Acta Physiol Scand 2001, **171**, 277–294

Skeletal muscle disorders in heart failure

P. K. LUNDE, I. SJAASTAD, H.-M. SCHIØTZ THORUD and O. M. SEJERSTED

Institute for Experimental Medical Research, University of Oslo, Ullevaal Hospital, Oslo, Norway

ABSTRACT

Heart failure is associated with reduction of exercise capacity that cannot be solely ascribed to reduced maximal oxygen uptake ($\dot{V}O_{2max}$). Therefore, research has focused on changes in skeletal muscle morphology, metabolism and function. Factors that can cause such changes in skeletal muscle comprise inactivity, malnutrition, constant or repeated episodes of inadequate oxygen delivery and prolonged exposure to altered neurohumoural stimuli. Most of these factors are not specific for the heart failure condition. On the other hand, heart failure is more than one clinical condition. Congestive heart failure (CHF) develops gradually as a result of deteriorating contractility of the viable myocardium, myocardial failure. Is it possible that development of this contractile deficit in the myocardium is paralleled by a corresponding contractile deficit of the skeletal muscles? This question cannot be answered today. Both patient studies and experimental studies support that there is a switch to a faster muscle phenotype and energy metabolism balance is more anaerobic. The muscle atrophy seen in many patients is not so evident in experimental studies. Few investigators have studied contractile function. Both fast twitch and slow twitch muscles seem to become slower, not faster as might be expected, and this is possibly linked to slower intracellular Ca^{2+} cycling. The neurohumoural stimuli that can cause this change are not known, but recently it has been reported that several cytokines are increased in CHF patients. Thus, the changes seen in skeletal muscles during CHF are partly secondary to inactivity, but the possibility remains that the contractility is altered because of intracellular changes of Ca^{2+} metabolism that are also seen in the myocardium.

Keywords calcium, energy metabolism, excitation–contraction coupling, fatigue, heart failure, skeletal muscle.

Received 12 December 2000, accepted 24 January 2001

Most patients with chronic heart failure experience skeletal muscle fatigue and muscle weakness. These patients have reduced cardiac output and low maximal oxygen uptake ($\dot{V}O_{2max}$) because of impaired left ventricular function, and increased peripheral resistance caused by high sympathetic nerve activity, increased plasma concentrations of vasoconstrictors and accumulation of sodium (Braunwald 1997a). However, these changes cannot explain the observed fatigue in this patient group because there is a weak association between clinical symptoms and left ventricular function (Harrington & Coats 1997). Administration of angiotensin-converting enzyme (ACE) inhibitors increases cardiac output and skeletal muscle blood flow by reducing peripheral resistance, but has no immediate effect on skeletal muscle function (Drexler *et al.* 1989). Even cardiac transplantation does not lead to rapid alleviation of exercise intolerance (Stratton *et al.* 1994a, Sorensen *et al.* 1999). Furthermore, several disturbances of intrinsic skeletal muscle function and biochemistry have been observed. Key issues are why these changes occur in skeletal muscle and to what extent they are responsible for the fatigue symptoms. This is especially important in the light of favourable results of training heart failure patients (Coats 1999).

To address these issues the following questions are considered in this review. First, what characterizes cardiac function in heart failure? Braunwald (1997a) defines heart (or cardiac) failure as the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues, or to do so only from an elevated filling pressure. This definition encompasses several different pathophysiological states of the heart, a fact that is not taken into account by many investigators who only use the New York Heart Association (NYHA) classification to categorize patients into four functional groups depending on the functional impairment (class 1 – little impairment, class 4 – severe

Correspondence: Professor Ole M. Sejersted, Institute for Experimental Medical Research, Ullevaal Hospital, N-0407 Oslo, Norway.

symptoms at rest). This simple categorization might therefore preclude insight into cellular and molecular mechanisms. Also, the definition is relative because the requirements of the metabolizing tissues are highly variable which means that heart failure might become evident only during exercise. However, the cardiac defect prevails also during rest. A further categorization of the type of heart failure is therefore required. Second, it is still unclear whether skeletal muscle dysfunction is linked merely to low cardiac output and local perfusion incommensurate with the metabolic requirements of the resting or exercising muscle? The alternatives include adaptations of skeletal muscle caused by increased reliance upon anaerobic metabolism, detraining effects, or some alterations unrelated to altered energy metabolism and muscle usage. Third, if the latter is the case, is it feasible that some signals other than those linked to metabolic needs might affect skeletal muscle function? In order to throw some light on these questions, we will first discuss the concept of heart failure, especially congestive heart failure (CHF) and review some clinical studies. However, it has become quite clear to us that a deeper understanding of these questions calls for experimental studies, and we have made an extensive perusal of existing experimental data.

A word is also required about the concept of fatigue. Fatigue is not simple to define. Most people refer to fatigue as a subjective feeling that makes it impossible to keep up work rate. Thus, the cause of fatigue in this sense may reside anywhere in the central or peripheral nervous system or within the muscles. In relation to heart failure, we are here discussing causes of fatigue that can be localized to the muscles. However, the definition is still complicated because at the time when work rate can no longer be maintained, processes responsible for reduced muscle performance have probably been going on inside the muscle cells for a long time. Therefore, we prefer to use the term 'exhaustion' for the condition that requires cessation of exercise or reduction of exercise intensity. Fatigue, on the other hand, can be measured as reduced maximum force, and develops gradually as long as exercise is going on (Sejersted & Vøllestad 1992, Lunde *et al.* 1998).

THE CONCEPT OF HEART FAILURE

Disregarding valvular diseases and congenital cardiac defects, heart failure may in principle be caused either by a ventricular mass too small to maintain cardiac output and/or by reduced contractility of otherwise viable and normal myocardium. The latter is called myocardial failure (Braunwald 1997a). In myocardial failure, the viable muscle tissue of the ventricles most often show signs of hypertrophy. It is at present unclear whether hypertrophy is a pre-requisite for myocardial failure (Hunter & Chien 1999). Even so, several investigators have considered myocardial hypertrophy and failure as one entity (Bishop & Altschuld 1970, Hasenfuss 1998, Vescovo *et al.* 1998a). Clearly, cardiac hypertrophy can exist without myocardial failure, and alterations observed in hypertrophied cardiac muscle may therefore be unrelated to any contractile deficit that subsequently develops.

The mechanisms of myocardial failure are at present unclear. It can occur during a variety of conditions, but leading causes are hypertension and myocardial infarction (MI). Hypertension leads to concentric hypertrophy, while following an MI that is too small to cause acute heart failure, eccentric hypertrophy develops. Most investigators agree that the function of the hypertrophied viable myocardium may deteriorate over time (Hasenfuss 1998) and a transition from asymptomatic compensated failure to decompensated symptomatic failure may occur. The decompensation first of all becomes manifest through pulmonary congestion and oedema. This understanding of the development of CHF has gradually emerged over the years (Mann 1999).

In patients and animal models of decompensated heart failure, the myocardium alters its contraction characteristics; time to peak force is delayed (Hasenfuss *et al.* 1992, Pieske *et al.* 1995, Skomedal *et al.* 1997, Holt *et al.* 1998), relaxation velocity is slower (Hasenfuss *et al.* 1992, Pieske *et al.* 1995, Holt *et al.* 1998) and fractional shortening is reduced (Gomez *et al.* 1997). These characteristics are only seen in CHF, not in animals with myocardial injury without failure (Pfeffer *et al.* 1979, Pfeffer & Braunwald 1990, Sjaastad *et al.* 2000).

These various aspects of heart failure must be kept in mind when gauging skeletal muscle function. An interesting hypothesis could be that the contraction defects found in the myocardium in CHF as a result of myocardial failure are akin to the contraction defects found in skeletal muscle. It is therefore important to evaluate myocardial function in patients or in animals used in studies on skeletal muscle function in heart failure.

Evaluation of cardiac function in animal models of CHF

It is necessary to distinguish between compensated and decompensated cardiac failure. In humans cardiac function is readily assessable, and patients with CHF have multiple symptoms, so the diagnosis is usually not difficult. In animal models, however, the diagnosis of CHF is more complicated to establish. Symptoms such as oedema, tachypnoea, weight loss, pleural effusion, ascites, increased heart weight and increased lung

weight are indices of CHF, but other criteria should be fulfilled to establish a safe diagnosis.

Haemodynamic parameters such as the maximum rate of left ventricular pressure development (LV dP/dt_{max}) might distinguish failing from non-failing animals. However, this parameter directly reflects contractility of the entire left ventricle (LV) including any scar tissue (Veragut & Krayenbuhl 1965, Nejad *et al.* 1971) rather than contractility of the viable myocardialum tissue. We have previously found reduced LV dP/dt_{max} in rats with MI, but the parameter did not separate those with CHF from those without failure (MI_{nf}). For this reason it is not feasible to use this parameter as a main criterion of CHF.

Left ventricular end diastolic pressure (LVEDP) has been used to identify CHF in rats (Drexler *et al.* 1985, Sabbah *et al.* 1993, Perreault *et al.* 1993b, Simonini *et al.* 1996a, b, 1999b, Delp *et al.* 1997, Holt *et al.* 1998, Wasserstrom *et al.* 2000). LVEDP is usually elevated in CHF signifying congestion, and is close to normal in animals without myocardial failure. The cut-off pressure is often set to 15 mmHg as an administrative limit to distinguish between CHF and non-failure. In Fig. 1, we illustrate the distribution of LVEDP values from sham-operated rats (SHAM), rats with MI_{nf} and rats with CHF. The diagnosis of CHF was made on the basis of heart weight, left atrial size, infarct size, pleural fluid accumulation, presence of ascites and tachypnoea. The figure shows that 15 mmHg is a cut-off value that discriminates well between infarct animals with and without myocardial failure. There are few false positive and negative classifications, and LVEDP above 15 mmHg is thus a reliable indicator of CHF in rats with MI (unpublished data from our laboratory).

In some studies on post-infarction heart failure, infarct size has been estimated (see Table 1), because it is generally appreciated that LV dilation occurs mainly after large transmural infarctions (Pfeffer & Braunwald 1990). However, infarct size is probably not the parameter of choice to separate animals with and without myocardial failure because in both groups extensive infarcts comprising most of the LV have been reported (Sjaastad *et al.* 2000).

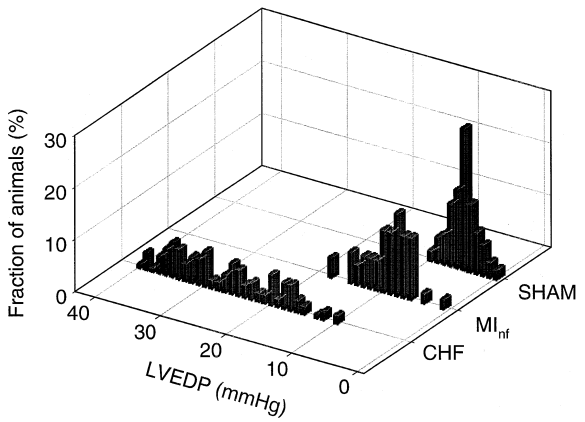

Figure 1 Distribution of LVEDP in groups of rats classified as SHAM, MI_{nf}, and CHF. Criteria for classification are given in the text. The LVEDP was measured in anaesthetized rats by means of a micromanometer-tipped pressure transducer catheter (Micro-Tip Transducer SPR-407, Millar Instruments, TX, USA).

Echocardiography is a non-invasive method to evaluate cardiac function. The diagnosis of CHF, regardless of experimental model, should preferably be based on echocardiographic findings in addition to symptoms, clinical signs, and haemodynamic characteristics according to the recommendations presented by the American Society of Echocardiography (Schiller *et al.* 1989) or the guidelines from the European Society of Cardiology (Anonymous 1995). In most animal studies echocardiographic validation of the model has not been performed and consequently the data do not allow assessment of the degree of contractile failure.

There are several cardiac parameters that can be measured by echocardiography, but only some of them are related to CHF. LV dilation follows large transmural infarcts, but we recently showed that dilation of the LV was not always associated with failure. Some animals with LV dilation had no signs of CHF, because the left atrium (LA) had normal dimensions and LVEDP was within the normal range (Sjaastad *et al.* 2000). The LA dilates at a later stage in development of CHF than the LV (Braunwald 1997a, Sjaastad *et al.* 2000). This indicates that dilation of the LA occurs as decompensation is in progress. Left ventricle posterior wall shortening velocity can be measured in M-mode, which is a cross-sectional display of the left ventricular dimensions over time. Reduced posterior wall shortening velocity has a high predictive value for CHF and separates infarct animals with and without CHF (Sjaastad *et al.* 2000). In human studies indices of CHF are reduced ejection fraction and reduced fractional shortening of the left ventricle.

In conclusion, CHF caused by myocardial failure should be clearly distinguished as a special and severe case of chronic heart failure. The diagnosis of CHF in patients is readily achieved, but in experimental models in which symptoms are difficult to judge, reliable indices of CHF include LVEDP > 15 mmHg, LA dilation and reduced posterior wall shortening velocity.

Experimental models of CHF

Studies on skeletal muscle function in patients with CHF have provided important information about the human pathological condition. Clinical evaluation of cardiac function is a routine procedure, and the measurements are reliable and valid. However, there are several other problems that may confound the

Table 1 Studies of skeletal muscle dysfunction in heart failure

Reference	Failure model	Species	LVEDP (mmHg)	MAP	Infarct size (%)	Right ventricle	dP/dt_{max}	Lung Weight	Ascites/ pleura fl.	Failure evaluation
Drexler *et al.* (1985)	CAL	Rat	27	13% ↓	42					MI_{nf}/ CHF?
Musch *et al.* (1988)	CAL	Rat			34					MI_{nf}
Musch *et al.* (1990)	CAL	Rat		NS	34					MI_{nf}
Arnolda *et al.* (1991)	CAL	Rat			39	71% ↑				MI_{nf}
Arnolda *et al.* (1991)	CAL	Rat			52	171% ↑				CHF
Musch *et al.* (1992)	CAL	Rat								MI_{nf}
Musch & Terrell (1992)	CAL	Rat			22	NS				MI_{nf}
Musch & Terrell (1992)	CAL	Rat			38	NS				MI_{nf}
McAllister *et al.* (1993)	CAL	Rat			37	28% ↑		NS		MI_{nf}
Perreault *et al.* (1993b)	CAL	Rat	27	13% ↓		61% ↑	39% ↓			CHF
Thompson *et al.* (1994)	CAL	Rat		NS	12	NS		NS		MI_{nf}
Brunotte *et al.* (1995)	CAL	Rat			44	126% ↑		135% ↑		CHF
Brunotte *et al.* (1995)	CAL	Rat			21	NS		NS		MI_{nf}
Hirai *et al.* (1995)	CAL	Rat		NS	25	NS				MI_{nf}
Hirai *et al.* (1995)	CAL	Rat		NS	44	21% ↑				MI_{nf}
Thompson *et al.* (1995)	CAL	Rat		19% ↓	49			64% ↑		CHF
Schieffer *et al.* (1995)	CAL	Rat			24	18% ↑				MI_{nf}
Simonini *et al.* (1996a)	CAL	Rat	24		35	74% ↑				CHF
Simonini *et al.* (1996a)	CAL	Rat	10		8	NS				MI_{nf}
Simonini *et al.* (1996b)	CAL	Rat	26		35	90% ↑				CHF
Pickar *et al.* (1997)	CAL	Rat	11	16% ↓		43% ↑		25% ↑		MI_{nf}
Delp *et al.* (1997)	CAL	Rat	11		45	36% ↑	29% ↓	NS		MI_{nf}
Delp *et al.* (1997)	CAL	Rat	25		59	81% ↑	44% ↓	53% ↑		CHF
Williams & Ward (1998b)	CAL	Rat			Identified	Increased				MI_{nf}
Williams & Ward (1998b)	CAL	Rat			Identified	Increased				MI_{nf}
Xu *et al.* (1998)	CAL	Rat	18	NS	46	52% ↑		NS		MI_{nf}
Simonini *et al.* (1999b)	CAL	Rat	20.4				36% ↓			CHF
Kindig *et al.* (1999a)	CAL	Rat	11	NS	33	27% ↑	24% ↓	NS		MI_{nf}
Drexler *et al.* (1987)	CAL?	Rat			36					
Peters *et al.* (1997)	SHR	Rat								CHF
Wilson *et al.* (1992)	Pacing	Dog		25% ↓		13% ↑ (HW)		62% ↑	Yes	CHF
Comini *et al.* (1996a)	Monocrotaline	Rat				180% ↑		62% ↑	Yes	RVD
Comini *et al.* (1996b)	Monocrotaline	Rat				96% ↑		50% ↑	Yes	RVD
Bernocchi *et al.* (1996)	Monocrotaline	Rat				88% ↑		70% ↑	Yes	RVD
Bernocchi *et al.* (1996)	Monocrotaline	Rat				105% ↑		NS		RVD
Vescovo *et al.* (1998a)	Monocrotaline	Rat				71% ↑		47% ↑	Yes	RVD
Vescovo *et al.* (1998b)	Monocrotaline	Rat							Yes	RVD
Libera *et al.* (1999)	Monocrotaline	Rat								RVD
Sabbah *et al.* (1993)	Microspheres	Dog	21				34% ↓			CHF
Chati *et al.* (1994)	Aortocaval fistula (Vol. overload)	Rat				24% ↑ (HW)				

Changes are given in percentage of SHAM values. NS: not significant; LVEDP: left ventricular end diastolic pressure; MAP: mean arterial pressure; dP/dt_{max}: maximum first derivative of left ventricular pressure; CAL: coronary artery ligation; MI_{nf}: myocardial infarction without congestive heart failure; CHF: congestive heart failure; RVD: right ventricular dysfunction; SHR: spontaneously hypertensive rats; ↑/↓: increased/decreased compared with SHAM; HW: heart weight.

conclusions that can be drawn as regards the mechanism of skeletal muscle dysfunction in patients with CHF: (1) the extent of the cardiac disease, cardiac hypertrophy and atherosclerosis is variable and other organs may be severely affected, such as the kidneys and the liver. The patient population in human studies is therefore usually quite heterogeneous; (2) patients included in the studies are usually heavily medicated, which might affect skeletal muscle function; and (3) patients with CHF become physically inactive, possibly resulting in detraining effects and skeletal muscle atrophy.

Animal models of CHF are therefore used to study skeletal muscle dysfunction. The population under study will be more homogeneous although outbred animals are most often used. The animals with CHF

seem to be as physically active as the control animals (Simonini *et al.* 1996a, 1999b). In Table 1, we have summarized these studies and categorized them on the basis of information offered about the models. The criteria used in the studies to evaluate cardiac function were varied. Some offered thorough documentation on their model, while others present so few data that it is impossible to evaluate cardiac function. Echocardiographic validation of the models used has not been performed in any of the studies.

In this review we refer to studies performed on four animal models (Table 1). (1) We have found 27 studies of skeletal muscle function in rats following coronary artery ligation (CAL). Many of the studies provide few data that could help us to determine whether the animals had developed CHF or not. In the absence of echocardiographic data, the presence of typical symptoms, large infarcts, high LVEDP and substantially increased lung weight were interpreted as indices of CHF. The majority of studies presented in Table 1 are studies on well compensated post-infarction rats that probably have no myocardial failure (MI_{nf}). We could confirm the CHF diagnosis only in eight, possibly nine investigations (Drexler *et al.* 1985, Arnolda *et al.* 1991, Perreault *et al.* 1993b, Brunotte *et al.* 1995, Thompson *et al.* 1995, Simonini *et al.* 1996a, b, 1999b, Delp *et al.* 1997). (2) In one study spontaneously hypertensive rats (SHRs) were used, and they eventually developed CHF (Peters *et al.* 1997). There is no obvious control group that can be used in studies on SHR rats because they are genetically quite different from other rats. For this reason, it is difficult to interpret results from studies on SHR rats. (3) Pacing induced heart failure in dogs has been used in one study (Wilson *et al.* 1992). These dogs develop combined left and right ventricular heart failure with clinical symptoms of CHF (Galione 1993). This is a good model of CHF, but is infrequently used because of high costs. (4) Monocrotaline is an alkaloid that causes progressive lung injury, pulmonary hypertension, compensatory right heart hypertrophy and eventually right ventricular heart failure (Schultze & Roth 1998). This model simulates development of cor pulmonale which is a serious outcome of some pulmonary diseases, e.g. emphysema. The LV is basically normal. Investigators should be cautious when comparing the monocrotaline model with, e.g. models 1, 2 and 3, that are all characterized by LV failure and do not have pulmonary disease. Monocrotaline is injected into the animal, and the substance is toxic. Although the effects reported on monocrotaline are mainly related to toxic effects on the pulmonary artery (Schultze & Roth 1998), it is difficult to rule out toxic effects also on other organs, such as skeletal muscles.

HEART FAILURE AND SKELETAL MUSCLE FUNCTION IN PATIENTS

The skeletal muscle abnormalities observed in heart failure patients have been extensively reviewed (Drexler 1992, 1995, Coats 1996, Drexler & Coats 1996, Poole-Wilson & Ferrari 1996, Harrington & Coats 1997). As it has not been possible to relate exercise intolerance unequivocally to any common indices of heart failure, it is possible that a number of factors contribute to exertional fatigue and that the contribution of each of these factors is very difficult to sort out in patients (Harrington & Coats 1997). In most studies patients have been classified as NYHA group II or III and a further subclassification is rarely given. We will briefly summarize some studies pertaining to the main conclusions that can be drawn from patient studies. In Fig. 2, we have compiled the various factors that may affect skeletal muscle function in this condition.

These factors are all extrinsic to the muscle. Some of them, for instance oxygen delivery, will limit performance of an otherwise completely normal muscle. However, some of them may also cause long-term alterations of muscle morphology and/or biochemistry that will reduce performance.

As peak $\dot{V}O_{2max}$ is low in heart failure patients, oxygen delivery to the skeletal muscles may become lower than the demand even at a very modest exercise intensity. As long as the arterial oxygen saturation of arterial blood remains high, peak $\dot{V}O_{2max}$ is first of all a function of cardiac output. Perfusion of skeletal muscles cannot exceed maximum cardiac output, and therefore, in order to maintain blood pressure, the vascular conductance in muscles reaches a maximum with increasing exercise intensity (Gullestad *et al.* 1993, Rowell 1993). This maximum is probably set by the activation of the sympathoadrenergic system and overrides the local vasodilator mechanisms (Rowell *et al.* 1986, Rowell 1993). A logical property of this regulatory system is that as maximum cardiac output is reached, the conductance of any exercising muscle will depend on the total muscle mass that is active. Normally maximum cardiac output is so large that flow to a single muscle does not become restricted although a large muscle mass is working (Savard *et al.* 1989). Saltin's group has shown that when only the quadriceps muscles of one or two legs are exercising, perfusion is linearly related to power even at the highest attainable intensities (Andersen & Saltin 1985, Radegran *et al.* 1999). The important implication for the heart failure condition is that as maximum cardiac output is low, perfusion of skeletal muscles becomes limited even with moderate whole body exercise. However, it is still possible that the heart can provide sufficient oxygen delivery for a small muscle mass that is exercising at

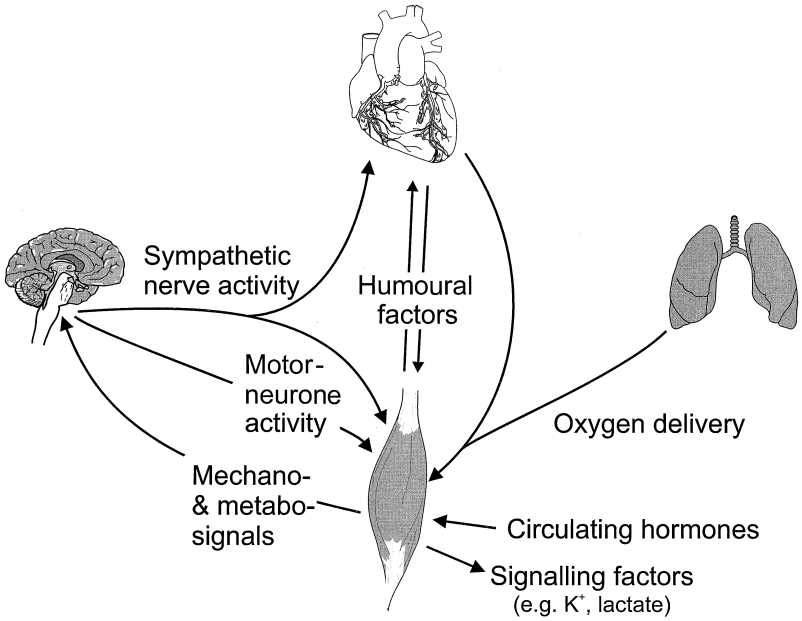

Figure 2 Factors that affect skeletal muscle structure, metabolism and function, and signals that emanate in muscle.

high power. This was demonstrated by Magnusson *et al.* (1997b). In their group of patients local perfusion was lower than normal during exercise of the two quadriceps muscles than during exercise of only one quadriceps muscle. Also earlier studies using plethysmographic technique have indicated that blood flow in exercising muscle can be normal in heart failure patients (Wiener *et al.* 1986, Massie *et al.* 1987). Thus, oxygen delivery is probably an important limiting factor for exercise like bicycling and running in heart failure patients as demonstrated by very low oxygenation levels in the muscle and in venous blood from the muscle (Wilson *et al.* 1989, Katz *et al.* 2000). This does not seem to be the case when only a small muscle mass is engaged as tissue oxygenation seems adequate (Mancini *et al.* 1994). However, fatigue is more prominent in heart failure patients even if they only exercise one quadriceps muscle (Buller *et al.* 1991, Minotti *et al.* 1993, Yamani *et al.* 1995, Magnusson *et al.* 1997b) or do plantar flexion (Okita *et al.* 1998). In addition, fatigue also occurs earlier in heart failure patients during complete ischaemia of the exercising muscle (Massie *et al.* 1988, Buller *et al.* 1991). These findings have prompted investigators to look for changes of the oxidative metabolic pathways in the skeletal muscles with the hypothesis that the rate limiting step might be located inside the muscle in situations where oxygenation is adequate (Wilson *et al.* 1993).

Numerous studies utilizing both ^{31}P magnetic resonance spectroscopy (^{31}P-MRS) and biochemical techniques have identified significant changes in skeletal muscles of heart failure patients. In spite of adequate oxygenation, lactate production starts at a lower than normal work load, and lactate turnover in the working muscle is significantly increased even at exercise intensities that do not cause a rise of arterial lactate concentrations (Katz *et al.* 1993, Wilson *et al.* 1993). This seems to fit with reduced mitochondrial capacity, and reduced fatty acid uptake, but maintained or increased glycolytic capacity (Sullivan *et al.* 1990, Poole-Wilson & Ferrari 1996, Schaufelberger *et al.* 1996, Kemp *et al.* 1996a). In line with this there is a more rapid breakdown of phosphocreatine and lower intramuscular pH during exercise in heart failure patients as compared with healthy subjects. Also the rate of resynthesis of phosphocreatine is significantly delayed (Mancini *et al.* 1992, Adamopoulos *et al.* 1993a). It is therefore concluded that changes intrinsic to the skeletal muscle may also limit performance in heart failure patients. It should be noted that these changes are sometimes difficult to interpret as few authors relate exercise intensity to the individual exercise capacity. Exercise protocols are often standardized in terms of absolute power so that muscle metabolism in patients and control subjects is compared at the same power output (Mancini *et al.* 1989, Wilson *et al.* 1993, Adamopoulos *et al.* 1993a, Stratton *et al.* 1994b, Kemp *et al.* 1996a). CHF patients have reduced maximum power output, therefore in these studies endurance will be reduced merely because the relative load was higher for the heart failure patients. This may also to some extent explain the more rapid breakdown of phosphocreatine at the onset of exercise. Although they did not estimate muscle mass or individual maximum work capacity of the muscle, Kemp *et al.* (1996a) have to some extent corrected the lack of these important background data in their interpretation of the NMR spectra and still conclude that oxidative metabolism is

reduced and glycogenolysis increased in exercising skeletal muscles of heart failure patients.

Barlow *et al.* (1994a) compared arterial lactate, K^+, catecholamine concentrations, heart rate and ventilation in CHF patients and controls at exercise intensities normalized to $\dot{V}O_{2max}$. They found that the controls actually reached higher lactate and K^+ concentrations at the same relative intensity or at the same heart rate as the CHF patients. This underscores the importance of relating metabolic parameters to the individual capacity. It is interesting that arterial K^+ concentration was so closely related to relative exercise intensity, because exercising muscle mass and electrical activity in the muscle determine the K^+ loss from the muscle during exercise (Sejersted & Sjøgaard 2000). Therefore, taking muscle atrophy in the patients into account, at a given power the CHF patients must recruit a larger number of motor units, possibly at a higher firing frequency than the controls in order to maintain power output.

A number of morphological changes can also be observed in skeletal muscles of heart failure patients. Atrophy may be prominent and there is a fibre type switch from type I (slow twitch, oxidative) to type II, especially type IIab and b (fast twitch, glycolytic) (Mancini *et al.* 1989, Sullivan *et al.* 1990, Drexler *et al.* 1992, Mancini *et al.* 1992). These changes may contribute importantly to reduced exercise capacity and greater reliance on anaerobic metabolism.

An important question is whether these changes are specific for the heart failure condition or whether they can also be seen in other conditions. It is interesting that ageing leads to muscle atrophy and reduced oxidative capacity (Conley *et al.* 2000a, b). Conditions that are even more relevant for comparison are peripheral vascular disease and deconditioning because of disuse. In peripheral vascular disease oxygen delivery to the skeletal muscles will be compromised and these patients have abnormalities of phosphocreatine metabolism similar to those seen in chronic heart failure (Hands *et al.* 1986). Detraining or deconditioning (less stimulation of the muscle through the motor neurones (Fig. 2)) leads to muscle atrophy, switch to faster fibre types and heightened glycolytic activity (Booth & Gollnick 1983, Thomason & Booth 1990). Heart failure patients often become more sedentary. Many heart failure patients also lose appetite and experience muscle wasting caused by low caloric intake and malnutrition. If the observed skeletal muscle changes in heart failure are indeed indirectly caused by inactivity and a state of chronic ischaemia, they should be reversible with appropriate training regimes.

Several studies have confirmed that training improves skeletal muscle function in heart failure patients, but we cannot give an extensive review of this literature. The patients in the study of Magnusson *et al.* (1996b) trained the quadriceps muscle, and those of Stratton *et al.* (1994b) the forearm muscles, whereas Adamopoulos *et al.* (1993a) let the patients do bicycle exercise, but monitored the effect on plantar flexion. Atrophy was reversed, strength and endurance increased and the alterations of oxidative metabolism were partly reversed. This indicates that inactivity, possibly in combination with low oxygen delivery to the muscles during daily life activities may be the cause of atrophy, fibre type switching to faster subtypes and altered oxidative metabolism in heart failure patients.

However, so far the patient studies do not clarify whether skeletal muscle is altered in other ways. Only one recent prospective study takes into account that an extensive MI may or may not lead to myocardial failure (Adamopoulos *et al.* 1999). These authors retrospectively divided the patients into two groups, one group who remained asymptomatic, but had low ejection fraction and reduced exercise capacity (low $\dot{V}O_{2max}$, in our terms MI_{nf}) and another group that developed pulmonary congestion, oedema and symptomatic exercise limitation (CHF). Interestingly, the latter group did not have lower ejection fraction than the former group. Surprisingly, the two groups had similarly reduced exercise capacity during handgrip exercise and phosphocreatine was nominally reduced to the same extent during submaximal exercise. These changes in skeletal muscle function developed over months. The authors point out that the important difference between the two groups at an early stage, before they could be separated on the basis of their symptoms, was a significantly higher sympathoadrenergic activation in the CHF group as measured by reduced heart rate variability and increased noradrenaline spillover. It is still possible that prolonged exposure of skeletal muscle to noradrenaline, atrial natriuretic factor and renin-angiotensin will alter muscle morphology and metabolism.

A recent publication points to a very interesting relationship between a specific genetic polymorphism of the β_2-adrenoceptor, reduced exercise capacity and increased mortality in heart failure patients (Wagoner *et al.* 2000). Also the strong downregulation of β-adrenoceptor responsiveness in the myocardium (Lefkowitz *et al.* 2000, Vatner *et al.* 2000) points to an important pathogenetic role of the sympathoadrenergic system in heart failure.

Another signalling system that has received considerable interest lately and that may play a pathogenetic role in heart failure comprises the cytokines (Mann & Young 1994) and among them the chemotactic cytokines, the chemokines (Aukrust *et al.* 1998, Damås *et al.* 2000). In Fig. 2, we have tentatively indicated that these signalling molecules, for instance

TNF-α, that may originate in the failing heart can have a detrimental effect on several processes in skeletal muscle (Wilcox *et al.* 1996, Li *et al.* 1998). On the other hand, it has also recently been shown that exercising muscle can produce certain cytokines (Ostrowski *et al.* 1998), and we speculate that these in turn can affect cardiac function. The role of the cytokines in heart failure pathogenesis and especially the accompanying exertional intolerance is an exciting new field of research.

This brief review of the literature concerning exercise intolerance and fatigue in heart failure patients shows that skeletal muscle morphology and metabolism are altered because of a variety of stimuli. It seems to us that inactivity and possibly a state of ischaemia may explain a large fraction of the changes. However, it remains an intriguing possibility that other aspects of skeletal muscle function may be altered, for instance the excitation–contraction–relaxation cycle, either as a consequence of exposure to neuroendocrine factors or in some way directly related to the contractile state of the myocardium itself. The patient studies cannot answer this question and we have therefore included a thorough review of animal studies.

SKELETAL MUSCLE AND HEART FAILURE IN EXPERIMENTAL DESIGNS

Table 2 shows that skeletal muscles are both qualitatively and quantitatively altered in various animals with experimentally induced heart failure. The table is separated into two sections. The first section lists animals that in our opinion have CHF. In this section, we have also included the studies with right sided heart failure as a consequence of monocrotaline injections. The second section comprises of animals with MI_{nf}.

Bigard *et al.* (1998a) recently showed that muscle unloading in rats induces atrophy, phenotype transition to faster muscles and a switch towards anaerobic metabolism that closely resembles the changes seen in patient studies. However, some key pieces of evidence strongly suggest that inactivity is not the only important factor mediating skeletal muscle dysfunction in experimental heart failure. First, no differences in locomotor activity was observed between rats with CHF and their controls (Simonini *et al.* 1996a, 1999b). Second, almost half of the studies listed in Table 2 report no atrophy in CHF rats. Third, shift in fibre type and changes in MHC-composition precedes atrophy (Simonini *et al.* 1996a, Vescovo *et al.* 1998b). These observations indicate that deconditioning does not contribute much to the skeletal muscle changes observed in experimental heart failure.

Blood flow and capillary structure

Musch & Terrell (1992) showed that total blood flow to the hindlimb was lower in rats with large myocardial infarcts as compared with the SHAM operated animals, both in resting conditions and during exercise. This difference was not apparent in most individual muscles in the resting condition, but during exercise blood flow was lower also at the individual muscle level. They also found that blood flow decreased linearly with an increasing percentage of fast twitch glycolytic fibres and a decreasing percentage of fast-twitch oxidative glycolytic (FOG) fibres. The reduced vascular conductance fits with the picture in patients that exercise a large muscle group because the increased sympathoadrenergic drive prevents the resistance vessels to dilate adequately.

In recent years research has focused on NO as a potential vasodilator in the exercising muscle. Hirai *et al.* (1995) found that the NO synthesis inhibitor L-NAME reduced blood flow and vascular conductance in normal rats during submaximal exercise, whereas this effect was variably attenuated in different hindlimb muscles from MI_{nf} rats. This indicates that impairment of the NO pathway could also be involved in the reduced blood flow to skeletal muscle in MI_{nf} rats. Blood flow has not been measured during stimulation of a single skeletal muscle in a CHF animals.

Patient studies referred to above have shown that in order to compensate reduced oxygen delivery, oxygen extraction may become maximal in heart failure patients during exercise (Sullivan *et al.* 1990). In the spinotrapezius muscle from CHF rats Kindig *et al.* (1999a) found reduced number of capillaries that were continuously perfused with red blood cells (RBCs), but at rest this was compensated by a reduction in RBC velocity allowing more complete oxygen extraction. The number of RBC adjacent to the muscle fibre as well as transit time is critical for adequate oxygen extraction (Federspiel & Popel 1986). Although there are no experimental data on exercising muscle, it is quite possible that also in animal models of heart failure oxygen extraction can become maximal so that oxygen delivery can limit the aerobic metabolism. However, again, with a small exercising muscle mass the limiting step might reside distal to the RBC.

Metabolic enzymes and metabolites

Several groups have examined mitochondrial enzymes in MI models. The most prominent finding is a reduction in activity of the citrate synthase (CS) in both fast, slow and mixed muscles (Brunotte *et al.* 1995, Thompson *et al.* 1995, Simonini *et al.* 1996a, Delp *et al.* 1997). The alteration varies with the degree of heart

Table 2 Selected findings in skeletal muscle after CHF or MI compared with SHAM operated rats

Reference	Failure model	Muscle studied	Species	Observed significant changes	Not significantly changed parameters
CHF					
Perreault *et al.* (1993b)	CAL	EDL	Rat	Reduced twitch and tetanic force and Ca^{2+} signal; Reduced relaxation rate and decay of Ca^{2+} signal; Increased fatiguability	Muscle weight, resting $[Ca^{2+}]_i$
Simonini *et al.* (1999b)	CAL	SOL	Rat	Reduced SERCA 2 protein and mRNA; reduced weight	Physical activity
Arnolda *et al.* (1991)	CAL	SOL–PL–GC	Rat	^{31}P-MRS: During exercise: Reduced PCr and pH, increased ADP; Enzymes: reduced CS	Twitch tension; At rest: ATP, Cr, PCr; Enzymes: PFK, HK, LDH
Thompson *et al.* (1995)	CAL	SOL–PL–GC	Rat	^{31}P-MRS: End of exercise: Reduced pH; Recovery: Prolonged PCr, reduced mitochondrial ATP synthesis rate	At rest: P_i, PCr, pH, ADP; End of exercise: ADP, PCr
Brunotte *et al.* (1995)	CAL	PL–GC–SOL	Rat	^{31}P-MRS: Prolonged PCr recovery; Enzymes: Reduced CS Muscle weight: reduced	At rest: PCr and pH; Enzymes: HADH and GPT; CSA
Delp *et al.* (1997)	CAL	SOL, PL, GC-W, GC-M, GC-R	Rat	Enzymes: SOL: CS reduced; PL: HADH reduced; GC-R: CS, MDH and HADH reduced; GC-W: PFK, CS and MDH reduced; Fibre types: PL: IID/X reduced and IIB increased; CSA: SOL: I and IIA reduced; PL: I, IIA and IIB reduced	Enzymes: SOL: PFK, LDH, MDH, HADH PL: PFK, LDH, CS, MDH GC-R: PFK, LDH GC-M: PFK, LDH, CS, MDH, HADH GC-W: LDH, HADH Fibre types: SOL: All types; PL: I, IIa; CSA: SOL: IID/X; PL: IID/X
Simonini *et al.* (1996a)	CAL	SOL	Rat	Reduced MHC content and synthesis; Reduced relative muscle weight; Reduced mRNA for βMHC, actin, COX, SDH	Muscle weight
Simonini *et al.* (1996b)	CAL	SOL, PL	Rat	mRNA in SOL: βMHC and COX III: reduced; MHC IIb and IIx increased; Fibre type: SOL: type I reduced, type IIab increased; PL: type IIa reduced, type IIab increased; CS: SOL and PL reduced; Muscle weight: SOL and PL reduced	Physical activity; SOL and PL: Capillary density; CSA
Drexler *et al.* (1985)	CAL	Skeletal muscle	Rat	At rest: Diltiazem increases blood flow to muscle in SHAM, but not in CHF Exercise: Blood flow lower in CHF; Diltiazem increases blood flow to muscle in CHF but not in SHAM	Blood flow at rest; vascular resistance at rest and during exercise

Table 2 (Continued)

Reference	Failure model	Muscle studied	Species	Observed significant changes	Not significantly changed parameters
Vescovo *et al.* (1998a)	Monocrotaline	EDL, SOL	Rat	MHC alterations, Reduced blood flow in SOL, Muscle weights reduced	Relative muscle weight and CSA Blood flow in EDL
Comini *et al.* (1996a)	Monocrotaline	EDL, SOL	Rat		Muscle weights; ecNOS; iNOS not detected
Comini *et al.* (1996b)	Monocrotaline	EDL, SOL, TA	Rat		HSP72
Bernocchi *et al.* (1996)	Monocrotaline	TA, SOL, EDL	Rat	Metabolites: SOL: Reduced PCr, ATP, NAD, increased NADH	TA, SOL, EDL: Muscle weights and water content
				EDL: Reduced PCr, ATP, NAD	TA: PCr, AMP, ADP, ATP, NAD, NADH
Vescovo *et al.* (1998b)	Monocrotaline	TA, SOL, EDL	Rat	EDL: Reduced MHC2a, increased MHC2b; SOL: Reduced MHC1;	No atrophy
				TA: Reduced CSA; Reduced Bcl-2; Apoptotic myonuclei: increased	TA: Bax
Libera *et al.* (1999)	Monocrotaline	SOL	Rat	Reduced MHC1and Bcl-2; Increased Caspase-3; Increased TUNEL+ apoptotic nuclei (interstitial and myonuclei)	No atrophy Ubiquitin
Sabbah *et al.* (1993)	Micro-embolization	TRI	Dog	Fibre type: Reduced type I, increased type II	Fibre area
Chati *et al.* (1994)	Aortocaval fistula	GC	Rat	^{31}P-MRS; During exercise: Increased PCr depletion	At rest: P_i/PCr, ATP, pH; During exercise: pH, ATP PDE; Recovery: P_i/PCr
Wilson *et al.* (1992)	Pacing	GRA, GC, TRI	Dog	GRA and TRI weight reduced; Fibre area: Reduced Type II;	Force–frequency; Contraction and relaxation time; Fatigue index; Fibre area: Type I; Enzymes: CS, HADH, LDH; GRA: Blood flow, oxygen uptake, pH, P_i/PCr
Peters *et al.* (1997)	SHHF	TA, GC, PL	Rat	TA, PL: Reduced mRNA for SERCA1 TA, GC: Reduced SERCA1 protein Not appropriate control groups	
MI_{nf}					
Williams & Ward (1998b)	CAL	GC	Rat	6 and 12 weeks; SR vesicles: Increased Ca^{2+} release, uptake and Ca^{2+} ATPase activity:; Increased $\pm dF/dt$	Force–frequency; Muscle weights
Arnolda *et al.* (1991)	CAL	SOL–PL–GC	Rat	PCr/(PCr + P_i) reduced after intense exercise;	Twitch tension; ^{31}P-MRS: At rest: pH and PCr/(PCr + P_i); During exercise: PCr and ADP; Enzymes: CS, PFK, HK, LDH
Brunotte *et al.* (1995)	CAL	PL–GC–SOL	Rat	Muscle weight: reduced	^{31}P-MRS; At rest: PCr and pH; Recovery PCr; Enzymes: CS, HADH and GPT; CSA

Table 2 (Continued)

Reference	Failure model	Muscle studied	Species	Observed significant changes	Not significantly changed parameters
Thompson *et al.* (1994)	CAL	GC	Rat	^{31}P-MRS: End exercise: Reduced pH, PCr, and ADP; Reduced PCr recovery; Reduced CS	At rest: pH, PCr, P_i and ADP
Musch & Terrell (1992)	CAL	28 hindlimb muscles	Rat	At rest: Blood flow reduced in GC-M; After exercise: Blood flow reduced in all muscles except GC-W, ankle flexors, some knee flexors and some thigh adductors Flow reduction dependent on infarct size	
Musch *et al.* (1988)	CAL	GC-W, PL, SOL	Rat	SHAM rats exercised longer	At rest, after exercise, after recovery: Glycogen concentration
Musch *et al.* (1990)	CAL	VI, PL, SOL, GC-W, TA-W	Rat	During exercise: VI and PL: Increased glycogen depletion	SOL, TA-W and GC-W: glycogen depletion
Xu *et al.* (1998)	CAL	PL, SOL	Rat	PL: Reduced CSA and capillary to fibre ratio	SOL: CSA and capillary to fibre ratio SOL and PL: Cap. surface area/fibre volume
Kindig *et al.* (1999a)	CAL	ST	Rat	Reduced capillarization, reduced CSA Reduced RBC flux	
McAllister *et al.* (1993)	CAL	Hindquarter	Rat	Regional flow differences; Increased post-capillary resistance	Total flow; Pre-capillary resistance
Hirai *et al.* (1995)	CAL	SOL, VL-R, and other	Rat	Large MI: Pre-L-NAME administration: Reduced blood flow and conductance in hindquarter muscle	Large MI after L-NAME Administration: Blood flow and conductance
Hirai *et al.* (1995)	CAL	SOL, VL-R, and other	Rat		Small MI: Before and after Administration of L-NAME Blood flow and conductance in hindquarter muscle
Delp *et al.* (1997)	CAL	SOL, PL, GC-W, GC-M, GC-R	Rat	Enzymes: GC-W: Reduced CS and PFK; CSA: PL: Type I	SOL, PL, GC-R and GC-M: PFK, LDH, CS, MDH, HADH; GC-W: LDH, MDH and HADH Fibre types: SOL and PL: All types CSA: SOL: All fibre types; PL: IIA, IID/X, IIB
Simonini *et al.* (1996b)	CAL	SOL, PL	Rat		Muscle weight; CSA
Schieffer *et al.* (1995)	CAL	Hindlimb	Rat	Collagen volume fraction increased Capillary density and capillary/fibre ratio reduced	High dose ACE for 1 year: Collagen volume fraction and capillary density
Pickar *et al.* (1997)	CAL	SOL, PL	Rat	SOL and PL: ^{3}[H]Ouabain binding reduced	SOL and PL: Dissociation Constant

CAL: coronary artery ligation; SOL: soleus; PL: plantaris; GC: gastrocnemius; VL: Vastus lateralis; VI: Vastus intermedius; ST: spinotrapezius; TRI: triceps; GRA: gracilis; CS: citrate synthase; PFK: phosphofructokinase; HK: hexokinase; LDH: lactate dehydrogenase; MDH: malate dehydrogenase; HADH: 3-hydroxyacyl-CoA dehydrogenase; COX: cytochrome C oxidase; GPT: glutamate pyruvate transferase; NOS: NO synthase; CSA: cross-sectional area; $[Ca^{2+}]_i$: intracellular calcium concentration; RBC: red blood cells; L-NAME: NG-nitro-L-arginine methyl ether; MRS: magnetic resonance spectroscopy; NS: not significant at 0.05 level.

failure, with no changes in muscles from rats with MI_{nf} (Brunotte *et al.* 1995, Delp *et al.* 1997) to a 15–25% reduction in various muscles from animals with during CHF (Brunotte *et al.* 1995, Thompson *et al.* 1995, Delp *et al.* 1997). Also other mitochondrial enzymes, such as malate dehydrogenase (MDH) and 3-hydroxyacyl-CoA-dehydrogenase (HADH) were reduced by 16–19 and 25–29%, respectively, in various skeletal muscles from CHF animals compared with SHAM (Delp *et al.* 1997). However, in a dog model in which CHF was induced by rapid ventricular pacing for 3 months there were no differences in either CS or HADH activity in skeletal muscle biopsies (Wilson *et al.* 1992). In rat models reduced HADH activity was not found in all muscle types, and the activity of this enzyme was not related to the degree of heart failure (Brunotte *et al.* 1995, Delp *et al.* 1997). This indicates that there might be a muscle type specific regulation of the various enzymes, and also that a fibre type shift might be partially responsible for these changes (see below). It seems clear that reduced activity of these enzymes depends on the severity of the heart failure with no or small changes as compared with SHAM operated rats in MI_{nf}, and significant changes in CHF.

The two glycolytic enzymes lactate dehydrogenase and phosphofructokinase show small or no differences in activity in various muscles from various models of heart failure in keeping with the patient data (Wilson *et al.* 1992, Delp *et al.* 1997).

The possibility that the rate limiting step in oxidative metabolism could reside in the skeletal muscles themselves has also been examined in animal models using ^{31}P-MRS (Arnolda *et al.* 1991, Chati *et al.* 1994, Thompson *et al.* 1994, 1995, Brunotte *et al.* 1995). In resting leg muscles there are no differences in CrP, ATP, ADP, P_i or pH between CHF, MI_{nf}, and SHAM animals. However, the results during and after stimulation are more variable. The most prominent finding is an increased breakdown of CrP during stimulation either measured as CrP or relative to CrP + P_i (Arnolda *et al.* 1991, Chati *et al.* 1994, Thompson *et al.* 1994, Brunotte *et al.* 1995) in the CHF group (Table 2). During stimulation the muscles from CHF animals also tended to become more acidic and to accumulate more ADP than the muscles of SHAM animals (Arnolda *et al.* 1991, Thompson *et al.* 1994). In contrast, the ATP concentration was reduced at the same rate in CHF rats as in SHAM (Chati *et al.* 1994, Thompson *et al.* 1994, 1995). Using biochemical techniques we found the same in the *in situ* perfused soleus muscle of CHF rats. The muscles were stimulated for 1 h at 5 Hz in trains lasting 6 s separated by 4 s pauses to allow adequate perfusion. We did not find any accumulation of lactate in these muscles (Lunde & Sejersted 1999).

Interestingly, Hammond *et al.* (2000) found that at a given exercise intensity the muscle metaboreflex (Fig. 2) was strongly amplified in a dog model of CHF as a result of rapid cardiac pacing for a month. The skeletal muscle metaboreflex is the activation of afferent free nerve endings within the skeletal muscle because of increased accumulation of metabolites leading to a powerful pressor response. The implication is that the muscle metaboreflex seems to be so much stronger in the CHF condition that it contributes to the tonic activation of the sympathoadrenergic system. Both increased lactate and K^+ release from the muscles may contribute to the stronger activation of afferent nerve fibres (Barlow *et al.* 1994a), but again it should be kept in mind that it is possible that these deviations from normal controls may disappear when exercise intensity is normalized to individual maximum exercise capacity (e.g. $\dot{V}O_{2max}$).

In some studies severe slowing of the recovery of phosphocreatine has been observed both in MI_{nf} and CHF rats (Thompson *et al.* 1994, 1995, Brunotte *et al.* 1995). Recovery after muscle stimulation is an aerobic process, so these findings strongly suggest a reduced rate of mitochondrial ATP synthesis in the muscle.

Taken together, these data confirm the patient studies by showing reduced oxidative, but maintained glycolytic capacity in skeletal muscle during heart failure (Fig. 3). They also indicate that these changes may occur in spite of maintained physical activity. In addition, it seems that these changes depend on the severity of the condition, because they most often are detectable only during CHF and not in MI_{nf}.

Muscle atrophy, apoptosis and fibre type composition

Experimental studies in rats have revealed contradictory results with respect to skeletal muscle atrophy. Some investigators report a significant decrease in muscle weight in rats with heart failure compared with controls (Brunotte *et al.* 1995, Simonini *et al.* 1996a, b, 1999b, Peters *et al.* 1997, Vescovo *et al.* 1998a, b) while others have not observed any change (Perreault *et al.* 1993b, Bernocchi *et al.* 1996, Comini *et al.* 1996a, Didion *et al.* 1997, Williams & Ward 1998b, Libera *et al.* 1999). Furthermore, a reduced cross-sectional area (CSA) of single muscle fibres has been observed in CHF (Delp *et al.* 1997, Xu *et al.* 1998, Vescovo *et al.* 1998b, Kindig *et al.* 1999a), but again this is not a general finding (Brunotte *et al.* 1995, Simonini *et al.* 1996a, Xu *et al.* 1998, Vescovo *et al.* 1998a). The latter observations are carried out in both fast-twitch (EDL, plantaris, tibialis anterior (TA)), slow-twitch (soleus), and mixed muscles (gastrocnemius, spinotrapezius). The observations are independent of the heart failure model used, the severity of heart failure (MI_{nf} or CHF),

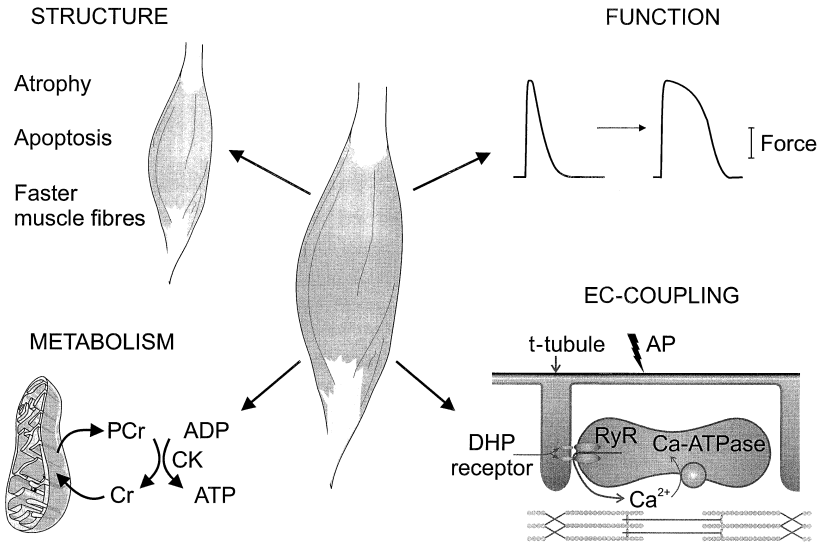

Figure 3 Sites of altered skeletal muscle structure, metabolism and function in heart failure.

duration of the disease state, and type of muscle. Except for one case, these studies did not last for more than 8 weeks. The single long-term study lasted for 5 months and showed that soleus weight and total amount of soleus MHC isoenzymes were reduced in CHF rats indicating myofibrillar atrophy (Simonini *et al.* 1996b). One study did not reveal any ultrastructural signs of atrophy in skeletal muscle fibres, such as a decrease in size of the myofibrils and/or disorder of the peripheral myofibrils, widening of the intermyofibrillar spaces, or a high incidence of lysosomes in heart failure rats (Perreault *et al.* 1993b). We therefore conclude that muscle atrophy probably occurs later during the development of CHF, and is not significant in short-term experimental studies lasting less than 2 months.

There is a progressive rise (up to 4 weeks) in the number of apoptotic interstitial and myocyte nuclei in the TA and soleus muscles in monocrotaline induced heart failure rats. The apoptosis preceded the appearance of muscle atrophy observed in TA. The amount of myocyte apoptosis in soleus was smaller than in TA and no atrophy was observed in soleus (Vescovo *et al.* 1998b, Libera *et al.* 1999). Skeletal myocytes are multinucleated and nuclear apoptosis of some nuclei may not result in an immediate myocyte death, delaying the appearance of muscle bulk loss. It could be questioned if myocyte apoptosis is ultimately responsible for muscle atrophy. Also in the failing heart the role of apoptosis is unclear (Kang & Izumo 2000).

In experimental studies of heart failure there is a shift in fibre type composition towards a faster phenotype. In general, observations on rats show a decrease in relative preponderance of the slow twitch fibres and an increase in fast twitch fibres during CHF (Simonini *et al.* 1996a, b, Delp *et al.* 1997, Vescovo *et al.* 1998a, b, Libera *et al.* 1999). In the slow twitch soleus muscle the fraction of type IIa fibres had increased whereas the percentage of type I fibres had decreased. In the fast muscles plantaris and extensor digitorium longus the percentage of type IId/x and IIa fibres was found to be reduced and the relative content of type IIb fibres was higher. These fibre type shifts indicate adaptation to a more anaerobic metabolism in skeletal muscles in heart failure rats. This is substantiated by the analysis of the mRNA expression for the various myosin heavy chain (MHC) proteins. There is a reduced expression of slow/β-MHC mRNA and a *de novo* synthesis of IIb and IIx MHC mRNA in soleus in CHF rats compared with SHAM. The plantaris muscle showed a lower content of IIa and IIb MHC mRNA (Simonini *et al.* 1996a, b, 1999b). These findings provide evidence that heart failure is associated with altered transcriptional regulation of skeletal muscle specific genes.

There are conflicting observations on fibre type shift in dogs with heart failure. Whereas a study on gracilis, gastrocnemius, and triceps muscle failed to show any changes in skeletal muscle fibre type composition (Wilson *et al.* 1992), another study showed reduced percentage of type I fibres and an increased percentage of type II fibres in the triceps muscle (Sabbah *et al.* 1993). These contradictory findings may be caused by differences in the experimental model of heart failure (rapid ventricular pacing vs. multiple sequential intracoronary microembolizations) and to the specific skeletal muscle used for analysis.

Contractile properties and Ca^{2+}-handling

The main muscle dysfunctions in heart failure patients are reduced force production and increased

fatiguability. Reduced intracellular Ca^{2+} transients have been proposed as a cause of fatigue in healthy individuals (Allen *et al.* 1995). In animal heart failure models there are only some studies on contractile properties, fatiguability and intracellular Ca^{2+} homeostasis of skeletal muscle.

In rats fulfilling our CHF criteria Perreault *et al.* (1993b) found reduced peak tension of both twitches and tetanic contractions in the isolated fast twitch EDL muscle, and they also observed increased fatiguability. We have preliminary data from rats with CHF compared with SHAM showing significantly more rapid reduction of developed force during a 1-h stimulation protocol on an *in situ* model of fully perfused soleus (Lunde & Sejersted 1999). Also in MI_{nf} rats both twitch and tetanic force in the gastrocnemius muscle was reduced compared with SHAM and swimming performance was poor (Musch *et al.* 1988, Williams & Ward 1998b).

Perreault *et al.* (1993b) found that relaxation rate of both twitch and tetanic contractions was prolonged in rested EDL muscle. The slowing of relaxation was associated with a slower decay of the light emitted from the Ca-sensitive protein aequorin. As opposed to this, in the *in situ* soleus model we found normal contraction and relaxation rates in resting muscle from CHF rats, but after about 5 min of stimulation both contraction and relaxation rates became slower in muscles from CHF as compared with SHAM rats (Lunde & Sejersted 1999) (Fig. 3). In this soleus model the muscles had completely recovered within 2 min with regard to maximal force of both twitch and tetanic contraction (Lunde *et al.* 2000).

In contrast, in their MI_{nf} model Williams & Ward (1998b) found nearly 50% increase in relaxation and contraction rates which fits in with accelerated rate of release and uptake of Ca^{2+} from SR vesicles isolated from the gastrocnemius muscle. Cytosolic Ca^{2+} is predominantly removed by the Ca^{2+}-ATPase of the SR during the Ca^{2+} transient and the amount and the activity of the SR Ca^{2+}-ATPase will to a great extent determine the relaxation rate. These highly divergent results as regards the effect on contractile properties can probably be ascribed to the different muscles that were used in the experiments (fast twitch or slow twitch) and/or the degree of heart failure. Also Perreault *et al.* (1993b) and Williams & Ward (1998b) used very different methods to measure kinetics of Ca^{2+} release and reuptake.

In support of slowed intracellular Ca^{2+} turnover Simonini *et al.* (1999b) found a reduction in both protein and mRNA for the Ca^{2+}-ATPase (SERCA 2a) in the slow twitch soleus muscle from CHF rats. On the other hand, by steady state ^{32}P incorporation we found a 43% increase in SR Ca^{2+}-ATPase in soleus from CHF (Lunde & Sejersted 1999) which seemingly contrasts with the gradual slowing of relaxation. However, both the amount of Ca^{2+}-ATPase as well as the activity of the pump is important for the rate of removal of Ca^{2+} from the cytosol. The activity of the Ca^{2+}-ATPase in heart, which is the same isoform (SERCA 2) as in slow skeletal muscle, is regulated by the small protein phospholamban that can be phosphorylated leading to increased activity of the Ca^{2+}-ATPase. We speculate that Ca^{2+} reuptake in the SR of slow skeletal muscle is regulated in a similar manner and that this regulation is altered in CHF (Fig. 3). The findings from slow twitch muscle cannot explain the altered kinetics of Ca^{2+} release and reuptake observed by Perreault *et al.* (1993b) in the EDL because the Ca^{2+}-ATPase isoform is different in the fast twitch EDL muscle (SERCA 1). Clearly, it would be timely with well controlled experimental studies on contractile properties and Ca^{2+} cycling in skeletal muscles from animals with CHF, especially in the light of a possible specific relationship between myocardial failure and skeletal muscle failure.

CONCLUSIONS

One of the main symptoms of CHF is intolerance to exercise. This decreased exercise capacity seems, at least in part, to be caused by abnormalities in the skeletal muscle itself. The main findings in these muscles comprise switching to faster fibre type and myosin heavy chain composition, fibre atrophy and a reduction in the activity of oxidative enzymes. These changes are not specific for the heart failure condition, but may to some extent be related to inactivity and chronic ischaemia. However, it remains an intriguing possibility that failure of the myocardium itself also may be linked to alterations of the skeletal muscle, especially slow twitch muscle, possibly through altered control of intracellular Ca^{2+} cycling that could lead to increased fatiguability and slowing of the muscle.

REFERENCES

Adamopoulos, S., Coats, A.J., Brunotte, F. *et al.* 1993a. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. *J Am Coll Cardiol* **21,** 1101–1106.

Adamopoulos, S., Kemp, G.J., Thompson, C.H. *et al.* 1999. The time course of haemodynamic, autonomic and skeletal muscle metabolic abnormalities following first extensive myocardial infarction in man. *J Mol Cell Cardiol* **31,** 1913–1926.

Allen, D.G., Lännergren, J. & Westerblad, H. 1995. Muscle cell function during prolonged activity: cellular mechanisms of fatigue. *Exp Physiol* **80,** 497–527.

Andersen, P. & Saltin, B. 1985. Maximal perfusion of skeletal muscle in man. *J Physiol (Lond)* **366,** 233–249.

Anonymous 1995. Guidelines for the diagnosis of heart failure. The task force on heart failure of the European society of cardiology. *Eur Heart J* **16,** 741–751.

Arnolda, L., Brosnan, J., Rajagopalan, B. & Radda, G.K. 1991. Skeletal muscle metabolism in heart failure in rats. *Am J Physiol* **261,** H434–H442.

Aukrust, P., Ueland, T., Muller, F. *et al.* 1998. Elevated circulating levels of C–C chemokines in patients with congestive heart failure. *Circulation* **97,** 1136–1143.

Barlow, C.W., Qayyum, M.S., Davey, P.P., Conway, J., Paterson, D.J. & Robbins, P.A. 1994a. Effect of physical training on exercise-induced hyperkalemia in chronic heart failure. Relation with ventilation and catecholamines. *Circulation* **89,** 1144–1152.

Bernocchi, P., Ceconi, C., Pedersini, P., Pasini, E., Curello, S. & Ferrari, R. 1996. Skeletal muscle metabolism in experimental heart failure. *J Mol Cell Cardiol* **28,** 2263–2273.

Bigard, A.-X., Boehm, E., Veksler, V., Mateo, P., Anflous, K. & Ventura-Clapier, R. 1998a. Muscle unloading induces slow to fast transitions in myofibrillar but not mitochondrial properties. Relevance to skeletal muscle abnormalities in heart failure. *J Mol Cell Cardiol* **30,** 2391–2401.

Bishop, S.P. & Altschuld, R.A. 1970. Increased glycolytic metabolism in cardiac hypertrophy and congestive failure. *Am J Physiol* **218,** 153–159.

Booth, F.W. & Gollnick, P.D. 1983. Effects of disuse on the structure and function of skeletal muscle. *Med Sci Sports Exerc* **15,** 415–420.

Braunwald, E. 1997a. Pathophysiology of heart failure. In: E. Braunwald (ed.) *Heart Disease. A Textbook of Cardiovascular Medicine*, pp. 394–418. W.B. Saunders Company, Philadelphia.

Brunotte, F., Thompson, C.H., Adamopoulos, S. *et al.* 1995. Rat skeletal muscle metabolism in experimental heart failure: effects of physical training. *Acta Physiol Scand* **154,** 439–447.

Buller, N.P., Jones, D. & Poole-Wilson, P.A. 1991. Direct measurement of skeletal muscle fatigue in patients with chronic heart failure. *Br Heart J* **65,** 20–24.

Chati, Z., Zannad, F., Michel, C. *et al.* 1994. Skeletal muscle phosphate metabolism abnormalities in volume – overload experimental heart failure. *Am J Physiol* **267,** H2186–H2192.

Coats, A.J.S. 1996. The 'muscle hypothesis' of chronic heart failure. *J Mol Cell Cardiol* **28,** 2255–2262.

Coats, A.J. 1999. Exercise training for heart failure: coming of age [editorial]. *Circulation* **99,** 1138–1140.

Comini, L., Bachetti, T., Gaia, G. *et al.* 1996a. Aorta and skeletal muscle NO synthase expression in experimental heart failure. *J Mol Cell Cardiol* **28,** 2241–2248.

Comini, L., Gaia, G., Curello, S. *et al.* 1996b. Right heart failure chronically stimulates heat shock protein 72 in heart and liver but not in other tissues. *Cardiovasc Res* **31,** 882–890.

Conley, K.E., Esselman, P.C., Jubrias, S.A. *et al.* 2000a. Ageing, muscle properties and maximal O_2 uptake rate in humans. *J Physiol (Lond) 526* **1,** 211–217.

Conley, K.E., Jubrias, S.A. & Esselman, P.C. 2000b. Oxidative capacity and ageing in human muscle. *J Physiol (Lond) 526* **1,** 203–210.

Damås, J.K., Gullestad, L., Ueland, T. *et al.* 2000. CXC-chemokines, a new group of cytokines in congestive heart failure – possible role of platelets and monocytes. *Cardiovasc Res* **45,** 428–436.

Delp, M.D., Duan, C., Mattson, J.P. & Musch, T.I. 1997. Changes in skeletal muscle biochemistry and histology relative to fiber type in rats with heart failure. *J Appl Physiol* **83,** 1291–1299.

Didion, S.P., Carmines, P.K., Ikenaga, H. & Mayhan, W.G. 1997. Enhanced constrictor responses of skeletal muscle arterioles during chronic myocardial infarction. *Am J Physiol* **273,** H1502–H1508.

Drexler, H. 1992. Skeletal muscle failure in heart failure. *Circulation* **85,** 1621–1623.

Drexler, H. 1995. Changes in the peripheral circulation in heart failure [Review]. *Curr Opin Cardiol* **10,** 268–273.

Drexler, H. & Coats, A.J. 1996. Explaining fatigue in congestive heart failure [Review]. *Annu Rev Med* **47,** 241–256.

Drexler, H., Depenbusch, J.W., Truog, A.G., Zelis, R. & Flaim, S.F. 1985. Effects of diltiazem on cardiac function and regional blood flow at rest and during exercise in a conscious rat preparation of chronic heart failure (myocardial infarction). *Circulation* **71,** 1262–1270.

Drexler, H., Banhardt, U., Meinertz, T., Wollschlager, H., Lehmann, M. & Just, H. 1989. Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure. A double-blind, placebo-controlled trial. *Circulation* **79,** 491–502.

Drexler, H., Faude, F., Hoing, S. & Just, H. 1987. Blood flow distribution within skeletal muscle during exercise in the presence of chronic heart failure: effect of milrinone. *Circulation* **76,** 1344–1352.

Drexler, H., Riede, U., Münzel, T., König, H., Funke, E. & Just, H. 1992. Alterations of skeletal muscle in chronic heart failure. *Circulation* **85,** 1751–1759.

Federspiel, W.J. & Popel, A.S. 1986. A theoretical analysis of the effect of the particulate nature of blood on oxygen release in capillaries. *Microvasc Res* **32,** 164–189.

Galione, A. 1993. Cyclic ADP-ribose: a new way to control calcium. *Science* **259,** 325–326.

Gomez, A.M., Valdivia, H.H., Cheng, H. *et al.* 1997. Defective excitation–contraction coupling in experimental cardiac hypertrophy and heart failure. *Science* **276,** 800–806.

Gullestad, L., Hallén, J. & Sejersted, O.M. 1993. Variable effects of β-adrenoceptor blockade on muscle blood flow during exercise. *Acta Physiol Scand* **149,** 257–271.

Hammond, R.L., Augustyniak, R.A., Rossi, N.F., Churchill, P.C., Lapanowski, K. & O'Leary, D.S. 2000. Heart failure alters the strength and mechanisms of the muscle metaboreflex. *Am J Physiol* **278,** H818–H828.

Hands, L.J., Bore, P.J., Galloway, G., Morris, P.J. & Radda, G.K. 1986. Muscle metabolism in patients with peripheral vascular disease investigated by ^{31}P

nuclear magnetic resonance spectroscopy. *Clin Sci* **71,** 283–290.

Harrington, D. & Coats, A.J. 1997. Skeletal muscle abnormalities and evidence for their role in symptom generation in chronic heart failure. *Eur Heart J* **18,** 1865–1872.

Hasenfuss, G. 1998. Animal models of human cardiovascular disease, heart failure and hypertrophy. *Cardiovasc Res* **39,** 60–76.

Hasenfuss, G., Mulieri, L.A., Leavitt, B.J., Allen, P.D., Haeberle, J.R. Jr & Alpert, N.R. 1992. Alteration of contractile function and excitation–contraction coupling in dilated cardiomyopathy. *Circ Res* **70,** 1225–1232.

Hirai, T., Zelis, R. & Musch, T.I. 1995. Effects of nitric oxide synthase inhibition on the muscle blood flow response to exercise in rats with heart failure. *Cardiovasc Res* **30,** 469–476.

Holt, E., Tonnessen, T., Lunde, P.K. *et al.* 1998. Mechanisms of cardiomyocyte dysfunction in heart failure following myocardial infarction in rats. *J Mol Cell Cardiol* **30,** 1581–1593.

Hunter, J.J. & Chien, K.R. 1999. Signaling pathways for cardiac hypertrophy and failure. *N Engl J Med* **341,** 1276–1283.

Kang, P.M. & Izumo, S. 2000. Apoptosis and heart failure: a critical review of the literature. *Circ Res* **86,** 1107–1113.

Katz, S.D., Bleiberg, B., Wexler, J., Bhargava, K., Steinberg, J.J. & LeJemtel, T.H. 1993. Lactate turnover at rest and during submaximal exercise in patients with heart failure. *J Appl Physiol* **75,** 1974–1979.

Katz, S.D., Maskin, C., Jondeau, G., Cocke, T., Berkowitz, R. & LeJemtel, T. 2000. Near-maximal fractional oxygen extraction by active skeletal muscle in patients with chronic heart failure. *J Appl Physiol* **88,** 2138–2142.

Kemp, G.J., Thompson, C.H., Stratton, J.R. *et al.* 1996a. Abnormalities in exercising skeletal muscle in congestive heart failure can be explained in terms of decreased mitochondrial ATP synthesis, reduced metabolic efficiency, and increased glycogenolysis. *Br Heart J* **76,** 35–41.

Kindig, C.A., Musch, T.I., Basaraba, R.J. & Poole, D.C. 1999a. Impaired capillary hemodynamics in skeletal muscle of rats in chronic heart failure. *J Appl Physiol* **87,** 652–660.

Lefkowitz, R.J., Rockman, H.A. & Koch, W.J. 2000. Catecholamines, cardiac beta-adrenergic receptors, and heart failure. *Circulation* **101,** 1634–1637.

Li, Y.P., Schwartz, R.J., Waddell, I.D., Holloway, B.R. & Reid, M.B. 1998. Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-κB activation in response to tumor necrosis factor alpha. *FASEB J* **12,** 871–880.

Libera, L.D., Zennaro, R., Sandri, M., Ambrosio, G.B. & Vescovo, G. 1999. Apoptosis and atrophy in rat slow skeletal muscles in chronic heart failure. *Am J Physiol* **277,** C982–C986.

Lunde, P.K. & Sejersted, O.M. 1999. Skeletal muscle dysfunction in heart failure. *Biophys J* **76,** a298.

Lunde, P.K., Verburg, E., Vøllestad, N.K. & Sejersted, O.M. 1998. Skeletal muscle fatigue in normal subjects and heart failure patients. Is there a common mechanism? *Acta Physiol Scand* **162,** 215–228.

Lunde, P.K., Eriksen, M. & Sejersted, O.M. 2000. Prolonged relaxation in slow twitch skeletal muscle from rats with heart failure. *Biophys J* **78,** 376a.

Magnusson, G., Gordon, A., Kaijser, L. *et al.* 1996b. High intensity knee extensor training, in patients with chronic heart failure. Major skeletal muscle improvement. *Eur Heart J* **17,** 1048–1055.

Magnusson, G., Kaijser, L., Sylven, C., Karlberg, K.-E., Isberg, B. & Saltin, B. 1997b. Peak skeletal muscle perfusion is maintained in patients with chronic heart failure when only a small muscle mass is exercised. *Cardiovasc Res* **33,** 297–306.

Mancini, D.M., Coyle, E., Coggan, A. *et al.* 1989. Contribution of intrinsic skeletal muscle changes to 31P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation* **80,** 1338–1346.

Mancini, D.M., Walter, G., Reichek, N. *et al.* 1992. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure [see comments]. *Circulation* **85,** 1364–1373.

Mancini, D.M., Wilson, J.R., Bolinger, L. *et al.* 1994. In vivo magnetic resonance spectroscopy measurement of deoxymyoglobin during exercise in patients with heart failure. Demonstration of abnormal muscle metabolism despite adequate oxygenation. *Circulation* **90,** 500–508.

Mann, D.L. 1999. Mechanisms and models in heart failure: a combinatorial approach. *Circulation* **100,** 999–1008.

Mann, D.L. & Young, J.B. 1994. Basic mechanisms in congestive heart failure. Recognizing the role of proinflammatory cytokines. *Chest* **105,** 897–904.

Massie, B., Conway, M., Yonge, R. *et al.* 1987. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. *Circulation* **76,** 1009–1019.

Massie, B.M., Conway, J., Rajagopalan, B. *et al.* 1988. Skeletal muscle metabolism during exercise under ischemic conditions in congestive heart failure. Evidence for abnormalities unrelated to blood flow. *Circulation* **78,** 320–326.

McAllister, R.M., Laughlin, M.H. & Musch, T.I. 1993. Effects of chronic heart failure on skeletal muscle vascular transport capacity of rats. *Am J Physiol* **264,** H689–H691.

Minotti, J.R., Pillay, P., Oka, R., Wells, L., Christoph, I. & Massie, B.M. 1993. Skeletal muscle size: relationship to muscle function in heart failure. *J Appl Physiol* **75,** 373–381.

Musch, T.I. & Terrell, J.A. 1992. Skeletal muscle blood flow abnormalities in rats with a chronic myocardial infarction: rest and exercise. *Am J Physiol* **262,** H411–H419.

Musch, T.I., Moore, R.L., Riedy, M. *et al.* 1988. Glycogen concentrations and endurance capacity of rats with chronic heart failure. *J Appl Physiol* **64,** 1153–1159.

Musch, T.I., Ghaul, M.R., Tranchitella, V. & Zelis, R. 1990. Skeletal muscle glycogen depletion during submaximal exercise in rats with chronic heart failure. *Bas Res Cardiol* **85,** 606–618.

Musch, T.I., Nguyen, C.T., Pham, H.V. & Moore, R.L. 1992. Training effects on the regional blood flow response to

exercise in myocardial infarcted rats. *Am J Physiol* **262,** H1846–H1852.

Nejad, N.S., Klein, M.D., Mirsky, I. & Lown, B. 1971. Assessment of myocardial contractility from ventricular pressure recordings. *Cardiovasc Res* **5,** 15–23.

Okita, K., Yonezawa, K., Nishijima, H. *et al.* 1998. Skeletal muscle metabolism limits exercise capacity in patients with chronic heart failure. *Circulation* **98,** 1886–1891.

Ostrowski, K., Rohde, T., Zacho, M., Asp, S. & Pedersen, B.K. 1998. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. *J Physiol (Lond) 508* **3,** 949–953.

Perreault, C.L., Gonzalez-Serratos, H., Litwin, S.E., Sun, X., Franzini-Armstrong, C. & Morgan, J.P. 1993b. Alterations in contractility and intracellular Ca^{2+} transients in isolated bundles of skeletal muscle fibers from rats with chronic heart failure. *Circ Res* **73,** 405–412.

Peters, D.G., Mitchell, H.L., McCune, S.A., Park, S., Williams, J.H. & Kandarian, S.C. 1997. Skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase gene expression in congestive heart failure. *Circ Res* **81,** 703–710.

Pfeffer, M.A. & Braunwald, E. 1990. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* **81,** 1161–1172.

Pfeffer, M.A., Pfeffer, J.M., Fishbein, M.C. *et al.* 1979. Myocardial infarct size and ventricular function in rats. *Circ Res* **44,** 503–512.

Pickar, J.G., Mattson, J.P., Lloyd, S. & Musch, T.I. 1997. Decreased [^{3}H]ouabain binding sites in skeletal muscle of rats with chronic heart failure. *J Appl Physiol* **83,** 323–327.

Pieske, B., Kretschmann, B., Meyer, M. *et al.* 1995. Alterations in intracellular calcium handling associated with the inverse force–frequency relation in human dilated cardiomyopathy. *Circulation* **92,** 1169–1178.

Poole-Wilson, P.A. & Ferrari, R. 1996. Role of skeletal muscle in the syndrome of chronic heart failure. *J Mol Cell Cardiol* **28,** 2275–2285.

Radegran, G., Blomstrand, E. & Saltin, B. 1999. Peak muscle perfusion and oxygen uptake in humans: importance of precise estimates of muscle mass. *J Appl Physiol* **87,** 2375–2380.

Rowell, L.B. 1993. *Human Cardiovascular Control.* Oxford University Press, New York.

Rowell, L.B., Saltin, B., Kiens, B. & Christensen, N.J. 1986. Is peak quadriceps blood flow in humans even higher during exercise with hypoxemia. *Am J Physiol* **251,** H1038–H1044.

Sabbah, H.N., Hansen-Smith, F., Sharov, V.G. *et al.* 1993. Decreased proportion of type I myofibers in skeletal muscle of dogs with chronic heart failure. *Circulation* **87,** 1729–1737.

Savard, G.K., Richter, E.A., Strange, S., Kiens, B., Christensen, N.J. & Saltin, B. 1989. Norepinephrine spillover from skeletal muscle during exercise in humans: role of muscle mass. *Am J Physiol* **257,** H1812–H1818.

Schaufelberger, M., Eriksson, B.O., Held, P. & Swedberg, K. 1996. Skeletal muscle metabolism during exercise in patients with chronic heart failure. *Br Heart J* **76,** 29–34.

Schieffer, B., Wollert, K.C., Berchtold, M. *et al.* 1995. Development and prevention of skeletal muscle structural alterations after experimental myocardial infarction. *Am J Physiol* **269,** H1507–H1513.

Schiller, N.B., Shah, P.M., Crawford, M. *et al.* 1989. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocard* **2,** 358–367.

Schultze, A.E. & Roth, R.A. 1998. Chronic pulmonary hypertension – the monocrotaline model and involvement of the hemostatic system. *J Tox Environ Health Part B, Crit Rev* **1,** 271–346.

Sejersted, O.M. & Sjøgaard, G. 2000. Dynamics and consequences of potassium shifts in skeletal muscle and heart during exercise. *Physiol Rev* **80,** 1411–1481.

Sejersted, O.M. & Vøllestad, N.K. 1992. Increased metabolic rate associated with muscle fatigue. In: P. Marconnet, P.V. Komi, B. Saltin & O.M. Sejersted (eds) *Muscle Fatigue Mechanisms in Exercise and Training (Med Sport Sci Vol 34)*, pp. 115–130. Karger, Basel.

Simonini, A., Long, C.S., Dudley, G.A., Yue, P., McElhinny, J. & Massie, B.M. 1996a. Heart failure in rats causes changes in skeletal muscle morphology and gene expression that are not explained by reduced activity. *Circ Res* **79,** 128–136.

Simonini, A., Massie, B.M., Long, C.S., Qi, M. & Samarel, A.M. 1996b. Alterations in skeletal muscle gene expression in the rat with chronic congestive heart failure. *J Mol Cell Cardiol* **28,** 1683–1691.

Simonini, A., Chang, K., Yue, P., Long, C.S. & Massie, B.M. 1999b. Expression of skeletal muscle sarcoplasmic reticulum calcium-ATPase is reduced in rats with postinfarction heart failure. *Heart* **81,** 303–307.

Sjaastad, I., Sejersted, O.M., Ilebekk, A. & Bjornerheim, R. 2000. Echocardiographic criteria for detection of post-infarction congestive heart failure in rats. *J Appl Physiol* **89,** 1445–1454.

Skomedal, T., Borthne, K., Aass, H., Geiran, O. & Osnes, J.B. 1997. Comparison between alpha-1 adrenoceptor-mediated and beta adrenoceptor-mediated inotropic components elicited by norepinephrine in failing human ventricular muscle. *J Pharmacol Exp Ther* **280,** 721–729.

Sorensen, V.B., Wroblewski, H., Galatius, S., Haunso, S. & Kastrup, J. 1999. Exercise blood flow and microvascualr distensibility in skeletal muscle normalize after heart transplantation. *Clin Transplant* **13,** 410–419.

Stratton, J.R., Kemp, G.J., Daly, R.C., Yacoub, M. & Rajagopalan, B. 1994a. Effects of cardiac transplantation on bioenergetic abnormalities of skeletal muscle in congestive heart failure. *Circulation* **89,** 1624–1631.

Stratton, J.R., Dunn, J.F., Adamopoulos, S., Kemp, G.J., Coats, A.J. & Rajagopalan, B. 1994b. Training partially reverses skeletal muscle metabolic abnormalities during exercise in heart failure. *J Appl Physiol* **76,** 1575–1582.

Sullivan, M.J., Green, H.J. & Cobb, F.R. 1990. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation* **81,** 518–527.

Thomason, D.B. & Booth, F.W. 1990. Atrophy of the soleus muscle by hindlimb unweighting. *J Appl Physiol* **68,** 1–12.

Thompson, C.H., Kemp, G.J., Rajagopalan, B. & Radda, G.K. 1994. Metabolic abnormalities in skeletal muscle after myocardial infarction in the rat. *Clin Sci* **87,** 403–406.

Thompson, C.H., Kemp, G.J., Rajagopalan, B. & Radda, G.K. 1995. Abnormal ATP turnover in rat leg muscle during exercise and recovery following myocardial infarction. *Cardiovasc Res* **29,** 344–349.

Vatner, S.F., Vatner, D.E. & Homcy, C.J. 2000. β-adrenergic receptor signaling: an acute compensatory adjustment – inappropriate for the chronic stress of heart failure? Insights from $G_{s\alpha}$ overexpression and other genetically engineered animal models. *Circ Res* **86,** 502–506.

Veragut, U.P. & Krayenbuhl, H.P. 1965. Estimation and quantification of myocardial contractility in the closed-chest dog. *Cardiology* **47,** 96–112.

Vescovo, G., Ceconi, C., Bernocchi, P. *et al.* 1998a. Skeletal muscle myosin heavy chain expression in rats with monocrotaline-induced cardiac hypertrophy and failure. Relation to blood flow and degree of muscle atrophy. *Cardiovasc Res* **39,** 233–241.

Vescovo, G., Zennaro, R., Sandri, M. *et al.* 1998b. Apoptosis of skeletal muscle myofibers and interstitial cells in experimental heart failure. *J Mol Cell Cardiol* **30,** 2449–2459.

Wagoner, L.E., Craft, L.L., Singh, B. *et al.* 2000. Polymorphisms of the β_2-adrenergic receptor determine exercise capacity in patients with heart failure. *Circ Res* **86,** 834–840.

Wasserstrom, J.A., Holt, E., Sjaastad, I., Lunde, P.K., Ødegaard, A. & Sejersted, O.M. 2000. Altered excitation–contraction coupling in rat ventricular myocytes from failing hearts 6 weeks after myocardial infarction. *Am J Physiol* **278,** H818–H828.

Wiener, D.H., Fink, L.I., Maris, J., Jones, R.A., Chance, B. & Wilson, J.R. 1986. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. *Circulation* **73,** 1127–1136.

Wilcox, P., Milliken, C. & Bressler, B. 1996. High-dose tumor necrosis factor alpha produces an impairment of hamster diaphragm contractility. Attenuation with a prostaglandin inhibitor. *Am J Respir Crit Care Med* **153,** 1611–1615.

Williams, J.H. & Ward, C.W. 1998b. Changes in skeletal muscle sarcoplasmic reticulum function and force production following myocardial infarction in rats. *Exp Physiol* **83,** 85–94.

Wilson, J.R., Mancini, D.M., McCully, K., Ferraro, N., Lanoce, V. & Chance, B. 1989. Noninvasive detection of skeletal muscle underperfusion with near-infrared spectroscopy in patients with heart failure. *Circulation* **80,** 1668–1674.

Wilson, J.R., Coyle, E.F. & Osbakken, M. 1992. Effect of heart failure on skeletal muscle in dogs. *Am J Physiol* **262,** H993–H998.

Wilson, J.R., Mancini, D.M. & Dunkman, W.B. 1993. Exertional fatigue due to skeletal muscle dysfunction in patients with heart failure. *Circulation* **87,** 470–475.

Xu, L., Poole, D.C. & Musch, T.I. 1998. Effect of heart failure on muscle capillary geometry: implications for O_2 exchange. *Med Sci Sports Exerc* **30,** 1230–1237.

Yamani, M.H., Sahgal, P., Wells, L. & Massie, B.M. 1995. Exercise intolerance in chronic heart failure is not associated with impaired recovery of muscle function or submaximal exercise performance. *J Am Coll Cardiol* **25,** 1232–1238.

