Role of ion channels in heart failure and channelopathies

Ann-Kathrin Rahm¹ · Patrick Lugenbiel¹ · Patrick A. Schweizer¹ · Hugo A. Katus¹ · Dierk Thomas¹

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Abstract

Heart failure (HF) is a complication of multiple cardiac diseases and is characterized by impaired contractile and electric function. Patients with HF are not only limited by reduced contractile function but are also prone to life-threatening ventricular arrhythmias. HF itself leads to remodeling of ion channels, gap junctions, and intracellular calcium handling abnormalities that in combination with structural remodeling, e.g., fibrosis, produce a substrate for an arrhythmogenic disorders. Not only ventricular life-threatening arrhythmias contribute to increased morbidity and mortality but also atrial arrhythmias, especially atrial fibrillation (AF), are common in HF patients and contribute to morbidity and mortality. The distinct ion channel remodeling processes in HF and in channelopathies associated with HF will be discussed. Further basic research and clinical studies are needed to identify underlying molecular pathways of HF pathophysiology to provide the basis for improved patient care and individualized therapy based on individualized ion channel composition and remodeling.

Keywords Arrhythmia · Channelopathy · Heart failure · Ion channel · Pathophysiology

Introduction

Heart failure (HF) is a complication of multiple cardiac diseases and is characterized by impaired contractile and electric function. Patients with HF are not only limited by circulatory

failure but are prone to life-threatening ventricular arrhythmias as well in up to 50% of cases (Kjekshus 1990).

HF itself is accompanied by remodeling of ion channels, gap junctions, and intracellular calcium handling abnormalities that in combination with structural remodeling, e.g., fibrosis, produce a substrate for arrhythmogenesis. Arrhythmogenesis on the basis of remodeling processes in HF is not limited to the ventricles. Rather, atrial arrhythmias, especially atrial fibrillation (AF), are common in HF patients and contribute to morbidity and mortality (Ehrlich et al. 2002; Mene-Afejuku et al. 2018). Nevertheless, this review focuses on ventricular changes remodeling of ion channels, and channelopathies, and their impact on structural remodeling. By contrast, ion channel remodeling in AF and its potential implications for arrhythmogenesis and treatment have been assessed in depth elsewhere (Dobrev and Ravens 2003; Nattel et al. 2008; Workman et al. 2008; Schotten et al. 2011; Grunnet et al. 2012; Heijman et al. 2014; Hancox et al. 2016).

The ion channel composition of each cardiac cell contributes to the formation of the cardiac action potential that is important for propagation of excitation. In addition, ion channel complexes form the basis for excitation contraction coupling including calcium-induced calcium release and mechanical contraction. Changes in action potential duration and QT interval in LQTS patients not only affect electrical but also mechanical function of the heart,

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✉ Dierk Thomas
dierk.thomas@med.uni-heidelberg.de

Ann-Kathrin Rahm
ann-kathrin.rahm@med.uni-heidelberg.de

Patrick Lugenbiel
patrick.lugenbiel@med.uni-heidelberg.de

Patrick A. Schweizer
patrick.schweizer@med.uni-heidelberg.de

Hugo A. Katus
sekretariat.katus@med.uni-heidelberg.de

¹ Department of Cardiology, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

highlighting the role of mechano-electrical dysfunction in channelopathies.

Moreover, ion channel remodeling processes may lead to HF development. Ion channels have recently been implicated in structural heart development, e.g., in patients carrying HCN4 mutations associated with left ventricular non-compaction, as outlined in this article. Ion channel remodeling processes in HF and in channelopathies associated with HF will be discussed below.

Ion channels and cardiac action potential

The cardiac action potential (AP) provides the basis for conduction of electricity throughout the heart and provides the basis for electro mechanic coupling which is essential for normal heart function. The AP is shaped by its underlying ionic currents, shown in Fig. 1, and transporters [for detailed reviews see Nerbonne and Kass 2005] and varies depending on the specific electric localization including the sinoatrial node, atria, atrioventricular node, His-Purkinje system, and ventricles shown in Fig. 2 (Schram 2002, Nerbonne and Kass 2005). Phase 0 is the initial depolarization that is carried by the fast sodium current I_{Na} , followed by a brief rapid repolarization (Phase 1), carried by I_{to1} and the plateau phase (Phase 2) which is balanced by calcium inflow through

Fig. 1 Cardiac action potential and its underlying ionic currents. Schematic representation of a human ventricular action potential. Numbers denote the different phases of the ventricular action potential outlined above. The dashed line represents phase 4 depolarization normally present in cells from the conduction system and not in ventricular cardiomyocytes. Underlying ionic membrane currents are depicted below. I_{Na} , Na^+ current; $I_{Ca,L}$, L-type Ca^{2+} current; $I_{Ca,T}$, T-type Ca^{2+} current; I_{to1} , transient outward current type 1; $I_{Cl(Ca)}$, Ca^{2+} activated Cl^- current, also called I_{to2} ; I_{Kur} , ultra rapid component of the delayed rectifier K^+ current; I_{Kr} , rapid component of the delayed rectifier K^+ current; I_{Ks} , slow component of the delayed rectifier K^+ current; I_{K1} , inward rectifier K^+ current; I_f , funny current; I_{NCX} , Na^+/Ca^{2+} exchange current (adapted from Hoekstra et al. 2012)

Fig. 2 Morphologies of cardiac action potential throughout the heart. Schematic drawing of cardiac action potential morphologies in the SA and AV node and atrial and ventricular action potentials. RA right atrium, LA left atrium, RV right ventricle, LV left ventricle [adapted from Chahal and Somers, 2016]

L-type calcium currents ($I_{Ca,L}$) and repolarizing potassium currents; the latter also terminate the action potential in Phase 3, the final repolarization. Phase 4 constituted the resting state with a potential around -80 to -90 mV and is mainly held by inwardly rectifying potassium currents (I_{K1}).

Various forms of cardiac diseases and rhythm disturbances may lead to changes in ion channels and transporters. These alterations can be part of homeostatic response mechanism or may worsen cardiac dysfunction by maladaptive processes through further rhythm disturbances (Nattel et al. 2007).

Mechanism of arrhythmogenesis in HF

Remodeling processes during the development of heart failure increase the susceptibility to arrhythmias. These remodeling processes include changes in ion channel composition, function, and localization as well as histological changes including fibrosis.

Ventricular tachyarrhythmias are responsible for sudden cardiac death in up to 50% of heart failure patients (Kjekshus 1990). Therefore, implantation of implantable cardioverter defibrillators was shown to improve survival in heart failure collectives (Al-Khatib et al. 2017).

Not only ventricular but also atrial arrhythmias in HF patients contribute to increased morbidity and mortality. In particular, the occurrence of atrial fibrillation increases with worsening ejection fraction (Ehrlich et al. 2002; Lugenbiel et al. 2015). Normal sinus rhythm may also be slowed or impaired in HF due to abnormal sinoatrial node function (Ophthof

et al. 2000; Sanders et al. 2004, and Zicha et al. 2005). In a dog model, tachypacing-induced heart failure led to downregulation of HCN4 and HCN2 expression and contributed to HF-induced sinus node dysfunction (Zicha et al. 2005), as shown in Fig. 3a.

Early afterdepolarizations (EADs; Fig. 3b) represent a different trigger of arrhythmias. Remodeling of ion channels leads to a prolongation of the AP by reduction of repolarizing currents (I_{Ks} , I_{K1} , and I_{to}) and increasing of depolarizing plateau currents (I_{NaL}). In contrast, delayed afterdepolarizations (Fig. 3c) are caused by calcium handling abnormalities in diastole. In HF, DADs are promoted by increased leak from the sarcoplasmic reticulum (SR) and increased function levels of the sodium-calcium antiporter that depolarizes the cardiomyocyte by transporting on Ca^{2+} ion out for three Na^{+} ions transported intracellularly. Delayed afterdepolarizations are also promoted by the decrease of $IK1$ current in HF and subsequent increase in diastolic membrane resistance. If these afterdepolarizations suffice to activate, a new action potential arrhythmias can be started.

Reentry mechanisms are prone by remodeling processes that lead to slowed conduction and spatial inhomogeneities in conduction velocities. Reduction of connexin 43 and alteration in connexin 43 localization and spatially increased variability of action potential duration (Akar and Rosenbaum 2003) can increase susceptibility to reentry.

Specific ion channel changes and ion channel mutations leading to channelopathies and impaired cardiac function are described in the following sections.

Ion channel remodeling in heart failure

Multiple ion channels are remodeled during the development of heart failure. Several animal models of heart failure have been used to assess specific ion channel alternations in past studies. These models include mostly rapid ventricular pacing. Also, human samples obtained from HF patients were assessed. For a more detailed review, see, e.g., Nattel et al. 2007.

Potassium channels

Potassium channels are the most important ion channels contributing to repolarization in cardiomyocytes. A consistent feature of cardiomyocytes from patients or animals with HF is prolonged action potential duration (Nuss et al. 1999; Akar and Rosenbaum 2003; Janse 2004), and it becomes obvious that K^{+} channel remodeling is of great importance for repolarization abnormalities. Some of these changes in HF mimic inherited channelopathies that cause long QT syndrome. The interplay between the various K^{+} channel subtypes during the progression to HF is dynamic. The underlying transcriptional, posttranscriptional, and posttranslational remodeling of the individual K^{+} channel types changes their activity and their significance respectively, and they must be viewed together to understand their role in maintaining a stable heart rhythm.

Studies that examined changes in K^{+} channels in ventricular cardiomyocytes are listed in Table 1. Differences in remodeling are seen which may be attributed to different animal models or stages of HF. The so far most consistent observation

Fig. 3 Mechanism of arrhythmogenesis in HF. Schematic drawing of mechanism underlying arrhythmogenesis in heart failure. **a** Highlights the changes in the SA node. **b**, **c** The mechanism of the initiation of EADs and DADs. **d** Reentry supporting remodeling processes [reproduced with permission from Nattel et al. 2007]

Table 1 Altered K^+ currents in heart failure in ventricular cardiomyocytes

Current	Changes in HF	References
I_{to}	↓	Beuckelmann et al. (1993), Kääb et al. (1996), Rozanski et al. (1997), Li et al. (2000), Tsuji et al. (2006), Pogwizd et al. (2001), Li et al. (2002), Zicha et al. (2004), Rose et al. (2005)
I_{Ks}	↓	Tsuji (2000), Tsuji et al. (2006), Li et al. (2000), Li et al. (2002)
I_{Kr}	↓	Tsuji (2000), Tsuji et al. (2006)
	→	Li et al. (2000), Li et al. (2002)
I_{ss}	→	
I_{K1}	↓	Beuckelmann et al. (1993), Kääb et al. (1996), Li et al. (2000), Pogwizd et al. (2001), Li et al. (2002), Rose et al. (2005)
	→	Rozanski et al. (1997), Tsuji (2000)
I_{K2P}	↓	Schmidt et al. (2017)

is a downregulation of I_{to} in HF. This occurs by a downregulation on mRNA and protein level (Kaab et al. 1998; Zicha et al. 2004). Results for the principal I_{Kr} subunit ERK show unaltered expression levels. Most studies also confirmed a downregulation in the inward-rectifier current I_{K1} .

Two-pore-domain potassium (K_{2P}) channels modulate cellular excitability. The significance of stretch-activated cardiac K_{2P} channels ($K_{2P2.1}$, TREK-1, KCNK2; $K_{2P4.1}$, TRAAK, KCNK4; $K_{2P10.1}$, TREK-2, KCNK10) has only been studied in recent years. HF- and AF-associated downregulation of KCNK2 ($K_{2P2.1}$) mRNA and protein levels suggest a mechanistic contribution to cardiac arrhythmogenesis (Schmidt et al. 2017).

Sodium channels

I_{Na} is important for the fast upstroke of the cardiac action potential (phase 0) and defines propagation velocity in normal cardiac tissue (Schram 2002). In HF peak, I_{Na} has been shown to be reduced by posttranslational reduction of the alpha subunit $Na_v1.5$ and other posttranslational modifications (Ufret-Vincenty et al. 2001). Slowed cardiac conduction favors reentry mechanism and contributes to inefficiently synchronized cardiac conduction.

Abnormalities in inactivation of I_{Na} lead to a late persistent sodium current that antagonizes repolarization and leads to APD prolongation and EADs that cause arrhythmia (Ufret-Vincenty et al. 2001; Yu et al. 2018).

Chloride channels

Chloride channels in the heart may influence both repolarization and depolarization (Bers and Lederer, 2008). They have been implicated in cardiac arrhythmogenesis, myocardial hypertrophy, and heart failure, as well as cardioprotection against

ischaemia–reperfusion (Duan 2009). The swelling sensitive chloride channel appears to be of particular interest. $I_{Cl,swell}$ is distributed throughout the heart and is activated by osmotic and hydrostatic increase in cell volume, by changes in membrane tension, and by direct mechanical stretch (Baumgarten and Clemo 2003). $I_{Cl,swell}$ leads to APD shortening, resting membrane potential depolarization, and reduces cell volume. In HF cardiomyocytes, constitutively active swelling-sensitive chloride channel currents $I_{Cl,swell}$ have been observed (Clemon et al. 1999).

Altered calcium handling and calcium currents

Significant changes in Ca^{2+} handling occur during the development of HF (Hasenfuss et al. 1997, Lugenbiel et al. 2015). Detailed reviews have been provided by Bers and Guo (2005) and Beuckelmann and Erdmann (1992).

The L-type-current itself has been studied in HF samples with different results, some showing a decrease of I_{CaL} (Ouadid et al. 1995; Mukherjee et al. 1998; Li et al. 2000) and others not reporting significant changes. The membrane density of the L-type Ca^{2+} currents is decreased (Mukherjee et al. 1998, Chen 2002, He 2001); however, phosphorylation increases and leads to increases in single-channel open probability.

Proteins involved in Ca^{2+} -induced Ca^{2+} release, cycling, and storage of Ca^{2+} in the SR are changed in activity (Fig. 4). Ryanodine receptors (RyRs) are hyperphosphorylated by protein kinase A (PKA) and/or calmodulin-dependent kinase II (CamKII), causing abnormal Ca^{2+} leaks to the SR. NCX activity is enhanced promotion of the occurrence for triggered activity by DADs (Vermeulen et al. 1994, Pogwizd et al. 2001, Pogwizd and Bers 2002). Finally, SERCA function is reduced, both by reduction in expression level as well as the concomitant dephosphorylation of phospholamban that detaches from

Fig. 4 Cycling of Ca^{2+} in a ventricular myocyte and changes in heart failure. RyR ryanodine receptor, PLB phospholamban, NaCaX $3\text{Na}^+-1\text{Ca}^{2+}$ -antiporter, SR sarcoplasmic reticulum [reproduced with permission from Pogwizd and Bers 2002]

SERCA and reduces transporting capacities of Ca^{2+} to the SR. These changes in Ca^{2+} handling lead to higher diastolic Ca^{2+} and increased diastolic Ca^{2+} loss from the SR which finally impairs Ca^{2+} -induced Ca^{2+} release mechanism and excitation–contraction coupling with reduced contractile force.

Altered connexin expression and distribution

Connexins form pores and enable cardiomyocytes to form electrical cell-to-cell coupling. The expression of the main ventricular connexin isoform, connexin 43, is downregulated in heart failure which was experimentally shown to reduce cell-to-cell coupling by luciferase yellow transfer (Dupont et al. 2001, Ai and Pogwizd 2005, Akar et al. 2004). Reduction of connexin amount of 90% has shown to decrease conduction velocity to 50% (van Rijen et al. 2004). But not only changes in protein amount increase susceptibility to arrhythmias. Additionally, HF causes changes in phosphorylation state of connexins that impair function (Akar et al. 2004) and localization disorders from the intercalated discs to lateral membrane occur (Severs et al. 2008, Kostin 2007).

Functionally altered connexin expression and function leads to conduction slowing in the failing heart (Akar et al. 2004; Ai and Pogwizd 2005) which contributed to mechanical dysfunction and adverse ventricular remodeling. In addition, APD heterogeneity is promoted by altered connexin expression pattern that favor reentry (Poelzing and Rosenbaum 2004).

T-tubular remodeling and ion channel sub-localization

Cardiomyocytes are functionally well-adapted cells that propagate electrical activity across their long axis. In support of structured and fast electrical transmission of cardiac electricity, T-tubules promote ion fluxes, e.g., calcium handling and

excitation–contraction coupling and influence conduction velocity (Bers and Lederer 2008, Fu and Hong 2016, Manfra et al. 2017). In heart failure and cardiomyopathies, a decrease in T-tubules has been observed (Caldwell et al. 2014). The protein bridging integrator 1 (BIN1) appears to be essential for normal T-tubule formation and is downregulated in failing hearts. BIN1 affects calcium channel trafficking. Downregulation of BIN1 in a mouse model decreased T-tubule formation accompanied by prolonged APD and increased prevalence of ventricular arrhythmias (Hong et al. 2014).

In addition to changes in T-tubular count and morphology, HF is characterized by redistribution of L-type Ca^{2+} channels from the T-tubules to the surface membrane in animal models.

Channelopathies and heart failure

Channelopathies are inherited genetic disorders with mutations in mainly specific ion channels that predispose patients to arrhythmias which among others include LQTS, short-QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Bezzina et al. 2015) (Table 2). Although most mutations accounting for channelopathies are located in specific ion channel genes, other mutations occur in genes encoding proteins involved in ion channel synthesis, membrane trafficking, and/or posttranslational modifications and regulation (Curran and Mohler 2015). The protein MOG1 for example interacts with Nav1.5 by regulating Nav1.5 membrane expression, and silencing of MOG1 was associated with BrS (Kattynarath et al. 2011).

Channelopathy syndromes are often characterized by specific ECG abnormalities either at baseline or during specific stressing conditions such as exercise (in CPVT and LQTS), fever (BrS), or pharmacological challenge (BrS). Depending on the respective ion channel mutation, function and/or expression level of the respective ionic current will change with effect on the cardiac action potential (Garcia-Elias and Benito 2018). The list of familial arrhythmia syndromes has been expanded by two other syndromes, early repolarization syndrome (Gourraud et al. 2013) and idiopathic ventricular fibrillation (Alders et al. 2009), which will not be discussed in this review.

Long-QT-syndrome

Clinically, long-QT-syndrome (LQTS) is characterized by prolongation of the QT-interval on the surface ECG that predispose patients to ventricular arrhythmias especially torsades-des-pointes-tachycardias. Patients present with syncope or during evaluation for risk of sudden cardiac death in families with affected members. The QT prolongation may be caused from

Table 2 Inherited channelopathies and underlying gene mutations

Syndrome	Gene	Functional alteration	References
LQTS	KCNQ1	IKr ↓	Ackerman et al. (2011), Schwartz et al. (2012)
	KCNH2	IKr ↓	
	SCN5A	INa↑	
	ANK2	INa,K ↑	
Brugada syndrome	SCN5A	INa↓	Brugada and Brugada (1992), Antzelevitch et al. (2007)
	GPD1L	INa↓	
	SCN1B	INa↓	
	CACNA1C	ICa↓	
	CACNB2B	ICa↓	
SQTS	KCNQ1	IKr ↑	Brugada et al. (2004), Bellocq et al. (2004), Priori et al. (2005), Antzelevitch et al. (2007), Harrel et al. (2015)
	KCNH2	IKr ↑	
	KCNJ2	IK1↑	
	CACNA1C	ICa ↓	
	CACNB2B	ICa ↓	
CPVT	RYR2	Abnormal Ca ²⁺ release from SR	Bhuiyan et al. (2007), Napolitano and Priori (2007), Mohamed et al. (2007)
	CASQ2		

either a decrease in repolarizing ionic currents or an increase in depolarizing currents late in the cardiac cycle (Moss and Kass 2005). Mutations in three ion channel genes KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) account for 75% of all LQTS cases (Ackerman et al. 2011, Schwartz et al. 2012). The genes associated with LQTS have been numerically ordered by the chronology of their discovery. Interestingly, triggers for arrhythmia differ among the LQTS subtypes. Genetic testing in affect patients and in first-degree relatives of patients who have a causative mutation for long-QT syndrome is recommended (Al-Khatib et al. 2017).

Channelopathies were initially thought to be mainly problems in cardiac electrophysiology. Nevertheless, recent studies show that patients with LQTS exhibit mechanical problems like diastolic dysfunction and prolonged contraction duration (Brado et al. 2017) and confirmed LQTS as an electromechanical disorder.

Short-QT-syndrome

Clinically, short-QT-syndrome (SQTS) is characterized by drastic shortening of the QT interval. As genetic causes gain-of-function mutations in potassium channel genes, KCNH2 (Brugada et al. 2004), KCNQ1 (Bellocq et al. 2004), KCNJ2 (Priori et al. 2005), or loss-of-function mutations in the L-type calcium channel (Antzelevitch et al. 2007) have been identified. These mutations shorten the effective refractory period and increase dispersion of repolarization and susceptibility to reentry in the ventricles and the atria.

Brugada syndrome

Clinically, Brugada syndrome is characterized by a typical ECG pattern (coved-type ST-segment elevation in right precordial leads and an increased risk to develop ventricular tachyarrhythmias and sudden cardiac death; Brugada and Brugada 1992). From experimental studies, it is known that the characteristic ECG pattern correlate with imbalances between depolarizing and repolarizing currents in the early phase of the cardiac action potential. Mutations in *SCN5A* account for the majority of Brugada syndrome cases with an identified gene mutation.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a syndrome characterized by stress-induced polymorphic beats and ventricular tachycardias. CPVT-causing mutations encode the cardiac ryanodine receptor (RYR2) or for cardiac calsequestrin (CASQ2) in 60% of affected patients (Ackerman et al. 2011); in the remaining patients, the molecular basis still needs to be identified. Calcium leak from the sarcoplasmic reticulum is assumed to be involved in the pathophysiology of AF in CPVT patients to trigger arrhythmia through calcium-handling abnormalities as outlined previously.

Ion channels cause electrical and structural overlap syndromes

Inherited arrhythmias were thought to be primarily electrical defects. Growing evidence shows that ion channel

dysfunction can also contribute to myocardial disorders. As one example, the HCN4 overlap syndrome comprising sinus node dysfunction and non-compaction cardiomyopathy (Milano et al. 2014, Schweizer et al. 2014) is highlighted here to show the pathophysiological relevance of ion channels in both electrical and structural heart disease.

Sinus node dysfunction and biventricular non-compaction cardiomyopathy (NCCM) were diagnosed in a German family with an autosomal-dominant inheritance pattern. Sequencing revealed a novel hyperpolarization-activated cyclic nucleotide channel 4 (HCN4)-G482R mutation (Schweizer et al. 2014). HCN4, known to importantly contribute to cardiac pace-making, is expressed mainly in the sinoatrial node and the conduction system in the adult heart. Abundant expression of HCN4 throughout cardiac development suggests a putative contribution of this channel to signaling pathways involved in myocardial compaction (Fig. 5). Furthermore, “loss-of-function” mutations in HCN4 were also associated with atrial fibrillation and dilation of the aorta ascending (Duhme et al. 2013, Vermeer et al. 2016), supporting the view that ion channel mutations often do not solely show arrhythmic symptoms but contribute to complex electrical and structural phenotypes (Akhirome and Jay, 2015).

Impact of ion channels on HF therapy

Treatment of arrhythmias in HF

Arrhythmias contribute to significant morbidity and mortality in HF patients. Treatment of ventricular arrhythmias can be

performed by diminishing potential causing factors as electrolyte imbalances and treatment of newly acquired ischemia by coronary interventions. Furthermore, acute ventricular arrhythmias can be terminated by electrical therapy, either cardioversion or defibrillation, and antiarrhythmic therapy or ablation regimen depending on the patient's status.

Patients suffering from high risk for ventricular arrhythmias can be planned for primary prophylactic implantation of an implantable cardioverter-defibrillator (ICD) according to the guidelines (Al-Khatib et al. 2017). Patients that already survived a sudden cardiac death are protected as well with an ICD for secondary prophylaxis.

Antiarrhythmic therapy concepts are limited and mostly include the class III antiarrhythmic drug amiodarone and have to take into considerations each patient's individual risk profile.

Gene therapy for ion channel alterations in HF

Gene therapy has emerged as a powerful tool for targeting molecular mechanism implicated in heart failure. Refinements in vector technology, including the development of recombinant adeno-associated vectors, have allowed for safe, long-term, and efficient gene transfer to the myocardium. After success in animal models with mainly structural and calcium-handling-associated proteins as targets [junctophilin-2 (Reynolds et al. 2016) and S100A1 (Ritterhoff et al., 2015)] besides L-type Ca^{2+} current (Cingolani et al. 2007), first clinical trials in patients have already been started. However, after promising early-phase clinical trials, the more recent larger clinical trials targeting SERCA2 (CUPID gene therapy trial) (Greenberg et al. 2016)

Fig. 5 Spatial and temporal HCN4 activity. Schematic drawing of spatial and temporal expression pattern and activity of the cardiac pacemaker current HCN4 and possible explanation for the development of non-compaction cardiomyopathy. SAN sinoatrial node, C conus arteriosus, LA left atrium, LV left ventricle, RV right ventricle, RA right atrium, VCS ventricular conduction system [adapted with permission from Schweizer et al. 2014]

did not improve functional indices of heart failure. Unfortunately, transfection efficiency was not controlled in the study making it highly likely that transgene dosing and transfection rate were too low to provide beneficial effects and raise the need to re-evaluate vectors, delivery systems, targets, and endpoints (Hulot et al. 2016).

As new targets, ion channels also may play a major role despite major challenges that need to be faced. Individual cross-talk between ion channels, ion exchangers, and transporters has to be considered.

Conclusion

HF in general is a complex and heterogeneous disease in which various remodeling processes including changes in ion channel composition and function. Further basic research and clinical studies are needed to identify underlying molecular pathways of HF pathophysiology to provide the basis for improved patient care and individualized therapy based on individualized ion channel composition and remodeling.

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Compliance with ethical standards

Conflict of interest D.T. reports receiving lecture fees/honoraria from Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer Pharma, Sanofi-Aventis, St. Jude Medical, and ZOLL CMS, and research grant support from Daiichi Sankyo.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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