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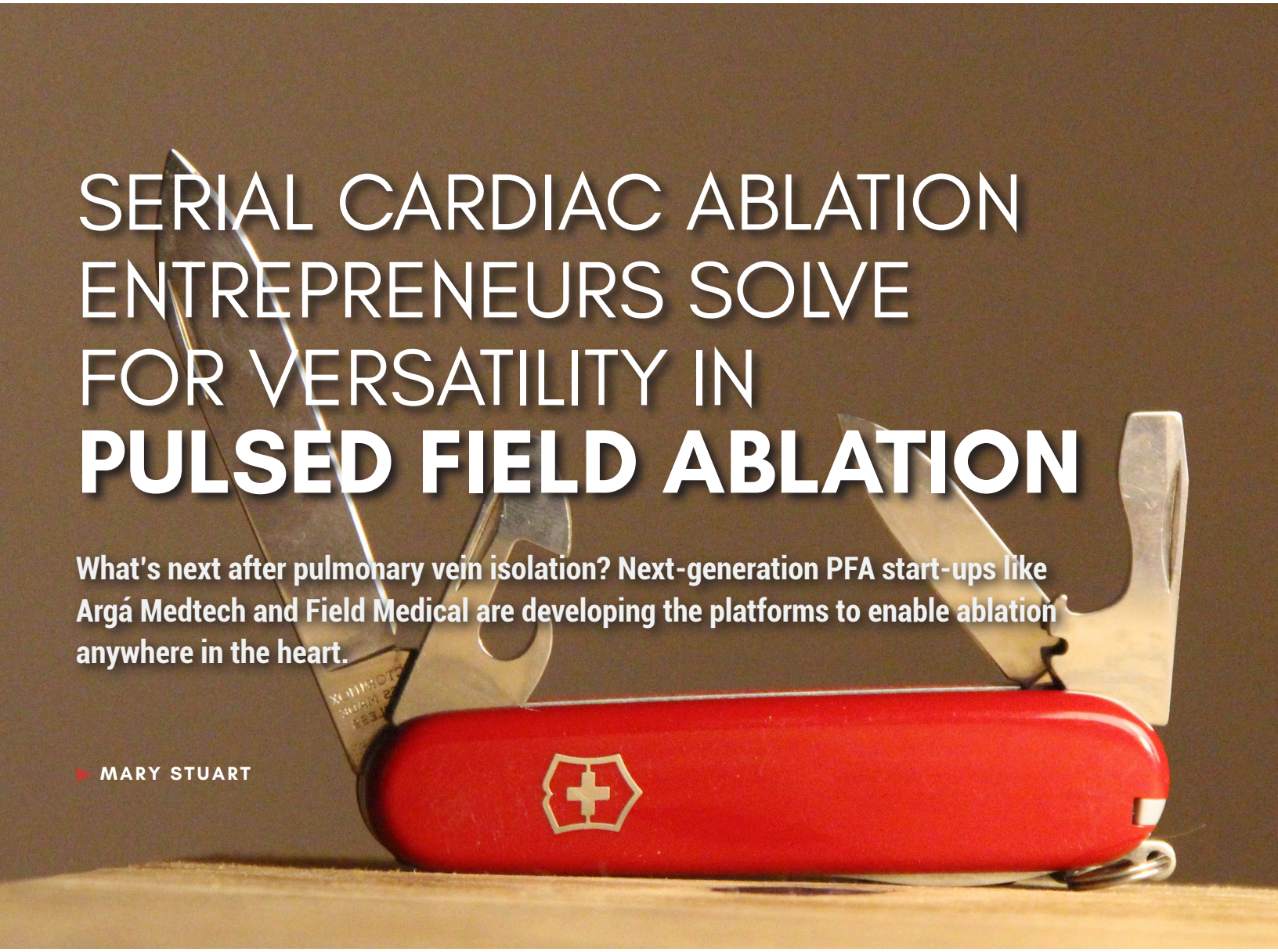
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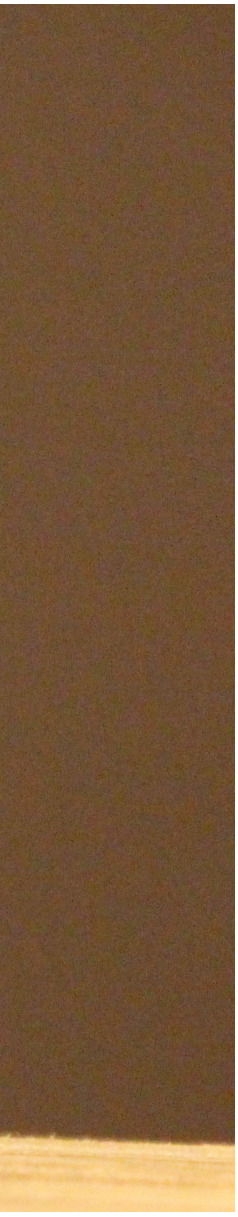
SERIAL CARDIAC ABLATION ENTREPRENEURS SOLVE FOR VERSATILITY IN **PULSED FIELD ABLATION**

What's next after pulmonary vein isolation? Next-generation PFA start-ups like Argá Medtech and Field Medical are developing the platforms to enable ablation anywhere in the heart.

▶ MARY STUART

Argá Medtech: The Power of the Sine Wave

Randy Werneth, co-founder and chief technology officer of pulsed field ablation start-up **Argá Medtech**, notes that his company's accented name comes from Greek, reflecting the concept "late to the party" in a field where the first generation began ten years ago, although one could say his new company is actually an early entrant to the second generation. It's easy for Werneth to be facetious in naming his company thus because in fact, in the field of atrial fibrillation and cardiac ablation, he has always been quite early. In 2004, he co-founded Ablation Frontiers, one of the first companies to develop a circular high-powered phased radiofrequency (RF) system for the treatment of atrial fibrillation. He founded **Acutus Medical** in 2011, the developer of a novel mapping system able to guide substrate ablation strategies, and in 2019 he created Maxwell Biomedical, to innovate a cardiac rhythm approach to patients with AF. (See *"Atrial Fibrillation Symposium 2023: Experts Debate Cosmic Questions,"* MedTech Strategist, *March 21, 2023*.)



It's Werneth's experience at Ablation Frontiers that's most relevant to his PFA start-up. Ablation Frontiers invented high-power short duration ablation and the concept of using monopolar and bipolar delivery of current together. At Ablation Frontiers, he says, "We would come on at 1,000 watts for microseconds, getting filling between lesions and in depth." Watching the development of pulsed field ablation, Werneth asked a friend, an engineer with whom he'd worked at Ablation Frontiers: "Just how difficult would it be to take the idea of what we did at Ablation Frontiers and transform the thinking and design to perform electroporation?" It took them about two years to master the challenge, but they did. At the recent Atrial Fibrillation Symposium, the team presented 60-day results of the first five patient experiences. "We went from up-and-running to human studies in two years,"notes Werneth, with a team that's expert in building ablation catheters and energy delivery systems.

Werneth also partnered with Switzerland-based David Neale to lead the company as co-founder and CEO. They'd worked together at Ablation Frontiers within Medtronic, which had acquired the start-up in 2009. The two decided to headquarter Argá Medtech in Switzerland, where there are more active early-stage VCs. Neale was instrumental in raising $10 million for the company, from European investors Advent Life Sciences in the UK, and Earlybird Venture and High-Tech Gründerfonds (HTGF) in Germany.

Argá Medtech's PFA platform is called *Coherent Sine-Burst Electroporation* (CSE). The main differentiating feature of the Argá platform is the ability to use a sine-wave approach to create bipolar energy, monopolar energy, or phased combinations of the two used simultaneously to tailor lesions.

According to Werneth, sine waves enabled the development of a multi-electrode catheter that offers better titration of depth and lesion volume. Where square waves step abruptly from one level to another, sine waves transition more smoothly because they consist of a single frequency. "By changing the start time delay, or phase, of a sinusoidal monopolar field applied to one electrode from the phase of a second sinusoidal monopolar field on an adjacent electrode, you mathematically create a third, bipolar sinusoidal field between them," Werneth explains. "You can offset the phase angle to deliver these at different time points. You can deliver a sine wave that's different from the next one."

That allows users to choose pure monopolar energy with no phase delay, for depth of penetration, bipolar delivery with phase delay of 180 degrees to localize the field (minimizing unwanted skeletal muscle contraction) or both together, combining both fill (contiguity of lesions) and depth. Electrophysiologists can thus achieve the lesion they want for the location of the catheter in the heart. "If they are in an area that is 5 millimeters thick, they can adjust for that. If they are ablating tissue one centimeter thick, they can change the waveform to ablate it," Werneth says.

Further, unlike conventional monophasic or biphasic square waves, sine waves are compatible with isolation transformers. As the name implies, these transformers completely isolate the patient from the high-power electronics needed to generate PFA fields, maximizing patient safety. Transformers also allow the system to increase the amplitude of the field being delivered. "We believe we can achieve transmural lesions where others can't. With sine waves we know we won't be underpowered."

To avoid the need for multiple catheter exchanges with their attendant workflow and safety drawbacks, Argá Medtech has developed an all-in-one catheter that deflects into different configurations—it can be used straight, for focal and linear lesions (precise targeting at individual points), addressing not only AF, but also atrial flutter, ventricular tachycardia (VT) and supraventricular tachycardia (SVT). The curved configuration is useful for circular linear lesions, and the circular form, for pulmonary vein isolation (PVI). Clinicians can accomplish all three ablation strategies with a single device.

"This design is in contrast to all systems under development by the competition," Werneth says, continuing, "companies have mostly focused either on single-shot devices for pulmonary vein isolation or on focal catheters, with larger or smaller footprints."

> "Everybody does PVI really well, so the search for what to do next is becoming more important. A catheter and generator like ours give physicians the flexibility to ablate anywhere in the heart, without having to get a second system and without having to do catheter exchanges."
>
> —Randy Werneth

Focal catheters, which ablate in a point-by-point manner, require more user skill and longer procedure times. Single-shot devices are specifically designed to conform to the pulmonary vein for PVI to provide procedural efficiencies. Argá combines both, with a catheter that is efficient as a single-shot device for pulmonary vein isolation while offering the flexibility of a focal or linear catheter for any other lesion required. In doing so, the company will improve procedure flow, shorten procedure times and reduce catheter exchanges. These efficiencies, and the fact that hospitals will require fewer devices, will save time and money for all stakeholders, according to Werneth.

The company expects to complete treatment of 35 patients in its first-in-human study, and also finalize follow-up by the end of the year. "If all goes well, we will file for an FDA feasibility study for AF at the end of the year. Because Argá's CSE System will have the ability to better titrate and form the lesion of choice, Werneth believes it offers the opportunity to go beyond the atria and also address VT, an enormous unmet need. The company plans to conduct a US feasibility study for VT in the first quarter of next year.

The goal of innovators in pulsed field ablation for cardiac ablation isn't necessarily to incrementally improve what's already being done; it's ultimately about achieving better outcomes for patients for whom existing therapies are inadequate. "Everybody does PVI really well," says Werneth, "so the search for what to do next is becoming more important. A catheter and generator like ours give physicians the flexibility to ablate anywhere in the heart, without having to get a second system and without having to do catheter exchanges. We can help them determine what, after PVI, will make a difference."

Field Medical: Bending the Conventions

Steven Mickelsen, MD, is out to beat himself at his own game. A cardiac electrophysiologist by training, he invented the first pulsed field ablation platform for cardiac ablation and licensed it from the University of Iowa to found Farapulse in 2012. Farapulse has led the way in terms of firsts and mosts. It was the first exit for a pulsed field ablation start-up, and its platform, *Farapulse* PFA, was the first product to make it to market when it gained CE mark in 2021. Finally, it's the most studied PFA system. (*See "The Arms Race in Pulsed Field Ablation," this issue.*)

Boston Scientific had held a 27% equity stake in Farapulse since 2014, and in June 2021 exercised its right to acquire the remaining 73%, paying $295 million up front, with an additional $92 million contingent upon the achievement of clinical, regulatory, and revenue-based milestones. After the acquisition, Mickelsen spent two years with Acutus Medical, where, as chief translational science officer, he was enlisted to expand the company's *AcQblate Force* catheter, which today delivers both RF and PFA energy.

In 2022, Mickelsen founded **Field Medical** to solve what he saw as short-sightedness in an industry where many companies are adopting the same approach to PFA; that is, adapting conventional RF catheters so they can deliver PFA. To explain what Field Medical is doing differently, he says, "Electric field strength isn't the same thing as volts. It's a function of volts divided by meters squared. Everyone is focusing on pulsed waveforms but not the meters-squared part; the geometry."

Mickelsen and his team at Field Medical are paying a lot of attention to electrode geometry. "The *FieldForce* catheter is quite a departure from conventional RF ablation catheters used today," says Mickelsen. It's an 8.5Fr. cylindrical catheter

with one of the therapy electrodes located on the inside irrigation lumen. The electric current path is forced to bend around the non-conductive tip to the external return electrode. "The result is something we call *FieldBending*. This electrode orientation attenuates the unwanted far field but concentrates the therapeutic effects favorably around the catheter tip." The *FieldForce* ablation catheter is magnetically enabled to facilitate visualization within 3D mapping systems and has contact force sensors to assist with safe navigation within the heart. The catheter is specifically built to provide precision and versatility required over the entire range of ablation procedures performed by RF catheters today (see *Figure 1*).

Field Medical is particularly focused on shaping electrical fields to reduce the far field effects seen with current PFA systems. Skeletal muscle contraction, unwanted stimulation, and vasospasm, for example, make current PFA therapies less tolerable to patients. According to Mickelsen, tolerability can be improved by several strategies related to PFA waveforms, but these approaches tend to create more heating and potentially impact procedural workflow unfavorably. "By changing the geometry of the electrodes, we can reduce the far-field effects by about half compared to a bipolar PFA catheter like Farapulse, and still have the same depth of tissue penetration." Also, Mickelsen notes, in cases where physicians need full thickness ventricular ablation the *FieldForce* system has theoretic capabilities to reach more than 2cm in lesion depth. "That's why I felt I had to start another company. To show the world what is possible with this technology, and that we can address VT and SVT alongside AF," he says.

Speaking at the recent Atrial Fibrillation Symposium, Usman Siddiqui, MD, a clinical electrophysiologist at Florida Cardiology in Orlando, FL, noted that the *FieldForce* electrode reduced far-field effects by 81% as compared to monopolar energy delivery and 46% compared to bipolar energy delivery.

Beyond PVI for AF there are millions of patients with heart arrhythmias who might benefit from focal ablation. Mickelsen notes, "Most electrophysiologists are very interested in seeing new tools to treat ventricular tachycardia. This is going to be the clinical regulatory path forward for Field Medical because it is a big unmet need." Ventricular arrhythmias pose a high risk of sudden cardiac arrest, at a rate, in the US, of 300,000 deaths per year, according to Medscape. It's difficult to get a good estimate of the prevalence of VT, but there is a high association with coronary artery disease and heart failure. "A large portion of patients could be treated more effectively by ablation than drugs," he adds.

Cardiac pulsed field ablation is only in its infancy. Mickelsen notes, "The heart is exquisitely sensitive to this means of ablation. It is an ideal place to evolve the technology." He believes that Field Medical has hit upon a couple of key concepts for which patents are pending and the company has also licensed external patents. "We have gained exclusive licenses to 172 enabling patents, because we are at the beginning of an evolution for a very effective application. There is room for really strong IP to be developed over the next several decades," he says.

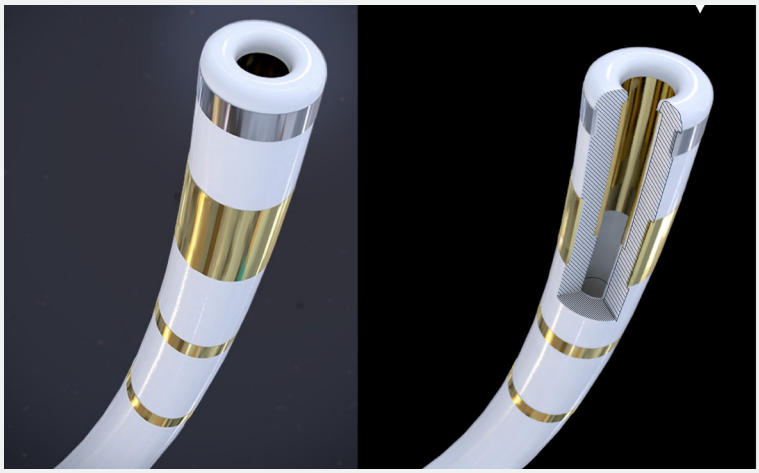
Field Medical is in the process of finishing its dosing work and has designed a series of human pilot studies that will begin within the next 12 months, Mickelsen estimates, after which he anticipates more than two years of development work before the company begins its pivotal trial.

Mickelsen believes the *FieldBending* technology to be robust. "This is the fourth cardiac PFA project I've been a part of. Of those, two have been tested in humans—Farapulse and Acutus—so I feel fairly confident that I know the development steps and, more, importantly where the pitfalls are." According to Mickelsen, Field Medical is on track to transform first generation PFA, which is narrowly focused on treating atrial fibrillation, to second-generation PFA optimized for therapy in the entire heart. MTS

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Figure 1

FieldForce PFA catheter



Source: Field Medical

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