

Origin of Symptoms in Heart Failure

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Abstract

In heart failure, the cardinal symptoms of breathlessness, reduced exercise capacity and muscle fatigue bear little correlation to conventional measures of left ventricular function or central haemodynamics. They are associated with objective abnormalities in ventilation, autonomic nervous system control and muscle metabolism, but controversies exist on the origin of these symptoms. Changes in the periphery may be partly responsible for the maintenance of sympatho-excitation and other neuro-hormonal activation and therefore may play a role in the progression of the syndrome.

This paper reviews some of the abnormalities that can occur secondarily in cardiac and extra-cardiac systems during heart failure and explains how they may contribute to exercise limitation and be harmful during the progression of the syndrome. The clinical and therapeutic implications are also discussed.

Key words: autonomic dysfunction, dyspnea, exercise, fatigue, ventilation

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Hear failure is a syndrome, not a diagnosis. The term refers to the clinical pattern in which left ventricular impairment produces a constellation of secondary changes in other organs, leading to symptoms and exercise limitation. Patients often complain of breathlessness, reduced exercise capacity and muscle fatigue, symptoms that, although partially treated with modern drug therapy, including the angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockade, aldosterone inhibitors and diuretics, bear little correlation to conventional measures of left ventricular function or central haemodynamics [25, 48]. These symptoms may cause patients to avoid physical activity, which may adversely affect not only the quality of life but also prognosis [22]. They are associated with objective abnormalities in ventilation, autonomic nervous system control and peripheral metabolism, but controversies exist on the origin of these symptoms. With acute heart failure the classic patho-physiologic explanation for the genesis of dyspnoea is increased pulmonary wedge pressures and the development of pulmonary oedema and inadequate peripheral blood flow due to poor cardiac output is usually cited as the explanation for fatigue. More recent investigations attest to the importance of abnormalities in peripheral blood flow and skeletal muscle for the genesis of the symptoms limiting exercise in the syndrome of chronic heart failure (CHF) [17].

It is now evident, in addition, that changes in the periphery may be partly responsible for the maintenance

of sympatho-excitation and other neuro-hormonal activation in CHF and therefore may play a role in the progression of the syndrome [17, 48]. This chapter reviews some of the abnormalities that can occur secondarily in extra-cardiac systems during heart failure and explains how they may contribute to exercise limitation and be harmful during the progression of the syndrome.

Pathophysiology of Chronic Heart Failure

Cardiac patho-physiology

Structural changes

Structural changes in the heart are of paramount importance for generating the clinical disorder. The clinical picture of systolic heart failure includes enlargement of the left ventricular cavity usually with a change of shape, to a more spherical contour. This change can occur relatively rapidly after a myocardial infarction via a passive process of stretching of the infarcted territory (infarct expansion) or more slowly by a process termed "remodeling." The remodeled and enlarged ventricle has increased stress on the myocardial wall, which may worsen myocardial ischaemia. The latter has important implications for myocardial functional performance and energetics.

Cardiac enlargement has long been known to be an adverse prognostic sign, even when estimated crudely as the cardio-thoracic diameter on the chest radiograph [44].

Origin of symptoms in heart failure

More precise measurements of the internal dimensions of the left ventricle by echocardiography have confirmed the prognostic value of cardiac enlargement. Cardiac enlargement is also incorporated into the information derived from calculating the ejection fraction by radionuclide ventriculography, long known to be a useful clinical and prognostic measure in CHF [58]. Prevention of the late remodeling process was the theory behind the use of ACE inhibitors given early after myocardial infarction [46]. These agents have been shown to reduce the ventricular enlargement that occurs in some patients after a large myocardial infarction, and this mechanism may, at least in part, contribute to the reduction in mortality seen in the post-infarct setting for these agents [45].

The failing heart also shows alterations in cardiac structure at microscopic and ultrastructural levels. There is an increase in the collagen content of the extracellular matrix, a process thought to be related in part to increased wall stress and in part to neuro-hormonal activation, particularly aldosterone. These changes are important for progression of the syndrome and for the generation of symptoms and cardiac output limitation. Increased ventricular collagen content reduces ventricular wall distensibility and may affect the efficiency with which active restorative forces can assist the diastolic filling process. As a result, this microscopic structural change may help explain the frequent coexistence of systolic and diastolic dysfunction of the enlarging ventricle during CHF. Enlargement of the ventricle is associated with thinning of the ventricular wall, which must involve a realignment of the intercellular attachments between individual myocytes. This process, wherein there is continual breaking and reforming of cell-to-cell junctions to allow remodeling, has been termed "cell slippage," although exactly how it occurs has not been established. Improvements in our understanding of this process may help explain how effective therapies work and how we can improve these treatments. They may explain why some treatments aimed specifically at the heart during heart failure are effective, whereas historically most that have had this purpose behind their development have not proved successful in practice [70].

Functional abnormalities of the myocardium

The description of an objective measurement of systolic function in intact humans has proved difficult. In simplest terms the left ventricle is a pump that generates both pressure and flow. It has a theoretic operating range from a pure pressure generator to a pure flow generator, although it always functions as a mixed pump. The function of this pump can be described in terms of the kinetic and potential energy it imparts to the blood ejected at each beat or in terms of the average power output of the circulation (flow $\times$ mean pressure drop, described as cardiac power output) assuming the left ventricle is the only significant power source in the circulation [67].

Cardiac power output is well preserved at rest, even with severe heart failure. The maximal reserve of car-

diac power output is reduced, however, and it can be studied during either maximal exercise or inotropic stimulation of the heart. Low maximal power output during inotropic stimulation is a poor prognostic sign [68]. Cardiac power output is a global measure, however, and tells us little of the mechanisms responsible. Ventricular filling or emptying or wasted myocardial power such as with aortic stenosis may be the predominant cause; and therapeutic interventions differ depending on the circumstances.

Attempts have been made therefore to define the components of ventricular function in order to explain the nature of reduced overall circulatory function. The difficulty lies in trying to separate the interacting components. There is no method that can measure the pure inotropic or diastolic (or "lusitropic") function of the myocardium of the heart independent of reflex control systems and the loading conditions of the circulation in the intact human. Even studies of isolated myocytes from patients with heart failure have led to differing conclusions about the relevant importance of inotropic dysfunction of the myocyte versus abnormalities in cardiac dysfunction due to the environment or cellular connections of the myocytes. Extrapolating these data to the intact patient with neuro-hormonal and reflex system abnormalities and altered ventricular loading conditions is orders of magnitude more complex, and attempts to do so may prove misleading or even futile. The alternative is to study the function of the integrated system and devise treatments based on the abnormalities detected by this approach.

Global cardiac function

Systole can be defined clinically, as the ejection phase between mitral valve closure and aortic valve closure, or in terms of ventricular dynamics as the phase of contraction of the myocytes within the ventricle. These two definitions do not coincide, as there is a period of isovolumic contraction at the onset of ventricular systole during which myocyte contraction generates a pressure increase within the ventricle and a conformational change in its shape but during which no blood is ejected. Similarly, during the latter phase of ventricular ejection the blood is flowing out of the left ventricle passively, and the myocardial elements may be already relaxing. Systolic dysfunction can be documented by abnormalities of the pressure or flow-generating properties of the left ventricle or by measurements of ventricular wall function. Useful haemodynamic measurements include the peak rate of pressure rise within the ventricle (positive dP/dt max), filling pressures, e.g., left ventricular end-diastolic pressure or pulmonary capillary wedge pressures, and measurements of ventricular volumes (by echocardiography, radionuclide ventriculography, or other imaging modalities). Although not a direct measure of ventricular performance, the ejection fraction (fractional emptying of the ventricle with each beat) carries information about ventricular volumes and global ventricular function. The left ventricular ejection fraction has proved to be the most

Origin of symptoms in heart failure

convenient global summary of systolic function when clinically evaluating the CHF patient [8].

Diastolic dysfunction of the heart can be quantified by a variety of measurements – haemodynamic, echocardiographic, radionuclear, ventriculographic – but overall objective measurements of diastolic function are more problematic than those of systolic function; no single global summary measurement is acceptable for routine clinical and research use [23]. The most commonly employed are the rate of constant of isovolumic relaxation of the ventricle during early diastole (τ), the early/late peak filling velocity ratio (E/A) across the mitral valve on Doppler echocardiography, and the peak rate of ventricular filling on radionuclear gated acquisition scans (in end-diastolic volumes per second). None of these parameters is independent of the loading conditions of the ventricle, atrio-ventricular delay, or heart rate, or the effect of systolic dysfunction. Pure diastolic dysfunction is rare, as indeed is pure systolic dysfunction, as the two are almost inseparably interdependent. One can speak, however, of cases where the heart failure is predominantly due to systolic or diastolic impairment of the ventricle. The simplest distinction is via the size of the end-diastolic volume; if it is large, systolic dysfunction is likely to be the major abnormality; if small, there is a diastolic problem. This differentiation is important because of differing effects of treatment, in particular vasodilators, which may be less useful for diastolic dysfunction because of the requirement for high ventricular filling pressures in this condition.

Circulatory function

Integrated function of the heart and blood vessels involves delivery of oxygen and elimination of carbon dioxide and other metabolic products of metabolism at a rate sufficient for resting or stressed metabolism, without excessively high filling pressures. Historically, cardiac output was measured, but it proved to be a poor discriminator between degrees of heart failure. In fact, during progressive exercise in heart failure the cardiac output may be near normal until the patient ceases exercise. Blood pressure, heart rate, peripheral vascular resistance, and ventricular filling pressures are important central haemodynamic parameters, but like cardiac output they only poorly describe the degree of limitation in a patient with CHF [25].

Non-cardiac patho-physiology

Although initiated by ventricular dysfunction, CHF as a clinical syndrome includes many characteristic patho-physiologic changes in other organ systems. The cause of many of the disparate organ pathologies that develop are poorly understood, as are the mechanisms by which these pathologies are corrected, often after some delay, by effective therapies. The genesis of the classic symptoms and the exercise limitation of patients with CHF may depend more on these changes than on a derangement of central haemodynamics [48].

Peripheral microvasculature

Changes occur in the microvasculature in many organ systems and may contribute to the organ underperfusion seen with this syndrome and are particularly important for renal, hepatic, and pulmonary vascular impairment [21, 72]. Structural changes in the microvasculature are subtle and remain poorly evaluated. We know more about the importance of functional endothelial deficiencies, such as impaired endothelial-dependent vasodilatation and exaggerated endothelial vasoconstrictor activity [69]. Therapeutically, little has developed to address these systems specifically, although endothelin receptor antagonists are under evaluation [60].

Large-artery function

Large-artery function is abnormal during heart failure owing to a combination of high sympathetic tone, increased activity of the local renin-angiotensin system within the arterial wall, and a high prevalence of atherosclerotic arterial disease in this population [42]. These changes decrease the compliance of the central aorta and large conduit arteries and reduce the efficiency of ventricle-aortic coupling. The net effect is increased impedance to ventricular output, which further worsens global cardiovascular function while at the same time increasing myocardial wall stress and oxygen consumption, possibly reducing effective myocardial blood flow. Direct-acting vasodilators do not specifically address these alterations, and other, more specific therapeutic interventions have not been developed; hence practical applications of our knowledge about these large-artery changes remain elusive.

Autonomic and neuro-endocrine systems

Many neuro-endocrine systems are activated during CHF [43]. Many of them evolved, in a teleologic sense, as a way of compensating for blood or fluid loss or sodium depletion; but during heart failure, although initially helping to support the circulation, continuous activation may be harmful [29]. Such systems include the renin-angiotensin-aldosterone system, sympathetic nervous system, vasopressin system, and the counteracting cardiac natriuretic peptide systems. Simultaneous with neuro-endocrine activation there is a reduction in vasodilator influences and vagal tone, which when maintained chronically may be harmful. Adverse consequences have been described, such as organ hypoperfusion, myocardial toxicity, and increased susceptibility to ventricular arrhythmias. These neuro-hormonal systems are so important to the development of the CHF syndrome that many experts consider neuro-endocrine activation to be an essential part of the recognition of the syndrome and an equally essential target of therapeutic strategies to improve the syndrome.

Renin-angiotensin-aldosterone system

With untreated heart failure there is mild activation of the renin system, which is dramatically augmented by the

Origin of symptoms in heart failure

first use of diuretics for treatment of the heart failure [5]. After that there is a reasonable relation between the severity of the heart failure and further increases in circulating renin and angiotensin II levels. The components of the circulating renin angiotensin system exist in tissue sites as well, and these local tissue systems are probably activated in the heart, kidney, brain, and blood vessel walls. Their role and effects in health and in the progression of heart failure have been proposed, and some of the beneficial effects of ACE inhibition stress how important these systems may be to the syndrome of CHF. The effects of activation of local systems in the kidney can cause either preservation or reduction of the glomerular filtration rate depending on whether the glomeruli are already dependent on angiotensin II mediated efferent arteriolar constriction to maintain an adequate filtration pressure in Bowman's capsule. Such dependence can be seen with bilateral renal artery stenosis. In the heart local increases in angiotensin II can cause coronary vasoconstriction and toxic effects on the myocytes, and in the periphery local angiotensin activation can contribute to vasoconstriction and abnormal large-artery function. This constitutes the patho-physiological basis for the therapeutic indication also for angiotensin II receptors inhibitors in CHF treatment: no definitive and clear indications are still available, besides the use in those patients where ACE-inhibitors are not tolerated [34].

Autonomic nervous system

The persistent overactivity of sympathetic discharge and the concomitant reduction in vagal tone are seen early in the progression of heart failure due to mild asymptomatic left ventricular dysfunction and are enhanced by the administration of diuretics. Our understanding of these systems and their importance to the syndrome is limited by the lack of clear methods of quantitation, so we are often left with indirect estimates, such as circulating levels of plasma norepinephrine, as an indirect estimate of the highly complex regional sympathetic nerve discharge pattern in a patient with heart failure. There is no clear mechanism for either activation of the sympathetic system during mild heart failure or its persistence and increase during the chronic syndrome. Understanding of the sympatho-excitation of CHF requires an appreciation of the excitatory and inhibitory inputs to the sympathetic nervous system [24]. These inputs are predominantly the cardio-pulmonary reflex systems, arterial baroreflex, low-pressure receptor systems, and arterial and central chemoreflexes. Most attention has been devoted to chronic loss of an inhibitory input from the arterial baroreflex. With asymptomatic left ventricular dysfunction or mild heart failure, no perceptible change in blood pressure occurs at a stage when sympathetic activation commences; even complete denervation of the baroreceptors does not lead to such persistent sympatho-excitation as is seen with CHF. Hence the baroreflex system alone does not seem to explain the persistent sympatho-excitation. Two other

candidate reflex systems are excitatory, and both are overactive during heart failure: the skeletal muscle ergoreceptor system [47] and the arterial chemoreflex system [13]. Both the ergoreflex and the chemoreflex cause sympathetic activation and may be abnormal throughout the progression of CHF, as discussed below. Analysis of heart rate variability has identified characteristic harmonic oscillations in cardiovascular parameters, the relative oscillatory power of which shows promise for estimating sympatho-vagal balance. The pattern during heart failure is abnormal with a dramatic reduction in total heart rate variability and a selective loss of the higher frequency (predominantly vagally mediated) rhythm characteristic of respiratory sinus arrhythmia and relative preservation of low frequency and very low frequency rhythms. The latter have their genesis more in the action of the sympathetic system (low frequency) and renin-angiotensin or chemoreflex system (very low frequency) [26, 54]. Analysis of total heart rate variability and, in particular, individual frequency components has shown that the pattern seen with heart failure is one associated with high risk for the development of unstable ventricular arrhythmias and cardiac sudden death: a causative role of hypersensitivity of peripheral neural reflexes has been implicated by us [53].

With chronic sympathetic activation there is a depletion of myocardial catecholamine stores and down-regulation of beta-1 receptors on the myocardium. There is also decoupling of receptors from the post receptor response, all of which lead to a loss of myocardial response to increased sympathetic drive. Clinically, it manifests as chronotropic incompetence, loss of response to sympatho-mimetic stimulation, and further impaired exercise tolerance. Specific treatments are few, but there has been some improvement after beta-blockade, ACE inhibition, and even short-duration, intermittent sympathomimetic stimulation [3].

Natriuretic peptide systems

The atria and ventricles contain granulated cells that release peptides, atrial natriuretic peptide (ANP or ANF), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) in response to stretch or volume distension. These peptides are weak natriuretic agents that also relax the peripheral vasculature and thereby mildly oppose the actions of the sympathetic and renin-angiotensin systems. The levels of these hormones reflect the degree of cardiac enlargement, but they appear to be too weak as vasodilators or natriuretic agents in their own right to be useful therapeutically. They may have an interesting role in the differential diagnosis of congestive heart failure [40].

Other hormonal systems

Vasopressin (antidiuretic hormone, or ADH), a hormone released from the posterior pituitary gland, has a role in free water handling by the distal convoluted tubule in its passage through the hypertonic renal medulla and

Origin of symptoms in heart failure

has a direct vasoconstrictor effect on the peripheral systemic resistance vessels. It is found in elevated plasma concentrations in patients with CHF, but its importance to the patho-physiology of the syndrome remains uncertain.

Abnormalities have been described in several other hormonal systems during CHF, but the significance of these changes is uncertain. Thyroid hormone handling in the cells is deranged, with an increase in reverse T3 similar to that seen with the "sick euthyroid syndrome" [49]. Plasma insulin levels are increased during heart failure, whether of ischaemic, valvular, or idiopathic aetiology; and the increases are associated with decreased sensitivity to the glucose transport effects of insulin. Alterations in sex hormones and growth factors are seen with advanced cardiac cachexia, leading to a loss of anabolic function (or resistance to their effects) and activation of catabolic systems.

Kidney

The kidney is of major importance during heart failure for understanding the development of the symptoms. The kidney is only partly a passive organ responding to neuro-endocrine activation outside its control; it is also an active endocrine and autocrine organ that responds to the reduced renal perfusion pressure during heart failure. The juxtaglomerular apparatus adjacent to the distal convoluted tubule senses the reduction in the rate of delivery of sodium to the distal tubule and releases renin in response. This action is an important part of the activation of the circulating renin-angiotensin system described above. The homeostatic role of this system is that blood flow is diverted to the kidney, the glomerular filtration rate (GFR) is increased, and there is increased active reabsorption of sodium. Angiotensin II has additional effect on thirst and possibly salt hunger, which completes the response, ensuring an increase in salt and water intake.

The components of the renin-angiotensin system also exist within the kidney, and there can be local autocrine activation, which can have important effects on intrarenal haemodynamics. These effects may either increase or decrease the GFR depending on the level of renal perfusion pressure and other factors operating on the kidney, such as the renal sympathetic nerves and circulating vasoactive factors.

Lungs and respiratory system

Despite the frequency of dyspnoea as the central complaint of a patient with heart failure, relatively little is known of the role of the lung and the abnormalities of ventilatory control in symptom generation during CHF. With acute heart failure, changes within the lung are profound and easily explain much of the acute respiratory distress of the syndrome.

Few changes are detected in the lung histology of well diuresed and non-oedematous CHF patients. The changes of pulmonary siderosis seen with chronic untreated mitral stenosis are not seen with well treated CHF. Even pulmonary venous pressures may be normal

if diuretic treatment is effective. The question of lung function in CHF remains controversial. Some authors report a reduction in oxygen-diffusing capacity, suggesting an alveolar-arterial block to oxygen transfer [57], whereas others find oxygen transfer to be nonlimiting and that arterial oxygen desaturation during exercise is rare with otherwise uncomplicated CHF [14]. Similarly, although intermittent, non-asthmatic bronchial constriction has been reported by some authors and even made a target for therapeutic intervention [12], in a detailed evaluation of well diuresed patients we could find no excessive broncho constriction or bronchial reactivity over that seen in a carefully matched control group. An increase in deadspace ventilation has been reported, thought by some to account for the exaggerated ventilatory response to exercise by patients with CHF [63]; but there is no anatomic substrate for this explanation. It may be a functional abnormality related to abnormal ventilatory control rather than a primary defect in the lung or pulmonary circulation.

One patho-physiologic change that can lead to respiratory distress is an alteration in the volume, structure, strength, and fatigability of the respiratory musculature. Early muscle de-oxygenation, respiratory muscle fatigue, and histologic changes have been described [37], and they may contribute to the sensation of dyspnoea. Whether these abnormalities can explain the excessive ventilatory response to exercise remains unknown. Whatever the cause, the increased ventilatory response to exercise appears to be an important abnormality in CHF, with a close correlation to objective measures of exercise intolerance [11].

Ventilatory control

The mechanisms of normal respiratory control during exercise are not fully understood, nor are the mechanisms underlying the abnormal respiratory response seen with CHF. Patients with heart failure, even in the absence of pulmonary oedema, have an increased ventilatory response to exercise while maintaining normal arterial blood gas tensions. They show reduced maximal oxygen consumption, early dependence on anaerobic metabolism, and an increased ventilatory equivalent for carbon dioxide even at low work levels. The latter feature can be best appreciated by the plot of minute ventilation (V_E) against CO_2 production (VCO_2) during progressive exercise: the V_E/VCO_2 slope [15]. The relation is approximately linear for most subjects at least until near-maximal exercise, but its slope is significantly (up to three-fold) steeper throughout both aerobic and anaerobic levels of exercise in patients with CHF, and its steepness correlates closely with the reduction of maximal oxygen consumption. There are deviations from linearity in more severe heart failure cases [15].

Although often thought to be due to ventilation perfusion mismatch within the lung, causing excessive but noncontributory ventilation [63], there are flaws in this argument. The ventilatory compensation is excessive,

Origin of symptoms in heart failure

with arterial blood gases being normal or even supernormal during CHF so whatever is causing the hyperventilation cannot be sensing abnormalities in arterial blood gases. An alternative explanation is that there is enhanced sensitivity of ventilatory control mechanisms to progressive exercise during CHF. Two reflexes with enhanced gain in CHF patients are the arterial chemoreceptors and the muscle ergoreflex system [13, 47]. Either reflex abnormality could explain increased ventilation and abnormal sensitivity to dyspnoea during exercise. The ergoreflex system senses the metabolic state of exercising skeletal muscle and reflexly increases ventilation. It is sensed by small work-sensitive afferents and carried by small myelinated or unmyelinated nerve fibres [1]. These fibres are histologically inseparable from pain fibre afferents, and it is possible that they serve a sensory as well as a reflex function, perhaps mediating to some extent both the sensation of fatigue and the exaggerated ventilatory and cardiovascular reflex responses to exercise. Overactivity of these fibres and the resultant reflex responses has been described for CHF [56].

Other overactive ventilatory control systems in CHF are the arterial and central chemoreflex systems [13]. We have described augmentation of peripheral hypoxic and central CO₂ sensitivity in CHF patients. These alterations could explain the heightened ventilatory responses and could lead to excessive sympathoexcitation. The cause of the heightened chemosensitivity itself remains undetermined, but it is possible that there is central augmentation of the handling of chemoreflex inputs or peripheral interaction and positive feed-back from other reflex overactivity [55].

Oscillatory ventilatory pattern

The presence of oscillatory breathing pattern in CHF has been described in CHF patients, occurring both during day-time and sleeping state [50]: its presence has been associated with poor prognosis (Figure 1) [32, 52].

Detailed sleep physiology studies have revealed that dips in oxygen saturation in CHF patients, often to below 80-85 percent, are not uncommon [9] despite the

relative rarity of exercise-induced desaturation, mentioned above. These episodes coincide with episodes of apnoea and often follow episodes of relative hyperventilation [41]. The episodes are followed by semiarousal from sleep and hyperventilation, which may awaken and frighten the sleeping partner. The pattern is reminiscent of the Cheyne-Stokes respiratory pattern, which is well recognised in severe heart failure. The mechanisms of both abnormalities of respiratory rhythm are incompletely understood, but their detection in CHF during sleep suggest that the ventilatory control is abnormal, rather than it being a structural obstructive sleep apnoea seen in obese patients with sleep disorders. The central abnormality may be an alteration in the central sensitivity to carbon dioxide, so oscillating levels of the respiratory drive and hence arterial oxygen saturation develop. A possibly related finding is that patients with CHF exhibit reduced total and high frequency heart rate variability but a relatively enhanced variability of heart rate at very low frequencies (< 0.01 Hz, or 1 cycle every 100 seconds), a specific rhythm we have shown to be related to hypoxic chemosensitivity and that can be abolished by supplemental oxygen. Several features of this very low frequency rhythm suggest that chemoreflex activity may play a role in its genesis. (Figure 2) First, the rhythm is particularly prominent during heart failure, where circulation time is long. Second, it has a frequency similar to that of the more obvious rhythm of Cheyne-Stokes breathing. Third, the chemoreflex loop has sufficient delay characteristics and sufficient interactions with the baroreflexes and control of heart rate for a harmonic of oscillatory arterial gas concentrations to set up a similar harmonic oscillation in respiration, which would then entrain the heart rate via an effect of the baroreflex. Lastly, similar rhythms are particularly prominent in pulmonary arterial pressure tracing during heart failure. Thus it may be that periodic sleep apnoea, very low frequency rhythms of heart rate variability, and Cheyne-Stokes respiration may be reflections of harmonic oscillations of chemoreflex-baroreflex interactions, a finding of particular importance given that it would lead to nocturnal surges of chemoreflex induced sympathoexcitation coinciding with profound arterial deoxygenation, a potent mix that would allow opportunistic ventricular arrhythmias to develop. The promising reports of nocturnal oxygen supplementation and of nasal positive-pressure ventilation for treatment of CHF may support this contention [26, 53, 54].

Respiratory muscle function

Respiratory muscle is abnormal in CHF. Early muscle deoxygenation, respiratory muscle fatigue, and histologic changes have been described [37] and may contribute to the sensation of dyspnoea (Figure 2). Whether these abnormalities can explain the excessive ventilatory response to exercise seen frequently in CHF patients remains unknown. Whatever the cause, the increased ventilatory response to exercise appears to be an

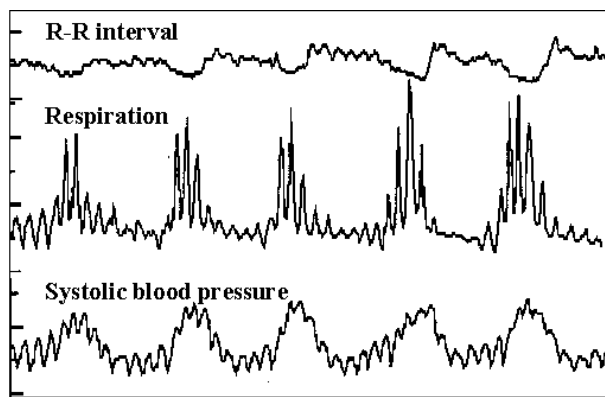


Figure 1. Recordings of R-R interval, respiratory and systolic blood pressure in a heart failure patients with oscillatory breathing pattern during sleeping.

Origin of symptoms in heart failure

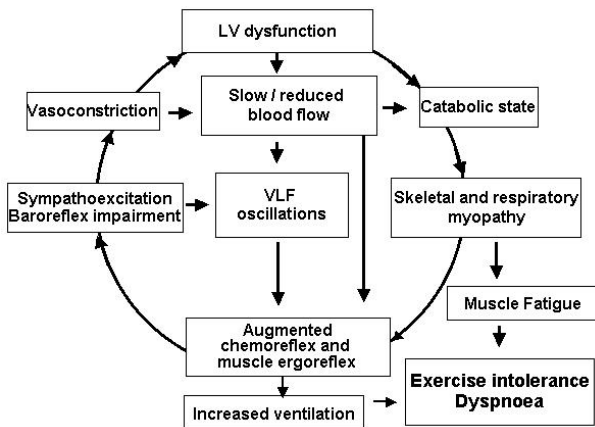


Figure 2. Origin of the most common symptoms of heart failure (exercise intolerance and dyspnoea) according to the skeletal muscle hypothesis.

important abnormality in CHF, with a close correlation to objective measures of exercise intolerance [11].

Skeletal muscle

Patients with CHF can have markedly reduced exercise tolerance and evidence of early muscular lactate release despite normal skeletal muscle blood flow [73]. An inherent defect in skeletal muscle metabolism independent of blood flow has been described in association with this condition along with many reports of abnormalities in histology, mitochondrial structure and function, oxidative enzymes, and a shift in fibre type distributions [38, 62]. Metabolic abnormalities have also been described, including early dependence on anaerobic metabolism, excessive early depletion of high energy phosphate bonds, and excessive early intramuscular acidification. Biopsy studies have confirmed defects in oxidative and lipolytic enzymes, succinate dehydrogenase and citrate synthetase, and, α -hydroxyacyl dehydrogenase. Muscle also has abnormal gross function, showing in particular early fatigability and reduced maximal strength [51].

Muscle ergoreflex effects

The muscle ergoreflex system is a system of small, free receptor endings within skeletal muscle that connect to group III and IV small myelinated or unmyelinated fibres that travel in the lateral spino-thalamic tract to the brain stem. This receptor/reflex system contributes to the reflex cardiovascular responses that support and augment the early circulatory adjustments to the onset of muscular exercise, such as a vasoconstrictor sympathetic output to non exercising muscle vascular beds. It has long been known that this system can mediate the sympatho-excitatory and vasoconstrictor responses to exercise [1], but they also play a role in generating and maintaining the early ventilatory responses. We have demonstrated the importance of this system to ventilatory control in normal subjects and in patients with CHF. Furthermore, we have demonstrated a dramatically enhanced dependence on this system during heart

failure, possibly explaining the exaggerated ventilatory response during heart failure [47]. The abnormalities of muscle in this syndrome means that there is an early and exaggerated build up of metabolites within the muscle, which could then stimulate the ergoreceptors and explain the heightened reflex responses. The potential importance of this reflex lies in its multiple effects. With chronic and repetitive recruitment of this exaggerated reflex there could be persistent and progressive sympathetic activation and persistently adverse loading conditions due to a diverse and persistent vasoconstrictor drive. Thus like the renin-angiotensin-aldosterone system, the muscle ergoreflex system could contribute to the progression of the syndrome by its dual effects on the load on the heart and the level of harmful neuro-endocrine activation. It has been proposed that skeletal muscle abnormalities during heart failure contribute to a vicious cycle of deterioration, coined the “muscle hypothesis” (Figure 2) [17]. The cause and most appropriate management of these muscle changes are uncertain. Physical inactivity is likely to play a role in some cases, along with activation of catabolic processes, loss of normal anabolic function (e.g., insulin resistance) [65], elevated levels of tumor necrosis factor, and excessive norepinephrine levels [6]. Anorexia and intestinal malabsorption may also play a role in some patients. We have demonstrated in the rat coronary artery ligation model of heart failure by use magnetic resonance spectroscopy that some of the metabolic disturbances of peripheral muscle (early high energy phosphate bond depletion and early acidification) can be completely avoided by regular exercise training commencing [6] weeks after the myocardial infarction [10]. In humans with CHF we have demonstrated partial correction of these muscle abnormalities by exercise training [2].

Haematologic system

A reduced arterial haemoglobin content has been described during heart failure, possibly secondary to chronic bone marrow tissue hypoxia, and impaired renal function via a reduced erythropoietin production. It is possible that the reduction in haemoglobin is important for symptoms generation of impaired exercise tolerance and poor prognosis [66].

Reduced peripheral blood flow and habitually reduced exercise could predispose patients to venous thromboses, so the interactions of these conflicting complications could lead either to bleeding or to thromboembolic events. The use of aspirin or formal anticoagulation is common in CHF patients. The white blood cell count may be mildly elevated during heart failure as part of a generalised but poorly understood immune activation in this syndrome.

Liver and gastrointestinal tract

During heart failure the liver can be affected by increased venous back-pressure, an impaired arterial supply, and the metabolic complications of the syndrome.

Origin of symptoms in heart failure

The underlying process that leads to the heart failure (e.g., alcohol excess or haemochromatosis) can also affect it. The most common hepatic abnormality seen with CHF is congestion due to high right atrial pressure. Persistent venous engorgement can result in a noticeable increase in hepatic size, local tenderness, and minor derangement in liver function, varying from the common modest increases in transaminase levels to profound hepatic dysfunction, including loss of clotting factor production and impaired hepatic metabolism of drugs or alcohol. In more severe cases nausea and right hypochondrial discomfort develop, and in severe cases jaundice, impaired albumin and clotting factor production and malabsorption of fats may result. The nausea and malabsorption can worsen the catabolic state of the patient and can contribute to the wasting seen with cardiac cachexia. Intestinal malabsorption and bacterial overgrowth are common in those with severe heart failure when the intestinal mucosa becomes congested.

Cardiac valvular abnormalities are also associated with a high rate of intestinal angiodysplasia, which can lead to recurrent blood loss, a considerable management problem for a patient who requires anticoagulation. The combination of intestinal oedema, sluggish blood flow, and intestinal overgrowth allows endotoxic stimulation of lipopolysaccharide, which can set in motion a cascade of cytokine release, including tumor necrosis factor, which may itself be associated with muscle wasting, impaired endothelial-dependent blood flow, and an adverse prognosis. Like many systems in this complex syndrome, the integrated whole is far more complex than the isolated and apparently independent components.

Symptoms of Heart Failure

Dyspnoea versus fatigue

The two cardinal symptoms of CHF are dyspnoea and fatigue, and the classic physiologic explanation for their genesis describes different processes for each. It has long been taught that the dyspnoea results primarily as a manifestation of “backward” heart failure (i.e., increased ventricular filling pressures). This theory was based on the patho-physiology of acute heart failure, where increased left ventricular end-diastolic pressure as a result of systolic impairment produces an increase in left atrial and pulmonary venous pressures, which in turn eventually leads to pulmonary oedema. Even before fluid extravasation into the alveoli occurs, the increased pulmonary venous pressures can increase the stiffness of the alveolar wall and can reduce the effective area for gas exchange. It might also increase the resistance to airflow in the small bronchioles, although experimental evidence of this phenomenon is sparse. A hallmark of this theoretic construct is that pulmonary arterial or wedge pressures should increase, and this increase generates the sensation of dyspnoea at a fairly reproducible level of wedge pressure.

Numerous lines of evidence argue against this theory. The limiting symptom during progressive exercise in an individual can be altered by changes in the details of the exercise test. The use of a rapidly incremental exercise load leads more frequently to dyspnoea, whereas a slower workload leads to fatigue [33]. There appears to be no substantial difference in the level of pulmonary arterial and wedge pressures achieved, but the limiting symptom differs [17]. Second, studies of 24-hour ambulatory pulmonary arterial pressure monitoring in patients with CHF showed no significant relation between the levels of pulmonary arterial pressures achieved by various forms of exercise and the symptoms reported by the patients at the time [27]. In fact, the highest levels of pulmonary arterial pressure were seen during supine rest, when the patients were comfortable.

Lastly, we have compared the physiologic and clinical characteristics of patients limited by fatigue to those limited by dyspnoea on a standard incremental cardiopulmonary exercise test [16]. There were no significant differences in the clinical, haemodynamic, or functional characteristics between the two groups, leading us to propose that the patho-physiologic processes generating dyspnoea may have more in common with those generating muscle fatigue that we had previously imagined. Two alternatives have been discussed: (i) The same receptors that carry the sensation of muscular fatigue could also carry the sensory input perceived as dyspnoea; or (ii) The patients are experiencing an unpleasant sensation that is different from the conventional fatigue or dyspnoea perceived by a normal subject. This idea might help explain why, with deterioration during heart failure, fatigue and dyspnoea often worsen simultaneously and why, with improvement, they similarly disappear together: They may represent the same underlying patho-physiologic abnormality.

Fatigue

Impaired muscular blood flow, deficient endothelial function, and disordered skeletal muscle structure and function play an important role [20]. Fatigue within skeletal muscle depends on excessive build-up of metabolic products (including potassium, adenosine, lactate, and acid) within the extracellular space. This build-up has two effects. (1) It contributes to objective fatigue of the muscle itself and neuro-physiologic fatigue of the neuromuscular apparatus; and (2) it leads to the perception of fatigue by the cortex. The sensory endings that carry this sensation have not been characterised, but it is possible that they are similar or indeed identical to the receptors that carry the afferent part of the muscle ergoreflex described above. It is not difficult to understand why the CHF patient develops muscular fatigue. The extensive range of structural and functional abnormalities described for CHF could all produce early muscular fatigue. In addition, there may be a heightened sensory mechanism to carry the sensation of this muscular distress to the cortex. What is of interest is how this theory fits with what we

Origin of symptoms in heart failure

know about objective limitation to exercise. We have known for years that objective measures of cardiac output-left ventricular ejection fraction or central haemodynamics-correlate poorly with exercise tolerance in well treated patients with CHF. In contrast, several groups have reported strong correlations between exercise intolerance and objective independent measures of muscle function, such as those derived from magnetic resonance spectroscopy studies of in vivo metabolism [35] or structural measures of skeletal muscle bulk or maximal quadriceps strength, which predominantly reflects the bulk of the leg muscle [71]. In addition, the delayed improvement in exercise capacity after vasodilator, positive inotropic, or even cardiac transplant therapy suggests that a structural abnormality is being overcome; and muscle changes leading to muscular fatigue are prime candidates for this limiting factor (Figure 2) [59].

Dyspnoea

Dyspnoea is poorly understood in normal subjects despite our understanding its associations and features. It has been studied in chronic lung disease, and there remains little consensus as to the primary cause of dyspnoea in this setting [4]. It is likely that several candidate physiologic processes can be invoked, including the sensation of abnormal blood gases sensed via a chemoreceptor afferent input, a perception of the effort of ventilation, a mismatch between the desired level of ventilation and that achieved, and a feeling of difficult or restricted airflow arising from within the lung.

Despite many reviews, even less is known about the processes operative in the genesis of the dyspnoea associated with heart diseases, with the exception of the simple case of acute heart failure with pulmonary oedema described above. There is a good correlation between the level of achieved ventilation during progressive exercise and the perception of dyspnoea associated with that level of exercise effort. This correlation has led cardiologists to consider the control of ventilation during exercise as an objective measurement that tells us something about the patho-physiology of ventilatory control and the symptoms limiting the patients with CHF. A normal subject during progressive exercise below the level of anaerobic threshold increases the level of minute ventilation in proportion to the increasing rate of carbon dioxide production (the V_E/VCO_2 slope described above). The increased V_E/VCO_2 slope seen with CHF is closely correlated with objective limitation to exercise and appears to be a good surrogate for the patho-physiologic processes causing dyspnoea. Furthermore, in the presence of normal blood gases during exercise this increased slope suggests relative hyperventilation during exercise rather than an appropriate response to abnormalities of lung function, where we would expect some residual error signal and mild hypoxemia or hypercapnia on exercise. If anything, the opposite is seen: almost supernormal blood gases in patients with CHF. This finding led us to search for alternative ventilatory stimuli that may be exaggerated in

CHF. We have described two candidate control systems as having an increased gain: the muscle ergoreflex system and hypoxic chemosensitivity and central CO_2 chemosensitivity [13, 47]. Either could lead to an exaggerated ventilatory response to exercise in CHF patients. Of interest is the finding that both these reflex systems, in addition, are potent stimuli for activation of the sympathetic nervous system, so they may help explain the persistent sympatho-excitation that is so much a part of the syndrome of CHF.

Exercise limitation

In normal subjects, exercise is usually possible until maximal cardiac output is achieved; at which time a further increase in workload produces extra CO_2 but no increase in O_2 uptake. This condition is termed maximal oxygen uptake (VO_{2max}). At 85-95 percent VO_{2max} the anaerobic threshold is reached, where skeletal muscle begins to depend on anaerobic metabolism for the continued production of adenosine triphosphate. Despite much use of this quantity, it is doubtful that a distinct transition point from aerobic to anaerobic metabolism occurs.

In well treated patients with CHF who have no residual pulmonary congestion, exercise proceeds along normal lines with little difference in submaximal cardiac output but with an exaggerated ventilatory response even at low level exercise. Most patients with CHF fail to achieve their VO_{2max} , and it has been shown that in contrast to normal subjects the addition of arm exercise to a patient already performing maximal leg exercise leads to a further increase in the rate of O_2 uptake [30]. Hence O_2 delivery, and by extrapolation cardiac output, was not maximal during the maximal leg exercise test in the CHF patients. The limitation to exercise therefore appears to be peripheral: either the vasculature is unable to accept an adequate blood flow or the exercising muscle is unable to take up or metabolise O_2 efficiently. Both defects are present in patients with CHF, as discussed earlier.

Wilson et al. described a subset of patients in whom exercise was clearly limited by skeletal muscle metabolic inefficiency despite nonlimiting cardiac output and normal leg blood flow responses [73]. Distinguishing the effects of limiting blood flow from skeletal muscle limitation may to some extent be artificial, as the process of skeletal muscle wasting characteristic of CHF reduces the vascular conductance of the limb, leading to an apparently increased vascular resistance even with no change in endothelial function or vascular resistance tone. Although this situation does not reduce the potential importance of endothelial, vasodilatory, and large-vessel functional defects, it does highlight the importance of the pathologic skeletal muscle of this condition.

Implications for Treatment

Effective therapies for exercise tolerance and prognostic benefit have been established for heart failure. Foremost among them is the use of ACE inhibitors, beta-blockade, and aldosterone inhibitor. The mechanisms

Origin of symptoms in heart failure

underlying the reduction in mortality rate and the improved tolerance to exercise are unknown, but reduction of persistent and exaggerated neuro-endocrine activation appears important. There are some suggestions that peripheral actions are necessary for improved exercise tolerance. The increase in exercise tolerance with ACE inhibition is delayed and is closely related to improvements in skeletal muscle blood flow [19]. In the future we may look to therapeutic approaches for improving symptoms and exercise capacity that are different from those designed to enhance survival.

Exercise training prescriptions

Exercise training in carefully selected patients with stable, mild to moderate CHF can increase exercise capacity and lessen dyspnoea, fatigue [18, 22] and may improve survival [7]. Such improvement has been shown for asymptomatic left ventricular dysfunction and mild to moderate CHF with no consistent effect on left ventricular ejection fraction. Most of the beneficial effects seem to depend on training-induced adaptations in the periphery [31], but a potential benefit on myocardial perfusion has been reported [7].

In normal subjects training is known to be able to increase endothelial, large-vessel, and resistance vessel function [39]. During heart failure exercise training can reduce peripheral vascular resistance and increase skeletal muscle blood flow and endothelial function. Partial corrections of skeletal muscle abnormalities have been demonstrated after training in heart failure patients. Single-limb and whole-body training can improve histology, mitochondrial structure, oxidative enzymes, and metabolic function [51]. Training, particularly with a resistive training component, has the potential to stabilise or reverse skeletal muscle wasting [61]. These improvements may explain the reduction in muscular fatigue seen after training [28].

Specific respiratory muscle training has been reported for CHF patients that leads to improved exercise tolerance [36]. It may have a particular role of alleviating dyspnoea in these patients. Training has also been shown to alleviate some of the abnormalities of neuro-hormonal overactivity, including a reduction in norepinephrine spillover, an increase in the vagal high frequency component of heart rate variability, and a relative diminution in the more sympathetically mediated low frequency component [22]. These changes are all consistent with what is known of training effects in normal subjects, although the mechanisms, even in normal subjects, have not been fully established. Given the absence of effects on central haemodynamics and the prominence of peripheral training effects, it is possible that these autonomic training effects are secondary to skeletal muscle or peripheral vascular training effects. In this regard the finding that single-limb training has been shown to reduce the overactivity of the skeletal muscle ergoreflex has important implications [47]. It could explain the removal of a major sympatho-

excitatory influence as well as removing a stimulus to the exaggerated ventilatory response to exercise.

Conclusions

The symptoms limiting exercise performance in CHF patients appear to be related to alterations in the physiology of the periphery: skeletal muscle, endothelium, regional blood flow, and reflex cardiopulmonary control systems. These alterations may set in motion a vicious cycle of deterioration, involving catabolic activation and reflex neuro-hormonal overactivity, that may lead to progressive disease severity. Understanding the complex patho-physiology of the syndrome of CHF may allow us to develop novel therapeutic strategies for this complex but common condition.

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