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REVIEW

When Calcium Turns Arrhythmogenic: Intracellular Calcium Handling during the Development of Hypertrophy and Heart Failure

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Alterations of intracellular Ca^{2+} handling in hypertrophied myocardium have been proposed as a mechanism of ventricular tachyarrhythmias, which are a major cause of sudden death in patients with heart failure. In this review, alterations in intracellular Ca^{2+} handling and Ca^{2+} handling proteins in the development of myocardial hypertrophy and the transition to heart failure are discussed. The leading question is at what stage of hypertrophy or heart failure Ca^{2+} handling can turn arrhythmogenic. During the development of myocardial hypertrophy and the transition to failure, Ca^{2+} handling is progressively altered. Recordings of free myocyte Ca^{2+} concentrations during a cardiac cycle (Ca^{2+} transients) are prolonged early in the development of hypertrophy. However, resting (or diastolic) Ca^{2+} does not increase before end-stage heart failure has developed. These alterations are due to progressively defective Ca^{2+} uptake into the sarcoplasmic reticulum that seems to be caused by quantitative changes of gene expression of the Ca^{2+} ATPase of the sarcoplasmic reticulum. Increased expression and activity of the Na^{+}/Ca^{2+} exchanger might compensate for this defective Ca^{2+} uptake, probably at the expense of increased arrhythmogenicity. When the Ca^{2+} handling proteins no longer efficiently counterbalance increasing intracellular Ca^{2+} – during stress conditions, resulting Ca^{2+} overload can lead to spontaneous intracellular Ca^{2+} oscillations, after depolarizations. Thus, after the transition to heart failure, Ca^{2+} overloaded sarcoplasmic reticulum, increasing resting intracellular Ca^{2+}, and increased Na^{+}/Ca^{2+} activity may all provoke afterdepolarizations, triggered activity, and finally, life-threatening ventricular arrhythmias. This increased susceptibility to ventricular arrhythmias in heart failure should not be treated with calcium antagonists.

Keywords: *arrhythmia; calcium; heart; hypertrophy, left ventricular; hyperthrophy, right ventricular; myocardium; death, sudden, cardiac; ventricular fibrillation*

Sudden death is the major cause of death in patients with heart failure, accounting for 30% to 70% of total mortality (1). Ventricular tachyarrhythmias, particularly ventricular fibrillation, contribute importantly to sudden death in patients with heart failure (2). These tachyarrhythmias may be caused by various arrhythmogenic factors that are pertinent to the failing heart. One of these factors is ventricular hypertrophy that commonly (but not always) precedes and accompanies heart failure (1,3). Ventricular hypertrophy is characterized by several electrophysiological abnormalities, including prolonged duration of the action potential, decreased resting membrane potential, slowed conduction velocity (by interstitial fibrosis), heterogeneous recovery following depolarization, and prolonged refractoriness (2,4). All of these abnormalities may facilitate the genesis and maintenance of ventricular tachyarrhythmias. In the failing heart, continuous sympathetic activation as well as decreased outward K^{+} currents and altered serum levels of K^{+} and Mg^{2+} further contribute to ventricular tachyarrhythmias (2,5).

Among the abnormalities in hypertrophied and failing myocardium are also alterations of intracellular Ca^{2+} handling. The handling of intracellular Ca^{2+} might already be affected in the hypertrophied heart (6-8) and is clearly altered in end-stage heart failure (9-13). Although never experimentally documented, these alterations could theoretically increase the susceptibility to ventricular arrhythmias. However, it is not clear at what stage of hypertrophy or heart failure alterations of intracellular Ca^{2+} handling occur and at what stage they can turn arrhythmogenic.

The purpose of this review is to discuss alterations of intracellular Ca^{2+} handling as well as its molecular ba-

sis in the development of myocardial hypertrophy and in the transition to heart failure. Based on theoretical considerations and recent experimental data, we herein propose that intracellular Ca^{2+} handling itself does not contribute to the increased incidence of ventricular arrhythmias associated with hypertrophy *before* the transition to heart failure.

This discussion about arrhythmogenic Ca^{2+} handling does not differentiate underlying causes or various models for myocardial hypertrophy and/or failure. Instead, alterations in intracellular Ca^{2+} handling are assigned to particular stages in the development of hypertrophy and the transition to heart failure. This simplification, however, should not deceive about the fact that underlying causes of myocardial hypertrophy and failure are important factors in the contribution of other arrhythmogenic factors and the prognosis of patients.

Alterations in Intracellular Ca^{2+} Handling in the Development of Hypertrophy and the Transition to Heart Failure

Progressive alterations in intracellular Ca^{2+} handling have been reported during the development of hypertrophy and heart failure (Table 1). In hypertrophied myocardium, recordings of free myocyte Ca^{2+} concentrations during a cardiac cycle (Ca^{2+} transients) may be prolonged (6,7) but are generally unchanged in their amplitude (6,14,18). Although not consistently observed (18), the decline rate of Ca^{2+} transients appears to decrease early in the development of hypertrophy (14) reflecting slowing of Ca^{2+} handling, particularly of Ca^{2+} removal from the cytosol. However, resting (or diastolic) Ca^{2+} is unchanged (14,18) and peak (or systolic) Ca^{2+} may be unchanged (7,14,18) or decreased (20).

In animal models of heart failure, intracellular Ca^{2+} handling is progressively altered (15,18). Ca^{2+} transients are clearly prolonged. However, resting intracellular Ca^{2+} is not different from control animals (15,18) and peak Ca^{2+} may be normal (15) or decreased (18). In end-stage human heart failure, finally, Ca^{2+} transients are further prolonged (9,10), the transient decline is slowed (13,21), peak Ca^{2+} is decreased (21), and resting Ca^{2+} is increased (9,10,21) as shown in bioluminescence and fluorescence studies of isolated myocytes or myocardial tissue. Thus, intracellular Ca^{2+} transients are progressively altered during the development of hypertrophy and heart failure. Importantly, however, resting intracellular Ca^{2+} does not increase before end-stage heart failure.

Intracellular Ca^{2+} and Ventricular Tachyarrhythmias

Increased intracellular Ca^{2+} has been suggested to be directly responsible for the initiation of potentially lethal ventricular tachyarrhythmias (22-24). The accumulation of Ca^{2+} in myocytes (Ca^{2+} overload) of the failing heart is believed to cause delayed afterdepolarizations and triggered activity (4). Recently, myocardial Ca^{2+} overload has been closely related to the initiation of tachyarrhythmic activity in isolated hearts or cardiomyocytes of rats and ferrets, as bioluminescence or fluorescence of intracellular Ca^{2+} indicators has shown (22,23,25). Moreover, controlled intracellular Ca^{2+} accumulation by programmed ventricular stimulation revealed a close correlation between intracellular Ca^{2+} and ventricular fibrillation threshold under nonischemic conditions (23). When Ca^{2+} loading of cardiomyocytes becomes sufficiently high, the sarcoplasmic reticulum can generate spontaneous Ca^{2+} oscillations that are not triggered by sarcolemmal depolarizations (22,24,25). If sufficiently synchronized, these Ca^{2+} oscillations may cause delayed afterdepolarizations and initiate ventricular fibrillation or modulate the initiation of ventricular fibrillation (24). Furthermore, myocardial Ca^{2+} overload may also facilitate the initiation of ventricular fibrillation by Ca^{2+}-induced cell-to-cell uncoupling (26), thereby slowing the conduction and amplifying the tendency for reentrant arrhythmias. This tendency is further amplified by slowed conduction velocity, heterogeneous recovery following depolarization, and prolonged refractoriness in the hypertrophied heart (4). Finally, as ventricular fibrillation itself causes Ca^{2+} overload (23,27), Ca^{2+} could contribute to sustaining ventricular fibrillation (22,25) and deterring of myocardial metabolism during ventricular fibrillation (28) as well as cause postarrhythmic contractile dysfunction (27,29).

Although most studies cited above point at a role that increased intracellular Ca^{2+} plays in the initiation and/or maintenance of ventricular fibrillation, none of these studies could experimentally link altered Ca^{2+} handling to arrhythmias in hypertrophied or failing hearts. Indeed, a causal role of altered Ca^{2+} handling in the increased incidence of arrhythmias in hypertrophied and failing hearts has been inferred but never experimentally demonstrated.

Table 1. Alterations of intracellular Ca^{2+} handling in the development of hypertrophy and heart failure[a]

Alteration of Ca^{2+} handling	End-stage heart failure			
	Hypertrophy	Heart failure		References
Intracellular Ca^{2+} transient duration	↑↑↔	↑↑	↑↑↑	6-10,14-17
decline time	↑↔	↑↑↔	↑↑↑↔	7,9,13-21
amplitude	↓↔	↓	↓	6,8,14,18,21
Peak or systolic Ca^{2+}	↓↔	↓↔	↓	7,14,15,17-21
Resting or diastolic Ca^{2+}	↔	↔↓	↑↑↑	7,9,10,13-15,18,19,21

[a]Symbols: ↑ increase; ↓ decrease; ↔ unchanged. Number of arrows represents body of supporting evidence for corresponding effect, disregarding species and underlying causes or models of hypertrophy/heart failure.

Linking Intracellular Ca^{2+} Handling to Ventricular Tachyarrhythmias in Hypertrophy and Heart Failure

While resting intracellular Ca^{2+} remains normal in *non-failing* hypertrophied myocardium (7,14,18), alterations in Ca^{2+} handling are unlikely to cause arrhythmias directly, unless Ca^{2+} handling is further perturbed (30). Such perturbation may occur during hypokalemia, hypoxia, ischemia, and increased inotropy or chronotropy (the latter frequently occurs in heart failure due to sympathetic activation). These conditions all lead to increased intracellular Ca^{2+} and challenge Ca^{2+} removal from the cytosol. Consequently, Ca^{2+} can turn arrhythmogenic when its handling is altered to a degree where a stress-induced increase of intracellular Ca^{2+} can no longer be efficiently counterbalanced and the resulting Ca^{2+} overload leads to spontaneous Ca^{2+} oscillations and afterdepolarizations.

Therefore, the stage at which Ca^{2+} handling turns arrhythmogenic can be experimentally estimated by analyzing both intracellular Ca^{2+} handling and the susceptibility to ventricular tachyarrhythmias during stress conditions at various stages of hypertrophy and heart failure. This analysis was recently applied to spontaneously hypertensive rats, a genetic model of early hypertrophic adaptation to hypertension and subsequent transition to heart failure. As in previous reports (31,32), non-failing hypertrophied hearts of hypertensive rats were more susceptible to ventricular fibrillation than hearts of control rats that had no myocardial hypertrophy (16). Surprisingly, however, during stimulation stress, such as rapid ventricular pacing or preprogrammed ventricular stimulation, isolated perfused hearts from both groups of rats handled intracellular Ca^{2+} similarly (16). Moreover, in spontaneously hypertensive rats, the correlation between the ventricular fibrillation threshold and intracellular Ca^{2+} was unaltered, indicating that the susceptibility to ventricular fibrillation was increased without any changes in Ca^{2+} handling (16). The analysis of intracellular Ca^{2+} transients could not detect potentially arrhythmogenic local Ca^{2+} oscillations or focal non-propagating release of Ca^{2+} from the sarcoplasmic reticulum, the so-called Ca^{2+} sparks (16). However, overall Ca^{2+} handling, as reflected in intracellular Ca^{2+} transients, appeared normal in hypertrophy and is therefore unlikely to cause an arrhythmogenic elevation of resting Ca^{2+}(16).

The finding of unaltered intracellular Ca^{2+} handling in hypertrophied myocardium may be explained by recent reports of altered gene expression and function of the proteins involved in myocardial Ca^{2+} handling in hypertrophy and heart failure. In the nex chapters, we will therefore review the molecular basis of altered Ca^{2+} handling in hypertrophied and failing myocardium.

Molecular Basis of Myocardial Intracellular Ca^{2+} Handling

Myocardial Ca^{2+} handling is under the control of various proteins that regulate the Ca^{2+} fluxes to and from the cytosol (33). Simplified for the purpose of this review, these proteins include the Ca^{2+} ATPase of the sarcoplasmic reticulum and its inhibitor – phospholamban, which are responsible for the reuptake of Ca^{2+} from the myofilaments and cytosol into the sarcoplasmic reticulum (Fig. 1). Other Ca^{2+} handling proteins include the sarcolemmal Na^{+}/Ca^{2+} exchanger and Ca^{2+} ATPase, both extruding Ca^{2+} from cytosol, however, with only minor contribution from the sarcolemmal Ca^{2+} ATPase. Furthermore, L-type Ca^{2+} channels and probably also reversed Na^{+}/Ca^{2+} exchange mediate Ca^{2+} entry in cardiomyocytes. Subsequently, entering Ca^{2+} can directly activate the contractile filaments or trigger Ca^{2+}-induced Ca^{2+} release at the calcium release channel of the sarcoplasmic reticulum (ryanodine receptor) to potentiate the activation of the contractile filaments (33).

The regulatory proteins calsequestrin (storage protein of the sarcoplasmic reticulum) and calmodulin (probably regulating sarcolemmal Ca^{2+} ATPase, the Na^{+}/Ca^{2+} exchanger, and phospholamban) are not included in this review. Although these proteins significantly contribute to myocardial Ca^{2+} handling, they are either not functionally changed (calsequestrin) (34-36) or insufficiently studied (calmodulin) at different stages of hypertrophy and heart failure. Similarly, a role of the Na^{+}/K^{+} exchanger and its complex expression of subunits in hypertrophy and heart failure (37) would be too speculative to discuss in this review on arrhythmogenic Ca^{2+} handling.

Molecular Basis of Altered Intracellular Ca^{2+} Handling in Myocardial Hypertrophy and Heart Failure

Various changes of proteins involved in intracellular Ca^{2+} handling in myocardium have been demonstrated at different stages of myocardial hypertrophy or failure (Table 2). In severely hypertrophied or failing myocardium, the Ca^{2+} ATPase of the sarcoplasmic reticulum is decreased at the mRNA (36,43,51-55,58) and the protein levels (11,35,36,40). Similarly, phospholamban is decreased at the mRNA level (36,52,53,58) and the protein levels (40). Interestingly, in early myocardial hypertrophy, mRNA levels (43,50,51) and protein levels (43) of the Ca^{2+} ATPase of the sarcoplasmic reticulum are increased (50) or unchanged (40,43,51), whereas in severe hypertrophy, these levels are decreased (43,50,51). Accordingly, in early hypertrophy, Ca^{2+} uptake into the sarcoplasmic reticulum is increased (38,39) or unchanged (39,40), whereas in severe hypertrophy or in heart failure, this uptake is decreased, as demonstrated in animal models of heart failure (40,41,43,45,46) and in human failing hearts (11,48). These findings may explain the limited function and the reduced capacity of failing myocardium to maintain low resting intracellular Ca^{2+}. However, several investigators found unaltered levels of the Ca^{2+} ATPase of the sarcoplasmic reticulum (34,49) and of phospholamban (34,35, 49) as well as unaltered Ca^{2+} uptake into the sarcoplasmic reticulum (47) in patients with terminal heart failure. Although the data concerning protein levels of the Ca^{2+} ATPase of the sarcoplasmic reticulum and phospholamban have not been uniform, most investigators agree on reduced activity of the Ca^{2+} ATPase of the sarcoplasmic reticulum as a cause of altered Ca^{2+} handling in hypertrophied and failing myocardium.

Table 2. Changes in the expression and function of intracellular Ca^{2+} handling proteins in the development of hypertrophy and heart failure[a]

Protein		Hypertrophy	Heart failure	End-stage heart failure	References
Sarcoplasmic reticular Ca^{2+}	uptake	↓↓↔	↓↓↔	↓↓↓	8,11,38-49
SERCA	mRNA	↓↓↔	↓	↓↓↓	11,36,42,43,49-57
	protein	↓↓↔	↓↓	↓↓↔	8,11,34-36,38,40,42,43,49, 56,57
Phospholamban	mRNA	↓	↓↔	↓↓↓	36,42,43,49,51-53,58
	protein	↔	↓	↔	34,35,40,49
Na^+/Ca^{2+} exchanger	activity	↑↓	↑	↑↑	57,59-63
	mRNA			↑↑	56,64,65
	protein			↑↑	56,57,63-65
Sarcoplasmic reticular Ca^{2+}	release	↓↔			8,39
Ryanodine receptor	density	↓↓↔	↓↓	↑	39,46,50,61,66-68
	mRNA	↓↓		↓↓↔	8,36,42,50,53,68-70
	protein	↓		↔	35,68
L-type Ca^{2+} channel	binding density	↔	↓	↑↓↔	55,61,71-74
	mRNA			↓	55
Sarcolemmal Ca^{2+} ATPase	activity	↑	↓		75

[a]Symbols: ↑ increase; ↓ decrease; ↔ unchanged. Number of arrows represents body of supporting evidence for corresponding effect, disregarding species and underlying causes or models of hypertrophy/heart failure.

In contrast to the Ca^{2+} ATPase of the sarcoplasmic reticulum, the Na^+/Ca^{2+} exchanger has recently been shown to be increased in failing rabbit and human myocardium at the mRNA (56,57,65) and protein levels (56,57,63,65) as well as more active (57,63). This increase could be of functional relevance for the modulation of cardiac contractility by increasing intracellular Na^+ concentrations *via* reversed Na^+/Ca^{2+} exchange (65) and/or by Ca^{2+} removal in Ca^{2+} overloaded myocytes. This way, increased Na^+/Ca^{2+} exchanger activity might compensate for depressed activity of the Ca^{2+} ATPase of the sarcoplasmic reticulum. Such compensation might be activated at an early stage of hypertrophy because mRNA and protein levels (64) as well as the activity (59,62) of the Na^+/Ca^{2+} exchanger are increased in animal models of myocardial hypertrophy (59,62,64). The activity of another Ca^{2+} extrusion system, the sarcolemmal Ca^{2+} ATPase, appears to be reduced in failing hamster hearts (75). However, the sarcolemmal Ca^{2+} ATPase does not contribute significantly to cytoplasmic Ca^{2+} removal on a beat- to-beat basis in cardiomyocytes (33).

Unfortunately, the data about L-type Ca^{2+} channels and ryanodine receptors in hypertrophied and failing myocardium have been contradictory. Specifically, mRNA levels (55) and density (55,61,72) of L-type Ca^{2+} channels have been reported to be decreased (55), increased (72), or unchanged (61) in end-stage heart failure. Similarly, the Ca^{2+} current density may be decreased (76) or unchanged (13,77) in hypertrophied myocardium (76,77) or terminally failing myocardium (13). Furthermore, ryanodine receptor mRNA levels (36,53,68-70), but not as well its protein levels (35,68), are decreased in severely hypertrophied (42) or failing hearts (36,53,68-70). Accordingly, ryanodine receptor density may be increased (68), unchanged (39), or decreased (46,66,67) in severely hypertrophied or failing hearts (8,46,66,67). Similar to the Ca^{2+} ATPase of the sarcoplasmic reticulum, mRNA levels of the ryanodine receptor appear to be increased in mild myocardial hypertrophy and decreased in severe hypertrophy (50). Other proteins, such as sarcolemmal Ca^{2+} ATPase, calsequestrin, calmodulin, or Na^+/K^+ ATPase, are currently unlikely or uncertain to contribute to the alterations in the intracellular Ca^{2+} handling in the hypertrophied or failing myocardium.

Thus, at present, defective Ca^{2+} uptake into the sarcoplasmic reticulum is the main candidate to be accused of causing alterations in intracellular Ca^{2+} handling in hypertrophied or failing myocardium. This defect is likely to be associated with the degree of myocardial hypertrophy and failure, and appears to be caused, at least in part, by quantitative changes of gene expression of the Ca^{2+} ATPase of the sarcoplasmic reticulum. Furthermore, de-

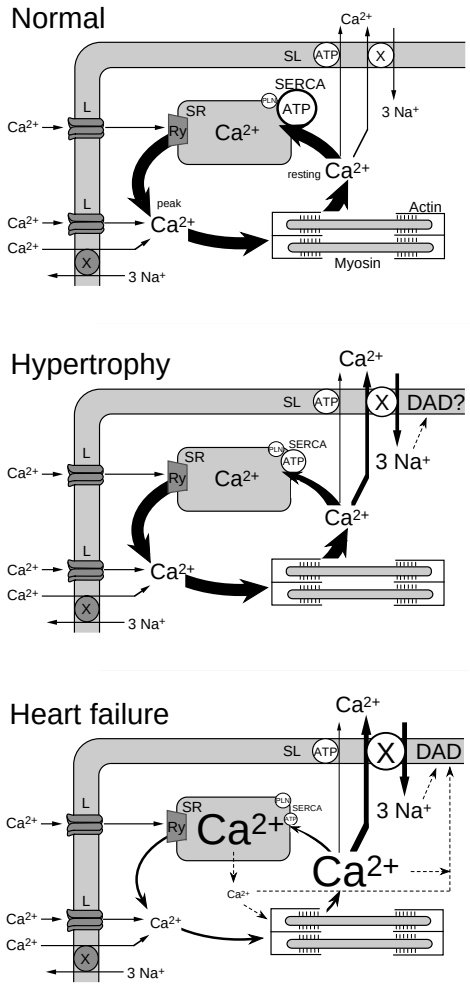

Figure 1. Schematic representation of proposed arrhythmogenic Ca^{2+} handling in a cardiomyocyte with the major Ca^{2+} handling proteins and pathways at the normal (top), hypertrophied (middle), and failing stage (bottom). Proteins mediating Ca^{2+} entry into the cytosol are shown in dark gray (L – L-type Ca^{2+} channel; X – Na^+/Ca^{2+} exchanger; Ry – ryanodine receptor) and those removing Ca^{2+} in white (PLN – phospholamban; SERCA – sarcoplasmic reticular Ca^{2+} ATPase). Arrows indicate the direction of Ca^{2+} transport and dashed arrows indicate pathways leading to delayed afterdepolarizations (DAD). **Top:** in normal cardiomyocytes, stress-induced increase of cytosolic Ca^{2+} is efficiently counterbalanced by SERCA and, to a lesser extent, the sarcolemmal (SL) Na^+/Ca^{2+} exchanger, both maintaining low arrhythmogenicity. **Middle:** in hypertrophied cardiomyocytes, defective sarcoplasmic reticular Ca^{2+} uptake is compensated for by increased Na^+/Ca^{2+} exchanger activity, preserving efficient cytosolic Ca^{2+} removal. The rate of cytosolic Ca^{2+} removal and accumulation is unaltered, and resting (diastolic) and peak (systolic) Ca^{2+} remain normal. However, electrogenic Na^+/Ca^{2+} exchange may increase arrhythmogenicity. **Bottom:** in failing cardiomyocytes, severely defective sarcoplasmic reticular function can no longer be compensated for by increased Na^+/Ca^{2+} exchange. Resting Ca^{2+} increases and peak Ca^{2+} decreases. Increasing resting intracellular Ca^{2+}, a Ca^{2+} overloaded sarcoplasmic reticulum, and increased Na^+/Ca^{2+} activity may all provoke afterdepolarizations, triggered activity, and thus life-threatening ventricular arrhythmias.

fective Ca^{2+} uptake into the sarcoplasmic reticulum might be (partially) compensated for by increased expression and activity of the Na^+/Ca^{2+} exchanger. Taking this hypothesis of compensation a step further, it may be speculated that during the development of myocardial hypertrophy and failure, the contribution of the Ca^{2+} ATPase of the sarcoplasmic reticulum and the competing Na^+/Ca^{2+} exchanger to cytosolic Ca^{2+} removal shifts towards the Na^+/Ca^{2+} exchanger (Fig. 1). As observed in hypertrophied hearts of spontaneously hypertensive rats (16), this shift may not be reflected in the decline rate of intracellular Ca^{2+} transients before the Ca^{2+} ATPase of the sarcoplasmic reticulum function is significantly deteriorated after the transition to heart failure. This is because the Ca^{2+} removal rate by Na^+/Ca^{2+} exchanger is just slightly slower than that by the Ca^{2+} ATPase of the sarcoplasmic reticulum (33).

When Ca^{2+} Turns Arrhythmogenic

Although a shift towards the Na^+/Ca^{2+} exchanger would facilitate diastolic Ca^{2+} removal, it could increase arrhythmogenicity because Na^+/Ca^{2+} exchange is electrogenic. Removal of one Ca^{2+} ion from the cytosol *via* sarcolemmal Na^+/Ca^{2+} exchange is coupled with the influx of three Na^+ ions that potentially produce afterdepolarizations (24,78). Thus, compensating the Ca^{2+} ATPase of the sarcoplasmic reticulum and preserving efficient Ca^{2+} removal from the cytosol *via* increased Na^+/Ca^{2+} exchange may therefore be achieved at the expenses of increased arrhythmogenicity in the hypertrophied myocardium.

As the sarcoplasmic reticular function deteriorates further during the progression of heart failure, compensation through increased activity of Na^+/Ca^{2+} exchange may no longer suffice to maintain normal resting intracellular Ca^{2+} levels (Fig. 1). Consequently, a Ca^{2+} overloaded sarcoplasmic reticulum, elevated resting intracellular Ca^{2+}, and increased Na^+/Ca^{2+} exchange may all contribute to generation of afterdepolarizations and trigger activity in the failing myocardium. Ultimately, this may give rise to re-entrant tachyarrhythmias on the basis of Ca^{2+}-induced cell-to-cell uncoupling, slowed conduction velocity, heterogeneous recovery following depolarization, and prolonged refractoriness in the hypertrophied failing heart (2,4,26).

In summary, we propose that the functional state of the sarcoplasmic reticulum may determine when intracellular Ca^{2+} handling turns arrhythmogenic. During hypertrophy before the transition to heart failure, increased activity of Na^+/Ca^{2+} exchange presumably suffices to compensate for the decreased sarcoplasmic reticular function without causing a significant slowing of cytosolic Ca^{2+} removal during stress conditions or sympathetic activation (as it occurs in heart failure). In this case, the increased activity of Na^+/Ca^{2+} exchange, but not Ca^{2+} itself, would contribute to the increased susceptibility to ventricular tachyarrhythmias. After the transition to heart failure, however, a Ca^{2+} overloaded sarcoplasmic reticulum, increasing resting intracellular Ca^{2+}, and increased Na^+/Ca^{2+} activity may all provoke afterdepolarizations, triggered activity, and thus life-threatening ventricular arrhythmias. The individual contribution of these mechanisms to increased arrhythmogenicity remains to be determined and might

well depend on both the state and the underlying cause(s) of heart failure.

Treating Increased Arrhythmogenesis

Calcium antagonists should not be used to treat the increased susceptibility to ventricular arrhythmias in heart failure. In general, the use of calcium antagonists in heart failure is not advised, even when used for the treatment of angina or hypertension (79). So far, no calcium antagonist has been shown to produce sustained improvement in symptoms in heart failure patients with predominant systolic ventricular dysfunction. Indeed, these drugs appear to worsen symptoms and may actually increase mortality in patients with systolic dysfunction. The reason for these adverse effects of calcium channel blockers in heart failure is unclear. It may be related to the negative inotropic effects of these drugs, reflex neurohumoral activation, or a combination of these and other effects (80). New calcium channel antagonists of the dihydropyridine class, particularly amlodipine, appear to have fewer negative inotropic effects than earlier drugs and no adverse effects on survival. Similar to calcium antagonists, amiodarone is not recommended for general use in prevention of sudden death in heart failure patients already treated with angiotensin-converting enzyme inhibitors and beta-blockers (79). Accordingly, effective strategies to reduce the incidence of sudden death and, thus, mortality in heart failure patients include angiotensin-converting enzyme inhibitors, beta-blockers, and probably aldosterone antagonists, angiotensin II antagonists, and implantable cardioverter defibrillators.

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