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Atrial fibrillation is a serious medical problem—worst case, AF carries a five-fold risk of stroke. At best, its symptoms, which include feelings of dizziness, shortness of breath, and fatigue, make millions of people highly uncomfortable (33 million people in the world have AF, according to a recent investor presentation by Johnson & Johnson).

One of the principle treatments for AF is cardiac catheter ablation. A $5 billion-plus market that’s about 20 years old, its massive size belies the fact that there are many unmet clinical needs in the space having to do with issues as basic as safety and efficacy. Alarmingly, the disease is growing in prevalence much faster than the healthcare system can treat the rapidly growing patient population, estimated at five million new patients globally per year, according to the recent J&J presentation.

It’s clear that it’s an attractive market for innovative companies that can solve the current problems of this gold standard therapy, and hundreds of millions of dollars in venture funding have gone into the space in the past five years.

New atrial fibrillation companies are proliferating at such a rapid pace that, as medtech journalists, we could probably write about 12 companies a year, and indeed, MedTech Strategist has devoted quite a bit of ink to the subject in recent months. (See “New Atrial Fibrillation Mapping, Information Systems Lay Down Evidence Base,” MedTech Strategist, September 28, 2018 and “Atrial

Vytronus aims to become the Intuitive Surgical of ablation technologies, offering visualization, automation, machine learning, non-contact therapy delivery, and the ability to ablate in any application where catheters are delivered into the bloodstream. Its first application is an enormous one: catheter ablation for atrial fibrillation, where the company aims to boost efficacy rates by offering the first personalized approach.

Vytronus believes that personalization is the answer. The company offers an ablation platform able to tailor the delivery of ablative energy to the tissue beneath the non-contacting catheter tip. This is important, since patients’ hearts differ very much from one another as to thickness of tissue and the presence of scar and fibrosis.

Today’s cardiac catheter ablations are skill-intensive procedures with large variabilities in techniques and outcomes. Vytronus has brought robotics to the most challenging steps, so that more clinicians will be able to successfully treat even the most difficult patients with persistent AF, high fibrosis, or unusual anatomies.

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Fibrillation Ablation after CABANA: What are We Missing?” MedTech Strategist, August 24, 2018.)

One fundamental issue driving innovation in cardiac ablation is the high rate of recurrence of atrial fibrillation after a first ablation procedure. Single-procedure efficacy at one year in patients with paroxysmal AF (which terminates quickly on its own) stand at 65%-70%; only 45%-50% of patients with non-paroxysmal (i.e. persistent or long-standing persistent AF, where fibrillation lasts more than a week or doesn’t terminate on its own) are free of AF at one year. These efficacy rates are just averages; different operators and different centers have varying success rates, a problem having to do with skill levels and the definitions of success. At any rate, recurrence and the need for repeat ablation procedures is obviously undesirable from both the patient and economic standpoint.

During episodes of atrial fibrillation, the firing of cells from certain areas of the heart cause the heart to flutter. The goal of cardiac ablation is to wall off these trigger areas so they can’t disrupt the heart’s electrical patterns, by the use of catheters that deliver energy to the heart wall to create unbroken lines of scar tissue around them. There is consensus that isolating the pulmonary veins in this manner is an effective strategy for paroxysmal AF (PAF), but some patients with PAF and many with non-paroxysmal AF need additional ablation in other sites of the heart as well.

Much innovation revolves around making sure that clinicians are able to create lesions that are completely transmural in continuous lines, such that they don’t allow any signals to break through and cause trouble. Studies have demonstrated that much of the post-procedure recurrence of AF has to do with inadequate lesion creation (when lesions aren’t durably transmural, or the fence of scar that’s been created has gaps that allow signals to break through).

There are still other problems to solve. Safety remains an issue, since it is possible with most energy sources (except for some implementations of non-thermal electroporation, which is selective for cell types) to cause collateral damage to important structures like the pulmonary veins, esophagus, phrenic nerve, or other extracardiac structures. Other barriers to higher efficacy include the fact that operators with different levels of skill achieve different results. With regard to skill-dependence, it’s important to note one study that found that the majority of catheter ablation procedures for AF have been done by operators who do fewer than 25 cases a year. (See A. Deshmukh et al, “In-Hospital Complications Associated with Catheter Ablation of Atrial Fibrillation in the United States Between 2000 and 2010,” Circulation, November 5, 2013.)

Another drawback: many procedures are lengthy, creating a bottleneck in the electrophysiology lab when there are so many patients with atrial fibrillation to treat and so many repeat procedures. Balloon technologies (such as the cryoballoon balloon from Medtronic plc) look like they can solve the latter two challenges for pulmonary vein isolation, by enabling procedures that are rapid and consistent from one operator to another, and they’re rapidly taking market share (as discussed in our August 24, 2018 issue, cited above).

Moving an Anatomic Strategy to a Patient-Specific Treatment

Atrial fibrillation researchers are increasingly discovering that the current treatment paradigm is also fundamentally flawed. Many argue that it is only a strategy, based on the delivery of a predetermined level of energy to tissue in locations known to be sources of trouble, and not a patient-specific treatment that takes into account a patient’s own patterns of AF and heart tissue. This becomes important when one considers that scar tissue responds differently to thermal energy than healthy tissue, and every patient’s heart has unique anatomic differences including highly variable atrial wall thickness.

Vytronus Inc. offers a cardiac ablation platform that tailors energy delivery to the kinds of tissue it finds (it is already able to detect wall thickness, wall motion, edema, and other tissue parameters and will be able to integrate MRI fibrosis). It also replaces the most challenging and skill-dependent part of the procedure—the manipulation of catheters in the heart to deliver therapy—with a robotic platform that automates the process. Its platform uses ultrasound to both image the heart and deliver ablative energy. So far, it is the only integrated imaging and therapy delivery platform capable of making continuous lesions without contacting the tissue. The non-contact therapy delivery is what enables the use of robotics to precisely make continuous lesions anywhere in the left atrium.

In short, by using ultrasound to reveal the thickness and quality (various parameters including fibrotic or healthy) of tissue and also to ablate target tissue, the company has devised a way to tailor ablation to the heart of the patient on the table, and as such, it will be the first personalized cardiac ablation therapy for atrial fibrillation.

The ability to detect tissue thickness and other tissue properties is highly appealing in electrophysiology and at least two other companies are describing such capabilities: MRI-guided RF Ablation company Imricor Medical Systems and EPD Solutions, which, acquired by Royal Philips in June 2018, is offering a novel imaging and electrical mapping platform. (MedTech Strategist discusses Imricor in the...
August 24 issue, and EPD Solutions in the September 18 issue, both cited above.) According to Vytronus CEO John Pavlidis, “flying blind without knowing a ton of information about the nearby tissue properties prior to ablation will soon no longer be competitive. Delivering personalized patient therapy without relying on extraordinary operator skills will become a prerequisite for any state-of-the-art system.”

The company completed its first-in-man study in 2013, upgraded the system in 2016 and since then has conducted clinical trials with more than six operators on 70-plus patients at two centers in Europe, where the company is now expanding to multiple centers. Vytronus recently submitted for CE mark. In 2019, the company expects to conduct feasibility work in the US and apply for pivotal IDE approval.

Granted, there are still some clinical hurdles ahead, but if all goes well, Vytronus will pursue a large market for cardiac rhythm disorders—as mentioned, the multibillion-dollar AF market (growing at 11% CAGR according to market leader J&J), with additional growth opportunities in persistent AF, an indication the company will seek in its FDA labelling, since those patients account for 70% of the population eligible for AF ablation.

In the cardiac ablation market, the company will also address supraventricular and ventricular tachycardia, the latter an important emerging market as well. And that’s only the beginning. Renal denervation for the treatment of drug-resistant hypertension is a future application, and indeed, says Pavlidis, the platform is useful “any time you need to visualize and ablate tissue without touching the tissue and from within a blood vessel.”

Real-Time Imaging and Ablation from a Single Catheter

Vytronus was founded in 2006 by Hira Thapliyal, PhD (a co-founder of ArthroCare Corp.), the late David Gallup, and Jim Arenson, PhD, a biomedical/electrical engineer who worked for many years at Acuson Corp. The company raised some $40 million prior to 2015, early years that it spent doing fundamental research and validation on a platform called low intensity focused ultrasound (LICU). Unlike HIFU (high-intensity focused ultrasound), which is powerful, focuses on a particular location and mechanically cavitates the tissue, LICU is intentionally unfocused ultrasound, delivered in a beam with a diameter of approximately 2mm for its entire length. Says Pavlidis, who joined as CEO in 2015, “It’s not focused energy and it cannot inadvertently focus on the wrong tissue. The maximum level of energy is delivered to the myocardium, and the energy builds inside the tissue.”

Since Pavlidis joined, the company has raised an additional $80 million up through its Series C round. (Vytronus was recapitalized in 2014 and the original founders no longer play active roles within the company.) The current roster of investors includes Apple Tree Partners, New Enterprise Associates, BioStar Ventures, Windham Venture Partners, and Abbott Ventures.

The company’s vision was to overcome the limitations of current technologies in a single platform. Current approaches to cardiac ablation for atrial fibrillation fall roughly into two categories; the first includes point-by-point catheters, the goal of which is to make adjacent single point ablations to try to create an unbroken line of scar. These can be used for both pulmonary vein isolation and the ablation of substrate elsewhere. However, the results of single point ablations are dependent upon the skill of the operator and the accuracy of electroanatomic mapping and registration.

Balloon ablation catheters, which are effective for pulmonary vein isolation, make up the second category. The operator places a balloon in the ostia of the pulmonary veins, and the balloon delivers one or more shots of energy that create a circumferential line of ablation. The balloons offer rapid and reproducible procedures in the hands of operators of all skill levels and are not dependent upon detailed electroanatomic maps. However, they can’t accomplish strategies for substrate ablation in sites other than the ostia of the pulmonary veins, such as WACA (wide area circumferential ablation), an increasingly common strategy. Balloons are also susceptible to the large human anatomic variations and there are some complex or large patient anatomies that cannot be efficiently ablated with current balloon sizes. Most balloons deliver the same amount of energy around the entire circumference and cannot titrate the energy delivered to account for patient variations in wall thickness.
In a radically different platform, Vytronus has combined the flexibilidad and versatility of point-by-point ablation technologies with the ease-of-use and lesion continuity of balloons.

A Powerful Platform that’s Easy to Use

Indeed, the Vytronus system makes the most difficult parts of point-by-point procedures easy. As is customary in cardiac ablation procedures, the operator inserts the sheath, crosses the septum from the right atrium into the left atrium, inserts the catheter and aims it towards the posterior wall. “All of this is done manually,” says Pavlidis, “We aren’t applying automation to this step, which people are amazingly good at doing safely.”

The same catheter is used to both image/map the atrium and to deliver energy; both are accomplished by the catheter tip, which is robotically controlled (see Figure 1).

First the system uses M-mode ultrasound to map the endocardial geometry in three-dimensions. “In fact, we also capture motion over time, so it’s really four dimensions,” says Pavlidis. The robotically-controlled catheter tip, which houses both an ultrasound transducer and location sensors, is highly deflectable and moves in a spiral pattern to collect thousands of data points. From this ultrasound and location sensor data, a rich color-coded representation of the heart wall is created, where colors indicate the distance from the catheter tip and thus zones amenable to therapeutic ablation. The Vytronus system can ablate at a distance of more than 1.5 centimeters and a lesion depth of more than 1 centimeter. This high-resolution anatomic mapping procedure takes about two-to-three minutes.

Using this information, the clinician designs a free-form lesion path by simply using the computer mouse on the 3D anatomic map. Next, the catheter, again under robotic control, takes a practice run along that trajectory, automatically detecting tissue thickness, distance, and motion as it goes, and calculating the suitable energy dosage. Once the electrophysiologist hits the “go” button, the same catheter traces the same path, this time delivering enough energy to ablate the tissue without directly contacting it (see Figure 2).

Electrophysiologist Vivek Reddy, MD, director of cardiac electrophysiology and Helmsley Trust Professor of Medicine at the Icahn School of Medicine at Mount Sinai and a thought-leader in the field of cardiac ablation, is a consultant to the company. Reddy, who has conducted preclinical work with the catheter, says “It often gets glossed over that when we use a mapping system to create a map, the quality of that map is dependent on operator experience and technical expertise [in addition to the fact that ablation also depends on the catheter skills of the operator]. But this [Vytronus] system uses ultrasound to define the anatomy itself. It removes operator dependence from creating the anatomy.” Moreover, he notes, mapping and ablation all occur with the same framework of coordinates, which also increases accuracy.

“Most difficult part of the procedure, which is delivering the correct amount of energy along a flexible lesion path, is done automatically,” says Pavlidis. The energy dosage level is a function of the distance from the tissue, the angle of attack, the speed of the catheter, and how much energy is absorbed, all of which is captured without contacting the tissue. Pavlidis notes that only a small portion of the energy attenuates as it goes through blood; most ends up in the tissue. “You’re not coagulating blood, you’re not creating char. You’re not getting anywhere close to 100 degrees centigrade, and you’re making continuous lesions.” Operators can create dots, lines, circles, curves, whatever they need to. “We are replacing subjective and skill-based variations in technique with objective and reproducible technology,” says Pavlidis.

Although the Vytronus system is very different from anything out there, it’s easy to adopt. “You insert the catheter through the groin, put it in the heart, and push a button,” says Vivek Reddy. The operator monitors the procedure from the console and since the system can be operated remotely, is not necessarily at the side of the patient. “Obviously there are numerous safeguards. We always know the exact location of the catheter tip. If anything changes, there are built-in safeguards for stopping or pausing.” The clinician can decide to pause and draw a new path, if so desired.

Reddy notes that it can be uncomfortable, at first, for electrophysiologists to step away from the patient, but he says “don’t forget—the field has had 10-plus years of experience with Stereotaxis Inc. and Hansen Medical Inc.” He points out that a nurse in the room is also monitoring vital signs minute to minute. “And in one sense, it’s even easier
to be close to the patient because you’re not using fluoro.” Radiation exposure is an obvious disadvantage of the x-ray based modalities used to guide catheter ablation procedures, but there are ergonomic disadvantages as well. “The chance of developing cancer because of radiation might be a worry in the back of your mind, but every day you think about the fact that your back hurts from wearing lead,” says Reddy.

Again, the system knows the tissue thickness and the motion, and the dosing is very specific to that patient, Pavlidis says, noting that the imaging beam is about 6 centimeters long, so it can image beyond the atrium, “and we’re getting better and better at visualizing extracardiac structures.” The system can also visualize edema and confirm lesion transmurality and will continue to improve in all of these procedural aspects because it is collecting thousands of data points from each procedure. These will be run through artificial intelligence and machine-learning algorithms to continually evolve and improve the platform. The company can analyze and “replay” the steps of the entire procedure and retrospectively look at prior data to evaluate the impact of dosing or other algorithm changes. The software nature of this development enables a learning system with development cycles that are faster than typical catheter or hardware development.

Nassir Marrouche, MD, Executive Director of the Comprehensive Arrhythmia Research and Management Center (CARMA) at the University of Utah in Salt Lake City, a consultant to Vytronus and a researcher who’s studied the technologies of many atrial fibrillation companies, says, “Imagine the amount of data that ultrasound in real-time can generate. Yes, you are delivering the lesion objectively [with the Vytronus system] and you are also visualizing the damage to the tissue. If it is too deep it will tell you. If it is too little, it will tell you. The power of AI is that with all this data from every single case, the system is learning and getting more powerful all the time.”

One Heart is Unlike Another

Marrouche has spent much of his career looking to improve the outcomes of cardiac ablation by studying structural changes in the atrium. In 2006 he pioneered the use of magnetic resonance imaging, at the University of Utah, during cardiac ablation procedures, and founded CARMA in 2009, which has focused on atrial fibrosis and precision AF medicine.

After safety, atrial fibrillation recurrence is at the top of the list of problems electrophysiologists would like to solve. Repeat procedures to eliminate atrial fibrillation are not only undesirable for patients, but they’re costly to healthcare systems, representing a significant portion of the $26 billion in health care costs attributable to patients with AF. One study estimated that repeat ablations are necessary in more than 17% of patients within 12 months after their first cardiac ablation procedure, and in the year following the second ablation procedure, patients costs about $40,000 more than those whose disease was well managed by a single ablation (according to Moussa Mansour, MD et al, “The Impact of First Procedure Success Rates on the Economics of Atrial Fibrillation Ablation,” JACC: Clinical Electrophysiology, Vol. 3, No. 2, 2017).

Recurrence is not only a function of the inability of current technologies to create lesions that are transmural and continuous 100% of the time; differences between patients are also factors. Marrouche was lead investigator of the DECAAF study, published in 2014, which identified extensive left atrial fibrosis as contributing to poor outcomes after catheter ablation. Marrouche also spearheaded the CASTLE-AF trial, which found that in patients with co-existing atrial fibrillation and heart failure, catheter ablation significantly reduced hospitalizations due to worsening heart failure and death. (See sidebar, “Precision AF: Towards a More Objective Treatment of Atrial Fibrillation.”)

“Not every patient is the same,” says Marrouche. “We know that you if you have heart failure symptoms, they can improve if you fix Afib. But if the ventricle is scarred, the chance of improvement is lower. That isn’t something that we took into consideration until we started studying it at CARMA.” It’s not likely that the patient with extensive scar tissue will have the same outcomes as the patient with a healthy heart that has no sign of scarring, he says.

“We should be armed with this information before we do the procedure. Ideally, when I see scarring, my energy levels should change, because if I ablate too much or too little, I might have a problem.” In the former, you are killing more heart tissue than you need to, in the latter, under-ablation might result in recurrence. “If we could get this [Vytronus] product into action, then we would be way ahead, because then anyone anywhere could do this objectively, without relying on the operator’s level of experience. It is all based on information that you could standardize.”

As noted, Vytronus is capable of executing a variety of tailored ablation strategies (pulmonary vein isolation, WACA, substrate ablation) and could potentially be used in every single patient. That role, of course, will ultimately depend on the kinds of economic arguments—cost-benefit analyses—the company will be able to make once it has gathered widespread experience.

Will clinicians reach for quick and easy balloons when odds are that pulmonary vein isolation will suffice, and reserve Vytronus for only the most complex types of cases? Time will tell. It’s not a new conundrum; the same arguments that cause hospitals to adopt surgical robots for prostate cancer
Robotics Comes to Cardiac Ablation

Intuitive Surgical Inc. has become perhaps the most successful medical device company ever: a start-up in 1995, it now has a $60 billion market cap. Its da Vinci brand is almost synonymous with robotically-enabled surgery itself (see "Intuitive Surgical: As Robotics Heats Up, Can the Market Leader Stay Ahead of the Pack?" MedTech Strategist, December 19, 2018 and "Intuitive Faces the Future of Surgical Robotics," this issue).

And the number of successful robotics companies is growing. Large strategics have acquired robotics companies in orthopedics, including Mazor Robotics (which is now part of Medtronic plc) and Mako Surgical (now part of Stryker Corp.). And what has driven these successes? According to Pavlidis, "Large markets with high procedure volumes, and very importantly, skill-intensive procedures with large variations in techniques and outcomes, where superior visualization with 3D resolution is critical." All of that is certainly true for cardiac catheter ablation.

These businesses are further attractive, because they offer revenues from disposables, market differentiation for hospitals in their local markets, and a short learning curve. Vytronus again checks off all the boxes. It might allow a hospital to be the only one in its region performing personalized cardiac ablation; Vytronus will sell disposable sheaths and catheters, and as noted, it is easy to adopt. "We found that the learning curve for our procedure is short. Three to five procedures is our experience, which seems to be much shorter than it is for other robotic approaches."

On the other hand, the Vytronus robotics platform has some advantages that robotic platforms for other applications don’t. For example, the upfront capital investment is relatively low. It will priced at a level that “is actually quite comparable to systems used with other commercially avail-

and orthopedics apply here, and indeed, Pavlidis says that it is the goal of Vytronus “To become the Intuitive Surgical of Ablation.”

Indeed, beyond atrial fibrillation, Vytronus has a broad platform suitable for many potential applications requiring minimally-invasive ablation from within blood vessels. Ventricular tachycardia is another important clinical application. Says Vivek Reddy, “The need in ventricular tachycardia is extraordinary, and there has yet to be a single tool to be developed for VT ablation.” He says some early-stage companies are working on the problem, but to date, clinicians have used tools designed for AF and repurposed for VT. “The need is great, the opportunity is great, and if the patient volume doesn’t seem to be that high right now, that’s because the efficacy hasn’t been that good. But if they build it, patients will come,” he says.

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—Nassir Marrouche, MD

And there is one other important distinction, Pavlidis says. “An Intuitive Surgical robot has amazing visualization and it does things very precisely and reproducibly inside the body, but it is operated by a very well-trained operator; it is precisely reproducing those motions inside the body. In other words, it is a highly sophisticated tele-operation.” Vytronus, in contrast, increases the skill level brought by any operator. “The catheter always senses its environment. There is an element of autopilot here, under physician supervision, of course,” Pavlidis says. “The catheter knows where it is, and knows the tissue around it, how thick it is, and how it’s moving. The 3D anatomic mapping is done in an automated fashion. The lesion planning is on the 3D map on the computer screen. The continuous lesion is delivered automatically within numerous safety parameters.”

The next benchmark for the company is the publication of its initial clinical study on paroxysmal patients and the initiation of a feasibility study and then a pivotal IDE on persistent patients. Initial results will be presented by Vivek Reddy at the AF Symposium in Boston at the end of January.

What Vytronus is doing is extraordinary, but of course a lot of companies in the space are doing extraordinary things. Clinicians can try out and adopt only so many new technologies, though, especially when many of them address only a few of the limitations on the list. Says CARMA’s Nassir Marrouche, “I think we really can’t continue like this with a new ablation catheter every year. People are still inventing because there is no solution, but they are missing the point. You need to make this procedure objective,” he says. It’s still early, but Vytronus, in offering the first personalized therapy for cardiac ablation procedures, does appear to have meaningful differentiation that might allow it to pull ahead of the pack.
Twenty years ago electrophysiologist Nassir Marrouche, MD, began working to improve the outcomes of catheter ablation for atrial fibrillation. For the past 12 years, his research has homed in on structural changes in the atrium and how they influence the prognosis of atrial fibrillation and impact co-morbidities such as heart failure.

As the founder and executive director of the Comprehensive Arrhythmia Research and Management Center (CARMA) at the University of Utah in Salt Lake City, he has spearheaded initiatives to use 3D MRI to look at tissue structure in patients undergoing catheter ablation for AF, with the goal of developing individual treatment strategies that improve outcomes. His research looks at how both patient selection and the treatments themselves could be tailored to the quality of heart tissue in each patient, that is, the presence and extent of scar or fibrosis in the atrium or the ventricle.

Marrouche was a lead investigator on the DECAAF trial, which sought to look at the impact of atrial fibrosis on outcomes after AF ablation. Published in 2014, DECAAF was a prospective study at 15 centers in the US, Europe and Australia. It enrolled 329 AF patients (including paroxysmal and non-paroxysmal AF) undergoing a first ablation procedure. Images of the each patient’s heart were taken up to 30 days before the procedure (by delayed enhancement MRI) and the extent of fibrosis in each patient was quantified by a core lab blinded to the participating center, ablation approach and outcome.

The study found atrial tissue fibrosis to be a factor that increased the likelihood of atrial fibrillation recurrence. (See “N. Marrouche, et al, “Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Study: The DECAAF Study, JAMA, February 5, 2014.”)

Marrouche was also a lead investigator for the CASTLE-AF trial, published in February 2018, which looked at the impact of catheter ablation on patients with co-existent atrial fibrillation and heart failure. Patients who received ablation fared better than the control group on medical therapy, on the composite endpoint of death from any cause and hospitalization for worsening heart failure. (Sub-group analyses of the landmark CABANA trial, published last year, also found a clear benefit for catheter ablation in heart failure patients with AF.)

As a preclinical and clinical researcher, Marrouche sees many new atrial fibrillation technologies; he consults for Abbott Laboratories Inc., Medtronic plc, Vytronus Inc., Johnson & Johnson’s Biosense Webster, Boston Scientific Corp., GE Health Care and Siemens AG, and holds equity in Marrek Inc., a new company developing software to enable the MRI-based guidance of catheter ablation for atrial fibrillation.

Marrouche says the spate of innovation in atrial fibrillation is not slowing down, because the problems with AF recurrence haven’t yet been solved. But most companies, he says, “are missing the point. You need to make this procedure objective.” MedTech Strategist recently spoke with this thought-leader in catheter ablation for atrial fibrillation to learn what, in his opinion, needs to change.
MedTech Strategist: We hear a lot about the high rates of recurrence of atrial fibrillation after a single procedure, which is obviously expensive and not very good for patients either. When you—or let’s just say physicians in general—are going into an AF ablation procedure, with what kind of certainty can you predict that AF won’t recur?

Nassir Marrouche: [After a moment of silence]. You are starting with a loaded question already!

I’m leading up to asking you to what extent innovative technology can have an influence on recurrence!

Recurrence is the most important question for every physician, except for safety, which is number one. If, as a patient, you go to three different hospitals, they will say that their success rate is such and such and they are talking about recurrence. But how do you define recurrence? That is a topic for a whole article that needs to be written.

I have been trying to find a way to deliver ablation lesions that are safe and lower the chance of recurrence for the past 20 years. And that is the challenge for every single new technology we hear about. But none of them, until the One-Shot system came along [first-generation ablation balloon from Medtronic] considered a major issue that we face across the world: the objectivity of this procedure, which continues to be operator dependent.

By ‘objectivity,’ you mean...

If you go to five different electrophysiologists today, they will give you five different ways of doing AF ablation, and we have been struggling with that as well. So if you were to ask me the top three things I worry about: safety, delivering good lesions to avoid recurrence, and, to make these procedures widely adopted and standardized—to increase the objectivity of the procedure.

How many of these issues can be solved by technology, and how many of them have to do with variations between patients—whether or not they also have scar tissue, heart failure, or other co-morbidities?

That was why, in the beginning, I was careful to say that how we define success is important. If we ablate AF, what are we looking for? Is it based only on recurrence of arrhythmia and patients’ symptoms? Is this enough?

After the CASTLE-AF trial, we now know that in the heart failure population we can save lives with this procedure and also that lowering the Afib burden by 50% is associated with an improvement in mortality and hospitalization. You don’t even have to eradicate Afib completely. Lowering the burden can save lives.

In practice, however, if you go to any clinic, EPs ablate AF to treat its symptoms, and that’s why I ablate my patients. If drugs aren’t working or they don’t want to take drugs and in addition they have symptoms of heart failure, we ablate them to minimize their symptoms. [Editor’s note: more than 50% of AF patients do not respond to or cannot tolerate drug therapy, according to Calkins et al, Arrhythmia and Electrophysiology, 2009; 2:349-361.)

So by ‘objectivity’ you didn’t necessarily mean standardizing the procedure. You meant having more objective goals for the therapy, or endpoints?

Patients aren’t all the same, and that is a challenge. Objectivity of the procedure includes a personalized approach to this patient. That means that I want to go in not only based on heart failure, which is an expression of symptoms—shortness of breath, a failing ventricle—which has been known to improve after ablation. But if the atria and ventricle are too scarred, the chance of improvement is lower. That isn’t something that we took into consideration until we started studying it at CARMA.

We could take these criteria today and characterize them to create the concept of an objective procedure. You can see from our work and because of the DECAAF study that many people have scarring in the atrium, acquired over a lifetime or because of disease, and the amount of scarring or fibrotic tissue impacts the outcome. So going to a patient with a lot of scar and doing the same thing as you would to a patient with a healthy heart probably wouldn’t have the same odds of success because you haven’t taken into account how different tissues react differently to the therapy. But people are starting to do that with MRI now. We are getting to a more personalized approach.
You would personalize the ablation strategies based on where the scar tissue is?

Even before I get to the procedure, I could say that I should not ablate this particular heart because of the amount of scarring in the atrium and ventricle based on the MRI image. In that case, I would want to work with your symptoms in a way that is not invasive.

On the other hand, if I go into the procedure knowing this information, and again, that’s what I mean by objectivity, and if I had a tool that could deal with this tissue, based on its structure and identity, rather than just ‘yes’ or ‘no’, if I could integrate this structural information into a system that would change energy levels when it sees these changes instead of ‘one shot fits all’, then we would be way ahead. Then anyone anywhere could do this objectively without relying on the operator’s level of experience. It is all based on information that you could standardize.

Do you think cardiac ablation device companies do, or are able to do, within the constraints of timing and budgets, the kinds of clinical trials that demonstrate the value of their technologies for treating AF? Or let me put it this way: does anything need to change in the way clinical trials are being done here?

We need to define outcomes differently. The FDA has been asking for endpoints along the “30 second rule.” [The FDA defines AF elimination as freedom from atrial flutter or atrial tachycardia episodes of 30 seconds or longer as detected by Holter or event recorder.]

How should we define outcomes in ways other than recurrence? For tools, we need to start looking at MRI scans and lesion formation. For example, if we want to test five different catheters, the FDA mandates that we do a study and look at safety and recurrence at three months. What is safety? Did the patient die, have a stroke, or is he bleeding?

But if you do an MRI scan within three months or even two weeks of the procedure, which is the way it should be designed, you could see whether the catheter did the one thing it was designed to do: deliver a lesion that ablates tissue. That is the endpoint of the catheter. If you have a threshold by which the catheter is measured irrespective of scar, fibrosis, or whatever in this patient, you don’t have a standardized endpoint and you cannot make the procedure more objective. Outcome is a different measure, and we will never have an objective measurement using outcome. I am talking to the FDA about this.

Plus you could obviously look at other measures. Where is the Afib? Could we change the outcomes from the “30-second rule” to lowering the AF burden?

I haven’t seen much more written about the CABANA trial, after the flurry of press at the release of the original results last May. What is your takeaway from the trial?

Unfortunately, there was a lot of crossover in CABANA, so we lost a lot of potential and power in the data. In the drug arm, 30% of patients crossed over to the ablation arm, so it was difficult to analyze from an intention to treat standpoint. It depends on who you ask. It was a neutral study, but with a lot of positive data. If you look at the per-protocol treatment, CABANA showed that ablation did save lives and improve outcomes. And what was interesting is that if you look at the heart failure population in CABANA, they did as well as CASTLE-AF. It clearly made a difference in that population.

But in the trial clinicians used ablation tools from the past 10 years and meanwhile catheters have been changing. Can you imagine how messy that data was—different catheters, different kinds of energy delivery, different operators, different labs? The only way to do a study like this is to have the lesion created in an objective way, and Vytronus is the only technology that can offer objectivity today. [See “Vytronus Poised to Offer the First Personalized Approach to Cardiac Ablation,” this issue.) Then you could detail the lesion sets in patients based on tissue characterization. You would know for sure that it was objective and the same in any two labs in the world.

What is the most important thing you’ve learned from your work in characterizing heart tissue in patients with AF?

We need to personalize this procedure. We can’t ablate everybody. But we are missing a lot of patients who are waiting and taking drugs and meanwhile their hearts are scarring. We need to personalize each procedure so we will be able to intervene before it’s too late.