Editorial

The failing human heart

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1. Introduction

Heart failure remains a significant public health problem with an unacceptably high morbidity and mortality affecting about three persons per thousand per year [1]. The percent survival following diagnosis decreases significantly as a function of the severity of the disease with survival rates for NYHA (New York Heart Association) I–II being 65% at the end of 4 years, for NYHA III it is 50% at the 4-year period and for NYHA IV it is 50% after only 1 year [2,3]. In the patients with heart failure, there is a significant correlation between survivability and ejection fraction [4]. The deficits in ventricular function in failing human hearts led us to examine the contributions of the contractile (acto–myosin interaction) and excitation–contraction–coupling (EC) (calcium cycling) systems to that insufficiency.

2. The contractile system

2.1. Myofibrillar ATPase activity and velocity of shortening

The first demonstration of a molecular alteration in the contractile system of human failing hearts was found in studies carried out on myofibrils from failing hearts (secondary to hypertensive heart disease) and non failing hearts (accident victims) [5]. The myofibrillar ATPase activity in the failing human hearts was reduced from non failing values (mean±S.D.)^2 of 0.99±0.05 to 0.69±0.04 μmole Pi/mg myofibrillar protein/15 min (P<0.001). The functional consequences of the depressed ATPase activity were not completely clear at the time these experiments were carried out although we believed the depressed activity was associated with a decrease in contractility of the heart muscle. This view was supported by a decrease in the contractility of actomyosin strands [6] and glycerinated fibers [7] from failing heart muscle. From the perspective of ventricular function, the decreased contractility involves contractile force, velocity of shortening or a combination of the two. The relationship between force and velocity of shortening was thoroughly described by Hill [8] where the hyperbolic relationship was believed to be a mechanical expression of the myosin cross-bridge’s cyclic interaction with actin and the obligatory hydrolysis of MgATP [9]. In a study where the force velocity relation and myofibrillar ATPase activity were determined in a population of rats ranging in age from 100 to 1000 days, there was a clear linear relation between velocity of shortening at each load and myofibrillar ATPase activity (Fig. 1) [10]. It would appear then that if one can extrapolate from the rat data to the human situation, the reduced myofibrillar ATPase activity is very likely associated with a reduced velocity of shortening. The correlation of myosin ATPase activity and the speed of muscle shortening was clearly demonstrated for various muscle types [11]. Since power output of the heart is the product of the force and velocity, the reduced velocity of shortening would result in a reduction of power output if force is unchanged and thus could readily contribute to the deficit in ventricular function found in the failing hearts. Despite the attractiveness of this view, extrapolation from rat data to the human should be

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1The classification of heart failure patients is based on physiological alterations such as shortness of breath and fatigue resulting from activity with severest degree of failure NYHA III–IV involving symptoms with minimal activity or at rest, respectively.

2Unless otherwise indicated the mean±the standard error of the mean is used.
experiments under physiological conditions (temperature 37 °C and 60–180 bpm stimulation frequency). The results were disappointing in that the low force values obtained limited the usefulness of the preparations [14,15]. The use of a protective solution consisting of Krebs–Ringer, 30 mM 2,3-butanedione monoxime (BDM), 11.2 mM glucose, 2.5 mM Ca²⁺ and 10 IU insulin per liter permitted dissection of thin strips (<0.30 mm²) which are electrically excitable and produce high tension [12,16] because diameters below 0.6 mm permit adequate oxygenation at 37 °C and 180 bpm. Tension values obtained with the BDM-dissected myocardial strips are 2.8–6.0 times larger than preparations from left ventricular papillary muscles by others [14,15]. These thin preparations are ideal for mechanical and myothermal experiments carried out at 37 °C.

2.3. Mechanical studies on human heart tissue

Muscle strips were obtained from six patients with end stage dilated cardiomyopathic heart failure “DCM” (NYHA IV) undergoing transplant surgery [19,20]. For controls, muscle strips were prepared from left ventricular biopsies during coronary artery bypass surgery from seven patients with normal left ventricular function [20]. The time course for a typical isometric myogram from non failing and DCM failing preparations is shown in Fig. 2A, top panel. At 37 °C and optimal muscle length, peak twitch tensions for the non failing and DCM failing myocardium were 25.9±3.9 and 13.9±2.0 mN/mm², respectively (P<0.02). The maximal rates of tension development and relaxation were reduced from 193±26 and 148±23 to 95±11 and 80±13 mN/mm² s (P<0.02). Thus in tissue from the failing hearts, isometric tension was reduced as was the rate of rise and fall of tension. In order to gain insight into the molecular events contributing to this deficit, thermo–mechanical measurements of the contractile and excitation–contraction–coupling system were employed.

2.4. Thermo–mechanical studies of human heart tissue

The time course of myocardial energy consumption along with mechanics provides a window for viewing the rate and extent of molecular and cellular mechanical phenomena along with the underlying chemical reactions. Ultra sensitive, thin-film thermopiles in conjunction with a capacitance force transducer were used to evaluate heat production and mechanics of thin strips from human hearts [17]. In a repetitively stimulated muscle strip, under steady state conditions, all mechanical and metabolic conditions at the start of each contraction are identical. Accordingly, average pH, ATP, ADP, CrP, and Pi levels are constant. Since contraction and relaxation are energy consuming phenomena this implies that the recovery processes (also energy consuming) take place throughout the contraction relaxation cycle [18]. Following the depolarization of the

Fig. 1. The velocity of papillary muscle shortening as a function myofibrillar ATPase activity. Force velocity curves were measured from tensions for the non failing and DCM failing myocardium 2rat papillary muscles isolated from rats ranging in age from 100 to 1000 days (see top of figure) in Krebs phosphate solution containing 0.5 mM 0.02). The maximal rates of tension development and2 of tension were reduced from 193±26 and 148±23 topopulation of hearts using glycerol stored myofibrils. The relationship of 2 95±11 and 80±13 mN/mm² s (P<0.02). Thus in tissue from the failing hearts, isometric tension was reduced as was the rate of rise and fall of tension. In order to gain insight into the molecular events contributing to this

2.2. Protection of human left ventricular myocardium during dissection and transport

The feasibility of using strips from human hearts was first demonstrated by Sonnenblick et al. who established that viable muscle preparations could be obtained during corrective cardiac surgery [13]. These methods resulted in strips with a cross sectional area of 5.5±3.9 mm², a thickness which does not permit sufficient oxygenation for

accepted with caution. In order to overcome this difficulty, experiments must be performed on failing and non-failing human heart tissue using methods that provide a window to examine the contractile and excitation–contraction coupling behavior of these tissues more directly. This requires the use of thin strips of human heart muscle for thermo–mechanical studies. A key obstacle is the requirement that heart tissue be protected during dissection into thin viable strips and during transportation from the surgical suites (local and at transplant centers) to the laboratory [12].
Fig. 2. (A) Top panel: peak isometric force for strips from non-failing (NF) and failing (F-DCM, dilated cardiomyopathic [transplant]) human hearts; lower panel: initial (I), tension dependent (TDH) and tension independent (TIH) heat production during the isometric twitch from non-failing (NF) and failing F-DCM heart strips. (B) Top panel: sources of recovery (R), tension dependent (TDH) and tension independent (TIH) heat production during the isometric twitch. Middle panel: time course of total activity related (TA), recovery (R), initial (I), tension dependent (TDH), tension independent (TIH) and resting (RH) heat production during the isometric twitch. Bottom panel: Isometric force production, the twitch force–time integral (IPdt) and twitch time (TT). (C) Left panel: average cross-bridge force–time integral for non-failing (NF) and failing (F-DCM) human hearts. Middle panel: isometric peak force versus calcium cycled per beat for non-failing (NF) and failing (F-DCM) human hearts. Right panel: rate of isometric relaxation as a function of the rate of calcium uptake for non-failing (NF) and failing (F-DCM) human hearts.

Sarcolemma, the principal events are (1) the release and subsequent uptake of calcium and (2) the actin–myosin cross-bridge cycle where the myosin head attaches to actin, rotates developing force or movement and then detaches. The calcium and cross-bridge cycling are immediately powered by the energy contained in the terminal phosphate of ATP and it’s associated hydrolysis (ATP→ADP+Pi). ATP is then resynthesized from ADP by the closely coupled creatine transphorylase reaction (CrP+ADP→ATP+Cr). Under steady-state conditions, the mus-
cle and thermopile system measuring temperature change can be viewed as a thermodynamically closed system. For a closed system at equilibrium the enthalpy change ($\Delta H$) is equal to the heat liberated ($q$) and the work done ($w$): 

$$q + w = -\Delta H$$

The enthalpy change is the sum of all the enthalpy changes that occur in all of the reactions coupled to the overall contraction relaxation cycle. If $n_i$ is the number of moles involved in the $i^{th}$ reaction and $\Delta H_i$ is the enthalpy change per mole of the $i^{th}$ reaction then:

$$-\Delta H = \sum_{i=0}^{n} n_i (-\Delta H_i)$$

Since we know that the key reaction involved is the hydrolysis of ATP, under isometric conditions where external work is zero, we can use the rate and quantity of heat production to calculate the rate and extent of ATP hydrolysis during the contraction–relaxation cycle and the accompanying recovery processes.

A resting muscle strip (optimum length [$l_o$]), in contact with the thermopile system, liberates heat at a steady rate (Fig. 2B). This is the resting heat production (RH) and is a reflection of the energy requirement for maintaining the internal environment (metabolites, electrolytes, pH, proteins). Following stimulation, the muscle goes through its contraction relaxation and recovery cycle (Fig. 2B) with the total activity related heat ($T_A$ = total heat–resting heat) liberated at an initial rapid ($I$) and a secondary slower rate ($R$) (Fig. 2B). The secondary heat production occurs at a mono exponentially decreasing rate. The mono exponential timecourse of this latter heat production can be extrapolated back to zero time to represent the recovery heat process, $R$. The initial heat ($I$) is partitioned into a tension dependent component (TDH, cross-bridge cycling) and a tension independent component (TIH, calcium cycling) (Fig. 2B) [21]:

$$T_A = R + I$$

$$I = TDH + TIH$$

2.5. Determination of the average cross-bridge force–time integral from the tension dependent heat during the isometric contraction–relaxation

The initial heat and tension dependent heat for the non-failing myocardium were $3.89 \pm 0.66$ and $3.39 \pm 0.59$ mJ/g. In the DCM failing myocardium, these values were reduced to $1.50 \pm 0.26$ and $1.34 \pm 0.22$ mJ/g (Fig. 2A, bottom panel). The tension dependent heat is a reflection of the number of molecules of ATP hydrolyzed by the cross-bridge cycling and thus of the number of cross-bridge cycles that occur during the isometric twitch duration. Dividing the tension dependent heat, produced during the contraction relaxation cycle, by the enthalpy change per molecule of ATP hydrolyzed (56 pnJ) gives the number of cross-bridge cycles that occur in the muscle ($XBrCyc_{muscle}$) during the contraction and relaxation:

$$TDH/56\text{pnJ} = XBrCyc_{muscle}$$

To ascertain the cross-bridge cycles per half sarcomere ($XBrCyc_{hs}$), the $XBrCyc_{muscle}$ is divided by the number of half sarcomeres (#$hs_{muscle}$) in the length ($l_{max}$) of the muscle. The muscle force–time integral ($FTI_{muscle}$) for the contraction relaxation cycle is equal to the number of cross-bridge cycles that occur during this period in a half sarcomere ($XBrCyc_{hs}$) multiplied by the average cross-bridge force time integral ($FTI_{XBr}$). Accordingly, the average cross-bridge force–time integral equals the muscle force–time integral divided by the number of cross-bridge cycles per half sarcomere:

$$#hs_{muscle} = l_{max} / hs$$

$$XBrCyc_{hs} = XBrCyc_{muscle} / #hs_{muscle}$$

$$FTI_{XBr} = FTI_{muscle} / XBrCyc_{hs}$$

2.6. The average cross-bridge force–time integral in failing hearts

In light of the reduction in the peak isometric force in the DCM failing hearts, it was surprising to find a 33% increase in the average cross-bridge force–time integral (Fig. 2C, left panel) [19]. In heart failure secondary to mitral regurgitation (MR) the overall mechanics was similar to that found for DCM failure with the average cross-bridge force–time integral being 85% greater than that for controls [22]. At the molecular level, the average cross-bridge force–time integral is the product of the unitary force ($F_{uni}$) developed by the myosin cross-bridge head as it attaches to actin and rotates and the period of time that it stays attached to actin ($T_{uni}$, attachment time). An increase in the average cross-bridge force–time integral can result from an increase in the unitary force, the attachment time or both of these:

$$FTI_{XBr} = F_{uni} T_{uni}$$

We know that myofibrillar ATPase activity and the the velocity of unloaded shortening in failing heart muscle is reduced (See Fig. 1). At a molecular cross-bridge level the velocity of unloaded shortening is determined by the ratio of the unitary displacement of the cross-bridge as it undergoes its power stroke ($D_{uni}$) and the attachment time ($T_{uni}$) following the power stroke:

$$V \approx D_{uni} / T_{uni}$$

Accordingly, the decrease in velocity might result from a decrease in $D_{uni}$ or an increase in $T_{uni}$. 
These observations apply to unloaded shortening conditions. We wished to assess whether there were comparable explanations for the increase in the isometric cross-bridge force–time integral in the failing heart preparations. In order to evaluate the determinants of the increase in the force–time integral, mechanical studies were carried out using sinusoidal length-perturbation analysis to obtain the frequency dependence of viscoelasticity in skinned MR-failing and non-failing human myocardium. Based on this analysis, the dynamic visco-elastic properties could be ascribed to both the kinetics and mechanical properties of the myosin cross-bridge population. In fact, we could model these visco-elastic properties as evidence for potential changes in the lifetime of the strongly bound AMADP cross-bridge state. Based on these modeling efforts, we estimate that this lifetime may be 75% greater in MR compared with NF ($P = 0.02$). This suggests the mechanism for the previously observed increase in cross-bridge FTI results from increased $T_{on}$ rather than from increased $F_{max}$.

Since these myothermal and mechanical studies indicate increased cross-bridge force generating capacity per cross-bridge cycle it is very clear that the decreased isometric twitch force in DCM myocardium cannot be accounted for by changes in cross-bridge molecular mechanics. If anything, the increase in cross-bridge force–time integral found in the failing heart would increase the muscle peak force and force–time integral. Accordingly we examined aspects of the excitation–contraction coupling system to evaluate whether changes in it might contribute to the depressed isometric mechanics.

3. The excitation–contraction coupling system

3.1. Calcium cycling

The tension independent heat, an index of excitation–contraction coupling phenomena and, thus, of calcium pump activity predominantly, was reduced from 0.51±0.13 mJ/g in muscle strips from the non-failing hearts to 0.16±0.05 mJ/g in DCM failure ($P < 0.03$) [19].

The TIH and TIH rates can be used to calculate the amount of calcium released into the muscle cell per beat and the rate at which it is removed. This relationship is described best by the following equation:

$$\text{Ca}^{2+}/\text{g beat} = K \times \left( [(\text{TIH/g})/(34 \text{kJ/mole})] \times (\text{Ca}^{2+:}\text{CrP coupling ratio}) \right)$$

where $K (K = 0.75)$ takes into consideration the amount of excitation–contraction coupling energy not associated with the calcium pumps and the $\text{Ca}^{2+:}\text{CrP}$ is 2 [21,22]. The calcium cycled (nmol/g beat) is reduced from 21.7±5.7 in the non failing hearts to 7.0±1.9 for DCM failure ($P < 0.03$). The average rate of calcium removal from the cytosol following activation can be calculated from the above equation by substituting measured average TIH/g s per beat for measured TIH/g beat. In the non-failing preparation the rate of $\text{Ca}^{2+}$ removal from the cytosol (nmol/g s) is 35±10.3 in contrast to 10.7±3.9 for the DCM failing hearts. The amount of calcium released into the cytosol correlates directly with the peak isometric force (Fig. 2C, center panel). This can well account for the depression in force production found in the failing myocardium. Since we know that calcium removal from the cytosol is associated with relaxation, it is not surprising to find the rate of calcium uptake is directly related to the rate of isometric relaxation (Fig. 2C, right panel). Comparable results are found in the failing myocardium secondary to mitral regurgitation [22]. An explanation for the profound depression in calcium cycling in the failing myocardium resides in the changes found in sarcoplasmic reticulum and in the sarcolemma. In the failing human heart the sarcoplasmic reticular calcium uptake system (SERCA 2a) was shown to be reduced and the sarcolemmal Na±Ca exchanger to be increased [23–26,32,34–36]. These changes result in a deficit in calcium storage in the SR and thus a decrease in the subsequent calcium release upon activation as well as a decrease in the rate of calcium uptake [33]. The decrease in the calcium release results in a reduction in the degree of activation and thus of the peak isometric force while the depression in the rate of uptake slows the rate of relaxation.

3.2. The force–frequency relationship

A key element in the response of the non-failing myocardium to an increase in demand is the increase in force normally present when the frequency of stimulation (heart rate) increases (Fig. 3A & B) [27,28]. Under these conditions, the stroke volume increases as the frequency is increased until the optimum frequency is reached and then it begins to decline. Thus in the ascending portion of the force frequency relationship, the stroke volume increases and the cardiac output (stroke volume×heart rate) increases. In contrast in the failing myocardium, there is a dramatic blunting of this relationship (Fig. 3A & B) [27,28]. This blunting of the frequency treppe in conjunction with the reduction in force contributes substantially to the deficit in cardiac output. These findings have been corroborated and extended by direct measurements of intracellular calcium concentration. In the non-failing heart, as the frequency of stimulation and the force of contraction are increased, there is a correlative increase in the aequorin light signal indicating an increase in calcium concentration with each beat. In contrast for the failing...
preparations, the depression in force that occurs as the frequency of stimulation is increased, is associated with a diminution in the aequorin light signal [29,30]. Based on post-rest potentiation and rapid cooling contracture studies of failing and non-failing preparations [30,31], the most likely explanation for the blunted force frequency relation in the failing heart preparations is the decrease in sarcoplasmic reticulum calcium storage found in the failing hearts and the exacerbation of this decrease found as the frequency of stimulation is increased.

4. Familial hypertrophic cardiomyopathy

4.1. Background

It was surprising to find that the constellation of intracellular changes in the failing heart were similar despite the etiology of the heart failure (DCM or MR). The question is raised as to whether all forms of heart failure have the same constellation of intracellular changes. To answer this question we present data from one form of familial hypertrophic cardiomyopathy in which mutation of the myosin molecule is accompanied by myocardial hypertrophy, heart failure and sudden death.

4.2. R403Q and L908V mutations in familial hypertrophic cardiomyopathy

Familial hypertrophic cardiomyopathy is a disease of the sarcomere with an incidence of about 1 in 500. The disease includes mutations in many of the sarcomeric genes, for example (genes, incidence): β-myosin heavy chain, 35%; cardiac troponin T, 15%; myosin binding protein C, 15%; α-tropomyosin, <5% and to a lesser extent cardiac troponin I, actin, the regulatory and essential light chains. Most of the population with the disease have no symptoms...
or only mild symptoms. The remainder of the group suffer from heart failure and to a somewhat lesser extent sudden death [37]. Two mutations studied were the arginine to glutamine substitution at position 403 (R403Q) located in the actin binding area of the myosin molecule and a leucine to valine substitution at position 908 located about 15 nm from the motor domain at the terminal portion of the lever arm (Fig. 4, panel A [38,39]). The phenotypic expression of R403Q compared with L908V involves earlier onset, greater hypertrophy, higher penetrance and greater incidence of failure and sudden death [40].

4.3. The mechanical performance of R403Q and L908V myosin

The two major contributors to myocardial performance are velocity and force with the product being power output. The fundamental contribution of the mutant myosin to velocity was assessed by means of the in vitro motility assay for measuring the ability of the myosin to propel actin filaments [41]. It was surprising that the mutant myosins moved actin filaments faster than that seen for control myosin (actin filament velocity: control, 1.39±0.03 \( \mu \)m/s; R403Q, 1.87±0.07 \( \mu \)m/s; L908V, 1.76±0.15 \( \mu \)m/s [control vs. 403 or 908, \( P < 0.05 \)].) The molecular determinants of actin filament velocity measured in the in vitro motility assay were evaluated using the laser trap system. This allows separate assessment of the contributions of unitary displacement and attachment time to alterations in actin filament sliding velocity [41]. The three bead, double similar, set-up raises the question as to how the 908 mutation, unitary displacement and attachment time to alterations in kinetic alterations for of the 403 and 908 mutants are.

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Under these circumstances, the average force for the mutant myosins was found to be similar to that for the control myosin (actin filament velocity: control, 29\( \pm \)2 ms; R403Q, 28\( \pm \)2 ms; L908V, 29\( \pm \)2 ms) (Fig. 4D [41]). Accordingly the increase in actin filament velocity seen in the presence of the mutant myosins is most likely the result of the decrease in the attachment time. One can speculate that this is the result of an increase in the rate of ADP release [45]. The force capability of the mutant myosin molecules was evaluated using the mixture technique based on a mechanical interaction model where actin filament velocity is assessed with mixtures of cardiac myosin (control, R403Q or L908V) and the faster chicken skeletal myosin [46]. Under these circumstances, the average force for the mutant myosins was found to be similar to that for the control myosin. Since the qualitative mechanical and kinetic alterations for the 403 and 908 mutants are similar, it raises the question as to how the 908 mutation, located 15 nm from the actin and nucleotide binding regions of the myosin molecule can alter the performance (Fig. 4A).

Speculation on this point invokes the possibility that the relay helix (Fig. 4A, green), extending from the catalytic site to the converter region, acts as a force or displacement transducer and thus transmits information from the 908 region to the catalytic site [41]. Experimental evidence to support this speculation might involve molecular manipulation of the relay helix along with the assessment of the mechanical performance with 908 mutants.

How does the presence of a mutant motor molecule that moves actin faster lead to the phenotypic changes associated with this disease? We hypothesize that since an individual has both a normal and mutant allele, every muscle cell should have both the slower (wild type) and faster (mutant) myosin present. This tug of war between the two myosin species, having substantially different mechanical capacities, can lead to internal stress within the muscle cell which in turn leads to the hypertrophy and cellular disarray.

5. Heart failure: summary and conclusions

The reduction in myocardial power output in the failing heart results in a cardiac output inadequate to meet the
systemic metabolic needs. Power is the product of velocity and force so that a deficiency in either will result in diminished power. The discovery of depressed myofibrillar ATPase in the failing human heart [5] and the possibility of an associated reduction in shortening velocity (Fig. 1) was the first indication that intracellular molecular alterations might be associated with human myocardial pump failure. The extension of these studies by means of thermo–mechanical techniques added additional information about changes in the cross-bridge cycle. It was shown that the cross-bridge force–time integral (unitary force $F_{uni} \times$ attachment time $T_{att}$) was increased in failing hearts from patients with dilated cardiomyopathy or mitral regurgitation [19,22]. Additional studies using perturbation analysis suggest that the increase in cross-bridge force–time integral is explained primarily by an increase in the attachment time ($T_{att}$). Since velocity is proportional to ratio of unitary displacement to attachment time ($V \propto d_{uni} / T_{att}$), this change might account for the reduction in velocity. At the same time the marked decrease in peak isometric force is proportional to the decrease in beat-to-beat calcium cycling (Fig. 2) [19]. At a molecular level these changes are associated with a decrease in the calcium cycling proteins SERCA 2A in the sarcoplasmic reticulum and an increase in the Na$^+$–Ca$^{2+}$-exchange protein in the sarcolemma [26]. The alteration in calcium cycling also leads to the blunted force frequency relationship (Fig. 3) and the decrease rate of relaxation (Fig. 2) [19,22]. The latter further compromise survival by impairing ability to increase cardiac output during even mild exercise.

These changes in the contractile and excitation–contraction coupling systems in MR or DCM failure readily account for the depressed power output of the failing human heart (mitral regurgitation, dilated cardiomyopathy). In contrast to MR and DCM in familial hypertrophic cardiomyopathy (R403Q, L908V myosin mutations), the mutant myosin molecular motor generates greater velocities with normal average force. We speculate that the mixture of fast myosin (FHC mutant) in series with normal myosin leads to hypertrophy and cellular disarray resulting in failure or sudden death.

Although modern therapeutic measures provide excellent relief from acute heart failure, in most cases these measures do not arrest the steady decline of cardiovascular function. The alterations in subcellular systems and function described above in human myocardial failure continue deteriorating as heart failure progresses. Progress in developing means of arresting this unremitting worsening of subcellular function is needed to truly improve the outcome in heart failure patients. This progress will undoubtedly come from increased understanding of the large number of significant additional changes involving the cytoskeleton and the neuro–hormonal, the cytokine systems and, most importantly, associated alterations in signaling pathways that have been discussed in an excellent recent review [47].

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References


