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Review

Electrophysiological remodeling in hypertrophy and heart failure

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1. Introduction

Over 2 million Americans suffer from heart failure and more than 200 000 die annually. The incidence is estimated to be 400 000 per year with a prevalence of over 4.5 million, numbers that will 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 over 15% of patients dying within 1 year of initial diagnosis and greater than 80% 6 year mortality [2]. Of the deaths in patients with heart failure, up to 50% are sudden and unexpected.

The failing heart undergoes a complex series of changes in both myocyte and non-myocyte elements. In an attempt to compensate for the reduction in cardiac function the sympathetic nervous (SNS), renin–angiotensin–aldosterone (RAAS) systems and other neurohumoral mechanisms are activated. The altered signal transduction in heart failure initiates changes in gene expression that produce myocyte hypertrophy. Ultimately the changes in gene expression that initially maintain tissue perfusion prove to be maladaptive, predisposing to further myocyte loss, ventricular chamber remodeling and interstitial hyperplasia resulting in a progressive reduction in force development and impairment of ventricular relaxation.

The intrinsic cardiac and peripheral responses to myocardial failure adversely alter the electrophysiology of the heart predisposing patients with heart failure to an increase in arrhythmic death. With progression of heart failure there is an increase in the frequency and complexity of ventricular ectopy [3,4]. Total mortality in heart failure patients correlates with LV function and the presence of complex ventricular ectopy [5–7]. However, there is no clear correlation between SCD and LV function or ventricular ectopy. In fact, data from VHeFT (Veteran's Administration Heart Failure Trial) and other trials suggest that death is disproportionately sudden in patients with more modest myocardial dysfunction [8]. A major caveat is that the mechanism of sudden death is highly heterogeneous; even if one considers only those patients with death due to a tachyarrhythmia, several mechanisms may prevail.

This review will consider the cellular electrophysiological changes that have been observed in myocardial hypertrophy and failure that predispose to cardiac arrhythmias.

2. Cellular electrophysiology in hypertrophy and heart failure

2.1. Changes in the action potential profile and duration

An elementary and distinctive signature of any excitable tissue is its action potential profile. Myocardial cells possess a characteristically long action potential (Fig. 1): after an initial rapid upstroke, there is a plateau of maintained depolarization before repolarization. The duration of the action potential is primarily responsible for the time course of repolarization of the heart; prolongation of the action potential produces delays in cardiac repolarization.

Changes in the action potential duration and profile result from alterations in the functional expression of depolarizing and repolarizing currents. Prolongation of the action potential is characteristic of cells and tissues isolated from ventricles of animals with heart failure independent of the mechanism, which may include pressure and/or volume overload [9–23], genetic [24–26], metabolic [27], ischemia/infarction [28–31] and chronic pacing tachycardia models [32–34]. Similarly, tissues [35–37] and cells [38,39] from failing human ventricles exhibit action potential prolongation.

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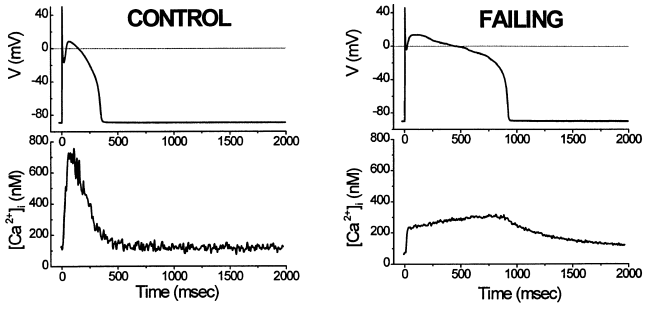

Fig. 1. Action potential and Ca^{2+} transients recorded in canine ventricular myocytes isolated from a normal heart (left) and failing heart (right). The action potentials are recorded at 37°C, a stimulation frequency of 0.5 Hz with indo-1 in the pipet for determination of the intracellular Ca^{2+} concentration. The transient of the failing cell is smaller with a slowly rising phase during the action potential plateau and delayed decay after repolarization.

The pathophysiological significance of action potential prolongation in cells isolated from hypertrophied and failing hearts has been questioned on several grounds. First, most action potential recordings from ventricular myocytes are made at unphysiologically slow rates and indeed the difference in duration between cells from failing and control ventricles converges at high stimulation frequency [34,37]. However, slow heart rates and pauses after premature contractions are common in heart failure, and the post-pause prolongation of the action potential duration may be highly significant. Second, isolated myocytes are no longer electrically coupled to other cells in the cardiac syncytium; however, intact muscle preparations from failing hearts (e.g. [36]) and monophasic action potential recordings in whole hearts [40] also exhibit action potential prolongation. Finally, the duration of the action potential is quite sensitive to mechanical load and increasing the load tends to shorten action potential duration and refractoriness more in failing than in normal hearts [41].

An important and understudied question is the effect of hypertrophy and failure on the regional differences in action potential duration. Action potential durations vary across the myocardial wall [42–45] and in different regions [46] of the mammalian heart. Data from experimental animal models of hypertrophy suggest regional inhomogeneity in action potential prolongation [12,15]. The finding of enhanced spatial and temporal dispersion and of monophasic action potential duration, refractoriness and electrocardiographic QT intervals in humans [47,48] and animals with heart failure [40] is consistent with an exaggerated dispersion of action potential duration that may predispose to ventricular arrhythmias.

2.2. Down-regulation of potassium currents

The duration and shape of the action potential is the result of a delicate balance between the depolarizing and repolarizing currents that are active during the plateau phase (Fig. 2). Repolarization in the mammalian heart is achieved primarily by the activity of potassium-selective ionic currents, although the exact molecular composition of these currents varies considerably from species to species. Functional down-regulation of K currents is a recurring theme in hypertrophied and failing ventricular myocardium. Ventricular myocytes contain several distinct classes of voltage-dependent K channels. The inward rectifier K current, I_{K1}, sets the resting membrane potential and contributes to the terminal phase of repolarization. Another important K current is the calcium-independent transient outward current, I_{to}. Unlike the inward rectifier, I_{to} is expressed in heart cells in a species- and cell type-specific fashion. This current plays a crucial role in the early phase of repolarization. The delayed rectifier K current (I_K), composed of molecularly distinct rapid (I_{Kr}) and slow (I_{Ks}) components, is important in phase 3 of repolarization. I_K density varies regionally in the hearts of some species [49,50] and I_{Kr} is the target of several antiarrhythmic drugs with Vaughan–Williams class III action.

A reduction in the current density of I_{to} is arguably the most consistent ionic current change in cardiac hypertrophy and failure (Table 1). Several notable exceptions are studies of compensated pressure overload hypertrophy which were associated with either no change [11] or an increase in I_{to} density [17,51]. Down-regulation of I_{to}, without a significant change in the voltage dependence or kinetics of the current has also been observed in cells isolated from terminally failing human hearts [39,52,53]. I_{to} is a transient current and as such down-regulation itself may not produce large effects on the action potential duration, particularly in larger mammals with long action potential durations such as dog and man. Nevertheless, I_{to} does profoundly influence phase 1 and the level of the plateau (Figs. 1 and 2), thereby affecting all of the currents that are active later in the action potential.

The density of I_{to} varies regionally and transmurally in the heart, and there is some evidence that the density of I_{to} may be reduced differentially in heart failure [52,53]. The mechanism underlying regional and transmural differences in I_{to} current density in the heart is not clear. Some data suggest that there are differences in the level of expression of the same K channel gene; alternatively, distinct gene products may underlie I_{to} in different regions of the heart and at various stages of development [54,55]. In humans [56] it has been hypothesized that the K channel, Kv1.4 is the predominant gene that encodes endocardial I_{to}, while Kv4.3 underlies mid-myocardial and epicardial I_{to}. Interestingly, these two K channels (Kv1.4 and [Kv4.3 or Kv4.2]) exhibit distinct kinetic behavior when heterologously expressed, with Kv1.4 having much slower inactivation recovery kinetics than Kv4.x [57–60]. Preferential expression of Kv1.4 in the endocardium may underlie the different electrophysiological behavior of I_{to} in human cells isolated from the subendocardium and subepicardium [52,53].

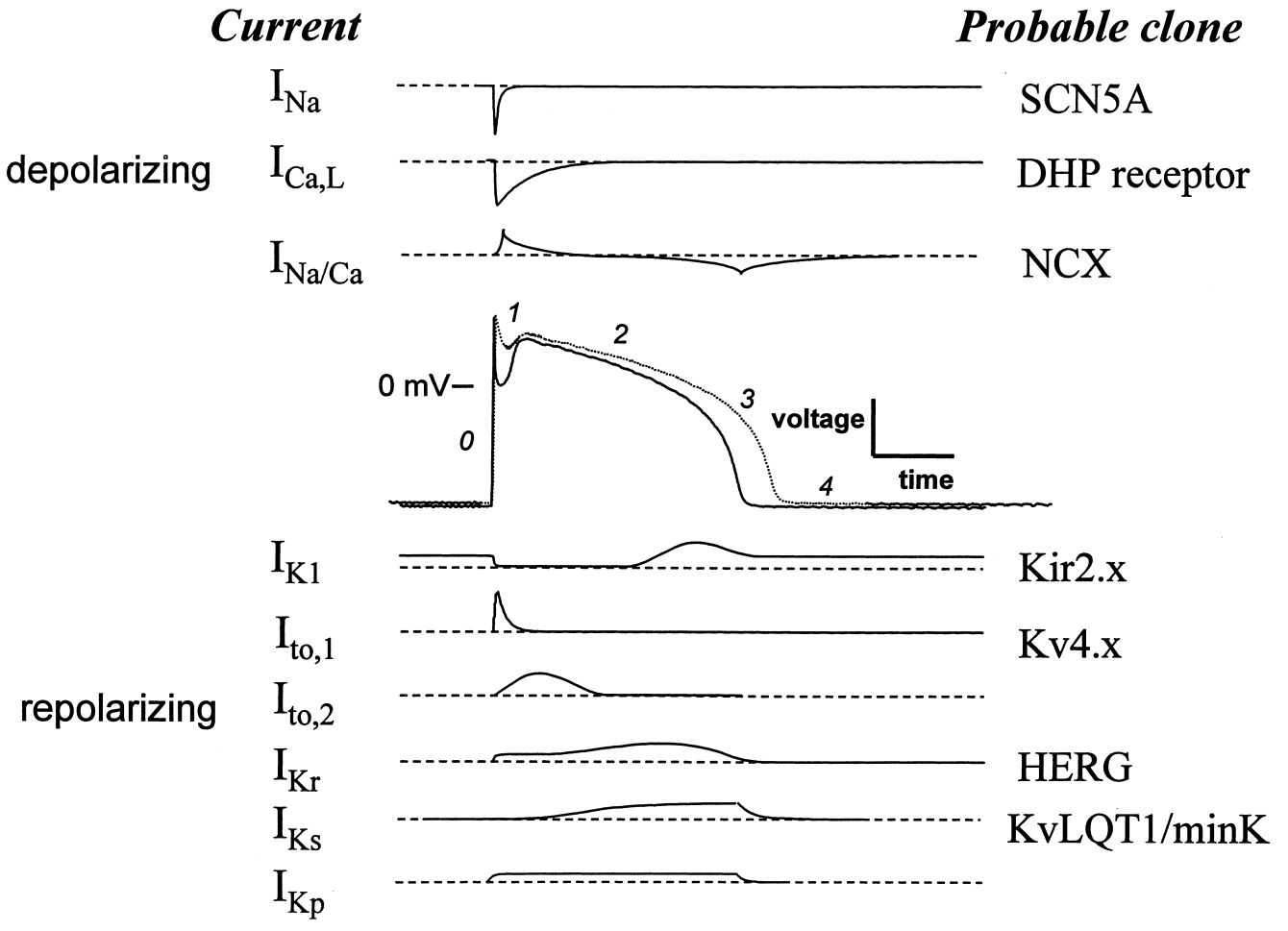

Fig. 2. Schematic of the depolarizing and repolarizing currents that underlie the action potential in the mammalian ventricle. A control (solid line) and failing (dotted line) action potential profile are shown in the center. The phases of the action potential are labeled. A schematic of the time course of each of the currents is shown as well as the gene product that underlies the current.

The molecular mechanism of I_{to} down-regulation in heart failure is likely to be multifactorial. I_{to} is regulated by neurohumoral mechanisms, specifically α_1-adrenergic stimulation reduces the current size [61–63]. In animal models [31] and human heart failure [64] a reduction in the steady-state level of Kv4 mRNA has been associated with down-regulation of I_{to}. In the rat reduction in the steady-state level of mRNA is associated with a commensurate decrease in the level of immunoreactive Kv4 protein [31]. The reduction in mRNA level results from a change in the balance between transcription and mRNA degradation, the precise molecular mechanism of which is unknown. It is interesting to note that regulated expression of I_{to} and Kv4 mRNA and protein occurs during development [54] and exposure to thyroid hormone [55,65].

Because I_{to} is brief, its role in setting the action potential duration in larger animals and humans remains controversial. Most of the studies examining I_{to} in heart failure have used Ca^{2+}-buffered internal solutions, thus eliminating any possible role of calcium-dependent processes. Under these conditions, several lines of evidence suggest that I_{to} can influence overall action potential duration [32,33,39]. Nevertheless, it is not clear whether this conclusion would also apply under more physiological conditions. Winslow et al. have simulated the role of I_{to} in setting the action potential duration in a novel canine ventricular action potential model [66]. They find that I_{to} has a sizable effect when intracellular Ca^{2+} is buffered, but not when Ca^{2+} cycling occurs unimpeded. More experiments will be required to resolve the physiological importance of I_{to} down-regulation in heart failure.

Changes in other K currents in hypertrophy and heart failure have been reported, but not with the consistency of down-regulation of I_{to} (Table 1). The inward rectifier K current (Kir2 family of genes) maintains the resting membrane potential and contributes to the terminal phase of repolarization in the ventricular myocyte. The important component of I_{K1} for action potential repolarization is the outward current at voltages positive to the equilibrium potential for K^+ (E_K). In mild ventricular hypertrophy increased [16], decreased (but no change at voltages positive to E_K) [11] and unchanged [13,20] I_{K1} density has

Table 1
K currents in hypertrophy and heart failure

	Model	APD	I_{to}	I_{K1}	I_K	Comment
Pressure/volume overload						
Kleiman and Houser, 1989 [16]	Cat/RVH			↑	↓	I_K slowed activation, faster deact
Benitah et al., 1993 [10]	Rat/Ao		↓			I_{to} density LVFW>apex>septum
Brooksby et al., 1993 [11]	SHR	↑	↔	↓	↔	
Furukawa et al., 1993 [68]	Cat/Ao	↑			↓	Slowed act and faster deact of I_K
Ryder et al., 1993 [20]	gp/Ao	↑		↔	↔	
Cerbai et al., 1994 [13]	SHR	↑	↓	↔		
Coulombe et al., 1994 [14]	DOCA/salt	↑	↓			Small negative shift gating
Li and Keung, 1994 [17]	RVHTN rat	↑	↑			Slowed I_{to} decay
Tomita et al., 1994 [21]	Rat/Ao	↑	↓			No change in I_{to} gating/kinetics
Potreau et al., 1995 [22]	Ferret/RVH		↓			Slowed TTP, decay and recovery
Takimoto et al., 1997 [23]	RVHTN rat					↓ Kv4.2/4.3 mRNA
						No change Kv1.2, 1.4, 1.5, 2.1,LQT1
Pacing-tachycardia						
Kääb et al., 1996 [32]	Dog	↑	↓	↓		No change in I_{to} gating/kinetics
Rozanski et al., 1997 [33]	Rabbit	↑	↓	↔		No change in I_{to} recovery
Ischemia/infarction						
Lue and Boyden, 1992 [28]	Dog	↓	↓			Infarct vs non-infarct zone
Qin et al., 1996 [29]	Rat	↑	↓			No change: RMP, I_{to} kinetics/gating
Gidh-Jain et al., 1996 [31]	Rat					↓ Kv1.4, 2.1, 4.2 mRNA
						↓ Kv2.1, 4.2 protein
Genetic/misc						
Thuringer et al., 1996 [25]	Hamster	↑	↓			Slowed I_{to} recovery
Xu and Best, 1991 [27]	Rat/GH	↑	↓			No change I_{to} gating/kinetics
Human						
Beuckelmann et al., 1993 [39]		↑	↓	↓	↔	
Wettwer et al., 1994 [52]			↓Subendo			
Näbauer et al., 1996 [53]			↓Subepi			Slow recovery of I_{to} in subendo
Kääb et al., 1998 [64]						↓Kv4.3, : Kv1.4, Kvβ1, Kir2.1, herg

RVH=right ventricular hypertrophy; Ao=aortic constriction; gp=guinea pig; SHR=spontaneously hypertensive rat; DOCA=deoxycorticosteroneacetate; RVHTN=renovascular hypertension; GH=growth hormone.

been reported. Similar inconsistencies have been observed in pacing tachycardia models: reduced I_{K1} density has been demonstrated in the dog [32] and both decreased [Rose et al. unpublished] and unchanged current density have been found in the rabbit [33]. In human heart failure, ventricular myocytes exhibit significantly reduced current density at negative voltages. The underlying basis of the down-regulation of I_{K1} in human heart failure is uncertain, but Kääb et al. reported no change in the steady-state level of Kir2.1 mRNA in failing compared to control hearts [64]. In studies of human ventricular I_{K1}, a differential reduction in the current was noted between cells isolated from failing hearts with dilated versus ischemic cardiomyopathy. The whole-cell slope conductance at the reversal potential for K^+ was significantly smaller in cells from hearts with dilated cardiomyopathy; these cells also had longer action potential durations with slower terminal (phase 3) repolarization [67]. Ventricular myocytes isolated from controls and hearts with ischemic myopathy exhibited voltage dependence of the open probability of I_{K1}, a response that was absent in cells from hearts of patients with dilated cardiomyopathy [67].

Studies of the delayed rectifier K current in hypertrophic and failing hearts are sparse. Myocytes isolated from hypertrophied right [16] and left ventricles [68,69] of the cat have reduced I_K current density with slowed activation and faster deactivation. The reduction in the outward current over the plateau voltage range in cells from the hypertrophied feline left ventricle exhibit a greater predisposition to developing potentially arrhythmogenic early afterdepolarizations (EADs) [68]. In contrast, studies of cells isolated from pressure-overload guinea pig [20] or spontaneously hypertensive rat [11] ventricles demonstrate no change in I_K. There are no studies comparing I_K in control and failing human hearts. The rapid component of the delayed rectifier current is encoded by the HERG (human ether a go-go related gene), we found no change in the steady state level of HERG mRNA [64] but others have reported a decrease in failing compared to control hearts [70].

The ATP-gated potassium channel ($I_{K\text{-}ATP}$) is the principal mediator of action potential shortening in response to ischemia in the heart. Differences in the behavior of $I_{K\text{-}ATP}$ in hypertrophied or failing hearts may have profound implications for susceptibility to arrhythmias induced by myocardial ischemia. Human ventricular $I_{K\text{-}ATP}$ in cells

isolated from failing ventricles is fundamentally similar to that observed in myocytes from control ventricles but less sensitive to ATP inhibition [71]. Action potential shortening that occurs in response to ischemia or metabolic inhibition is exaggerated in cells from hypertrophied compared to normal ventricles [69]. The differential sensitivity of the action potential duration to ischemic stress may be a result of altered $I_{K\text{-}ATP}$ sensitivity to intracellular [ATP]; however, the L-type Ca current in myocytes from hypertrophied hearts is also more profoundly suppressed by metabolic inhibition than the current in cells from control hearts [69].

2.3. Alterations in Ca^{2+} homeostasis

Heart failure is characterized by depression of developed force, prolongation of relaxation and blunting of the frequency-dependent facilitation of contraction. The fundamental changes in Ca^{2+} handling that attend ventricular failure are thought to account for the abnormalities in excitation–contraction coupling; however, the cellular and molecular basis of the Ca^{2+} handling deficits in ventricular hypertrophy and failure remain controversial. Intracellular Ca^{2+} and the action potential are intricately linked through Ca^{2+}-modulated cell surface channels and transporters such as the L-type Ca current, I_K and the Na^+–Ca^{2+} exchanger (NCX).

The voltage-dependent L-type Ca channel is a multisubunit protein that is ubiquitous in the heart. The L-type Ca current is the primary source of Ca^{2+} entry, triggering release of Ca^{2+} from the sarcoplasmic reticulum and initiating actin–myosin crossbridge cycling. The density of Ca current has been studied in a number of animal models of ventricular hypertrophy and failure (see review by Hart [72]). The severity of hypertrophy or failure appears to influence the density of the L-type current [11,13,20,29,32,69,73–86] or number of dihydropyridine (DHP) binding sites [80,87–94]. In general, when a difference in L-type Ca current density has been detected, the current is increased in mild-moderate hypertrophy and decreased in more severe hypertrophy and heart failure (Table 2). Studies of L-type Ca current in cells isolated from failing human hearts parallel the findings in animal models with severe hypertrophy or failure; human cells exhibit either no change [38,95–97], or a decrease in current density [98] or DHP binding sites [99,100] (Table 2). Ventricular myocytes isolated from failing hearts exhibit attenuated augmentation of the L-type Ca current by beta-adrenergic stimulation [96,98] and depression of rate-dependent potentiation [101] compared to cells isolated from control hearts.

The basic electrophysiological features of the L-type current are altered in some studies of hypertrophy and failure. The most common change is a slowing of the decay of the whole-cell current (e.g. [11,20,74,79]), a change that could alter excitation–contraction coupling and would tend to prolong the action potential duration. Prolongation of the decay of the Ca current is curious particularly in view of the common association of elevation of the intracellular [Ca^{2+}] in cardiac hypertrophy and failure, a change that should promote calcium-induced inactivation of the current [102,103]. However, the slowed decay of the L-type current may reflect deficiencies in Ca^{2+} handling as exemplified by the reduction in the peak of the Ca^{2+} transient causing less Ca^{2+}-induced inactivation of the Ca current. The underlying mechanism of the prolonged whole-cell current decay is unknown; however, a recent single-channel comparison of Ca current in human ventricular myocytes has suggested an increase in open probability of channels consistent with a dephosphorylation defect in the cells isolated from failing hearts [104].

The molecular basis of changes in the density of the L-type Ca current is unknown. In failing human hearts the steady state level of the α_{1C} mRNA has been reported to decrease by Northern blot [99,104] but was unchanged by ribonuclease protection assay [64]. It is not known whether there is a change in the level of immunoreactive protein, although a reduction in the number of DHP binding sites has been reported in various studies (Table 2). Hypertrophy after myocardial infarction in the rat is associated with re-emergence of expression of the fetal isoform of the α_{1C} gene [85]. Two reports of changes in human Ca channel β subunit mRNA exhibit disparate findings. Northern blots of samples from the left ventricle of terminally failing hearts revealed no change in β subunit (or α_{1C}) mRNA [104]. In contrast, samples from right ventricular endomyocardial biopsies revealed an inverse relationship between β subunit mRNA levels measured by competitive PCR and LV end diastolic pressure in transplanted hearts [105].

Up-regulation or re-expression of the T-type Ca current is a prominent feature of some animal models of ventricular hypertrophy [84]. The T-type current activates at hyperpolarized voltages and may participate in automaticity in some cells and tissues in the heart. The distribution of the T-type current is more restricted in the heart (for review see Vassort et al. [106]) than the L-type current, particularly in the adult ventricle. Normal maturation of cardiomyocytes is associated with loss of the T-type current, but myocytes grown in primary culture [107], exposed to insulin-like growth factor (IGF-1) in short-term culture [108] or isolated from the atria of rats with growth hormone-secreting tumors [109] reexpress this current. The T-type current has not been detected in cells isolated from either normal or failing human ventricles [38,96,110], therefore a role for this current in progression of human heart failure and associated arrhythmogenesis is unlikely.

The amplitude of the intracellular Ca^{2+} transient and its rate of decay are reduced in intact muscles [36] and cells [34,38,96,111] isolated from failing ventricles compared with normal controls (Fig. 1). The changes in the Ca^{2+} transient are the result of defective function of the sarcop-

Table 2
Calcium current changes in hypertrophy and failure

Reference	Model	Current density/binding sites	Comment
Animal models			
Mild–moderate hypertrophy			
Mayoux et al., 1988 [87]	Ao/rat	↑ DHP-binding sites	
Keung, 1989 [74]	RVHTN rat	↑ $I_{Ca\text{-}L}$	Slowed decay
Scamps et al., 1990 [75]	Ao/rat	↔ $I_{Ca\text{-}L}$	↓β-adrenergic responsiveness
Qin et al., 1996 [29]	Post-MI/rat	↔ $I_{Ca\text{-}L}$	No change in kinetics
Santos et al., 1995 [76]	Post-MI/rat	↓ $I_{Ca\text{-}L}$	No significant change in kinetics
Gomez et al., 1997 [77]	SHR	↔ $I_{Ca\text{-}L}$	No change in kinetics
Xiao and McArdle, 1994 [78]	SHR	↑ $I_{Ca\text{-}L}$ (10 weeks)	
Kleiman and Houser, 1988 [79]	PA banding/cat	↑ $I_{Ca\text{-}L}$	No change in kinetics
Finkel et al., 1987 [88]	Syrian hamster	↑ DHP binding sites (early)	
Wagner et al., 1989 [89]	Syrian hamster	↑ DHP binding sites (early)	
Creazzo, 1990 [80]	Chick PDA	↑ $I_{Ca\text{-}L}$	No change DHP binding sites
Ryder et al., 1993 [20]	Ao/gp	↑ $I_{Ca\text{-}L}$	Slowed decay, depolarizing shift of SS inactivation
Mukerjee et al., 1998 [81]	Pacing pig (1 week)	↓ $I_{Ca\text{-}L}$	No change in kinetics, ↓β-adrenergic responsiveness
Severe hypertrophy and failure			
Momatz et al., 1996 [82]	DOCA–salt/rat	↔ $I_{Ca\text{-}L}$	No change in kinetics
Gomez et al., 1997 [77]	SHR	↔ $I_{Ca\text{-}L}$	No change in kinetics
Brooksby et al., 1993 [11]	SHR	↔ $I_{Ca\text{-}L}$	Slowed decay
Cerbai et al., 1994 [13]	SHR	↔ $I_{Ca\text{-}L}$	
Dixon et al., 1990 [91]	Post MI/rat	↓ DHP binding sites	
Gopalakrishnan et al., 1991 [90]	Post-MI/rat	↓ PN200-110 binding sites	
Furukawa et al., 1994 [69]	Post-MI/cat	↔ $I_{Ca\text{-}L}$	Slowed decay
Finkel et al., 1987 [88]	Syrian hamster	↓ DHP binding sites (late)	
Wagner et al., 1989 [89]	Syrian hamster	↓ DHP binding sites (late)	
Bouron et al., 1992 [83]	PA banding/ferret	↓ $I_{Ca\text{-}L}$	
Nuss and Houser, 1991 [84]	PA banding/cat	↓$I_{Ca\text{-}L}$	Re-expression of $I_{Ca\text{-}T}$
Gidh-Jain et al., 1995 [85]	Post-MI/gp	↓$I_{Ca\text{-}L}$	Increase in the fetal splice variant of α1C
Ming et al., 1994 [86]	RVHTN/gp	↓ $I_{Ca\text{-}L}$	No change in kinetics, ↓β-adrenergic responsiveness
Colston et al., 1994 [92]	Pacing rabbit	↓ DHP binding sites	
Vatner et al., 1994 [93]	Pacing dog	↓ DHP binding sites	
Kääb et al., 1996 [32]	Pacing dog	↔ $I_{Ca\text{-}L}$	No change in kinetics
Gengo et al., 1992 [94]	MI dog	↓ DHP binding sites	
Aggarwal and Boyden, 1996 [73]	MI dog	↓$I_{Ca\text{-}L}$	No change in kinetics,↓β-AR sensitivity
Mukerjee et al., 1998 [81]	Pacing pig (3 week)	↓$I_{Ca\text{-}L}$, ↓ DHP binding sites	No change in kinetics, ↓β-adrenergic responsiveness
Human studies			
Beuckelmann et al., 1992 [96]		↔ $I_{Ca\text{-}L}$	No change in kinetics, ↓β-AR sensitivity
Mewes and Ravens, 1994 [97]		↔ $I_{Ca\text{-}L}$	No change in kinetics or voltage dependence
Ouadid et al., 1995 [98]		↓$I_{Ca\text{-}L}$	↓β-AR sensitivity
Piot et al., 1996 [101]			Blunted upregulation of $I_{Ca\text{-}L}$ by rapid stimulation in hearts with EF<40%
Rassmussen et al., 1990 [95]		↔ DHP binding sites	
Takahashi et al., 1992 [99]		↓ DHP binding sites, α1C mRNA	
Gruver et al., 1994 [100]		↔ DHP binding sites	Normal vs. DCM LV
		↓ DHP binding sites	Normal vs. IsCM LV
Schroder et al., 1998 [104]		↑Ensemble average $I_{Ca\text{-}L}$	↑P_{open}, single channel availability
		↔ α_{1C}, β mRNA	

MI=myocardial infarction; PA=pulmonary artery; PDA=patent ductus arteriosus. For other abbreviations see Table 1.

lasmic reticulum, but the precise molecular mechanism(s) of this defect is controversial. The sarcoplasmic reticulum Ca^{2+}–ATPase (SERCA2a) and the Na^{+}–Ca^{2+} exchanger (NCX) are primary mediators of Ca^{2+} removal from the cytoplasm. SERCA2a is inhibited by unphosphorylated phospholamban (PLB) by direct protein-protein interaction [112], when PLB is phosphorylated SERCA2a inhibition is relieved. Ca^{2+} entry into the cell through the L-type Ca channel stimulates release of Ca^{2+} from the SR by the ryanodine receptor (RyR) in a process known as Ca^{2+}-induced Ca^{2+} release. The level of ventricular RyR mRNA decreases in some studies of terminal human heart failure [113,114] but no change in RyR protein level has been demonstrated [115].

Many studies have demonstrated a reduction in SERCA2a mRNA [99,116–124], but fewer studies have shown a reduction in immunoreactive protein [34,124–126]. Despite unanimity of opinion that Ca^{2+} sequestration by the SR is defective in failing myocardium, there is controversy about whether there is a change in SERCA

pump function (for discussion see reviews by Hasenfuss [127] and Movsesian [128]). SERCA2a function may also be altered in hypertrophy and heart failure by changes in the relative expression or function of PLB. PLB mRNA is consistently reduced in failing human hearts [116,119–121,129], but this has not translated into a decrease in PLB protein in all studies (Table 3 [119–121,130].

Intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) is an important modulator of the cellular electrophysiology of the heart, affecting the function of a number of ion channels and transporters and increasing the resistance between cells by reducing gap junctional conductance [131]. The NCX importantly contributes to control of $[Ca^{2+}]_i$, extruding cytoplasmic Ca^{2+} by electrogenically exchanging it for extracellular Na^+ . Most studies from hypertrophied and failing hearts have demonstrated an increase in both NCX mRNA and protein [34,118,132,133] (Table 3), suggesting that enhanced NCX function compensates for defective SR removal of Ca^{2+} from the cytoplasm in the failing heart. O'Rourke et al. [34] have reported functional evidence for a prominent role of NCX in myocytes from failing canine hearts, which they interpreted as being compensatory for a decrease in Ca^{2+} reuptake by the SR. However, direct studies of NCX function in failing hearts are limited; Na^+-dependent [45] Ca^{2+} flux into sarcolemmal vesicles has been shown to be increased in a human sarcolemmal preparation [133]. In contrast, no change in the Ni^{2+}-sensitive exchanger current was observed in cells isolated from failing hearts compared with normal controls in the rabbit pacing tachycardia heart failure model [134]. This, however, does not imply that the current carried by the NCX is the same in cells from failing hearts compared with controls. In the context of a prolonged Ca^{2+} transient, the NCX is likely to play a significant role in reshaping the action potential profile. Forward-mode exchanger function (Na^+ in and Ca^{2+} out) compensates for defective SR Ca^{2+} removal at the expense of depletion of the releasable pool of Ca^{2+} with repetitive stimulation (flat or negative force–frequency relation) [135-137], increasing depolarizing current. Reverse mode exchange (Na^+ out and Ca^{2+} in) has been suggested to provide inotropic support to the failing heart [132,138]. Computer simulations based on the canine pacing tachycardia model suggest that augmentation of reverse mode exchanger function during the early plateau will tend to shorten the action potential duration. However, with exaggerated forward mode function and changes in the decay rate of the L-type Ca current the net effect is prolongation of the action potential [66].

2.4. Pacemaker current, I_f

The hyperpolarization-activated 'funny' or pacemaker current (I_f) in the heart is a nonselective cation current that was originally described in automatic tissues such as the sinoatrial node [139–141]. More recently I_f has been demonstrated in ventricular cells from animal [142,143] and human hearts [144,145], activating at very negative voltages outside the physiological range. The channel gene underlying this current has recently been cloned [146]. I_f generates an inward current that drives the membrane voltage toward threshold, thus significantly contributing to diastolic depolarization in automatic cells. In the rat, I_f density increases with the severity of cardiac hypertrophy [147]. In contrast, although I_f is found in higher density in ventricular myocytes from failing human hearts, the difference from controls did not reach statistical significance. Furthermore, no differences in the voltage dependence, kinetics or isoproterenol-induced gating shift were noted in cells from failing compared to control hearts [145]. Nonetheless, the trend toward an increase in I_f in the

Table 3
Alterations in Ca^{2+} regulatory proteins in human heart failure

Reference	SERCA		NCX		PLB		RYR	
	mRNA	Protein	mRNA	Protein	mRNA	Protein	mRNA	Protein
Mercadier et al., 1990 [117]	↓							
Feldman et al., 1991 [129]					↑			
Takahashi et al., 1992 [99]	↓							
Brilliantes et al., 1992 [113]							↓ ICM ↔ DCM	
Arai et al., 1993 [116]	↓				↓		↓	
Studer et al., 1994 [118]	↓DCM, ICM		↑ DCM, ICM	↑ DCM, ICM				
Movsesian et al., 1994 [130]		↔ Function				↔		
Hassenfuss et al., 1994 [125]		↓ Function						
Go et al., 1995 [114]							↓DCM, ICM	
Meyer et al., 1995 [115]		↔				↔		↔
Flesch et al., 1996 [132]			↑ DCM, ICM	↑ DCM, ICM				
Flesch et al., 1996 [120]	↓	↔			↓	↔		
Reinecke et al., 1996 [133]			↑ Trend	↑ Trend				
Schwinger et al., 1995 [119]	↓	↔			↓	↔		
Linck et al., 1996 [121]	↓	↔			↓	↔		
Hasenfuss et al., 1997 [136]		↓				↑		

setting of reduced I_{K1} current density may predispose ventricular myocytes isolated from failing hearts to enhanced automaticity.

2.5. Na^+–K^+ ATPase

The Na^+–K^+ ATPase (Na, K pump) transports K^+ into the cell and Na^+ out with a stoichiometry of 2:3 therefore generating an outward repolarizing current. The Na^+–K^+ ATPase is dimeric consisting of α- and β-subunits each of which has three isoforms. The α-subunit determines the glycoside sensitivity of the pump. The majority of experimental data suggest that the expression and function of the Na^+–K^+ ATPase are reduced in failing compared with control hearts [148–152]. Decreased pump function in heart failure has several consequences that might be relevant to production of arrhythmias. First is the reduction in the outward repolarizing current that would tend to prolong action potential duration. Second, all else being equal, reduced pump function would lead to an increase in intracellular $[Na^+]$ and enhanced reversed mode NCX, increasing depolarizing current. Finally, cells with less Na^+–K^+ ATPase activity have greater difficulty handling changes in extracellular $[K^+]$: low $[K^+]_o$ itself tends to inhibit the ATPase, while increases in $[K^+]_o$ would tend to be cleared less rapidly in the setting of relative pump inhibition.

2.6. Modulation of channel and transporter function

In the face of impaired left ventricular pump function, the body attempts to maintain circulatory homeostasis through a complex series of neurohumoral changes. Prominently, the sympathetic nervous (SNS) and renin–angiotensin–aldosterone (RAAS) systems are activated. Activation of the SNS increases heart rate and contractility and redistributes blood flow centrally by peripheral vasoconstriction. The RAAS similarly causes vasoconstriction and increases circulatory volume. The neurohumoral changes are initially adaptive, maintaining systolic function and vital organ perfusion, but ultimately lead to progression of the heart failure phenotype. Elaboration of catecholamines chronically can be directly cardiotoxic and results in a series of changes in adrenergic receptor densities that are maladaptive. The volume overload and vasoconstriction produced by chronic activation of both the SNS and RAAS increases myocardial wall stress with increased oxygen demand and the possibility of progressive myocyte damage and dropout. The combination of neurohumoral activation and mechanical stress activates signal transduction cascades that produce myocyte hypertrophy and result in the elaboration of trophic factors that increase the interstitial content of collagen; both effects combine to impair both systolic and diastolic function of the heart. The changes in neurohumoral signaling have prominent effects on the electrophysiology of the failing heart.

Since the initial observations of Bristow et al. [153], adrenergic signaling in human heart failure has been the subject of extensive study (for reviews see [154,155]). The β_1, β_2 and α_1 adrenergic receptors mediate the effects of increased catecholamines (both circulating epinephrine and norepinephrine released from cardiac nerve terminals) in the heart. These receptor subtypes are coupled to different signaling systems. The β_1 and β_2 receptors are coupled by stimulatory G proteins to adenylyl cyclase; activation results in increased cellular levels of cAMP, which may be quite local in the case of β_2 receptors [156]. The α_1 receptor is coupled by a G protein to phospholipase C (PLC) which hydrolyzes inositol phospholipids increasing cellular inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). Angiotensin II (AT1) receptors are similarly coupled to PLC. Activation of the AT1 receptor or the α-adrenergic pathway initiates a kinase cascade triggering cell growth and altering the level of intracellular Ca^{2+}. Indeed, a byproduct of local catecholamine excess in the heart is an increase in cellular Ca^{2+} load. The possible adverse consequences of increased Ca^{2+} load is activation of phospholipases, proteases and endonucleases culminating in cell necrosis or apoptosis and progression of the failing phenotype.

The β and α signaling pathways significantly affect the function of a number of ion channels and transporters. The net effect of β-adrenergic stimulation is to shorten the ventricular action potential duration due to an increase in the current density and a hyperpolarizing shift of the activation of I_K [157], despite β_1 receptor stimulation of depolarizing current through the L-type Ca channel. α_1-adrenergic receptor stimulation inhibits several K currents in the mammalian heart, including I_{to}, I_{K1} and I_K in rat ventricle with the net effect of prolonging action potential duration [158].

Mechanical load is an important modulator of excitability in the heart. The effect of altered hemodynamic load may be exaggerated in the failing compared with the normal ventricle. In doxorubicin-induced heart failure in the rabbit increased load produced exaggerated shortening of the action potential duration and enhanced arrhythmia susceptibility in failing compared to control hearts [41]. The effect of load is not likely to be distributed uniformly across the ventricular wall or throughout the myocardium, and thus has the potential to increase dispersion in action potential duration with arrhythmogenic consequences.

2.7. Electrical remodeling and arrhythmia mechanisms in cardiac hypertrophy and failure

Sudden death due to ventricular arrhythmias associated with cardiac hypertrophy and failure is likely to involve multiple arrhythmic mechanisms. The variability in the reported electrophysiological changes are certainly in part methodological, but also reflect a high degree of heterogeneity in the pathobiology of hypertrophy and heart

failure in animal models and human disease. The stage of disease is crucial in determining the degree and character of electrical remodeling and arrhythmic risk. Data from human heart failure trials support this concept; in VHeFT the risk of sudden and presumed arrhythmic death was proportionately greater in patients with less severe heart failure [8]. The changes in risk of sudden death with progression of heart disease are likely to be a reflection of changes in electrophysiological substrate. The great challenge remains to use insights provided by in vitro studies to more completely understand arrhythmic mechanisms in the intact heart and to prevent sudden death in patients.

It is useful to consider the possible mechanisms of ventricular arrhythmias in terms of cellular electrophysiological parameters and the molecular changes in hypertrophy and heart failure that modulate these parameters (Table 4) [159]. Abnormal automaticity may arise in hypertrophied and failing hearts in the setting of a reduction in resting membrane potential or acceleration of phase 4 diastolic depolarization such that the threshold for activation of the Na current is reached rapidly. Re-expression of $I_{Ca\text{-}T}$ in ventricular cells changes in the voltage dependence, β-adrenergic sensitivity, or an increase in the density of I_f, and reduced I_{K1} density could conspire to enhance automaticity in ventricular myocytes in failing hearts.

Triggered automaticity arising from afterdepolarizations could be enhanced by several electrophysiological changes described in the failing and hypertrophied heart. Cells isolated from failing animal and human hearts consistently reveal a significant prolongation of action potentials compared to those in normal hearts, independent of the mechanism of CHF (Table 1). The plateau phase of the action potential is known to be quite labile: this is a time of high membrane resistance, during which small changes in current can easily tip the balance either towards repolarization or maintained depolarization. As a rule, the longer the action potential, the more labile is the repolarization process [160]. Action potential lability may be manifest as variability in duration and/or secondary depolarizations that interrupt action potential repolarization, such as EADs that can initiate triggered arrhythmias including torsades de pointes ventricular tachycardia. Indeed, enhanced susceptibility to afterdepolarization-mediated ventricular arrhythmias has been demonstrated experimentally. Prolongation of repolarization [161–163], enhanced dispersion of repolarization and susceptibility to cesium-induced action potential prolongation have been demonstrated in the canine pacing-tachycardia heart failure model, an animal model with a high incidence of sudden death [40]. Ventricular myocytes isolated from the failing canine heart exhibit more spontaneous EADs than cells from control hearts and have an exaggerated response (more frequent and complex EADs) to reduction of the bath K^+ concentration and the addition of the non-specific K channel blocker CsCl [164]. Complex afterdepolarizations and triggered arrhthythmias are more common in hypertrophied rat ventricular myocardium exposed to K channel blockers [165] and dogs with LVH exposed to the Ca channel agonist BayK 8644 [166]. Alterations in Ca current density or kinetics can predispose to EAD- or DAD-mediated arrhythmias [160]. Changes in the cellular environment such as hypokalemia, hypomagnesemia, and elevated levels of catecholamines may further increase the susceptibility to afterdepolarization-mediated triggered arrhythmias [37].

The changes in Ca^{2+} handling in the hypertrophic and failing heart may also contribute to electrical instability. The characteristic slow decay of the Ca^{2+} transient and increased diastolic [Ca^{2+}] can predispose to oscillatory release of Ca^{2+} from the SR and DAD-mediated triggered arrhythmias. The slow decay of the Ca^{2+} transient will

Table 4
Arrhythmia mechanisms in cardiac hypertrophy and heart failure

	Arrhythmogenic mechanism	Molecular changes in hypertrophy/HF
Abnormal automaticity		
↓RMP-$V_{threshold}$	Phase 4 diastolic depolarization (enhanced) Maximum diastolic potential (reduced)	↑$I_{Ca\text{-}T}$, ↓I_{K1}, ↑I_f
Triggered automaticity		
EAD-mediated	AP duration (↑AP duration and altered profile)	↓K currents, ↑ NCX, Altered $I_{Ca\text{-}L}$ density and kinetics,
Late EAD or DAD-mediated	$[Ca^{2+}]_i$ (increased)	Slowed Ca^{2+} transient, ↑NCX
Reentry		
Reactivation (short excitable gap)	APD (prolonged)	
↓Conduction and block (long excitable gap)	Anisotropic conduction (altered)	Microfibrosis in the interstitium

influence ion flux through the NCX and may also predispose to late phase 3 EAD-mediated triggered arrhythmias.

The most common mechanism of ventricular arrhythmias is reentry due to abnormal impulse conduction. There are a number of changes characteristic of failing myocardium, in both the myocyte and interstitial compartments that create substrates for reentry. In hearts that are failing as the result of myocardial infarction a macroreentry circuit may exist in the border zone of the infarction. Although in the absence of prior infarction, macroreentry is less likely to be a mechanism, hence patients with non-ischemic cardiomyopathy are less likely to be inducible at electrophysiological study. Normally there is a dispersion of action potential duration in the ventricle of both man [45] and animals [167], it is possible that changes in the expression of K currents (and other currents) could enhance this dispersion of action potential duration. There is clinical evidence that spatial [47] and temporal dispersion of repolarization [48] are enhanced in the failing human heart. Such dispersion of repolarization may predispose to non-excitable gap reentry such as that proposed to underlie polymorphic ventricular tachycardia and ventricular fibrilation.

Alterations in anisotropic conduction may contribute to the production of arrhythmias in hypertrophic and failing hearts. Alterations in intracellular [Ca^{2+}] [131,168] and redistribution of gap junctions [169,170] will affect intercellular conduction, microfibrosis will alter anisotropic conduction [171] leading to spatial non-uniformities of electrical loading resulting in conduction block and reentry.

3. Conclusions

The increased risk of sudden cardiac death in patients with myocardial hypertrophy and heart failure is the result of remodeling that occurs in both the myocyte and interstitial compartments of the heart. The key components of ventricular myocyte remodeling are the functional expression of a number of ion channels, transporters and receptors that result in action potential prolongation, abnormal Ca^{2+} handling and aberrant adrenergic signaling. The remodeling process creates a substrate that is highly sensitive to triggers for potentially lethal ventricular arrhythmias.

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