The role of action potential prolongation and altered intracellular calcium handling in the pathogenesis of heart failure

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Abstract

Action potential prolongation is a common finding in human heart failure and in animal models of cardiac hypertrophy. The mechanism of action potential prolongation involves altered expression of a variety of depolarising and hyperpolarising currents in the myocardium. In particular, decreased density of the transient outward potassium current seems to play a prominent role, regardless of species, precipitating factors or the severity of hypertrophy. The decreased density of the transient outward current appears to be caused by reduced transcription of Kv4.2 and Kv4.3 and may be caused in part by an inhibitory effect of α-adrenoceptor stimulation. During the early stage of the disease process, action potential prolongation may increase the amplitude of the intracellular calcium transient, causing positive inotropy. We argue therefore, that action prolongation may be a compensatory response which may acutely support the compromised cardiac output. In severe hypertrophy and end-stage heart failure however, despite continued action potential prolongation, the amplitude of the calcium transient becomes severely reduced. The mechanism underlying this event appears to involve reduced expression of calcium handling proteins, and these late events may herald the onset of failure. At present the events leading to the late changes in calcium handling are poorly understood. However, chronic activation of compensatory mechanisms including action potential prolongation may trigger these late events. In the present article we outline a hypothesis which describes a potential role for action potential prolongation, and the associated elevation in the levels of intracellular calcium, in maladaptive gene expression and the progression toward cardiac failure. © 1998 Elsevier Science B.V.

Keywords: Heart failure; K⁺ channels; Action potential; Calcium

1. Introduction

Cardiac failure has numerous etiologies including myocardial infarction, hypertension, myocarditis and cardiomyopathy resulting from genetic abnormalities (such as mutations in the β-myosin heavy chain, dystrophin or mitochondrial t-RNA genes). About 50% of heart failure cases result from coronary artery disease with the remainder arising from non-ischaemic, and often unknown, etiologies.

Myocyte loss or systolic dysfunction is typically associated with activation of the sympathetic nervous system, inducing positive inotropy and chronotropy, which acutely support the compromised cardiac output. Myocyte adaptation including concentric myocyte hypertrophy and altered gene expression, further attempt to reverse diminished cardiac function [1–4]. However, in spite of the compensatory response, cardiac function may continue to decline. Chronic myocyte adaptation appears to be associated with diminished systolic and diastolic function and myocyte loss, perhaps as a result of maladaptive hypertrophy and ongoing apoptosis, and these factors have been postulated to be involved in the progressive decline in pump function and the onset of heart failure [5–9]. In addition, myocyte...
adaptation seems to predispose the heart toward lethal ventricular arrhythmia, a leading cause of death (50–80%) in patients with dilated or hypertrophic heart disease. Thus, whilst myocyte hypertrophy and remodelling may compensate for the original changes in load, these adaptations may ultimately contribute to arrhythmogenesis, mechanical dysfunction and progressive cardiac dysfunction.

The mechanism by which myocyte adaptation leads ultimately to failure is unclear. However, an understanding of the molecular events that occur following an insult to pump function may shed some light on this process. One of the most commonly reported aspects of the remodelling process is action potential prolongation. In the present article we review the data on action potential duration in hypertrophy and failure and its probable causes. We conclude that action potential prolongation represents an early compensatory event. A second common finding in human and animal models of heart failure is altered calcium handling. In the present article we also review the calcium handling literature and show that, unlike action potential prolongation, calcium handling is most severely impaired late in the progression of heart disease. In the final section of the article we present a hypothesis that links the early compensatory action potential prolongation to the eventual impairment of calcium handling, via chronically elevated intracellular calcium, and provide a model for the progression from compensated hypertrophy to heart failure.

2. Action potential prolongation in human cardiac failure and in animal models of cardiac failure

Action potential prolongation is a consistent finding in human heart failure and animal models of cardiac insufficiency. The evidence for action potential prolongation in heart failure has been reviewed in detail previously [10,11]. In 1970, Coltart and Meldrum reported that action potential duration was prolonged in septic tissue from a patient with hypertrophic cardiomyopathy [12]. Action potential duration was also shown to be prolonged in cardiac trabeculae from the hearts of patients with end-stage heart failure caused by either dilated cardiomyopathy and hypertrophic cardiomyopathy [13,14] and, more recently, in single cells isolated from hearts of patients with end stage heart failure caused by either dilated cardiomyopathy or ischaemic heart disease [15,16]. Prolongation of the cardiac action potential duration also occurs in a variety of animal models of cardiac hypertrophy, disease and failure. For example, action potential prolongation was shown in the hypertrophied cat right ventricle following pulmonary artery banding [17–20]. In the rat, action potentials were prolonged in association with hypertrophy induced by hypertension in the Goldblatt [21–23] and SHR models [24,25] and following deoxycorticosterone acetate treatment [26]. Action potential prolongation is also associated with hypertrophy secondary to left coronary artery ligation [27,28], pulmonary artery ligation [29], thoracic or abdominal aortic banding [30,31], acromegaly [32] and catecholamine treatment [33]. Prolongation of action potential duration occurs following pulmonary artery constriction in the ferret [34], in Syrian hamsters with hereditary cardiac hypertrophy [35,36], in guinea pigs following thoracic or abdominal banding [37,38], in rabbits with hypertrophy induced by perinephritis hypertension [39] and in dogs with pacing induced heart failure [40]. In our laboratory, we have used a rat model in which ligation of the left anterior descending coronary artery induces a large (> 35%) left ventricular infarction leading to the development of a compensatory right sided ventricular hypertrophy [41], and we find that this right ventricular hypertrophy is also associated with action potential prolongation (Fig. 1).

2.1. The mechanism of action potential prolongation

Action potential profiles depend on a delicate balance between depolarising (L-type calcium current, \( I_{\text{Ca,L}} \), sodium current, \( I_{\text{Na}} \), and the sodium–calcium exchanger, \( I_{\text{NaCa}} \)) and hyperpolarising currents (the transient outward potassium current, \( I_{\text{Ko}} \), the delayed rectifier, \( I_{\text{Kr}} \), the inward rectifier, \( I_{\text{K1}} \), chloride current, \( I_{\text{Cl}} \) and the sodium-potassium ATPase). The role of the L-type calcium current has been studied in human heart failure and in animal models and these data have been reviewed in detail previously.

Fig. 1. (A) Action potentials, (B) the transient outward K current (\( I_{\text{Ko}} \)) and (C) calcium transients in rat heart. Action potentials and \( I_{\text{Ko}} \) were recorded from single right ventricular myocytes using the whole cell voltage clamp technique. Calcium transients were recorded from fura-2 loaded trabeculae from the right ventricle. The figure shows that action potential duration is prolonged 6–8 weeks post-myocardial infarction (MI) compared to sham control and that action potential prolongation is associated with a decrease in the density of \( I_{\text{Ko}} \) and an elevation in the amplitude of the calcium transient. Pharmacological inhibition of \( I_{\text{Ko}} \) in control cells with 4-aminopyridine (4-AP, 5 mM) similarly prolongs action potential duration and elevates the calcium transient. Horizontal lines represent (A) 0 mV and (B) 0 pA/pF. \( I_{\text{Ko}} \) density was determined at 70 mV. 

\( \text{Sham} \quad \text{Post-MI} \quad 5 \text{mM 4-AP} \)
Table 1

<table>
<thead>
<tr>
<th>Species</th>
<th>Model</th>
<th>Stage</th>
<th>APD</th>
<th>IK</th>
<th>Ref.</th>
</tr>
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<tr>
<td>human</td>
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<td>↑</td>
<td>↓ I_{to}, ↓ I_{K1}, → I_{sus}</td>
<td>[16]</td>
</tr>
<tr>
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</tr>
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<td>[28,41]</td>
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<tr>
<td></td>
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<td>[68]</td>
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<td>↓ I_{to}</td>
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</tr>
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<td>↓ I_{to}</td>
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<td>[71]</td>
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<td></td>
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<td>↑</td>
<td>↓ I_{to}, → I_{sus}</td>
<td>[72]</td>
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<td>↑ I_{to}</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>guinea pig</td>
<td>aortic coarctation</td>
<td>↑</td>
<td>→ I_{sus}, → I_{K1}</td>
<td>[38]</td>
</tr>
<tr>
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<td>cat</td>
<td>pulmonary artery banding</td>
<td>↑</td>
<td>↓ I_{to}</td>
<td>↑ I_{K1}</td>
</tr>
<tr>
<td></td>
<td>dog</td>
<td>chronic pacing</td>
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<td>↓ I_{to}, ↓ I_{K1}</td>
<td>[40]</td>
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<tr>
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<td>coronary artery ligation</td>
<td>↑</td>
<td>↓ I_{to}</td>
<td>→ I_{sus}</td>
</tr>
<tr>
<td>hamster</td>
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<td>↑</td>
<td>↓ I_{to}, → I_{sus}</td>
<td>[75,76]</td>
</tr>
</tbody>
</table>

↑ = increased.
↓ = decreased.
→ = unchanged.

I_{to} = the transient outward current. I_{sus} = the sustained, non-inactivating outward current. I_{K1} = the inward rectifier. Moderate hypertrophy indicates compensated hypertrophy without pulmonary congestion. Severe hypertrophy indicates end-stage hypertrophy with pulmonary congestion.

In two studies, L-type calcium current has been reported to increase [38,42]. However, more commonly, the L-type calcium current is either unchanged [15,20,28,31,41,43–45], or decreased [46–49] and therefore, appears unlikely to be responsible for the prolongation of action potential duration seen in these studies. I_{Na/Ca} may be increased in the hypertrophied heart [38] (although contradictory data has been published [50,51]) and pressure overload can induce increases in NaCa exchanger expression [52], suggesting that this electrogenic exchanger may also contribute to action potential prolongation in some animal models. More importantly, the expression of Na/Ca exchanger is consistently found to increase in end-stage human heart failure (Table 2).

Altered background hyperpolarising currents could also impact on the action potential profile of hypertrophied and failing hearts, although the extent to which these currents contribute to action potential prolongation is unclear. Thus, in animal models of cardiac hypertrophy, the activity of the Na\(^{+},K^{+}\)-ATPase is decreased [53–58], along with altered Na\(^{+},K^{+}\)-ATPase isoform expression [59–63]. In human heart failure there is evidence for reduced concentration of the Na\(^{+},K^{+}\)-ATPase (ouabain binding sites) but no evidence for any subunit isoform switch [64–66]. One study to date has shown evidence for de-novo expression of a background chloride current (which would tend to counteract action potential prolongation) [67].

Potassium currents are the major repolarising currents active during the plateau of the action potential in myocytes isolated from a variety of model species and human hearts. Several groups have now measured K\(^{+}\) currents in human heart failure and in animals models of cardiac hypertrophy and these data are summarised in Table 1. Of all the mechanisms that may contribute to action prolongation, decreased K\(^{+}\) currents appear to be the most reproducible. Thus, in the studies outlined in Table 1, the density of the transient outward current (I_{to}) is reduced in hypertrophied hearts, regardless of species, precipitating factors or the disease stage. Indeed, preliminary evidence suggests that reduced I_{to} density represents a very early event in the response to decreased pump performance [74,68]. Decreased I_{to} therefore, would appear to be a significant contributor to action potential prolongation in cardiac hypertrophy and failure. The role of other repolarising K\(^{+}\) currents is not as clear. Delayed rectifier currents (I_{K2}) can be separated into several components including a rapid component (I_{K1}), a slow component (I_{K2}) and a poorly characterised sustained component (I_{sus}). Detailed analyses of the expression of each of these components during the development of cardiac hypertrophy have not been performed. In the majority of studies, the density of I_{sus} is not significantly altered in hypertrophied myocytes, although I_{sus} has been reported to be decreased in one report (see Table 1 for references). The inward rectifier (I_{K1}) contributes to the late phase of repolarisation and, more importantly, to the setting of the resting membrane potential. The density of I_{K1} has been shown to be decreased in human heart failure and in some animal models (see Table 1 for references). Decreased I_{K1} density may contribute to the reduced resting membrane potential which accompanies cardiac hypertrophy in some models [17,20,37,41,43]. In other studies however, I_{K1} is either unchanged, or increased.

### 2.2. Altered K\(^{+}\) channel gene transcription

Recently, we and others [41,77–79] have applied molecular and biochemical techniques to address the
mechanism underlying the reduced K⁺ current density in cardiac hypertrophy. These studies show that compensated hypertrophy following MI in the rat is associated with a decrease in the transcription of Kv4.2 and Kv4.3, the probable molecular correlates of \( I_{\text{Ks}} \) in rat. The transcription of some K⁺ channel genes encoding \( I_{\text{Ks}} \)-like currents (Kv2.1, ERG) is also decreased during hypertrophy in animals and human hearts [79] although the functional consequences of decreased transcription have not been identified. In contrast, we find that mRNA levels for genes encoding inward rectifiers, IRK1 and IRK2, are unchanged in the hypertrophied heart, despite electrophysiological evidence for decreased \( I_{\text{Ks}} \) in the same model [41]. These findings suggest that decreased K⁺ current density (and action potential prolongation) may be the result of reduced K⁺ channel gene expression at both the transcriptional and post-transcriptional level. Interestingly, the fetal K⁺ channel gene, Kv1.4 [80,81] appears to be re-expressed in the hypertrophied myocyte [41,82] suggesting that altered K⁺ channel gene expression represents yet another facet of the re-expression of fetal genes in cardiac hypertrophy.

2.3. The role of the sympathetic nervous system

The mechanism by which K⁺ channel expression is reduced (and action potential duration is increased) in hypertrophy and failure is not clear. However, reflex activation of the sympathetic nervous system occurs immediately in response to an insult to pump function. Acute administration of \( \alpha \)-adrenergic agonists is known to prolong action potential duration [83–85] by a mechanism that involves inhibition of repolarising K⁺ currents (\( I_{\text{Ks}} \) [86–88], \( I_{\text{K}} \) [89,90] and \( I_{\text{K1}} \)[91]) without significant effects on \( I_{\text{Ca}} \) [86,92–94]. Thus, while chronic activation of the sympathetic nervous system is associated with a reduction in the positive inotropic effects of \( \alpha \)-agonists [95], it seems plausible that \( \alpha \),-adrenoreceptor stimulation following activation of the sympathetic nervous system contributes to the initial action potential prolongation following acute alterations in loading of the myocardium.

2.4. The consequences of action potential prolongation-elevated intracellular calcium and positive inotropy: a compensatory response

It has long been recognised that action potential height and/or duration is an important regulator of the amount of calcium released from intracellular storage sites [96–100]. Furthermore, interventions that induce a prolongation of the action potential, such as \( \alpha \)-adrenoreceptor stimulation, increase the amplitude of the calcium transient in cardiac myocytes [86]. In rat cardiac trabeculae, we find that inhibition of the transient outward potassium current (\( I_{\text{to}} \)) and prolongation of the action potential with 4-aminopyridine also enhances the amplitude of the calcium transient (Fig. 1). Prolongation of simulated action potentials using the action potential clamp technique has shown unequivocally that prolonged depolarisation can directly increase the amplitude of the calcium transient [101]. The mechanism by which action potential duration influences the amount of calcium released during cardiac excitation probably involves the two key sarcolemmal proteins involved in calcium cycling, the L-type calcium channel and the Na⁺/Ca exchanger, since the function of both these proteins is directly influenced by the membrane potential. Prolonged depolarisation during the plateau of extended action potentials enhances calcium entry via the L-type calcium channel and retards calcium extrusion via the Na⁺/Ca exchanger, thereby loading the cell with calcium [101,102].

Elevated calcium transients have also been recorded in animal models of moderate cardiac hypertrophy. Differences in systolic calcium that exist between hypertrophied and normal myocytes are abolished under voltage clamp conditions where the duration of depolarisation is normalised [103], suggesting that action potential prolongation is responsible for the elevated systolic calcium seen in the hypertrophied myocyte. Since increases in the amplitude of the calcium transient are inotropic, it seems plausible that the reduction in K⁺ channel expression and action potential prolongation represents and early compensatory response of the heart to an increased load, thereby increasing contractility.

Compensatory action potential prolongation is, however, potentially arrhythmogenic and as such this compensatory mechanism may predispose the heart to lethal arrhythmias [104]. In addition, in Section 4 we propose that chronic elevation in intracellular calcium (as a result of action potential prolongation) may potentiate mitogenic signalling cascades, leading to maladaptive gene expression (see below), over-riding any short term benefit and contributing to disease progression.

3. Calcium handling in hypertrophy and failure

Release and reuptake of intracellular calcium are essential for efficient contraction and relaxation of the heart. Intracellular calcium is released via ryanodine sensitive calcium channels located in the SR, in response to calcium entering during the plateau phase of the action potential. The two main pathways for calcium removal are the SR CaATPase, which resequesters calcium into the SR, and the sarcolemmal NaCa exchanger. The available data from animal models suggest that the calcium handling properties of hypertrophied myocytes are highly stage dependent. In moderate hypertrophy in animal models the expression of genes encoding calcium handling proteins is relatively normal [105–109]. Indeed, during compensated hypertrophy, we and others find that systolic calcium is actually increased [41,103,110–112] without slowing in the rate of relaxation of the calcium transient. The elevation in the
amplitude of the intracellular calcium transient could result from prolongation of the cardiac action potential, as observed following adrenergic receptor stimulation [86] and may represent a compensatory response (see Section 2.4).

Despite continued action potential prolongation however, systolic calcium is severely reduced [15], the calcium transient is significantly prolonged [13–15,112] and Ca$^{2+}$ uptake activity may be reduced [113–115] in more advanced stages of hypertrophy in animal models and in end-stage heart failure in humans. In animal models of severe hypertrophy, these events correlate with the finding that the expression of genes encoding calcium handling proteins is markedly reduced [105–109]. Although the mechanisms underlying altered calcium handling in end-stage human heart failure are not entirely clear, and there is currently controversy concerning the extent to which RNA levels are predictive of protein levels, a number of studies have demonstrated altered expression of genes encoding calcium handling proteins (including SR CaATPase (SERCA2), ryanodine receptor (RYR2), NaCa exchanger and phospholamban genes), and these are summarised in Table 2.

Unlike the changes that lead to action potential prolongation (see Sections 2.1 and 2.2) therefore, impaired calcium handling appears to be a relatively late event in the progression toward failure. In contrast to altered K$^+$ channel expression, it appears that changes in calcium handling may be maladaptive rather than compensatory, and may lead to severely impaired systolic and diastolic cardiac function, heralding the onset of failure [105].

At present the events leading to the late changes in calcium handling are poorly understood. However, chronic activation of compensatory mechanisms including action potential prolongation may trigger these late events. In the following sections we outline a hypothesis which describes a potential role for action potential prolongation, and the associated elevation in the levels of intracellular calcium, in the regulation of calcium handling gene expression.

4. The contribution of action potential prolongation and elevated intracellular calcium to altered gene expression and the progression of heart failure: a hypothesis

The potential role for prolonged action potential duration in the progression of heart failure is outlined in Fig. 2. Decreased pump function as a result of myocardial infarction, hypertension or genetic abnormalities triggers a compensatory response which involves altered K$^+$ channel gene expression. Prolonged action potential depolarisation results in elevated intracellular calcium which may acutely support the compromised heart. Elevated intracellular calcium however, may also potentiate mitogenic signalling cascades, leading to maladaptive gene expression, which may initially blunt the compensatory response and ultimately depress cardiac function, accelerating the progression toward failure.

Membrane depolarisation and calcium entry are important determinants of gene expression in a number of excitable cells [127–132]. Similarly, and consistent with the hypothesis, gene expression in cardiac myocytes has also been shown to be dependent on calcium. For example, NE treatment of cultured neonatal myocytes induces a decreased expression of SERCA2 and the decrease in SERCA2 can be abolished in contractile arrested and verapamil treated myocytes [133], implying that excitation-contraction coupling and calcium current through

Table 2
Altered calcium handling gene expression in end-stage human heart failure

<table>
<thead>
<tr>
<th>Species</th>
<th>Model</th>
<th>Stage</th>
<th>Changes in Ca$^{2+}$ handling genes</th>
<th>Ref.</th>
</tr>
</thead>
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<tr>
<td>human</td>
<td>dilated/ischaemic cardiomyopathy</td>
<td>severe</td>
<td>↓CaATPase protein, ↑NaCa exchanger protein, ↓RyR mRNA, ↓calsequestrin protein, ↑calreticulin protein</td>
<td>[116]</td>
</tr>
<tr>
<td>human</td>
<td>dilated cardiomyopathy</td>
<td>severe</td>
<td>↑NaCa exchanger (mRNA and protein)</td>
<td>[117]</td>
</tr>
<tr>
<td>human</td>
<td>dilated cardiomyopathy</td>
<td>severe</td>
<td>↓CaATPase mRNA, →CaATPase protein, ↑NaCa exchanger (mRNA and protein)</td>
<td>[113]</td>
</tr>
<tr>
<td>human</td>
<td></td>
<td>severe</td>
<td>↓RyR mRNA, ↑IP3R mRNA</td>
<td>[119]</td>
</tr>
<tr>
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<td>dilated cardiomyopathy</td>
<td>severe</td>
<td>→CaATPase protein, →phospholamban protein, →calsequestrin protein</td>
<td>[120]</td>
</tr>
<tr>
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<td>severe</td>
<td>↓CaATPase protein, ↑NaCa exchanger (mRNA and protein)</td>
<td>[121]</td>
</tr>
<tr>
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<td>↓CaATPase mRNA</td>
<td>[122]</td>
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<td>severe</td>
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<td>→CaATPase protein, →CaATPase protein, ↓phospholamban mRNA</td>
<td>[126]</td>
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† = increased.
↓ = decreased.
→ = unchanged.
CaATPase = sarcoplasmic reticulum calcium ATPase, RyR = ryanodine receptor, IP3R = inositol trisphosphate receptor.
Fig. 2. The role of action potential prolongation in the response to decreased pump function. Decreased pump function from numerous causes is associated with action potential prolongation. The increased amplitude of the intracellular calcium transient as a result of action potential prolongation is inotropic and may acutely compensate for the reduced cardiac output. Chronic elevations in the amplitude of the calcium transient however, may trigger maladaptive gene expression (such as decreased SR Ca\(^{2+}\) ATPase expression), which blunts the compensatory response and ultimately contribute to the progression from compensatory hypertrophy to cardiac failure. ---- shows the compensatory response which supports cardiac output, ---- shows the maladaptation which may contribute to failure.

the L-type calcium channel are important in the phenotypic response to \(\alpha\)-adrenergic agonists. Furthermore, the induction of the immediate early genes c-fos and Egr-1 by ET and ANGII in cultured adult cardiocytes is inhibited by the calcium antagonist, nisoldipine [134] and in neonatal myocytes, induction of the muscle specific genes MLC-2, \(\alpha\)-actin and troponin I by ET could be mimicked by the calcium ionophore, ionomycin [135].

Given the potential role for altered gene expression in the pathogenesis of heart failure, the signalling cascades that lead to altered gene expression in heart failure have been the subject of intense research over the last decade. In-vitro and in-vivo studies have shown that altered gene expression can be induced by a number of stimuli including \(\alpha\)- and \(\beta\)-adrenergic agonists, angiotensin II, endothelin, growth factors and mechanical activity. These diverse stimuli converge on the MAPK cascade [136–139]. Once activated, MAPK may translocate to the nucleus, where it phosphorylates transcription factors and regulates gene expression [140,141]. The MAPK cascade can be activated by calcium [127,142–148] and calcium sensitive mechanisms seem important for activation of the MAPK cascade by the hypertrophic stimuli, mechanical stretch [138], \(\beta\)-adrenergic agonists [148] and ANG II [149] in cardiac myocytes.

Additional calcium dependent second messenger systems may also play a role in altered gene expression in response to mitogenic stimuli. For example, over-expression of calmodulin in transgenic mice causes myocyte hypertrophy [150] while the calmodulin antagonist W-7 can inhibit the induction of ANF by PE in cultured neonatal myocytes [151]. Calmodulin, when activated by calcium (CaM), modulates the activity of a number of enzymes including CaM-dependent protein kinases (CaM kinases) and adenylate cyclases, both of which are capable of phosphorylating transcription factors and regulating gene expression [152,153]. A role for PKC-dependent pathways has also been suggested [154,155] and the activation of many isoforms of PKC is calcium dependent [156]. PKC may directly regulate gene expression following translocation to the nucleus [157] or may regulate gene expression via activation of the MAPK cascade [158].

5. Implications for treatment

Morbidity and mortality in heart failure remain unacceptably high. Despite recent advances in medical treatment, heart failure remains a highly lethal disease. As we have argued, action potential prolongation and the associated elevation in systolic calcium may contribute to maladaptive gene expression and the progression toward cardiac failure, as well as to the high incidence of sudden cardiac death in patients with heart failure. Accordingly, it is possible to predict that agents that further prolong action potential duration (such as class III anti-arrhythmic agents) or increase calcium availability (such as positive inotropic agents) would be detrimental in the setting of cardiac hypertrophy and failure. Indeed, clinical practise supports this contention since the class III anti-arrhythmic agent, d-sotalol [159] and positive inotropic agents [160,161] have generally been found to be detrimental in this patient group. On the contrary, agents that normalise action potential duration or reduce the availability of calcium may be beneficial. Reductions in the availability of calcium may explain some recent findings showing the long acting calcium antagonist, amlodipine [162], and the T-type calcium channel antagonist, mibefridil [163], are beneficial in human heart failure and in animal models of cardiac hypertrophy.

Since action potential prolongation in heart failure involves a reduction the net outward repolarising K\(^+\) current, a novel approach to the treatment of heart failure would be to normalise K\(^+\) channel gene expression. Conceivably, this could be achieved by gene transfer [164] or pharmacologically. With regard to the latter we and others have recently shown that thyroid hormone is capable of increasing K\(^+\) channel expression at the transcriptional level in rat ventricular myocytes [81,165]. The possibility exists therefore, that agents with thyroid hormone-like properties may find a role in the treatment of heart failure.

6. Future directions

In order to determine the role of action potential prolongation in the pathogenesis of cardiac failure we have
created transgenic mice which over-express an N-terminus fragment of the rat Kv4.2 gene in a cardiac restricted manner [166]. Over-expression of this fragment in vitro abolishes functional expression of full length Kv4.2 in heterologous expression systems. We hypothesised that in mice this construct should suppress functional expression of I_K, leading to action potential prolongation in the absence of any other trophic stimuli. Preliminary data suggest that these mice develop frank congestive heart failure resulting in death at 2–3 months of age [166]. An understanding of the mechanism by which dominant negative inhibition of K^+ channels in the mouse heart leads to failure may help clarify the role of K^+ channel down-regulation in the pathogenesis of heart disease.

Since action potential prolongation and the associated increase in intracellular calcium may play a central role in the pathogenesis and progression of heart failure, it is of particular interest to note that membrane depolarisation and intracellular calcium may also be capable of regulating K^+ channel gene expression [82,129,167]. It is possible therefore, that elevated intracellular calcium may reduce expression of adult K^+ channel isoforms, further prolonging action potential duration and accelerating disease progression. This possibility warrants further study.

A number of recent studies have implicated myocyte loss as an important factor in the progressive mechanical dysfunction that leads ultimately to cardiac failure [5]. While cell death can occur by necrosis or apoptosis, the latter appears predominant in the dog model of chronic pacing induced heart failure [6], in dogs with heart failure induced by multiple intracoronary microemboli [7] and in rats following experimental left ventricular infarction [8,9]. The factors that trigger apoptosis in the hypertrophied myocardium are unknown. However, studies using non-cardiac cells have identified intracellular calcium as an important regulator of programmed cell death [168,169]. In cardiac myocytes, stretch [170] and angiotensin II [171] have been shown capable of inducing apoptosis and, consistent with an important role for calcium, apoptosis induced by angiotensin II in adult rat ventricular myocytes can be inhibited by the calcium chelator BAPTA/AM and mimicked by the calcium ionophore, A23187 [171]. Further studies to explore the possible link between increases in intracellular calcium (secondary to action potential prolongation) and apoptosis in the overloaded heart are clearly warranted.

7. Summary

Altered K^+ channel expression and action potential prolongation is a common finding in heart disease. Previous studies have focused on the arrhythmogenic consequences of these alterations. However, given the connection between action potential profile, intracellular calcium concentration and myocyte gene expression, it seems plausible that altered K^+ channel expression and action potential prolongation may also play a more insidious role in disease progression.

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