Magnetic Nanoparticles and Neurotoxins for Treating Atrial Fibrillation
A New Way to Get Burned?

Dara L. Kraitchman, VMD, PhD, FACC; Jeff W.M. Bulte, PhD

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, with over 2.6 million Americans affected. Partly due to the high risk of stroke in these patients, AF is associated with significant morbidity and mortality. The number of individuals affected with AF is expected to rise ≈6-fold over the next 40 years. Catheter-based ablation may offer a more effective means of treating AF than conventional medical therapy. Ablation techniques have been adopted after limited clinical trials with a relatively small number of patients. In an effort to guide the best treatment strategies, a registry has been established to follow the increasing numbers of AF patients who are being treated with ablation. Although the generally accepted initial ablation strategy is isolation of the pulmonary veins, which are often the source of ectopic beats that initiate AF, animal models have shown that the cardiac ganglionated plexi play a role in inducing and maintaining AF. Initial clinical studies indicate that ablation of the ganglionated plexi, in addition to pulmonary vein isolation, may improve ablation outcome. Indeed, fortuitous ablation of the ganglionated plexi during pulmonary vein isolation may contribute to procedure success. However, targeting the ganglionated plexi for selective ablation requires their localization, presently achieved by additional mapping to detect sites where high-frequency stimulation elicits heart rate slowing and then ablation at that site, which, for endocardial catheter techniques, includes the surrounding atrial myocardium. Better methods to identify and ablate these focal neural networks are desirable for potential use as adjunct treatments to conventional cryoablotion or radiofrequency ablation.

Interestingly, Yu et al have proposed a technique using injected iron-core nanoparticles to target the ganglionated plexi for ablation. The use of magnetic particles has a long history in medicine. Ultrasmall superparamagnetic iron oxide particles have been widely used in magnetic resonance angiography applications in cardiovascular magnetic resonance imaging (MRI) due to their ability to remain in the blood pool for long periods of time. The toxicity of these particles is low due their biocompatibility with recycling of iron into the normal body iron pool, similar to hemoglobin. Clearance of these particles by activated macrophages has also been used as a method by which to identify the potentially vulnerable atherosclerotic plaque. The ability of these particles to remain intravascular for long periods of time makes them ideal candidates to attach ligands for active targeting to specific cells. Yu et al used a superparamagnetic nanoparticle, which is larger than commonly used ultrasmall superparamagnetic iron oxide particles, and was coated with a heat-sensitive polymer to enable the release of a neurotoxin at body temperature. They employed the simple approach of surgically placing a permanent magnet adjacent to the plexus to trap the nanoparticle after intracoronary delivery. Unfortunately, this straightforward approach eliminated the ability to image the nanoparticle directly with MRI. In a less invasive manner, Wilson et al used a permanent magnet placed outside the body to localize magnetic particles that contained a chemotherapeutic drug injected under conventional fluoroscopic guidance to hepatocellular carcinoma. Other methods—perhaps adding magnets to ablation catheters—might be envisioned as means to enjoy the simplicity of magnets for targeting combined with the advantages of MRI’s high spatial resolution and serial imaging capabilities for anatomic imaging of particle delivery.

Polymer hydrogels have also been an area of great interest for controlled drug release. Unlike liposomes, polymer-based coatings offer superior stability characteristics and can be engineered to decompose at a specific pH or temperature. Poly-N-isopropylacrylamide-coacrylamide, the polymer used by Yu et al, is hydrophilic and thus hydrated at temperatures below body temperature. However, the polymer is hydrophobic at body temperature, so the structure collapses once injected and can release any incorporated drugs for a localized therapeutic effect. The critical temperature for disintegration of poly-N-isopropylacrylamide-coacrylamide can be altered by the addition of residues. Potentially, this would offer the ability to combine radiofrequency ablation for the release of the incorporated drugs at a higher temperature trigger. Unfortunately, poly-N-isopropylacrylamide-coacrylamide is not biodegradable, which means that it would permanently remain within the body. Consequently, other...
hydrogels with similar heat-sensitive properties, but with enhanced breakdown properties, are being explored for drug delivery and in combination with iron oxides for imaging. An appealing secondary mechanism by which to realize the benefits of the targeted agent may be microvascular plugging of the nanoparticle in the tissue. While this was not explored in detail by Yu et al, histopathology demonstrated the embolization of the particle. Clearly, if this was not a desirable effect, there are many polymer-coated iron oxide agents of much smaller size (eg, ultrasmall superparamagnetic iron oxide particles) that exhibit less clumping, which could provide a viable alternative approach.

Iron-based nanoparticles have also shown promise for hyperthermia-based treatments for cancer. While heating of devices in MRI is a concern, in magnetic hyperthermia treatments, the deposition of thermal energy occurs as superparamagnetic nanoparticles are exposed to rapidly alternating positive and negative magnetic fields and relax toward an equilibrium state. This heating is exploited for tumor cell destruction. Particle conjugation, including overall particle size, size distribution, and core size, is important in determining the efficiency of heating. Fortuitously, superparamagnetic nanoparticles appear not only to be good for imaging, but also for the enhancement of the heating effect through surface modification of the nanoparticles. Targeting of these iron nanoparticles to the tumor is critical to avoid killing normal cells. For example, Ito et al have shown antibody targeting to Her2-positive breast cancer cells of magnetic liposomes in combination with hyperthermia treatment. The success of nanoparticle delivery was further confirmed by MRI. One can imagine that the nanoparticle developed by Yu et al could be extended to provide not only tracking with MRI, but also for ganglionated plexi ablation using hyperthermia as an adjunct to radiofrequency ablation. If hyperthermic heating of cells was insufficient, the polymer coating could be designed to have a higher critical temperature that would release only the endotoxin with the use of alternating magnetic field hyperthermia, providing additional targeting of the drug delivery.

Yu et al have provided an interesting first step toward targeted drug-based treatment of atrial fibrillation. As the population ages, increasing procedural risk, minimally invasive treatments that can provide complementary means to monitor therapeutic response will become increasingly sought as alternatives to conventional medical or surgical therapies. The combination of catheter ablation techniques with magnetically targeted nanoparticles for ablation of autonomic ganglia involved in initiating and perpetuating AF can be envisioned. Yu et al have just scratched the surface of a new approach to ablation for treatment of arrhythmias.

Disclosures

Drs. Kraitchman and Bulte receive grant support from Siemens Medical Systems.

References


**Key Words:** Editorials, atrial fibrillation, autonomic function, cardiovascular magnetic resonance imaging, electrophysiology, iron oxide labeling
Magnetic Nanoparticles and Neurotoxins for Treating Atrial Fibrillation: A New Way to Get Burned?
Dara L. Kraitchman and Jeff W.M. Bulte

_Circulation_. 2010;122:2642-2644; originally published online December 6, 2010; doi: 10.1161/CIRCULATIONAHA.110.000166
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/122/25/2642

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/