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Authors

Morotti, Stefano
Grandi, Eleonora

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Quantitative systems models illuminate arrhythmia mechanisms in heart failure: Role of the Na^+-Ca^{2+}-Ca^{2+}/calmodulin-dependent protein kinase II-reactive oxygen species feedback

Stefano Morotti and

Department of Pharmacology, University of California Davis, Davis, CA, 95616, USA

Eleonora Grandi

Department of Pharmacology, University of California Davis, Davis, CA, 95616, USA

Abstract

Quantitative systems modeling aims to integrate knowledge in different research areas with models describing biological mechanisms and dynamics to gain a better understanding of complex clinical syndromes. Heart failure (HF) is a chronic complex cardiac disease that results from structural or functional disorders impairing the ability of the ventricle to fill with or eject blood. Highly interactive and dynamic changes in mechanical, structural, neurohumoral, metabolic, and electrophysiological properties collectively predispose the failing heart to cardiac arrhythmias, which are responsible for about a half of HF deaths. Multi-scale cardiac modeling and simulation integrates structural and functional data from HF experimental models and patients to improve our mechanistic understanding of this complex arrhythmia syndrome. In particular, it allows investigating how disease-induced remodeling alters the coupling of electrophysiology, Ca^{2+} and Na^+ handling, contraction, and energetics that lead to rhythm derangements. The Ca^{2+}/calmodulin dependent protein kinase II, which expression and activity are enhanced in HF, emerges as a critical hub that modulates the feedbacks between these various subsystems and promotes arrhythmogenesis.

Graphical/Visual Abstract and Caption

Correspondence to: Eleonora Grandi.

Stefano Morotti, ORCiD: 0000-0001-8679-665X
Eleonora Grandi, ORCiD: 0000-0002-4401-8857

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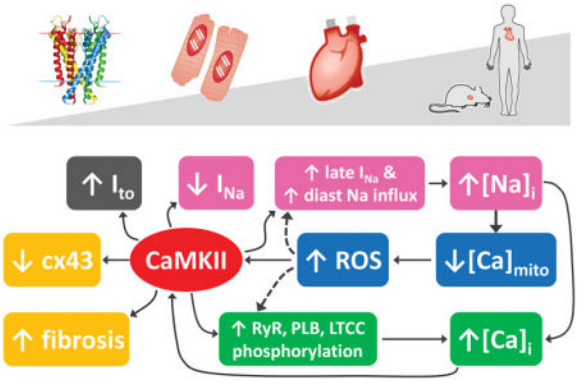

Structural and functional data integration via multi-scale quantitative cardiac modeling illuminates arrhythmia mechanisms in heart failure by investigating how disease-induced remodeling alters the coupling of electrophysiology, Ca^{2+} and Na^{+} handling, contractile function, and energetics.

Introduction

Complex systems interplay in heart failure

Heart failure (HF) is a rapidly growing health problem in the US. The number of adults diagnosed with HF increased from about 5.7 million (2009–2012) to about 6.5 million (2011–2014) and is projected to rise to more than 8 million people by 2030.[6] HF is a pathological state in which the heart is unable to pump blood at a rate commensurate with the requirements of metabolizing tissues, resulting in inadequate perfusion of tissues during exertion, or is able to do so only with an elevated diastolic filling pressure. HF biology involves multiple adaptive and maladaptive pathways that work on multiple biological scales to maintain end-organ perfusion. These include increase in the sympathetic drive, renin-angiotensin-aldosterone system (RAAS), and oxidative stress (Fig. 1, top).

While advances in high-throughput experimental approaches have allowed identifying and characterizing many individual actors in this multifaceted disease process, one major challenge is to mine this massive amount of information from high-throughput biological data to generate novel mechanistic insights in HF pathophysiology. Systems biology, enabled by multidisciplinary expertise from different fields, often including mathematics, physics, engineering, and computer science, allowed developing many tools and approaches to **(a)** integrate data in physiological networks; **(b)** reveal emergent mechanisms of disease; and **(c)** facilitate prediction and development of therapeutic intervention. These approaches apply a wide spectrum of mathematical formalisms and integrate multiple data types across interacting biochemical and biophysical functions and multi-scale models that are structurally integrated over physical scales (Fig. 1, bottom).

Alterations in cardiac electrophysiology, contractile function and their neurohormonal regulation, accompanied by ventricular hypertrophy and structural remodeling, all contribute to the HF phenotype (Fig. 1, top). Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) is upregulated and more active in HF,[1, 47, 58] and is a key regulator of cellular subsystems contributing to acute mechanical and electrical dysfunction as well as chronic cardiac

remodeling in HF. In the context of a complex cardiac disease like HF multiple signaling pathways are likely to be altered, many of which might crosstalk with CaMKII signaling. Among these, enhanced sympathetic activation is one of the most well characterized forms of neural remodeling in HF and has been clearly linked to ventricular arrhythmias in animal models and humans.[101] Altered CaMKII signaling has been associated to all major aspects of HF at various spatial and time scales, which makes this kinase an attractive candidate for therapy and the ideal center piece in our systems analysis. CaMKII phosphoregulates many proteins that are important in excitation-contraction (EC) coupling.[7, 75] Upregulated expression and activity of CaMKIIδ (the predominant cardiac isoform) is seen in human HF,[47] and cardiac-specific overexpression of CaMKIIδ_C leads to severe HF and arrhythmias in mice,[118, 136] whereas mice lacking CaMKIIδ develop ventricular hypertrophy following aortic banding, but do not decompensate into HF.[70] However, despite a growing body of work detailing the molecular, cellular and functional aspects of CaMKII-dependent remodeling, key questions remain to be addressed regarding the extent to which CaMKII upregulation itself can explain the individual alterations that contribute to HF, and whether there exist interaction and synergy among the plethora of downstream CaMKII effects and other signaling pathways.

Systems approach to understanding cardiac arrhythmia

Failing hearts are at increased risk of arrhythmias, accounting for half of HF deaths (the other half due to pump failure). While sinus node dysfunction and atrial fibrillation are commonly seen in HF (and associated with increased risk of stroke), ventricular tachyarrhythmia is the most common cause of death in HF patients, and is usually associated to disease-induced ionic and structural remodeling. Derangements in cardiac rhythms emerge from abnormalities in gene or protein expression or function, cell signaling pathways, cell-to-cell coupling, tissue heterogeneity that can promote or exacerbate cardiac disease. There are several challenges in the study of arrhythmia mechanism in HF that still preclude translation of basic research findings to the clinic. Model organisms (large mammals) are expensive, and, while genetically engineered mice are valuable because there are now many mouse models that recapitulate major clinical features of HF with specifically defined molecular triggers, electrophysiologic properties for mouse are quite different than human. Use of human preparations is complicated by procurement issues and confounding clinical variables, including comorbidities and pharmacological therapies. Patient-specific induced pluripotent stem cell-derived cardiomyocytes are a powerful option providing potentially unlimited supplies of human cardiomyocytes, but they have inherent limitations: **(a)** myocyte immaturity, **(b)** restricted to known genetic HF causes and **(c)** lack of adult patient hearts for myocyte and organ-level study. The wealth of multi-scale data on alterations in cell signaling, electrophysiology, Ca^{2+} handling, myofilament function and tissue structure that can be measured in the adult animal models cannot be obtained in humans, but integrative mathematical models provide a systematic framework to extrapolate findings in the mouse to the clinical setting. Here, we review recent advances in our comprehensive mechanistic understanding of arrhythmia in this complex clinical syndrome through mechanism-based mathematical models.

Arrhythmia mechanisms in HF: abnormalities in impulse formation and conduction

It is generally accepted that lethal ventricular arrhythmias occur when triggering events (e.g., ectopic foci) propagate in tissue as they encounter substrate for sustainability (e.g., reentrant loop). Premature ventricular contractions are prototypical triggers in the myocardium that are thought to emerge from cellular events known as early and delayed afterdepolarizations (EADs and DADs). DADs occur during diastole and arise from a transient inward current I_{ti} carried by the Na^+/Ca^{2+} exchanger (NCX), which is evoked by diastolic increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) due to abnormal spontaneous Ca^{2+} release (SCR) from the sarcoplasmic reticulum (SR) (Fig. 2, bottom left). In contrast, EADs initiate during action potential (AP) repolarization and involve complex dynamical interaction among the currents that are available late in the AP (Fig. 2, middle left). EADs occur predominantly at slow heart rates in the setting of reduced repolarization reserve and prolonged AP duration (APD) due to increased inward Ca^{2+} and Na^+ or decreased outward K^+ currents, but can also arise from Ca^{2+} handling abnormalities that activate depolarizing NCX current (I_{NCX}). Regardless the mechanism, in large mammals, the L-type Ca^{2+} current (I_{CaL}) eventually carries the majority of inward charge during the EAD upstroke – but recovery from inactivation and reactivation of the Na^+ current (I_{Na}) has been shown to lead to EAD takeoff in specific conditions (and species).[20, 84] Ectopic activity could also result from automatic firing, which occurs when an increase in time-dependent depolarizing inward currents carried by Na^+ or Ca^{2+} or a decrease in repolarizing outward K^+ currents cause progressive time-dependent cell depolarization. When threshold potential is reached, the cell fires, producing automatic activity (Fig. 2, top left).

Reentry can occur when an electrical impulse is able to re-excite areas that have already recovered, thereby providing a perpetuation of electrical activity. Reentry can be caused by a fixed anatomical obstacle (fibrosis), or be functional reentry, favored by spatially heterogeneous APD and conduction slowing (Fig. 2, right). For reentry to be sustained, all points in the reentrant path need to become excitable before the arrival of the reentrant impulse (termed ‘excitable gap’). When wavelength (i.e., the distance an impulse travels within a single refractory period) decreases due to shortening of the effective refractory period or due to conduction slowing, reentry will be more likely and more reentrant circuits can fit in the same area, making the arrhythmia more stable and less likely to terminate.

HF-induced changes alter both individual myocytes properties (e.g., ion channel dysfunction or expression remodeling) and cell-to-cell coupling, thus affecting impulse formation and propagation and enhancing both arrhythmia triggers and substrate.

Arrhythmia Triggers in HF

Triggered activity is facilitated by HF-induced modifications in ionic currents and intracellular Ca^{2+} dynamics. Dysregulation of Ca^{2+} handling is the most established cause of arrhythmias in failing myocytes, and it is due to the progressive change in the expression and function of many proteins involved in Ca^{2+} cycling. Compared to nonfailing ventricular myocytes, failing cells are characterized by reduced Ca^{2+} transient (CaT) amplitude and

enhanced SR Ca^{2+} leak, which are not only responsible for hypocontractility and impaired relaxation, but also for increased the propensity for EADs[121] and DADs[108] (Fig. 3).

CaMKII has been linked to the triggering of arrhythmias via both EADs and DADs.[5] CaMKII activation of ryanodine receptors (RyRs) enhances EC coupling[65] and increases SR Ca^{2+} leak, Ca^{2+} sparks and waves.[42] In HF, where NCX is upregulated and I_{K1} downregulated, these spontaneous SR Ca^{2+} release events are more likely to induce DADs.[96] CaMKII-dependent phosphorylation of L-type Ca^{2+} channels (LTCCs) enhances the influx of Ca^{2+} thereby fueling a positive feedback mechanism that enhances CaMKII activation, and mediates facilitation of I_{CaL},[8, 44] which in turn favors the development of EADs and modulates RyR fluxes.[43] All these effects are expected to be more pronounced during sympathetic stimulation, when protein kinase A (PKA)-dependent phosphorylation of LTCC, RyR and phospholamban (PLB) further enhances Ca^{2+} cycling[111] and thereby CaMKII activation. CaMKII-dependent phosphorylation also modulates the voltage-gated Na^+ channel (Na_V) kinetics similarly to a human mutation (SCN5A 1795InsD) associated with heritable arrhythmias.[118] CaMKII-dependent enhancement of late I_{Na} could contribute to increased propensity for EADs in HF[81] (Fig. 3).

CaMKII activity directly influences Na^+ homeostasis, another key regulator of EC coupling that is altered in HF.[38] It is well established that intracellular Na^+ concentration ($[Na^+]_i$) is increased in myocytes from failing hearts compared to nonfailing myocytes by 2–6 mM, but the precise mechanistic and quantitative aspects remain unclear.[38] Emerging evidence suggests that perturbed Na^+ homeostasis and CaMKII hyperactivity are closely interrelated, and critically involved in electrophysiological and mechanical dysfunction in HF.[46, 118, 132] Indeed, it has been suggested that CaMKII and enhanced late I_{Na} contribute to $[Na^+]_i$ elevation in HF, as CaMKIIδ_C-overexpressing mice with HF exhibit prominent late I_{Na} and have increased Na^+ content.[118] Cellular Na^+ loading might cause, via outward shift in I_{NCX}, excessive Ca^{2+} load, which is associated with a number of deleterious cellular consequences, including abnormalities in myocyte shortening, electrical instabilities, and metabolic imbalance.[38] It has been proposed that the $[Na^+]_i$-induced increase in Ca^{2+} further activates CaMKII, thus fueling a vicious cycle that favors spontaneous SR Ca^{2+} release and predisposes to Ca^{2+}-related arrhythmia (Fig. 3). We have confirmed and analyzed quantitatively the extent of this feedback in models of healthy and failing mouse myocytes.[82] Similar results were obtained with our model of the human atrial myocyte.[91] Nevertheless, further studies are required to assess the details and extent of such feedback in cells characterized by a more positive AP plateau (i.e., human ventricular myocytes). In such condition, increase in late I_{Na} would favor AP prolongation (and EAD formation), likely contributing to greater $[Na^+]_i$ loading.

Altered Na^+ homeostasis also impacts mitochondrial function. Increased $[Na^+]_i$ influences production of reactive oxygen species (ROS) by augmenting mitochondrial Ca^{2+} efflux via the mitochondrial NCX (mNCX) and thus reducing mitochondrial Ca^{2+} concentration ($[Ca^{2+}]_m$).[60, 73] Notably, higher oxidative stress may further exacerbate $[Na^+]_i$ loading by enhancing late I_{Na} through direct effects on $Na_V1.5$ or secondarily by activating CaMKII[21, 119] (Fig. 3). A direct link between oxidative stress and CaMKII-dependent arrhythmias has been suggested by computational studies investigating mechanisms of EAD

formation upon H_2O_2 administration [27, 124], which showed that phosphorylation of $Na_V1.5$ and LTCC (caused by ROS-dependent CaMKII activation) are both required in the generation of these EADs.

Oxidative phosphorylation is the main source of energy for metabolic/contractile works in cardiac myocytes. Mitochondria provide the ATP needed for contractile function and sarcoplasmic and sarcolemmal ion transport, which is responsible for the myocyte electrical activity. Coupling mitochondrial energetics to EC coupling models is therefore needed to investigate the key role of energetics in modulating myocyte mechanical activity and ion concentration gradients, especially during impaired metabolic states in pathological conditions, such as HF. Thus, it is surprising that only a few computational models have been developed to link mitochondrial activity to membrane electrophysiology and cytosolic Ca^{2+} handling, despite the large number of modeling studies investigating in detail mitochondrial energetics, Ca^{2+} handling, pH regulation and ROS production,[18, 31, 32, 55, 120] and mitochondrial oscillations and waves.[89, 130] Cortassa *et al.* integrated the description of mitochondrial energetics into a model of EC coupling to study the dynamic changes in ADP, NADH, and $[Ca^{2+}]_m$ induced by changes in pacing frequency.[17] Extensions of this model have been used to investigate the effect of ROS on AP dynamics during ischemia-reperfusion [137] mediated by the sarcolemmal ATP-sensitive K^+ (K_{ATP}) channels, and the interplay between of local Ca^{2+} and ROS signaling.[45] Recently, Li *et al.* developed a multi-scale model including a mitochondria-SR microdomain and simulating ROS-dependent modulation of RyR and SR Ca^{2+}-ATPase (SERCA).[66] Their simulations showed that elevated ROS production (as in disease) increases cytosolic Ca^{2+} by stimulating RyRs and inhibiting SERCA. Enhanced Ca^{2+} signal in turn activates I_{NCX}, Ca^{2+}-sensitive nonspecific cationic channels, and Ca^{2+}-induced Ca^{2+} release, indirectly affecting I_{CaL} and leading to abnormality in AP shape.

Oxidative stress plays an important role in the pathophysiology of cardiac remodeling and HF. ROS production is increased within the mitochondria from failing hearts,[60] and directly impairs myocyte function by modifying proteins central to EC coupling.[22] Not only does oxidative stress activate CaMKII directly,[22] but CaMKII-induced $[Na^+]_i$ loading can induce an increase in ROS[60] (Fig. 3). Studying the deleterious arrhythmogenic consequences of chronic CaMKII activation and oxidative stress is an important next step integrative modeling efforts should tackle.

Arrhythmia Substrates in HF

Development and progression of HF are accompanied by an extensive remodeling of the whole organ, which leads to maladaptive changes in the size of heart chambers and in the mechanical properties of the myocardium. Typical HF features are indeed hypertrophy, increased thickness of the ventricular wall, and abundance of fibrosis. These modifications initially occur as part of a compensatory mechanism in response to pathologic conditions like pressure or volume overload. Number and size of cardiomyocytes increase to accommodate the need of more mechanical work to maintain the cardiac output within the normal range. At the same time, the composition of the connective tissue changes increasing myocardium stiffness. Cardiac hypertrophy is regulated by an intricate web of signaling

pathways that influence myocyte growth, including those of CaMKII[61] and calcineurin/NFAT.[48, 80] Computational models of cardiomyocyte hypertrophic signaling networks have successfully been used to gain a quantitative understanding of the contributions of individual pathways and their interactions, and to predict which signaling nodes are most important for cardiomyocyte hypertrophy,[54, 102, 103] and apoptosis.[54] Other computational studies have instead investigated the factors responsible for cycling of specific mediators like IP3 and NFAT.[15, 16] Along the same lines, computational models have also begun to provide important insights into the development of fibrosis. The Saucerman group has developed a large-scale computational model of the cardiac fibroblast signaling network in order to identify the key drivers of differentiation in myofibroblast and extracellular matrix remodeling.[134] Extension of modeling approaches to account for longer time scales is an important step to gain a comprehensive understanding of HF pathophysiology.

Conduction defects

While a decrease in refractoriness seems critical to the development of sustained classical (especially atrial) tachyarrhythmia, reentrant substrate in HF has been rather associated to structural/anatomic abnormalities and conduction delay, whereas refractoriness is actually increased (due to APD prolongation). Thus, structural remodeling including hyperthrophy and enhanced interstitial fibrosis might play a dominant role in sustaining ventricular tachyarrhythmia in HF. However, HF-induced alterations in Na^+ and Ca^{2+} handling (possibly mediated by CaMKII) can functionally affect cell properties and tissue susceptibility to reentry. For example, King *et al.* recently highlighted novel arrhythmogenic consequences of abnormal Ca^{2+} handling resulting from catecholaminergic polymorphic ventricular tachycardia (CPVT) mutations, which may play a critical role in arrhythmia maintenance. Specifically, they found a reduced upstroke velocity of monophasic APs, inter-atrial conduction delays and slowed epicardial conduction velocity (CV) in structurally normal RyR2-P2328S hearts, which were more susceptible to atrial arrhythmia triggering than wild type hearts.[57] This strongly suggested that Ca^{2+}-dependent alterations in Na_Vs[56] may promote functional reentry also in other disease conditions, such as HF. The increased SR Ca^{2+} leak in CPVT mice may result in increased CaMKII activity, which is also enhanced during rapid paging[13] and can alter cardiac Na_V function. Indeed, CaMKII induces loss-of-function effects on peak I_{Na},[118] which can explain conduction slowing[40] independent of structural and anatomical changes (Fig. 3). Delaying recovery of Na_Vs from inactivation can increase the slope of the APD restitution curve and hence the likelihood of alternans and reentry,[99] and reducing Na_V conductance increases the vulnerable window.[123] Christensen *et al.* used a multicellular mathematical model of the cardiac fiber to demonstrate that enhanced CaMKII activity in the infarct border zone, due primarily to increased oxidation, and CaMKII effects on Na_Vs are associated with reduced CV, prolonged refractoriness, and increased susceptibility to formation of conduction block at the border zone margin, a prerequisite for reentry.[14] Heterogeneous Na^+ and Ca^{2+} loading in cardiac tissue can predispose to reentrant arrhythmia, as shown in both ventricular[128] and atrial simulations.[63] Ca^{2+}-dependent regulation of other ion channels/transporters may also affect CV and APD restitution. For example, Ca^{2+}-dependent inhibition of inward rectifier K^+ current (I_{K1}) has been suggested,[25] which could indirectly reduce I_{Na} availability by depolarizing the resting membrane potential (RMP).

Impaired cell-cell electrical coupling might also affect AP propagation and contribute to the formation of a reentrant substrate. Indeed, connexin43 (cx43), the principal gap-junctional protein in ventricular myocytes, is seen downregulated[2, 19] and heterogeneously distributed[9] in HF. Dysregulation of cx43 has been associated to reduced electrical coupling among cells, decreased CV, and increased propensity for arrhythmias[9, 95, 107] (Fig. 3). Interestingly, a recent study showed that both acute and chronic calmodulin/CaMKII inhibition improved conduction and enhanced localization of cx43 in the intercalated disc.[114]

Whether they are electrically coupled to myocytes[59] or only passive obstacles, myofibroblasts can alter AP propagation in cardiac tissue. The first model coupling a cardiomyocyte to an electrically active fibroblast predicted a depolarizing effect on myocyte MRP and AP shortening.[74] Jacquemet and Hernandez first described an opposite effect on APD (and a decrease in CV),[50] then determined that the different outcome depends on the fibroblast resting membrane potential, whereby lower resting potentials shorten the AP, while depolarized resting potentials prolong the AP.[51] Other computational investigations confirmed that, depending on the context, fibroblasts can differentially affect the electrical activity of myocytes by acting as a current source or sink,[76, 86, 104, 105, 126, 127] and increasing/decreasing arrhythmia risk.[76, 112] Investigating how different degrees of HF-induced remodeling affect vulnerability to reentry, Gomez *et al.* showed that, while a moderate amount of fibrosis and cellular uncoupling is sufficient to elicit reentrant activity, very high fibrotic content and/or very low conductivity hinder the development of reentry.[35]

Spatially heterogeneous APD and Ca^{2+} signal

Transmural dispersion of repolarization (DOR) and APD gradients are altered in HF.[4, 34, 71] Computational studies have shown that electrophysiological and structural HF-induced remodeling (including fibrosis and tissue heterogeneity) increases APD dispersion. For example, while a certain degree of transmural DOR is normal and may be attributed in part to differential expression of I_{to} (which is larger at the epicardial side), CaMKII-dependent upregulation of I_{to} shortens APDs in the epicardium but prolongs APDs in the endocardium (where I_{to} is small) thus amplifying transmural DOR[40] (Fig. 3). However, it has been proposed that heterogeneous remodeling modulates repolarization gradients and can even reduce transmural APD dispersion and APD gradients in HF *vs.* control.[36] Notably, HF enhances susceptibility to arrhythmogenic cardiac alternans,[62, 122] which amplifies electrical heterogeneities in the heart and has been closely associated with sudden cardiac death.

Subcellular heterogeneity in EC coupling and Ca^{2+} handling, either anatomical[3] or dynamically induced,[28, 29, 109, 125] is one very clear contributor to intracellular Ca^{2+} waves (and triggered activity) and Ca^{2+}-driven AP alternans in ventricular cells. Using a ventricular myocyte model with detailed spatiotemporal Ca^{2+} cycling, Nivala *et al.* demonstrated that t-tubular disruption contributes to dyssynchronous Ca^{2+} release and impaired contraction in HF.[90] Comparing results obtained with normal or downregulated SERCA, they also characterized different mechanisms responsible for the development of Ca^{2+} alternans at different stages of HF-induced remodeling. Studying a mouse model of congestive HF, Louch *et al.* observed regions of cells characterized by both slow Ca^{2+} sparks kinetics and slow CaT rise during the AP, suggesting a link between greater variability in spark kinetics

and dyssynchronous Ca^{2+} release in HF.[72] A computational analysis showed that alterations in Ca^{2+} sparks can be explained by rearrangement of RyRs within the Ca^{2+} release units, and excluded a direct role of t-tubule disruption.[72] In a later investigation, the same group showed that synchrony of Ca^{2+} release in HF is also determined by the interplay between RyR sensitivity and SR Ca^{2+} loading.[92]

Fibrosis also affects the formation of alternans. Xie *et al.* showed that fibroblast-myocyte coupling prolongs the myocyte refractory period, facilitating induction of reentry in cardiac tissue.[126] In a more detailed investigation, the same group also showed that such coupling generates a gap junction current that flows into the myocyte and is characterized by two main components: an early transient outward current and a background current present during the repolarizing phase. Depending on the relative prominence of the two, fibroblast-myocyte coupling can either prolong or shorten the AP, promoting or suppressing both voltage-driven and Ca^{2+}-driven alternans.[127]

It has also been shown that impairment of mitochondrial function adversely affects cardiac Ca^{2+} cycling leading to proarrhythmic Ca^{2+} alternans.[26] Investigating the mechanisms linking metabolic stress and membrane instabilities, Zhou *et al.* analyzed how oscillations in mitochondrial inner membrane potential ($\Delta\Psi_m$) affect electrical activity in tissue.[138] They showed that ROS-induced regional $\Delta\Psi_m$ loss activates K_{ATP} channels that cause regional AP shortening, leading to the formation of a metabolic sink. Propensity for reentry and fibrillation resulted increased because of the disparity in refractoriness inside and outside the sink.[138]

Source-sink

Synchronization mechanisms are required for EADs and DADs to overcome the robust protective effects of electrotonic source-sink mismatch (especially in well-coupled ventricular tissue) and trigger premature ventricular complexes. Structural and electrophysiological remodeling in HF decreases the number of cells displaying EADs or DADs that are required to trigger an arrhythmia in tissue, as elegantly demonstrated in ventricular tissue simulations.[129] Notably, whole-heart AP and Ca^{2+} optical mapping mimicking various HF-related conditions showed results for DADs that were in qualitative agreement with these modeling predictions.[85] In failing cardiac tissue, Lang *et al.* observed a higher than normal (*vs.* nonfailing cardiac tissue) number of myocytes that did not synchronize with neighboring myocytes, and these asynchronous myocytes also often exhibited independent spontaneous Ca^{2+} waves. While in normal well-coupled tissue asynchronous Ca^{2+} waves did not produce detectable depolarizations, poor electrical coupling between failing myocytes enabled local Ca^{2+}-induced inward current of sufficient source strength to overcome a weakened current sink to depolarize the membrane potential in the actual myocyte exhibiting the Ca^{2+} wave, and even depolarize nearby neighboring myocytes appreciably.[64]

Influence of mechanical dysfunction on electrophysiology and arrhythmia

Since the myofilaments dynamically and cooperatively buffer large amounts of cytosolic Ca^{2+},[11] developing computational models coupling myofilament contraction to Ca^{2+} cycling

and membrane electrophysiology is critical to study how HF-induced changes in ion channel and Ca^{2+} dynamically affect contraction, and quantifying how impaired myofilament function in HF feeds back into Ca^{2+} and AP dynamics.[10, 41, 77, 78, 88, 100] We have developed a model that describes electrophysiology, Ca^{2+} handling, myofilament activation and crossbridge (XB) cycling to understand the effects of β-adrenergic activation on cardiac mechanics in rabbit and mouse heart.[87, 113] We showed that distinct changes in myofilament Ca^{2+} sensitivity and XB cycling influence CaT and contraction responses to β-adrenergic stimulation, but the changes in Ca^{2+} buffering by the myofilaments have a limited impact on membrane currents and AP morphology in nonfailing ventricular myocytes.[87, 113] Zile and Trayanova simulated Ca^{2+} and mechanical remodeling in a coupled human electromechanical model and showed that HF-induced remodeling of mechanical parameters alters electrical, Ca^{2+} and mechanical alternans, and myofilament protein dynamics play an important role in EAD formation.[139, 140]

Myofilament contraction requires ATP, hence it is also important to combine energetics and contraction to understand how the heart adapts the rate of ATP production to energy demand (and HF-associated changes thereof), as for example done in.[131] Tewari *et al.* built a multi-scale model linking myofilament energetics to whole-body cardiovascular function[116] and demonstrated that metabolic dysfunction in HF directly impairs myofilament contractile function and, consequently, systolic function.

The expression of ion channels sensitive to mechanical load (in particular to changes in cell strain or volume) creates a feedback mechanism (called mechano-electric feedback) that directly affects the membrane electrical activity. Acting like mechanoreceptors, these channels contribute to the regulation of the cardiac function that has to continuously adapt to the mechanical load. Despite the fact that a large numbers of channels are modulated by mechanical stress,[94] modeling studies have primarily focused on stretch-activated channels (SACs), shown to be involved in the generation of arrhythmias induced by mechanical stimulation,[30, 67] and in the termination of arrhythmias by precordial thump.[68] Recruitment of SACs has also been shown to play a role in the regulation of scroll waves that underlie reentrant arrhythmias,[49] though a more recent study showed that both SAC activation and stretch-induced Ca^{2+} release from myofilaments are associated to triggered propagating contractions, and that both phenomena are required to significantly perturb the AP.[117]

Using a cell-in-gel system that imposes an afterload during cardiomyocyte contraction, Jian *et al.* found that nitric oxide synthase (NOS) was involved in transducing mechanical load to potentiate CaTs and Ca^{2+} sparks.[52] Stretch on ventricular cardiomyocytes during diastole also evokes changes in Ca^{2+} cycling via enhanced X-ROS signaling due to activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2).[97, 98] Elevated ROS directly increases RyR open probability and facilitates the formation of Ca^{2+} sparks and arrhythmogenic waves.[97] By modeling compartmentalized ROS signaling and ROS-dependent modulation of RyR gating, Limbu *et al.* analyzed the role of X-ROS signaling in Ca^{2+} cycling regulation and arrhythmogenesis.[69] They showed that, upon stretch, ROS levels in the dyadic space can be about an order of magnitude higher than the global ROS signal, suggesting the need of a better characterization of ROS signaling compartmentalization. They showed that X-ROS signaling can improve EC coupling in

physiological conditions (by enhancing CaT amplitude), but that can also increase the propensity for arrhythmias in response to oxidative stress.

Cardiomyocytes express also mechano-sensitive proteins that are not directly involved in the regulation of membrane potential or Ca^{2+} handling, but are instead responsible for signaling cascades associated to pathological remodeling and hypertrophy. Tan *et al.* developed a network model of cardiac mechano-signaling to identify the key sensors involved in the stretch-induced hypertrophic response.[115] This large-scale model integrates results from many published studies into one coherent platform that allows the identification of emerging behaviors and crosstalk mechanisms that could not be seen analyzing isolated pathways. The analysis revealed that cooperation between different pathways is necessary to cause growth and remodeling, suggesting potential targets for pharmacological treatment against HF.

Conclusion

Development of computational frameworks for simulation of cardiac electromechanical activity has improved our comprehensive understanding of complex cardiac arrhythmias, such as those occurring in HF patients. By integrating data describing different cell functions (membrane electrophysiology, intracellular signaling, contraction, and metabolism) in different time and spatial scale, these models allow for identification of emergent mechanisms and can potentially facilitate the development of therapeutic strategies. Nevertheless, there exist areas in which our understanding is incomplete and future modeling efforts are needed to advance the field.

We focused our review on CaMKII as a key nodal point in HF pathophysiology. An important extension HF modeling is the inclusion of spatio-temporal characteristics of CaMKII activation in myocytes and of mechanisms of CaMKII activation independent from Ca^{2+}/calmodulin and ROS signaling: O-GlcNAcylation,[24] S-nitrosylation,[23] and Epac/NOS-dependent pathway.[93] This extension will be important to elucidate the potential synergy among the different activation mechanisms, and could be important for the development of CaMKII inhibitors for clinical applications.[37]

Complex network relationships are emerging through comparative analyses of large-scale genomic, transcriptomic, proteomic, and metabolomic profiles that can be integrated into detailed mechanistic models. Although still rarely done, integrating “omics” approaches with mathematical mechanism-based biology models might be a powerful strategy to both understand the data and improve the predictive ability of the models. While advancements in experimental research will provide modelers with novel data for further improvement of computational frameworks, the parallel systematic use of sensitivity analysis and uncertainty quantification methods will also contribute to enhance the robustness of models and their predictions.[53, 79, 83, 106, 110]

Finally, an important priority will be to translate the mechanistic insights obtained from the studies to new clinical interventions. The use of clinically-derived patient-specific computer models to optimize catheter ablation strategies[133] is a relevant example of the application of systems biology and computational modeling approaches to therapy. The safety screening

FDA proposal, Comprehensive *in vitro* Proarrhythmia Assay (CiPA), also involves the use of computational models for mechanism-based *in silico* assessment of drug toxicity and overall proarrhythmic risk.[33, 39] Indeed, computational models are now poised to deliver breakthroughs at the bedside.

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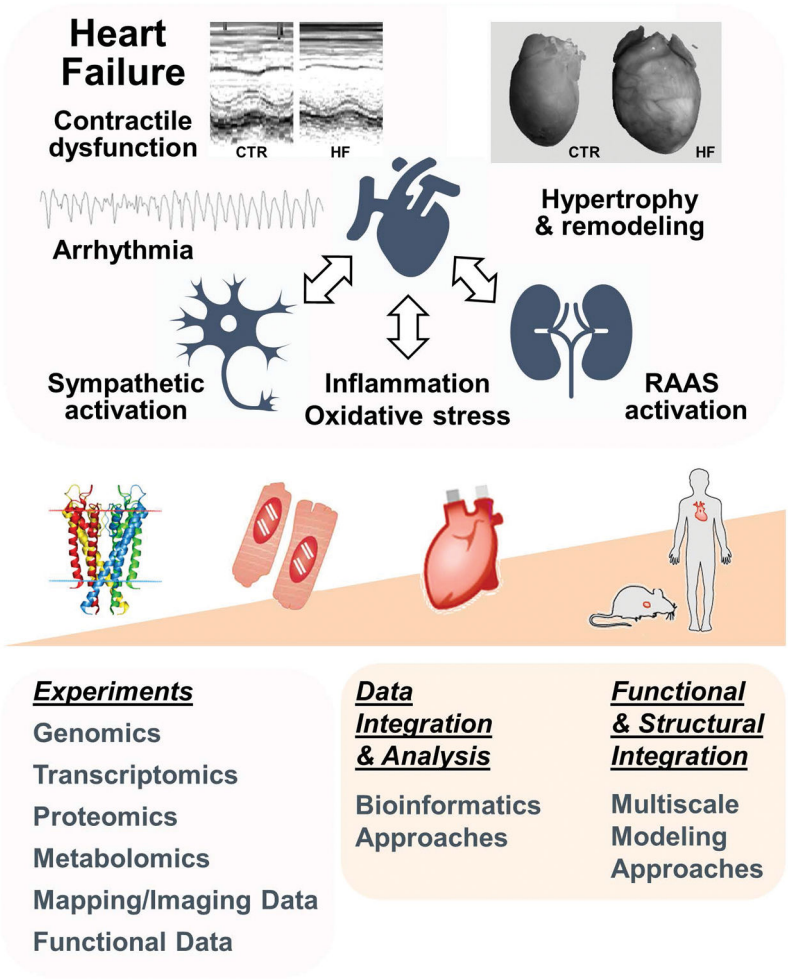

Fig. 1. Systems interplay in HF and multi-scale systems biology approaches

Top: schematic of systems involved in HF pathophysiology. HF phenotype includes ventricular hypertrophy, ionic and structural remodeling, and neurohormonal dysregulation leading to both impaired contractile function, and increased arrhythmia susceptibility. Bottom: systems biology approaches for data collection, analysis, and functional and structural integration. The data images in the upper panel are reproduced with permission from [12, 135].

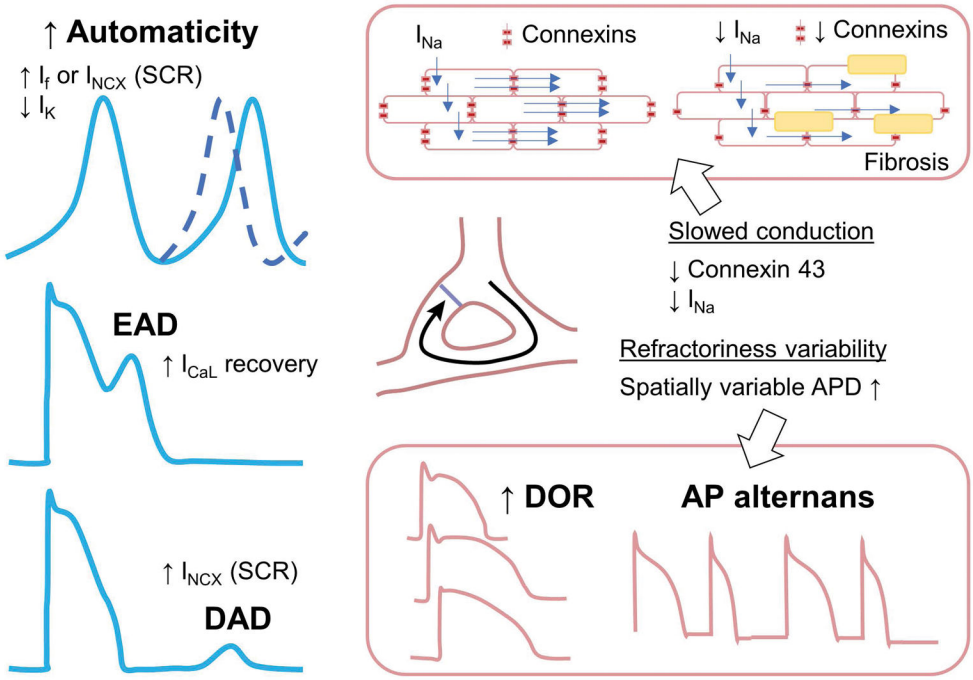

Fig. 2. Mechanisms of arrhythmias

Abnormalities in impulse formation include altered automaticity, early and delayed afterdepolarizations (left). Alterations in impulse conduction include slowing of conduction and increase in spatial APD heterogeneity (right).

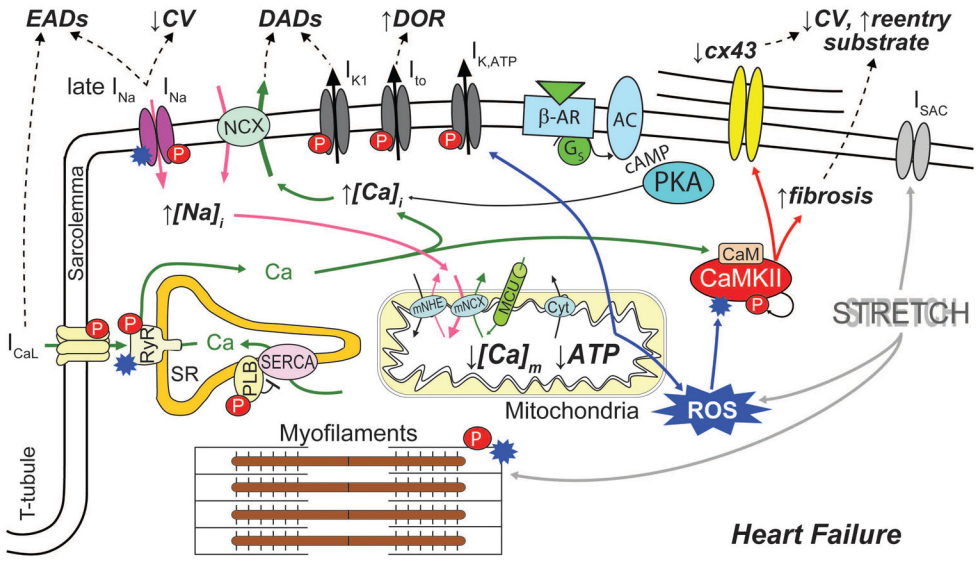

Fig. 3. Arrhythmogenic crosstalk and feedback of Na^+-Ca^{2+}-CaMKII-ROS in HF

Schematic of the main cellular processes linking Na^+ and Ca^{2+} cycling, CaMKII activity and metabolism to increased propensity for arrhythmia in failing myocytes. CaMKII, which expression and activity are enhanced in HF, phosphorylates multiple targets (red symbol "P"), directly influencing membrane electrophysiology and Na^+ and Ca^{2+} signals, thereby facilitating the development of ectopic activity (EADs and DADs). Increased Na^+ load enhances $[Ca^{2+}]_i$ and reduces $[Ca^{2+}]_m$, leading to further CaMKII activation via both Ca^{2+}/calmodulin- and oxidation-dependent mechanisms. In turn, increased ROS production (oxidative stress) can directly affect membrane electrophysiology, Ca^{2+} handling, and myofilament function (blue starred symbol). CaMKII is also involved in HF-induced structural remodeling that facilitates the formation of reentrant substrate.