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Electrical Remodeling in the Failing Heart

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Abstract

Purpose of review—We focus on the molecular and cellular basis of excitability, conduction and electrical remodeling in the heart failure with dyssynchronous LV contraction (DHF) and its restoration by cardiac resynchronization therapy (CRT) using a canine tachy-pacing heart failure (HF) model.

Recent findings—The electrophysiological hallmark of cells and tissues isolated from failing hearts is prolongation of action potential duration (APD) and conduction slowing. In human studies and a number of animal models of HF, functional downregulation of K currents and alterations in depolarizing Na and Ca currents and transporters are demonstrated. Alterations in intercellular ion channels and matrix contribute to heterogeneity of APD and conduction slowing. The changes in cellular and tissue function are regionally heterogeneous particularly in the DHF. Furthermore, β -adrenergic signaling and modulation of ionic currents is blunted in HF.

CRT partially reversed the DHF-induced downregulation of K current and improved Na channel gating. CRT significantly improved Ca homeostasis especially in lateral myocytes, and restored the DHF-induced blunted β -adrenergic receptor responsiveness. CRT abbreviated DHF-induced prolongation of APD in the lateral myocytes and reduced the LV regional gradient of APD, and suppressed development of EADs.

Summary—CRT partially restores DHF-induced electrophysiological remodeling, abnormal Ca homeostasis, blunted β -adrenergic responsiveness and regional heterogeneity of APD, thus may suppress ventricular arrhythmias and contribute to the mortality benefit of CRT as well as improve mechanical performance of the heart.

Keywords

Ion channels; action potential; gene expression; heart failure; remodeling

Introduction

Heart failure (HF) is highly prevalent, accounting for more than 250,000 deaths annually in the US. The incidence and prevalence has continued to increase with the aging of the US population [1]. Despite remarkable improvements in medical therapy the prognosis of patients with myocardial failure remains poor with almost 20% of patients dying within one year of initial diagnosis and greater than 80% eight-year mortality. Of the deaths in patients with HF, up to 50% are sudden and unexpected; indeed, patients with HF have 6–9 times the rate of sudden cardiac death of the general population [1].

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HF is associated with anatomic and functional remodeling of cardiac tissues in both animal models and humans, which alters cardiac electrophysiology. Indeed, abnormalities of atrial and ventricular electrophysiology in diseased human hearts have been recognized for over four decades. Remodeling of myocyte electrophysiology in HF is well described, recent data suggests that the pattern of electrical and mechanical activation may influence this remodeling.

Prolongation of APD and development of EADs

The hallmark of cells and tissues isolated from failing hearts independent of the etiology is action potential (AP) prolongation [2–8]. The AP reflects a delicate balance between the activity of several depolarizing and repolarizing ionic currents, transporters, and exchangers, which are not uniformly expressed in the ventricular wall (Figure 1). The prolongation of AP in HF is heterogeneous, exaggerating the physiological inhomogeneity of electrical properties in the failing heart.[3,9] The AP prolongation in HF is highly arrhythmogenic with frequent early afterdepolarizations (EADs) that are not observed in ventricular myocytes isolated from control hearts.

K⁺ current remodeling

K⁺ current down regulation is a regular finding in the failing heart. The detailed changes in currents and channels vary with the model of HF; however, the consistent effect is the generation of heterogeneous prolongation of APD.

Transient outward K⁺ current (I_{to})

Although expressed cardiac K⁺ channels vary in different species. The transient outward potassium current (I_{to}) down regulation is the most consistent ionic current change in failing hearts [2,4,5,7,10]. Since, I_{to} is an early transient current; it may not directly affect the ventricular action potential duration (APD) in large mammalian hearts as it does in rodent ventricle. Interestingly, down-regulation of I_{to} in cells isolated from terminally failing human hearts is not associated with a change in its voltage dependence or kinetics [2]. The molecular mechanism of I_{to} down-regulation in HF is likely to be multifactorial. Reduced steady-state levels of Kv4 mRNA are highly correlated with functional down-regulation of I_{to} in human HF [5,10–13]. In a canine model, tachycardia down regulates I_{to} expression, with the Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) and calcineurin/NFAT systems playing key Ca²⁺-sensing and signal-transducing roles in rate-dependent I_{to} control.[14]

Inward rectifier K⁺ current (I_{K1})

Reduced inward I_{K1} density in HF may contribute to prolongation of APD and enhanced susceptibility to spontaneous membrane depolarizations including delayed afterdepolarizations (DADs) [6,9,15,16] Changes in I_{K1} functional expression are more variable than I_{to}, and controversial. Even within the same experimental model of HF induction (e.g. pacing-tachycardia), inconsistencies have been observed across species: reduced I_{K1} density in canine [4,9] but no change in rabbit [17]. In terminal human HF, I_{K1} is significantly reduced at negative voltages,[2] but the underlying basis for such down-regulation appears to be post-transcriptional in light of the absence of changes in the steady-state level of Kir2.1 mRNA. [5]

The molecular basis of I_{K1} down regulation in HF remains controversial without consistent changes in the expression of Kir2 family of genes. Even the specific subunit(s) that underlie I_{K1} vary as function of species and cardiac chamber, although Kir2.1 and 2.2 knockout [18] and Kir2.1 dominant negative over expressing mice [19] exhibit prolonged APDs.

Delayed rectifier K currents (I_{Kr} and I_{Ks})

The delayed rectifier K^+ currents play a prominent role in the late phase of repolarization, [20] therefore changes in either the slow (I_{Ks}) or fast (I_{Kr}) activating components of this current could contribute significantly to AP prolongation in HF. Reduced I_K density, slower activation, and faster deactivation kinetics have been observed in hypertrophied feline ventricles.[21] Down regulation of both I_{Kr} and I_{Ks} have been reported in a rabbit model of rapid ventricular pacing HF,[7] whereas I_{Ks} but not I_{Kr} was down regulated in all layers of the left ventricular myocardium in a canine model of same tachy-pacing HF.[9] The molecular basis for I_K down regulation in HF remains uncertain. We recently measured mRNA levels of the genes encoding the α subunits for the rapidly (HERG) and slowly (KvLQT1) activating components of I_K in normal and failing canine hearts and found no statistical difference [5].

Ca^{2+} currents and Ca^{2+} transients

Altered Ca^{2+} homeostasis underlies abnormalities in excitation-contraction coupling and arrhythmic risk in HF. Intracellular $[Ca^{2+}]$ and the AP are intricately linked by a variety of Ca^{2+} -mediated cell surface channels and transporters such as I_{Ca-L} , I_K , Ca^{2+} -activated Cl^- current, and NCX. I_{Ca-L} density is unchanged or reduced in HF, the latter typically occurring in more advanced disease.[22] Remarkably in human HF baseline I_{Ca-L} density is consistently unchanged; [23] although single channel studies suggest a reduction in channel number with an increase in open probability perhaps due to altered phosphorylation or subunit composition. [24] The molecular bases of changes in the density of I_{Ca-L} are incompletely understood, subunit mRNA expression in HF is variable. [25] The complexity of the molecular Ca channel remodeling is highlighted by reports of isoform switching of both α_1C [26] and β subunits in the failing heart. [27]

The amplitude of the calcium transient (CaT) and its rate of decay are reduced in intact preparations and cells isolated from failing ventricles. [28] Systematic comparisons of the CaT profile and dynamics in cells isolated from different regions of the failing heart are limited. Sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a), its inhibitor phospholamban (PLN) and NCX are primary mediators of Ca^{2+} removal from the cytoplasm. In HF, ventricular myocytes exhibit a greater reliance on NCX for removal of Ca^{2+} from the cytosol and an increase in NCX function,[29] which leads to defective SR Ca^{2+} loading.[30] Altered NCX function in HF significantly influences CaT and AP dynamics.[31] SR Ca^{2+} release is also defective in the failing heart and is associated with altered regulation of the ryanodine receptor (RyR).[32] Hyperphosphorylation of RyR by protein kinase A [33] or CaMKII [34] may increase diastolic Ca^{2+} leak and generate spontaneous Ca^{2+} waves underlying triggered arrhythmias in HF. The role of RyR regulation and gating in altered systolic function and arrhythmic risk in HF remains controversial [35–37]. Recently, increased inositol 1,4,5-trisphosphate receptors (InsP₃Rs) expression has been suggested to be a general mechanism that underlies remodeling of Ca^{2+} signaling during heart disease, and in particular, in triggering ventricular arrhythmia during hypertrophy.[38] On the other hand, CaMKII δ contributes to cardiac decompensation by enhancing RyR2-mediated SR Ca^{2+} leak and that attenuating CaMKII δ activation can limit the progression to heart failure.[39] The HF-related alterations in RyR2 function mimic the changes caused by posttranslational modification by reactive oxygen species, thus redox modification of RyR may contribute to SR Ca^{2+} leak in chronic HF.[40]

Na^+ channel and late I_{Na}

Studies of I_{Na} in a canine infarct model of HF revealed a significant down regulation of the current, an acceleration of its inactivation properties, and a slowing of its recovery from inactivation in myocytes isolated from the infarct border zone.[41] Normal impulse formation and conduction depend on the fast inward I_{Na} . Also, an increase in the late component of Na

current (late I_{Na}) can markedly prolong APD and promote polymorphic VT. Therefore, changes in I_{Na} density and kinetics may predispose to arrhythmias either by disrupting conduction and/or prolonging repolarization.

In a canine model of ischemic HF, significant down-regulation of I_{Na} , acceleration of its inactivation properties, and slowing of its recovery from inactivation were observed.[41] a significant increase in the late I_{Na} was demonstrated in human and canine HF.[42] [43] A recent study has shown that intracellular Ca^{2+} CaMKII signaling increases late I_{Na} by slowing inactivation kinetics and shifting steady state inactivation.[44] [45] Changes in I_{Na} are likely to depend on the specific disease etiology, and may have profound implications for arrhythmogenesis given the relative abundance and importance of this current to wavefront propagation.

Conduction and connexin remodeling in HF

Slowed intraventricular conduction is a prominent feature of HF and is associated with a reduction in the density, altered distribution and post-translational modification of the major cardiac gap junction protein (connexin 43, Cx43).[46] Similar findings have been observed in hypertrophied and ischemic human ventricular myocardium, Cx43 is down regulated and redistributed from the intercalated disk to the entire cell border (lateralization) [47–49], a pattern observed in early cardiac development. We observed down regulation and lateralization of Cx43 in HF[46] that is progressive with duration of tachypacing[50] and associated with conduction slowing. The mechanism of Cx43 down regulation is not completely understood but may involve altered rennin-angiotensin signaling [51,52] changes in binding partners [53,54] or altered membrane domain localization [55]. In the pacing tachycardia HF, Cx43 down regulation is associated with a reduction in Cx43 mRNA.

DHF and the effect of CRT on electrical remodeling

In HF with dyssynchronous contraction (DHF), bi-ventricular pacing referred to as CRT improves symptoms and reduces mortality in subsets of patients,[56] CRT is widely applied in patients with DHF, but the electrophysiological consequences of CRT are not well understood.

Clinical Effects of CRT

Is CRT pro-arrhythmic or anti-arrhythmic? Soon after starting bi-ventricular pacing, QT prolongation and development of Torsades de pointes, the arrhythmia characteristic of the long QT syndrome, has been reported [57]. LV epicardial pacing further increased QTc and JTc intervals compared to Bi-V pacing.[58] In an acute study using a canine wedge preparation, reversal of activation by the epicardial pacing compared to the endocardial pacing increased QT, JT interval and transmural dispersion of repolarization, creating the substrate for TdP under LQT condition.[59] In patients with advanced HF and a prolonged QRS interval, CRT decreases the combined risk of death from any cause or first hospitalization and, when combined with an ICD, significantly reduces mortality.[60] On the other hand, in patients treated with CRT defibrillators, ventricular arrhythmias were reduced during the initial 12 months after implant.[61,62]

CRT and regional effects on APs and ionic currents

AP prolongation in DHF is most prominent in cells isolated from the late-activated lateral LV wall. CRT significantly shortens the AP in lateral myocytes and reduces the LV regional heterogeneity in APD (Figure 2).[12] AP prolongation in DHF is highly arrhythmogenic with frequent early afterdepolarizations (EADs) that were not observed in myocytes isolated from

control hearts. CRT dramatically reduces the frequency of EADs in cells isolated from both the anterior and lateral LV.

The mechanisms of regional AP remodeling in the DHF and CRT are controversial. At the molecular level, tumor necrosis factor- α (TNF- α) and CaMKII were increased in DHF prominently in the lateral wall and these differences were absent in CRT.[63] TNF- α decreases I_{to} and prolongs the APD in rat ventricular myocytes.[64] Recently, Xie *et al.* suggested an increased oxidative stress in HF induced CaMKII activation and triggers of ventricular arrhythmias. [65] CaMKII influences Ca^{2+} current, SR function,[66,67] and increases persistent Na^{+} current [44,45] resulting in prolongation of APD.[68] It is possible and indeed likely, that other regional alterations in Ca^{2+} handling or increased persistent Na^{+} current contribute to regional differences in the APD and AP profile in DHF, and the regionally-specific effects of bi-ventricular pacing on this phenotype.

K^{+} current changes associated with CRT are variable. The down regulation of I_{to} is regionally uniform in the left ventricle in DHF and is unique among regulated K^{+} currents in HF in that it is *not* reversed by CRT. In parallel, Kv4.3 and KChIP2 mRNA and protein expression are down regulated in DHF without restoration by CRT.[12] CRT even in the setting of continued HF partially restores I_{K1} density and decreases membrane resistance and in the setting of improved Ca^{2+} handling in CRT may reduce the frequency of arrhythmogenic DADs. Kir2.1 mRNA and protein levels are partially restored by CRT in the canine model; suggesting that different mechanisms of regulation of current are operative in some animal models and human HF. CRT partially restores DHF-induced downregulation of I_K density in both anterior and lateral LV myocytes without a significant change in mRNA or protein levels of KvLQT1 or minK compared with DHF, whereas ERG mRNA level was restored by CRT in either the anterior or lateral LV wall.[12]

CRT restores Ca current and handling

In DHF there are intraventricular regional changes in I_{Ca-L} that are partially restored by CRT [12]. DHF produced a reduction peak I_{Ca-L} density and slowed current decay in myocytes isolated from the late-activated lateral LV wall. In contrast, peak I_{Ca-L} density in anterior myocytes was increased compared with non-failing controls, thus DHF produced regional heterogeneity of Ca^{2+} current density and kinetics. CRT restored the peak current density but did not alter the I_{Ca-L} decay in the lateral cells, eliminating the anterior-lateral I_{Ca-L} density gradient. Neither DHF nor CRT exhibit consistent changes in Ca^{2+} channel subunit mRNA or protein levels.

In canine pacing DHF, CaT amplitudes are depressed and kinetics slowed particularly in cells isolated from the late-activated lateral LV myocardium and partially restored by CRT (Figure 2)[12]. In DHF, mRNA and protein levels of SERCA2a, PLN and RyR2 were down regulated and NCX up regulated *without* a change in CRT. There were also no regional differences in mRNA and protein expression in any of these mediators of Ca^{2+} handling in DHF and CRT, suggesting that the global and regional differences of Ca^{2+} handling function in DHF and its restoration by CRT are post translational.

The mechanisms underlying the differences in regional remodeling of K^{+} currents and Ca^{2+} handling in DHF remain obscure. Plotnikov et al. reported that cardiac dyssynchrony by left ventricular pacing (120–150 bpm for 3 weeks) produced a slower decay of I_{Ca} inactivation [69] consistent with our results. Moreover, this phenomenon was suppressed by a β -adrenergic blockade. These findings suggest that DHF-induced changes of I_{Ca} inactivation kinetics might be mediated by regionally heterogeneous β -adrenergic receptor stimulation. Furthermore, the Ca^{2+} -handling proteins are functionally regulated by phosphorylation, prominently by key

intracellular enzymes protein kinase A and CaMKII,[66,67,70] and a variety of phosphatases which may be regionally regulated.[63]

Reduced β -adrenergic receptor (β -AR) function is a key feature of HF. CRT restores the DHF-induced baseline reduction of $I_{Ca,L}$ and the blunted response to β -adrenergic ($\beta_1 \gg \beta_2$) receptor stimulation. Moreover, CRT improves baseline Ca^{2+} handling and its adrenergic responsiveness, which may contribute to improvement in contractility and altered arrhythmia susceptibility. [71] And, these electrophysiological data is consistent to our previous molecular results that CRT increased β_1/β_2 -AR ratio. [72]

Gene Expression changes by CRT

We have described regional changes in signaling and protein expression in DHF, notably in stress-response kinases and cytokines with enhanced levels in the late-activated, lateral wall [46,63,73]. In some instances CRT can reverse these changes and produce salutary effects on overall LV function [63]. In order to better understand the breadth of signaling changes we have studied transcriptomic changes in DHF and CRT.[74] In these studies we demonstrated that genes in mitochondrial energetic pathways are similarly over represented in the lists of down regulated genes in the failing LV. In contrast, genes localized in nucleus and related to transcriptional regulation are over represented in the genes up regulated in failing LV.

In a microarray study comparing intraventricular changes in gene expression in DHF and CRT, we found that dyssynchrony-induced changes in gene expression were more pronounced in the anterior compared with the lateral LV. The genes that exhibited regional heterogeneity with dyssynchrony are involved in critical cellular processes such as metabolic pathways, extracellular matrix remodeling, and myocardial stress responses. Remarkably, dyssynchrony-induced regional expression changes were reversed to levels in normal hearts by CRT, with prominent reversal of dysregulation of expression of transcripts with metabolic and cell signaling function [75].

Conclusions

Electrophysiological remodeling of the failing heart involves changes in both active membrane properties of heart cells and network attributes of the myocardium. The pattern of electrical activation and mechanical contraction impact the cellular and tissue physiology and all seem to exaggerate the normal heterogeneity of electrophysiological properties of the heart when it is failing. The remodeling poses unique and complex challenges to the treatment of arrhythmias in the failing heart. Studies of antiarrhythmic therapy have targeted ion channels and the cardiac AP as well as changes in the cardiac interstitium with variable success. CRT alters electrical activation of the failing heart that exhibits intraventricular conduction delays and resynchronizes mechanical contraction. CRT undoubtedly benefits some patients, improving symptoms of HF and reduces sudden death when implemented with defibrillator therapy. The reversal of the exaggerated electrophysiological heterogeneity of the failing heart would suggest that CRT is antiarrhythmic, however this has yet to be demonstrated clinically.

Acknowledgments

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Ionic Basis for Altered Ventricular AP by Heart Failure

Figure 1.

Schematic of inward and outward ionic currents, pumps, and exchangers, which inscribe the mammalian ventricular action potential. A schematic of the time course of each current is shown (left), and the gene product that underlies the current is indicated (right).

Figure 2. Regional heterogeneity of action potential (AP) and Ca transient (CaT) in DHF and its restoration by CRT. CRT abbreviates DHF-induced prolongation of APD and restores amplitude and decay of CaT in the lateral cells, thus reduced regional heterogeneity of repolarization and Ca handling.