Cellular and molecular aspects of contractile dysfunction in heart failure

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1. Introduction

Heart failure is a syndrome in which dysfunction of the heart causes a mismatch between blood supply and demand of the organs. This activates neurohumoral systems and water and salt retention by the kidneys. These counter-regulatory mechanisms in turn influence cardiac function. The pump failure can comprise systolic and diastolic dysfunction that depend on preload, afterload, frequency, and the systolic and diastolic myocardial patterns of contraction, the former often referred to as ‘contractility’. Preload in the intact heart is determined by the enddiastolic ventricular pressure, which, depending on ventricular distensibility, determines enddiastolic volume. On a cellular basis the elongation of the sarcomere (strain) depends on diastolic stress and fiber stiffness [1]. Afterload is defined as the wall stress during contraction and is determined by the forces opposing ventricular ejection, chamber diameter, and the wall thickness. Glower et al. (1985) [2] stated that, in the intact heart in vivo, “no potential index for the determination of contractility” independent of preload and afterload exists. Therefore, it might be useful to distinguish between ‘working capacity’ of the whole heart [3] and myocardial ‘contractility’ of isolated myocardium or of isolated cells in a defined experimental setting. Opie (1995) [4] even suggested the use of ‘contractility’ on a molecular basis as the pattern of “the calcium–contractile protein interaction”. This distinction has the advantage that ventricular heterogeneity, asynchrony and geometrical influences, which change cardiac function, can be described by changes in ‘working capacity’ of the heart even if, on a cellular or molecular basis, ‘contractility’ is unchanged. The present review focuses on how alterations in gene expression that cause cellular and molecular dysfunction of the myocytes can explain changes of contractility and diastolic myocardial function in chronic heart failure.

2. Cellular and molecular alterations in heart failure

Cellular and molecular changes in heart failure occur in myocytes or in nonmyocytes and in interstitial tissue. Among the changes of myocytic gene expression and function three aspects will be discussed: the composition and function of contractile proteins, calcium homeostasis, and signal transduction pathways. These changes of the myocytes will be reviewed first in order to discuss the intrinsic myocardial characteristics of contractile dysfunction in heart failure.

2.1. Contractile proteins

In the failing human heart the expression pattern of myosin heavy chain isoforms [5–7] as well as the ATPase-activity of isolated myosin preparations is unchanged [8]. However, some changes of function of intact myofibrils have been described (Fig. 1C). The calcium-dependent Mg2+-ATPase activity is lower in heart failure [6]. Correspondingly, Hajjar and Gwathmey (1992) [9] found a slowing of the cross bridge cycling rate, and Hasenfuss et al. (1992) [10] concluded from heat measurements in isometrically contracting myocardial strip preparations, that the number of cross bridge interactions per time was reduced, but that on the other hand the force–time integral of an individual crossbridge cycle was increased. Summarizing these results, it appears that the mechanical output per crossbridge cycle requires less energy in the failing ventricular myocardium. This may give rise to a decreased maximal force developed, but keeps the contraction on a more economical level. These changes cannot be explained by the reduction of the relative amount of myofibrils as reported in failing myocardium [7,10,11]. Therefore, additional changes in the regulatory proteins of the myofibrils were postulated. Indeed, some data suggest an enhanced expression of the fetal isoform of troponin T [12–14] and, although controversial, changes in myosin light chain expression [14–16]. Recently the phosphorylation state of troponin I was reported to be reduced in failing myocardium.

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dium [17]. This was most likely due to the blunted adenylyl cyclase–cAMP–protein kinase A pathway [18] and therefore did not imply intrinsic changes of the myofilaments. Such changes in the regulatory proteins in heart failure could theoretically affect the calcium sensitivity of the myofilaments which additionally depends on the length of the sarcomere and on intracellular pH (for review see [19,20]). Indeed, some authors reported an increased calcium sensitivity [21,14] and a decreased change in myofibrillar calcium sensitivity in response to changes in length [22] in failing myocardium. However, most groups found that the calcium sensitivity and its increase with stretching is unchanged [23–26].

In summary, despite of a lack of a myosin heavy chain isoform shift the reported biochemical changes in the myofilibrils seem to favor a more economical myocardial contraction, but most likely do not produce intrinsic changes of the calcium sensitivity.

2.2. Calcium homeostasis

Since activation of the myofibrils depends on cytosolic calcium concentrations, an altered handling of intracellular calcium could contribute to contractile dysfunction in failing myocardium. First evidence of an impaired calcium homeostasis was provided by Gwathmey et al. [24,27]. Investigating isometrically contracting ventricular muscle strips at 30°C they reported increased diastolic calcium concentrations and a prolonged calcium transient. These two findings were confirmed under isotonic conditions in isolated human ventricular myocytes [28] and in isolated ventricular muscle strips at 37°C [29], even if at this temperature under isometric conditions no differences could be demonstrated between failing and nonfailing myocardium [29]. Corresponding to the slowed decline in intracellular calcium concentrations, the action potential duration was prolonged in isolated ventricular myocardium and myocytes from failing hearts [28,30]. In summary, there is ample evidence to suggest that the failing heart exhibits a prolonged action potential and calcium transient and increased diastolic calcium concentrations (Table 1). However, it is less clear whether systematical changes occur in systolic calcium concentrations, since they were elevated [29], unchanged [24,27], or decreased [28] under different experimental conditions. Possibly, differences in systolic calcium concentrations might become relevant at higher heart rates since systolic calcium concentrations decreased in failing, but increased in nonfailing isometrically contracting myocardium with increasing stimulation frequencies [30].

On a molecular basis there are no clear changes in the proteins involved in the rise of cytosolic calcium concentrations in failing human hearts (Fig. 1B). The number of L-type calcium channels and maximal currents were reported to be unchanged [28,31]. However, decreased protein levels have also been found [32]. In addition, no changes were found in the amount of calcium release channels [33] and the sarcoplasmic calcium release rate was normal despite of an increased threshold of activation [26]. Recently, as a new concept of systolic disturbances of the calcium homeostasis, an impaired coupling between L-type calcium channels and calcium release channels was described in hypertrophied and failing rat hearts [34]; however, corresponding data from human hearts are lacking.

More clearly, the calcium uptake of the sarcoplasmic reticulum was found to be reduced by most investigators in failing human myocardium [30,35–38]. Only one group reported contradictory results [39]. The decreased transport rate could explain the increase in diastolic calcium concentrations mentioned above. Interestingly, the reduced diastolic calcium concentration cannot easily be explained by changes in protein concentration of the calcium ATPase of the sarcoplasmic reticulum or the regulatory protein phospholamban, since both of these proteins were found to be unaltered by most [38–40] although not all groups. Possibly compensating in part for the decreased transport capacity of the sarcoplasmic reticulum, the sarcolemmal Na+/Ca2+-exchanger is increased in the failing myocardium [41–43].

In conclusion, the failing human myocardium exhibits a prolonged action potential duration, a prolonged calcium transient and increased diastolic calcium concentrations that correspond to a decreased calcium uptake rate of the sarcoplasmic reticulum.

2.3. Signal transduction

Changes in G-protein mediated signal transduction pathways in human heart failure have gained much attention (Fig. 1A). A decrease in β-adrenoceptor number was found, which was selective for the β1-subtype in dilated cardiomyopathy, affected both β1- and β2-subtypes in mitral valve stenosis and β1- and possibly β2-subtype in ischemic cardiomyopathy ([44], for rev. [45]). These biochemical alterations were accompanied by a decreased β-adrenoceptor mediated stimulation of the adenylyl cyclase [46] and intracellular cAMP levels [47]. More recently, an increased expression of the β-adrenoceptor kinase that participates in receptor desensitization [48] and

Table 1

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<th>Molecular and functional alterations of calcium homeostasis in failing human myocardium</th>
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<tr>
<td>Alterations</td>
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<tr>
<td>Prolonged action potential</td>
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<tr>
<td>Prolonged Ca2+ transient</td>
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<tr>
<td>≈ Systolic Ca2+ concentrations</td>
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<tr>
<td>↓ Threshold for Ca2+ release from sarcoplasmic reticulum</td>
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<tr>
<td>↑ Diastolic Ca2+ concentrations</td>
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<tr>
<td>↓ Ca2+ uptake of sarcoplasmic reticulum</td>
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<td>↑ Na+/Ca2+ exchanger protein content</td>
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↑ increase; ↓ decrease; ≈ conflicting results.
Fig. 1. Adenylyl cyclase signalling pathway, calcium homeostasis and contractile filaments in nonfailing (left side) and failing (right side) myocardium. A: Stimulation of β-adrenoceptors (β-AR) activates the adenylyl cyclase (AC) via heterotrimeric stimulatory G-proteins consisting of α, β, and γ-subunits. Receptor coupled inhibitory G-proteins (α, β, γ) inhibit AC function. In failing myocardium the total number of β-ARs is reduced, the activity of β-AR kinase (βARK) that inhibits activated β-ARs by phosphorylation (P), and the amount of inhibitory G-proteins is increased. This results in a decreased production of cAMP and a decreased activation of protein kinase A (PKA). B: Calcium that enters the myocyte via the L-type calcium channel (DHP) triggers calcium release from the sarcoplasmic reticulum (SR) via the calcium release channel (Rya). Cytosolic calcium is removed into the SR by the Ca²⁺-ATPase of the SR (SERCA) which is modulated by phospholamban (PLB) and into the extracellular space via the Na⁺/Ca²⁺ exchanger (NCX). In the failing heart protein content and transport rate of DHP and Rya are unchanged, whereas the threshold of activation of the Rya is increased. The concept of a possibly impaired coupling between DHP and Rya is illustrated by an increased distance between DHP and Rya on the right side. Diastolic calcium reuptake via SERCA into the SR is reduced, which is compensated for in part by an increased expression of the NCX. C: Contraction is achieved by the interaction between myosin heads and actin which is regulated by tropomyosin and the troponin complex consisting of troponin I, C, and T, and is dependent on ATP hydrolysis of the Mg²⁺-ATPase. In failing myocardium changes regarding the myofilaments include a reduced Mg²⁺-ATPase activity, a decreased phosphorylation state of troponin I, and an increased expression of the fetal isoform of troponin T (TnT4).

an increase in inhibitory G-proteins (Giα) have been described [49–53]. The latter finding can explain the heterologous nature of desensitization of cardiac adenylyl
cyclase activity in failing myocardium, i.e. the blunted response to other cAMP elevating receptor systems. It is important to note that the blunted cAMP response to
catecholamines results in less phosphorylation of phospholamban and thereby deteriorates the Ca\(^{2+}\) uptake capacity of the sarcoplasmic reticulum. Desensitization of the adenyl cyclase, both biochemically and functionally, can be induced in animal models and cell culture experiments by chronic β-adrenergic stimulation, indicating that it is secondary to neurohumoral activation in heart failure [53].

In summary, cAMP generating receptor pathways are desensitized in the failing myocardium, which contributes to the relative refractoriness to catecholamines in patients with heart failure.

3. Systolic dysfunction of the failing myocardium

Systolic function of the myocardium can be characterized by the response (1) to increased preload, the Frank–Starling mechanism, (2) to increased frequency of stimulation, and (3) to positive inotropic compounds (Table 2).

3.1. Frank–Starling mechanism

Studies in dogs with pacing-induced heart failure suggested that the failing heart in vivo is almost unable further to augment end-diastolic volume and stroke volume in response to acute volume load indicating an exhausted Frank–Starling mechanism [54]. The ability of the failing human heart to use the Frank–Starling mechanism has been the subject of controversy. Schwinger et al. (1994) [21] found that isolated papillary muscle strips from terminally failing human hearts were generally unable to develop a Frank–Starling mechanism. This finding was explained by an increased calcium sensitivity of the myofibrils, which would be unable to further augment their calcium sensitivity in response to an increase in length. However, the majority of studies, using strip preparations or trabeculae carneae or isovolumically contracting intact hearts, revealed that the Frank–Starling mechanism may increase in systolic function during isovolumic contraction or trabeculae carneae or isovolumically contracting intact In healthy subjects an increase in frequency leads to an enhanced diastolic calcium inlux via the calcium channel, which might at least in part be explained by a frequency induced increase in functional L-type calcium channels, which was shown in human atrial and to a lesser degree in ventricular myocytes [61]. This system is modulated by intracellular levels of cAMP, because calcium uptake by the sarcoplasmic reticulum and sarcлемmal calcium influx are increased by protein kinase A dependent phosphorylation of phospholamban and the L-type calcium channel, respectively [62].

In healthy subjects an increase in frequency leads to an increase in systolic function during isovolumic contraction and the ejection phase [63–65] and to enhanced diastolic performance [65,66]. On the other hand, patients with congestive heart failure showed little or no changes of systolic or diastolic function upon atrial stimulation [66,67]. This difference between failing and nonfailing hearts is also seen in vitro. Electrically driven preparations isolated from hypertrophied [27,68,69] and terminally failing human hearts [70,71] showed a blunted or negative, whereas nonfailing myocardium showed a positive ‘staircase’. Studies in isolated ventricular myocytes from terminally failing hearts confirmed that this difference was inherent to the myocytes [72]. Most likely, an impaired activation of the myofibrils is responsible for the negative ‘staircase’ in failing myocardium, possibly due to a decreased calcium sensitivity of the myofilaments at higher stimulation frequencies, to alterations in the action potential with increasing stimulation frequencies or to an unchanged Ca\(^{2+}\) sensitivity of the myofibrils and an increase in calcium sensitivity with stretching [23–26]. On the other hand, in patients with heart failure the ability of the heart to recruit the Frank–Starling mechanism to compensate for increases in afterload may be limited. High end-diastolic pressures may result in an ‘afterload–inotropic state mismatch’ when the limit of the preload reserve is reached [57]. Similarly, an upwardshift of the left ventricular end-diastolic pressure–volume relation, resulting from a decreased ventricular distensibility, prohibits left ventricular diastolic filling. Therefore, patients with left ventricular diastolic dysfunction may present with congestive heart failure even when systolic function is normal [58].

### 3.2. Force–frequency relationship

An increase in force with increasing stimulation frequency, the so-called ‘Treppe’ or ‘staircase’ phenomenon, was first described by Bowditch (1871) [59]. The mechanisms of the ‘staircase’ phenomenon are not completely understood but seem to depend on changes of the balance between intracellular sodium and calcium concentrations [60]. An increase in heart rate may lead to an increased sarcolemmal sodium influx by the Na\(^+\)/K\(^+\)-ATPase and may cause a secondary decrease in calcium efflux by the Na\(^+\)/Ca\(^{2+}\)-exchanger. Frequency dependent changes of the calcium homeostasis also include an increased systolic calcium influx via the calcium channel, which might at least in part be explained by a frequency induced increase in functional L-type calcium channels, which was shown in human atrial and to a lesser degree in ventricular myocytes [61]. This system is modulated by intracellular levels of cAMP, because calcium uptake by the sarcoplasmic reticulum and sarcolemmal calcium influx are increased by protein kinase A dependent phosphorylation of phospholamban and the L-type calcium channel, respectively [62].

In summary, cAMP generating receptor pathways are desensitized in the failing myocardium, which contributes to the relative refractoriness to catecholamines in patients with heart failure.

### Table 2

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<th>Contractile characteristics of failing human myocardium in vitro</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Preserved Frank–Starling mechanism</td>
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<tr>
<td>Negative staircase phenomenon</td>
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<tr>
<td>Inotropic drug response</td>
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<tr>
<td>↓ response to cAMP elevating drugs</td>
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<tr>
<td>= response to PLC activating drugs</td>
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<tr>
<td>unchanged response to extracellular calcium</td>
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<tr>
<td>unchanged maximal effect of Na(^+) elevating drugs</td>
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<tr>
<td>unchanged maximal effect of calcium sensitizer</td>
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<tr>
<td>Unchanged isometric relaxation at 37°C</td>
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<td>↓ decrease; =: conflicting results.</td>
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impaired calcium handling [24,27,73]. Pieske et al. [30]
supported the latter concept. For isolated ventricular
muscle strips, they reported a good correlation between
twitch amplitude, the maximum of the respective systolic
aequorin signal, and the Ca\(^{2+}\) uptake of the sarcoplasmic
reticulum. The importance of sarcoplasmic reticulum
calcium handling is further emphasized by the effect of
cAMP increasing agents that increase phosphorylation of
the regulatory protein phospholamban and thereby enhance
Ca\(^{2+}\) uptake by the sarcoplasmic reticulum. At low
concentrations they reversed the negative 'staircase' [73–
76] and improved diastolic abnormalities of calcium handling [24].

3.3. Responsiveness of the failing myocardium to
positive inotropic drugs

Positive inotropic agents mediate their effects by in-
creasing either intracellular calcium concentrations or the
sensitivity of the myofilaments for calcium.

Elevation of intracellular calcium concentrations can be
achieved by several mechanisms: (1) Most importantly,
cAMP increasing agents increase transsarcomembral cal-
cium influx via the L-type calcium channel and diastolic
calcium reuptake of the sarcoplasmic reticulum via phos-
phorylation of phospholamban and decrease the sensitivity
of the myofilaments for calcium. Agents that increase
cAMP by coupling to the stimulatory G-protein include
agonists at β1- and β2-adrenoceptors (e.g. adrenaline,
noradrenaline, dobutamine) and at H\(_2\)-histamine receptors;
these receptors are coupled to stimulatory G-proteins.
Other cAMP increasing agents include direct activators of
the adenylyl cyclase (e.g. forskolin), and inhibitors of the
cAMP hydrolyzing phosphodiesterase III (e.g. milrinone,
amrinone). The positive inotropic effect of these agents is,
in contrast to cAMP-independent agents, accompanied by
shortening of the contraction and relaxation time.

(2) An increase in intracellular calcium can also be
achieved directly: calcium channel agonists or experimen-
tal elevation of extracellular calcium concentrations in-
crease calcium influx through the L-type calcium channel.

(3) Higher intracellular sodium levels enhance Na\(^{+}\)–
efflux and Ca\(^{2+}\) influx via the Na\(^+\)–Ca\(^{2+}\)-exchanger. This
can be mediated by inhibitors of the Na\(^+\)–K\(^+\)-ATPase
(digitalis glycosides) or by agents that prolong the open
state of the Na\(^+\)-channel (e.g. DPI 201-106, BDF 9148).

The mechanism of action of α-adrenoceptor agonists or
of endothelin and angiotensin II (at the atrium), which
mediate their positive inotropic effects via an activation of
the phospholipase C, is unclear in human myocardium. It
has been questioned whether they increase intracellular
calcium concentrations sufficiently, and it has been pro-
posed that an increase in action potential duration, inositol
tris phosphate content, diacylglycerol, pH, or in the
sensitivity of the myofilaments to calcium may play a role
([77,78], for review [79,80]).

In heart failure, the positive inotropic effect and the
potency of β\(_1\)-adrenoceptor agonists is progressively re-
duced with an increasing degree of the disease, both in
isolated myocardium [81,82] and in vivo [83]. The reason
lies in the desensitization of the adenylyl cyclase signaling
pathways as discussed above. This desensitization also
applies to positive inotropic effects of other cAMP increas-
ing agents, such as histamine, β\(_3\)-adrenoceptor agonists
[84], and compounds that increase cAMP by inhibiting
phosphodiesterases (PDE). Since the sensitivity of the four
cardiac PDE isoenzymes to the inhibitory effect of the
PDE inhibitors did not differ, the blunted response cannot
be explained by an alteration at the level of the PDEs, but
rather by a diminished formation of cAMP [84–86].

In contrast, the positive inotropic effect of agents that
increase calcium independently of G-proteins and cAMP,
is preserved in heart failure, as is that of an increased
external calcium [23,87–89]. This reflects an unchanged
systolic capacity of the contractile proteins. The maximal
positive inotropic effect of agents that increase intracellular
sodium is also maintained, regardless of whether they are
primarily acting by prolonging the open state of the Na\(^+\)
channel or by inhibition of the Na\(^+\)/K\(^+\)-ATPase
[87,89,90]. Some groups even found an increased potency
of these agents [87,90]. This could be explained by an
increased expression of the Na\(^+\)/Ca\(^{2+}\) exchanger [40–43]
or by a decreased expression of the Na\(^+\)/K\(^-\)–ATPase,
which also was reported by some [91,92], but not by all
groups [90].

Whether the positive inotropic effect mediated by
phospholipase C activating receptors is maintained in
failing myocardium is controversial. Steinfath et al. [84]
reported a reduced positive inotropic effect of α-adreno-
ceptor agonists. Their efficacy correlated with that of
β-adrenoceptor agonists [88,93]. Since the α-adrenoceptor
number is not decreased or even increased in failing
human myocardium [84,94], a post-receptor defect was
suggested, possibly involving G proteins. However, this
remained speculative, since in general the mechanism of
the action of α-adrenoceptor agonists is as yet not well
understood [79,80]. In contrast to these data, other groups
did not find a reduction in the efficacy of α-adrenoceptor
agonists in failing human myocardium [95].

Agents that do not increase systolic intracellular calcium
concentrations but increase the sensitivity of the myofil-
laments to calcium, e.g. EMD 57033, are equally effective in
failing and nonfailing human myocardium in increasing
force of contraction [96]. This supports the concept of the
unchanged systolic capacity of the contractile proteins.

4. Diastolic dysfunction in the failing heart

In experiments on isolated myocardium, isometric,
isotonic, and auxotonic relaxation can be investigated by
measuring rate and time of force decline and of lengthening,
respectively (for review, see [97]). In the intact heart
the concept of isometric and isotonic relaxation can be

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applied to the force decline during predominantly isovolumic relaxation (i.e. isometric) and the predominantly isotonic relaxation during early ventricular filling. However, in general the behaviour of the ventricle can better be described as auxotonic. Load, inactivation of myofilibrils, and nonuniformity have been proposed to determine relaxation. The latter means that some fibers are still contracting, whereas others are already in the phase of isometric relaxation or are increasing in length. The important role of the extracellular matrix for diastolic function in heart failure and the changes in chamber stiffness and myocardial stiffness has been reviewed elsewhere (e.g. [97,98]).

Given the changes in calcium homeostasis discussed above with a prolonged calcium transient and increased diastolic calcium concentrations in the failing myocardium, one would expect dissociation of calcium from the contractile proteins to be slowed and therefore relaxation to be prolonged. Indeed, one group [27,73,87] described an increase in the time of relaxation in isometrically contracting muscle strips from failing myocardium at a temperature of 30°C. However, under similar conditions but at 37°C only one further group found slightly prolonged times of relaxation [30]. In contrast, the majority of investigators reported that the duration of relaxation is unchanged or at the most marginally prolonged in only some of the preparations [10,21,22,36,76]. This holds true for the whole range of stimulation frequencies between 0.2 Hz and 3 Hz [71].

Do these data allow one to conclude that disturbances of the calcium homeostasis in failing myocardium do not influence relaxation? Most likely not, because according to Bruttsaert and Sys (1989) [97] the mechanisms of relaxation depend on the experimental setting. During isotonic relaxation of cardiac muscle, load and the sarcomplasmic reticulum are of major relevance. On the other hand, isometric relaxation depends predominantly on the instantaneous force and the intrinsic properties of the contractile filaments, modulated by muscle lengths, and only to a minor degree on load and on the function of the sarcomplasmic reticulum. In experimental models where no functional sarcomplasmic reticulum was present the load dependence of isotonic relaxation disappeared and the relaxation curves met the respective curves of the isometric relaxation [99–101]. Therefore, the finding of most groups of an unchanged isometric relaxation does not conflict with the assumption that the disturbances of the sarcomplasmic calcium reuptake affect muscle lengthening, but would imply that the function of the myofilaments during relaxation, at least in the absence of calcium sensitizing agents, is unchanged. This is in accordance with the unchanged calcium sensitivity reported by most groups as discussed above [23–26].

In conclusion, the molecular and functional changes of the sarcomplasmic reticulum, as outlined above, will cause dysfunction primarily during the phase of isotonic relaxation. However, since the mode of early relaxation in the intact heart is best characterized as auxotonic, it is to some degree dependent on the sarcomplasmic reticulum. Furthermore, the temporal and spatial nonuniformity of heart muscle relaxation in vivo adds some load dependency and increases the influence of the sarcomplasmic reticulum. Therefore, even during early relaxation, changes in diastolic calcium handling can contribute to the dysfunction in patients with heart failure, which are well known since the studies of Grossman et al. [66].

5. Summary

A number of molecular and cellular alterations have been identified in the failing human heart that help to understand contraction and relaxation abnormalities. Cyclic AMP dependent pathways are desensitized due to quantitative changes in β-adrenoceptors, β-adrenoceptor kinase, and inhibitory G-proteins. Calcium homeostasis is impaired, characterized by a decreased calcium reuptake rate of the sarcoplasmic reticulum, an increased threshold of the calcium release channel, and an increased Na⁺/Ca²⁺ exchanger expression. Myofibrillar function may be affected by a decrease in Mg²⁺-ATPase activity and in troponin I phosphorylation, and by changes in TnT isofrom expression. These alterations seem to occur independently of the underlying etiology of heart failure and are most likely consequences rather than primary causes of the disease. Most likely, chronic neurohumoral activation and abnormal mechanical load initiate the majority of the hitherto known changes in the myocardium and promote the further progression of cardiac failure as part of a vicious circle. Further extension of knowledge of pathophysiological mechanisms should improve therapeutic strategies which aim at slowing the progression of heart failure and at reversing secondary alterations by interrupting the deleterious influence of neurohumoral activation. Future progress will depend on answers to current gaps in our knowledge of heart failure, including the unknown primary cause of idiopathic dilated cardiomyopathy, factors underlying the greatly variable progression of pump failure, as well as the exact pathophysiologic role of the molecular alterations as described in this review.

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