

The Year in Cardiovascular Medicine: Arrhythmias 2021

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2021 yielded remarkable societal impact arrhythmia papers reporting on important public health issues, the latest ESC 2021 pacing guidelines, randomised trials on atrial fibrillation (AF) and cardiac pacing, and intriguing multidisciplinary aspects of AF, with progress in ventricular arrhythmias, in particular an outstanding series of Brugada syndrome studies.

Public health and societal issues matter in AF

A range of papers indicate that foods and food supplements, health behaviours, work and sleep environment and life events may increase the incidence of AF in turn affecting health in the population and drawing attention to the need for reform. Dietary supplements were investigated in the VITAL Rhythm Study (Graphical Abstract).¹ Incident AF was not significantly reduced over 5.3 years by either omega-3 fatty acids or vitamin D supplementation. Indeed a meta-analysis of randomised trials in patients with increased vascular risk showed that supplementation with marine omega-3 fatty acids increases the 1.2% yearly risk of incident AF by 25% especially if >1gram per day is ingested, to be discussed with your patient when optimising AF management.² The mechanisms remain an area of future exploration.

Daily alcohol consumption of one standard drink is long said to be protective in myocardial infarction, heart failure and stroke but did not protect from new AF despite how low the alcohol dose was in 107,845 individuals in 5 prospective community-based cohorts (Figure 1).^{3,4} Furthermore, abstinence of alcohol after a new diagnosis of AF was associated with a 14% reduction in stroke compared to continued drinking in a population-based study from Korea.⁵ So, alcohol and AF seem to have an atypical relationship^{6,7} versus other cardiovascular disorders.

The incidence of AF is also impacted by social stressors with studies demonstrating increases in AF risk among night shift workers, regardless of their genetic background risk for AF.⁸ Parents losing a child also have an on average 15% increased AF risk, especially in the first week after the loss, with atrial arrhythmogenic sympathetic arousal, substance use, inflammation or the renin-angiotensin-aldosterone system as mediating factors.^{9,10} Sleep arousal burden is associated with long-term all-cause and cardiovascular mortality in community-dwelling elderly, but unknown if it increases the incidence of AF.¹¹

Resuscitation

From the Swedish Register for Cardiopulmonary resuscitation one paper showed that low socioeconomic status reduces chances of survival after in-hospital cardiac arrest due to lack of rhythm monitoring and delayed CPR¹², in line with out-of-hospital cardiac arrest.¹³ Socio-economic prejudices leading to inappropriate health inequalities demand re-engineering societal conditions.^{12,14} A second paper from this registry reported decreased 30-day survival from 9.8% to 4.7% in out-of-hospital arrests in patients suffering from COVID-19 compared to non-COVID-19 arrests, and from 39.5% to 23.1% for in-hospital cardiac arrests, respectively.¹⁵ Although this may relate to the early COVID-19 recommendation from the authorities to avoid bystander ventilation, arrests were more often associated with non-shockable rhythms and pulmonary failure. At the same time, due to COVID-19 restrictions an unexpected 32% reduction in ventricular arrhythmias needing device therapies was reported¹⁶, whilst the converse of a 33% increase pacemaker/ICD detected atrial arrhythmia episodes was found in otherwise stable rhythm device patients.¹⁷

A novel strategy of alert system-supported lay defibrillation and basic life-support was superior to usual resuscitation in a randomised study from the Netherlands with improved out-of-hospital cardiac arrest survival from 26 to 39%, and 50% more patients with neurologically favourable outcome.¹⁸ A spectacular new concept from Sweden concerned drone-delivery of an AED to the out-

of-hospital cardiac arrest scene integrated in the standard emergency medical services, showing that delivery was feasible with earlier arrival of AED by two minutes.¹⁹ Both papers illustrate that the chain-of-survival for cardiac arrest is boosted significantly by novel technologies, and implicitly they provide an example for regions with less advanced resuscitation infrastructure.

New pacemaker and resynchronisation guidelines

The 2021 ESC Guidelines on cardiac pacing and resynchronization therapy, updated from 2013, address many new areas including pacing in TAVI, conduction system pacing, novel insights into CRT indications, and leadless pacing.²⁰ Figures summarising management in the increasingly complex areas of seemingly simple conditions like suspected bradycardia or conduction system disease are provided (Figure 2). A long list of gaps in evidence are outlined as an invitation to perform randomised trials and observational big data studies. Gaps which could be addressed include optimal pre-implant programming, prediction of pacing-induced cardiomyopathy, long-term effects of conduction system pacing, prediction of AVB after TAVI, and acute device implantation in patients with an active infection. The Guidelines also highlight evidence gaps in the effects of patient education, patient-centred care, and shared decision-making.²⁰

Randomised controlled trials in AF with or without HF

Screening for AF is currently recommended on an opportunistic basis for patients over the age of 65, using pulse palpation or ECG rhythm strip.²¹ The LOOP study investigated a more strategic screening approach, utilising Medtronic LinQ® loop recorders for continuous heart rhythm monitoring.²² Elderly patients were randomised to loop recorder implant for AF screening or standard care. Anticoagulation was started for patients in whom more than six minutes of AF was detected. Subclinical AF was more frequently diagnosed in the loop recorder arm, but anticoagulation of these patients did not result in significantly reduced incidence of stroke or systemic arterial embolism over more than five years. Similarly, another randomised AF screening study published this year, STROKESTOP, which utilized a less intensive screening involving twice daily 12-lead ECGs for 14 consecutive days in a larger population of 75-76 year olds also did not find a significant benefit on ischemic stroke compared to usual care.²³ However, this study did report a significant modest 4% reduction conferred by AF screening on the primary composite outcome of ischemic or haemorrhagic stroke, systemic embolism, major bleeding leading to hospitalisation, or death compared to usual care.²³ Therefore, whilst strategic screening programs for AF may be of use in elderly patients, there do not appear to be marked benefits on ischemic stroke in unselected patients. Also, the specific role of long-term continuous monitoring and the precise burden of AF required to instigate anticoagulation remain unclear. A separate LOOP analysis assessed physical activity measured through the loop recorder showing that a 1-hour reduction in average daily physical activity was associated with an increased odds of AF onset the next day by $\approx 25\%$ ²⁴, a finding supported by a recent UK Biobank analysis using a wrist-based accelerometer.²⁵ These data strengthen the evolving links between modifiable risk factors, physical activity and AF; providing a foundation for new tools to evaluate and intervene in lifestyle modification programs.²⁶

RATE-AF compared bisoprolol with low-dose digoxin as first-line therapy in permanent AF and high ventricular rates.²⁷ Both drugs were found to be equally effective in reducing resting heart rate and there were no differences between the two arms in patient-reported quality of life at 6 months. Furthermore, digoxin was associated with fewer adverse events, suggesting that digoxin may have a place as an alternative to beta-blockade as first-line therapy despite previous observational studies suggesting increased mortality.²⁸⁻³⁰

The APAF-CRT trial compared medical rate control with a pace and ablate strategy^{31,32} using CRT as opposed to RV pacing in patients with permanent AF, heart failure and narrow QRS on ECG.³³ AVN ablation and CRT was superior to medical rate control, resulting in a 74% reduction in all-cause mortality and a 60% reduction in heart failure hospitalisation. These substantial reductions are compelling and highlight the utility of this strategy over medical rate control in a specific cohort of elderly patients with heart failure and permanent AF.

Syncope

Investigation and management of patients with recurrent reflex syncope remains a significant clinical challenge. The utility of tilt table testing in diagnosis has been questioned, but a state-of-the-art review³⁴ highlighted its advantages, which include the ability to correlate symptoms, blood pressure and heart rhythm, providing the ability to assess the temporal association between bradycardia and syncope optimise selection of patients who may benefit from pacing. Brignole et al.³⁵ studied patients over 40 years old with recurrent reflex syncope and tilt-induced syncope with an asystolic pause longer than three seconds who had dual chamber pacemakers with closed loop stimulation (CLS) function. Patients were then randomised to either active ('pacing on') or inactive ('pacing off'). The 'pacing on' group had a 77% reduction in risk of recurrent syncope compared to the 'pacing off' group, highlighting both the clinical utility of tilt-induced asystole as well as the efficacy of pacing with CLS.

Multidisciplinary AF

COPD shares common risk factors with AF and may cause AF-genic atrial structural remodeling and increased sympathetic nerve activity (the latter also boosted by beta-agonists), caused by hypoxemia and hypercapnia, increased thoracic pressure swings, systemic inflammation and accelerated ageing.³⁶ COPD in AF patients associates with sleep apnoea, heart failure, coronary disease, and diabetes. COPD contributes to AF progression and recurrences after rhythm control therapies, increases the risk of all-cause and cardiovascular death, stroke and major bleeding in AF patients, and therefore requires a multidisciplinary management approach.^{36, 37}

Verdonschot et al. clustered dilated cardiomyopathy in 4 phenotypes, one of which is the arrhythmia DCM-phenocluster mainly consisting of AF and pointing to either a common mechanism leading to DCM and AF (with atrial failure as one of presumed linking mechanisms) or AF causing reversible tachycardiomyopathy.³⁸ In a Mendelian randomisation study, AF was found to be a causal factor for renal impairment rather than the reverse.³⁹ Presumed linking mechanisms are hemodynamic or thromboembolic, but whether elimination of AF would reduce incidence of kidney failure is as yet uncertain.⁴⁰ In the LAAOS-III trial removal of the left atrial appendage during cardiac surgery reduced the risk of stroke in patients continuing oral anticoagulation⁴¹ and should be considered in all cardiac surgeries in high risk AF patients.⁴² Notably, one quarter of NOAC users appear to discontinue the drug leading to avoidable strokes⁴³ but LAAOS-III does not address stand-alone appendage closure in non-compliant patients.

Utilising serially assessed hsTnT and NT-proBNP improves the ABC stroke risk score and the same holds for GDF-15 incorporated in the ABC bleeding risk score.⁴⁴ Although this paper supports the notion that serial biomarkers may better reflect risk of adverse events in AF²¹ it may not immediately change practice: what if NT-proBNP and hsTnT increased in an already anticoagulated patient? Add platelet inhibitor and put in an appendage occluder? Or reduce anticoagulation and manage already well-managed bleeding risk factors in case of an increase in GDF-15?⁴⁵ By design, since all patients were CHA2DS2-VASc 2 or greater and treated with anticoagulation, the study could not answer whether serial assessment of biomarkers might help to identify patients at apparently low risk by

CHA2DS2-VASc who might benefit, and randomised clinical trials are dearly needed in this area. For the time being, for the low risk AF patients an easy to use decision tree for or against adding anticoagulation can be found at⁴⁶.

Ventricular arrhythmias and SCD

Studies in this area include elegant clinical observations from the humble surface ECG, epicardial mapping, to functional genetic studies. Two specific papers focus on the initiation of ventricular fibrillation (VF). Viskin and colleagues examined the behaviour of triggering ventricular ectopics in 87 patients with coronary artery disease who developed spontaneous polymorphic VT responsive to quinidine therapy in the absence of ischaemia.⁴⁷ In 32 patients, the QT interval was prolonged. However, when comparing the polymorphic VTs of these patients, which were termed 'pseudo-Torsade de Pointes (TdP)', with 53 patients with true TdP in the context of drug-induced LQTS they noted the coupling interval of the initiating ectopic beat was shorter than 400 ms in pseudo-TdP and (much) longer than 400 ms in true TdP. In addition, the QT interval in pseudo-TdP was shorter, the mode of onset was less often pause dependent, and the initial R-R intervals were shorter than in true TdP. Finally, patients with pseudo-TdP responded well to quinidine therapy, whereas quinidine is obviously detrimental in true TdP. Thus, in patients with pseudo-TdP, polymorphic VTs occur in the presence of a prolonged QT interval, but not due to a prolonged QT interval.⁴⁷ These observations have important implications in managing polymorphic VT/VF in coronary artery disease patients to identify 'quinidine responders'.⁴⁸ (Figure 3)

The CASPER investigators described a distinct novel phenotype of idiopathic VF initiated by a trigger PVC with a coupling interval of <350 ms, short-coupled ventricular fibrillation (SCVF).⁴⁹ Among 364 Unexplained Cardiac Arrest (UCA) survivors, 6.6% met diagnostic criteria for SCVF. Electrical storm occurred in 21% of these probands but not in other UCA probands ($P < 0.001$). Recurrent ventricular fibrillation resulted in quinidine administration in 50% SCVF cases with excellent arrhythmia control indicating this should be a first line treatment. The lesson learned from both these studies is to carefully evaluate VF initiation examining the coupling intervals of the initiating beat as this can have critical implications for polymorphic VT/VF drug management using quinidine. (Figure 3)

Over the past year, there has been increased recognition of the importance of considering competing risks of mortality when considering who might benefit from ICD therapy. The MADIT-ICD score quantified the risk of cardiac arrest versus other competing causes of death and reported on separate prognostic score models for VT and non-arrhythmic mortality.⁵⁰ The two scores were combined to create three MADIT-ICD benefit groups. In the highest benefit group, the 3-year predicted risk of VT/VF was three-fold higher than the risk of non-arrhythmic mortality (20% vs. 7%, $P < 0.001$). This personalised benefit score predicted the likelihood of prophylactic ICD therapy weighed against the risk of non-arrhythmic mortality enabling a more informed discussion with patients.

In a risk stratification study focusing on Brugada Syndrome (BrS), the Shanghai Brugada diagnostic score was compared to the Sieira score (which combines a number of risk factors including Type 1 resting Brugada ECG, family history of sudden death and inducibility of VT/VF at EP study): both scores differentiate equally between high and low risk patients but perform equally poorly for intermediate risk cases.⁵¹ Interestingly, there were very few sudden deaths with an overall risk of 0.15% per annum i.e. equivalent to the general population indicating that although risk assessment in BrS needs to be refined, very few sudden deaths occur using current individual clinician based risk stratification strategies⁵²; however, recent studies suggest that genetic profiling may identify higher risk subgroups.

To this end, Ishikawa et al demonstrated that loss of function (LOF) SCN5A mutation carriers identified on a functional cellular assay had more severe ECG conduction abnormalities and worse prognosis associated with earlier manifestations of lethal arrhythmic events (LAEs) (7.9%/year) than in silico algorithm-predicted SCN5A carriers (5.1%/year) or all BrS probands (2.5%/year). Importantly, non-LOF SCN5A variation carriers (n = 15) exhibited no LAEs during the follow-up period.⁵³ Multivariate analysis demonstrated that only LOF-SCN5A mutations and a history of aborted cardiac arrest were significant predictors of LAEs.⁵³ Rare variations of non-SCN5A BrS-associated genes did not affect LAE-free survival curves. This study highlights that specific LOF SCN5A mutations could enable more refined risk stratification in BrS. Indeed, Ciconte et al recently reported SCN5A-positive BrS patients exhibited a larger epicardial area of fractionated, prolonged electrograms and more frequent ECG late potentials.⁵⁴ The presence of an SCN5A mutation explained >26% of the variation in epicardial abnormal substrate area. These data indicate a link between SCN5A determined epicardial conduction abnormalities and ventricular arrhythmias in BrS supporting the conduction reserve hypothesis but requires further refinement in determining the genetic architecture of pro-arrhythmic phenotypes in BrS.⁵⁵

To conclude, The Year in Cardiovascular Medicine 2021 – Arrhythmias has produced a diverse range of papers, with many highlighting key knowledge gaps for further investigation.

Legends to Figures

Graphical abstract. Randomised trials reported on food supplements to prevent AF¹, screening for AF²² and left atrial appendage occlusion (LAAO)⁴¹ to prevent stroke, and novel pacing strategies to prevent death in heart failure patients³³ or syncope recurrence³⁵. In RATE-AF digoxin was superior to bisoprolol²⁷, illustrating an old drug can be effective if wisely applied with a patient-oriented endpoint. To improve impact of primary prevention ICD, the MADIT-ICD benefit score balances the risk of sudden cardiac death and the competing risk of non-arrhythmic death⁵⁰ (calculator at <https://redcap.urmc.rochester.edu/redcap/surveys/index.php?s=3H888TJ8N7>). The worldwide differences in ICD usage⁵⁶ further supports a unified approach focusing on ICD-benefit. Contrary to current guidelines, EAST-AFNET4 substudy suggests that (early) rhythm control benefits asymptomatic and symptomatic patients alike concerning cardiovascular endpoints.⁵⁷ Alcohol does not protect from AF no matter dose or type of alcohol (Csengeri study)³, although the latter is at variance with another recent BIOBANK study.⁷ Stopping consuming alcohol after detection of AF may reduce stroke⁵; it may also reduce recurrence of AF after ablation.⁶ Less AF^{24, 25} and stroke²⁵ was also seen with higher levels of physical activity (PA) as measured by modern day monitoring technology (#) in LOOP trial²⁴ and UK Biobank.²⁵ Also from the UK Biobank: long-term night shift work may cause AF.⁸

Figure 1. Alcohol consumption and risk of cardiovascular associations per one standard drink: finding the right balance.⁴

Figure 2. One of the didactic Figures from the ESC 2021 Guidelines on cardiac pacing and resynchronisation explaining the evaluation of bradycardia and conduction disease.²⁰

Figure 3. Coupling intervals at the initiation of various ventricular arrhythmias including short-coupled variants.

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