On the Beat: Key Articles from July 2017

"Hard Hitting" Article Summaries

Atrial Fibrillation
Cardiac mapping and ablation

DOI	Title
10.1111/jce.13225	*Catheter ablation for the treatment of atrial fibrillation is associated with a reduction in health care resource utilization*
Summary: Samuel, et al reviewed data from a large population based cohort in Quebec, Canada, evaluating the effect of catheter ablation in a cohort of 1,556 patients on resource utilization pre- versus post-ablation. They demonstrated that hospitalizations for atrial fibrillation, all-cause hospitalizations, emergency room visits, echocardiograms performed, and cardioversions needed were significantly reduced in the 12 months after index catheter ablation versus the 12 months prior. This decrease continued further up to 24 months after the index ablation.	
Commentary: The finding that catheter ablation has a sustained impact on overall resource utilization amongst patients with atrial fibrillation is important to decision making in clinical practice, especially when considering on a population basis. Current debates regarding the role of ablation in atrial fibrillation lie in performing a potentially high cost procedure that is not necessarily curative. However, the findings of there being a sustained, overall benefit in resource utilization is important when considering the potential benefits of ablation in terms of societal cost attributable to atrial fibrillation. Important considerations, however, include whether this effect is a byproduct of improved ambulatory care of these patients after ablation due to being tied more closely into care providers with expertise in management of atrial fibrillation, or whether the reduction in ER visits, etc is attributable to improved patient understanding of their condition after having had a complex, interventional procedure.	
10.1016/j.ijcard.2017.02.067	*Conduction recovery following catheter ablation in patients with recurrent atrial fibrillation and heart failure*
Summary: Anselmino, et al reviewed in a retrospective evaluation electrophysiologic findings during intracardiac mapping in patients undergoing redo atrial fibrillation ablation in the setting of underlying heart failure. They demonstrated that in this population, the most common finding was that of reconnection of the pulmonary veins, consistent with prior data. However, almost 1/3 had no pulmonary vein reconnection, and this population tended to suffer from more persistent atrial fibrillation,	

with longer durations of atrial fibrillation and larger left atrial volumes. They concluded that a large number of patients with heart failure and atrial fibrillation require consideration of atrial substrate beyond the pulmonary veins as a result.

Commentary: The study by Anselmino, et al highlights an important consideration in patients with otherwise complex myopathic processes – that pulmonary vein isolation may not be enough. This has underlay the basis for multiple studies over the past several years regarding the role of adjunctive CFE ablation, empiric linear ablation, and rotor ablation beyond pulmonary vein isolation to attempt to improve outcomes. While additive to an already existing literature highlighting the potential relevance of substrate beyond the PVs alone, other important publications from this past month further highlight the importance of trying to find better ways of identifying the right lesion set and the right approach based on a patient's individual substrate. Szilagyi, et al published in JACC EP this month regarding the outcomes of patients who had persistent pulmonary vein isolation at the time of redo ablation. Nearly 17% of patients had pulmonary vein isolation at the time of redo evaluation, with ablation at the time of redo consequently targeting non pulmonary vein triggers and inducible tachycardias or flutters. Outcomes amongst these redo patients were significantly worse (56% freedom from AF) than those who presented with PV reconnection (76%). However, adding to the existing body of evidence that more ablation up front may not necessarily add to outcomes, Fink, et al demonstrated that overall outcomes were no different in all comer persistent and long-standing persistent AF between catheter ablation involving PVI alone versus a stepwise approach involving PVI plus CFE and linear ablation. These studies support the need for continued study and potentially newer disruptive approaches to understand the optimal ablative intervention in individual patients with different AF presentations, whether in the setting of myopathic processes that may associate with more non-PV atrial substrate, or based on duration of AF (which is generally felt to correlate with the extent of substrate though data may be mixed in this regard as well).

Pathophysiology and mechanisms of disease

DOI	Title
10.1111/jce.13217	*Effects of extrinsic cardiac nerve stimulation on atrial fibrillation inducibility: The regulatory role of the spinal cord*

Summary: Dai, et al studied the effects of spinal cord stimulation and spinal cord block on atrial fibrillation inducibility. In a canine model, when added to vagal nerve stimulation, stellate ganglion stimulation, or superior left ganglionated plexus stimulation. They demonstrated that spinal cord stimulation enhanced the effects of vagal nerve stimulation while attenuating the effects of stimulation of the left stellate ganglion or ganglionated plexus. In turn, combinations of different levels of stimulation between spinal cord and whether vagal or stellate stimulation had different effects on AF inducibility, whether significantly increasing or decreasing that potential.

Commentary: The role of autonomic modulation in management of arrhythmias has been an evolving field of study. One critical limitation to this understanding is the complex interplay that exists between different elements of the autonomic nervous system – whether between intrinsic and extrinsic cardiac nerves or between the stellate, the vagus, and other sources of cardiac innervation. One of the major limitations of existing studies has been that different intervention models on extrinsic cardiac nerves may have variable effects on atrial electrophysiology and AF vulnerability. For example, whether low or high level vagal or stellate stimulation is used, different effects on atrial electrophysiology may be seen. These findings, especially in light of other data (eg, from the DEFEAT-HF trial) that may put a damper on the prospects for interventions such as spinal cord stimulation, highlights the importance of further study into the complex interplay between different elements of the autonomic nervous system when considering effects on cardiac electrophysiology, and the potential need for more complex design or targeted approaches to intervention that considers the extensive crosstalk that exists. Two reviews, one by Witt, et al in Europace this past month, and another by Schwartz, et al in the International Journal of Cardiology further discuss the role of the sympathetic nervous system in cardiac arrhythmogenesis, particularly as it relates to risk of ventricular arrhythmias and sudden death.

Risk stratification and management

DOI	Title
10.1016/j.jacc.2017.04.054	*Treating specialty and outcomes in newly diagnosed atrial fibrillation: From the TREAT-AF study*
Summary: Perino, et al present data from the TREAT-AF study regarding the effect of treating specialty on atrial fibrillation outcomes. In a large cohort of over 180,000 veterans, they demonstrated that cardiologist involvement in care was associated with an overall decrease in stroke and death, albeit with a concomitant increase in hospitalization for AF or supraventricular tachycardia and myocardial infarction. The stroke reduction seen appeared to be a result of earlier anticoagulation prescription within 90 days of diagnosis amongst patients seen by a cardiologist, though this did not mediate the mortality reduction.	
Commentary: The data presented by Perino, et al is provocative. Given rising healthcare costs, and the ever increasing numbers of patients with atrial fibrillation, particularly in light of an aging populace, a critical question is whether invoking more specialty care for common conditions, such as atrial fibrillation, early on impacts long-term outcomes. Perino, et al suggest that it does in this retrospective review of data. In a sense, these data are complementary to the results by Samuel, et al discussed earlier suggesting a sustained reduction in health resource utilization attributable to catheter ablation in patients with AF. However, understanding the reasons for these differences in outcomes will be critical to help streamline	

and improve care at the primary internist levels, especially in light of other articles published this past month. For example, Hernandez, et al in Stroke discussed the large degree of geographic variation that exists with regards to appropriate anticoagulation prescription for patients with AF. Whether there may be issues related to access to specialty care, or training on appropriate care pathways amongst internists when compared with specialists, is critical to understanding why gaps in care that may mediate differences in outcomes exist.

10.1136/heartjnl-2016-310357	*Chocolate intake and risk of clinically apparent atrial fibrillation: The Danish Diet, Cancer, and Heart Study*
Summary: Mostofsky, et al present data from the Danish diet, cancer, and heart study in Heart this month regarding the potential effect of chocolate intake on clinically apparent atrial fibrillation. They demonstrate in a population of over 55,000 patients that higher chocolate intake (more than once per month) was associated with decreased atrial fibrillation risk when compared with those consuming less than once per month. However, they note that despite attempts to account for multiple confounding variables, residual confounders could not be accounted for.	
Commentary: The debate on different lifestyle choices and risk of arrhythmias is common, and mediated in part by variable evidence. One critical limitation is most studies are retrospective, and given the large cohorts considered, causes of associations cannot always be readily teased out based on traditional statistical modeling. Thus, counseling patients based on these data becomes complex. However, the importance of these data from Mostofsky et al lies in the question of whether products such as chocolate (which tends to contain caffeine but perhaps other cardioprotective elements) may modulate arrhythmia risk. These data support other prior data that, from a cardiac perspective, moderate intake of chocolate ought not to have a negative effect on atrial fibrillation risk and may have some modest positive impact.	

ICDs, pacemakers and CRT

DOI	Title
10.1038/s41598-017-06493-5	*Inductively powered wireless pacing via a miniature pacemaker and remote stimulation control system*
Summary: Abiri, et al present a novel approach to pacing involving an inductively powered wireless approach in this month's issue of Nature Scientific Reports. Their approach presents potential novel opportunities beyond currently available lead-based and even leadless pacemakers, which are limited due to their need for a pacer-integrated battery. Using intermittent power transfer to control stimulation intervals, they were able to significantly reduce power requirements of an inductive wireless pacing system while also miniaturizing the pacing component such that it could be deployed into the anterior interventricular vein. This is a first report of such an inductively powered miniaturized pacing system with low	

enough power consumption that may prove viable for ambulatory human use.
Commentary: The ability to minimize the power supply from the intracardiac component of the pacemaker holds the potential to further miniaturize pacing devices and provide novel opportunities for deployment to various cardiac locations. The novelty of this work lies in their demonstration of a remote-controlled inductive power transfer system design that allows for miniaturization of the pacing portion and greatly reduces power requirements. Improving design of such systems to increase options for deployment holds potential value in future iterations of pacemakers and other implantable devices. Of note, also this month, Killu, et al published in JACC: Clinical Electrophysiology this month the initial results of a percutaneous epicardially delivered, partially insulated defibrillator lead. Work such as these holds the potential to improve options for patients in whom traditional vascular access is not desired due to any number of reasons, including lack of appropriate access, desire to avoid intravascular leads, and minimizing concomitant infectious risk.

Sudden Death / Cardiac Arrest

DOI	Title
10.1161/JAHA.117.005667	*Health insurance expansion and incidence of out-of-hospital cardiac arrest: A pilot study in a US metropolitan community*
Summary: Stecker, et al published this month the results of the effects of health insurance expansion conferred by the Affordable Care Act on out of hospital cardiac arrests in a large US metropolitan community of over 600,000 people. They used the middle-aged population in whom healthcare expansion would have had an effect on rates of insured individuals against a Medicare aged population whose rates of being appropriately insured should not have changed. They demonstrated that while the increased insurance amongst middle aged individuals correlated with a significant decline in rates of out of hospital cardiac arrest, no change was seen in the elderly Medicare population over the same time period, suggesting a direct population benefit of health insurance expansion.	
Commentary: The findings by Stecker, et al are provocative in that they suggest not just an individual but an overall population benefit in terms of outcomes attributable to increasing the proportion of individuals with adequate health insurance. While it would be impossible to state if other confounders, such as improvements in care beyond the combination of availability and mandates towards carrying health insurance, may have impacted these changes in out of hospital cardiac arrest rates, the time period considered (less than a decade) along with the lack of a change amongst the Medicare population are suggestive. Further evaluation at a national level in varying communities as well as consideration	

of population level cost-benefit analysis, however, will help further understand these findings.	
10.1056/NEJMoa1609758	*Declining risk of sudden death in heart failure*
Summary: Shen, et al present in the New England Journal this month data across 40,000 patients from multiple clinical trials over two decades regarding the change in rates of sudden death amongst heart failure patients. They noted a 44% reduction in sudden death rates across these trials over time, with a cumulative incidence of 2.4% in the earliest trial versus 1.0% in the most recent trial 90 days after randomization. They attributed part of this decline to improving usage and prescription of medications which may modulate heart failure outcomes.	
Commentary: The findings by Shen, et al complement a growing body of evidence that estimates of sudden death risk amongst heart failure patients that inform decision making regarding interventions such as defibrillator implantation, etc may not hold. These complement the DANISH study results that suggest, with improving heart failure care, the incremental benefit of defibrillator therapy in terms of life saving benefit might not be equivalent to what was seen based on trials from the 1990s and 2000s. One of the limitations of studies such as DANISH, however, lay in how the study was powered (in the case of DANISH, to see a 25% difference in mortality). Findings of a declining overall risk of sudden death in heart failure suggest that considerations to how we power future ICD trials needs to take into consideration improving overall outcomes amongst these patients. The importance of better stratifying heart failure patients has been raised in multiple articles this month, including in a review by Halliday, et al in Circulation and in a series of reviews published in volume 237 of the International Journal of Cardiology.	
10.1161/CIRCEP.116.005093	*Prevention of Sudden Cardiac Death in Adults with Congenital Heart Disease: Do the Guidelines Fall Short?*
Summary: Vehmeijer, et al review in this past month's edition the utility of existing guidelines in risk prediction and prevention of sudden death in adults with congenital heart disease. They demonstrated that amongst a population of almost 26,000 adults with congenital heart disease, less than half of patients who suffered sudden cardiac death would have had a guideline based recommendation for an ICD on the basis of either the 2014 consensus statement on arrhythmias or the 2015 European Society of Cardiology guidelines. In turn, about 15% of living controls who had not yet suffered a cardiac arrest met indications for an ICD.	
Commentary: Patients with adult congenital heart disease reflect a unique cohort as many of them have ventricular scar due to prior surgery or chronic hemodynamic stress imposed on their ventricle that can predispose to arrhythmias. In turn, the initial structural insult may result in conduction system abnormalities predisposing to ventricular arrhythmias, and, in turn, sudden death as well. As patients with congenital heart disease are living longer, the incidence of arrhythmias is	

increasing. As a result, many patients at risk of sudden death may not meet conventional guideline criteria. This highlights the need for better approaches to screening these patients at a population level.

Cellular Electrophysiology

DOI	Title
10.1038/s41467-017-00127-0	*Plakophilin-2 is required for transcription of genes that control calcium cycling and cardiac rhythm*
Summary: Cerrone, et al published in this month's edition of Nature Communications regarding novel mechanisms by which Plakophilin-2 (PKP2) may regular arrhythmogenesis. PKP2 is commonly associated with arrhythmogenic right ventricular cardiomyopathy (ARVC), with mutations in it affecting cell to cell adhesion given it is a component of desmosomes. However, Cerrone et al in this publication further demonstrate that PKP2 plays a significant role in maintaining gene transcription that controls intracellular calcium cycling. Absence of PKP2 reduces expression of the ryanodine receptor, ankyrin-B, calsequestrin, and others. They further showed that this reduced expression leads to isoproterenol-induced arrhythmias that can be suppressed with flecainide.	
Commentary: These findings are important in that they point to a novel arrhythmogenic mechanism underlying mutations in PKP2. Further, it suggests that abnormal PKP2 could result in arrhythmogenesis even in the absence of structural heart abnormalities. Thus, PKP2 abnormalities may regulate both electrical *and* mechanical elements of the heart, potentially independent of one another. The implications of these findings include the possibility of PKP2 mutations mediating arrhythmias beyond clinically evident ARVC and potentially novel targets for treatment. Furthermore, due to the effects on expression of a variety of channels that mediate calcium cycling, including the ryanodine receptor and others, it is theoretically possible that PKP2 abnormalities may recapitulate clinical findings associated with primary mutations in these other receptors, such as catecholaminergic polymorphic ventricular tachycardia (CPVT).	
10.1126/sciadv.1603081	*Deregulated Ca^{2+} cycling underlies the development of arrhythmia and heart disease due to mutant obscurin*
Summary: Hu, et al, in this edition of Science Advances, review the role of obscurin in calcium cycling and the resultant risk of arrhythmias. Obscurins are cytoskeletal proteins, mutations of which have been associated with both hypertrophic and dilated cardiomyopathy. Interestingly, knockout animal models for obscurin exhibit abnormal calcium handling, likely	

mediated through SERCA2 and pentameric phospholamban expression. They demonstrated that knockout animal models could exhibit both principally electrical phenotypes (as exhibited by frequent PVCs) or mechanical phenotypes when a chronic, pathologic stress is added (as exhibited by dilated cardiomyopathy).
Commentary: Similar to the work by Cerrone, et al, Hu, et al demonstrate the relevance of a gene associated with structural abnormalities of the heart to cardiac arrhythmogenesis. These findings are important to understand because they imply that the arrhythmias to attributable to myopathies associated with these specific mutations may not reflect a substrate-related myopathy (as one would see with an infarcted heart) alone, but also an electrical imbalance secondary to direct electrophysiologic effects, even in the absence of obvious structural abnormalities. Understanding the pathways via which these effects are mediated may, in turn, afford novel therapies or improved understanding of a patient's risk. One theoretical clinical condition in which the findings by Hu, et al may apply is to that of PVC-related cardiomyopathy, in which there is a clear electrical component but potentially a structural component as well which may be mediated by subcellular events such as impaired calcium cycling.

Genetic Channelopathies (LQTS, Brugada, CPVT, etc)

DOI	Title
10.1016/j.jacc.2017.05.022	*Contemporary Outcomes in Patients with Long QT Syndrome*
Summary: Rohatgi, et al present outcomes in modern practice amongst patients with long QT syndrome. Amongst a large cohort of over 600 patients predominantly affected by LQT1 or LQT2, 92% of patients did not experience any breakthrough cardiac events with tailored individual therapies. It was noted, however, that the incidence of breakthrough cardiovascular events over long-term follow-up were far more common in patients who were symptomatic prior to first evaluation versus asymptomatic (25% vs 2%). Of 30 patients with 2 or more breakthrough cardiac events, 5 either died or required heart transplantation.	
Commentary: The work by Rohatgi, et al highlights the advances thus far in the care of patients with long QT syndrome in terms of long-term outcomes, but also the need for continued advances. While overall most patients did well, as many as one in four patients with a history of symptoms attributable to their long QT syndrome will have breakthrough events after initiation of appropriate treatment. Thus, specialized and individualized care may have the potential to significantly prolong life in patients with long QT syndrome in the modern era.	

10.1001/jamacardio.2017.1320	*Efficacy of Flecainide in the Treatment of Catecholaminergic Polymorphic Ventricular Tachycardia: A Randomized Clinical Trial*
Summary: Kannankeril, et al published a prospective, single-blind, placebo-controlled crossover trial regarding the efficacy of flecainide in treating CPVT in JAMA Cardiology this month. All patients had an ICD and were continued on maximal beta-blocker therapy. Amongst 14 patients included (of whom 13 completed the study), flecainide when compared with placebo significantly reduced median ventricular arrhythmia score during exercise, and resulted in complete suppression in most (85%).	
Commentary: Currently, flecainide is a class IIa indication according to both the 2015 ESC guidelines and 2013 HRS/EHRA/APHRS consensus statement. However, no prospective clinical trial regarding use of flecainide to suppress arrhythmias had been well evaluated in these patients prior to the work by Kannankeril, et al. Thus, these findings add to the existing literature in terms of the potential incremental value of flecainide in achieving adequate arrhythmia suppression, when used in conjunction with maximal tolerated beta-blockers.	
10.1113/JP273142	*A multiscale computational modelling approach predicts mechanisms of female sex risk in the setting of arousal-induced arrhythmias*
Summary: Yang, et al published in the Journal of Physiology this past month regarding the mechanism potentially underlying how female gender increases risk of inherited and acquired prolonged QT related torsades. They demonstrate using experimental and computational approaches that hormone concentrations partly mediate this risk, specifically as it relates to hERG related mutations. Interestingly, females with high progesterone exhibited a protective effect against arrhythmias while estrogen enhanced torsadogenic potential, particularly in the setting of sympathetic stress. The mechanism by which this occurs was thought to be via interaction of estrogen with the pore loop or intra-cavity binding site of the hERG channel. In turn, they demonstrated that pore channel blockade can occur simultaneously with both estrogen and dofetilide.	
Commentary: The findings by Yang, et al suggest one mechanism for sex-based arrhythmias. The findings carry the potential to offer improved methods of risk stratification amongst patients with both inherited and acquired long QT syndromes. In addition, the fact that dofetilide and estrogen can concurrently block the pore of the hERG channel carries theoretical implications when considering drug loading, particularly in actively menstruating younger women. Thus, these findings may also be hypothesis-generating in terms of potential future research to further clarify at risk patients.	

Ventricular Arrhythmias

DOI	Title
10.1016/j.jacep.2017.02.024	*Real-Time Localization of Ventricular Tachycardia Origin from the 12-Lead Electrocardiogram*
Summary: Sapp, et al present a methodology for rapidly determining in real-time the approximate origin of a ventricular tachycardia using the 12-lead electrocardiogram. In 38 patients with scar-related VT, they used different methods including 1) a discrete method estimating segment of activation based on template matching; 2) a population-based multiple linear regression method; and 3) a patient-specific multiple linear regression method using at least 10 training set pacing sites in the individual patient. They demonstrated that a localization accuracy of as much as 5 mm could be achieved with the patient specific method, with that accuracy further increasing with additional pacing sites.	
Commentary: These findings support the continued utility of the standard 12-lead ECG in localizing the exit of ventricular tachycardia. The ECG reflects a predictable reflection of global cardiac activation pattern. However, due to variability in cardiac anatomy that may often be subtly, as seen by Sapp, et al, applying a system by which there is continuous, real-time optimization of the system via use of additional information regarding the resultant ECG from individual patients' specific pacing sites further optimizes results. Several papers this past month discuss the role of the ECG in understanding a patient's specific disease pattern. Yadav, et al also in JACC: Clinical Electrophysiology reviewed the use of standardized ECG algorithms in distinguishing idiopathic VT from SVT with aberrancy, noting severe limitations in their use when idiopathic VT arises from a septal or Purkinje site. Zhang, et al in the same issue reviewed addition of a posterior ECG lead to further localizing idiopathic outflow tract arrhythmias.	
10.1016/j.jacep.2017.01.020	*Long-Term Outcomes of Catheter Ablation of Electrical Storm in Nonischemic Dilated Cardiomyopathy Compared with Ischemic Cardiomyopathy*
Summary: Muser, et al review outcomes of ablation in nonischemic versus ischemic cardiomyopathy. They reviewed 267 patients who were predominantly ischemic (196 ischemic vs 71 non-ischemic). Over a nearly 4 year median follow-up, nearly 1/3 of the overall population had recurrence of VT. A low EF, VT recurrence, and NYHA class were associated with death or transplant over follow-up. There was no significant difference, however, in long-term outcomes between patients with a nonischemic versus ischemic etiology of their cardiomyopathy.	
Commentary: Outcomes data regarding utility of ventricular tachycardia ablation in nonischemic as compared with ischemic patients is varied. In these results from a high volume center, the outcomes were similar between both groups.	

Most prospective trials of ventricular tachycardia ablation have focused on ischemic patients, largely because they are expected to have a fixed, predictable substrate. The findings that outcomes are similar regardless of etiology highlghts that ablation may provide a reasonably effective therapy irrespective of the cause of the myopathy.

10.1016/j.jacbts.2017.02.002	*Increased afterload following myocardial infarction promotes conduction-dependent arrhythmias that are unmasked by hypokalemia*
Summary: Motloch, et al studied the role of increased afterload after myocardial infarction in eliciting arrhythmias in a porcine infarct model. They demonstrated that in this animal model of myocardial infarction with increased afterload, there is increased interstitial fibrosis that is widespread, resulting in increased propensity to pacing-induced arrhythmias. Most interestingly, these arrhythmias were due to effects on hypokalemia-associated conduction rather than repolarization. It was hypokalemia specifically that served to unmask these inducible, re-entrant arrhythmias.	
Commentary: Concomitant hypertension with myocardial infarction is common. In addition, ventricular arrhythmias in the early phases after myocardial infarction are not uncommon. However, the mechanism by which these arrhythmias happen, whether due to repolarization abnormalities or other mechanism, is unclear. The work by Motloch, et al support the role of associated fibrosis and conduction abnormalities unmasked by hypokalemia as being a significant mediator of ventricular arrhythmogenesis in this specific animal model. One clinical implication of these findings is that of the potential pro-arrhythmic effect of antitachycardia pacing in patients with increased afterload, as their findings were specific to pacing-associated arrhythmias. Furthermore, hypokalemia and perhaps other treatments that impair cardiac excitability (eg, sodium channel blockade) may similarly confer an increased risk of ventricular arrhythmias when in the presence of increased afterload and myocardial infarction.	

EP Relevant Myopathies (ARVC, HCM, etc)

DOI	Title
10.1016/j.jacep.2017.01.009	*12-Lead Electrocardiogram to Localize Region of Abnormal Electroanatomic Substrate in Arrhythmogenic Right Ventricular Cardiomyopathy*
Summary: Tschabrunn, et al reviewed the utility of the 12-lead electrocardiogram in localizing the electroanatomic substrate in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). Out of 30 patients included, 25 had	

depolarization abnormalities as defined by fractionation in the QRS complex. They found that evidence of a fractionated QRS was associated with more extensive substrate. Furthermore, distribution of QRS fractionated to specific leads (inferior, anterior, basal superior) was 100% specific but variably sensitive (45-82%) for identifying substrate localizing to associated cardiac regions.

Commentary: The utility of the ECG in defining cardiac substrate may be useful in helping invasive electrophysiologists define expected areas of involvement that may require close attention during mapping. Furthermore, understanding the extent of substrate may correlate with outcomes of ablation. The utility of findings on a commonly obtained test such as the 12-lead ECG in counseling patients or defining relevant substrate is a simple approach Rudy, et al also reviewed how the addition of multiple leads, via noninvasive electrocardiographic imaging, could be used to specifically hone in on relevant substrate in arrhythmogenic right ventricular cardiomyopathy. Furthermore, they demonstrated that additional repolarization abnormalities colocalized with origination sites for ventricular ectopy. These studies in combination highlight the utility of simple and more advanced methods of electrocardiographic “imaging” in identifying arrhythmogenic substrate in ARVC.

10.1038/s41598-017-05001-z	*MiR-320a as a Potential Novel Circulating Biomarker of Arrhythmogenic Cardiomyopathy*

Summary: Sommariva, et al studied whether a circulating biomarker could help distinguish ventricular arrhythmias of an idiopathic origin versus those due to arrhythmogenic cardiomyopathy. They evaluated circulating microRNAs in 36 arrhythmogenic cardiomyopathy patients, 53 healthy controls, and 21 idiopathic VT patients. Circulating MiR-320a was significantly higher in arrhythmogenic cardiomyopathy patients compared with either other group. Furthermore, when compared with other non-invasive diagnostic parameters for arrhythmogenic cardiomyopathy, MiR-320a increased accuracy in differentiating between patients.

Commentary: Diagnosis of arrhythmogenic cardiomyopathy may often be difficult. Prior studies have suggested significant overlap amongst patients presenting with idiopathic VT, with seemingly idiopathic VT reflecting a form of “concealed” arrhythmogenic cardiomyopathy that has yet to fully manifest itself in the form of structural abnormalities. This possibility is borne out by the work of Cerrone, et al discussed earlier in which PKP2 mutations may lead to alteration in electrical activity in the absence of obvious structural abnormalities. Thus, identifying methods to further discriminate between patients who have truly idiopathic VT or perhaps a “not fully manifested” form of arrhythmogenic cardiomyopathy could be useful, particular as it relates to long-term risk stratification. Future study into novel biomarkers, such as MiR-320a, may provide improved methods of accurately differentiating such patients.

Other EP Concepts

DOI	Title
10.1093/eurheartj/ehx156	*Alcohol consumption, sinus tachycardia, and cardiac arrhythmias at the Munich Octoberfest: results from the Munich Beer Related Electrocardiogram Workup Study (MunichBREW)*
Summary: Brunner, et al studied the effect of alcohol consumption on manifestation of cardiac arrhythmias in the MunichBREW study. 3028 voluntary participants were included and underwent breath alcohol concentration (BAC) measurements as well as electrocardiographic recordings via SmartPhone. In addition, they evaluated the effects of chronic alcohol consumption on arrhythmias in a separate cohort of 4131 patients from the KORA S4 Study. In the acute study of effects of alcohol consumption, a variety of arrhythmias (most commonly sinus tachycardia) were seen in nearly 1/3 of patients. There was a direct correlation between BAC and the occurrence of arrhythmias. In addition, respiratory sinus arrhythmia was seen to be significantly reduced in the setting of alcohol use. In terms of chronic alcohol consumption, an apparent significant association was seen with the occurrence of sinus tachycardia.	
Commentary: The effect of alcohol intake on incidence of cardiac arrhythmias, in particular atrial fibrillation, is of particular concern to patients. However, while retrospective analyses suggest association between supraventricular arrhythmias and alcohol use, prospective data are wanting. This was a rigorous study done on thousand of volunteers engaged in alcohol consumption and demonstrated that there was a significant and direct effect of alcohol intake on sius rates and, in particular respiratory sinus arrhythmia. This suggests a potential autonomic influence which could underlie some other elements of arrhythmogenesis related to alcohol intake, in particular atrial fibrillation. These findings serve to further elucidate such mechanisms of disease in a large real-world patient sample.	