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COMMENTARY

Could Ablation for AF Be an Elaborate Placebo?

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Maybe electrophysiologists are too close to see it: the possibility that ablation of atrial fibrillation is no more effective than a placebo.

Turkish authors boldly raised[1] this question in a recent editorial in the *International Journal of Cardiology*. They likened AF ablation to renal denervation, a procedure that promised to transform the treatment of hypertension. That is, until the SYMPLICITY HTN-3[2] trial showed that renal ablation was no better than a sham procedure. Before the properly controlled trial, nearly all of the data and most of the experts predicted a new era in hypertension. Think about the massiveness of that reversal: millions of people have high blood pressure.

Millions of people also have atrial fibrillation. And, unlike renal ablation, ablation in the left atrium has never been tested against a true placebo. In thousands of reports of AF ablation in the literature, not one is a true test—a sham-controlled study.

I concede that burns (radiofrequency ablation) or freezes (cryoablation) in the left atrium, with the clear end point of electrical isolation of the pulmonary veins, is different from ablation in the renal arteries.

But AF ablation is not just unproven, it's *inelegant*. This month, almost 2 decades after the first report of AF ablation, German authors called the 2-year results after cryoballoon ablation in patients with persistent AF "promising."[3] How promising? The procedure failed in 22 of the 50 patients (44%).

Not only are the results poor, but the procedure is big—ablation lesions in the left atrium, often millimeters away from the esophagus or phrenic nerve, general anesthesia, transseptal puncture, multiple vascular entries, and hours of bed rest put patients at significant risk. Creating scar to treat a disease that is often caused by scar hardly seems elegant.

This vision of catheter ablation of AF is not hyperbole. In a systematic review of 3471 citations, researchers for the Agency for Healthcare Research and Quality (AHRQ) did not find enough evidence to draw conclusions regarding efficacy or safety for cryoablation.[4] Regarding radiofrequency ablation, they found:

- Insufficient evidence to draw conclusions regarding its effectiveness and safety in the Medicare population.
- Moderate level evidence that RF ablation was superior to medical therapy for enhancing freedom from recurrence of atrial arrhythmia in the general population, but reablation was common.
- No impact on all-cause mortality.
- No firm conclusions regarding health-related quality of life due to heterogeneity across studies.

You could criticize this report because none of the authors ablate AF, but perhaps it is those removed from the expectations of benefit who see most clearly. Perhaps we ablationists are like Pygmalion—we have sculpted the atria so precisely, we cannot help but expect good results.

No doubt, ablation of AF can eliminate episodes of AF. All ablation doctors have pacemaker recordings that show total elimination of AF after the procedure. But what does that mean? Is AF just a surrogate? Like HDL cholesterol, for instance?

Then there are the inconvenient cases: a patient has incapacitating AF. He has an ablation or cardioversion. He feels better. At follow-up 3 months later, he thanks me for giving him his life back. But the ECG shows AF!

These are not just anecdotes. In the DISCERN-AF study, Canadian researchers found that the ratio of asymptomatic to symptomatic AF episodes increased more than threefold after ablation[5].

We are doing something with this procedure. The question is, would it be more effective than a sham procedure—especially if those judging its success were not ablation doctors?

The Argument for Doing a Sham-Controlled Ablation Trial

Ethics: Let's first dispense with the ethical argument. Critics might say no electrophysiologist would willingly submit a patient to a sham AF ablation.

Here it's worth thinking about the ethics of *not* doing sham-controlled trials.

If not for SYMPLICITY HTN-3, we'd be exposing thousands, perhaps millions, of humans to renal artery ablation.

In the VPS-1 trial,[6] a comparison of pacemaker or no pacemaker for patients with vasovagal syncope, pacemakers proved superior to no pacemakers. But in the VPS-2 trial,[7] which was double-blinded and sham-controlled, pacing therapy did not work. Imagine a world where pacemakers are used to treat benign fainting.

Neurosurgeons can teach cardiologists a bit of bravery when it comes to the use of sham controls. In a study comparing intracranial transplants of embryonic dopamine neurons for the treatment of Parkinson's disease, both control and active arms got craniotomies (holes drilled in the head). Researchers found no difference in outcomes.[8] Similarly, it took a properly done sham-controlled trial to debunk the common practice of injecting cement into a fractured vertebra (vertebroplasty) for the treatment of compression fractures.[9]

Transmyocardial revascularization (drilling holes in the heart),[10] pacing for hypertrophic cardiomyopathy,[11] and ligation of coronary arteries[12] were practices that required the courage of sham controls to be proven ineffective.

Benefit from CRT may partially come from placebo effects. In the control arm (CRT-off) of the MIRACLE trial, one in three patients improved a single heart-failure functional class and 12 patients (6%) improved two functional classes.[13]

Previous Data: Another argument ablation doctors might make is that we have strong evidence showing that AF ablation works better than drugs. That's true, but even a cursory look at placebo and nocebo effects casts doubt on that comparison.

First is the notion that placebo effects depend on the strength of the placebo. The buildup to an AF ablation, the bigness of the procedure, and the expectations of patient and doctor outmatch the promise of any pill. Dr Brian Olshansky (University of Iowa) discusses these effects in a state-of-the-art review paper in the *Journal of the American College of Cardiology*.[14]

Then there are the real (bradycardic/negative inotropic/proarrhythmic) and perceived (nocebo) adverse effects of antiarrhythmic drugs. In other words, in a comparison of ablation vs drugs, the

ablation procedure could be neutral but look positive *relative* to drugs. Is it a stretch to posit that a class IC antiarrhythmic drug worsens symptoms when it converts intermittent AF to sustained flutter?

A nocebo effect occurs when a patient or doctor perceives harm solely from the appearance that treatment has occurred. The most recent example of nocebo effect with drugs was seen in the first phase of the GAUSS-3 trial, in which patients with a strong history of statin intolerance were rechallenged with atorvastatin or placebo. Researchers found that 27% of those in the placebo arm reported muscle symptoms.[15]

The nocebo effect of rhythm drugs should be obvious. Patients expect to be better with ablation, but they don't expect that with drugs. Most patients who come to ablation have already had one drug failure, and the internet streams with information about the adverse effects of rhythm drugs.

Mechanism of Placebo Effect: Another argument made against a sham-control AF ablation trial is implausibility.

The placebo effect occurs because of a complex interplay of many factors. In AF, one of these issues is disease fluctuation. Clinicians know this effect well: a patient with AF due to a flare of stress, infection, or injury often has remission of the episodes if given time and support. If an ablation is done during (or soon after) this flare, the improvement attributed to ablation may simply be regression to the mean.

Placebo effects can also cause changes in neurophysiology, which may then feed back to the heart. Like the Pygmalion effect, other expectation responses include the Hawthorne effect (subjects respond to knowledge of being evaluated), the Jastrow effect (subjects respond to explicit expectation of outcome), and the Halo effect (subjects respond to treatment novelty).

Maybe this seems a bit too soft—perhaps it's too much mind-body connection.

By email, Dr Kalyanam Shivkumar, a professor of medicine, radiology, and bioengineering at the University of California, Los Angeles, wrote, "I think we are at the total infancy of understanding neurovisceral sciences, and areas like autonomics and metabolism are going to provide new insights into arrhythmia biology." Explaining the complexity of doing a sham-control trial in AF, he writes, "The fact that the heart is a sensory organ and has very rich afferent innervation, even a single RF [ablation] or even mechanical stretching of a part of the atrium (say the stretch of the lower interatrial septum during transseptal access) can influence neuron-neuron communication in the heart's intrinsic nervous system; therefore, a 'sham' intervention is also an 'intervention.' "

Summary

I've ablated AF many hundreds of times over the past 12 years. I do fewer AF ablations now. I go slower. Patients and I have long chats about AF; we discuss their symptoms, the reasons for these symptoms, the vast uncertainty of AF and its treatment, and, mostly, the expectations of ablation or no ablation. Could a nurturing, respectful, and optimistic doctor-patient interaction deliver antiarrhythmic effects?

Something clicked when I read the Turkish authors call for a sham-control trial. Their words reminded me how little we know about AF. The truth is we lack a true scientific understanding of what causes the arrhythmia, and we have little basic scientific insights into what *is* fibrillation itself.

It was a big step we made going from Haïssaguerre and colleagues first description of focal tachycardia in the pulmonary veins to extensive left atrial ablation.[16]

It is time to rethink our strategy. Better late than never.

JMM

Editors Note : An earlier version of this commentary mistakenly said of the Tscholl study that "the procedure failed in 16 of the 22 patients (73%)." The total failure rate was 22 of 50, which is 44%. This error was introduced during editing.

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