

On the Beat: Key Articles from August 2017

“Hard Hitting” Article Summaries

Atrial Fibrillation

Cardiac mapping and ablation

DOI	Title
10.1016/j.jacc.2017.06.008	<i>Temperature-Controlled Radiofrequency Ablation for Pulmonary Vein Isolation in Patients With Atrial Fibrillation</i>
<p>Summary: Iwasawa et al present on use of a novel irrigated ablation catheter with a diamond-embedded tip for rapid cooling to improve thermal feedback. The catheter also included high resolution electrograms from split tip electrodes. They tested the catheter in both pigs and humans for evaluation of utility in pulmonary vein isolation. In patients, they compared use of the novel catheter against a control group using a standard catheter with plan to remap for pulmonary vein reconnection after 3 months. In porcine hearts, they demonstrated a high frequency of transmural lesion application with the novel catheter. In the patient example, there was significantly less ablation time needed to achieve PVI compared to standard catheters (26 vs 90 minutes) and there was less frequent of apparent acute dormant pulmonary vein conduction. The majority of patients (74%) had durable PV isolation at the time of remapping.</p>	
<p>Commentary: This is the first study of a novel catheter consisting of a diamond embedded tip and novel thermocouple distribution to facilitate temperature controlled irrigated radiofrequency ablation. In a small subset of patients, using less ablation duration with shorter fluoroscopy times, there was a high frequency of durable PV isolation (though the control group was not remapped). Given the ongoing evolution of catheters for the purpose of achieving more effective or more efficient cardiac ablation, consideration of new designs and their implications on safety and efficacy is critical. This reflects the first study of this novel catheter, though further randomized analysis to prove incremental benefit is required.</p>	
10.1016/j.jacep.2017.02.018	<i>Atrial Tachycardias After Surgical Atrial Fibrillation Ablation: Clinical Characteristics, Electrophysiological Mechanisms, and Ablation Outcomes From a Large, Multicenter Study</i>
<p>Summary: Gopinathannair reviewed from a multicenter cohort the mechanisms and outcomes from atrial tachycardia ablation in the setting of prior surgical atrial fibrillation ablation. A total of 137 patients were evaluated with a total 149 atrial arrhythmias mapped. The majority were of left atrial origin with nearly a third having a focal mechanism and the remaining</p>	

majority being reentrant. The majority of patients (93%) had at least one vein reconnected. Acute success rates were 97% for right atrial origin and 93% for left atrial origin atrial arrhythmias. One year freedom from recurrence was 80%.

Commentary: Recurrent arrhythmias after prior surgical atrial fibrillation ablation is not uncommon. However, counseling patients on likelihood of success given the complexity of the substrate can be difficult. As noted by the authors, the distribution of arrhythmias can be highly variable, with both right and left origins. Thus, care must be taken to consider that 1) multiple mechanisms may exist in the same patient; 2) there is a high frequency of pulmonary vein reconnection; and 3) despite the substrate complexity, overall success rates can be quite high (in excess of three-fourths of patients).

[10.1016/j.hrthm.2017.04.043](https://doi.org/10.1016/j.hrthm.2017.04.043)

Epicardial-endocardial breakthrough during stable atrial macroreentry: Evidence from ultra-high-resolution 3-dimensional mapping

Summary: Pathik, et al reviewed evidence for epicardial – endocardial breakthrough during atrial macroreentry evaluated using ultra high-resolution mapping. Epicardial-endocardial breakthrough was defined as presence of focal endocardial activation with radial spread that could not be accounted for by an endocardial wavefront which had to present with the same timing at each beat in the tachycardia cycle. A total of 26 patients were included A total of 14 examples of breakthrough were seen, with the majority in the posterior right atrium. Of these, 4 were involved in maintenance of the reentry circuit, with 1 appearing critical to arrhythmia propagation.

Commentary: These findings lend further support to the importance of consideration of the epicardial circuitry as relevant to atrial arrhythmia substrate. While the need for epicardial block is commonly considered for mitral flutter, the importance of the epicardial circuitry is often not considered. There is the potential for complex reentry not just utilizing the endocardium but differential endocardial versus epicardial conduction. Ultra high-density mapping systems may better allow for appreciation of these situations. However, consideration of an epicardial contribution not affected by endocardial ablation should be considered in particularly difficult to treat cases of macro-reentry.

[10.1161/JAHA.117.006043](https://doi.org/10.1161/JAHA.117.006043)

The Impact of Cryoballoon Versus Radiofrequency Ablation for Paroxysmal Atrial Fibrillation on Healthcare Utilization and Costs: An Economic Analysis From the FIRE AND ICE Trial

Summary: Chun et al review the economic impact of use of cryoballoon versus radiofrequency ablation from the FIRE and ICE trial. In this study, patients were randomized 1:1 to cryoballoon versus radiofrequency ablation for pulmonary vein isolation. Results of the trial had been previously presented. There was a cost saving of up to \$355,000 attributable to use of cryoballoon over the trial period presumed secondary in part due to lower resource utilization.

Commentary: With increasing diagnosis of atrial fibrillation in the population, the need for less resource-intensive approaches to treatment is increasingly clear. With introduction of any novel technology, the balance between cost and efficacy is important. This trial adds an important cost-analysis to the use of cryoballoon for pulmonary vein isolation versus the more long-standing radiofrequency approach.

Anticoagulation

DOI	Title
10.1056/NEJMoa1707278	<i>Idarucizumab for Dabigatran Reversal — Full Cohort Analysis</i>
<p>Summary: Pollack et al review the full analysis of idarucizumab for achieving dabigatran reversal. In this multicenter, prospective open-label study, they studied whether or not idarucizumab could completely reverse the effects of dabigatran safely in those with uncontrolled bleeding or about to undergo an urgent invasive procedure. A total of 503 patients were included and median maximum percentage reversal was 100%. In those with uncontrolled bleeding, mean time to bleeding cessation was 2.5 hours. In those undergoing surgery, periprocedural hemostasis was considered normal in 93% of patients performed an average 1.6 hours after administration. Thrombotic events were seen in 6.3% of the uncontrolled bleeding cohort and 7.4% of the surgery cohort, with mortality rates above 18% in each group.</p>	
<p>Commentary: Overall, these data demonstrate a high level of safety and efficacy in use of idarucizumab for rapid reversal of dabigatran in acute situations. While the outcomes suggest a high incidence of thrombotic events and mortality, these patients reflected a high-risk cohort overall given the presence of uncontrolled bleeding or need for urgent surgery for various indications. Whether the thrombotic risk after immediate reversal is reflective of a prothrombotic state in the immediate post reversal period that exceeds normal situations where a patient is either not on a blood thinner, is on a blood thinner but allowed to gradually have it wear out, or is on a different blood thinner such as warfarin which is subsequently reversed is unclear.</p>	
10.1136/heartjnl-2016-310672	<i>Early non-persistence with dabigatran and rivaroxaban in patients with atrial fibrillation</i>
<p>Summary: Jackevicius, et al report the persistence of patients on therapy with novel oral anticoagulants when compared with warfarin. The justification for their study was that while NOACs are increasingly being utilized in clinical practice, the lack of monitoring strategies to ensure patients are compliant with the prescription is not as straightforward as with warfarin where checking an INR may give that information. In this retrospective cohort study, non-persistence was defined as a gap of at least 14 days in NOAC prescription. Amongst almost 16,000 dabigatran users and over 10,000 rivaroxaban users,</p>	

around a third were not persistent with their medication. Stroke, TIA, and death were more common in those patients who were non-persistent with their NOAC prescription.

Commentary: These findings support the importance of clinical counseling of patients on the importance of being persistent with their anticoagulant prescription in the setting of novel oral anticoagulants. Novel oral anticoagulants, while easier to use given the lack of need for blood monitoring, are also exposed to the compliance issues regarding their continued compliance. These data highlight the importance of counseling patients on the increased risk of incident stroke, TIA, or death that may occur with failure to persist with anticoagulant prescriptions.

[10.1093/eurheartj/ehx403](https://doi.org/10.1093/eurheartj/ehx403)

Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study

Summary: Godier, et al reviewed in a prospective multicenter study the various predictors of direct oral anticoagulant concentrations prior to procedures. Amongst 422 patients, there was a wide range of time of cessation relative to the procedure timing, but it was demonstrated that after a 49-72 hour period of discontinuation, nearly 95% of the anticoagulant was at a low enough level to be considered safe to proceed. A 72 hour period of discontinuation predicted a low residual DOAC level with 91% specificity. However, low creatinine clearance and antiarrhythmic use were predictors of needing a longer time off DOACs to achieve a low concentration (with the former being more relevant for dabigatran and the latter for anti-Xa treated patients). They also demonstrated the routine hemostasis assays did not correlate with DOAC concentrations.

Commentary: The study by Godier, et al highlights that a 72 hour period of DOAC discontinuation can predictably result in a low enough concentration as to be safe to proceed with an invasive procedure. However, certain factors such as antiarrhythmic use or moderate renal impairment predicted the need for longer duration off a DOAC prior to achieving a low enough DOAC concentration to be safe to proceed with an invasive procedure. These data can be used to guide hospital policies on peri-procedural anticoagulant management.

[10.1007/s10840-017-0274-2](https://doi.org/10.1007/s10840-017-0274-2)

The anticoagulant effect of heparin during radiofrequency ablation (RFA) in patients taking apixaban or rivaroxaban

Summary: Brendel, et al reviewed the role of heparinization during ablation on apixaban and rivaroxaban given the activated clotting time (ACT) does not often reflect accurately the total anticoagulant effect. 90 patients were assessed in terms of anticoagulant effect on either rivaroxaban or apixaban while on heparin targeted to an ACT of 250-300 seconds based on blood samples taken 10, 60, and 360 minutes after heparin administration. Rivaroxaban-treated patients exhibited

a lower anti-Xa activity with heparin than apixaban treated patients. However, differences in anticoagulant state in vitro did not translate into differences in clinical outcomes.

Commentary: There is variability between different anti-Xa anticoagulants in terms of summative effects on overall anticoagulant activity when in conjunction with heparin. These differences, while they did not translate into significant bleeding or thromboembolic complication differences in this study, are important to take into account when considering potential implications for clinical management.

Risk stratification and management

DOI	Title
10.1016/j.jacc.2017.06.034	<i>Increasing Prevalence of Atrial Fibrillation and Permanent Atrial Arrhythmias in Congenital Heart Disease</i>
Summary: Labombarda, et al review the changes in prevalence of atrial arrhythmias in patients with adult congenital heart disease. Amongst a large multicenter cohort of 482 patients with atrial arrhythmias. The most common arrhythmia was intra-atrial reentrant tachycardia which increased in overall frequency with higher levels of complexity of congenital heart disease. In older patients (above 50 years of age), atrial fibrillation surpassed reentrant tachycardia as the most common rhythm. While most patients (nearly two-thirds) were paroxysmal, the remainder were persistent or considered permanent). Permanent atrial arrhythmias were more common in older patients.	
Commentary: Paroxysmal intra-atrial reentrant tachycardias are the most common atrial arrhythmia in patients with adult congenital heart disease, particularly in younger (<50 years of age) and those with more complex substrates. However, older patients more commonly get atrial fibrillation that is more permanent. These findings suggest that while a discrete substrate characterizes the majority of younger adult congenital patients' arrhythmia burden, older patients often get atrial fibrillation. This may have repercussions for decision making regarding ablation or other treatment approaches in these patients.	

Cellular Electrophysiology

DOI	Title
10.1161/CIRCRESAHA.116.310396	<i>Transient Notch Activation Induces Long-Term Gene Expression Changes Leading to Sick Sinus Syndrome in Mice</i>
Summary: Qiao et al whether transient Notch activation alters atrial ion channel gene expression and arrhythmia inducibility in a murine model. In those mice in whom there was transient Notch activation, there was resultant dysregulation of Nkx2-5, Tbx3 and Tbx5. These findings resulted in both decreased heart rates and lower atrial conduction velocities. Pacing near the pulmonary veins also suggested a higher susceptibility to arrhythmia inducibility.	
Commentary: These findings suggest that transient Notch reactivation in the adult heart may lead to a variety of atrial arrhythmias including sick sinus syndrome, sinus bradycardia, and a higher likelihood of atrial arrhythmia inducibility. This is achieved through a variety of direct effects on ion gene channel expression. Further study is required to see if effects can be reversed through pharmacologic intervention on the downstream effects and whether transient Notch activation may be the relevant pathophysiologic factor underlying the development of sick sinus syndrome or other arrhythmias in adult humans.	

Electrocardiography

DOI	Title
10.1161/CIRCGENETICS.116.001667	<i>Fifteen Genetic Loci Associated With the Electrocardiographic P Wave</i>
Summary: Christopherson, et al review the results of large scale GWAS studies of over 44,000 individuals to determine if there may be specific predictors of features of the electrocardiographic P wave. They demonstrated several known genes (including SCN10A, SCN5A, TBX5, and CAV1/CAV2, associated with P wave duration and PR interval. In addition they demonstrated 6 other novel loci associated with the P wave terminal force. In addition, some of these loci also associated with overall atrial conduction.	
Commentary: Identification of novel determinants of atrial conduction and activation may be critical to finding new targets that may both be patient-specific as well as offer benefit to larger populations of patients. While in the early phase and still requiring further characterization of what these novel loci encode, the potential for novel targets for atrial arrhythmia therapy is important.	

Sudden Death / Cardiac Arrest

DOI	Title
10.1161/CIRCIMAGING.117.006446	<i>Denervated Myocardium Is Preferentially Associated With Sudden Cardiac Arrest in Ischemic Cardiomyopathy</i>
Summary: Fallavollita, et al performed a pilot competing risks analysis to evaluate the incremental value of sympathetic innervation PET imaging in stratifying sudden cardiac death risk amongst patients with ischemic cardiomyopathy. Sudden cardiac arrest was shown to significantly correlate with a greater volume of denervated myocardium, elevated BNP, and lack of angiotensin inhibitory therapy.	
Commentary: These findings are complementary to older data regarding the potential value of sympathetic innervation imaging in stratifying sudden death risk amongst patients with ischemic cardiomyopathy. New approaches to improve risk stratification and identify those patients most likely to benefit from an implantable defibrillator are necessary. Whether these findings may be useful as prospective risk predictors when combined with EF in improve risk determination and decision making regarding primary prevention ICD implantation remains to be seen.	

Genetic Channelopathies (LQTS, Brugada, CPVT, etc)

DOI	Title
10.1016/j.hrthm.2017.04.020	<i>Lidocaine attenuation testing: An in vivo investigation of putative LQT3-associated variants in the SCN5A-encoded sodium channel</i>
Summary: Anderson, et al review the value of lidocaine attenuation testing in specifically evaluating the likely pathogenicity of variants of uncertain significance in the SCN5A gene and putative cases of long QT type 3. They reviewed the results of 25 patients and demonstrated that a positive lidocaine attenuation test correlated with abnormal in vitro channel function in 86%. In the case of one variant of uncertain significance, the positive lidocaine attenuation test in combination with abnormal in vitro function pointed towards consideration of reclassification as likely pathogenic.	
Commentary: Lidocaine acts as a late sodium current blocker. Thus, it may have a role in evaluating likelihood of pathogenicity of SCN5A variants in putative cases of long QT type 3. This may assist in classifying patients with variants of uncertain significance and also in risk stratifying patients.	

10.1136/heartjnl-2016-310617	<i>Arrhythmia risk and β-blocker therapy in pregnant women with long QT syndrome</i>
<p>Summary: Ishibashi, et al review arrhythmia risk and beta-blocker safety in pregnant women with long QT syndrome. Of 136 pregnancies among 76 long QT patients (a mix of LQT 1, 2, and 3 with 42 on beta-blockers and the remainder not), only 2 events occurred in the post-partum period amongst those treated with beta-blockers whereas 12 events occurred amongst the untreated group (half during pregnancy and half in the post-partum period). Premature delivery and low birth weight were more common in the beta-blocker group, though rate of congenital malformations or fetal growth rate were no different.</p>	
<p>Commentary: These findings support a role for continuation of beta-blockers (or initiation of) in pregnant patients with long QT syndrome given a relatively higher risk of both intra-partum and post-partum events. From these data, it appears that beta-blockers are relatively well tolerated by fetuses during growth, though with a higher incidence of low birth weight and premature delivery.</p>	
10.1161/CIRCEP.117.005282	<i>Loss-of-Function KCNE2 Variants: True Monogenic Culprits of Long-QT Syndrome or Proarrhythmic Variants Requiring Secondary Provocation?</i>
<p>Summary: Roberts, et al reviewed loss of function KCNE2 variants to determine if they were the culprit for long QT syndrome or proarrhythmic variants acting in concert with other provoking factors. 44 probands were reviewed and they found that 16 only developed QT prolongation and arrhythmia in the setting of other stressors, 10 had other LQTS pathologic mutations, and 10 did not exhibit an LQTS phenotype. The remaining 8 had an LQTS phenotype but evidence suggested that the KCNE2 variant was not the primary culprit.</p>	
<p>Commentary: These findings are provocative in that they indicate most if not all of the suggested KCNE2 disease-causing variants are in fact not causative of LQTS. Instead they may confer proarrhythmic susceptibility in concert with other stressors that may be other genetic factors or environmental (eg, QT prolonging drugs). This work highlights the importance of reconsidering what is known regarding genetic association with disease when counseling patients and particularly when counseling other family members on the conferred genetic risk.</p>	

Ventricular Arrhythmias

DOI	Title
10.1152/ajpheart.00129.2017	<i>Spinal cord stimulation reduces ventricular arrhythmias during acute ischemia by attenuation of regional myocardial excitability</i>
Summary: Howard-Quijano, et al reviewed the effect of spinal cord stimulation on ventricular arrhythmia burden during acute ischemia. In this porcine model, stimulation of the epidural space in T1-T4 was done in addition to a multielectrode mesh placed over the heart for multielectrode mapping. They demonstrated that spinal cord stimulation reduced sympathetically mediated repolarization shortening in the ischemic myocardium, attenuated any increases in repolarization dispersion, reduced ability to induce ventricular arrhythmias, and improved myocardial function. However, there was no change in electrical parameters in nonischemic myocardium.	
Commentary: These findings are provocative in that they seem to suggest spinal cord stimulation primarily regionally effects the ischemic myocardium without altering activity in the nonischemic. These data suggest mechanisms by which the beneficial effects of spinal cord stimulation are conferred. Whether these effects are recapitulated in humans, however, is as of yet unclear.	
10.1093/europace/euw217	<i>A new cryoenergy for ventricular tachycardia ablation: a proof-of-concept study</i>
Summary: Berte et al review a novel cryoenergy source for treatment of ventricular tachycardia. In an ovine model, they demonstrated using a novel catheter using liquid nitrogen that with 3 minute freezes in the RV or 6 minute freezes in the LV, transmuralty was achieved in nearly 2/3 with an at least 10 mm depth in three-fourths. Vascular structures including the mid-left anterior descending and coronary sinus were also targeted and they appeared macroscopically normal on pathologic evaluation.	
Commentary: The need for better technology to target ventricular substrate and achieve deeper or more transmural lesions is critical. Research into bipolar ablation, needle ablation and now novel cryoenergy sources may afford novel ways to target mid-myocardial and even epicardial substrate from an endocardial approach. However, most of these technologies are still in animal phases of testing and require human studies.	

10.1161/CIRCEP.117.005175	<i>Unipolar Endocardial Voltage Mapping in the Right Ventricle: Optimal Cutoff Values Correcting for Computed Tomography–Derived Epicardial Fat Thickness and Their Clinical Value for Substrate Delineation</i>
<p>Summary: Venlet et al revisit unipolar endocardial voltage criteria for assessment of epicardial scar in the right ventricle, noting the limitations of prior studies not taking into account the presence of epicardial fat. Amongst 33 patients undergoing combined endocardial and epicardial mapping, along with CT integration to delineate fat regions, they demonstrated that the optimal endocardial unipolar voltage cutoff to identify epicardial bipolar voltage <1.5 mV was 3.9 mV, and to identify any abnormal epicardial electrogram was 3.7 mV. They further demonstrated that there was incremental benefit of coupling sites of abnormal unipolar voltage with normal bipolar voltage may identify all epicardial abnormal electrograms in regions with <1.0 mm of fat.</p>	
<p>Commentary: These data reconsider traditionally accepted voltage cutoffs for endocardial unipolar voltage assessment of epicardial abnormality in the right ventricle. This may be in part due to lack of consideration of epicardial fat in the consideration of what adequate cutoffs ought to be. These are important to the practicing electrophysiologist in delineating when there is true epicardial scar.</p>	
10.1161/JAHA.117.006447	<i>Physiological Assessment of Ventricular Myocardial Voltage Using Omnipolar Electrograms</i>
<p>Summary: Magtibay, et al review the utility of omnipolar electrograms in assessing ventricular myocardial voltage. Using orientation-independent omnipolar electrodes in 5 isolated hearts from a variety of species, they derived bipolar voltage electrograms from different electrode orientations relative to the underlying tissue as well as omnipolar electrograms. They demonstrate that catheter orientation can result in a change in the bipolar electrogram voltage of on average 0.25 mV. The largest assessed bipolar voltage, however, was consistent with the omnipolar voltage.</p>	
<p>Commentary: Given the tendency of bipolar voltage assessment to be impacted by catheter orientation relative to the underlying myocardium, the authors review the use of orientation independent omnipolar electrodes. They demonstrate that use of such electrodes affords more consistent electrogram voltage determination in keeping with the maximal bipolar voltage appreciated. Whether use of such electrodes may improve substrate evaluation remains to be seen.</p>	

EP Relevant Myopathies (ARVC, HCM, etc)

DOI	Title
10.1111/jce.13228	<i>Tailored approach for management of ventricular tachycardia in cardiac sarcoidosis</i>
Summary: Yalagudri, et al review their single center experience of management of patients with ventricular arrhythmias in the setting of cardiac sarcoidosis to offer a tailored approach to treatment. While retrospective, they suggest that the phase of disease (whether active inflammatory, or post-inflammatory) ought to determine method of treatment. They demonstrated that those with arrhythmias in the setting of active inflammation tended to respond well to immunosuppression while those without active inflammation but scar responded better to ablation.	
Commentary: These data support decision making based on the results of tests evaluating for active inflammation or not. If there is active inflammation in the setting of presumed cardiac sarcoid, these data support aggressive immunosuppression over ablation, though prospective work is required to help delineate how this tailored approach will work for patients.	

Other EP Concepts

DOI	Title
10.1038/s41598-017-07653-3	<i>Virtual cardiac monolayers for electrical wave propagation</i>
Summary: Kudryashova, et al report on the first mathematical model of the formation of cardiac tissue. They characterized the morphology of cardiac tissue in rat ventricular cells and coupled these with detailed electrophysiological models. They then demonstrated that the in vitro cellular models demonstrated the same anisotropy ratio and wavefront complexity as their mathematical models.	
Commentary: Accurate mathematical models simulating the morphological and physiological properties of cardiac tissue are critical to ex vivo and in vitro studies of the effects of a variety of approaches to therapy on arrhythmogenesis. Models such as these based on simplified in vitro cellular groupings require further validating given the additional complexity conferred by the 3-dimensional nature of the normal heart, however.	

[10.1103/PhysRevE.96.022206](https://arxiv.org/abs/10.1103/PhysRevE.96.022206)

Controlling three-dimensional vortices using multiple and moving external fields

Summary: Das and Dutta report on using changing external thermal and electrical fields to alter the path of three-dimensional scroll waves. They demonstrate that a scroll wave may alter the trajectory of motion of scroll waves such that they can be extrinsically controlled.

Commentary: These data are intriguing in that they suggest a method for controlling phenomena thought to underlie the pathogenesis of atrial and ventricular fibrillation using extrinsic / non-contact thermal and electrical external fields. However, application to electrical phenomena in the heart remains to be evaluated.