ESC European Society of Cardiology

Europace (2023) **25**, 1–11
https://doi.org/10.1093/europace/euad210

25 years of basic and translational science in *EP Europace*: novel insights into arrhythmia mechanisms and therapeutic strategies

Carol Ann Remme [1,2]*, Jordi Heijman [3], Ana M. Gomez [4], Antonio Zaza [5], and Katja E. Odening [6]

[1]Department of Experimental Cardiology, Amsterdam UMC location University of Amsterdam, Heart Centre, Academic Medical Center, Room K2-104.2, Meibergdreef 11, 1105 AZ Amsterdam, The Netherlands; [2]Amsterdam Cardiovascular Sciences, Heart Failure & Arrhythmias, Amsterdam, The Netherlands; [3]Department of Cardiology, Cardiovascular Research Institute Maastricht, Faculty of Health, Medicine and Life Sciences, Maastricht University, 6229 ER Maastricht, The Netherlands; [4]Signaling and Cardiovascular Pathophysiology, UMR-S 1180, Inserm, Université Paris-Saclay, 91400 Orsay, France; [5]Department of Biotechnology and Biosciences, University of Milano-Bicocca, 20126 Milan, Italy; and [6]Translational Cardiology, Department of Cardiology and Department of Physiology, Inselspital University Hospital Bern, University of Bern, 3012 Bern, Switzerland

Received 19 June 2023; accepted after revision 19 June 2023; online publish-ahead-of-print 25 August 2023

In the last 25 years, *EP Europace* has published more than 300 basic and translational science articles covering different arrhythmia types (ranging from atrial fibrillation to ventricular tachyarrhythmias), different diseases predisposing to arrhythmia formation (such as genetic arrhythmia disorders and heart failure), and different interventional and pharmacological anti-arrhythmic treatment strategies (ranging from pacing and defibrillation to different ablation approaches and novel drug-therapies). These studies have been conducted in cellular models, small and large animal models, and in the last couple of years increasingly *in silico* using computational approaches. In sum, these articles have contributed substantially to our pathophysiological understanding of arrhythmia mechanisms and treatment options; many of which have made their way into clinical applications. This review discusses a representative selection of *EP Europace* manuscripts covering the topics of pacing and ablation, atrial fibrillation, heart failure and pro-arrhythmic ventricular remodelling, ion channel (dys)function and pharmacology, inherited arrhythmia syndromes, and arrhythmogenic cardiomyopathies, highlighting some of the advances of the past 25 years. Given the increasingly recognized complexity and multidisciplinary nature of arrhythmogenesis and continued technological developments, basic and translational electrophysiological research is key advancing the field. *EP Europace* aims to further increase its contribution to the discovery of arrhythmia mechanisms and the implementation of mechanism-based precision therapy approaches in arrhythmia management.

Keywords Basic electrophysiology • Translational electrophysiology • Atrial fibrillation • Ventricular arrhythmias • Sudden cardiac death • Ion channels • Pathophysiology • Genetics • Modelling

Introduction

In the last 25 years, *EP Europace* has published more than 300 basic and translational science articles covering different arrhythmia types [ranging from atrial fibrillation (AF) to ventricular tachyarrhythmias (VT)], different diseases predisposing to arrhythmia formation [such as genetic arrhythmia disorders and heart failure (HF)], and different interventional and pharmacological anti-arrhythmic treatment strategies (ranging from pacing and defibrillation to different ablation approaches and novel drug therapies) (*Figures 1* and *2*). These studies have been conducted in cellular models, small and large animal models, and in the last couple of years increasingly *in silico* using computational approaches (*Figure 3*). In sum, these articles have contributed substantially to our pathophysiological understanding of arrhythmia mechanisms and treatment options; many of which have made their way into clinical applications. This review discusses a selection of representative manuscripts on pacing and ablation; AF; HF and pro-arrhythmic ventricular remodelling; ion-channel (dys)function and pharmacology; as well as inherited arrhythmia syndromes and arrhythmogenic cardiomyopathies to highlight some of the advances of the past 25 years.

Pacing and ablation

The basic and translational articles on pacing and ablation published in the last 25 years in *EP Europace* range from 'classical' translational experimental studies investigating novel pacing or ablation strategies conducted in larger experimental animal models,[2,3] via mechanistic studies exploring the impact of pacing, scar formation after ablation, to novel

* Corresponding author. Tel: +31-20-5663262/3, *E-mail address*: c.a.remme@amsterdamumc.nl

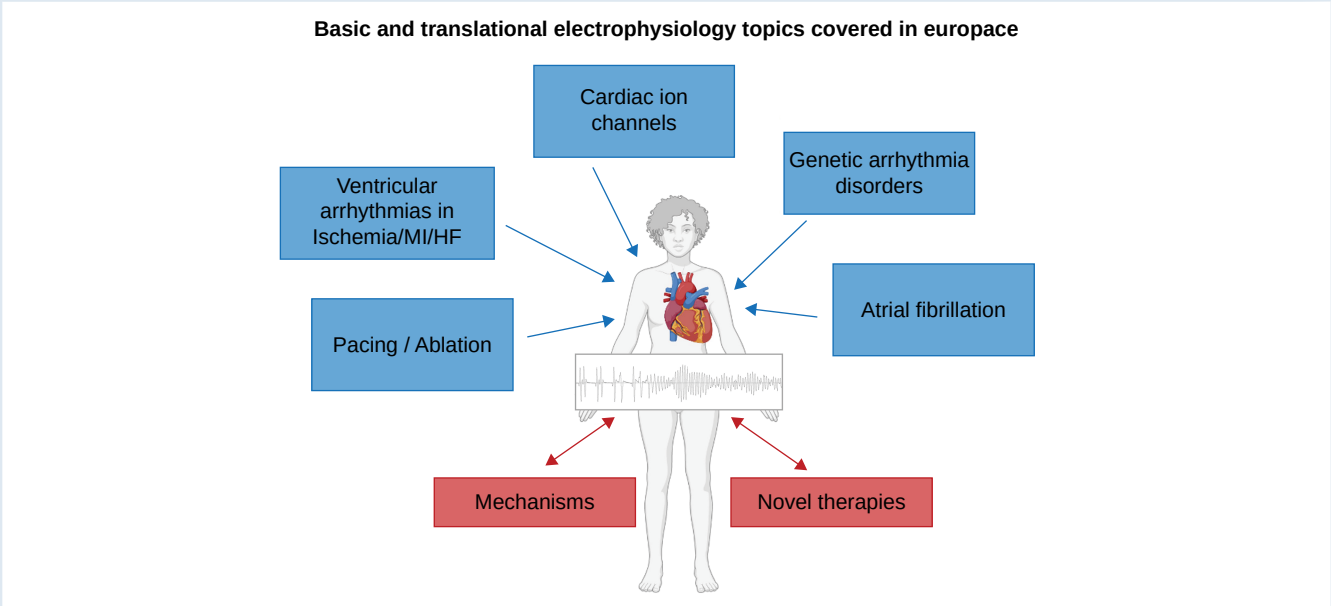

Figure 1 Overview of the basic and translational cardiac electrophysiology topics that have been covered in *EP Europace*. In all topics, pathophysiological mechanism and novel therapy approaches are investigated. Generated with *biorender*.

innovative investigations of bio-artificial pacemakers or optical pacing. In recent years, these experimental studies have been complemented by several computational whole-heart electro-mechanical studies providing insight into the electrophysiology of pacing and ablation.

The classical translational experimental studies—and particularly their consequences for current state-of-the-art clinical approaches—will be discussed in dedicated reviews on 'Cardiac pacing', 'Clinical EP and AF ablation', and 'Clinical EP and VT ablation' published in this issue. Here, we will focus primarily on the mechanistic insights obtained.

Ablation—insights into scar formation

Several manuscripts investigated the biophysical consequences and scar formation after ablation and factors facilitating recurrency. Among them, a sophisticated ablation study conducted in mice characterized spatio-temporal diverse electrophysiological changes within the lesion and beyond the border zone.[4] Moreover, they showed that late recovery of electrical conduction in individual lesions can lead to arrhythmia recurrence—consistent with the clinical observation of the association between loss of bi-directional conduction block and arrhythmia recurrence. Other studies investigated the differences in scar/lesion formation in healthy and diseased myocardium (low- to intermediate-voltage areas),[5,6] identifying differences in the depth, width, and homogeneity of the lesions, which has clinical implications for performing ablations in diseased myocardium.

Pacing—impact on synchronicity and heterogeneity in repolarization

Basic/translational articles have focused on the impact of pacing the heart at different anatomical sites and/or different parts of the myocardial wall (e.g. endo- vs. epicardium) and the potential pathophysiological consequences of the associated dyssynchrony.[7] Xu *et al.* demonstrated in arterially perfused canine left-ventricular (LV) wedge preparations that epicardial pacing promoted transmural repolarization dispersion and re-entry formation, while this was reduced by midmyocardial LV pacing.[8] By contrast, endocardial vs. epicardial LV pacing had no differential effects on cardiac re-synchronization in an experimental model of non-ischaemic cardiomyopathy, while baso-apical differences were observed, with improved re-synchronization upon basal stimulation—regardless of endo- or epicardial origin.[9] Similarly, Tsvetkova *et al.* demonstrated increased dispersion of repolarization with apical pacing compared to basal pacing, and could additionally demonstrate that the acute haemodynamic response of the ventricle was better when pacing originated in the region with the longest rather than the shortest repolarization duration, indicating that baseline repolarization characteristics may be important for lead position selection.[10] Studies investigating the differences between LV epicardial and right ventricular (RV) endocardial pacing in explanted Langendorff-perfused human myopathic hearts revealed that despite a lack of a decrease in global epicardial activation delays by LV epicardial pacing (as compared to RV endocardial pacing), LV endocardial activation was obtained earlier,[11] indicating importance of LV endocardial activation for re-synchronization. All these investigations have potential translational impact for further optimization of re-synchronization therapies. How the efficacy of such therapies can be evaluated best has also been studied in-depth, with the LV end-systolic volume,[12] the so-called heart-arterial coupling[13] and the pulse arrival time (the time the pulse waves need to travel from the LV to the lower limb[14]) as potential markers of an acute response to cardiac re-synchronization therapy in experimental studies. These results require further clinical validation. To complement these insights into dys-synchronicity and re-synchronization approaches, combined experimental and *in silico* modelling approaches have facilitated the evaluation and optimization of lead placement for re-synchronization therapy.[15–17] Moreover, computational model-computed 3D LV activation times were shown to correlate strongly with the reduction in LV end-systolic volume and simulated CRT correlated strongly with end-systolic volume reduction in patients.[18] Furthermore, modelling has shown that septal infarctions or RV dysfunction negatively affect the magnitude of the 'pre-ejection leftward septal motion' in the left bundle branch block, which has been proposed as another marker to assess the efficacy of re-synchronization therapy.[19]

Novel pacemaking approaches

Not only pacing with 'standard' pacemaker devices but also investigations with modified and bio-artificial pacemakers have been published

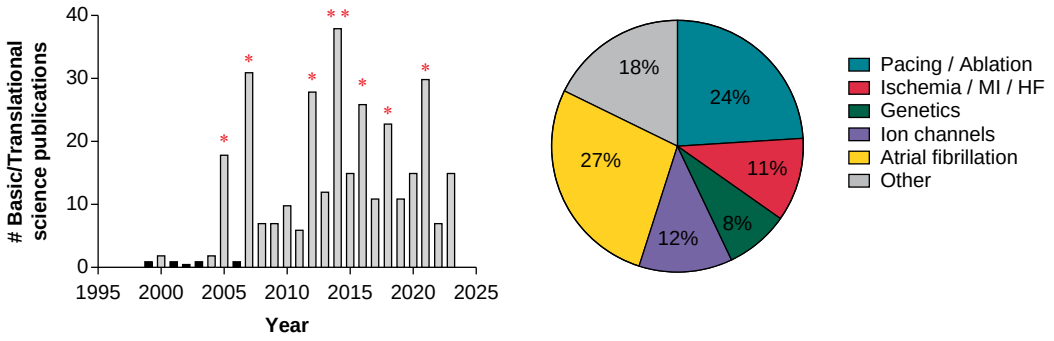

Figure 2 Left panel: number of basic/translational science articles published per year in *EP Europace*. Years with supplemental issues dedicated to basic/translational science topics are indicated with a * for each supplemental issue. Right panel: Percentage distribution of the different topics within basic/translational science articles.

in *EP Europace*. Among these, Haeberlin *et al.* investigated the feasibility of sunlight-powered cardiac pacing and demonstrated successfully that a battery-less pacemaker could be powered by a solar module and could pace a pig *in vivo*.[20] In a completely different approach, Chan et al. investigated the impact of different ion currents for bio-artificial pacemaker design in a monolayer of neonatal rat ventricular cardiomyocytes. The authors concluded that the combination of I_{K1} and I_f determined the threshold for pacemaker activity, while I_f additionally functioned as a membrane potential oscillator to determine the basal firing frequency.[21]

Mapping and mechanistic insights into activation patterns and conduction

Several studies have used high-density mapping of the atria to increase the understanding of atrial conduction heterogeneities[22] and antiarrhythmic mechanisms of drugs based on a reduction of these complex atrial propagation patterns.[23] Moreover, some approaches have been developed to generate patient-specific *in silico* models—using atlas-based methods to characterize patient-specific ventricular activation patterns,[24] or to improve VT substrate identification[25] or antitachycardia pacing efficacy.[26] Additionally, it has been demonstrated that automatic reconstruction of the left atrial activation from sparse intracardiac contact recordings can be achieved by an inverse estimate of fibre structure and anisotropic conduction in a patient-specific computational model.[27] *In silico* pace mapping has also been employed to predict left vs. right outflow tract origin in idiopathic ventricular arrhythmias in patient-specific electrophysiological simulations.[28]

Atrial fibrillation

AF remains the most common clinically relevant cardiac arrhythmia, negatively affecting the morbidity and mortality of millions of individuals worldwide.[29] Accordingly, AF has received significant attention in *EP Europace* over the last 25 years, with more than 80 basic/translational papers published on this topic. These papers span the full spectrum of mechanisms of atrial remodelling and arrhythmogenesis, therapeutic strategies, and biomarkers, employing a wide range of model systems to investigate disease-mechanisms, including isolated cardiomyocytes, human atrial samples, animal models, and computer models.

Insights into atrial fibrillation mechanisms

Conceptually, the mechanisms of AF involve a vulnerable substrate, often characterized by structural remodelling, and electrophysiological changes that promote ectopic activity, which in turn can initiate re-entry as the primary AF-maintaining mechanism.[30] Both cellular electrophysiological and calcium-handling remodelling associated with AF or AF-promoting conditions, as well as structural remodelling and its consequences for conduction and re-entry have been extensively investigated in *EP Europace*. For example, advancing age is one of the most consistent risk factors for AF development: Biliczki *et al.* revealed that electrical remodelling occurs in a qualitatively similar manner in the left- and right atrium of patients and that age-related miR-328 dysregulation and reduced $I_{Ca,L}$ may contribute to increased AF susceptibility with age.[31] Animal models have been extensively used to characterize genetic determinants and potential adverse consequences of the disease- or AF-induced atrial remodelling.[32] O'Reilly *et al.* investigated the p.M1875T variant in *SCN5A*, revealing a gain-of-function of I_{Na} that increases excitability, promotes familial AF, and reduces the antiarrhythmic effects of flecainide.[33] Likewise, Koo *et al.* identified that atrial tachycardia-induced upregulation of constitutively active acetylcholine-activated inward-rectifier K^+ current contributes to prothrombotic atrial hypo-contractility in dogs.[34] In addition, large animal models have been used to study the signalling pathways involved in atrial remodelling, including the role of oxidative stress and inflammation.[35,36] Finally, histological and mapping studies in human atria have provided insight into the structural remodelling and conduction abnormalities associated with AF.[22,37] However, establishing a causal link between structural remodelling and conduction abnormalities in patients is highly challenging. As such, computer models have been used extensively to characterize in detail the electrophysiological consequences of structural remodelling.[38,39] Together, these studies have established a wide array of potential AF-promoting mechanisms.

Rhythm-control therapy approaches for atrial fibrillation

AF therapy comprises anticoagulation, rate- or rhythm control therapy, and risk-factor management.[29] The basic/translational science papers on AF therapy published in *EP Europace*, however, have primarily focused on advances in rhythm-control therapy. There has been a long history of translational studies evaluating the antiarrhythmic effects of existing or novel antiarrhythmic drugs (AADs) in large animal models. In one of the first of these studies, Chandra *et al.* compared the effects of the Class IC AAD propafenone, Class III AAD dofetilide, and KCB-328, a novel inhibitor of the rapid delayed-rectifier K^+ current in dogs with complete atrio-ventricular block, demonstrating pronounced differences in efficacy and safety.[40] Propafenone was most effective in terminating AF, and both propafenone and KCB-328 were

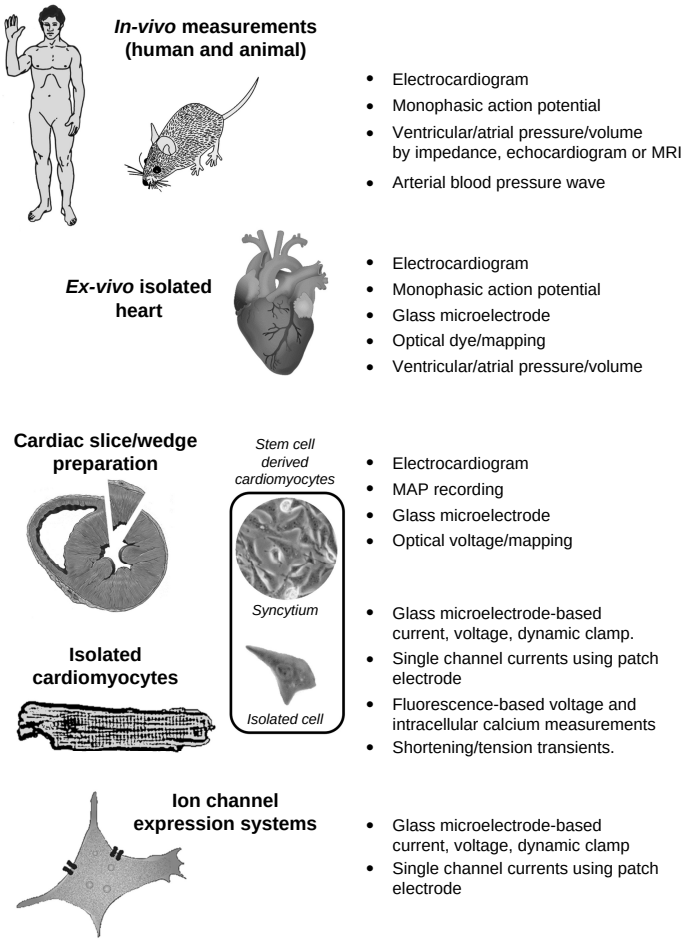

Figure 3 Overview of methods utilized in basic/translational cardiac electrophysiology articles in *EP Europace*. Preparations range from intact organism (animal-to-human), isolated heart, multicellular preparation (i.e. slice/wedge of papillary/trabeculae preparations), isolated cardiac cells (i.e. atrial, ventricular, nodal, or Purkinje cells), and ion channel expression systems (e.g. human embryonic kidney cells). The associated techniques for measuring cardiac function are shown on the right. Modified from *Odening et al. EP Europace 2021*.[1]

less pro-arrhythmic than dofetilide.[40] Other studies have employed Langendorff-perfused hearts to study the electrophysiological effects of AADs to provide more control over the pro-arrhythmic trigger. For example, Milberg *et al.* showed that acute atrial dilatation significantly increased the incidence of AF in isolated rabbit hearts.[41] Ranolazine and flecainide, but not sotalol, suppressed stretch-induced AF. Since then, various novel AADs have been evaluated but none have made it to clinical approval for rhythm control of AF.[42] At present, one of the few targets still actively pursued in clinical studies is the small-conductance Ca^{2+}-activated K^+ (SK) channel. Gatta *et al.* have shown that the SK-channel inhibitor AP14145 can effectively terminate persistent AF in goats.[43] Termination of AF was preceded by an abrupt organization of the arrhythmia, with a decline in the number of fibrillation waves. In contrast to the declining interest in AADs, catheter ablation of AF has developed rapidly in the past 25 year.[42] The number of experimental preclinical studies on this topic has been relatively limited, with available basic/translational studies primarily evaluating the histopathological effects of different ablation modalities (see above).[2,3] In addition, translational studies in large animal models have investigated the effects of other invasive AF therapies such as renal sympathetic denervation.[44] There has furthermore been significant interest in the development of computational models to improve ablation therapy,[45] evaluating, e.g. the emergence of new arrhythmia sources following virtual ablation of re-entrant drivers,[46] or the synergistic antiarrhythmic effects of ablation and AAD therapy targeting the inward-rectifier K^+ current.[47] These studies have highlighted the potential value of patient-tailored therapeutic approaches, but several challenges, e.g. related to the acquisition and implementation of atrial imaging data remain. For example, the specific representation chosen to model fibrosis has a large effect on rotor dynamics,[48] and microstructural variations in cardiac tissue (not detectable with current clinical imaging modalities) may facilitate the formation of isolated sites of wavefront breakthrough, potentially enabling abnormal electrical activity in small tissue regions to develop into more widespread re-entrant activity.[49]

Biomarkers for risk stratification and predictors of therapeutic response

Despite these advances, the success rate of currently available AF therapies remains variable. Moreover, a significant fraction of AF patients is asymptomatic, hindering early diagnosis and subsequent initiation of anticoagulation and rhythm-control therapies to reduce the likelihood of adverse AF-associated events. Biomarkers can be used for risk stratification and as predictors of therapeutic response, potentially facilitating

earlier detection and adjustments in AF therapy to maximize therapeutic success. Both blood-derived molecular markers and ECG features have been used as biomarkers. For example, Berger *et al.* have shown that post-ablation changes in circulating galectin-3 levels, but not baseline values, predict AF recurrence after thoracoscopic ablation.[50] Similarly, Zeemering *et al.* have shown that biomarkers of AF complexity obtained from 12-lead ECGs are better predictors of successful pharmacological cardioversion and progression to persistent AF compared with common clinical and echocardiographic predictors.[51] More recently, these blood-based and ECG-derived biomarkers have been combined with modern machine-learning approaches to improve risk prediction.[52,53] While these biomarkers have shown some promise in predicting incident AF or AF recurrence, most are not used in routine clinical practice.

Taken together, it is apparent that the papers in *EP Europace* have contributed significantly to our understanding of AF pathophysiology and treatment. Nevertheless, translating these insights into improved clinical management of patients with AF has proven difficult and many knowledge gaps remain.[54,55] Future basic/translational studies are expected to address some of these gaps, helping to establish the most effective and safe mechanism-based therapy in an individual AF patient based on clinical parameters, as well as blood-based and ECG- or imaging-derived biomarkers.

Heart failure, remodelling, and arrhythmogenesis

In the last 25 years, basic/translational research published in *EP Europace* has contributed to a better understanding of electrical alterations that induce arrhythmias in cardiac hypertrophy and HF, as well as new approaches to prevent those arrhythmias. Since about half of the patients with cardiac hypertrophy or HF die suddenly due to fatal ventricular arrhythmias, a better understanding of the intimate mechanisms is needed to prevent sudden death. Cardiac remodelling in hypertrophy and HF affects the individual cardiac myocytes, but also the communication, regional characteristics, extracellular matrix, neurohormonal regulation, etc.[56] Studies published in *EP Europace* have elucidated various aspects of the relationship between contractile dysfunction and arrhythmogenesis, addressing basic mechanisms as well as risk predictors.

Myocardial remodelling and repolarization

At the cardiomyocyte level, myocardial remodelling is associated with alterations in the expression, location, and function of ion channels, which collectively induce a prolongation of the action potential (AP) duration (APD). APD prolongation *per se* may induce focal arrhythmogenic events (early afterdepolarizations [EADs]); however, several observations point to the role of remodelling in disrupting the physiological repolarization pattern. Arrhythmogenesis has been intensively studied in the atrioventricular-(AV-)block dog model, characterized by bradycardia-induced APD prolongation and, in the long run, by myocardial remodelling. In this setting, arrhythmia facilitation (during anaesthesia) only occurred at a time compatible with myocardial remodelling.[57] Nonetheless, cellular studies suggest that even in non-remodelled myocytes, adrenergic activation during bradycardia may induce a profound imbalance between inward and outward currents promoting EADs.[58] The observations in the AV-block model do not argue against this further possibility, because they were conducted under conditions (anaesthesia) minimizing autonomic activity. In the chronic AV-block model, arrhythmias were consistently initiated at the site of maximal local gradients in repolarization time (RT), as opposed to APD gradients. Initiation was consistently found at the site with shorter RT,[59] which may suggest phase 2 re-entry. Unlike APD, RT includes the time for impulse conduction to the recording site, which adds perturbed propagation as a factor. Notably, TdP continuation was associated with conduction slowing.[59] In accordance, Munkler *et al.* found that the best predictor of arrhythmia degeneration to ventricular fibrillation (VF), even superior to the steepness of APD restitution, was the ratio between RT and cycle length (CL).[60] While stressing again the role of local repolarization timing, this result points to excitation prematurity as a crucial factor in the transition between organized and chaotic electrical activity.

Structural remodelling is common in HF, both in the setting of reduced and preserved ejection fraction, and is expected to contribute to arrhythmogenic risk. Computer modelling may integrate structural and electrophysiological abnormalities, e.g. by tuning a reaction–diffusion model of the human heart to reproduce measured ECGs and electrogram data.[61] Deng *et al.* demonstrate that virtual heart simulations personalized based on MRI data may provide a novel risk stratification modality to non-invasively and effectively identify patients with LV ejection fraction (LVEF) > 35% who could benefit from an implantable cardioverter-defibrillator (ICD).[62]

Sarcoplasmic Ca^{2+} release and arrhythmogenesis

Sarcoplasmic reticulum (SR) Ca^{2+} release through ryanodine receptors (RyR) plays an important role in arrhythmogenesis in the remodelled and failing heart. Once released from the SR, Ca^{2+} can induce a depolarizing current when extruded from the cell through the Na^{+}/Ca^{2+} exchanger, which may provoke delayed after depolarizations (DADs) and influence AP repolarization. Highly relevant to HF-related SR instability is the 'vicious loop' linking enhanced RyR open probability to activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII): enhanced RyR opening during rest increases cytosolic Ca^{2+}, which activates CaMKII; this, in turn, phosphorylates RyRs, increasing open probability.[63] The role of such a vicious loop in arrhythmogenesis was assessed by Sosalla *et al.* in human atrial cardiomyocytes from patients with AF.[64] Albeit performed in atrial cardiomyocytes, this study nicely illustrates a principle likely also applicable to ventricular cardiomyocytes and identifies therapeutic targets. Blocking RyRs, and/or inhibiting CaMKII, decreased the occurrence of Ca^{2+} sparks (visible events of RyR2 openings) in these cardiomyocytes. To get better insight into the role of CaMKII, atrial cells from CaMKII overexpressing mice were compared to wildtype. RyR blockade decreased Ca^{2+} sparks, Ca^{2+} waves, and after depolarizations (both EADs and DADs) in transgenic cardiomyocytes, but not in wildtype cells.[64] CaMKII inhibition had similar effects in the two genotypes, but it did not add to the effect of RyR blockade; moreover, RyR blockade suppressed AF inducibility *in vivo*.[64]

The cardiomyocyte ultrastructure is also remodelled in HF, contributing to pro-arrhythmic alterations. Specifically, a rarefication of transverse (T) tubules is often found in HF. T-tubules are membrane invaginations penetrating into the cell, which synchronize Ca^{2+} release across the cell with the AP. The decrease in the T-tubule network is associated with delayed Ca^{2+} release, which affects the AP shape. A deficiency of dysferlin, a protein involved in T-tubule stabilization, has been reported to sensitize to adrenergically induced arrhythmias.[65] Indeed, dysferlin gene deletion was found to cause loss of transverse T-tubules, with 'transverse-axial tubule system axialization', associated with I_{CaL} downregulation and arrhythmogenic SR instability.[65]

Neurohumoral activation and arrhythmogenesis

The role of neurohumoral activation in arrhythmogenesis is a classical concept, supported by innumerable studies. Nonetheless, novel information continues to emerge, suggesting potential therapeutic targets and strategies. Coutinho *et al.* showed that pharmacologic activation

of the type 2 angiotensin converting enzyme (ACE2) reverts electrophysiological remodelling in diabetic cardiomyopathy.[66] This extends previous evidence of the cardioprotective effect of ACE2 activation to electrophysiological aspects of remodelling in diabetes and suggests ACE2 as a pleiotropic target, also affecting arrhythmias, in this condition. Also relevant to arrhythmogenesis in metabolic disorders is the observation by Chen *et al.* that renal denervation may prevent sympathetic hyperactivity and VF inducibility in rabbits fed a high-fat diet (HFD) with or without HF, thus showing the protective role of this procedure.[67] Concerning the role of inflammation-activated signals, Zuo *et al.* showed that TNFα destabilizes the SR in adult atrial myocytes, mainly through increased reactive oxygen species (ROS) and CaMKII activation.[68] This work provided the first demonstration of TNFα effects in native atrial myocytes at clinically relevant cytokine concentrations.

Regarding the more classical pro-arrhythmic effect of beta-adrenergic activation, a computational study proposed that the kinetics of autonomic changes are important in triggering the transition from VT to VF.[69] In a two-dimensional rabbit myocardial model, including kinetic aspects of adrenergic target modulation; this study showed that the transition between VT and VF occurred only if β-adrenergic stimulation was sudden.[70] This occurred because adrenoreceptor-induced I_{CaL} enhancement preceded I_K increase, resulting in a transient dysbalance of repolarizing currents promoting repolarization delay and instability. Sala *et al.* showed that APD response to adrenergic stimulation differs between guinea-pig and canine myocytes because of differences in the early repolarization course, thus emphasizing the importance of AP contour *per se* in setting its response to autonomic modulation.[71] Sex-related differences in the effect of adrenergic activation on SR Ca^{2+} release through RyRs channels (viewed as Ca^{2+} sparks) were studied by Fisher *et al.* in human remodelled hearts,[72] evaluating ventricular myocytes from hypertrophied and failing hearts. While only a trend for sex differences was found in hypertrophy, in HF spontaneous Ca^{2+} release events were significantly more frequent in males.[72]

Sympathetic cardiac innervation is also altered in several other cardiac diseases, including ischaemic cardiomyopathy. Indeed, studies in *EP Europace* have demonstrated that ventricular electrical remodelling and function could be improved in ischaemic cardiomyopathy by targeting remodelling of cardiac sympathetic re-innervation with thoracic spinal cord stimulation[73] or targeted ablation of cardiac sympathetic neurons.[74]

Cardiac desynchronization and electro-mechanical derangements

A further point of interest is the crosstalk between electrical and mechanical derangements in cardiac desynchronization, a common and at least partially correctible feature of cardiac disease. Van Weperen *et al.* evaluated the effect of dyssynchronous activation in the chronic AV-block model.[75] Mechanical dyssynchrony, resulting from idioventricular rhythm, was paralleled by increased arrhythmia inducibility and could be partially reversed by cardiac re-synchronization therapy. Van Middendorp *et al.* assessed the relationship between drug-induced conduction slowing and mechanical dyssynchrony.[76] When administered in repeated doses to patients with left bundle branch block (LBBB), flecainide slowed ventricular conduction more than vernakalant, while the two drugs equally impaired both systolic and diastolic function.[76] Nonetheless, at least in the low dose range, a correlation between conduction slowing and mechanical impairment was observed, suggesting a primary role of dyssynchrony in the haemodynamic effect of both drugs and pointing to desynchronization as an important component of the haemodynamic deterioration induced by AADs.

The long-term impact of frequent ventricular ectopy on cardiac function widely varies among subjects. Therefore, whether otherwise benign extrasystoles should be treated is a frequent clinical conundrum. Gurukripa *et al.* investigated the value of post-extrasystolic potentiation (PESP) of LVEF, measured early, in predicting the impact of 12 weeks ventricular bigeminy on contractile function.[77] They found that strong initial PESP predicted less decay of LVEF during the bigeminy period. However, once bigeminy-induced reduction in LVEF had been installed, higher PESP correlated with lower LVEF.[77] Since LVEF PESP can be measured by a simple echocardiogram, the results of this work may assist in deciding whether frequent extrasystoles should be treated.

Ion channel (dys)regulation and pharmacology

Various ion channels contribute to cardiac depolarization and repolarization, with their concerted interplay underlying action potentials. Studies published in *EP Europace* have explored the role of ion channel (dys)regulation in arrhythmogenesis and their potential impact as anti-arrhythmic targets. These investigations have mostly addressed this in relation to AF, ventricular arrhythmias, and (inherited) sudden cardiac death.

Atrial ion channels and atrial fibrillation

In addition to structural alterations, AF is associated with remodelling of ion channels.[30] In particular, reduced L-type calcium ($I_{Ca,L}$) and increased inward-rectifier K^+ currents (I_{K1}) contribute to APD shortening, and more pronounced $I_{Ca,L}$ reduction has been shown in human atria of older patients.[31] Consequently, many studies have explored the therapeutic potential of targeting ion channels to prevent AF. Earlier publications employed compounds acting on multiple ion channels, demonstrating beneficial effects on atrial-effective refractory periods (atrial ERP), AF inducibility, and/or AF termination.[78,79] More specific approaches to prolong APD and prevent re-entrant arrhythmias include the use of I_{Kr} blockers. However, since these often display reverse use dependence, their atrial refractoriness prolonging effect is reduced at high rates and hence their efficacy is likely limited in the setting of AF. Attempting to circumvent this, Chandra and colleagues showed that KCB-328, an I_{Kr} blocker that prolongs APD without exhibiting significant reverse use dependence, terminated tachypacing-induced AF in 50% of dogs by prolonging the atrial ERP and increasing atrial activation time, while at the same time prolonging QT-intervals to a lesser extent than dofetilide.[40] While K^+ channel blockers can terminate re-entry by increasing APD and wavelength, a modelling study published in *EP Europace* showed that it can also promote wave breaks in the pulmonary vein (PV) region by increasing electrical heterogeneity and consequently act pro-arrhythmic.[80] Interestingly, such pro-arrhythmogenic effects were not observed for amiodarone, which not only prevented re-entry but also decreased the likelihood of wave break generation.[80] Moreover, Loewe *et al.* showed that there are also significant differences in the frequency and concentration-dependent effects of amiodarone and dronedarone and between different atrial substrates, providing possible explanations for the superior efficacy of amiodarone.[81] As discussed in the AF section above, atrial-selective ion channel modulators have been developed and investigated, including blockers of the ultra-rapid delayed-rectifier current K^+ (I_{Kur}), small-conductance Ca^{2+}-activated K^+-currents (SK), and the G-protein-gated acetylcholine-activated inward-rectifier current (I_{KAch}).[34,43,47] In addition to remodelling of K^+ and Ca^{2+} channels, alterations in sodium channel function have also been reported in AF. While reduced peak sodium current (I_{Na}) may contribute to conduction slowing, enhanced late I_{Na} leads to pro-arrhythmic intracellular Na^+ and Ca^{2+} dysregulation; both processes may, in fact, play a pro-arrhythmic role in the setting of various stages of AF, i.e. paroxysmal vs. persistent AF.[82]

Besides pharmacological strategies directly targeting ion channels, other approaches have also been reported in *EP Europace*. For instance,

Kharche *et al.* evaluated the potential 'pharmacological remodelling' effects of chronic beta blockade in mathematical models of human atrial cells and 3D tissue. They observed that beta blocker therapy, in addition to beneficial acute effects, may also chronically suppress AF by increasing ERP and preventing re-entry due to a long-term adaptational decrease in I_{to} and I_{K1}.[83] Other modelling work has shown that temporal variations in acetylcholine concentration can modulate the complexity of re-entrant atrial arrhythmias through modulation of $I_{K,ACh}$.[84] The anti-ageing protein klotho, which is mainly expressed in kidneys but also the heart, is reduced in patients with kidney disease and correlated with AF incidence. In isolated-rabbit PV tissue preparations and cardiomyocytes, klotho administration was found to reduce PV automaticity, $I_{Ca,L}$, late I_{Na}, and DAD occurrence by inhibiting PI3K/Akt signalling and CaMKII activation.[85] Another study demonstrated that macrophage migration inhibitory factor (MIF; an inflammatory cytokine highly expressed in the setting of AF) increased $I_{Ca,L}$, late I_{Na}, Ca^{2+} overload, ROS, and arrhythmogenesis in rabbit PV, which was prevented by pharmacological inhibition of late I_{Na} and CaMKII as well as increased ROS scavenging.[36] These studies show the rationale for identifying (molecular) pathways underlying AF-associated electrophysiological remodelling to develop novel therapeutic strategies.

Ion channels and ventricular depolarization, ventricular repolarization, and arrhythmias

Ventricular ion channels play a crucial part in cardiac depolarization, conduction, and excitation-contraction coupling. In addition, their proper function is crucial for maintaining normal cardiac repolarization and preventing arrhythmias such as TdP and VF; this is also reflected by the fact that mutations in ion channel genes are associated with arrhythmia syndromes (discussed in the next section). AP alternans is considered particularly pro-arrhythmic, and Orini *et al.* found that biopsies from human hearts showed higher RNA expression of calsequestrin, ryanodine receptor, and genes underlying I_{K1} and I_{to} at alternans-susceptible sites.[86] In addition, sarcolemmal ion-channel remodelling may indirectly modulate Ca^{2+} handling and contractility. Using computational modelling, Maleckar *et al.* showed that restoring APD of HF cardiomyocytes to its pre-failing state does not ameliorate Ca^{2+}-transient dysfunction; however, restoration of AP notch depth appeared to impart modest benefit.[87]

Ion channels are critically regulated by catecholamines, a process highly relevant for the regulation of excitation-contraction coupling during rest vs. activity (see also the section on HF). High, toxic levels of catecholamines are thought to contribute to Takotsubo syndrome, and a study by Huang *et al.* in *EP Europace* showed that high levels of epinephrine triggered arrhythmias and prolonged APD through activating alpha-adrenoceptors with subsequent effects on $I_{Ca,L}$ and I_{Na}.[88] Pro-arrhythmic APD prolongation may occur secondary to increased late I_{Na} or reduced I_{Ks} or I_{Kr}; the latter may also be a side-effect of certain (non-cardiac) drugs such as for instance fluconazole.[89] While many studies have focused on compounds that can counter such pro-arrhythmic APD prolongation, most of these are not specific and often block multiple ion channels. For example, commonly used Ca^{2+} channel blockers may also inhibit I_{Kr}, which according to a study using a multiscale human torso model may significantly affect the electrophysiological properties of the ventricle.[90] Moreover, multiple cardiac drugs are often prescribed to patients which may induce synergistic pro-arrhythmic effects. For instance, the co-existence of dronedarone and digitalis in patients with both AF and HF may prolong APD, post-repolarization refractoriness, and increase the vulnerability to VF, as demonstrated in rabbit hearts.[91]

Nevertheless, several studies published in *EP Europace* have demonstrated the beneficial anti-arrhythmic effects of drugs targeting (multiple) ion channels. Andersson and colleagues investigated the combined ion channel blocker AZD1305 in dog cardiomyocytes and rabbit ventricular preparations. They found that AZD1305 inhibited both late I_{Na} and I_{Kr} yet attenuated excessive APD prolongation and repolarization instability induced by a short-long-short CL pattern, indicating that block of late I_{Na} may attenuate I_{Kr}-induced repolarization liability following sudden slowing of rhythm.[92] Vernakalant is another drug displaying a mixed block of both Na^+ and K^+ channels, which has been investigated for potential atrial-specific benefits in the setting of AF. However, a study published in *EP Europace* demonstrated that vernakalant also prolongs ventricular APD, ERP, and post-repolarization refractoriness in rabbit hearts; nevertheless, in contrast to sotalol, vernakalant neither increased dispersion of repolarization nor facilitated arrhythmias.[93] Interestingly, a later study reported anti-arrhythmic effects in a rabbit model of drug-induced, acquired long QT syndrome (LQTS), with vernakalant again decreasing dispersion in repolarization.[94] Similarly, the antihistamine antazoline, which is known to block $I_{K\text{-}ATP}$, reduced dispersion of repolarization and had anti-arrhythmic effects in drug-induced rabbit models of both short (SQTS) and LQTS syndromes, despite prolonging ventricular repolarization.[95] The same group reported that the sodium channel blocker mexiletine suppressed torsade de pointes in drug-induced LQTS2 and LQTS3 models by reducing spatial dispersion of repolarization, and eliminated VF in the SQTS model by increasing ERP.[96] Inhibitors of late I_{Na}, including mexiletine have shown APD shortening, anti-arrhythmic, and other beneficial effects and confirm late I_{Na} as an important target for the development of novel pharmacological approaches.[97–99] While whole-heart studies remain important for investigating the effects of drugs on arrhythmogenesis, human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are now increasingly used for drug safety studies, allowing for patch clamp and multi electrode array assessments of APD and beat-to-beat variability in repolarization as markers of pro-arrhythmic risk of compounds.[100] Altomare *et al.* have shown that although cardiac differentiation efficiency was improved in hiPSCs of cardiac vs. non-cardiac origin, no major functional differences were observed between hiPSC-CMs of different somatic cell origins.[101] It is expected that these *in vitro* approaches will be increasingly used for drug discovery, i.e. employing medium/high throughput electrophysiological assays and compound screens.

Inherited arrhythmia syndromes and arrhythmogenic cardiomyopathies

The basic and translational articles on inherited cardiac disorders published in the last 25 years in *EP Europace* range from review articles covering the main inherited channelopathies, cardiomyopathies, and conduction disorders to in-depth mechanistic studies revealing novel insights into the pathophysiology of these conditions, experimental research investigating pro- or anti-arrhythmic effects of endogenous modifiers or exogenous factors such as drugs and studies exploring novel therapeutic approaches.

The clinical characteristics of these inherited diseases and their genetic background will be discussed in detail in this issue's review on 'Clinical Cardiogenetics'. We focus here more on the mechanistic insights into arrhythmogenesis obtained through these articles and the resulting novel, mechanism-based anti-arrhythmic therapeutic approaches. Most mechanistic studies were published on LQTS, sodium channelopathies, and arrhythmogenic cardiomyopathy (ACM).

Long QT syndrome

Long QT syndrome is a genetic channelopathy caused mostly by either loss-of-function variants in genes encoding repolarizing K^+ currents (*KCNQ1*/I_{Ks} or *KCNH2*/I_{Kr}; LQTS1 and LQTS2) or gain-of-function variants in *SCN5A* encoding for the depolarizing sodium current (LQTS3); in sporadic cases, mutations in other genes such as those encoding

(subunits of) other ion channels or the cardiac RyR have been described.[102,103] All these variants lead to pathologically prolonged cardiac repolarization predisposing to ventricular polymorphic TdP tachycardia and sudden cardiac death. In LQTS1 and LQTS2, arrhythmias are typically triggered by sympathetic activation and rely on an arrhythmogenic substrate with regional heterogeneity in cardiac repolarization predisposing to functional block and re-entry formation. While arrhythmias related to LQTS3 occur mostly during rest and sleep, a study published in *EP Europace* revealed that also in (drug-induced) LQTS3 sympathetic activation by epinephrine increased pro-arrhythmic triggers—and importantly—had dose-dependent opposite effects on repolarization and triggering events.[104] As discussed above, the important role of regional heterogeneity of repolarization was also demonstrated in acquired LQTS.[59]

Despite being caused by variants in cardiac ion channels, leading primarily to electrical changes (e.g. of cardiac repolarization), more and more clinical and experimental evidence is accumulating that patients with LQTS also manifest with mechanical—particularly diastolic—dysfunction,[105] as demonstrated exemplarily in LQTS1 and LQTS2[106] and in a study published in *EP Europace* for the first time also in LQTS3 patients.[107] Regarding the latter, intracellular calcium dysregulation secondary to enhanced late I_{Na} may play an important role.[108] Interestingly, enhanced late I_{Na} has also been observed in LQTS2 rabbit cardiomyocytes and as such may contribute to both arrhythmogenesis and mechanical dysfunction.[109]

Sex differences are known to modulate the arrhythmogenic risk in LQTS with women having a higher risk than men in general; and particularly during the postpartum phase.[110] In transgenic LQTS2 rabbit models, it was demonstrated that the postpartum-associated hormones oxytocin and prolactin exert their QT/APD-prolonging, pro-arrhythmic effects primarily by blocking the slow delayed-rectifier current I_{Ks},[111] leading to the recommendation to avoid oxytocin applications during delivery in LQTS patients (www.azcert.com). Similarly, several studies have revealed the mechanisms by which sex hormones impact cardiac repolarization and triggered activity thereby causing the observed sex differences in arrhythmic risk in LQTS.[112] In addition, genetic modifiers are more and more recognized to play a role in determining the phenotype in LQTS.[102]

For LQTS3 a gene-specific mechanism-based therapy exists, namely mexiletine, which targets the pathologically enhanced late I_{Na}.[113] Several novel mechanism-based therapies have been tested in other LQTS models and genotype-specific efficacy could be revealed for the I_{Ks}-activator docosahexaenoic acid in LQTS2,[114] and the inhibition of the serum/glucocorticoid-regulated kinase 1—a modulator of pathologically enhanced late I_{Na} current—mainly in LQTS2 and to a lesser, variant-specific extent in LQTS1.[98] Similarly, in drug-induced LQTS2 and LQTS3, anti-arrhythmic APD-dispersion reducing effects were observed upon treatment with vernakalant, another blocker of late I_{Na},[94] further indicating that late I_{Na} is also—secondarily—increased in the potassium channelopathy LQTS2. In addition, novel gene therapy approaches have been developed and tested in hiPSC-CM derived from LQTS1 and LQTS2 patients.[115,116]

Sodium channelopathies (other than LQTS3)

While gain-of-function mutations in *SCN5A* lead to LQTS3, loss-of-function *SCN5A* mutations are known to be associated with other clinical phenotypes such as Brugada syndrome (BrS) and cardiac conduction disease.[102] In addition, both gain- and loss-of-function *SCN5A* mutations have also been linked to AF, dilated cardiomyopathy, and more recently also ACM.[108] Regarding the latter, alterations in Ca^{2+} dysregulation and/or non-ionic effects of sodium channel dysfunction on e.g. cytoskeletal or adhesion proteins may be involved in this process.[108] Ca^{2+} dysregulation secondary to enhanced late I_{Na} has furthermore been shown to affect AV-conduction in mice carrying the *Scn5a*-1798insD mutation.[97] Another phenotype linked to *SCN5A* mutations is multifocal ectopic Purkinje-related premature contractions (MEPPC), which is clinically characterized by atrial and ventricular ectopy as well as dilated cardiomyopathy and is thought to result from an increased window current and/or gating pore current. In a recent study, Calloe *et al.* demonstrated that flecainide treatment reduced the window current in hiPSC-CMs with the *SCN5A*-G231D mutation, and had beneficial effects in patients carrying this mutation.[117] Despite the well-established link with Na^+ channels, *SCN5A* mutations are found in only 20% of BrS patients, and their presence is not necessarily always causally related since *SCN5A* genetic variants are frequently observed in the general population, some of which do not affect Na^+ channel function.[118] Overall, BrS is characterized by extensive variability in disease severity as well as reduced penetrance, and a polygenic basis is now increasingly recognized.[102]

Arrhythmogenic cardiomyopathy

ACM is caused by mutations in genes encoding predominantly cardiac desmosomal proteins, leading to fibro-fatty replacement of the right (or both) ventricle and ventricular arrhythmias, particularly during exercise.[119] The mechanisms underlying pathogenic desmoglein-2 variants in the propeptide cleavage-site have been investigated in the human heart and epithelial and cardiac cellular models and it has been demonstrated that the variants impair desmosomal interactions between N-terminal extracellular domains upon cellular stress,[120] thus providing more evidence for the stress-/exercise-mediated deterioration of the disease. Imaging-based patient-specific computer simulations were used to better characterize the electro-mechanical substrate in ACM, revealing increased heterogeneity in regional RV contractility and most changes in the basal RV free wall.[121] The genetic culprit, however, remains elusive in up to 50% of ACM patients.[122] In some patients, large deletions or duplications are present but are difficult to detect by the conventional PCR-based Sanger sequencing method. Using the multiplex ligation-dependent probe amplification method, a patient with a complete deletion of all *PKP2* coding exons was identified.[123] As mentioned above, more recently *SCN5A* mutations have also been associated with ACM; Na^+ channels are located in close proximity to desmosomal proteins within the intercalated disc region, and as such may impact on cell–cell adhesion.[119] Ongoing research is increasingly uncovering involved signalling pathways in ACM, with the potential of identifying novel therapeutic targets.

Conclusions and outlook

Clearly, basic/translational research published in the last 25 years in *EP Europace* has made an enormous contribution to our current understanding of cardiac arrhythmias. The journal aims to continue publishing key studies to further increase our knowledge on arrhythmia mechanisms and define potential novel targets for therapy, maintaining the current basic-translational focus and keeping in mind potential clinical impact. With the growing complexity of cardiovascular disease management and the development of more precision medicine approaches, this will become increasingly important, and *EP Europace* aims to further increase its contribution to the discovery of arrhythmia mechanisms and implementation of mechanism-based precision therapy approaches in arrhythmia management.

Funding

This study was supported by the Netherlands CardioVascular Research Initiative (CVON-eDETECT 2015-12 and CVON-PREDICT2 2018-30 to CAR), the Netherlands Organisation for Health Research and Development (ZonMw; Innovational Research Incentives Scheme Vidi grant 09150171910029 to JH), the French National Research Agency (ANR-19-CE14-0031-01 to AMG), the European Joint Research Program on Rare

Diseases (EJP-RD grant 'Silence-LQTS' to CAR and KEO; SNF 31ER30_194836), and the Swiss National Science Foundation (SNF grant 310030_197595 to KEO).

Conflict of interest: None declared.

References

1. Odening KE, Gomez AM, Dobrev D, Fabritz L, Heinzel FR, Mangoni ME *et al.* ESC Working group on cardiac cellular electrophysiology position paper: relevance, opportunities, and limitations of experimental models for cardiac electrophysiology research. *Europace* 2021;**23**:1795–814.
2. Bhaskaran A, Chik W, Pouliopoulos J, Nalliah C, Qian P, Barry T *et al.* Five seconds of 50–60 W radio frequency atrial ablations were transmural and safe: an in vitro mechanistic assessment and force-controlled in vivo validation. *Europace* 2017;**19**:874–80.
3. Franceschi F, Bonan R, Khairy P, Dubuc M, Thibault B, Macle L *et al.* Histopathological effects and evolution of transvenous β-radiation applications in right and left atria: an animal study. *Europace* 2012;**14**:745–51.
4. Bernstein SA, Duggirala S, Floberg M, Elfvendal P, Kuznekoff LM, Lader JM *et al.* Spatiotemporal electrophysiological changes in a murine ablation model. *Europace* 2011;**13**:1494–500.
5. Tofig BJ, Lukac P, Nielsen JM, Hansen ESS, Tougaard RS, Jensen HK *et al.* Radiofrequency ablation lesions in low-, intermediate-, and normal-voltage myocardium: an in vivo study in a porcine heart model. *Europace* 2019;**21**:1919–27.
6. Sandhu U, Alkukhun L, Kheiri B, Hodovan J, Chiang K, Splanger T *et al.* In vivo pulsed-field ablation in healthy vs. chronically infarcted ventricular myocardium: biophysical and histologic characterization. *Europace* 2023;**25**:1503–9.
7. Auricchio A, Prinzen FW. Update on the pathophysiological basics of cardiac resynchronization therapy. *Europace* 2008;**10**:797–800.
8. Xu T, Wang H, Zhang J-Y, Zhang Y, Zhang R, Jiang L-Q *et al.* Effects of mid-myocardial pacing on transmural dispersion of repolarization and arrhythmogenesis. *Europace* 2012;**14**:1363–8.
9. Amorós-Figueras G, Jorge E, Raga S, Alonso-Martin C, Rodríguez-Font E, Bazan V *et al.* Comparison between endocardial and epicardial cardiac resynchronization in an experimental model of non-ischaemic cardiomyopathy. *Europace* 2018;**20**:1209–16.
10. Tsvetkova AS, Kibler NA, Nuzhny VP, Shmakov DN, Azarov JE. Acute effects of pacing site on repolarization and haemodynamics of the canine ventricles. *Europace* 2011;**13**:889–96.
11. Porta-Sánchez A, Angaran P, Massé S, Nair K, Farid T, Umapathy K *et al.* The effect of left ventricular pacing on transmural activation delay in myopathic human hearts. *Europace* 2018;**20**:719–28.
12. Boe E, Smiseth OA, Storsten P, Andersen OS, Aalen J, Eriksen M *et al.* Left ventricular end-systolic volume is a more sensitive marker of acute response to cardiac resynchronization therapy than contractility indices: insights from an experimental study. *Europace* 2019;**21**:347–55.
13. Zócalo Y, Bia D, Armentano R, González-Moreno J, Varela G, Calleriza F *et al.* Resynchronization improves heart-arterial coupling reducing arterial load determinants. *Europace* 2013;**15**:554–65.
14. Villegas-Martinez M, Odland HH, Hammersbøen LE, Sletten OJ, Stugaard M, Witsø M *et al.* Pulse arrival time variation as a non-invasive marker of acute response to cardiac resynchronization therapy. *Europace* 2023;**25**:1183–92.
15. Huntjens PR, Walmsley J, Ploux S, Bordachar P, Prinzen FW, Delhaas T *et al.* Influence of left ventricular lead position relative to scar location on response to cardiac resynchronization therapy: a model study. *Europace* 2014;**16**:iv62–8.
16. Pluijmert M, Bovendeerd PHM, Lumens J, Vernooy K, Prinzen FW, Delhaas T. New insights from a computational model on the relation between pacing site and CRT response. *Europace* 2016;**18**:iv94–103.
17. Crozier A, Blazevic B, Lamata P, Plank G, Ginks M, Duckett S *et al.* Analysis of lead placement optimization metrics in cardiac resynchronization therapy with computational modelling. *Europace* 2016;**18**:iv113–20.
18. Villongco CT, Krummen DE, Omens JH, McCulloch AD. Non-invasive, model-based measures of ventricular electrical dyssynchrony for predicting CRT outcomes. *Europace* 2016;**18**:iv104–12.
19. Remme EW, Niederer S, Gjesdal O, Russell K, Hyde ER, Smith N *et al.* Factors determining the magnitude of the pre-ejection leftward septal motion in left bundle branch block. *Europace* 2016;**18**:1905–13.
20. Haeberlin A, Zurbuchen A, Schaerer J, Wagner J, Walpen S, Huber C *et al.* Successful pacing using a batteryless sunlightpowered pacemaker. *Europace* 2014;**16**:1534–9.
21. Chan YC, Tse HF, Siu CW, Wang K, Li RA. Automaticity and conduction properties of bio-artificial pacemakers assessed in an in vitro monolayer model of neonatal rat ventricular myocytes. *Europace* 2010;**12**:1178–87.
22. Van Schie MS, Heida A, Taverne YJHJ, Bogers AJJC, De Groot NMS. Identification of local atrial conduction heterogeneities using high-density conduction velocity estimation. *Europace* 2021;**23**:1815–25.
23. Van Hunnik A, Podziemski P, Kuklik P, Kuiper M, Verheule S, Schotten U. Bi-atrial high-density mapping reveals inhibition of wavefront turning and reduction of complex propagation patterns as main antiarrhythmic mechanisms of vernakalant. *Europace* 2021;**23**:1114–23.
24. Vincent KP, Forsch N, Govil S, Joblon JM, Omens JH, Perry JC *et al.* Atlas-based methods for efficient characterization of patient-specific ventricular activation patterns. *Europace* 2021;**23**:I88–95.
25. Sung E, Prakosa A, Kyranakis S, Berger RD, Chrispin J, Trayanova NA. Wavefront directionality and decremental stimuli synergistically improve identification of ventricular tachycardia substrate: insights from personalized computational heart models. *Europace* 2023;**25**:223–35.
26. Qian S, Connolly A, Mendonca-Costa C, Campos F, Rodero C, Whitaker J *et al.* Optimization of anti-tachycardia pacing efficacy through scar-specific delivery and minimization of re-initiation: a virtual study on a cohort of infarcted porcine hearts. *Europace* 2023;**25**:716–25.
27. Lubrecht JM, Grandits T, Gharaviri A, Schotten U, Pock T, Plank G *et al.* Automatic reconstruction of the left atrium activation from sparse intracardiac contact recordings by inverse estimate of fibre structure and anisotropic conduction in a patient-specific model. *Europace* 2021;**23**:I63–70.
28. Doste R, Sebastian R, Gomez JF, Soto-Iglesias D, Alcaine A, Mont L *et al.* In silico pace-mapping: prediction of left vs. right outflow tract origin in idiopathic ventricular arrhythmias with patient-specific electrophysiological simulations. *Europace* 2020;**22**:1419–30.
29. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
30. Nattel S, Heijman J, Zhou L, Dobrev D. Molecular basis of atrial fibrillation pathophysiology and therapy: A translational perspective. *Circ Res* 2020;**127**:51–72.
31. Biliczki P, Boon RA, Girmatsion Z, Bukowska Alicia, Ördög Balázs, Kaess BM *et al.* Age-related regulation and region-specific distribution of ion channel subunits promoting atrial fibrillation in human left and right atria. *Europace* 2019;**21**:1261–9.
32. Nishida K, Michael G, Dobrev D, Nattel S. Animal models for atrial fibrillation: clinical insights and scientific opportunities. *Europace* 2010;**12**:160–72.
33. O'Reilly M, Sommerfeld LC, O'Shea C, Broadway-Stringer S, Andaleeb S, Reyat JS *et al.* Familial atrial fibrillation mutation M1875T-SCN5A increases early sodium current and dampens the effect of flecainide. *Europace* 2022;**25**:1152–61.
34. Koo SH, Wakili R, Heo J-H, Chartier D, Kim H-S, Kim S-J *et al.* Role of constitutively active acetylcholine-mediated potassium current in atrial contractile dysfunction caused by atrial tachycardia remodelling. *Europace* 2010;**12**:1490–7.
35. Lenaerts I, Driesen RB, Blanco NH, Holemans P, Heidbüchel H, Janssens S *et al.* Role of nitric oxide and oxidative stress in a sheep model of persistent atrial fibrillation. *Europace* 2013;**15**:754–60.
36. Chin CG, Chen Y-C, Lin Y-K, Lu Y-Y, Cheng W-L, Chung C-C *et al.* Effect of macrophage migration inhibitory factor on pulmonary vein arrhythmogenesis through late sodium current. *Europace* 2023;**25**:698–706.
37. Ravelli F, Masè M, Cristoforetti A, Avogaro L, D'Amato E, Tessarolo F *et al.* Quantitative assessment of transmural fibrosis profile in the human atrium: evidence for a three-dimensional arrhythmic substrate by slice-to-slice histology. *Europace* 2023;**25**:739–47.
38. Gharaviri A, Verheule S, Eckstein J, Potse M, Kuklik P, Kuijpers NH *et al.* How disruption of endo-epicardial electrical connections enhances endo-epicardial conduction during atrial fibrillation. *Europace* 2017;**19**:308–18.
39. Saliani A, Irakoze É, Jacquemet V. Simulation of diffuse and stringy fibrosis in a bilayer interconnected cable model of the left atrium. *Europace* 2021;**23**:I169–77.
40. Chandra P, Rosen TS, Yeom ZH, Lee K, Kim HY, Danilo P *et al.* Evaluation of KCB-328, a new IKr blocking antiarrhythmic agent in pacing induced canine atrial fibrillation. *Europace* 2004;**6**:384–91.
41. Milberg P, Frommeyer G, Ghezelbash S, Rajamani S, Osada N, Razvan R *et al.* Sodium channel block by ranolazine in an experimental model of stretch-related atrial fibrillation: prolongation of interatrial conduction time and increase in post-repolarization refractoriness. *Europace* 2013;**15**:761–9.
42. Heijman J, Hohnloser SH, John Camm A. Antiarrhythmic drugs for atrial fibrillation: lessons from the past and opportunities for the future. *Europace* 2021;**23**:II14–22.
43. Gatta G, Sobota V, Citerni C, Diness JG, Sørensen US, Jespersen T *et al.* Effective termination of atrial fibrillation by SK channel inhibition is associated with a sudden organization of fibrillatory conduction. *Europace* 2021;**23**:1847–59.
44. Wang X, Huang C, Zhao Q, Huang H, Tang Y, Dai Z *et al.* Effect of renal sympathetic denervation on the progression of paroxysmal atrial fibrillation in canines with long-term intermittent atrial pacing. *Europace* 2015;**17**:647–54.
45. Boyle PM, Zahid S, Trayanova NA. Towards personalized computational modelling of the fibrotic substrate for atrial arrhythmia. *Europace* 2016;**18**:iv136–45.
46. Hakim JB, Murphy MJ, Trayanova NA, Boyle PM. Arrhythmia dynamics in computational models of the atria following virtual ablation of re-entrant drivers. *Europace* 2018;**20**:III45–54.

47. Gharaviri A, Pezzuto S, Potse M, Conte G, Zeemering S, Sobota V *et al.* Synergistic antiarrhythmic effect of inward rectifier current inhibition and pulmonary vein isolation in a 3D computer model for atrial fibrillation. *Europace* 2021;**23**:I161–8.
48. Roney CH, Bayer JD, Zahid S, Meo M, Boyle PMJ, Trayanova NA *et al.* Modelling methodology of atrial fibrosis affects rotor dynamics and electrograms. *Europace* 2016;**18**: iv146–55.
49. Hubbard ML, Henriquez CS. Microscopic variations in interstitial and intracellular structure modulate the distribution of conduction delays and block in cardiac tissue with source–load mismatch. *Europace* 2012;**14**:v3–9.
50. Berger WR, Jagu Bt, van den Berg NWE, Chan Pin Yin DRPP, van Straalen JP, de Boer OJ *et al.* The change in circulating galectin-3 predicts absence of atrial fibrillation after thoracoscopic surgical ablation. *Europace* 2018;**20**:764–71.
51. Zeemering S, Lankveld TAR, Bonizzi P, Limantoro I, Bekkers SCAM, Crijns HJGM *et al.* The electrocardiogram as a predictor of successful pharmacological cardioversion and progression of atrial fibrillation. *Europace* 2018;**20**:e96–e104.
52. Toprak B, Brandt S, Brederecke J, Gianfagna F, Vishram-Nielsen JKK, Ojeda FM *et al.* Exploring the incremental utility of circulating biomarkers for robust risk prediction of incident atrial fibrillation in European cohorts using regressions and modern machine learning methods. *Europace* 2023;**25**:812–9.
53. Ganesan P, Deb B, Feng R, Rodrigo M, Ruiperez-Campillo S, Rogers AJ *et al.* Quantifying a spectrum of clinical response in atrial tachyarrhythmias using spatiotemporal synchronization of electrograms. *Europace* 2023;**25**:euad055.
54. Nattel S, Sager PT, Hüser J, Heijman J, Dobrev D. Why translation from basic discoveries to clinical applications is so difficult for atrial fibrillation and possible approaches to improving it. *Cardiovasc Res* 2021;**117**:1616–31.
55. Goette A, Auricchio A, Boriani G, Braunschweig F, Terradellas JB, Burri H *et al.* EHRA White paper: knowledge gaps in arrhythmia management—Status 2019. *Europace* 2019;**21**:993–4.
56. Wolk R. Arrhythmogenic mechanisms in left ventricular hypertrophy. *Europace* 2000; **2**:216–23.
57. Dunnink A, van Opstal JM, Oosterhoff P, Winckels SKG, Beekman JDM, van der Nagel R *et al.* Ventricular remodelling is a prerequisite for the induction of dofetilide-induced torsade de pointes arrhythmias in the anaesthetized, complete atrio-ventricular-block dog. *Europace* 2012;**14**:431–6.
58. Rocchetti M, Freli V, Perego V, Altomare C, Mostacciuolo G, Zaza A *et al.* Rate dependency of β-adrenergic modulation of repolarizing currents in the Guinea-pig ventricle. *J Physiol* 2006;**574**:183–93.
59. Dunnink A, Stams TRG, Bossu A, Meijborg VMF, Beekman JDM, Wijers SC *et al.* Torsade de pointes arrhythmias arise at the site of maximal heterogeneity of repolarization in the chronic complete atrioventricular block dog. *Europace* 2017;**19**:858–65.
60. Münkler P, Klatt N, Scherschel K, Kuklik P, Jungen C, Cavus E *et al.* Repolarization indicates electrical instability in ventricular arrhythmia originating from papillary muscle. *Europace* 2023;**25**:688–97.
61. Potse M, Krause D, Kroon W, Murzilli R, Muzzarelli S, Regoli F *et al.* Patient-specific modelling of cardiac electrophysiology in heart-failure patients. *Europace* 2014;**16**: iv56–61.
62. Deng D, Arevalo HJ, Prakosa A, Callans DJ, Trayanova NA. A feasibility study of arrhythmia risk prediction in patients with myocardial infarction and preserved ejection fraction. *Europace* 2016;**18**:iv60–6.
63. Zaza A, Rocchetti M. Calcium store stability as an antiarrhythmic endpoint. *Curr Pharm Des* 2015;**21**:1053–61.
64. Pabel S, Mustroph J, Stehle T, Lebek S, Dybkova N, Keyser A *et al.* Dantrolene reduces CaMKIIδC-mediated atrial arrhythmias. *Europace* 2020;**22**:1111–8.
65. Hofhuis J, Bersch K, Wagner S, Molina C, Fakuade FE, Iyer LM *et al.* Dysferlin links excitation-contraction coupling to structure and maintenance of the cardiac transverse-axial tubule system. *Europace* 2020;**22**:1119–31.
66. Coutinho DCO, Monnerat-Cahli G, Ferreira AJ, Medei E. Activation of angiotensin-converting enzyme 2 improves cardiac electrical changes in ventricular repolarization in streptozotocin-induced hyperglycaemic rats. *Europace* 2014;**16**:1689–96.
67. Yamada S, Lo L-W, Chou Y-H, Lin W-L, Chang S-L, Lin Y-J *et al.* Renal denervation ameliorates the risk of ventricular fibrillation in overweight and heart failure. *Europace* 2020;**22**:657–66.
68. Zuo S, Li L-L, Ruan Y-F, Jiang L, Li X, Li S-N *et al.* Acute administration of tumour necrosis factor-α induces spontaneous calciumrelease via the reactive oxygen species pathway in atrialmyocytes. *Europace* 2018;**20**:1367–74.
69. Xie Y, Grandi E, Bers DM, Sato D. How does β-adrenergic signalling affect the transitions from ventricular tachycardia to ventricular fibrillation? *Europace* 2014;**16**:452–7.
70. Xie Y, Grandi E, Puglisi JL, Sato D, Bers DM. β-adrenergic stimulation activates early afterdepolarizations transiently via kinetic mismatch of PKA targets. *J Mol Cell Cardiol* 2013;**58**:153–61.
71. Sala L, Hegyi B, Bartolucci C, Altomare C, Rocchetti M, Váczi K *et al.* Action potential contour contributes to species differences in repolarization response to β-adrenergic stimulation. *Europace* 2018;**20**:1543–52.
72. Fischer TH, Herting J, Eiringhaus J, Pabel S, Hartmann NH, Ellenberger D *et al.* Sex-dependent alterations of Ca21 cycling in human cardiac hypertrophy and heart failure. *Europace* 2016;**18**:1440–8.
73. Liao SY, Liu Y, Zuo M, Zhang Y, Yue W, Au K-W *et al.* Remodelling of cardiac sympathetic re-innervation with thoracic spinal cord stimulation improves left ventricular function in a porcine model of heart failure. *Europace* 2015;**17**:1875–83.
74. Xiong L, Liu Y, Zhou M, Wang G, Quan D, Shen C *et al.* Targeted ablation of cardiac sympathetic neurons improves ventricular electrical remodelling in a canine model of chronic myocardial infarction. *Europace* 2018;**20**:2036–44.
75. van Weperen VYH, ter Horst I, Dunnink A, Bossu A, Salden OA, Beekman HDM *et al.* Chronically altered ventricular activation causes pro-arrhythmic cardiac electrical remodelling in the chronic AV block dog model. *Europace* 2023;**25**:707–15.
76. Van Middendorp LB, Strik M, Houthuizen P, Kuiper M, Maessen JG, Auricchio A *et al.* Electrophysiological and haemodynamic effects of vernakalant and flecainide in dyssynchronous canine hearts. *Europace* 2014;**16**:1249–56.
77. Kowlgi GN, Ramirez RJ, Kaszala K, Joslyn M, Koneru JN, Ellenbogen KA *et al.* Post-extrasystolic potentiation as a predictor of premature ventricular contraction-cardiomyopathy in an animal model. *Europace* 2020;**22**:813–20.
78. Hashimoto N, Yamashita T, Fujikura N, Tsuruzoe N. NIP-141, a multiple ion channel blocker, terminates aconitine-induced atrial fibrillation and prevents the rapid pacing-induced atrial effective refractory period shortening in dogs. *Europace* 2007; **9**:246–51.
79. Löfberg L, Jacobson I, Carlsson L. Electrophysiological and antiarrhythmic effects of the novel antiarrhythmic agent AZD7009: A comparison with azimilide and AVE0118 in the acutely dilated right atrium of the rabbit in vitro. *Europace* 2006;**8**:549–57.
80. Colman MA, Varela M, Hancox JC, Zhang H, Aslanidi OV. Evolution and pharmacological modulation of the arrhythmogenic wave dynamics in canine pulmonary vein model. *Europace* 2014;**16**:416–23.
81. Loewe A *et al.* In-silico assessment of the dynamic effects of amiodarone and dronedarone on human atrial patho-electrophysiology. *Europace* 2014;**16**:iv30–8.
82. Casini S, Marchal GA, Kawasaki M, Fabrizi B, Wesselink R, Nariswari FA *et al.* Differential sodium current remodelling identifies distinct cellular proarrhythmic mechanisms in paroxysmal vs persistent atrial fibrillation. *Can J Cardiol* 2023;**39**:277–88.
83. Kharche SR, Stary T, Colman MA, Biktasheva IV, Workman AJ, Rankin AC *et al.* Effects of human atrial ionic remodelling by β-blocker therapy onmechanisms of atrial fibrillation: A computer simulation. *Europace* 2014;**16**:1524–33.
84. Matene E, Vinet A, Jacquemet V. Dynamics of atrial arrhythmias modulated by time-dependent acetylcholine concentration: A simulation study. *Europace* 2014;**16**: iv11–20.
85. Hung Y, Chen Y-C, Huang S-Y, Lu Y-Y, Lin Y-K, Kao Y-H *et al.* Klotho modulates electrical activity and calcium homeostasis in pulmonary vein cardiomyocytes via PI3K/akt signalling. *Europace* 2020;**22**:1132–41.
86. Orini M, Yanni J, Taggart P, Hanson B, Hayward M, Smith A *et al.* Mechanistic insights from targeted molecular profiling of repolarization alternans in the intact human heart. *Europace* 2019;**21**:981–9.
87. Maleckar MM, Lines GT, Koivumäki JT, Cordeiro JM, Calloe K. NS5806 Partially restores action potential duration but fails to ameliorate calcium transient dysfunction in a computational model of canine heart failure. *Europace* 2014;**16**:iv46–55.
88. Huang M, Fan X, Yang Z, Cyganek L, Li X, Yuecel G, *et al.* Alpha 1-adrenoceptor signalling contributes to toxic effects of catecholamine on electrical properties in cardiomyocytes. *Europace* 2021;**23**:1137–48.
89. Wang J, Wang G, Quan X, Ruan L, Liu Y, Ruan Y *et al.* Fluconazole-induced long QT syndrome via impaired human ether-a-go-go-related gene (hERG) protein trafficking in rabbits. *Europace* 2017;**19**:1244–9.
90. Zemzemi N, Rodriguez B. Effects of L-type calcium channel and human ether-a-go-go related gene blockers on the electrical activity of the human heart: A simulation study. *Europace* 2014;**17**:326–33.
91. Frommeyer G, Milberg P, Schulze Grotthoff J, Dechering DG, Kochhäuser S, Stypmann J *et al.* Dronedarone and digitalis: individually reduced post-repolarization refractoriness enhances life-threatening arrhythmias. *Europace* 2015;**17**:1300–8.
92. Andersson B, Abi-Gerges N, Carlsson L. The combined ion channel blocker AZD1305 attenuates late Na current and IKr-induced action potential prolongation and repolarization instability. *Europace* 2010;**12**:1003–10.
93. Frommeyer G, Milberg P, Clauss C, Schmidt M, Ramtin S, Kaese S *et al.* Electrophysiological profile of vernakalant in an experimental whole-heart model: the absence of proarrhythmia despite significant effect on myocardial repolarization. *Europace* 2014;**16**:1240–8.
94. Frommeyer G, Clauss C, Ellermann C, Bogossian H, Dechering DG, Kochhäuser S *et al.* Antiarrhythmic effect of vernakalant in an experimental model of long-QT-syndrome. *Europace* 2017;**19**:866–73.
95. Ellermann C, Sterneberg M, Kochhäuser S, Dechering DG, Fehr M, Eckardt L *et al.* Antiarrhythmic effect of antazoline in experimental models of acquired short- and long-QT-syndromes. *Europace* 2018;**20**:1699–706.

96. Frommeyer G, Garthmann J, Ellermann C, Dechering DG, Kochhäuser S, Reinke F *et al.* Broad antiarrhythmic effect of mexiletine in different arrhythmia models. *Europace* 2018;**20**:1375–81.
97. Rivaud MR, Marchal GA, Wolswinkel R, Jansen JA, van der Made I, Beekman L *et al.* Functional modulation of atrio-ventricular conduction by enhanced late sodium current and calcium-dependent mechanisms in Scn5a1798insD/+mice. *Europace* 2020;**22**:1579–89.
98. Giannetti F, Barbieri M, Shiti A, Casini S, Sager PT, Das S *et al.* Gene- and variant-specific efficacy of serum/glucocorticoid-regulated kinase 1 inhibition in long QT syndrome types 1 and 2. *Europace* 2023;**25**:euad094.
99. Portero V, Casini S, Hoekstra M, Verkerk AO, Mengarelli I, Belardinelli L *et al.* Anti-arrhythmic potential of the late sodium current inhibitor GS-458967 in murine *Scn5a*-1798insD$^{+/-}$ and human *SCN5A*-1795insD$^{+/-}$ iPSC-derived cardiomyocytes. *Cardiovasc Res* 2017;**113**:829–38.
100. Altrocchi C, de Korte T, Bernardi J, Spätjens RLHMG, Braam SR, Heijman J *et al.* Repolarization instability and arrhythmia by IKr block in single human-induced pluripotent stem cell-derived cardiomyocytes and 2D monolayers. *Europace* 2020;**22**:1431–41.
101. Altomare C, Pianezzi E, Cervio E, Bolis S, Biemmi V, Benzoni P *et al.* Human-induced pluripotent stem cell-derived cardiomyocytes from cardiac progenitor cells: effects of selective ion channel blockade. *Europace* 2016;**18**:iv67–76.
102. Offerhaus JA, Bezzina CR, Wilde AAM. Epidemiology of inherited arrhythmias. *Nat Rev Cardiol* 2020;**17**:205–15.
103. Hirose S, Murayama T, Tetsuo N, Hoshiai M, Kise H, Yoshinaga M *et al.* Loss-of-function mutations in cardiac ryanodine receptor channel cause various types of arrhythmias including long QT syndrome. *Europace* 2022;**24**:497–510.
104. Chinushi M, Izumi D, Iijima K, Ahara S, Komura S, Furushima H *et al.* Antiarrhythmic vs. pro-arrhythmic effects depending on the intensity of adrenergic stimulation in a canine anthopleurin-A model of type-3 long QT syndrome. *Europace* 2008;**10**:249–55.
105. Odening KE, Van Der Linde HJ, Ackerman MJ, Volders PGA, Ter Bekke RMA. Electromechanical reciprocity and arrhythmogenesis in long-QT syndrome and beyond. *Eur Heart J* 2022;**43**:3018–28.
106. Haugaa KH, Amlie JP, Berge KE, Leren TP, Smiseth OA, Edvardsen T. Transmural differences in myocardial contraction in long-QT syndrome: mechanical consequences of ion channel dysfunction. *Circulation* 2010;**122**:1355–63.
107. Hummel YM, Wilde AAM, Voors AA, Bugatti S, Hillege HL, van den Berg MP *et al.* Ventricular dysfunction in a family with long QT syndrome type 3. *Europace* 2013;**15**:1516–21.
108. Rivaud MR, Delmar M, Remme CA. Heritable arrhythmia syndromes associated with abnormal cardiac sodium channel function: ionic and non-ionic mechanisms. *Cardiovasc Res* 2020;**116**:1557–70.
109. Hwang J, Kim TY, Terentyev D, Zhong M, Kabakov AY, Bronk P *et al.* Late INaBlocker GS967 supresses polymorphic ventricular tachycardia in a transgenic rabbit model of long QT type 2. *Circ Arrhythmia Electrophysiol* 2020;**13**:E006875.
110. Seth R, Moss AJ, McNitt S, Zareba W, Andrews ML, Qi M *et al.* Long QT syndrome and pregnancy. *J Am Coll Cardiol* 2007;**49**:1092–8.
111. Bodi I, Sorge J, Castiglione A, Glatz SM, Wuelfers EM, Franke G *et al.* Postpartum hormones oxytocin and prolactin cause pro-arrhythmic prolongation of cardiac repolarization in long QT syndrome type 2. *Europace* 2019;**21**:1126–38.
112. Odening KE, Koren G. How do sex hormones modify arrhythmogenesis in long QT syndrome? Sex hormone effects on arrhythmogenic substrate and triggered activity. *Hear Rhythm* 2014;**11**:2107–15.
113. Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M *et al.* Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. *J Am Coll Cardiol* 2016;**67**:1053–8.
114. Castiglione A, Hornyik T, Wülfers EM, Giammarino L, Edler I, Jowais JJ *et al.* Docosahexaenoic acid normalizes QT interval in long QT type 2 transgenic rabbit models in a genotype-specific fashion. *Europace* 2022;**24**:511–22.
115. Dotzler SM, Kim CSJ, Gendron WAC, Zhou W, Ye D, Bos JM *et al.* Suppression-Replacement KCNQ1 gene therapy for type 1 long QT syndrome. *Circulation* 2021;**143**:1411–25.
116. Schwartz PJ, Gnecchi M, Dagradi F, Castelletti S, Parati G, Spazzolini C *et al.* From patient-specific induced pluripotent stem cells to clinical translation in long QT syndrome type 2. *Eur Heart J* 2019;**40**:1832–6.
117. Calloe K, Geryk M, Freude K, Treat JA, Vold VA, Frederiksen HRS *et al.* The G213D variant in Nav1.5 alters sodium current and causes an arrhythmogenic phenotype resulting in a multifocal ectopic Purkinje-related premature contraction phenotype in human-induced pluripotent stem cell-derived cardiomyocytes. *Europace* 2022;**24**:2015–27.
118. Giudicessi JR, Ye D, Stutzman MJ, Zhou W, Tester DJ, Ackerman M. Prevalence and electrophysiological phenotype of rare SCN5A genetic variants identified in unexplained sudden cardiac arrest survivors. *Europace* 2020;**22**:622–31.
119. van der Voorn SM, te Riele ASJM, Basso C, Calkins H, Remme CA, van Veen TAB. Arrhythmogenic cardiomyopathy: pathogenesis, pro-arrhythmic remodeling, and novel approaches for risk stratification and therapy. *Cardiovasc Res* 2020;**116**:1571–84.
120. Vite A, Gandjbakhch E, Hery T, Fressart V, Gary F, Simon F *et al.* Desmoglein-2 mutations in propeptide cleavage-site causes arrhythmogenic right ventricular cardiomyopathy/dysplasia by impairing extracellular 1-dependent desmosomal interactions upon cellular stress. *Europace* 2020;**22**:320–9.
121. Van Osta N, Kirkels F, Lyon A, Koopsen T, van Loon T Cramer MJ *et al.* Electromechanical substrate characterization in arrhythmogenic cardiomyopathy using imaging-based patient-specific computer simulations. *Europace* 2021;**23**:1153–60.
122. Gandjbakhch E, Vite A, Gary F, Fressart V, Donal E, Simon F *et al.* Screening of genes encoding junctional candidates in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Europace* 2013;**15**:1522–5.
123. Sonoda K, Ohno S, Otuki S, Kato K, Yagihara N, Watanabe H *et al.* Quantitative analysis of PKP2 and neighbouring genes in a patient with arrhythmogenic right ventricular cardiomyopathy caused by heterozygous PKP2 deletion. *Europace* 2017;**19**:644–50.