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Revisiting K⁺ channel-dependent electrical remodeling in the border zone

Jerry Curran¹ and Peter J. Mohler^{1,2,3}

¹The Ohio State University Wexner Medical Center, The Dorothy M. Davis Heart & Lung Research Institute, Columbus, OH

²Department of Internal Medicine, Columbus, OH

³Department of Physiology and Cell Biology, Columbus, OH

It is estimated that nearly seven million individuals within the United States are currently diagnosed with heart failure (HF).¹ One in nine deaths in the United States is directly related to HF. Despite great advances in both HF diagnostics and therapies, the 5-year mortality rate is approximately 50%.¹ HF is a multifactorial disease state with neither one singular cause, nor one singular progression path. The symptoms of HF can be subtle and practically unnoticeable, or they can be severe as dementia or complete incapacitation.

In both humans and animal models, HF is inextricably linked with structural and electrical remodeling of the heart. This remodeling is an adaptive response to maintain cardiac output following insult or injury to the heart. The most common trigger for remodeling is the myocardial infarct (MI). Large tracts of previously functional myocardium are damaged or destroyed ensuing from ischemia and necrosis and are eventually replaced by scar tissue (primarily non-contractile fibrotic tissue). Ultimately, the overall contractile force of the heart is diminished, and the remaining healthy muscle must strengthen (hypertrophy) and electrically remodel in order to compensate for this loss.

Electrophysiological changes in the myocardium (both atrial and ventricular) have been observed in HF and hypertrophy for well over 40 years. Slowed conduction and prolongation of the action potential (AP) are characteristics of HF in both the clinical and research setting.²⁻⁵ Conduction slowing is thought to be the result of reductions in the expression, subcellular localization, and post-translational modifications of connexin 43, a major cardiac gap junction protein,⁶⁻⁹ while the lengthening of the AP is the complex manifestation of overall changes in the expression and/or function of the various membrane ion channels, transporters, and exchangers expressed in the heart. These proteins mediate depolarizing and repolarizing currents that regulate AP duration and morphology.

Increases in the late Na current (I_{Na}) and Na/Ca exchanger-mediated current (I_{NCX}) are observed in failing and hypertrophied hearts.¹⁰⁻¹³ Both mediate inward depolarizing currents, and therefore increases in either would be expected to prolong the AP. However,

the changes in these proteins are relatively modest and by themselves would only account for a slight increase in AP duration. In fact, it is the reduction in K^+ current (I_K) density that largely accounts for AP prolongation in HF. The outward whole cell I_K is mediated by a numerous K^+ channels, each with varying biophysical properties expertly reviewed elsewhere.^{14, 15} These K^+ channels pull against the depolarizing effect of inward currents and are largely responsible for repolarizing the membrane following the initiation of an AP. Therefore, loss of these channels may prolong the AP as the inward depolarizing current would be less opposed. In HF, numerous K^+ -mediated currents are down-regulated. For example, I_{to} , I_{K1} , I_{Kr} , and I_{Ks} are all diminished in human HF and animal models of HF.^{2, 16, 17} The combination of the prolonged AP duration and the lack of repolarization reserve, resulting from the loss of I_K density, greatly increases propensity for arrhythmogenic early afterdepolarizations (EADs) and subsequent ventricular fibrillation or death. Interestingly, contrasting other K^+ channels, it was recently reported that the small-conductance calcium-activated potassium current (I_{KAS}) is up-regulated in the ventricles of end stage failing human hearts, where they are normally expressed at extremely low or non-existent levels.¹⁸ This increase may in part maintain repolarization reserve and promote well-ordered ventricular repolarization in HF patients.

In this issue of *The Journal of Cardiovascular Electrophysiology*, Lee *et al.* report that the AP duration in the peri-infarct zone (PZ) and remote zone (RZ) was significantly shorter in a rabbit model of MI.¹⁹ Using a pharmacological approach, the authors demonstrate that this decrease in APD is I_{KAS} -dependent. This increase in I_{KAS} was particularly pronounced in the PZ. Notably, this is the first study to report that MI results in an increase in I_{KAS} . The PZ has long been recognized to undergo acute electrical remodeling after MI and is considered a hot spot for arrhythmogenic activity post-MI. Both early- and delayed afterdepolarizations (EADs and DADs) may originate from the PZ depending on the extent and duration of the remodeling process.⁵ DADs are triggered by spontaneous Ca release events from the sarcoplasmic reticulum (SR) in the form of diastolic SR Ca leak or spontaneous Ca waves.²⁰⁻²² These spontaneous Ca waves manifest themselves under conditions of cellular Ca overload. It is interesting to speculate that in the infarcted heart, and particularly within the PZ, any electrical remodeling that decreases the AP duration is actually a cardioprotective mechanism. Decreasing the AP duration would limit the amount of Ca entering the cell, thus attenuating Ca overload and arrhythmogenesis. Feeding this speculation further, I_{KAS} channels are Ca-activated, which ideally suits them to respond to Ca overload and blunt this response. The exciting new work of Lee *et al.* appears to support this hypothesis directly. In fact, the authors show that in the infarcted heart the duration of the $[Ca]_i$ transient is significantly shorter when compared with healthy hearts. When the I_{KAS} blocker, apamin, is applied both the APD and $[Ca]_i$ transient duration are shifted back to those observed in healthy hearts. These data directly implicate I_{KAS} in the electrical remodeling of the myocardium post-MI.

However, as the authors appropriately point out, this potential cardioprotective mechanism is not without its complications. A shortening of the APD that relies on I_{KAS} , while protecting against Ca overload at rest, may actually increase myocardial susceptibility to a reentry circuit during rapid pacing. Tachypacing causes Ca to accumulate in the cytosol

leading to increased Ca-dependent activation of I_{KAS} . The resultant shortening of the AP would place the myocardium at higher risk for ventricular fibrillation (VF) especially in the presence of an MI-induced scar. This mechanism has been well-characterized in animal models of HF, and ventricles from failing human hearts exhibit increased I_{KAS} .^{23,24} Lee *et al.* observe a more pronounced effect of I_{KAS} -dependent shortening of the APD during rapid pacing. However, they did not observe an increase of VF under the same conditions. This highlights the complex nature of electrical remodeling after MI. Undoubtedly, other ion channels, transporters, and exchangers are also changing their expression and/or function in this model; these changes could conspire to be antiarrhythmogenic and resist any proarrhythmic effect resulting from increased I_{KAS} . It is important to note that the rabbits used in the study by Lee *et al.* did not yet show signs of overt HF even though the average MI size was 25% of the left ventricle. This suggests that remodeling in these rabbits—both structural and electrical—was incomplete. This leaves open the interesting hypothesis that I_{KAS} remodeling occurs acutely after MI and is cardioprotective during this phase.

There are obvious clinical implications in these findings. Potassium channel blockers have been utilized as therapies for arrhythmia. The compensatory increase of I_{KAS} observed could offset the loss of other K^+ channels during remodeling and play a critical role in maintaining repolarization reserve. However, this same mechanism may lead to arrhythmogenesis (as noted above). These new data suggest that blockers can be both proarrhythmic and antiarrhythmic depending on disease progression. Furthermore, as the authors point out, these new data demonstrate that I_{KAS} is increased in diseased ventricles; therefore, I_{KAS} blockers should not be considered as atrial-specific antiarrhythmic agent.

This study raises important new questions. It focused on one time point for the measurement of I_{KAS} in MI. While outside the scope of this particular study, the design leaves open the possibility for differential I_{KAS} -dependent APD remodeling at further time points of disease progression. The new data imply that I_{KAS} -dependent remodeling had taken place and was maintained in myocardial tissue remote to the infarct zone as soon as 5 weeks post MI. Recent data demonstrate that the shortening of the AP (as observed here) was observed as early as 30 minutes post-MI but was completely normalized by day 60.²⁵ Taken together, these data suggest that the I_{KAS} effect on APD may be transitory, or that other changes in K^+ channel expression and function that develop with time tip the scales in favor of APD prolongation. The temporal regulation of individual K channel function post-MI is not well known and has important clinical implications.

Electrical remodeling is a broad term encompassing the myriad of changes in expression and function of numerous ion channels, transporters, and exchangers embedded in the membrane of cardiomyocytes during hypertrophy and HF. Understanding the role of each individual protein integrated into this response furthers our ability to effectively treat cardiac disease. Of the greater than 250,000 deaths attributed to HF each year in the U.S., approximately 50% of these are sudden and unanticipated.¹ This highlights the gaps in our knowledge of both the disease state and our treatment paradigms. The work of Lee *et al.* draws underscores how revisiting established models and asking simple, novel questions can lead to critical insights.

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References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics--2012 update: A report from the American heart association. *Circulation*. 2012; 125:e2–e220. [PubMed: 22179539]
2. Beuckelmann DJ, Nabauer M, Erdmann E. Alterations of K^+ currents in isolated human ventricular myocytes from patients with terminal heart failure. *Circulation research*. 1993; 73:379–385. [PubMed: 8330380]
3. Kaab S, Nuss HB, Chiamvimonvat N, O'Rourke B, Pak PH, Kass DA, Marban E, Tomaselli GF. Ionic mechanism of action potential prolongation in ventricular myocytes from dogs with pacing-induced heart failure. *Circulation research*. 1996; 78:262–273. [PubMed: 8575070]
4. Rose J, Armondas AA, Tian Y, DiSilvestre D, Burysek M, Halperin V, O'Rourke B, Kass DA, Marban E, Tomaselli GF. Molecular correlates of altered expression of potassium currents in failing rabbit myocardium. *American journal of physiology. Heart and circulatory physiology*. 2005; 288:H2077–2087. [PubMed: 15637125]
5. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: Heart failure, myocardial infarction, and atrial fibrillation. *Physiological reviews*. 2007; 87:425–456. [PubMed: 17429037]
6. Akar FG, Spragg DD, Tunin RS, Kass DA, Tomaselli GF. Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy. *Circulation research*. 2004; 95:717–725. [PubMed: 15345654]
7. Kalcheva N, Qu J, Sandeep N, Garcia L, Zhang J, Wang Z, Lampe PD, Suadicani SO, Spray DC, Fishman GI. Gap junction remodeling and cardiac arrhythmogenesis in a murine model of oculodentodigital dysplasia. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104:20512–20516. [PubMed: 18077386]
8. Kostin S, Dammer S, Hein S, Klovekorn WP, Bauer EP, Schaper J. Connexin 43 expression and distribution in compensated and decompensated cardiac hypertrophy in patients with aortic stenosis. *Cardiovascular research*. 2004; 62:426–436. [PubMed: 15094362]
9. Peters NS, Green CR, Poole-Wilson PA, Severs NJ. Reduced content of connexin43 gap junctions in ventricular myocardium from hypertrophied and ischemic human hearts. *Circulation*. 1993; 88:864–875. [PubMed: 8394786]
10. Valdivia CR, Chu WW, Pu J, Foell JD, Haworth RA, Wolff MR, Kamp TJ, Makielski JC. Increased late sodium current in myocytes from a canine heart failure model and from failing human heart. *Journal of molecular and cellular cardiology*. 2005; 38:475–483. [PubMed: 15733907]
11. Hobai IA, O'Rourke B. Decreased sarcoplasmic reticulum calcium content is responsible for defective excitation-contraction coupling in canine heart failure. *Circulation*. 2001; 103:1577–1584. [PubMed: 11257088]
12. Hobai IA, O'Rourke B. Enhanced Ca^{2+} -activated Na^+ - Ca^{2+} exchange activity in canine pacing-induced heart failure. *Circulation research*. 2000; 87:690–698. [PubMed: 11029405]
13. Armondas AA, Hobai IA, Tomaselli GF, Winslow RL, O'Rourke B. Role of sodium-calcium exchanger in modulating the action potential of ventricular myocytes from normal and failing hearts. *Circulation research*. 2003; 93:46–53. [PubMed: 12805237]
14. Tinker A, Harmer SC. K^+ channels in the heart: New insights and therapeutic implications. *Expert review of clinical pharmacology*. 2010; 3:305–319. [PubMed: 22111612]

15. Jan LY, Jan YN. Structural elements involved in specific k⁺ channel functions. Annual review of physiology. 1992; 54:537–555.
16. Kaab S, Dixon J, Duc J, Ashen D, Nabauer M, Beuckelmann DJ, Steinbeck G, McKinnon D, Tomaselli GF. Molecular basis of transient outward potassium current downregulation in human heart failure: A decrease in kv4.3 mrna correlates with a reduction in current density. Circulation. 1998; 98:1383–1393. [PubMed: 9760292]
17. Tsuji Y, Zicha S, Qi XY, Kodama I, Nattel S. Potassium channel subunit remodeling in rabbits exposed to long-term bradycardia or tachycardia: Discrete arrhythmogenic consequences related to differential delayed-rectifier changes. Circulation. 2006; 113:345–355. [PubMed: 16432066]
18. Chang PC, Turker I, Lopshire JC, Masroor S, Nguyen BL, Tao W, Rubart M, Chen PS, Chen Z, Ai T. Heterogeneous upregulation of apamin-sensitive potassium currents in failing human ventricles. Journal of the American Heart Association. 2013; 2:e004713. [PubMed: 23525437]
19. Young SL, Chang PC, Hsueh CH, Maruyama M, Park HW, Rhee KS, Hsieh YC, Shen C, Weiss JN, Chen Z, Lin SF, Chen PS. Apamin-sensitive calcium-activated potassium currents in rabbit ventricles with chronic myocardial infarction. J Cardiovasc Electrophysiol. Accepted manuscript online: 7 MAY 2013 06:36AM EST | DOI: 10.1111/jce.12176.
20. Curran J, Brown KH, Santiago DJ, Pogwizd S, Bers DM, Shannon TR. Spontaneous ca waves in ventricular myocytes from failing hearts depend on ca(2+)-calmodulin-dependent protein kinase ii. Journal of molecular and cellular cardiology. 2010; 49:25–32. [PubMed: 20353795]
21. Bers DM, Pogwizd SM, Schlotthauer K. Upregulated na/ca exchange is involved in both contractile dysfunction and arrhythmogenesis in heart failure. Basic research in cardiology. 2002; 97(Suppl 1):I36–42. [PubMed: 12479232]
22. Schlotthauer K, Bers DM. Sarcoplasmic reticulum ca(2+) release causes myocyte depolarization. Underlying mechanism and threshold for triggered action potentials. Circulation research. 2000; 87:774–780. [PubMed: 11055981]
23. Chua SK, Chang PC, Maruyama M, Turker I, Shinohara T, Shen MJ, Chen Z, Shen C, Rubart-von der Lohe M, Lopshire JC, Ogawa M, Weiss JN, Lin SF, Ai T, Chen PS. Small-conductance calcium-activated potassium channel and recurrent ventricular fibrillation in failing rabbit ventricles. Circulation research. 2011; 108:971–979. [PubMed: 21350217]
24. Ogawa M, Morita N, Tang L, Karagueuzian HS, Weiss JN, Lin SF, Chen PS. Mechanisms of recurrent ventricular fibrillation in a rabbit model of pacing-induced heart failure. Heart rhythm: the official journal of the Heart Rhythm Society. 2009; 6:784–792. [PubMed: 19467505]
25. Huang C, Bao M, Jiang H, Liu J, Yang B, Wang T. Differences in the changing trends of monophasic action potential duration and effective refractory period of the ventricular myocardium after myocardial infarction in vivo. Circulation journal: official journal of the Japanese Circulation Society. 2004; 68:1205–1209. [PubMed: 15564708]