Don’t Forget to Gather the Evidence
Myocardial Effects of Cryoablation in the Immature Heart

J. Philip Saul, MD

In this issue of The Journal, Khairy et al1 present the results of an impeccably performed study comparing the effects of cryothermal (CRYO) and radiofrequency (RF) ablation on the developing swine heart. Despite the earlier report from my group in 1994 that RF lesions appear to grow when placed in the atria and ventricles of developing hearts,2 until now no parallel study has been published to assess the late effects of CRYO in the atria, ventricles, and AV groove of the immature heart. This lack of data may have come from a combination of limited funding sources and a form of complacency, perhaps based on early animal and human data demonstrating the relative safety of CRYO over RF techniques.3–7 All factors that may have led to acceptance of this new technology as preferable to RF for the developing heart. In fact, Khairy et al initially speculated that CRYO lesions would act differently than RF lesions at late follow-up, based on the different mechanisms of cell injury, and the distinct acute histological features of the lesions from the two techniques.4 When the data were in, they actually demonstrated that there were no differences between the late effects of CRYO and RF on developing myocardium, and both techniques led to long-term lesion growth and invasion of scar tissue into surrounding myocardium.1

New Devices and Drugs in Children
It is often the case in pediatrics that new technologies or drugs are adopted into clinical practice in the absence of animal or human data that sufficiently demonstrates both safety and efficacy in immature organs. This situation results from the combination of the immediate availability to pediatric providers of new drugs and devices once they are approved by the Food and Drug Administration (FDA) for adults and the lack of a requirement for pediatric testing for such therapies before approval. Because pediatric providers naturally desire to incorporate new therapies that might benefit their patients into their practices, in the absence of data they are required to make their own assessment of the balance between efficacy and safety. It would of course be preferable for data to be available before such decisions are made.

The FDA has addressed the issue much more aggressively for new drugs, in which a variety of regulations support the 2002 Best Pharmaceuticals for Children Act, which uses a carrot-and-stick approach to incentivize manufacturers to perform drug trials in children.8–10 The Pediatric Medical Device Improvement and Safety Act,11 passed by Congress in 2007, did identify the need for improved access for pediatric patients to new devices, as well as postmarketing safety monitoring. Further, the act encourages sale of devices under a Humanitarian Device Exemption for conditions affecting fewer than 4000 patients, which includes most pediatric conditions; however, there are no requirements or incentives to perform trials in children, as there are with the Best Pharmaceuticals for Children Act.

Important Observations From This Study
Khairy et al1 confirmed the findings of our earlier study of RF lesions that only atrial and ventricular lesions appeared to increase in size, whereas AV groove lesion did not change significantly for either technology. This finding, which was also confirmed by Kriebel et al,12 can provide some comfort to the physician, since most ablations at every age are performed for AV groove related substrates (71% in infants and 89% in children).13 Saul et al2 suggested that transmurality of the lesions may have been a factor in lesion expansion. The data presented by Khairy et al1 did not allow for such an assessment, but it is worth noting that atrial and ventricular lesions both appeared to increase in size, despite only 39% of ventricular lesions being transmural, compared with 70% of atrial lesions. Further, lesion width, depth, and volume all increased with age. Finally, Khairy et al1 found evidence of endocardial surface disruption frequently in RF lesions but only rarely in CRYO lesions, potentially related to the development of more surface thrombi for RF than CRYO lesions. The presence of thrombus early after ablation with either technology (27% for RF and 14% for CRYO), even though aspirin was administered both before ablation and until death, suggest that at a minimum aspirin, therapy is an important therapeutic option for at least 30 days after ablation, regardless of the ablation technology, particularly when applications are delivered to left-sided structures.

It is also important to note that Khairy et al1 did not report on ablation affects to nearby coronary arteries in this study. However, 2 prior studies did demonstrate that CRYO can have minimal effects on nearby coronary arteries of infant pigs, with increased mural echogenicity by intracoronary ultrasound in 1 of 5 animals, and some lesion extension into the medial coronary wall of the left circumflex, without

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
From the Medical University of South Carolina, Charleston, SC.
Correspondence to J. Philip Saul, MD, Medical University of South Carolina, 165 Ashley Ave, MSC 915, Charleston, SC 29425. E-mail saulp@musc.edu

(Circ Arrhythm Electrophysiol. 2011;4:123-124.)
© 2011 American Heart Association, Inc.
Circ Arrhythm Electrophysiol is available at http://circcep.ahajournals.org
DOI: 10.1161/CIRCEP.111.962316

Article see p 211

The FDA has addressed the issue much more aggressively for new drugs, in which a variety of regulations support the 2002 Best Pharmaceuticals for Children Act, which uses a carrot-and-stick approach to incentivize manufacturers to perform drug trials in children.8–10 The Pediatric Medical Device Improvement and Safety Act,11 passed by Congress in 2007, did identify the need for improved access for pediatric patients to new devices, as well as postmarketing safety monitoring. Further, the act encourages sale of devices under a Humanitarian Device Exemption for conditions affecting fewer than 4000 patients, which includes most pediatric conditions; however, there are no requirements or incentives to perform trials in children, as there are with the Best Pharmaceuticals for Children Act.
stenoctosis or flow abnormalities.12,14,15 These changes were far less than those observed with RF lesions in prior studies.16

CRYO Versus RF?
The report of Khairy et al1 demonstrates that both CRYO and RF energy application in immature hearts can cause late lesion expansion but does not directly address the acute safety issues of either technology. One conclusion might be that regardless of ablation technology, such procedures should not be performed in the youngest patients. The same could be said of cardiac surgery because there is evidence that cardiac surgical scars also expand with time in immature hearts.17,18 However, just as with cardiac surgery, in some infants, catheter ablation is clinically indicated, so the issue becomes one of using the safest available technology. In that regard, there are numerous features of cryoablation that raise its safety profile over RF energy when it comes to the smallest children.3 These include reversibility during testing, smaller lesion size, minimal effects on coronary arteries without reported stenosis, and minimal endocardial disruption with less thrombus formation.4–6,12,15 Many of these features were highlighted in the current study by Khairy et al.1

The Future
It is clear that information such as that provided by this important study of Khairy et al1 is critical to optimizing clinical decision-making in the management of arrhythmias in small children. It appears that in growing myocardium, no form of myocardial injury or destruction, including surgically induced, can be accomplished with complete long-term safety. However, it is somewhat comforting to note that despite the observed lesion growth in animals with fibrous extension into surrounding myocardium, to date, late arrhythmias (>2 months after the procedure) have not been reported as a complication of infant ablation procedures.

Khairy et al1 add to the speculation on some of the cellular and biochemical mechanisms that might account for scar tissue expansion in the immature postnatal heart. These factors include differences between neonatal and adult hearts in myocardial cell division, fibroblast activity, growth factors, cytokine responses, matrix metalloproteinases, and other growth mechanisms, which can all influence the fibrogenic response.3,19,20 They end their report by stating “Further studies are required to elucidate the pathogenesis of ablation lesion growth in immature myocardium, identify potential therapeutic targets to limit lesion expansion, and assess the efficacy of preventive approaches.” I cannot agree more and would add that regulatory activities could help ensure that such information is sought for children in advance of public release of new devices by the FDA and that long-term follow-up of ablations performed in small children is warranted.

Disclosures
None.

References
Don't Forget to Gather the Evidence: Myocardial Effects of Cryoablation in the Immature Heart

J. Philip Saul

Circ Arrhythm Electrophysiol. 2011;4:123-124
doi: 10.1161/CIRCEP.111.962316

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/4/2/123

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology 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: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org//subscriptions/