Larry Chinitz

SYMPLICITY AF: evaluating the potential of combination of pulmonary vein isolation and renal denervation for atrial fibrillation

Atrial fibrillation (AF) is a common disease that is associated with considerable morbidity and mortality. While management of AF has improved since the introduction of catheter-based ablation about 20 years ago, the disease still poses clinical problems. The autonomic nervous system has been implicated in both AF and hypertension, which can cause and exacerbate AF. One potential therapy for hypertension, renal denervation destroys sympathetic nervous tissue in the kidneys. *Confluence* spoke to Dr Larry A Chinitz, NYU Langone Medical Center, New York, USA, to find out more about how renal denervation might help patients with AF.

How common is AF and what are the major health concerns and complications associated with it?

Larry Chinitz (LC): AF is by far and away the most common electrical disorder that we deal with. There are an estimated four million people in the United States alone who have the condition, and that number has increased substantially as our population ages. AF is an arrhythmia that occurs both with and without the presence of underlying heart disease, so it's common in both young and old people.

The two most adverse outcomes associated with AF are stroke and reduced cardiac output. AF is a major cause of neurological disorders, including stroke. When the heart fibrillates and the blood does not circulate well, this can lead to blood clot formation. Indeed, thromboembolic disease, stroke or transient ischemic attack can be the first manifestation of the arrhythmia. When patients are in normal sinus rhythm, synchronized atrial contraction is present and maximises cardiac efficiency. This is lost in atrial fibrillation and may lower cardiac output by as much as 25%. That results in very substantial symptoms, such as shortness of breath, exercise intolerance, episodes of palpitation and light-headedness. There is an entire spectrum of symptoms and they can be quite limiting for patients, so this is a major health problem.

How do people with AF present to the clinic?

LC: First of all, some people are extremely symptomatic, and recognise the second the arrhythmia begins and the second it terminates. However, there are many others who are completely asymptomatic and who are only identified if they happen to be in AF while in the doctor's office or are undergoing an electrocardiogram. Therefore, we are not always aware of the presence of the arrhythmia.

The CRYSTAL AF trial that was recently presented in the *New England Journal of Medicine* investigated the link between ischemic stroke and AF, because the cause of stroke remains uncertain, despite a complete diagnostic evaluation in 20–40% of cases (cryptogenic stroke).[1] The study showed that if you monitor those people for as long as 3 or 4 months, the incidence of AF approaches 40%, so it can sometimes take a few months to show that they did in fact have AF.

How is AF treated at present?

LC: There are predominantly two modes of therapy. One is medical therapy, in which anticoagulant medications are given to lower the risk of stroke and additional medications are given to treat the AF. Medical therapy is never curative but controls the arrhythmia in many patients, in so much as it

reduces symptoms, decreases the frequency of episodes and slows the rate of the heart during an episode of AF.

The other approach is catheter ablation. Catheter-based therapy is designed to electrically isolate the pulmonary veins and posterior wall of the left atrium to suppress and prevent atrial fibrillation. Catheter-based therapy has come a really long way over the course of the last 20 years.

The final thing is there are many modifiable risk factors that contribute to the process of AF, such as hypertension, sleep apnoea, obesity or certain lifestyle factors. Therefore, we manage these aspects alongside medical therapy or catheter ablation because they have an impact on the long-term success of the primary treatment.

What impact has the introduction of catheter ablation had in terms of outcomes for patients?

LC: Twenty years ago, when we began addressing AF with catheter-based ablation therapy, it was a very difficult procedure. We weren't particularly clear on how much ablation needed to be done and we didn't have the right tools. It took a long time and collaboration between industry and the electrophysiology community to understand what type of lesion set should be given to patients.

Nowadays, in some populations of patients, it's an amazingly successful procedure with a very low complication rate. The incidence of stroke is less than 1%, as determined by a worldwide registry of AF published by Caputto et al.[2] However, outcomes can vary in different populations depending upon the presence of structural disease, how long they've had AF or how big their left atrium has become.

You mentioned modifiable risk factors such as hypertension. What is the association between AF and hypertension?

LC: There is a very strong association. We know that the factors associated with AF such as increased intracardiac pressure and changes in the structure of the myocardium that can occur as a result of the hypertension can influence the presence of AF. Studies have shown that patients with well-controlled hypertension have far more success with therapy. There are physiological effects associated with sleep apnoea, with hypertension, with obesity, that directly impact both the structure as well as the electrical properties of the atrium that contribute to the development of AF.

With this in mind, is there a relationship between the sympathetic nervous system and AF?

LC: That's an area of enormous discussion and research. We have known for a long time that the autonomic nervous system plays a direct role in the vulnerability of the atrium to AF. The influence of the sympathetic and the parasympathetic nervous system directly impacts upon the heart's electrical properties, such as how fast it can conduct, the refractory period and conduction velocity, and this neurological input influences AF.

Many years ago it was shown that the parasympathetic ganglia that innervate the heart are very close to the areas that we were ablating for AF. Subsequently, we showed that catheter ablation from the endocardial side actually influenced the parasympathetic innervation, which had a positive impact upon success of catheter-based therapy. Following this, surgical procedures were developed to resect the parasympathetic ganglia that exist on the epicardial surface of the heart, as another means of influencing the success of catheter ablation or even surgical ablation. That has been shown to truly have an impact.

Moreover, beta-blockers, which block the sympathetic nervous system, have been used to treat AF for decades, so we know that the autonomic nervous system has a role. However, the process of teasing out the precise roles of the sympathetic and parasympathetic nervous system, and understanding the best way to harness this knowledge is ongoing. We know that the autonomic nervous system is a major player, we know that it influences the structural and the electrical remodelling that occurs in patients with AF, and now we are just trying to figure out the best way of modulating it to improve our success with catheter or medical therapy.

You were speaking there about the surgical removal of ganglia on the cardiac surface as management for AF; how much impact can renal denervation in the kidney have on AF?

LC: Yes, what's most important is to recognise that the autonomic nervous system is a very complex

fig. 1

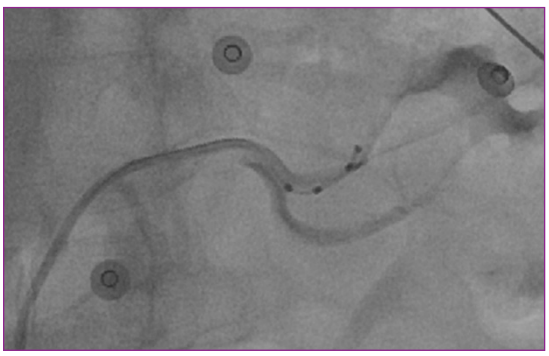
Symplicity Spyral™ catheter for renal denervation

fig. 2

Arctic Front Advance™ Cardiac CryoAblation Catheter

fig. 3

Circular ablation catheter in the renal artery



interplay between the brain, the parasympathetic ganglia adjacent to the spinal cord, and various organs, most notably the heart and the kidney.

Sympathetic innervations to the kidney result in a change in blood pressure, which signals back to the heart to change heart rate and blood pressure response, which signals back to the brain and spinal cord. There is an entire literature on the very important interaction between the brain and the spinal cord, the sympathetic nervous system and organs such as the heart and the kidney.

Adequate renal denervation is required and often takes special catheter skills, and ablation in multiple branches. Renal denervation, if done correctly, is an effective means of altering the autonomic input to the heart and to blood pressure regulation. The question now, is can we have that same effect on the heart's electrical disorders?

We need to investigate two potential mechanisms through which renal denervation may impact AF. Firstly, if renal denervation significantly affects sympathetic and parasympathetic output, resulting in lowering of blood pressure, will that lowering of blood pressure have a significant influence upon the heart's AF tendencies, which are very closely tied in to blood pressure? The second part of this is, can renal denervation affect the direct autonomic input into the heart, and achieve the same effects that a surgeon may get with surgical resection of parasympathetic ganglia or other modulations? We know that effective renal denervation is a relatively easy way of affecting the autonomic nervous system, which, at least theoretically, should have an impact on AF both through the blood pressure effects and other effects.

What clinical evidence supports the hypothesis that renal denervation might be useful in combination with pulmonary vein isolation?

LC: There is a series of small studies, a couple of which have been published, showing that renal denervation can have an influence on the development of AF: there is a study from Russia and a couple of others which have shown efficacy. This, combined with the theoretical influence, made it important to have a definitive trial investigating these things.

SYMPLICITY AF will be a definitive trial, and it has to do two things: it has to result in effective ablation using our current technology for managing AF, as well as truly effective renal denervation. The technology that Medtronic has can answer both of those points (figure 1 and 2).

Can you tell us more about the SYMPLICITY AF trial?

LC: We are looking at patients with paroxysmal or newly persistent AF who have concomitant hypertension with at least at 150 mm/Hg systolic blood pressure, and who are on at least two antihypertensive medications, one of which is a diuretic. It's not a population with severe refractory hypertension, as in previous SYMPLICITY trials, but they are hypertensive and remain hypertensive, despite two drugs. We intend to randomise 70 patients.

Patients will be randomised to catheter ablation for AF, either alone or with renal denervation using the Symplicity™ Sypral catheter (figure 1 and 3). The operator will not know the patient's randomisation at the time the initial AF ablation is carried out. We didn't want to bias the operator with the knowledge of whether he was going to do a renal denervation or not. Medtronic (who is supporting the trial) know the randomisation, but the operator does the initial catheter-based therapy for AF and then is told afterwards which way the patient randomised. All patients have a pre-procedure CT scan to look at the suitability of the aorta and the renal arteries for renal denervation, but again the results of that are not known to the operator.

We worked very hard to select operators who had the experience to do this well. Medtronic has a very sophisticated mentoring group who visit hospitals to make sure that everything is done appropriately to ensure adequate success. That's a very large change from SYMPLICITY. By enrolling experienced Electrophysiologists who are well-versed in catheter-based therapy who, in addition, are being mentored by both interventional cardiologists and electrophysiologists, we are playing a big part in ensuring the procedure is carried out as effectively as possible.

The primary endpoint is freedom from AF. We are going to implant loop recorders in all patients to monitor for atrial arrhythmias, as well as doing pretty extensive blood pressure monitoring. The first 3 months is given as a healing time, and we won't count recurrent atrial arrhythmias during that period; success or failure will be based on monitoring after the 3-month period. Unfortunately, we still don't have a measurable endpoint for renal denervation. We are also looking at lots of secondary endpoints, such as blood pressure control, AF symptoms, heart rate – the multiple factors that patients came in with – and how they influence success. Safety parameters such as haematomas, the safety of renal denervation, the safety of concomitant AF ablation and renal denervation, aortic dissections, injury to the renal arteries, will be looked at very carefully.

This is a different population of patients compared with those enrolled in the previous SYMPLICTY HTN trials. Is this population representative of what you see in your clinic?

LC: When I initially worked on the entry criteria, I thought that this would be a very easy population to find, and very representative of our patients. It turns out that nowadays there are not actually that many patients who have ongoing hypertension, despite reasonable medical therapy, at least among those who are referred to us.

It's important to use a hypertensive group, because it allows you to measure at least some effects of renal denervation and get a sense that you are doing something. I just don't know how long it will take to get the number of patients to show the difference. We have a lot of hypertensive patients, but most of them are on medical therapy that gets their blood pressure below 150 mm/Hg. Maybe cardiologists are doing a better job at controlling blood pressure and maybe they have better tools, but it's been harder than I had anticipated and I am somewhat disappointed about that.

What longer-term follow-up of these patients will be carried out?

LC: Because of the implantable loop recorder we are going to follow them for at least 6 months or maybe longer.

Most of the recurrences will probably occur within the first 6 months, and we usually have a sense early on of who is going to recur, but there is no question that there's late-term follow-up recurrence as well, sometimes a year, sometimes longer, so that's something that can be investigated. We know that many people who have ablation for AF require more than one procedure,

whether it is for recurring atrial tachycardias or for muscular reconnections. I believe the expectation is that some patients will need a recurrent procedure, but I also believe that the long-term outcome for those patients will be very positive.

With all catheter-based therapy it may be important to dispel the notion that you can do one procedure and it's going to cure this patient forever. AF can be a chronic disease and it does need to be managed. Some people will need medication, some people will need another procedure. The data are extremely positive in terms of our ability to maintain normal sinus rhythm long-term, but we have to get away from the idea that you are going to do it once and everything is going to be perfect. That's true in most other interventional areas. Coronary revascularisation with stents and balloons and such is a very effective means of controlling coronary disease, but there's no expectation that patients will have one procedure and be cured for life.

If the results from the SYMPLICITY AF trial are promising, what do you see as the next steps to really enthusing people about this technique and making sure that they're taking it through to their clinics?

LC: I'm really excited about some of the new information that Medtronic has brought to the community about how to go about achieving optimal renal denervation. Being able to denervate effectively is extraordinarily important, and information about ablating in the distal renal arteries and in the branches, where much of the nerve tissue lies, has been very interesting. Had this been appreciated sooner, it may have had an impact on the outcomes of SYMPLICITY.

It also brings out the understanding that there are many factors that influence the presence of AF, and that there may be multiple ways of manipulating the autonomic nervous system, but renal denervation may be the easiest and most effective when it's done correctly.

The results of HTN-3 have led to some incredulous thoughts about renal denervation.[2] I would counter these by saying, firstly, that it may not have been done optimally in the HTN-3 trial, and secondly, that catheters currently under investigation may allow for more effective and safe renal denervation.

I also think we should continue to work towards a measurable endpoint. There is a lot of ongoing work in terms of the direct measurement of norepinephrine and other parameters that can really show us when we have reached an endpoint. As with all other catheter-based therapy, the technology needs to catch up with what we anticipate should occur, but the future for that is really quite bright.

I just would like to emphasise the importance of improving our results for the treatment of AF, because definitive therapy for AF has the potential to greatly benefit patients. As we said, AF is associated with a very significant stroke risk and a significant increase in mortality. Taking a really concentrated approach to the treatment of AF has the potential to reduce the long-term risk of stroke, to reduce mortality, and to significantly improve lifestyle.

We have come a long way, but there is still so much more that we can do to improve outcomes and again, given the number of patients, young and old, that have to deal with this, it's a very important undertaking.

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DISCLOSURES: LC has provided consultancy services to St Jude Medical, Medtronic, Biotronik, Biosense Webster and Boston Scientific.