Introduction

Numerous cellular abnormalities of heart muscle are associated with ventricular dysfunction and the clinical syndrome of heart failure. Many of these changes have been described in animal models of heart failure where there is considerable species and model variation. The increasing use of cardiac transplantation has provided access to fresh myocardial tissue from severely failing human hearts and this has generated a large volume of experimental data.

A classification of the cellular abnormalities encountered in the failing human heart is provided in Table 1. The relative contributions of each mechanism depend on the underlying aetiology of heart failure and different mechanisms may predominate at various times in the natural history of a particular disease.

Myocyte death

Heart failure in the setting of acute cardiogenic shock secondary to an extensive myocardial infarction is an example where a relatively well defined single mechanism is operative i.e. insufficient numbers of viable myocytes remain to sustain effective contraction. Under these conditions a fairly close relationship exists between myocyte loss and functional impairment. Myocyte loss is also prominent in more chronic forms of heart failure secondary to both ischaemic and dilated cardiomyopathy, but here there is a weaker correlation between myocyte loss and functional impairment. Myocyte hypertrophy is an almost universal finding in chronic heart failure, whether attributed to increases in cell length, width or both. Whilst originating as a compensatory response to increased haemodynamic load, there is clear evidence of its deleterious long-term effects from mortality studies. In parallel with this there is slippage between adjacent myocytes resulting in a distortion of ventricular geometry, eventually resulting in the dilatation characteristic of systolic dysfunction. The degree of dilatation frequently exceeds the capacity to hypertrophy with resultant wall thinning. Although some

<table>
<thead>
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<th>Table 1</th>
<th>Possible mechanisms in human heart failure</th>
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<td>Myocyte death</td>
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<tr>
<td>Ventricular dilatation</td>
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<td>Structural changes in the cardiac myocytes</td>
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Disruption of the extracellular matrix

The role of the extracellular matrix in maintaining the physical structure of the heart and in the transmission of mechanical force to the circulation dictates that alterations in matrix composition have potentially important consequences for myocardial function. There is an increase in the collagen content of failing myocardium, due to increases in types I and III collagen with a proportionately greater increase in type I. Alterations in collagen architecture (but not increases in collagen volume) have been shown to correlate with abnormalities of passive relaxation in aortic valve disease, but in general attempts to correlate the degree of histological fibrosis with functional abnormalities in heart failure have yielded inconsistent results.

Structural change in cardiac myocytes

Changes in myocyte shape and size

Myocyte hypertrophy is an almost universal finding in chronic heart failure, whether attributed to increases in cell length, width or both. Whilst originating as a compensatory response to increased haemodynamic load, there is clear evidence of its deleterious long-term effects from mortality studies. In parallel with this there is slippage between adjacent myocytes resulting in a distortion of ventricular geometry, eventually resulting in the dilatation characteristic of systolic dysfunction. The degree of dilatation frequently exceeds the capacity to hypertrophy with resultant wall thinning. Although some
authors have demonstrated only weak correlations be-
 tween cell size and myocardial function[11,21], we have
recently demonstrated significant correlations between
ventricular hypertrophy and abnormalities of relaxation
in isolated ventricular myocytes[16]. We have also found
that myocytes of normal size selected from hypertro-
phied hearts still demonstrated these relaxation abnor-
malities, suggesting that physical cell size alone is not
responsible for the functional abnormalities.

There has been a considerable amount of animal
research directed at identifying the mechanisms involved
in coupling increased haemodynamic load to the pro-
duction of myocyte hypertrophy. Interest has centred on
changes in gene expression secondary to increases in cell
loading and the actions of peptide growth factors (re-
viewed in[22,23]). However, there is a paucity of data from
human studies on these mechanisms due to the non-
availability of appropriate human tissue. The elevated
levels of myotrophin[24] and endothelin[25] detectable in
human heart failure provide evidence of possible stimuli
to the hypertrophic process in man.

In contrast to the certainty as to the occurrence
of hypertrophy in heart failure, is the controversy
surrounding whether there might be progression to
hyperplasia and myocyte proliferation under certain
conditions[26]. Despite some evidence to the contrary[27],
the established view has been that the adult cardiac
myocyte is terminally differentiated and thus incapable
of mitotic division[28,29]. This view has recently been
challenged by careful morphometric studies demonstrat-
ing an increase in the number of myocytes in addition to
the well recognised increases in myocyte size[30,31]. This
appears to occur not during the early phases of adapta-
tion to increased load but in association with the latter
stages of dilatation and myocardial failure. These find-
ings await further confirmation, but they raise important
questions about a potential role for hyperplasia in the
transition from hypertrophy as a beneficial adaptation
to the one that is a cause of mortality.

Ultrastructural change

The most prominent feature is one of loss of myo-
fibrils[6,13,32,33]. This loss of contractile units provides an
obvious mechanism for the depression of systolic func-
tion and has been shown to correlate with both ejection
fraction[13] and prognosis[33]. In addition Scholtz et al.
have characterized a proliferation of T tubules, a diver-
sity of nuclear shapes and the occurrence of numerous
small mitochondria[32] occurring in a severe form in 30%
of the myocytes of patients with dilated cardiomyo-
pathy. Immunofluorescence has identified increased
amounts of the cytoskeletal components desmin, tubulin
and vinculin[6], disruption of which could result in
malalignment of the contractile proteins and inefficiency
of force transmission.

Recent experimental work on isolated cardiac
myocytes from hypertrophied cat myocardium has
suggested that microtubular proliferation might contrib-
ute to contractile dysfunction[34]. Unfortunately, the
methodological constraints imposed by the fragility of
microtubules makes it unlikely that this intriguing pos-
sibility can be investigated in human tissues in the near
future. Sarcomere length appears to remain constant in
studies of failing human heart[15,35,36], suggesting that
sarcomere replication must form an integral part of
changes in cell length.

Functional changes in ventricular myocytes

Although the structural changes outlined above are
clearly important in the pathogenesis of chronic heart
failure, there are additional functional changes that are
present in myocytes which appear morphologically
intact. There has been previous uncertainty as to
whether impaired contractility could be demonstrated in
isolated preparations, with some studies demonstrating
a reduction in contractility in isometric myocardial
preparations[57-60], whilst others have been unable to
demonstrate a difference[61-66]. Those studies employing
higher stimulation rates and physiological temperatures
have generally been those in which a depression of
contractility has been demonstrated, although results in
patients with ischaemic heart disease have been less
consistent[67]. Our findings with isotonically contracting
isolated ventricular myocytes from patients with ischae-
mic cardiomyopathy have demonstrated no depression
of contraction amplitude at lower stimulation rates[60],
but a 50% depression of contractility emerging at physi-
ological stimulation rates[68]. This frequency-dependent
impairment of function is consistent with clinical evi-
dence demonstrating that a reduced cardiac output in
heart failure is only apparent at higher heart rates[69].
With the demonstration of impaired myocardial func-
tion in heart failure at the level of individual myocytes
the question arises as to which components in the
excitation-contraction process are at fault.

Physiology of excitation-contraction
coupling

The proposed mechanisms responsible for excitation-
contraction (EC) coupling have been comprehensively
reviewed[50,51]. The finding that depressed contractility
in heart failure is dependent on stimulation rate has
focused interest on those sub-cellular mechanisms
thought to be responsible for frequency-dependent
behaviour in the myocardium: the L-type Ca$^{2+}$ channel,
the sarcoplasmic reticulum and the Na$^+$-Ca$^{2+}$
exchanger[52-55] (Figs 1 and 2).

Abnormalities of excitation-contraction
coupling in heart failure

Before setting out the abnormalities associated with
heart failure, it is important to bear in mind the
limitations of some of the biochemical techniques
Systole

Figure 1 Physiology of excitation–contraction coupling — systole. Membrane depolarization opens sarcolemmal L-type Ca\(^{2+}\) channels. The local rise in Ca\(^{2+}\) around the sarcoplasmic reticulum (SR) Ca\(^{2+}\) release channels (ryanodine receptors-SRRC) triggers Ca\(^{2+}\) release from the SR. This combines with smaller contributions from the Na\(^+\)-Ca\(^{2+}\) exchanger (working in Ca\(^{2+}\) influx mode) and the L-type trigger current itself to form the Ca\(^{2+}\) transient which interacts with the myofilaments to produce contraction.

Diastole

Figure 2 Physiology of excitation–contraction coupling — diastole. Ca\(^{2+}\) dissociates from the myofilaments and is removed from the cytosol via uptake into the SR via the SR Ca\(^{2+}\) ATPase (SERCA2a) and by the Na\(^+\)-Ca\(^{2+}\) exchanger working in Ca\(^{2+}\) efflux mode. The negligible contribution from the sarcolemmal Ca\(^{2+}\) ATPase is omitted for clarity.

involved. In particular the fact that changes in the concentration or activity of a particular substance must be interpreted with reference to a standard which is not itself subject to change in heart failure (typically per mg of total protein). Recent work by Böhm's group has challenged the tacit assumption that normalization per mg of total protein provides satisfactory standardization. Levels of the G protein \(G_\alpha\) were found to be elevated by 139% in dilated cardiomyopathy and by 58% in ischaemic cardiomyopathy when referenced to
may predispose to the development of re-entry and mode. Secondly, any inhomogeneity of prolongation of time for the exchanger to operate in Ca efflux +2+ Na+-Ca whilst allowing a shorter period exchanger flux into the myocyte via the +2+ +2+ -Ca (the transient outward current). This has two important L-type Ca current (see below). This has two important L-type Ca2+ channel

No functional abnormality has been detected in the L-type Ca2+ (Ica) current in isolated myocytes from failing hearts76,78, although Ica may contribute a proportionately greater amount to the calcium transient69. The assumptions made in using capacitance to correct for changes in cell surface area have been questioned70 but there is evidence to support a correlation between electrical capacitance and cell size (K. MacLeod; personal communication). These Ca2+ current studies are in agreement with descriptions of an unaltered number of dihydropyridine (DHP) binding sites71 but are in contrast to the finding of a reduction in DHP binding and receptor mRNA by Takahashi et al72. Nevertheless, the balance of functional evidence would seem to suggest that L-type channel conductance is not impaired in heart failure.

Sarcoplasmic reticulum Ca2+ release channels

This is an area of controversy with some groups reporting a reduction in the ryanodine sensitive release channel mRNA in ischaemic73 but not dilated cardiomyopathy74,75 with others describing reductions in both ischaemic and dilated cardiomyopathy73. It has been suggested that these reductions are associated with upregulation of the inositol 1,4,5-triphosphate (ins(1,4,5)P3) triggered Ca2+ release channel73. However, the role played by the ins(1,4,5)P3 channel in the physiology of human EC coupling is uncertain and the significance of this observation awaits confirmation. The sensitivity of mRNA techniques in general must be weighed against the fact that alterations in translation rates and protein turnover mean that changes in mRNA do not necessarily equate to changes in protein levels or to altered function. Single channel recordings have been unable to detect differences between ryanodine-sensitive release channel function in failing human heart compared with non-failing sheep hearts76.

Ca2+ transient

There is general agreement on the prolonged diastolic decay of the transient in heart failure (Table 2) and this is in accord with the prolonged relaxation noted in isolated ventricular myocytes46 from failing hearts and

<table>
<thead>
<tr>
<th>Study</th>
<th>Preparation</th>
<th>Temperature</th>
<th>Indicator</th>
<th>Load</th>
<th>Contraction in CHF</th>
<th>Peak Ca2+</th>
<th>Time for Ca2+ decay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gwathmey78</td>
<td>Papillary</td>
<td>30 °C</td>
<td>aequorin</td>
<td>M</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Hasenfuss79</td>
<td>Papillary</td>
<td>37 °C</td>
<td>aequorin</td>
<td>M</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Vahl64</td>
<td>Papillary</td>
<td>37 °C</td>
<td>fura-2</td>
<td>M</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Beuckelmann64</td>
<td>Myocyte</td>
<td>35 °C</td>
<td>fura-2</td>
<td>T</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

↑=increased; ↓=decreased; ↔=unchanged; M=isometric; T=isotonic; *=not measured; CHF=heart failure.

total protein, but to be increased by 135% and 155% respectively when normalized to the sarcolemmal membrane marker of 3H-ouabain binding sites (although this itself is not without its limitations — see below). The implication is that non-viable or non-myocyte tissue is diluting the sample in ischaemic but not dilated cardiomyopathy. Similar concerns have arisen concerning the use of β-actin as a standard in studies examining changes in mRNA levels in heart failure.

Na+-K+ ATPase

Several investigators have described a reduction in 3H-ouabain binding57-60 itself in heart failure, although the reduction was not statistically significant in one study61 and was absent in one45. The discrepancies in these findings are perhaps not surprising in view of the known limitations of ligand binding techniques that occur due to non-specific binding and the presence of receptors on cells other than myocytes. There is no evidence for either a depression in the levels of Na+-K+ ATPase mRNA or a change in the relative abundance of the three isoforms in man60,61. The presence of an endogenous ouabain in heart failure62 suggests that functional Na+-K+ ATPase inhibition may occur in the presence of undiminished enzyme concentrations. The confusion surrounding Na+ homeostasis in heart failure is compounded by observations that increases in intracellular Na+ normalize the abnormal force-frequency relationship38,63.

Action potential duration

Action potential duration is prolonged in heart failure64,65, and this appears to be secondary to reductions in both Ito (the transient outward current) and Ini (the inward rectifier current)65,66 but not to changes in the L-type Ca2+ current (see below). This has two important consequences, firstly the prolonged membrane depolarization increases Ca2+ flux into the myocyte via the Na+-Ca2+ exchanger500 whilst allowing a shorter period of time for the exchanger to operate in Ca2+ efflux mode. Secondly, any inhomogeneity of prolongation may predispose to the development of re-entry and arrhythmias.

Table 2 Abnormalities of the Ca2+ transient in human heart failure

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the frequent occurrence of diastolic dysfunction in clinical practice[7]. There remains uncertainty concerning
the magnitude of the peak Ca\textsuperscript{2+} transient with the
finding of Gwathmey's et al. that this was unchanged in
heart failure[78] contrasting with reports of a depressed
transient by Hasenfuss et al.[79] and Beukelmann et al.[64]. Some of these apparent discrepancies may
relate to the use of right ventricular samples and the
lower temperatures used by Gwathmey's group[79]. But
this observation does not explain the findings of Vahl et al.[80], in particular the increase in the calcium
transient in preparations from failing hearts under isotonic
conditions, which is in direct contradiction to the find-
ings of Beukelmann et al.[64] in isolated cells. One
possible explanation for these discrepancies lies in the
technical limitations associated with recording Ca\textsuperscript{2+}
transients from multicellular preparations where the
outer layers of myocytes may contribute disproportionate-
lly to the Ca\textsuperscript{2+} signal whilst damaged myocytes may
generate a Ca\textsuperscript{2+} signal but may not contribute to the
work of contraction. Unfortunately, the technical diffi-
culties in applying external load to cardiac myo-
cytes[80,81] have meant that there is no available data on the
effects of mechanical loading on the Ca\textsuperscript{2+} transient
in isolated myocytes from failing human hearts. There
thus remains no clear consensus surrounding this central
event in excitation–contraction coupling and further
careful studies are needed under both isometric and
isotonic conditions

\textbf{\textit{Ca}}\textsuperscript{2+} uptake and storage

As outlined above, there is clear evidence of prolonged
diastolic Ca\textsuperscript{2+} decay and attention has focused on
abnormalities of uptake into sarcoplasmic reticulum
(SR). The majority of functional studies have demon-
strated reduced Ca\textsuperscript{2+} uptake or storage (Table 3),
the only exception being the study of Movsesian et al.[82].
Studies of the mRNA of the SR Ca\textsuperscript{2+} ATPase
(SERCA2a) have uniformly demonstrated depressed
levels in failing heart[72,74,83-85]. There are, however,
conflicting estimates of SERCA2a protein, with some

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>SR function in heart failure</th>
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<tbody>
<tr>
<td>Harigaya[130]</td>
<td>Spectrophotometric</td>
<td>↓</td>
</tr>
<tr>
<td>Lentz[51]</td>
<td>45Ca\textsuperscript{2+} uptake</td>
<td>↓</td>
</tr>
<tr>
<td>Limas[132]</td>
<td>45Ca\textsuperscript{2+} uptake</td>
<td>↓</td>
</tr>
<tr>
<td>D'Agno[99]</td>
<td>Caffeine contractures</td>
<td>↓</td>
</tr>
<tr>
<td>Derviri[100]</td>
<td>Caffeine contractures</td>
<td>↓</td>
</tr>
</tbody>
</table>
| Beukelmann[62] | Ca\textsuperscript{2+} transient decay with  
zero intracellular Na\textsuperscript{+} | ↓                           |
| Beukelmann[64] | Ca\textsuperscript{2+} transient decay with  
high intracellular Na\textsuperscript{+} | ↓                           |
| Movsesian[82]  | 45Ca\textsuperscript{2+} uptake | ↔                           |

↓ = reduced; ↔ = unchanged.

There are, however, conflicting estimates of SERCA2a protein, with some studies demonstrating depressed levels[84,86] whilst Movsesian et al. were unable to confirm this[87].

Phospholamban inhibits SERCA2a at two separate sites, with this inhibition being attenuated by phosphorylation[88]. Although levels of phospholamban mRNA are depressed in heart failure[74,89] findings with respect to protein levels have been conflicting[86,87,90] and there has been no demonstration of functional impairment[91]. There is no evidence of a disturbance of the SR Ca\textsuperscript{2+} storage protein casqueleterin[72,74,85,87].

The other major pathway for Ca\textsuperscript{2+} removal from the cytosol involves the Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger[50] as the cytosolic Ca\textsuperscript{2+} ATPase contribution appears to be negligible[92]. There is recent evidence for upregulation of the exchanger both in terms of increases in mRNA and protein levels[93] in addition to an increase in the transport of Ca\textsuperscript{2+} across sarcolemmal membrane vesicles[94]. This appears to be functionally significant as inhibition of SERCA2a produces a greater prolongation of relaxation in myocytes from non-failing hearts than in those from patients with heart failure, implying that myocytes from failing hearts are better adapted to SR dysfunction[95]. Thus the weight of evidence, particularly from functional studies, would therefore seem to favour
an abnormality of SR Ca\textsuperscript{2+} uptake secondary to an
abnormality of SERCA2a with uncertainty surrounding the function of phospholamban.

\section*{Myofilament abnormalities}

\subsection*{Myofilament Ca\textsuperscript{2+} sensitivity}

Studies have been performed on skinned fibre prepara-
tions in an attempt to assess the function of the myofil-
ments separately from the controlling influence of the
Ca\textsuperscript{2+} regulatory apparatus. The majority of these have
failed to demonstrate an overall reduction in Ca\textsuperscript{2+}
sensitivity in heart failure[96-100]. Two studies have shown an increased myofilament Ca\textsuperscript{2+} sensitivity in dilated cardiomyopathy, those of Wankerl et al.[35] and that of Schwinger et al.[101]. Schwinger et al. have proposed that whereas the Ca\textsuperscript{2+} sensitivity in non-failing myocardium is dependent upon fibre length this is not the case in failing hearts[101] resulting in a failure of the Frank–Starling mechanism. D’Agno et al. have not confirmed these findings[100]. The fact that no study has demonstrated reduced myofilament Ca\textsuperscript{2+} sensitivity implies that this is not a mechanism for the impaired systolic function in the failing heart.

\subsection*{Alterations in myofilament composition}

The total myosin content and myofilibrillar Mg-ATPase are reduced in the failing heart[102,103] and although this is in keeping with the histological descriptions of a reduced number of myofilibrils[83,32,33], changes in thin filament composition may also play a role[104]. There is no evidence for any myosin isoform switch from the predominant V3 subtype[105] but there are two lines of evidence to suggest that abnormalities of myofilament composition may not be of primary importance in

\footnotesize{Eur Heart J, Vol. 17, February 1996}
Table 4  Alterations in unstimulated adenylate cyclase in the failing human heart

<table>
<thead>
<tr>
<th>Author</th>
<th>Parameter</th>
<th>Change in heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Böhm (121)</td>
<td>Basal adenylyl cyclase activity</td>
<td>↓</td>
</tr>
<tr>
<td>Feldman (133)</td>
<td>Basal cAMP levels</td>
<td>↓</td>
</tr>
<tr>
<td>Bristow (122)</td>
<td>Effect of phosphodiesterase</td>
<td>↓</td>
</tr>
<tr>
<td>Böhm (136)</td>
<td>Inhibition on contraction</td>
<td>↓</td>
</tr>
<tr>
<td>Von der Leyen (137)</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Böhm (138)</td>
<td></td>
<td>ertoire</td>
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<tr>
<td>Böhm (139)</td>
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<tr>
<td>Feldman (140)</td>
<td></td>
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</tr>
<tr>
<td>Böhm (141)</td>
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<td>ertoire</td>
</tr>
<tr>
<td>Von der Leyen (142)</td>
<td></td>
<td>ertoire</td>
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<td></td>
<td>↓ = reduced; ≣ = unchanged.</td>
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</table>

The pathogenesis of depressed systolic performance in heart failure. Firstly, the failure of skinned fibre preparations to demonstrate the reduced force development seen in intact preparations suggests that the major disturbance lies in the Ca²⁺ control mechanisms and not in the contractile units. Secondly, Hasenfuss et al., on the basis of myothermal measurements, have demonstrated no reduction in the efficiency of EC coupling to mechanical work, again supporting evidence in favour of an abnormality of Ca²⁺ control over one of myofilament function.

Could myofilament abnormalities play a role in diastolic dysfunction? There is some evidence to support this from myothermal work demonstrating prolongation of the crossbridge force–time integral in myocardium from failing hearts. Decreases in the atrial-like light chain 2 content of ventricular myocardium in dilated cardiomyopathy have been postulated to slow crossbridge dissociation as might the modest increases in the TnT isoform of troponin T that have been reported. The interest generated by these findings must be tempered by the fact that similar abnormalities of the crossbridge force–time interval are also found in elderly non-failing hearts and thus the contribution of these abnormalities to diastolic dysfunction remains uncertain.

Abnormalities of energy utilization

In a small series, Bashore et al. have described reduced ATP levels in endomyocardial biopsies from failing hearts and correlated these with the expression of ejection fraction, while Schultheiss et al. have demonstrated dysfunction of the mitochondrial ADP/ATP carrier in dilated but not ischaemic cardiomyopathy. In contrast, studies of ATP in heart failure using surgical biopsies (where the time between tissue harvest and freezing will have been shorter) have not demonstrated depression of ATP levels. Some investigators have described a reduction in the ratio of phosphocreatine to ATP levels in dilated cardiomyopathy using ³¹P MRI studies but this finding has not been confirmed by others.

There are several reasons to doubt that a depressed level of ATP is a significant cause of contractile dysfunction in chronic heart failure. Firstly, there are technical difficulties in the measurement of ATP in endomyocardial biopsy specimens and measurement of total adenine nucleotides has failed to show reduced levels in heart failure. Secondly, the Michaelis constants of both SERCA2a and myosin-ATPase are less than 1000 times cytosolic ATP levels suggesting that neither of these enzymes' activity is ATP-limited. Thirdly, intracellular addition of ATP does not reverse the abnormalities in the Ca²⁺ transient seen in heart failure.

Abnormalities of the β-adrenoceptor signalling system

The well-recognized β-adrenoceptor down-regulation, increases in G protein and up regulation of β-adrenoceptor kinase activity in heart failure have been recently reviewed in detail and will not be covered here. Although the importance of a depressed β-adrenoceptor axis in the impaired response to exercise is clear, recent interest has centred on a potential role for β-adrenoceptor desensitization in the pathogenesis of progressive heart failure. The SOLVD trial demonstrated that elevation of catecholamine levels in patients with asymptomatic left ventricular dysfunction preceded the development of heart failure, whilst sequential measurements in patients with stable heart failure have revealed progressive increases in plasma noradrenaline. Several studies have demonstrated that there is a reduction of both basal adenylate cyclase activity and basal levels of cAMP itself in heart failure, although these have not been universal findings. However, studies examining the effects of phosphodiesterase inhibition on contraction which provide a functional measurement of basal cAMP have consistently demonstrated reduced effects in heart failure (Table 4).

These observations have led to the hypothesis that reduced levels of basal cAMP might adversely affect basal myocyte contraction. Several authors have demonstrated that small (sub-inotropic) increases in cAMP can reverse the abnormal force–frequency relationship found in trabecular preparations from failing hearts and we have recently demonstrated that isoprenaline can normalize the abnormal time course of contraction observed in myocytes from patients with heart failure. Against this background it is somewhat surprising that cAMP analogues do not appear to normalize the abnormalities of the Ca²⁺ transient seen in heart failure and that levels of phosphorylated phospholamban are unaltered.
Conclusions

Structural changes are clearly of fundamental importance in the pathogenesis of heart failure, both in terms of a reduction in the total number of myocytes and in a reduction in the myofibril content of those remaining. Changes in the extracellular matrix probably play an important role both in the process of remodelling and in determining passive diastolic function (although conclusive evidence for this in humans is still lacking). In addition to this there are important functional abnormalities of the remaining viable myocytes contributing to both systolic and diastolic dysfunction. The evidence favours disturbance of the Ca\(^{2+}\) regulatory mechanisms over myofilament abnormalities as the predominant contributor to these functional disturbances. There remains uncertainty concerning the abnormalities of the various subcellular organelles involved in Ca\(^{2+}\) homeostasis, but the evidence is most convincing for an abnormality of sarcoplasmic reticulum Ca\(^{2+}\) uptake, possibly with partial compensation by upregulation of the Na\(^{+}\)-Ca\(^{2+}\) exchanger. Whether this abnormality could be reversed by pharmacological intervention is unknown, nor is it known whether these changes are beneficial by reducing cardiac contraction and delaying cell death or harmful by contributing to diminished function of the heart as a pump. Future therapies for heart failure will need to be directed towards avoiding cell necrosis, promoting and controlling cell growth and possibly regulating increases in myocardial cell numbers.

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