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Arrhythmogenic Ion-Channel Remodeling in the Heart: Heart Failure, Myocardial Infarction, and Atrial Fibrillation

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Nattel S, Maguy A, Le Bouter S, Yeh Y-H. Arrhythmogenic Ion-Channel Remodeling in the Heart: Heart Failure, Myocardial Infarction, and Atrial Fibrillation. *Physiol Rev* 87: 425–456, 2007; doi:10.1152/physrev.00014.2006.—Rhythmic and effective cardiac contraction depends on appropriately timed generation and spread of cardiac electrical activity. The basic cellular unit of such activity is the action potential, which is shaped by specialized proteins (channels and transporters) that control the movement of ions across cardiac cell membranes in a highly regulated fashion. Cardiac disease modifies the operation of ion channels and transporters in a way that promotes the occurrence of cardiac rhythm disturbances, a process called "arrhythmogenic remodeling." Arrhythmogenic remodeling involves alterations in ion channel and transporter expression, regulation and association with important protein partners, and has important pathophysiological implications that contribute in major ways to cardiac morbidity and mortality. We review the changes in ion channel and transporter properties associated with three important clinical and experimental paradigms: congestive heart failure, myocardial infarction, and atrial fibrillation. We pay particular attention to K^+, Na^+, and Ca^{2+} channels; Ca^{2+} transporters; connexins; and hyperpolarization-activated nonselective cation channels and discuss the mechanisms through which changes in ion handling processes lead to cardiac arrhythmias. We highlight areas of future investigation, as well as important opportunities for improved therapeutic approaches that are being opened by an improved understanding of the mechanisms of arrhythmogenic remodeling.

I. INTRODUCTION

The cardiac action potential represents cardiac transmembrane potential (measured at the inside of the cell) as a function of time. The action potential is a key determinant of cardiac electrical activity and is shaped by underlying ionic currents and transporters [for detailed reviews, see Nerbonne and Kass (219) and/or Schram et al. (280)]. A schematic representation of a cardiac action potential and the principal currents involved in its various phases are shown in Figure 1*A*. The phases of the cardiac action potential are designated by the numbers 0 through 4, beginning with initial depolarization (phase 0) to the return to the resting state (phase 4). The cellular resting potential is set by the resting K^+ conductance, which is normally large in non-nodal tissue (working atrial and ventricular muscle, specialized ventricular conducting tissue composed of Purkinje fiber cells) because of a high resting permeability through inward-rectifier current (I_{K1}) channels. The substantial resting I_{K1} conductance fixes the resting potential of non-nodal cardiac muscle near the K^+ equilibrium potential of about −80 to −90 mV. Upon activation, cells are depolarized by the rapid entry of Na^+ through Na^+ channels, generating a large inward-flowing (depolarizing) Na^+ current (I_{Na}). The maximum rate of voltage upstroke during phase 0 of the action potential, dV/dt_{max}, is determined by (and closely correlated with) the size of the depolarizing I_{Na}. After a brief rapid repolarization phase (phase 1) due to K^+ egress through a rapidly activating and inactivating transient outward current (I_{to}) K^+ channel, cardiac cells enter a plateau phase (phase 2) during which there is a balance between inward currents (Ca^{2+} through the L-type Ca^{2+} current, I_{CaL}) and outward K^+ currents. During this phase there is progressive time-dependent activation of delayed-rectifier currents, particularly the rapid delayed-rectifier I_{Kr}, which finally terminate the action potential with an appropriate delay by producing rapid phase 3 repolarization. Nodal-type cells in the sinoatrial node (also called the sinus node) and atrioventricular node maintain a more primitive phenotype, with a smaller resting K^+ conductance producing less negative resting potentials (further from the K^+ equilibrium potential) and a slow action potential upstroke generated by Ca^{2+} entry through the L-type Ca^{2+} channel. Typical examples of action potentials from various cardiac regions are illustrated in Figure 1*B*, along with a schematic diagram to show the normal pattern of electrical activation of the heart.

Action potential abnormalities associated with heart disease were first described in human atrial preparations by Trautwein et al. in 1962 (315). Gelband and Bassett (103) provided the first description of action potential abnormalities (including less negative resting potential and dV/dt_{max} and increased action potential duration, APD) in an experimental model of heart failure, based on observations in right ventricular tissue from cats subjected to partial pulmonary artery obstruction. In the early 1980s, Ten Eick and co-workers (305, 306) described alterations in outward K^+ currents (decreased inward-rectifier and delayed-rectifier currents) and inward Ca^{2+} currents in diseased hearts.

Various forms of cardiac disease and rhythm disturbances result in altered cardiac ion channel and transporter function. These alterations appear in many instances to be part of the homeostatic adaptive response to the primary abnormality (213), but often result in second-

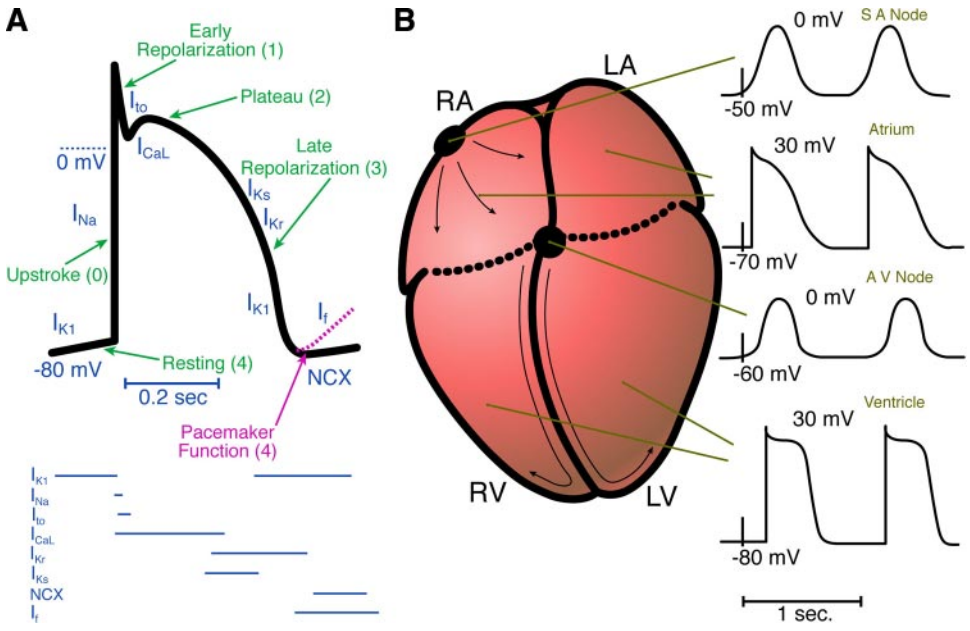

FIG. 1. Generation of cardiac electrical activity. *A*: schematic cardiac action potential with the various phases and principal corresponding ionic currents indicated. The horizontal lines at the *bottom* indicate schematically the portions of the action potential during which each current flows. *B*, *left*: the cardiac impulse is initiated by spontaneous regular firing of the sinoatrial (SA) node. It then spreads to the atria to cause them to fire and contract, and from the atria arrives at the atrioventricular (AV) node. The AV node is normally the only conducting pathway between the atria and ventricles, which are otherwise separated by nonconducting fibrous tissue. After a delay in the AV node to provide time for the ventricles to fill before they contract, the impulse spreads via the specialized Purkinje fiber ventricular conducting system to activate the ventricles. *Right*: typical action potentials (APs) corresponding to the tissues shown at *left*. The short vertical lines indicate the time of onset of activity in the SA node for one beat (for reference purposes). NCX, Na^+-Ca^{2+} exchanger.

ary cardiac dysfunction, including excessively rapid cardiac rhythms ("tachyarrhythmias"). Over the past 20 years, an enormous amount has been learned about the biophysical nature of arrhythmogenic ion-channel remodeling, as well as of its pathophysiological consequences and molecular basis. We review the available information with respect to three selected paradigms of conceptual and clinical importance: congestive heart failure, myocardial infarction, and atrial fibrillation (AF).

A. Channel Function as a Regulated Phenomenon

The classical notion of ion-channel function viewed ion-channel properties as essentially fixed in the absence of tissue damage; however, our understanding has evolved to appreciate that ion-channel properties are regulated and responsive to changes in ionic fluxes, neurohumoral environment, and hemodynamic state (212). It is logical that ion-channel function be regulated, because physiological action potential properties require fine balances among a wide range of currents. This would seem to necessitate some form(s) of feedback control on ion-channel production and function in relationship to action potential waveforms, frequency of activation, and cellular metabolism. How such mechanisms, designed to maintain physiological function under a broad range of normal conditions, come into play in the face of disease processes that are often associated with aging-related pathology remains to be clarified. A variety of mechanisms, including modulation of gene transcription, mRNA processing, mRNA translation, protein processing, subunit assembly, membrane transport, assembly into macromolecular complexes, and posttranslational regulation, have the capacity to mediate the remodeling of ion-channel expression and function (264). Although we know a great deal about the functional consequences of such processes, we are only beginning to learn about the fundamental mechanisms controlling their occurrence. Our ability to control remodeling-induced changes will ultimately depend on our understanding of how they come about; however, because remodeling may be part of an adaptive physiological program, any therapeutic manipulation will need to take into consideration the potentially negative consequences of interfering with homeostatic paradigms.

B. Regional Considerations

The various regions of the heart have highly specialized electrical functions, determined by a defined complement of ion channels and transporters (for detailed reviews of regional ion-channel expression properties and their relationship to electrophysiological function and arrhythmias, see Refs. 211, 219, and 280). Regional functional specialization is typified in part by characteristic action potential waveforms in various cardiac regions, as illustrated in Figure 1*B*. Emerging information is clarifying the molecular bases for the specificity of regional ion-channel complement patterns (116, 185, 193, 280). The principal arrhythmic consequences of ion-channel remodeling are related to these specialized functions and their underlying molecular/biophysical basis.

II. REMODELING OF IONIC CURRENTS ASSOCIATED WITH CARDIAC DISEASE: CONGESTIVE HEART FAILURE

A. Significance and Arrhythmic Consequences

Heart failure is a syndrome caused by significant impairments in cardiac function. Sudden death, generally due to arrhythmic causes, is responsible for up to ~50% of deaths among patients with cardiac failure (153). Cardiac dysfunction is the single most useful clinical predictor of the mortality-preventing effectiveness of implantable ventricular cardioverter/defibrillator devices, which automatically terminate ventricular tachyarrhythmias by giving an appropriately adjusted shock to the heart (201). This finding highlights the importance of ventricular tachyarrhythmias in heart failure patients, all of whom have impaired cardiac function. In addition to ventricular tachyarrhythmias, patients with heart failure experience a variety of other significant rhythm abnormalities. Atrial arrhythmias, particularly atrial fibrillation, are very common in heart failure and can contribute substantially to morbidity and mortality (82). Sinoatrial node function is abnormal in clinical and experimental heart failure (230, 273, 371), causing slow heart rhythms, "bradycardias," that may produce weakness, syncope, cardiac dysfunction, or circulatory collapse requiring artificial pacemaker implantation.

Many of the arrhythmic consequences associated with cardiac failure are due to disease-induced remodeling of ion-channel and ion-transport function that may initially be adaptive in nature. For example, the increases in ventricular APD that are typical of heart failure can improve contraction strength (270) and thereby support the weakened heart. The sinus bradycardia caused by remodeling due to cardiac failure may improve mechanical efficiency and have protective value (134). However, these adaptive responses, which presumably are intended to deal with physiological stresses, may have maladaptive consequences when invoked by chronic diseases associated with aging like heart failure, leading to arrhythmic syndromes and in some instances ultimately impairing contractile function (213). Specific heart failure-induced changes in ion-handling function and their significance are discussed below. The associated arrhythmia mechanisms, including enhanced automaticity, early and de-

layed afterdepolarizations, and reentry, are illustrated along with the major predisposing ion current modifications induced by heart failure in Figure 2.

B. Alterations in K^+ Currents

A consistent feature of action potentials recorded in ventricular myocytes from subjects with cardiac dysfunction is APD prolongation (6, 134, 171, 226). Early afterdepolarizations are frequently observed in relation to impaired repolarization (134, 171, 172, 226). Early afterdepolarizations are an important arrhythmia mechanism associated with delayed repolarization and are particularly prone to produce a specific form of ventricular tachyarrhythmia called Torsades des Pointes (85). K^+ currents play a key role in shaping the cardiac action potential, and remodeling-induced changes in K^+ currents are important contributors to repolarization abnormali-

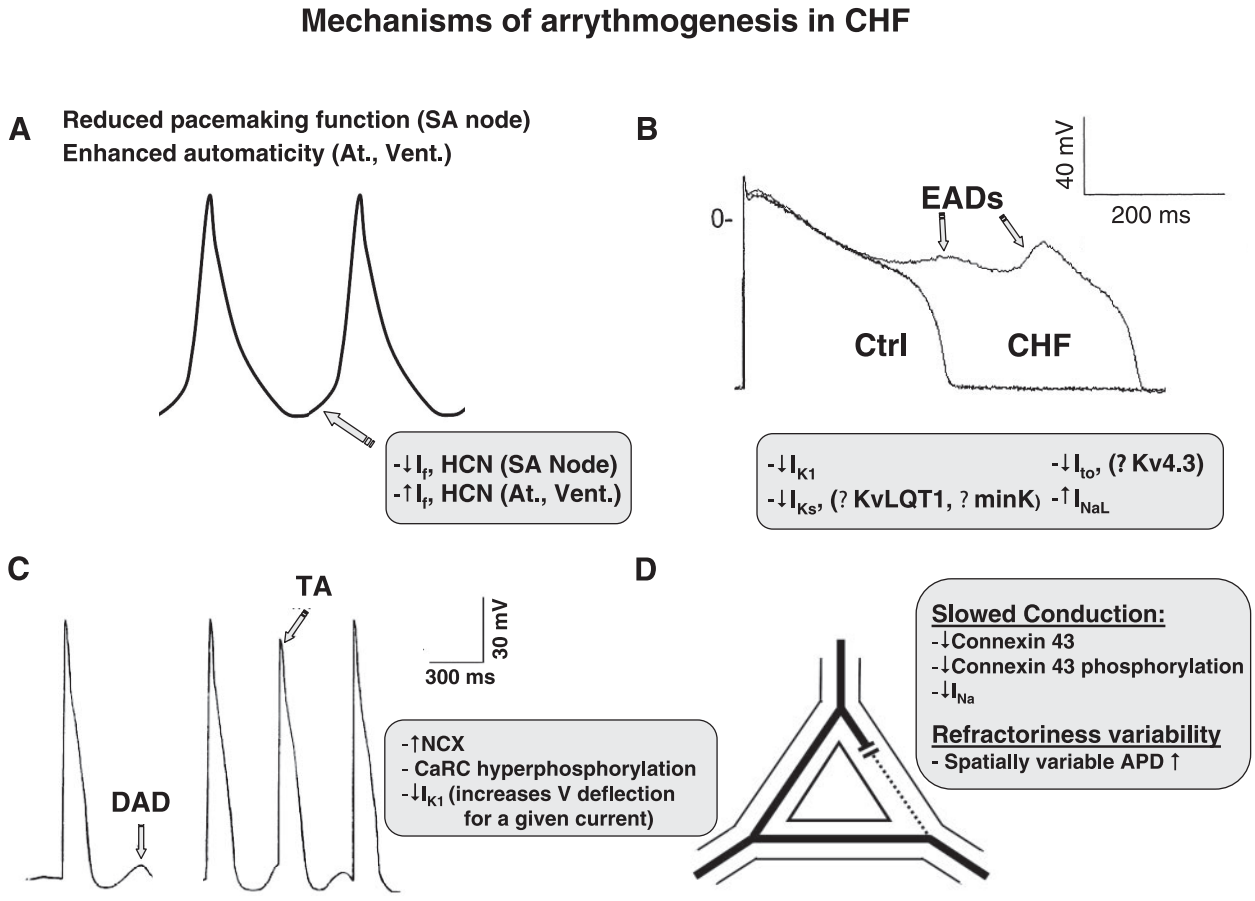

FIG. 2. Schematic summary of arrhythmia mechanisms in congestive heart failure (CHF). *A*: abnormalities in spontaneous pacemaking function (automaticity). Reductions in the nonselective cation current I_f and its underlying HCN subunit contribute to impaired SA node function and bradycardia in CHF. Increases in atrial and ventricular I_f may contribute to ectopic beat formation in CHF. *B*: repolarization impairment and early afterdepolarizations (EADs). CHF-induced reductions in repolarizing K^+ currents (including I_{K1}, I_{Ks}, and I_{to}) and increases in depolarizing plateau currents (like late I_{Na}, I_{NaL}) impair repolarization, prolong the APD, and promote formation of arrhythmogenic EADs. *C*: delayed afterdepolarizations (DADs). DADs are formed when cytoplasmic Ca^{2+} released by an abnormal diastolic SR Ca^{2+} discharge is exchanged for extracellular Na^+ via the Na^+-Ca^{2+} exchanger (NCX). Since NCX removes only 1 Ca^{2+} for every 3 Na^+ entering, it causes a net flow of positive ions to enter and depolarize the cell. If the DAD is large enough to raise the membrane voltage to threshold, an extrasystole is induced, a phenomenon known as triggered activity (TA). In CHF, DADs and TA are favored by *1*) increased NCX function; *2*) Ca^{2+} release channel (CaRC) phosphorylation, which increases the likelihood of abnormal diastolic Ca^{2+} release; and *3*) reduced I_{K1}, which increases diastolic membrane resistance and increases the voltage deflection caused by a given depolarizing current (see Fig. 4). *D*: reentrant activity. Reentry requires an impulse to block in one of two potential conducting pathways (unidirectional block), and then to return and reenter through the previously inexcitable zone. Reentry is favored by premature impulses (which can find one path refractory when the other can conduct, thereby triggering reentry), by variability in refractoriness (which provides the differences allowing for only one path to be activated) and by slow conduction, which allows enough time for the previously refractory pathway to recover by the time the returning impulse (stippled line) gets back to the site where it previously blocked. Factors favoring reentry in CHF include premature impulses arising from the mechanisms shown in *A–C*, refractoriness heterogeneity due to spatially variable APD increases, and slowed conduction caused by reduced connexin expression, decreased connexin phosphorylation, and reduced phase 0 I_{Na}. For a more detailed discussion of these mechanisms, see Reference 211.

ties associated with heart failure. Some of the changes in heart failure mimic congenital ion channelopathies that cause long QT syndromes, and congestive heart failure can be viewed as a form of acquired long QT syndrome (55).

1. Ion-current changes

Studies addressing K^+ current alterations in various models of cardiac failure are listed in Table 1. A variety of animal models have been used, with the most common involving rapid ventricular pacing (ventricular tachypacing) to produce an arrhythmic cardiomyopathy that parallels the clinical syndrome of tachycardiomyopathy associated with sudden death due to ventricular tachyarrhythmias (220). Twelve studies have assessed ventricular ion channels and one each changes in atrial, sinoatrial node, and Purkinje fiber cells from the specialized ventricular conducting system. The most consistent finding is a decreased Ca^{2+}-independent I_{to}, observed in all studies and all tissues other than the sinus node. In ventricular myocytes, seven studies show a decrease in the inward-rectifier current I_{K1}, but two other studies (268, 318) do not. In addition, the one study that has been performed on atrial cardiomyocytes (170) did not find any I_{K1} change with congestive heart failure. The variability in findings regarding I_{K1} is likely due, at least in part, to differences in the severity and duration of cardiac dysfunction. Most investigators have found no change in I_{Kr}, but Tsuji et al. (318) reported decreased I_{Kr} in ventricular-tachypaced rabbits. Of note, the current-voltage relation for I_{Kr} in the latter study was similar to that of I_{Ks}, with a half-activation potential of the order of +20 mV, whereas I_{Kr} typically activates ~30–40 mV more negatively than I_{Ks}, at −20 to −10 mV (275). Since I_{Kr} was defined by E-4031-sensitive current in the Tsuji study, it is possible that I_{Ks} rundown during E-4031 superfusion contributed significantly to the current differences between pre- and post-drug values. A subsequent study in the same model recorded I_{Kr} and I_{Ks} with more typical relative voltage dependencies, and noted no heart failure-induced change in I_{Kr} (319). Six studies found that heart failure decreases I_{Ks} in ventricular, atrial, and sinoatrial node cells; the only study that did not report I_{Ks} change was in Purkinje fibers (117), which require isolation by a "chunk" method that can artifactually suppress delayed-rectifier currents (363).

2. Molecular basis

The molecular basis of changes in K^+ current function associated with heart failure has been examined by several groups over the past 7 years (Table 2). Downregulation of transcript expression clearly plays a major role. Transcripts encoding I_{to} subunits, in particular Kv4.3, have been found to be reduced in heart failure by six studies. Protein expression changes are consistent with the mRNA data. The β-subunit KChIP2, which is critical for the formation of functional I_{to} channels (219), was found to be unaltered at the mRNA level by heart failure in two studies (8, 373) and downregulated in one (265); however, in all three studies KChIP2 protein expression was unaltered. Thus the evidence argues against a signif-

TABLE 1. *Changes in K^+ channel function in CHF*

Reference	I_{to}	I_{K1}	I_{Kr}	I_{Ks}	Other	Remarks
				Ventricular cardiomyocytes		
Beuckelmann et al. (22)	↓	↓				Explanted terminally diseased human hearts vs. undiseased donors
Kaab et al. (142)	↓	↓				VTP-induced CHF, dog
Thuringer et al. (311)	↓	↓			I_{SS} ↔	Syrian myopathic hamsters
Rozanski et al. (268)	↓	↔				VTP-induced CHF, rabbit
Tsuji et al. (318)	↓	↔	↓	↓		VTP-induced CHF, rabbit; I_{Kr}, I_{Ks} similar voltage dependence
Pogwizd et al. (246)	↓	↓				Volume/pressure overload rabbits
Li et al. (171)	↓	↓	↔	↓		VTP-induced CHF, dog
Li et al. (172)	↓	↓	↔	↓		Diseased human right ventricle
Zicha et al. (373)	↓					VTP-induced CHF, dog
Petkova-Kirova et al. (238)	↓			$I_{Kslow1,2}$ ↓	I_{SS} ↔	Mice overexpressing tumor necrosis factor-α
Rose et al. (265)	↓	↓		I_K ↓		VTP-induced CHF, rabbit
Tsuji et al. (319)			↔	↓		VTP-induced CHF, rabbit; characteristic I_{Kr},I_{Ks} voltage dependence
				Atrial cardiomyocytes		
Li et al. (170)	↓	↔	↔	↓		VTP-induced CHF, dog
				SA node cells		
Verkerk et al. (331)	↔	NP	↔	↓	I_f ↓	Volume/pressure overload rabbits
				Purkinje fiber cells		
Han et al. (117)	↓	↓	↔	↔		VTP-induced CHF, dog

CHF, congestive heart failure; NP, not present; VTP, ventricular tachypaced; SA, sinoatrial; ↓, decrease; ↔, no change.

TABLE 2. *CHF-related changes in K^+ channel subunit expression*

Reference	Subunit mRNA Changes Reported	Remarks
Kaab et al. (141)	Kv4.3 ↓; Kv1.4, Kir2.1, HERG ↔	
Wang et al. (337)	Kir2.1, Kir2.2, Kir2.3 ↔	Normal vs. CHF human hearts
Bodi et al. (25)		Protein: Kv4.2 ↓; Kv1.4 ↑
Borlak and Thum (28)	Kv4.3, Kir2.1 ↓; ERG↔; KvLQT1, minK ↑	Gene microarray analysis
Zicha et al. (373)	Kv4.3 ↓; KChIP2 ↔	Protein corresponds to mRNA
Akar et al. (8)	Kv4.3 ↓; KChIP2, Kir2.1, KvLQT1, minK ↔	Protein: Kv4.3 ↓; Kv1.4, ERG ↑; KChIP2, Kir2.1, KvLQT1, minK ↔
Rose et al. (265)	Kv1.4, Kv4.2, KChIP2, Kir2.1 ↓; Kv4.3, ERG, KvLQT1, minK ↔	Protein: Kv1.4, 4.2, 4.3, KChIP2, KvLQT1, Kir2.1 expression unchanged
Zicha et al. (371)	Atrial HCN4 ↑; SA node HCN2,4 ↓	Protein corresponds to mRNA
Tsuji et al. (319)	Kv1.4, Kv4.3, KvLQT1, minK ↓; ERG ↔	Protein corresponds to mRNA

CHF, congestive heart failure; ↓, decrease; ↔, no change; ↑, increase.

icant role for KChIP2 in heart failure-induced I_{to} downregulation. Three studies showed mRNA expression of Kir2.1, which encodes the principal cardiac I_{K1} subunit (337), to be unchanged in heart failure (8, 141, 337), whereas two studies (28, 265) showed it to be decreased. One study that noted decreased Kir2.1 mRNA expression found Kir2.1 protein levels to be unchanged (265). Thus the basis of I_{K1} suppression in congestive heart failure remains unclear, and the explanation may not simply involve decreased production of protein corresponding to the principal subunit. The results for the principal I_{Kr} subunit ERG have been consistent, with four studies noting unaltered mRNA levels. There is much more variability in results for the I_{Ks} subunits KvLQT1 and minK in studies of heart failure; one investigation showed a decrease, three no change, and one increased mRNA expression. Similar discrepancies exist in studies of I_{Ks}-related subunit protein expression. Thus posttranscriptional and posttranslational mechanisms may be important in heart failure-related I_{Ks} downregulation, a result that would not be surprising in view of the important regulation of I_{Ks} function by associated proteins in macromolecular complexes (187).

3. Arrhythmic consequences

The downregulation of K^+ currents can promote the occurrence of arrhythmogenic early afterdepolarizations, either by directly prolonging APD in the voltage range at which I_{CaL} reactivation generates afterdepolarizations (217, 334), or by reducing "repolarization reserve" (262), as illustrated in Figure 3. Repolarization reserve refers to the ability of cardiomyocytes to compensate for the loss of a repolarizing current by recruiting other outward currents, thereby minimizing the repolarization deficit. Loss of repolarization reserve can result in imperceptible repolarization changes at baseline because of remaining compensatory mechanisms, but greatly exaggerated repolarization abnormalities when a major compensating component is lost. Thus cardiac failure itself may not greatly prolong ventricular or Purkinje cell APD, but may result in exaggerated responses and tachyarrhythmias upon exposure to I_{Kr} blockers (117, 319). An additional, indirect

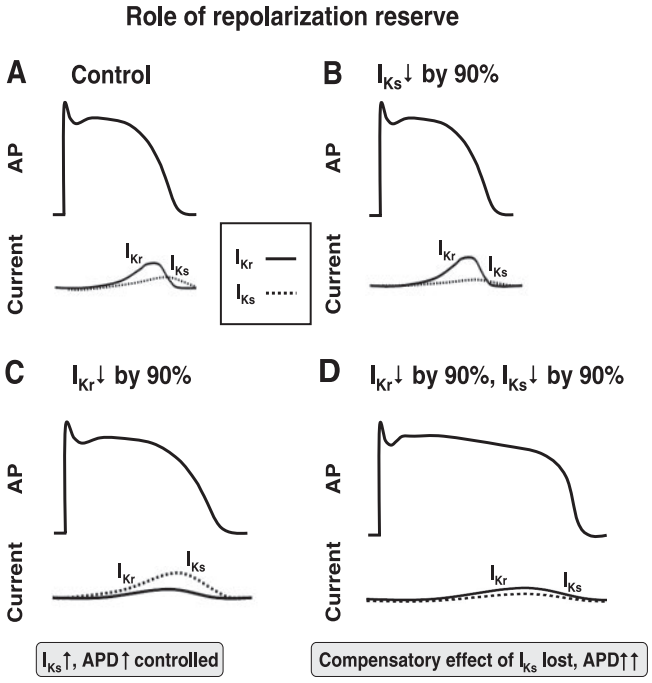

FIG. 3. The importance of repolarization reserve. *A*: normal action potential, along with a schematic diagram of corresponding rapid (I_{Kr}) and slow (I_{Ks}) delayed-rectifier current. For the normal action potential (AP), I_{Kr} is much larger than I_{Ks}. *B*: when I_{Ks} is reduced by 90%, the effect is very small because *1*) baseline I_{Ks} for the normal AP is small and *2*) I_{Kr} increases to compensate. *C*: when I_{Kr} is reduced by 90%, APD is prolonged, but because the longer AP leaves more time for activation of I_{Ks}, APD prolongation is limited. *D*: when I_{Ks} is now also reduced by 90%, the compensation is lost and APD increases substantially. Note that the APD-prolonging effect of blocking I_{Ks} when repolarization reserve is reduced by decreased I_{Kr} (compare *D* with *C*) is much greater than when repolarization reserve is intact (compare *B* with *A*). Similarly, the APD-prolonging effect of I_{Kr} inhibition is much greater when I_{Ks} is reduced (compare *D* with *B*) than when I_{Ks} is intact (compare *C* with *A*).

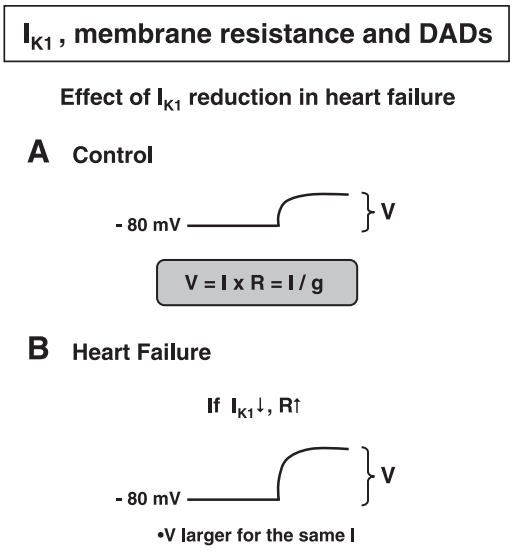

FIG. 4. Role of congestive heart failure (CHF)-induced I_{K1} reduction and consequent membrane resistance increase in delayed aftedepolarization promotion. *A*: the myocardial diastolic membrane resistance is determined by the normally high resting conductance (g) to K^+ through I_{K1}, which keeps the resistance very low. If an abnormal depolarizing diastolic current arises [e.g., generated by Na^+-Ca^{2+} exchange (NCX) of abnormally released Ca^{2+}], the resulting voltage deflection (V), given mathematically by the product of membrane resistance R and current amplitude I, will be small. *B*: if I_{K1} is reduced as in CHF, the membrane resistance increases and the voltage deflection caused by the same NCX-generated current will be greatly increased, potentially causing the cell to depolarize to threshold and fire an ectopic beat.

consequence of heart failure-induced K^+ current downregulation is the promoting effect of I_{K1} decreases on the occurrence of delayed afterdepolarizations. The large background I_{K1} conductance produces a very small resting membrane resistance. When I_{K1} is reduced, membrane resistance increases, causing a much bigger voltage deflection for a given quantity of depolarizing membrane current (Fig. 4). Pogwizd et al. (246) have shown this to be an important mechanism for the promotion of afterdepolarization-induced arrhythmias in a rabbit heart failure model.

C. Alterations in Ca^{2+} Currents and Cellular Ca^{2+} Handling

Cardiac failure has major effects on cellular Ca^{2+} handling. Some of the principal components of the Ca^{2+} handling system and associated abnormalities described in heart failure are illustrated in Figure 5. For a detailed discussion of cellular Ca^{2+} handling and coupled events, the interested reader is referred to some excellent recent reviews (19, 20). In brief, Ca^{2+} enters cardiomyocytes via a variety of Ca^{2+} conductances, of which that carrying L-type Ca^{2+} current (I_{CaL}) is the most prominent, with a potential but still controversial contribution of reverse-mode function of the Na^+-Ca^{2+} exchanger, NCX (164). The voltage-dependent transsarcolemmal entry of Ca^{2+} triggers the release of additional Ca^{2+} from sarcoplasmic reticulum Ca^{2+} stores through closely coupled sarcoplasmic reticulum Ca^{2+} release channels. This process is commonly called Ca^{2+}-induced Ca^{2+} release. The magnitude of Ca^{2+}-induced Ca^{2+} release is governed by a number of factors, including sarcoplasmic reticulum Ca^{2+} content and the function of Ca^{2+} release channels. Ca^{2+} release channel function is regulated by phosphorylation, which depends particularly on key intracellular phosphorylating enzymes like protein kinase A and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), as well as a variety of phosphatases which cause dephosphorylation. Sarcoplasmic reticulum Ca^{2+} content depends on cellular Ca^{2+} entry, particularly via I_{CaL}, Ca^{2+} removal from the cell (particularly via the sarcolemmal Ca^{2+} pump and forward-mode Na^+-Ca^{2+} exchange) and Ca^{2+} pumping into the sarcoplasmic reticulum by the Ca^{2+}-ATPase Ca^{2+} pump (the principal cardiac form of which is SERCA2a).

1. Changes in Ca^{2+} currents

Studies of I_{CaL} have produced varying results, with some showing a decrease (170, 203, 232) and others no change (21, 122, 142, 171, 194). These apparently discrepant results are likely due to two opposing heart failure-induced changes in I_{CaL}. The membrane density of I_{CaL} channels is reduced by cardiac failure (53, 122, 203). However, channel phosphorylation is increased, leading to reduced response to phosphorylating interventions (53, 232) and causing increased single-channel open probability (281) that compensates for the reductions in channel density.

2. Changes in Ca^{2+}-handling proteins

Heart failure causes very significant changes in Ca^{2+}-handling proteins. The results of relevant studies are summarized in Table 3. Na^+-Ca^{2+} exchange is enhanced by cardiac failure, and most studies show increases in Na^+-Ca^{2+} exchanger mRNA and protein expression. Decreases in SERCA2a function are also commonly observed, and most studies have shown decreases in corresponding mRNA. Studies of SERCA2a protein expression have provided discrepant results (Table 3): of five studies performed before 1998, three showed SERCA2a protein to be unchanged and two showed a decrease; however, six studies performed subsequently consistently show decreased SERCA2a protein expression. Phospholamban is a small regulatory peptide that controls sarcoplasmic reticulum Ca^{2+}-ATPase function: dephosphorylated phospholamban inhibits SERCA2a function by decreasing its affinity for Ca^{2+}, whereas phospholamban phosphorylation removes this inhibition. Phospholamban expression appears unchanged in heart failure; however, phospholamban phosphorylation is decreased, possibly because of

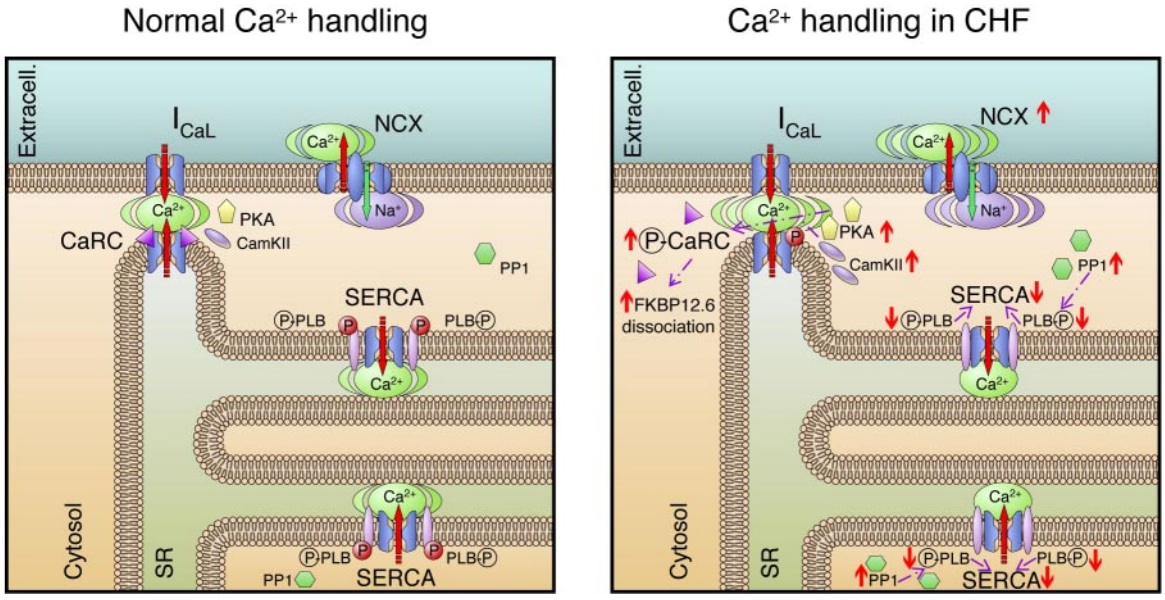

FIG. 5. Normal Ca^{2+} handling and Ca^{2+}-handling remodeling in congestive heart failure (CHF). *Left*: normal Ca^{2+} handling. Ca^{2+} entering through the L-type Ca^{2+} current (I_{CaL}) causes a triggered release of SR Ca^{2+} through the Ca^{2+} release channel (CaRC). CaRC function is stabilized by binding to calstabin (FKB12.6). When the cell repolarizes, cytoplasmic Ca^{2+} that has accumulated because of Ca^{2+} entry through I_{CaL} and consequent SR release is removed from the cytoplasm by two main processes: Ca^{2+} extrusion via Na^{+}-Ca^{2+} exchange (NCX) and Ca^{2+} uptake into the SR by the SR Ca^{2+}-ATPase (SERCA). SERCA function is regulated by phospholamban. *Right*: changes in Ca^{2+} handling with CHF. CaRCs are hyperphosphorylated by β-adrenergic controlled protein kinase A (PKA) and/or by Ca^{2+}/calmodulin kinase II (CaMKII). CaRC hyperphosphorylation dissociates FKB12.6, destabilizing the CaRC and causing abnormal diastolic Ca^{2+} leak from the SR. NCX activity is enhanced, promoting delayed afterdepolarization formation and reducing intracellular Ca^{2+} stores by extruding more Ca^{2+} out of the cell. SERCA function is reduced, both by reduced SERCA expression and by the action of protein phosphatase-1 (PP1)-mediated dephosphorylation of phospholamban. Decreased SERCA function further impairs SR Ca^{2+} stores and reduces contractility.

increased phosphatase activity and expression (113, 132), leading to reduced SERCA2a function (272, 283). Mishra et al. (198) found reduced Ca^{2+}/calmodulin kinase function in experimental heart failure, along with reduced phospholamban phosphorylation at both protein kinase A (Ser-16) and CaMKII (Thr-17) sites.

Sarcoplasmic reticulum Ca^{2+} leak is enhanced in congestive heart failure, likely because of abnormal Ca^{2+}-release channel function (284). Ca^{2+}-release channel protein expression is stable or decreased in heart failure, and important functional changes occur as a consequence of alterations in phosphorylation state and impaired interactions with calstabin (also commonly known by the abbreviation FKBP12.6). Calstabin binding modulates Ca^{2+}-release channel function, stabilizing open and closed states (38, 98, 356). A drug (JTV519) that stabilizes the calstabin-Ca^{2+} release channel interaction reduces sarcoplasmic reticulum Ca^{2+} leak and prevents adverse left ventricular remodeling in experimental heart failure (355). Manipulation of the calstabin-Ca^{2+} release channel interaction by changing its stoichiometry can rescue cardiac function (133).

Ca^{2+} release channels are found in macromolecular complexes along with protein kinase A, CaMKII, various phosphatases, and calstabin. Ca^{2+} release channel phosphorylation leads to calstabin dissociation (188). There is evidence for increased Ca^{2+} release channel phosphorylation by protein kinase A in heart failure (4, 188), with a potentially important role in progression of the condition (339). It has been suggested that protein kinase A phosphorylation destabilizes Ca^{2+} release channels by causing calstabin dissociation, thereby reducing sarcoplasmic reticulum Ca^{2+} stores via increased diastolic Ca^{2+} leak and producing triggered arrhythmias due to abnormal diastolic Ca^{2+} discharge (167). However, the precise role of protein kinase A phosphorylation of Ca^{2+} release channels in heart failure is controversial. Some studies failed to find increased protein kinase A hyperphosphorylation of Ca^{2+} release channels in experimental models of cardiac dysfunction (140, 221). Other investigators were unable to show significant effects of protein kinase A phosphorylation on Ca^{2+} release channel function (174, 298) and suggested that effects on phospholamban may be of greater importance for protein kinase A actions on Ca^{2+} release events (174). Whether heart failure causes protein kinase A hyperphosphorylation of Ca^{2+} release channels has been contested (347, 349), as has the ability of such phosphorylation to dissociate calstabin (348). There is evidence that abnormal Ca^{2+} uptake, rather than changed Ca^{2+} release channel function, may be crucial for sarcoplasmic reticulum Ca^{2+} handling abnormalities in heart failure (140). In at least one study, CaMKII-induced hy-

TABLE 3. *Changes in Ca^{2+}-handling proteins in CHF*

Reference	NCX	SERCA	CaRC	PLB	Remarks
Studer et al. (301)	M↑, P↑	M↓, P↓			Human CHF
Movsesian et al. (202)			P↔	P↔	Human CHF
Hasenfuss et al. (121)			F, P↓		Human CHF
Schwinger et al. (282)		F↓, M↓, P↔		M↓, P↔	Human CHF
Meyer et al. (195)		P↓	P↔	P↔	Human CHF
Kiss et al. (151)		P↓		P↓	Pressure-overload CHF guinea pigs
Go et al. (108)			P↓		IP_3R P↑; human CHF
Linck et al. (177)		M↓, P↔		M↓, P↔	Human CHF
Reinecke et al. (259)	F↑, P↑				Human CHF
Flesch et al. (94)		F↓, M↓, P↔		M↓, P↔	Human CHF
Flesch et al. (93)	F↑, M↑, P↑				Human CHF
Yao et al. (357)	F↓, M↓	F↓, M↓			VTP-induced CHF rabbits
Currie and Smith (61)		P↓		P↓	MI-induced CHF rabbits
O'Rourke et al. (231)	F↑, P↑	F↓, P↓		P↓	VTP-induced CHF dogs
Gupta et al. (112)		M↓, P↓		M↓, P↓	Coronary microemboli-CHF dogs
Yano et al. (356)			FKB12.6↓		Diastolic SR Ca^{2+} leak, VTP-induced CHF dogs
Netticadan et al. (221)		F, CaMK-P↓	CaMK-P↓ PKA-P↔		MI-induced CHF rats
Li et al. (170)	F↑, P↑				VTP-induced CHF dogs
Hobai and O'Rourke (126)	F↑				VTP-induced CHF dogs
Marx et al. (188)			PKA-P↑		Human CHF
Pogwizd et al. (246)	F↑				Rabbit pressure/volume overload
Jiang et al. (140)		P↓	F, PKA-P↔	P↔	Human CHF
Schillinger et al. (277)	P↑	P↓			Human CHF
Pogwizd and Bers (244)	F↑, M↑, P↑	F↓			Rabbit pressure/volume overload
Reiken et al. (258)			PKA-P↑		Human CHF
Xiong et al. (350)	F↑, M↑, P↑				VTP-induced CHF dogs
Ai et al. (4)			P↓, PKA-P, CaMK-P↑, FKB12.6↓		Diastolic SR Ca^{2+} leak due to CaMK-P CaRC, rabbit pressure/volume overload

F, function; M, mRNA expression; P, protein expression; VTP, ventricular tachypacing; MI, myocardial infarction; NCX, Na^+-Ca^{2+} exchanger; PKA-P, protein kinase A-phosphorylated moiety; SERCA, sarcoplasmic reticulum Ca^{2+}-ATPase; CaMK-P, Ca^{2+}/calmodulin kinase-phosphorylated moiety; CaRC, Ca^{2+} release channel; CHF, congestive heart failure; FKB12.6, calstabin; MI, myocardial infarction; SR, sarcoplasmic reticulum; IP_3R, inositol trisphosphate receptor; ↑, increase; ↓, decrease; ↔, no change.

perphosphorylation was quantitatively and functionally more important in heart failure-induced sarcoplasmic reticulum Ca^{2+} release channel dysfunction than that caused by protein kinase A, and produced important sarcoplasmic reticulum diastolic Ca^{2+} leaks (4). The deltaC isoform of CaMKII is particularly overexpressed in pressure overload-induced cardiac dysfunction, and targeted overexpression of this isoform leads to a cardiomyopathic phenotype with Ca^{2+} release channel hyperphosphorylation that precedes any signs of heart failure (366). Thus the weight of evidence suggests that CaMKII modulation of the Ca^{2+} release channel-calstabin interaction is particularly important for Ca^{2+}-handling abnormalities and triggered arrhythmias in heart failure.

3. Functional consequences

The changes in Ca^{2+} handling caused by heart failure have important implications for cardiac function and arrhythmogenesis. The cytoplasmic Ca^{2+} content increases resulting from Ca^{2+} entry through I_{CaL} and subsequent sarcoplasmic reticulum Ca^{2+} release are handled by two principal mechanisms: *1*) Ca^{2+} exchange for Na^+ across the sarcolemma to the extracellular space and *2*) SERCA2a-mediated transport back into the sarcoplasmic reticulum. Decreased SERCA2a activity and increased Na^+-Ca^{2+} exchange favor net Ca^{2+} efflux from the sarcoplasmic reticulum towards the extracellular space. This efflux reduces cellular Ca^{2+} stores and consequently decreases contractile function. Increased diastolic Ca^{2+} loss from the sarcoplasmic reticulum because of leaky Ca^{2+} release channels, resulting from hyperphosphorylation and decreased calstabin expression, further contributes to reducing Ca^{2+} stores and impairs contractility. In cardiomyocytes from dogs with heart failure, Na^+-Ca^{2+} exchange inhibition normalizes the systolic Ca^{2+} transient and sarcoplasmic reticulum Ca^{2+} load (125). Similarly, increasing SERCA2a function by adenoviral gene transfer of a dominant-negative construct of phospholamban improves SR Ca^{2+} stores and reverses contractile dysfunction (374). CaMKII overexpression by recombinant adenovirus infection into adult rabbit cardiomyocytes increases diastolic Ca^{2+} leak and reduces sarcoplasmic reticulum Ca^{2+} stores, but without suppressing contractility, suggesting active compensatory mechanisms (157). Enhanced calstabin binding improves function in heart failure, but only in wild-type, not calstabin-knockout, mice (338). Thus a variety of innovative interventions that

restore more normal Ca^{2+} homeostasis show promise for heart failure therapy.

Triggered activity related to delayed afterdepolarizations caused by spontaneous diastolic Ca^{2+} release is an important mechanism underlying ventricular tachyarrhythmias caused by cardiac failure (246, 332). Delayed afterdepolarizations occur in congestive heart failure despite reduced cell Ca^{2+} stores because of a number of features of cardiac failure-induced ion transport remodeling (4, 245, 246). *1*) Hyperphosphorylated Ca^{2+} release channels are prone to spontaneous diastolic Ca^{2+} release. *2*) For any given level of Ca^{2+} release, enhanced Na^+-Ca^{2+} exchange function increases the depolarizing current resulting from electrogenic Ca^{2+} extrusion, with three Na^+ (total charge +3) transported into the cell for every Ca^{2+} ion (charge +2) transported out. *3*) I_{K1} downregulation increases membrane resistance, resulting in a larger depolarization for a given inward current (Fig. 4).

D. Alterations in Na^+ Current

1. Na^+ current changes

I_{Na} is responsible for rapid initial (phase 0) action potential depolarization (280) and provides the electrical energy for electrical impulse propagation. As such, it is a key determinant of cardiac conduction speed. In addition, appropriate I_{Na} inactivation is essential for effective action potential repolarization; abnormalities in I_{Na} inactivation produce large inward Na^+ currents during the cardiac action potential plateau, causing repolarization failure, early afterdepolarizations, and life-threatening ventricular tachyarrhythmias (209). A variety of Na^+ channel abnormalities have been demonstrated in heart failure. Several studies suggest that peak I_{Na} is reduced (161, 321, 324, 372). Possible underlying mechanisms include posttranscriptional reductions in the cardiac I_{Na} α-subunit protein Nav1.5 (372) and posttranslational mechanisms (161, 321) such as deficient Nav1.5 glycosylation (321).

Additional data point to abnormalities in I_{Na} inactivation. Inactivation deficiencies result in an abnormally large late component of I_{Na}, which flows during the action potential plateau in failing human (183, 323, 324) and animal (321, 324) hearts. These abnormalities cause APD prolongation and early afterdepolarizations (321, 323). Single-channel studies show that both a bursting mode and scattered late openings are responsible for late I_{Na} (322).

2. Functional consequences

Since I_{Na} is a major determinant of cardiac conduction velocity, I_{Na} reductions contribute to conduction slowing in failing hearts. Slowed intracardiac conduction favors reentry (211) and contributes to dyssynergic and inefficient cardiac contraction. In addition, I_{Na} inactivation failure promotes arrhythmogenic early afterdepolarizations. The relative importance of I_{Na} dysfunction compared with other cardiac failure-related abnormalities causing conduction slowing (like connexin dysfunction and tissue fibrosis) and early afterdepolarizations (like K^+ channel abnormalities) is unclear.

E. Changes in Connexin Function

1. Cell-coupling and connexin changes

Conduction abnormalities are a common feature of cardiomyopathies, both clinical (149) and experimental (163). The underlying mechanisms have been a subject of intense investigation. In 1999, De Mello (66) described a decline in cell-to-cell coupling in cardiomyopathic hamsters. Subsequent studies showed substantial abnormalities in the expression, distribution, and regulation of the connexin proteins that effect electrical continuity between cardiomyocytes. The expression of the principal ventricular connexin isoform, connexin43, is downregulated by heart failure (5, 7, 78, 158, 243). Heart failure activates the mitogen-activated protein kinase C-Jun NH_2-terminal kinase (JNK), which downregulates connexin43 (239). In addition to decreasing connexin43 expression, heart failure causes phosphorylation changes that impair connexin43 function. Increased tyrosine phosphorylation by c-Src tyrosine kinase in cardiomyopathic hearts can impair connexin43 function (314), and more recent work points to defects in connexin43 phosphorylation (5, 7). Connexin43 dephosphorylation is due to increased colocalization with protein phosphatase-2, and impairments in cellular coupling can be improved by the phosphatase inhibitor okadaic acid (5). Changes in connexin43 expression may be regionally determined and aggravated by dyssynchronous contraction (243, 297). Increased heterogeneity of connexin43 expression is associated with an increased likelihood of ventricular tachyarrhythmias (152). Other connexins, including connexin45 (353) and connexin40 (78), are upregulated in failing hearts, possibly as a compensation for connexin43 downregulation. However, the functional importance of connexin40/45 upregulation in failing hearts is uncertain because neither is importantly expressed in the ventricles.

2. Functional consequences

Decreased connexin43 expression and phosphorylation contribute to conduction slowing in the failing heart (5, 7). Such conduction abnormalities in turn contribute to mechanical dysfunction and adverse ventricular remodeling (297), producing a deleterious positive feedback system: cardiac failure causes connexin dysfunction, which produces conduction abnormalities that result in dyssynchronous contraction, which further worsens the state of the failing heart. Conduction abnormalities also

predispose to the generation of reentrant arrhythmias. In addition, cellular uncoupling enhances APD heterogeneity (243), which favors the occurrence of reentry.

F. Hyperpolarization-Activated, Cyclic Nucleotide-Gated Nonselective Cation Channels

1. Changes in hyperpolarization-activated nonselective cation currents and corresponding subunits

Hyperpolarization-activated, cyclic nucleotide-gated (HCN) subunits encode the relatively nonselective cation channel I_f, which plays an important role in cardiac pacemaking (67, 300). Sinus node function is impaired in both clinical (273) and experimental (230, 371) heart failure. Downregulation of I_f causes the sinus node pacemaker dysfunction seen in failing rabbit hearts (331). Sinus node dysfunction in dogs with heart failure is associated with mRNA and protein downregulation of both HCN4 and HCN2 (371), suggesting that HCN subunit remodeling decreases I_f and impairs pacemaking. In contrast, HCN subunits are upregulated in failing atria (371), in which increased I_f function may contribute to heart failure-related arrhythmic activity from abnormal (ectopic) foci (127).

2. Functional consequences

Clinically significant sinus node dysfunction is common in patients with heart failure and may contribute to cardiac decompensation (9). Heart failure patients have an increased risk of bradycardia requiring artificial pacemaker implantation. When a pacemaker is needed, the pacing lead is usually installed in the right ventricle (because of ready access via peripheral veins), producing a dyssynchronous cardiac contraction pattern with left ventricular contraction lagging behind. Dyssynchronous contraction may cause adverse ventricular remodeling (297). Biventricular pacing, which is technically more complicated to install and more expensive, may be required to optimize cardiac function and prognosis in heart failure patients (50). Increased I_f in nonpacemaking tissues of heart failure patients may induce arrhythmias by causing abnormal impulse generation, which may be suppressible by recently introduced I_f blocking drugs (27).

III. REMODELING OF IONIC CURRENTS ASSOCIATED WITH CARDIAC DISEASE: MYOCARDIAL INFARCTION

A. Significance and Arrhythmic Consequences

Myocardial infarction refers to the death of cardiac tissue, most often caused by critical decreases in coronary artery blood flow induced by obstructive coronary artery disease. Prior myocardial infarction is an important risk factor for sudden cardiac death (144), due primarily to ventricular tachyarrhythmias. There is a very extensive experimental literature regarding ventricular arrhythmia mechanisms in myocardial infarction; for a detailed review, see Janse and Wit (135). Several mechanisms, including reentry and triggered activity due to early and delayed afterdepolarizations, contribute to ventricular tachyarrhythmia induction (63, 135, 253). Remodeling of ion-channel and transport processes cause important changes in cellular electrical activity and impulse propagation over days and weeks following acute infarction. Within the infarct zone itself, most ventricular cardiomyocytes die, leaving a surviving subendocardial Purkinje fiber layer with prolonged action potentials and enhanced automaticity (95, 296). Surviving cardiomyocytes in the viable border zone adjacent to a prior infarction have signs of reduced excitability: reduced action potential amplitude and dV/dt_{max} (181), along with postrepolarization refractoriness (44). Marked abnormalities of activation include very slow and sometimes discontinuous conduction (63, 99, 293). Features like electrotonic potentials and a decreased space constant suggest abnormal cell-to-cell coupling (294). These abnormalities cause severe conduction disturbances that strongly promote reentry. A particularly important arrhythmia mechanism is anisotropic reentry in the peri-infarction border zone (68, 192, 261). Acute myocardial infarction causes longer term (remodeling) changes over days to weeks, as well as important very early (within minutes to hours) functionally based ion-channel abnormalities caused by intracellular acidosis, K^+ loss, and membrane breakdown. In this review, we deal with only the longer term remodeling changes. Figure 6 illustrates how different forms of ion-channel remodeling contribute to anisotropic reentry in the presence of a healed myocardial infarction.

B. Alterations in K^+ Currents

Myocardial infarction causes substantial changes in K^+ current expression, density, and function. Key sources of postinfarction arrhythmias are situated in border-zone cells, including the often-spared epicardial rim, the lateral margins, and subendocardial Purkinje fibers nourished by left ventricular cavity blood (135). Alterations in border-zone tissues have been studied almost exclusively in large-animal models (dogs or cats). Studies in smaller-animal models (rats and rabbits) have examined changes in cells remote from the infarction, which reflect the effects of cardiac hypertrophy and/or failure caused by a loss of cardiac tissue in the necrotic infarct zone rather than infarction per se.

1. Changed K^+ current function in surviving border-zone cells

Increased border-zone cell APD, particularly in subendocardial Purkinje cells (95), causes early afterdepolar-

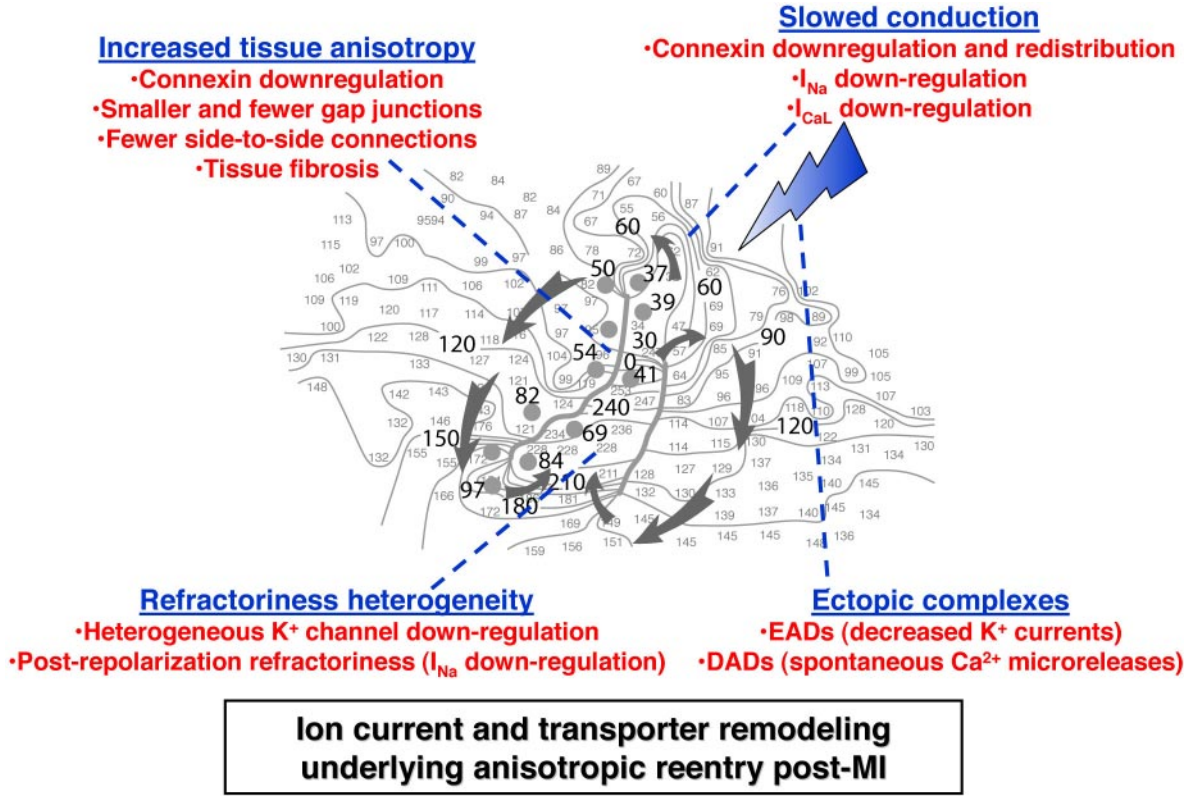

FIG. 6. Contributors to anisotropic reentry in myocardial infarction (MI). A principal mechanism underlying potentially lethal ventricular tachyarrhythmias post-MI is anisotropic reentry, represented schematically by the black activation map in the central part of the figure [From Peters et al. (237).] The numbers indicated on the map are times of electrical activation, and the curved lines (isochrones) indicate zones of tissue activated within 10 ms of each other. Crowded isochrones denote very slow conduction. Thicker black lines show lines of functional conduction block parallel to fiber orientation, due to the impaired transverse conduction (increased anisotropy) post-MI. The impulse travels slowly in two parallel streams (thick arrows) around the lines of block, which come together to conduct through the central corridor (thinner arrows) of the reentrant pathway. The ways in which ion-channel remodeling post-MI lead to this arrhythmia mechanism are indicated by the red points, organized into groups of dysfunction categories (blue underlined headings). Increased tissue anisotropy, which causes the unidirectional block needed for reentry initiation, arises because of connexin downregulation, reduced gap junction number and size, fewer side-to-side connections, and tissue fibrosis around muscle bundles. Unidirectional block is also favored by refractoriness heterogeneity due to spatially heterogeneous K^+ channel downregulation coupled with postrepolarization refractoriness. Slowed conduction, which allows enough time for the proximal part of the central corridor to recover excitability when the reentering impulse returns, is caused by connexin downregulation, I_{Na} decreases, and reduced I_{CaL} (I_{CaL} is particularly important for conduction in conditions of impaired coupling). Finally, the ectopic complexes needed to engage spatially variable refractoriness and initiate reentry are provided by early afterdepolarizations (EADs) promoted by K^+ current downregulation and delayed afterdepolarizations (DADs) caused by spontaneous diastolic Ca^{2+} releases from the SR.

izations and related arrhythmias (110). A variety of K^+ currents are downregulated in border-zone cells. Background K^+ conductance is reduced in surviving canine subendocardial Purkinje fibers (31), due to reduced I_{K1} and altered delayed-rectifier currents (240). Border-zone left ventricular cardiomyocytes show reduced I_{to} (181). I_{to} decreases are most prominent within days of acute infarction and tend to resolve over the subsequent 2 months (74). Delayed-rectifier currents are also reduced in border-zone cardiomyocytes (75, 139, 361). Both I_{Kr} and I_{Ks} decrease (139). The expression of subunits encoding I_{Kr} (ERG) and I_{Ks} (KvLQT1 and minK) is downregulated in 2-day postinfarction border-zone cells. ERG and KvLQT1 expression normalizes by day 5, whereas minK remains suppressed. Persistent decreases in minK with normalized KvLQT1 expression may underlie unusual delayed-rectifier currents with very rapid activation (75, 139), resembling currents produced by the expression of KvLQT1 in the absence of minK (18, 274). Overall, the multiple forms of K^+-channel dysfunction postinfarction impair repolarization and lead to early afterdepolarizations.

2. *Changes in K^+ currents in normal zones of hearts with prior myocardial infarction*

APD increases and ventricular arrhythmias are features of normal-zone tissues from postinfarction rat (130, 145, 146, 235, 253) and rabbit (179) hearts. Both reentry associated with spatial refractoriness heterogeneity and triggered activity are involved (179, 253). Decreases in I_{to}, I_{K1}, and total delayed-rectifier current (I_K) occur in rabbit

hearts (179). In rats, I_{to} decreases correlate most closely with downregulation of Kv4.2 subunits (106, 130, 145, 146, 235, 359). Metabolic disturbances contribute to postinfarction I_{to} decreases in rats (267, 269). There may be compensatory upregulation of Kv1.4 subunits (145, 146), although downregulation of Kv1.4 has also been reported (106). Decreases in rat I_K correlate with downregulation of the putative α-subunit Kv2.1 (130, 131). The effects of postinfarction remodeling on spatial dispersion of electrophysiological properties in noninfarcted tissues are controversial, with one study showing increases in dispersion (131) and another decreased spatial heterogeneity (145).

C. Alterations in Ca^{2+} Currents and Cellular Ca^{2+} Handling

Changes in Ca^{2+} handling contribute importantly to arrhythmogenesis postinfarction. Changes may be due to the infarct per se, and be restricted to the border zone, or may occur broadly in noninfarcted myocardium and be related to myocardial hypertrophy and/or failure. In this section, we limit ourselves to studies of Ca^{2+} handling in border-zone cells.

1. Changes in Ca^{2+} current

I_{CaL} is diminished in border-zone cells of dogs (2, 74), sheep (150), cats (241), and rabbits (178). I_{CaL} kinetic properties also change, with slowed recovery (74) and hyperpolarizing shifts in inactivation voltage dependence (241). The I_{CaL} response to dihydropyridine agonists (252) and tyrosine kinase inhibitors (351) is preserved in the border zone. T-type Ca^{2+} current (I_{CaT}) varies over time, being unchanged 5 days postinfarction (2) and increasing thereafter (74). In surviving subendocardial Purkinje cells, both I_{CaL} and I_{CaT} are reduced (34).

2. Changes in cellular Ca^{2+} handling

Ca^{2+} transients in border-zone cells are decreased in amplitude and show slowed recovery and decay (150, 176). SERCA2A is downregulated (150). The diminished and slowed Ca^{2+} transients are due to impaired spatial coordination of quantal Ca^{2+} releases, or sparks (178). Na^+-Ca^{2+} exchange function is unaltered, and action potential abnormalities are not responsible for Ca^{2+} handling abnormalities (251). Surviving subendocardial Purkinje cells show marked abnormalities in subcellular Ca^{2+} release events, with spontaneous and spatiotemporally nonuniform microreleases that can trigger arrhythmic episodes (32). Drugs that suppress Ca^{2+} microreleases by either inhibiting sarcoplasmic reticulum Ca^{2+} release channels or inositol trisphosphate receptors may constitute a novel antiarrhythmic approach postinfarction (33).

D. Alterations in Na^+ Current

1. Na^+ current changes

Surviving border-zone tissue is characterized by reduced phase 0 amplitude and upstroke velocity (dV/dt_{max}), suggestive of reduced I_{Na} (95, 293). These abnormalities in excitability favor unidirectional block and reentry (135). Isolated border-zone cardiomyocytes also have reduced dV/dt_{max} (181) and marked abnormalities in I_{Na}, including reduced current density, accelerated inactivation, and slowed reactivation (250). I_{Na} changes are related to abnormal cell-membrane localization of I_{Na} (Nav1.5) α-subunit protein (16). Computer simulations suggest that both I_{Na} and I_{CaL} abnormalities contribute to conduction abnormalities in the reentry circuit (16), in keeping with the key role of I_{CaL} in the context of reduced coupling (286). Protein kinase A activators partially improve I_{Na} in peri-infarct zone cells, and the response to phosphatase inhibitors suggests that I_{Na} is hyperphosphorylated (15). In late postinfarction rat cardiomyocytes, changes in I_{Na} properties and in ion-channel subunit expression suggest the appearance of atypical I_{Na} isoforms (12, 129); these changes may be due to generalized cardiac hypertrophy/dysfunction rather than infarction per se.

2. Functional consequences

Oxidative stress in postinfarction tissues produces reactive intermediates (especially E2-isoketals) that alter I_{Na} in a fashion similar to arrhythmogenic Nav1.5 subunit mutations and potentiate the effects of Na^+ channel-blocking drugs (96). The I_{Na} blocker lidocaine differentially affects peri-infarct zone cardiomyocytes (249). These differential effects may contribute to the tendency of I_{Na} blockers to cause malignant ventricular tachyarrhythmias postinfarction (216, 256). These paradoxical "proarrhythmic" effects of I_{Na}-blocking antiarrhythmic drugs on myocardial infarction tissues contribute to a mortality-enhancing potential (47).

E. Changes in Connexin Function

Cells in the surviving peri-infarct zone have prepotentials and notches on phase 0 upstrokes, reduced space constants, and discontinuous propagation due to abnormal cell-to-cell coupling (99, 294, 295). Marked changes in gap junction organization and connexin43 distribution occur within healed myocardial infarctions in human (236), canine (236, 237), and rat (190, 191) models. Gap junction changes precede the formation of the infarct scar and are thus a primary phenomenon unrelated to physical cell separation by scar tissue (236). Postinfarction remodeling of gap junction distribution in rats is linked to

desmosome and adherens junction alterations, with temporary intracellular junctional complexes formed as a component of complex remodeling of cell-to-cell and cell-to-extracellular matrix interactions (190). In healed myocardial infarctions from dogs, there are smaller and fewer gap junctions, with a decreased proportion of side-to-side versus end-to-end connections (236). Decreased side-to-side intercellular coupling contributes to transverse conduction block (perpendicular to fiber orientation) and anisotropic reentry (358). In hearts with inducible ventricular tachyarrhythmias, connexin43 disorganization extends through the full thickness of surviving myocardium at sites corresponding to the central common pathways of figure-8 reentrant circuits (237). Thus coupling abnormalities due to connexin changes are central to ventricular arrhythmogenesis postinfarction.

IV. REMODELING OF IONIC CURRENTS ASSOCIATED WITH ATRIAL FIBRILLATION

A. Significance and Arrhythmic Consequences

AF, which causes very rapid and highly irregular atrial firing, is the most common sustained arrhythmia in the developed world, with an age-dependent prevalence exceeding 10% in elderly populations (1, 316), and is a significant source of cardiovascular morbidity and mortality (215). AF results from a variety of conditions that cause ion-channel remodeling, including congestive heart failure and acute myocardial infarction, with features discussed in detail elsewhere in this review. In addition, however, AF itself causes ionic current remodeling, which plays a significant role in AF pathophysiology. AF alters atrial electrophysiological properties in a way that favors AF occurrence (this auto-perpetuation phenomenon has been called "AF begets AF"), both by increasing AF sustainability and by enhancing atrial vulnerability to AF induction by premature atrial beats (10, 71, 218, 342). The primary factor in AF-induced remodeling is the rapid atrial rate: any sufficiently rapid atrial tachycardia produces remodeling virtually indistinguishable from that caused by AF itself (303, 343). This form of remodeling, often called atrial tachycardia remodeling, is studied in experimental animals by rapidly pacing ("tachypacing") the atria for days or weeks. The principal mechanisms by which atrial tachycardia remodeling promotes AF involve facilitation of atrial reentry, via regionally heterogeneous atrial refractoriness abbreviation and abnormalities in atrial conduction properties (90, 101, 200, 342). In addition, there is evidence of enhanced focal atrial driver activity (200), possibly related to triggered activity associated with Ca^{2+}-handling abnormalities (333, 370). Figure 7 illustrates the role of ion-channel and transporter remodeling in atrial tachycardia remodeling. Conceptually, the atria adapt to AF in ways that enable them to maintain rapid atrial firing with minimal metabolic cost, but at the expense of making AF more likely to be sustained.

B. Alterations in K^+ Currents

1. Changes in voltage-dependent K^+ currents

Profound changes in K^+ current expression and function result from sustained atrial tachycardia. I_{to} is downregulated by atrial tachycardia, with reductions apparent at 24 hours and increasing over 6 weeks in animal models (29, 76, 362). I_{to} decreases also occur in patients with AF (30, 330, 345). The functional importance of I_{to} changes are not clear, because decreased I_{to} has complex and relatively small effects on human and canine atrial APD (59, 255). I_{to} reduction can favor impulse propagation under specific conditions (336). Results regarding the ultrarapid delayed-rectifier I_{Kur} are conflicting. In canine atrial tachycardia remodeling, I_{Kur} is unchanged (362). In cardiomyocytes from AF patients, results have been inconsistent (30, 36, 111, 330, 345), probably because of variability in patient populations. I_{Kur} changes in AF may be important because this current is atrial-specific in humans (91, 119) and is considered to be a potentially interesting target for atrial-selective anti-AF drug development. I_{Kur} downregulation could reduce the importance of the current (and thus the value of blocking it) in AF. However, the main factor determining the role of I_{Kur} in repolarization is the shape of the atrial action potential: the action potential-shortening associated with AF increases the contribution of I_{Kur} to atrial repolarization even when the current is downregulated (60, 340). Atrial tachycardia remodeling does not alter I_{Kr} or I_{Ks} in animal models (362). No voltage-clamp data are available regarding I_{Kr} and I_{Ks} in human atria, likely because of the technical difficulty of recording them in cells isolated with the "chunk" method (363).

AF-related changes in voltage-dependent (Kv) K^+ channel subunits are consistent with transcriptional downregulation. Kv4.3 is downregulated at both mRNA (29, 41, 43, 97, 111, 364) and protein (41, 43, 364) levels. Changes in subunits encoding I_{Kur}, principally Kv1.5, have been more variable, consistent with functional studies. Decreases in Kv1.5 protein (41, 43, 330) and mRNA (162) expression have been reported in some studies, but not others (97, 111). The discrepancies may be related to differences in underlying heart disease. Gaborit et al. (97) showed that the majority of the ion-channel mRNA changes in patients with AF and valvular heart disease are similar to changes in valve-disease patients with sinus rhythm and are therefore attributable to their underlying heart disease. It is thus very important to consider underlying heart disease in clinical studies of AF-related remod-

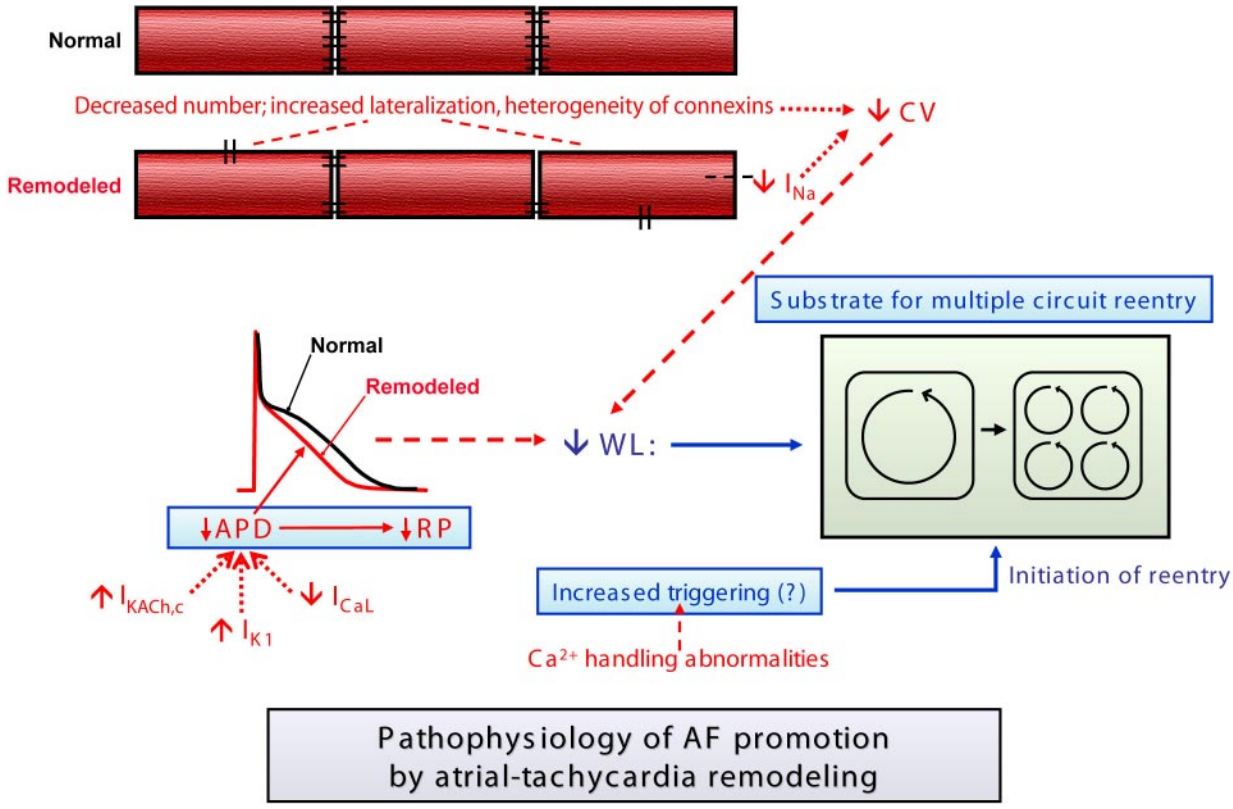

FIG. 7. Pathophysiology of AF promotion by atrial tachycardia remodeling (ATR). The ATR-induced changes in atrial-cardiomyocyte electrophysiology that result in AF promotion are indicated in red, with control-cell properties depicted in black. ATR creates a substrate for multiple circuit reentry; for a detailed review, see Nattel et al. (214). The reentry substrate is favored by decreases in refractory period (RP) and conduction velocity (CV). The minimum size of a functional reentry circuit is given by the wavelength (WL), or product of RP and CV. The shorter the WL, the larger the number of reentry circuits that can be maintained simultaneously. When the WL is reduced, the atria move from the condition shown at the *left* of the black *inset*, in which very few circuits are possible and the arrhythmia is unstable, to the situation at the *right*, for which many more circuits exist and simultaneous extinction of all circuits (as would be needed to stop arrhythmia) is unlikely. APD is decreased by decreased I_{CaL}, increased I_{K1}, and increased $I_{KACh,c}$. CV is decreased because of decreased I_{Na} and/or connexin changes, including decreased numbers, increased heterogeneity, and lateralization of connexins. Ca^{2+}-handling abnormalities producing abnormal diastolic Ca^{2+} release events have been reported with ATR, potentially causing delayed afterdepolarization-mediated ectopic complexes that could act as a trigger on the reentry substrate to initiate AF.

eling. Altered regulation of K^+ channels may also contribute to functional alterations. Increased CaMKII phosphorylation contributes to I_{to} changes in AF patients (307).

Several studies have reported alterations in delayed-rectifier K^+ channel subunits in AF patients, including decreased mRNA expression of ERG and KvLQT1 along with increased expression of minK (97, 162) and decreased ERG and minK protein expression (41). The significance of these differences is difficult to assess in the absence of information on I_{Kr} and I_{Ks} function.

2. Changes in inward-rectifier K^+ currents

Potentially important changes have been reported in inward-rectifier K^+ channel function in AF, particularly for I_{K1} and the acetylcholine-dependent K^+ current I_{KACh}. Several studies have reported increased background inward-rectifier current, attributed to I_{K1}, in atrial cardiomyocytes from AF patients (30, 70, 72, 97, 330, 345). Initial studies in dogs did not describe changes in I_{K1} (362), but increased I_{K1} was observed subsequently (52, 53). I_{K1} increases correspond to more negative resting potentials (reflecting greater resting I_{K1} conductance) in human (70) and canine (120) atrial tissues. Increased Kir2.1 mRNA (70, 97) and protein (97) expression have been reported in AF patients.

Stimulation of cardiac M_2 muscarinic cholinergic receptors by cholinergic agonists elicits a large K^+ current, I_{KACh}, which strongly promotes AF (156). Decreases in I_{KACh} subunit (Kir3.1 and 3.4) mRNA (41, 43, 70) and protein (41, 43) have been reported, corresponding to a decreased current response to M_2-receptor stimulation (70, 72). Canine cardiomyocytes possess constitutively active I_{KACh} (present in the absence of M_2-receptor agonists) that is upregulated by atrial tachycardia (81). Constitutive I_{KACh} is also upregulated in cardiomyocytes from AF patients (69) and contributes to atrial tachycardia remodeling-induced APD abbreviation and atrial-tachyarrhythmia promotion in canine atrium (51). The mechanism of atrial tachycardia-induced increases in constitutive I_{KACh} is unclear. The expression of the Kir3.1 and

Kir3.4 subunits that carry I_{KACh} is not increased and may even be decreased (41, 43, 70, 81). M_2-receptor protein is also decreased (81). Agonist-induced I_{KACh} is decreased to an extent similar to constitutive I_{KACh} increases, leaving total I_{KACh} unchanged (81). This observation suggests partial uncoupling of current from channel occupancy as a potential mechanism.

The ATP-sensitive K^+ current I_{KATP} is an important mediator of ischemia-induced electrophysiological changes (124), and a role for ischemia in atrial tachycardia remodeling has been suggested (136). Both increased I_{KATP} under simulated ischemic conditions (346) and decreased current with K_{ATP} agonists (17) have been reported with AF. Decreases, increases, and no change in the principal cardiac I_{KATP} α-subunit Kir6.2 have also been reported (41, 43). Thus the nature and significance of I_{KATP} changes remain obscure for the moment.

Recent analyses of changes in the human atrial action potential attributable to ion-current alterations in AF suggest a significant role for inward-rectifier current upregulation in AF-associated APD abbreviation and AF persistence (233, 365). Therefore, increases in I_{K1} and constitutive I_{KACh} probably play an important role in atrial tachycardia remodeling.

C. Alterations in Ca^{2+} Currents and Cellular Ca^{2+} Handling

1. Changes in L-type Ca^{2+} current and molecular basis

Tachycardia causes rapid increases in atrial cardiomyocyte Ca^{2+} loading (302). It would be logical for cells to adapt by reducing Ca^{2+} entry to minimize potentially lethal Ca^{2+} overload (211). Reductions in atrial cardiomyocyte I_{CaL} have been found consistently in atrial tachycardia remodeling (29, 30, 56, 329, 345, 352, 362). I_{CaT} does not appear to be similarly affected (362). Mimicking I_{CaL} downregulation by exposing normal atrial cardiomyocytes to I_{CaL} blockers reproduces cellular electrophysiological changes, like APD abbreviation and loss of APD adaptation, that are typical of atrial tachycardia remodeling (30, 329, 362). However, mathematical modeling suggests that the observed changes in I_{to} and I_{CaL} alone are insufficient to explain action potential abnormalities caused by atrial tachycardia (155, 255) and that additional factors like inward-rectifier current upregulation (365) and changes in intracellular Ca^{2+} handling (155) may contribute significantly.

Downregulation of mRNA encoding the Cav1.2 I_{CaL} α-subunit has been a consistent finding (29, 41–43, 326, 328, 364). In some experimental studies of atrial tachycardia remodeling, mRNA changes parallel those in I_{CaL} (362), while in others I_{CaL} decreases more rapidly than Cav1.2 mRNA and temporally corresponds better to changes in Ca^{2+} channel β-subunit mRNA (29). Some investigators have reported significant decreases in atrial Cav1.2 protein expression (41–43, 364) or dihydropyridine receptor density (102), whereas others have not (56, 279). Proteolysis due to activation of calpain protease may also contribute to I_{CaL} downregulation (39, 109). In an isolated tachypaced HL-1 atrial cell model, calpain inhibition prevents I_{CaL} protein-expression changes (40). Posttranslational regulatory changes have also been invoked. One study suggested a role for I_{CaL} dephosphorylation due to enhanced activity of protein phosphatase 2A (56). However, another study showed increased single-channel I_{CaL} open probability, which appeared to be caused by decreased phosphatase function (154). Some of the discrepancies in results may be due to differences in patient populations, given the many uncontrollable variables (patient disease, concomitant drug therapy, age distribution, varying cardiac function, etc.) in clinical studies.

Experimental heart failure also causes AF-promoting atrial remodeling, but with a distinct pattern from atrial tachycardia remodeling (170). APD is, if anything, increased. I_{K1} is unchanged and I_{Ks} is reduced (83), in contrast to atrial tachycardia remodeling in which they are increased and unchanged, respectively. In addition, atrial Na^+-Ca^{2+} exchange is increased in atria from failing hearts, potentially promoting triggered activity (170). There appears to be cross-talk between heart failure-induced and atrial tachycardia-induced remodeling, such that when both occur (as would happen when heart failure patients develop AF) the resulting remodeling is different from the sum of the individual effects produced by either condition (52).

2. Changes in cellular Ca^{2+} handling

Atrial cardiomyocytes from dogs subjected to atrial tachypacing show profound alterations in Ca^{2+} handling including reduced transients and slowed decay (303). These abnormalities cause cardiomyocyte contractile dysfunction (303). Corresponding phenomena are seen in atrial tissue from AF patients (278). Hypocontractility based on abnormal Ca^{2+} handling can be demonstrated with even short (several-minute) tachycardia (302) and likely contributes to the thromboembolic risk resulting from stasis in poorly contracting atria. Abnormal Ca^{2+} release channel function, with increased open probability at diastolic Ca^{2+} concentrations, is likely due to Ca^{2+} release channel hyperphosphorylation and calstabin unbinding (333). As in heart failure, enhanced diastolic Ca^{2+} leak may promote triggered activity. Spontaneous quantal Ca^{2+} release events (sparks) and Ca^{2+} waves are more frequently in atrial cardiomyocytes from AF patients (128). Sarcoplasmic reticulum Ca^{2+} stores and Na^+-Ca^{2+} exchange function are not different, consistent with a

primary abnormality in Ca^{2+} release channel function that could translate into triggered arrhythmias.

The results of biochemical studies of changes in Ca^{2+} handling proteins in AF are inconsistent. Some studies have reported no change in the mRNA or protein expression of important Ca^{2+} handling elements like phospholamban, calsequestrin, SERCA2a, and Ca^{2+} release channels (278, 320, 328). Other investigators found evidence for transcriptional downregulation of SERCA2a (42, 228) and Ca^{2+} release channels (228). Uemara et al. (320) showed no change in Na^+-Ca^{2+} exchange mRNA, whereas Schotten et al. (278) showed increased Na^+-Ca^{2+} exchange protein in AF. Clinical studies are difficult to standardize, because of variability in age, heart disease, drug therapy, and duration of AF, which probably explains the varying results in different studies.

D. Alterations in Na^+ Current

Relatively few studies have examined I_{Na} remodeling in AF. Gaspo et al. (100) showed that atrial tachypacing decreased I_{Na} over several weeks in dogs, roughly paralleling conduction changes. These I_{Na} reductions paralleled decreases in mRNA encoding the Na^+ channel α-subunit and corresponding protein (364). The development of AF does not further reduce I_{Na} in atrial tachypaced dogs (352). Decreased I_{Na} could promote AF by slowing conduction and promoting reentry, as proposed for loss-of-function Nav1.5 mutations associated with AF (229). In a study of ionic remodeling in AF patients, I_{Na} was not reduced (30). Gaborit et al. (97) noted decreased Navβ2 mRNA in valve-disease patients with AF compared with those in sinus rhythm, but Nav1.5 was unchanged. Similarly, goats with electrically induced AF do not show decreases in Nav1.5 mRNA (326). The discrepant findings regarding I_{Na} expression may be due to species differences.

E. Changes in Connexin Function

A variety of changes in connexin expression and distribution have been described in atrial tachycardia remodeling and AF, as summarized in Table 4. Unfortunately, there are many discrepancies among the available studies, which make interpretation difficult. The principal connexin subunits in atrium are connexin40 and connexin43, unlike ventricular tissue in which connexin43 appears to be the only functionally significant subunit (310). Upregulation of connexin43 was shown in two studies of atrial tachypaced dogs (86, 271), in one of which the ventricular response was not controlled and heart failure resulted (271). Neither study assessed connexin40 expression. Van der Velden and co-workers (325, 327) noted increased heterogeneity of connexin40 expression and reduced connexin40/43 expression ratio as a function of time with tachypacing-induced AF in the goat. The most consistent findings in AF patients are increased expression of connexins on lateral cell surfaces (159, 247) and increased heterogeneity (77, 143, 159). Increased overall connexin40 expression was noted in three studies (77, 247, 341), whereas three studies showed decreased connexin40 (159, 208, 344) and one study showed no change (143). For connexin43, one study showed an increase (341), one a decrease (159), and the other five no change. Overall, the only consistent finding is that the heterogeneity of connexin distribution increases, possibly because of a spatially variable redistribution from cell ends to lateral margins. Increased connexin heterogeneity could promote abnormal conduction patterns and favor

TABLE 4. *Changes in connexin expression in AF and atrial tachycardia remodeling*

Reference	Cx40	Cx43	Population (n)*	Remarks
			Experimental studies	
Elvan et al. (86)	ND	P↑	ATR dogs (AV block for rate control)	
Van der Velden et al. (327)	M/P↔	M/P↔	AF-induced ATR goats	Heterogeneous Cx40 in AF
Van der Velden et al. (325)	M↔	M↔	AF-induced ATR goats	Heterogeneous Cx40 in AF; ↓Cx40/43 P
Sakabe et al. (271)	ND	P↑	ATR + CHF dogs	↑Cx43 due to increased lateral staining
			Clinical studies	
Polontchouk et al. (247)	P↑	P↔	CAF (10); SR (10); rats with 24-h ATR	Lateralization; ↓anisotropic condxn (rats)
Dupont et al. (77)	M/P↑	M/P↔	Post-op AF (9); SR (36)	Heterogeneous Cx40 in AF
Kostin et al. (159)	P↓	P↓	CAF (31); SR (22)	Lateralization, regional variation
Nao et al. (208)	P↓	P↔	CAF-MVD (10); SR-MVD (10); SR (10)	Serine-phosphorylated Cx40 ↑
Kanagaratnam et al. (143)	P↔	P↔	CAF (13) vs. SR (27)	Increased Cx40 heterogeneity in AF
Wetzel et al. (341)	P↑	P↑	Lone AF (43); CAF-MVD (31); SR (15)	LA tissue
Wilhelm et al. (344)	P↓	P↔	CAF (12); post-op AF (12); SR (20)	Cx40↓ in CAF only; ↓Cx40/43 in CAF and post-op AF

P, protein; M, mRNA; ND, not done; CAF, persistent (chronic) atrial fibrillation; SR, sinus rhythm; MVD, mitral valve disease; ATR, atrial tachycardia remodeling; CHF, congestive heart failure; Cx, connexin; ↑, increase; ↓, decrease; ↔, no change. * For clinical studies, the number of patients in each group is indicated in parentheses.

reentrant excitation. A haplotype in the connexin40 promoter region that reduces connexin40 gene expression is associated with increased atrial vulnerability in a patient cohort (92), and connexin40-knockout mice are susceptible to induction of atrial tachyarrhythmias, including AF (115). The variability in connexin changes likely reflects different patient populations and experimental methods. Connexin changes may well play an important role in AF-related remodeling, but further clarification is needed.

V. A COMPARISON OF IONIC REMODELING IN VARIOUS ARRHYTHMOGENIC PARADIGMS

Although heart failure, healed infarction, and AF are quite different paradigms, they share a variety of common features. Table 5 compares the changes reported in various currents and transporters, as well as physiological consequences, for each. K^+ current remodeling is seen for all three, particularly in I_{to}; however, delayed-rectifier current remodeling occurs only for heart failure and myocardial infarction. A particular contrast occurs for inward-rectifier currents, with I_{K1} downregulated by heart failure and myocardial infarction, but I_{K1} (as well as constitutive I_{KACh}) being upregulated in AF. The stronger downregulation of K^+ currents in heart failure, as well as small (if any) changes in I_{CaL}, results in a propensity to generate early afterdepolarizations that is not seen in AF remodeling. Although Ca^{2+}-handling abnormalities have been described in AF, they are most clearly associated with reduced Ca^{2+} transients, whereas in cardiac failure and infarction Ca^{2+} release abnormalities associated with delayed afterdepolarizations and triggered activity have been described. There is evidence for abnormal Ca^{2+} release channel phosphorylation in atrial tachycardia remodeling, but its precise role in arrhythmia generation remains to be clarified. In contrast to the APD increases occurring with heart failure and infarction, APD is strongly reduced by atrial tachycardia. An increased likelihood of reentrant arrhythmia is a feature of all three paradigms: for cardiac failure and infarction, conduction abnormalities related to connexin dysfunction play a central role, whereas for AF, APD reduction is a central feature.

VI. MECHANISMS UNDERLYING THE DEVELOPMENT OF REMODELING

We know much less about the mechanisms underlying ion current and transporter remodeling than about the remodeling-induced changes themselves. A better understanding of the underlying mechanisms will be important in designing improved therapeutic strategies.

A. Factors Modulating Ion-Channel Transcription

As discussed above, for many ion-channel subunits that are remodeled in heart disease, changes in protein expression are paralleled by alterations in mRNA expression. Transcriptional regulation is a likely candidate mechanism (264, 308). Borlak and Thum (28) examined ion-channel mRNA expression changes in failing human hearts with the use of gene-expression microarrays and observed that induction of the transcriptional repressor m-Bop and the translational repressor NAT1 coincided with repressed cardiac gene expression. The most extensively studied transcriptional regulators are those for subunits underlying transient outward currents, the Kv4 and KChIP families. GATA transcription factors regulate

TABLE 5. *A comparison of ion current and transporter remodeling in CHF, healed MI, and AF/ATR*

Property	CHF	MI	AF	Remarks
I_{to}	↓ ↓	↓ ↓	↓ ↓	
I_{K1}	↓	↓	↑	Constitutive I_{KACh} ↑ in AF
I_{Kr}	↔	↓	↔	
I_{Ks}	↓	↓	↔	
I_{CaL}	↔(↓)	↓	↓ ↓	
SERCA	↓	↓	??	
CaRC	Ph ↑	DS	Ph ↑	
NCX	↑	↔	↔ (↑)	
I_{Na}	↓	↓	↔ (↓)	
Connexins	↓	↓	??	Increased lateralization in MI and AF Increased heterogeneity in all
APD	↑	↑	↓	
CV	↓	↓	↓ (↔)	
EADs	+	+	No	
DADs	+	+	?	
Reentry	+	+	+	

Ph, phosphorylation; DS, dyssynchronous release; (), effect reported less frequently than the primary effect shown; ?, unknown; ??, widely discrepant results in the literature; SERCA, sarcoplasmic reticulum ATPase; NCX, Na^+-Ca^{2+} exchanger; EADs, DADs, early, delayed afterdepolarizations; CHF, congestive heart failure; MI, myocardial infarction; AF, atrial fibrillation; ATR, atrial tachycardia remodeling; ↑, increase; ↓, decrease; ↔, no change.

Kv4.2 expression in cardiomyocytes, with GATA4 producing a larger increase of Kv4.2 transcription than GATA6 and the GATA coregulator FOG2 suppressing GATA regulation (137). The JAK-STAT pathway is involved in Kv4.2 downregulation following myocardial infarction in rats (84). Angiotensin II and phenylephrine independently downregulate Kv4.3 mRNA expression in neonatal rat cardiomyocyte hypertrophy, with phenylephrine suppressing mRNA transcription and angiotensin II destabilizing Kv4.3 mRNA (367). Aortic banding and phenylephrine exposure strongly downregulate KChIP2 expression in rat cardiomyocytes, with effects mediated by mitogen-activated protein kinases (138). A particularly important regulator of KChIP2 expression is the Iroquois transcription factor Irx, with Irx5 recruiting m-Bop to suppress KChIP2 transcription (58). Irx isoforms are expressed with a strong transmural gradient, with the Irx gradient generating transmural expression gradients in genes such as KChIP2 (58, 263). In addition to changes in transcription rate, changes in mRNA splicing can alter ion-channel and transporter expression in cardiac disease states (105, 204, 354).

It is conceivable that genetic factors are important determinants of ion-channel remodeling in response to cardiac disease. The regulation of gene expression patterns by common gene variants are thought to underlie congenitally based interindividual variation. Similarly, gene expression could be modified by interindividual variations in regulatory intronic or intergenic DNA elements responsive to cardiomyocyte stress, metabolic changes, neurohormonal messages, and other signaling pathways that underlie interindividual variability in acquired gene expression responses. However, there are presently no data regarding specific genetic haplotypes or polymorphisms that determine ion-channel expression changes and associated arrhythmia susceptibility patterns in response to cardiac disease.

B. Altered Regulation of Ion-Channel and Transporter Function

Ion-channel function is regulated by channel phosphorylation state, neurotransmitters, and interactions with other channels and transporters. Altered channel regulation is an important potential mediator of remodeling. There are potentially important changes in phosphorylation state of Ca^{2+} handling proteins in the failing heart. Phospholamban phosphorylation is reduced (132, 198, 222, 272, 283), contributing to SERCA2a dysfunction. Type 1 phosphatase activity is enhanced, contributing to dephosphorylation of Ca^{2+} handling proteins including phospholamban (49, 113, 132, 223). The enhancement in phosphatase activity is due to both increased expression of the catalytic subunit and reduced expression of a phosphatase-inhibitor protein, Inh-1 (113). Phosphatase inhibition can improve heart failure-induced abnormalities in Ca^{2+} transient relaxation (132). Enhanced Ca^{2+} release channel phosphorylation is important for the induction of spontaneous diastolic Ca^{2+} leak from the sarcoplasmic reticulum. Various isoforms of protein kinase C also importantly modulate the Ca^{2+} handling machinery. The α-isoform modulates dephosphorylation and cardiac contractility by phosphorylating protein phosphatase-1 (37). Protein kinase C inhibition reduces left ventricular dysfunction and remodeling postinfarction (35). β-Adrenergic regulation of ion-channel function may also be altered by remodeling. I_{CaL} is inhibited by β_3-adrenergic activation, which is enhanced in failing hearts (368). Heart failure-induced decreases in β_1-adrenoceptor expression in the face of preserved β_2-adrenoceptors leads to a blunted I_{CaL} response to adrenergic stimulation (123). Reduced basal I_{CaL} phosphorylation by protein kinase A may also contribute to atrial I_{CaL} downregulation by heart failure (26). The atrial muscarinic cholinergic receptors subtypes M2, M3, and M4 are downregulated by heart failure, along with their distinct coupled K^+ currents (287).

Relatively little is known about changed ion-channel regulation caused by prior infarction. Myocardial infarction induces an activator of G protein signaling (AGS8) that interacts directly with G$\beta\gamma$ subunits (276). Enhanced oxidative stress following infarction promotes dysfunction of both I_{to} (267) and I_{Na} (96). Isoproterenol-induced increases in I_{CaL} in cells from 5-day- and 2-mo-old infarcts are attenuated compared with the response of normal tissues (3, 241). The β-adrenergic receptor complex in epicardial border zone cells of 5-day-old infarctions shows multiple defects, including decreased β-adrenoceptor density; reduced basal, guanine nucleotide, isoproterenol, forskolin, and manganese-dependent adenylyl cyclase activities; diminished quantities of G_s protein α-subunits; and increased G_i protein α-subunit expression (299).

We are only beginning to learn about changes in channel regulation in AF. CaMKII upregulation in chronic AF may underlie changes in I_{to} kinetics (307), and hyperphosphorylation of Ca^{2+} release channels promotes sarcoplasmic reticulum diastolic Ca^{2+} leak (333). Reduced phosphorylation resulting from increased expression of the catalytic subunit of protein phosphatase 2a contributes to I_{CaL} decreases (56). Protein kinase C expression and function do not appear to be altered (46).

C. Altered Transport and Assembly Into Macromolecular Complexes

Recent work has highlighted the great importance of ion-channel membrane trafficking, as well as localization

in functional macromolecular complexes. Abnormal ion-channel trafficking is emerging as a key mechanism of congenital and drug-induced long QT syndromes (64, 80). We were unable to identify studies of cardiac ion-channel trafficking abnormalities in cardiac disease states, although congestive heart failure apparently causes increased trafficking of the water channel aquaporin-2 to the renal collecting duct apical membrane, contributing to water retention and hyponatremia (224). Angiotensin receptors form complexes with Kv4.3 channel subunits and provide an internalization scaffold regulating their cell-surface expression (73).

Another important area in rapid development is the study of ion-channel subunit assembly along with related and regulating proteins in specialized membrane microdomains (160, 182, 188). Altered regulation of Ca^{2+} release channels by physically associated proteins like protein kinase A, CaMKII, calstabin, and protein phosphatases 1 and A2 (188) is of paramount importance in failing hearts, as discussed in section II*C2*. Targeting of the components of this complex depends on binding via highly conserved leucine/isoleucine zippers (186). In addition to close physical interaction with Ca^{2+} release channels, Na^+-Ca^{2+} exchange protein localizes to the vertical T tubules and can be affected by perturbations of T-tubular organization (309) in cardiac disease. Dystrophin, an important component of lipid raft structures (182), is disrupted in various models of cardiac failure (148, 360), potentially leading to dysfunction of a variety of lipid-raft localized proteins. Calpain-induced dystrophin degradation in heart failure is suppressed by angiotensin converting enzyme (ACE) inhibition and angiotensin-1 receptor blockade, potentially contributing to their beneficial effects (304). The distribution of caveolins, a major protein constituent of lipid rafts, is markedly altered in failing hearts (257). An important interaction between annexin A5, caveolin-3, and NCX is altered by heart failure, with potential pathophysiological significance (45). Abnormalities in desmoplakin and cadherin localization postmyocardial infarction suggest that changes in connexin distribution and function may not necessarily be primary abnormalities, but may be due to alterations in macromolecular structures in which they are contained (190).

VII. THERAPEUTIC IMPLICATIONS OF IONIC CURRENT AND TRANSPORTER REMODELING

A. Remodeling-Induced Modification of the Response to Therapeutic Interventions

Disease-induced changes in ionic current and transport processes may significantly alter the responses to a variety of forms of clinical drug therapy. Changes may include reduced responsiveness, increased response, or increased susceptibility to adverse effects.

1. Heart failure-induced remodeling

Heart failure greatly increases the risk of arrhythmic death (153), and associated remodeling sensitizes patients to the proarrhythmic effects of a variety of drugs. The risk of drug-induced Torsades de Pointes arrhythmias caused by early afterdepolarizations is approximately doubled by heart failure (166, 196). This increased risk is caused by decreased repolarization reserve, which increases the repolarization-delaying effects of I_{Kr} blockers (117, 319). Drugs like β-adrenergic agonists and phosphodiesterase inhibitors, which increase cardiac contractility by increasing intracellular cAMP concentrations, Ca^{2+} loading, and Ca^{2+}-induced Ca^{2+} release, have been used extensively to improve cardiac function in patients with severe cardiac dysfunction. Unfortunately, in the longer term they have arrhythmogenic actions and increase mortality (13, 114, 180). Ionic remodeling likely contributes to these adverse responses. Heart failure-related Ca^{2+}-handling abnormalities that promote abnormal diastolic Ca^{2+} release and delayed afterdepolarizations are enhanced by agents that increase cAMP, enhancing protein kinase A activity and phosphorylation of the Ca^{2+} handling machinery. β-Adrenergic activation increases both I_{CaL} and I_{Ks}, with I_{Ks} acting as a "brake" to prevent excessive APD prolongation by the increased I_{CaL} plateau current (118). Congenital I_{Ks} deficiency predisposes to adrenergically induced ventricular tachyarrhythmias (147), a response that may be mimicked by functional I_{Ks} downregulation in heart failure (210). On the other hand, cardiac failure sensitizes to the anti-AF effects of I_{Kr} block by reducing repolarization reserve (169). Heart failure predisposes to the proarrhythmic effects of Na^+ channel blocking antiarrhythmic drugs (317), possibly by exaggerating drug-induced conduction slowing by suppressing I_{Na} and impairing connexin function.

2. Postmyocardial infarction remodeling

Many of the changes responsible for adverse effects of antiarrhythmic drugs in heart failure are also caused by postinfarction myocardial remodeling: increased APD, localized conduction slowing, downregulation of K^+ channels, abnormal diastolic Ca^{2+} handling, and impaired connexin function. It is not surprising, therefore, that myocardial infarction predisposes to the proarrhythmic actions of Na^+ channel blocking drugs (47, 216, 256) and I_{Kr} blocking agents (335). Responses to I_{Kr} blocking drugs may be reduced in postinfarction cells (361), perhaps because of I_{Kr} downregulation, illustrating the complexity of the electrophysiological substrate.

3. AF-related remodeling

The APD decreases caused by atrial tachycardia alter the contribution of different ionic currents during the action potential, increasing the relative contribution of I_{Kur} and decreasing that of I_{Kr} (60, 340). Consequently, the effects of I_{Kr} blockers are attenuated (79), and I_{Kr} blockers are rendered ineffective for AF occurring in tachycardia-remodeled atria (24, 169). The impairment in antiarrhythmic drug responsiveness caused by atrial tachycardia is reversible upon restoration of sinus rhythm (313).

B. Ionic Remodeling as a Target for Novel Therapeutic Approaches

With increasing awareness of the role of ionic current/transporter remodeling in the arrhythmic and functional consequences of cardiac disease, there has been growing interest in remodeling as a therapeutic target.

1. Heart failure-induced remodeling

Both β-adrenoceptor blockers and drugs suppressing the renin-angiotensin system (converting enzyme inhibitors and angiotensin receptor antagonists) suppress adverse remodeling and reduce mortality in patients with congestive heart failure (205). ACE inhibition reduced mortality and improved cardiac performance in rats with myocardial infarction-induced heart failure, while partially preventing Na^+-Ca^{2+} exchange upregulation as well as reduced SERCA2a and Ca^{2+} release channel activity (260). In addition, converting enzyme inhibition prevented downregulation of SERCA2a, phospholamban, and Ca^{2+} release channel mRNA and protein expression (285). Although converting enzyme inhibitors reduce mortality in heart failure patients, the primary effect seems to be on pump failure death rather than arrhythmic death, whereas β-adrenoceptor antagonists are more effective against lethal arrhythmias (205). This observation suggests that adrenergic effects that interact with remodeling, like Ca^{2+} release channel hyperphosphorylation or promotion of early afterdepolarizations by I_{Ks} downregulation, may be particularly important in heart failure-induced arrhythmias. Endothelin antagonists are being developed for clinical use in congestive heart failure (104). Administration of an endothelin receptor A antagonist to cardiomyopathic hamsters prevented APD prolongation; I_{Ca}, I_K, I_{K1}, and I_{to} downregulation; QT-interval prolongation; and ventricular arrhythmias, while improving overall survival (189). Early afterdepolarization mechanisms are being more specifically targeted. Drugs that enhance I_{Kr} suppress APD prolongation and early afterdepolarizations (369). Highly selective Na^+-Ca^{2+} exchange inhibitors are being developed, one of which was shown to suppress afterdepolarizations in cardiac Purkinje fibers (206).

Insights into the molecular basis of congestive heart failure-induced remodeling are leading to potential new avenues in molecular therapeutics. JTV519 stabilizes the calstabin-Ca^{2+} release channel interaction and prevents adverse ventricular remodeling in dogs with ventricular tachypacing-induced cardiomyopathy (355) and mice with heart failure caused by myocardial infarction (338). The beneficial effect of JTV519 is ablated in calstabin −/− mice, supporting the presumed molecular basis of action (338). Proof of principle has been achieved for a variety of gene therapy approaches. Adenoviral gene transfer of SERCA1 (the skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase isoform) increases Ca^{2+} pumping into the sarcoplasmic reticulum of rat ventricular myocytes (54). SERCA2a gene transfer restores normal sarcoplasmic reticulum Ca^{2+}-ATPase function and Ca^{2+} handling indices to neonatal rat myocytes with SERCA2a dysfunction induced by in vitro exposure to phorbol ester (107). In ventricular myocytes from patients with end-stage heart failure, overexpression of SERCA2a increases SERCA2a protein expression and function, reduces diastolic $[Ca^{2+}]_i$, and improves the systolic Ca^{2+} transient (65). SERCA2a gene transfer to aortic-banded failing rat hearts improves SERCA2a expression and ATPase activity to nonfailing levels, while restoring various indices of contractility to levels comparable to sham-operated rats (199). Gene transfer of K^+ channel encoding genes is being explored as an approach to restore normal K^+ channel function to the failing myocardium (225). A recently studied combined approach transfers both SERCA2a and Kir2.1 to improve contractile function and simultaneously abbreviate repolarization (87). Finally, transfer of HCN2 pacemaker genes is being studied as a way to create biological pacemakers for patients with bradyarrhythmias that can be associated with cardiac failure (242, 248, 254).

2. Postmyocardial infarction remodeling

Much less work has been done to study interventions targeting ion-handling processes postinfarction. An ACE inhibitor attenuated increases in refractoriness heterogeneity and prevented afterdepolarization formation in normal zones of rats with prior infarctions (175). The combined α- and β-adrenoceptor antagonist carvedilol suppresses downregulation of both Na^+ (184) and L-type Ca^{2+} (173) currents following myocardial infarction. Protein kinase A activators can partially restore suppressed I_{Na} in the infarct border zone (15); however, given the potentially deleterious effects of protein kinase A phosphorylation on Ca^{2+} release channels, this may not be a practical therapeutic approach.

3. AF-related remodeling

Considerable effort has been made to prevent the development of atrial tachycardia remodeling. There is evidence for a role of Ca^{2+} loading as a signal in tachy-

cardia remodeling (14, 168, 302). Early studies suggested that I_{CaL} blockers might prevent tachycardia-induced atrial electrophysiological changes (312); however, subsequent work showed that although I_{Ca} blockers prevent short-term (over 10–15 min) functional changes due to I_{CaL} inactivation caused by atrial tachyarrhythmias (59, 62), they are ineffective against changes caused by changes occurring over several days (88, 165). Other therapies reported to suppress shorter-term changes (11, 207) that failed to prevent longer-term remodeling (23, 288) include inhibitors of sarcolemmal Na^+-H^+ exchange and converting enzyme inhibitors. In contrast to the inefficacy of I_{CaL} blockers, drugs that target I_{CaT} prevent longer-term atrial tachycardia remodeling (88, 89, 227). The antiarrhythmic drug amiodarone has superior efficacy in clinical AF (266) and possesses I_{CaT} inhibiting properties (57). Dogs receiving amiodarone, but not the I_{Kr} blocker dofetilide or the I_{Na} blocker flecainide, during 7-day atrial tachypacing are protected against downregulation of Cav1.2 protein expression, APD shortening, and AF promotion (289).

There is evidence for oxidative injury in atrial tissues from AF patients (197) and atrial tachypaced-remodeled dogs (48). Simvastatin, which has both antioxidant and anti-inflammatory properties, is effective against experimental atrial tachycardia remodeling (292). In addition, the potent anti-inflammatory agent prednisone prevents tachycardia-induced electrophysiological changes and AF promotion (290).

Recent studies have examined the possibility of intervening in specific ion-channel changes of pathophysiological importance in atrial tachycardia remodeling. A gene therapy approach that targets K^+ channel β-subunit function prolongs porcine atrial APD in vivo (234). A highly selective inhibitor of cardiac I_{KACh} suppresses atrial tachyarrhythmias and APD shortening in left atrial preparations from atrial-tachypaced dogs, pointing to the importance of constitutive I_{KACh} enhancement in atrial tachycardia remodeling and the potential value of its inhibition as an antiarrhythmic approach (51). Evidence for cell-coupling abnormalities in AF has led to interest in gap junctions as a therapeutic target, and a gap junction coupling enhancing peptide (rotigaptide) has recently been developed. However, rotagaptide appears ineffective in canine tachypacing-related AF (291).

VIII. CONCLUSIONS

A great amount has been learned about remodeling of ion channels and transporters in heart disease. It is clear that such remodeling has major pathophysiological and therapeutic implications. It is also clear that an enormous amount remains to be learned and that the full implications of this knowledge are only beginning to be understood. Ion-channel function changes in response to cardiac disease represent the application of programs designed to adapt to physiological variation in a strongly pathological context. The undesirable consequences, like cardiac dysfunction and malignant arrhythmias, may be mitigated by understanding the response pattern and altering it in intelligent ways. The development of rationally based therapeutic interventions to suppress or modify remodeling presents exciting possibilities for therapeutic innovation.

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GRANTS

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