CARDIOVASCULAR REGULATION IN CHRONIC HEART FAILURE

C. GUNNAR BLOMQVIST, M.D.

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Southwestern Medical School

University of Texas Health Science Center

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Chronic cardiac dysfunction with failure to provide a systemic flow sufficient to meet metabolic demands induces a complex set of regulatory and anatomical adaptations. Initially, these adaptations serve to enhance pump performance and to distribute optimally a reduced cardiac output. However, at some later stage, they often become counterproductive.

The primary purpose of this presentation is to review the interactions between cardiac and extracardiac adaptations. Exercise is included as a major topic for several reasons. Exercise - particularly in the sense of moving one's own body around - imposes greater demands on the cardiovascular system than other activities during daily life. It is the immediate cause of many of the symptoms and signs associated with chronic heart failure (CHF). Measurement of the amount of exercise (or the increase in metabolic rate) that is required to precipitate symptoms and signs provides an objective means of quantitating the degree of CHF. The cardiovascular system in the average young normal individual can support at least a 10-fold increase in metabolic rate, i.e. there is a 10:1 ratio between maximal and basal oxygen uptakes. This ratio approaches 1:1 in the Class IV patient.

The complexity of the adaptations to CHF makes it difficult to use simple descriptors of cardiac function as estimates of the severity of failure. Exercise capacity, which translates into the highest rate of oxygen transport that the cardiovascular system can sustain, provides a reasonable alternative. Maximal oxygen uptake reflects the combined impact of the primary cardiac lesion and the compensatory mechanisms. Exercise has also proved to be an important tool for the study of CHF in applications ranging from pathophysiology to evaluation of therapy.

Natural history.

Chronic heart failure is a major health problem. Gorlin (1983) has reviewed current data on incidence. There were in the United States in 1980 more than 400,000 hospital discharges with a diagnosis of CHF, corresponding to a rate of 1.8/1,000 population. The incidence of CHF increases with increasing age and is higher among men than women. Table 1 presents recent data from the Framingham study (Kannel et al., 1982).

Table 1. Annual Incidence of CHF.

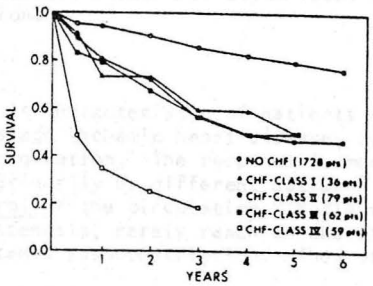
Data from a 20-year follow-up study in the Framingham population (Kannel et al., 1982).

	RATE PER 1,000	
AGE	MEN	WOMEN
45-54	1.8	0.8
55-64	4.3	2.7
65-74	8.2	6.8
Total	3.7	2.5

Hypertension was identified as the dominant precursor of CHF. Definite hypertension was documented in 75% of all subjects prior to the onset of CHF. Concurrent hypertension was the rule also in those subjects who had coronary or rheumatic heart disease. Clinical series are likely to show different distributions, reflecting special interests and facilities. Sixty-five per cent of the patients in Cohn's (1982) referral population had significant coronary artery disease. The remaining 35% represented a mixture of alcoholic and other forms of cardiomyopathy and corrected valvular lesions. Patients with angina or correctable valve disease were excluded.

Two-year survival in Cohn's series of patients, mostly with severe CHF, was only 30%. The Framingham data (Kannel et al., 1982) are less alarming with a 2-year survival rate of 70% in men and 75% in women. The corresponding 8-year rates were 20 and 35% with little or no difference between patients with and without coronary disease. Califf et al. (1982) have analyzed a large series of patients with coronary disease and CHF, who had been studied at Duke University. The prognosis was similar among patients in NYHA Functional Classes I-III with 2-year survival rates of about 70% compared to 25% in Class IV patients (Fig. 1).

Figure 1.



Survival probabilities in 236 patients with CHF and coronary disease according to NYHA Heart Failure Class compared 1728 patients with no history of congestive heart failure.

From Califf et al. (1982).

Pathophysiology of CHF - Overview.

Multiple compensatory mechanisms are activated in CHF (Zelis et al., 1981; Zelis and Flaim, 1982). The progression may be viewed as having three phases:

1. Maintenance of cardiac output.

   A reduction in contractile performance and stroke volume is compensated for by relative tachycardia and increased heart size with ventricular dilatation and hypertrophy. Ventricular filling is enhanced by fluid retention and blood volume expansion. Cardiac output is adequate, at least at rest.

2. Maintenance of arterial pressure and perfusion of critical organs.

   The mechanisms listed under (1) continue to be operative during Phase 2 but cardiac output can no longer be maintained at normal levels. Vasoconstriction is the hallmark of the second line response which serves to distribute optimally a reduced cardiac output. Perfusion of the brain and myocardium is maintained at the expense of the renal, splanchnic and cutaneous circulations, particularly during exercise. Both neurogenic (alpha-adrenergic) and humoral (circulating catecholamines, angiotensin, vasopressin) mechanisms contribute. Vasoconstriction may also be enhanced by structural changes in the resistance vessels (increased salt and water content of the arteriolar walls).

3. Inappropriate vasoconstriction.

   At some point, the degree of vasoconstriction becomes inappropriate. The failing ventricle faces an increased resistance to ejection, i.e. increased aortic impedance. Stroke volume and cardiac output decrease. A vicious circle is established in which increased vasoconstriction leads to further ventricular dysfunction.

This sequence is characteristic of patients with chronic congestive heart failure, e.g. end-stage ischemic heart disease, congestive cardiomyopathy, or chronic mitral regurgitation. The response is modified in certain other forms of heart disease, primarily by different patterns of ventricular hypertrophy and of neurogenic control of the circulation. Patients with severe pressure overload, e.g. aortic stenosis, rarely reach an end-stage characterized by ventricular dilatation and systemic vasoconstriction. They often succumb to sudden death.

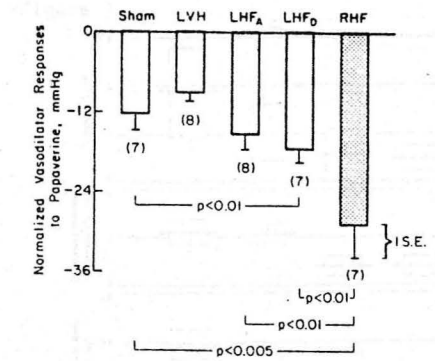
Lesion-specific differences in the rate of afferent impulse traffic originating in arterial and cardiac receptors affect hemodynamic conditions. The carotid and aortic baroreceptors and the cardiopulmonary receptors, including receptors in the ventricular wall, respond to distension with increased impulse flow. This activation of the receptors produces sympathetic inhibition with bradycardia, decreased contractile state, and vasodilatation. Increased vagal tone contributes to the bradycardia. Decreased wall tension and degree of deformation of the receptors, as with falling arterial pressures or decreased cardiac chamber size, cause increased sympathetic outflow with tachycardia and vasoconstriction.

Activation of arterial and ventricular baroceptors with reflex-induced sympathetic inhibition explains the vasodilatation that occurs in certain forms of heart failure. This mechanism has been referred to as endogenous impedance (or afterload) reduction (Zelis and Flaim, 1982). Systemic vasodilatation is often present in slowly progressing chronic aortic regurgitation that is associated with a wide arterial pulse pressure and a rapid rate of change in arterial

pressure during ejection. A reflex-induced dilator response may also occur during the early phase of CHF when fluid retention and blood volume expansion have produced cardiac enlargement and activated atrial and ventricular receptors. Activation of ventricular receptors by deformation may also be responsible for the vasodilatation and bradycardia that sometimes is seen in acute myocardial infarction, particularly inferior infarction. The ventricular receptors are concentrated to the inferoposterior left ventricular wall.

Schmid et al. (1981) have demonstrated (Fig. 2) that non-neurogenic vasoconstrictor mechanisms, e.g. increased vascular responses to circulating norepinephrine, angiotensin, and other vasoconstrictor agents, dominate in right heart failure (RHF) produced by banding of the pulmonary artery.

Figure 2.



Nonneurogenic control of peripheral circulation assessed by vasodilator responses to papaverine.

From Schmid et al. (1981).

On the other hand, neurogenic mechanisms are preeminent in left heart failure caused by banding of the ascending aorta (LHF_A). Reduced arterial baroceptor stimulation with a reflex-induced increase in sympathetic activity in aortic but not in pulmonary artery constriction is the likely explanation.

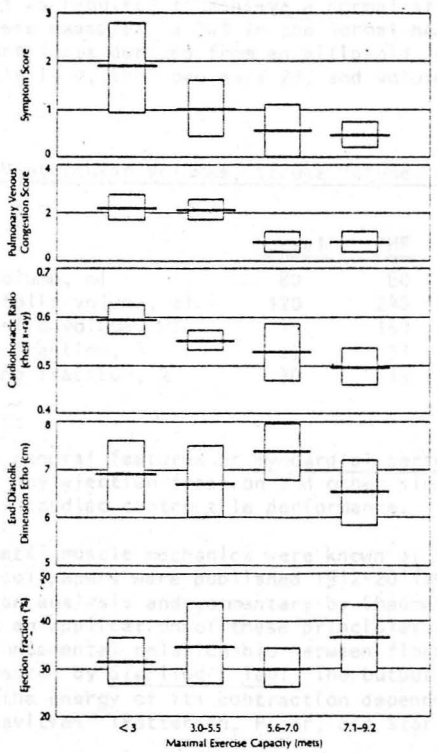
The modulating effects of the arterial and cardiopulmonary receptors are attenuated with progression of CHF. Decreased activity of the cardiac afferent nerves is a feature of late CHF (Abboud et al., 1982).

Determinants and descriptors of cardiac pump performance.

In current clinical practice, ventricular ejection fraction (the ratio stroke volume/end-diastolic volume) is by far the most widely used of all indices of cardiac performance. Ejection fraction has many attractive features, including simplicity. Comparable measurements may be obtained with relative ease both during catheterization and non-invasively by radionuclide ventriculography or echocardiography. However, ejection fraction is by itself a poor index of ventricular contractile state and of the severity or the degree of impairment in failure.

Figure 3 is a summary of data from a series of patients with CHF studied at U.C. San Diego (Ross, 1983).

Figure 3.



Patients with severe cardiomyopathy were categorized for this study according to maximum exercise capacity on a treadmill. Neither exercise capacity nor symptom scores were well correlated with standard hemodynamic measurements. For instance, left ventricular ejection fraction calculated by first-pass radionuclide technique was consistently between 30% and 35% and not significantly different among groups, and the same was true of left ventricular end-diastolic dimension calculated echocardiographically. The degree of pulmonary congestion on x-ray and the cardiothoracic ratio correlated better with symptoms or exercise capability.

From Ross (1983).

Exercise capacity was used as a measure of the overall functional capacity of the cardiovascular system and ranged from $\geq$ 7 mets to $\leq$ 3 mets. Patients were divided into 4 classes. The classes corresponded to average exercise capacities of about 25, 50, 75 and 100% of normal. Left ventricular ejection fraction was similarly depressed in all groups at approximately 35%. Measurement of left ventricular end-diastolic diameter also showed no significant differences between groups but there were significant correlations between loss of exercise capacity and the severity of symptoms and the severity of pulmonary congestion.

Simple geometrical relationships limit the power of ejection fraction to serve as a comprehensive index of cardiac pump function. The normal left ventricular end-diastolic volume is about 120 ml. A typical ejection fraction of 67% produces a stroke volume of 80 ml. A two-fold increase in diastolic size enables a patient with myocardial dysfunction to achieve a normal 80 ml stroke volume at an ejection fraction of only 33%. The effect of increased chamber size becomes even more dramatic when viewed in terms of the degree of circumferential fiber shortening that is required to achieve a normal stroke volume. Fractional shortening in these examples is 30% in the normal heart compared to only 13% in the dilated heart (data derived from an ellipsoid left ventricular model in which the short axis is d, the long axis 2d, and volume approximates d^3 (Pombo et al., 1971).

Table 2. Relation Between Ventricular Volumes, Stroke Volume, and Fiber Shortening.

	Normal	CHF
Stroke volume, ml	80	80
End-diastolic volume, ml	120	240
End-systolic volume, ml	40	160
Ejection fraction, %	67	33
Shortening fraction, %	30	13

A consideration of the general features of myocardial performance will also make apparent other reasons why ejection fraction and other simple variables are unable to measure accurately cardiac contractile performance.

The principles of skeletal muscle mechanics were known at the turn of the century. Starling's classical papers were published 1912-20 (and are available in facsimile reprints with an analysis and commentary by Chapman and Mitchell (1966)). They are based on an application of these principles to the analysis of cardiac function. The fundamental relationship between fiber length and cardiac performance is expressed by Starling's law: "The output of the heart is a function of its filling, the energy of its contraction depends on the state of dilatation of the heart's cavities" (Patterson, Piper, and Starling, 1914).

Figure 4a shows a Starling curve taken from the 1914 paper by Patterson and Starling. Right atrial pressure (isolated dog heart preparation) is given as a function of cardiac output. Reversal of the ordinate and abscissa produces the more familiar form of the function curve (Fig. 4b). Note that there is a prominent descending limb at high right atrial pressures. Patterson and Starling identified the responsible mechanisms: increased arterial pressure with increasing resistance to ejection at high filling pressures and increasing diastolic stiffness with little change in fiber length with further increases in right atrial pressure. In addition, the A-V valves eventually become incompetent with mitral and tricuspid regurgitation.

Figure 4a.

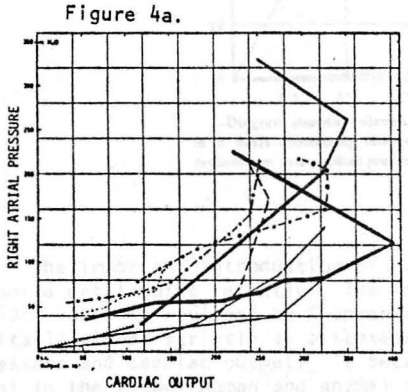


Figure 4b.

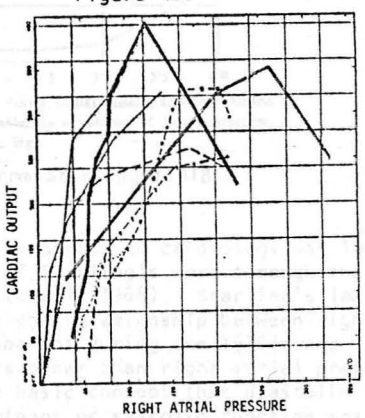
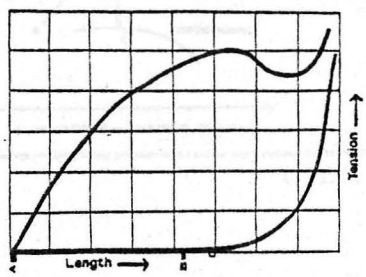


Figure 4. Relation between right atrial pressure and cardiac output. A. Original, B. X- and Y-axis reversed.

From Patterson and Starling (1914).

Starling also (Patterson, Piper, and Starling, 1914; Starling, 1918) applied to the intact heart the basic length-tension relationship that Blix (1895) had described in isometrically contracting isolated skeletal muscle (Fig. 5).

Figure 5.

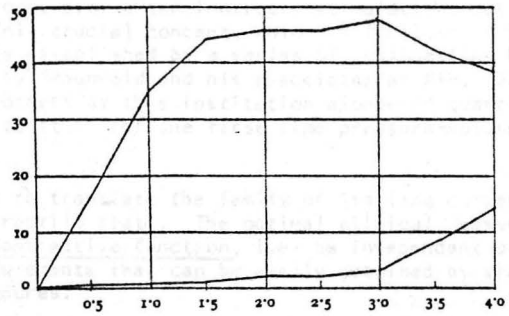


Curve showing the relation of tension, initial length, and energy evolved in isometric twitch. (Drawn from the results of one of Blix's experiments. *Skand. Arch. f. Physiol.* v, Tab. VI, Fig. 4.)
A = Condition of maximum shortening.
B = Position of maximum length of muscle in the body.

From Starling (1918).

This was translated into the ventricular volume-pressure relationship (Fig. 6), which now is the principal framework for the analysis of ventricular function. Similar concepts had been developed by Frank in Germany and Starling used Frank's data in a pressure-volume diagram.

Figure 6.

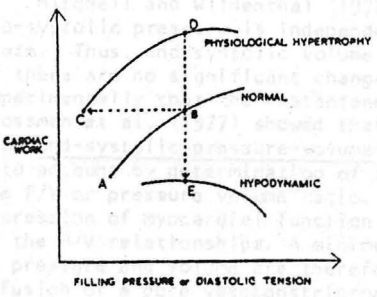


-Diagram showing relation between filling, initial tension, and final tension in a heart contracting isometrically (abscissa = volume of heart contents, ordinates = intracardiac pressure in mm. Hg).

From Starling (1918).

The important introduction of muscle mechanics to cardiology was largely ignored until quite recently. The impact of Starling's work through the mid 1960's has been reviewed by Chapman and Mitchell (1966). Starling's law was initally viewed strictly as a statement of the relationship between right atrial pressure and cardiac output. It became apparent during the 1930's and 1940's that in the intact human and animal factors other than right atrial pressure have major effects on cardiac output. The basic concept that diastolic fiber length is a principal physiological determinant of systolic function was rejected. Resurrection began when McMichael (1952) suggested on theoretical grounds (Fig. 7) and Sarnoff and Berglund (1954) experimentally showed (Fig. 8) that the relationship between diastolic fiber length and systolic performance is characterized not by a single curve but rather by a family of Starling curves.

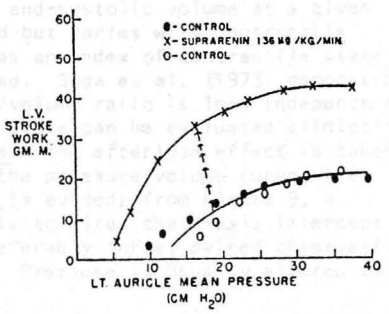
Figure 7.



Curves relating filling pressure and cardiac work devised by McMichael.

(1952).

Figure 8.



Ventricular function curves from Sarnoff and Berglund.

(1954).

The function relating end-diastolic pressure to stroke work may change with experimental conditions, e.g. after inotropic stimulation, but its basic shape remains the same. This crucial concept, which is implicit in Starling's series of papers, was firmly established by a series of publications by Sarnoff's group and extended to man by Braunwald and his associates at NIH. Drs. Chapman, Mitchell, Bonte and others at this institution pioneered quantitative ventriculography and were able to study for the first time pressure-volume relationship in the intact heart.

It is difficult to translate the family of Starling curves into a clinically useful index of contractile state. The optimal clinical measurement should describe intrinsic contractile function, i.e. be independent of loading conditions, and be based on measurements that can be easily obtained by standard clinical techniques and procedures.

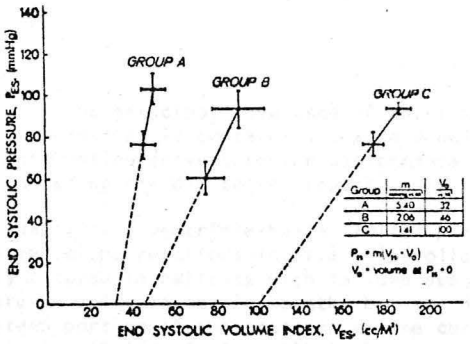
A large number of simple and composite measurements of cardiac performance, derived during the isovolumic phase of contraction or during ejection, have been described but no satisfactory simple expression of intrinsic contractile state has been found (Grossman, 1982).

Approaches to the clinical evaluation of ventricular function include isovolumic phase indices such as dp/dt (rate of change of ventricular pressure), dp/dt at a given pressure, and $d\sigma/dt$ (rate of change of wall stress). All these measurements require high-fidelity recording systems. Only measurements of the rate of wall stress development, which requires simultaneous accurate measurements of pressure, chamber radius, and wall thickness, accurately reflects intrinsic contractile state if the basic requirement of load independence is made more stringent by requiring also independence of muscle mass.

Ejection phase indices, among which are ejection fraction, mean normalized systolic ejection rate, and velocity of circumferential fiber shortening are markedly sensitive to afterload and also, to some extent, to preload (Grossman, 1982). However, mean velocity of circumferential fiber shortening, which can easily be derived by echocardiographic techniques, is independent of preload (Nixon et al., 1982).

Mitchell and Wildenthal (1972) noted that end-systolic volume at a given end-systolic pressure is independent of preload but varies with contractile state. Thus, end-systolic volume may be used as an index of contractile state if there are no significant changes in afterload. Suga et al. (1973) demonstrated experimentally that the instantaneous pressure/volume ratio is load independent. Grossman et al. (1977) showed that contractile state can be evaluated clinically from end-systolic pressure-volume relationships. The afterload effect is taken into account by determination of the slope of the pressure-volume curve, i.e. the P/V or pressure volume ratio. However, as is evident from Figure 9, a depression of myocardial function is also likely to alter the X-axis intercept of the P/V relationships. A minimum of two, preferably three, paired observations of pressure and volume are therefore required. Pressure is usually altered by infusion of a pure vasoconstrictor agent.

Figure 9.



Average values for left ventricular end-systolic volume and pressure at two levels of systolic load are plotted for subjects with normal contractile function (group A, ejection fraction ≥ 0.60), intermediate function (group B, ejection fraction = 0.41–0.59), and poor contractile function (group C, ejection fraction ≤ 0.40). Points represent average values for pressure and volume from table 1, and brackets indicate standard errors of the means. Volumes are indexed for body surface area in square meters (m^2).

From Grossman et al. (1977).

The development of radionuclide angiography has made it feasible to determine non-invasively pressure-volume relationships. Peak systolic pressure is taken as a measure of end-systolic pressure. Measurements of the P/V ratio during exercise have proved to be a useful predictor of prognosis in ischemic heart disease (Corbett et al., 1981) but this P/V ratio expresses manifest rather than intrinsic contractile state. Intrinsic or basal contractility is modulated by inotropic stimulation (beta-adrenergic activation) and also by the development of ischemia.

Major conceptual advances in the analysis of the function of the intact heart followed the introduction of instantaneous ventricular pressure-volume diagrams (Suga and Sagawa, 1974; Sagawa, 1978; Weber and Janicki, 1977; Weber et al., 1982). An example is shown in Figure 10.

Figure 10.

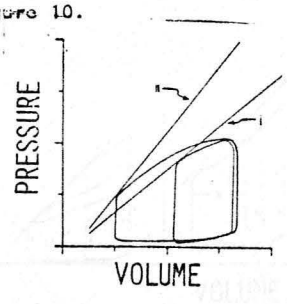


Figure 10. Left ventricular pressure-volume relationships in a normal subject (n) and a patient with ischemic heart disease and depressed myocardial function (i). The line defining the maximal end-systolic pressure that can be achieved at any given volume also defines contractile state. Downward and rightward displacement characterizes depressed contractility. The four corners of the loop represent (clockwise from upper left) end-systole, onset of ejection, end-diastole, and onset of diastolic filling. The distance between the two vertical limbs equals stroke volume. Diastolic pressure/volume characteristics are also defined. They are non-linear with a progressively larger increase in pressure for any further increase in volume.

From Weber and Janicki (1977).

The principal advantage of the instantaneous pressure-volume loop is that it contains within a single frame most of the essential information on ventricular performance and its determinants, including the diastolic properties of the heart.

The failing ventricle has a limited pre-load reserve. The basic diastolic pressure-volume relationship, i.e. diastolic stiffness, is usually not significantly altered in patients with failure due to volume overload or loss of myocardial cells in cardiomyopathy but the heart is likely to operate on or near the steep portion of the pressure-volume curve. This means that any increase in ventricular filling is less likely to produce a significant increase in fiber length and performance and more likely to cause symptoms and signs of congestion. Increased diastolic stiffness is a prominent feature of the hypertrophy induced by pressure overload and often is a major factor limiting stroke volume (Grossman, 1982).

An increased contractile state, e.g. after beta-adrenergic stimulation, is manifest as an upward and leftward displacement of the line defining end-systolic pressure-volume relationship. A higher end-systolic pressure can be developed from any given end-systolic volume. There is an increase in slope, intercept, or both. A depressed contractile state is reflected by a downward and rightward displacement.

Figure 11 diagrams the methods by which stroke volume can be increased: (1) Decreased afterload or end-systolic pressure, (2) Increased preload or end-diastolic volume, and (3) Increased contractile state.

Figure 11.

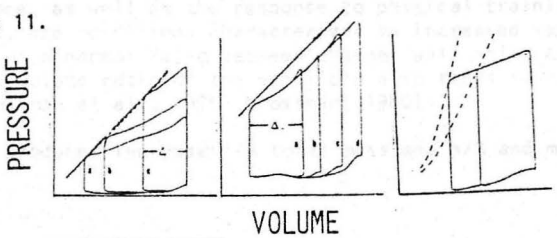


Figure 11. Effect of afterload/end-systolic pressure (left panel), preload (middle), and altered contractile state (right) on stroke volume (Δ volume).

Adapted from Weber et al. (1982).

As a whole, the instantaneous pressure volume relationship is the most satisfactory of the current approaches to the analysis of ventricular function but there are major limitations. The method is primarily conceptual and experimental. Only the analysis of the end-systolic pressure-volume relationship is readily applicable to clinical situations.

The stimulus to myocardial hypertrophy is more closely related to wall stress than to pressure. It is extremely difficult to quantitate accurately the forces developed by the intact heart. Average wall tension, which is balanced by the force produced by the myocardium, is a function of chamber size, shape, and pressure. The force exerted by any fiber will also vary with its orientation relative to the chamber. The myocardial muscle fibers are arranged in complex patterns. Total circumferential force is proportional to the product of chamber pressure (P) and surface area. Thus, the total force developed by a ventricle of a shape approximated by a hemisphere is proportional to $P \times \pi R^2$ where R is the internal radius.

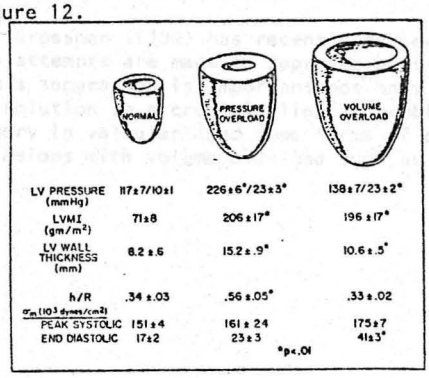
Wall stress is defined as force per crossectional area of myocardium. Circumferential wall stress is non-uniform across the thickness of the ventricular wall but a simplified model can provide some very important insights. A modification of LaPlace' law states that circumferential wall stress is directly proportional to the product of pressure (P) and internal radius (R) and inversely proportional to wall thickness (h):

$$\text{Wall stress} = P \times R/2h.$$

Chronic pressure or volume overload produces changes in wall thickness that tend to keep wall stress within normal limits. To maintain constant force per unit crossectional area, wall thickness has to increase in proportion to the increase in the product of pressure and volume. The normal growth during childhood and adolescence, as well as the response to physical training and chronic volume overload, are conditions characterized by increased ventricular chamber size and mass but a normal ratio between chamber wall thickness and radius (h/R). The mass/volume ratio of the ventricle also tends to remain normal (Ford, 1976; Grossman et al., 1975; Grossman, 1980).

Pressure overload produces increases in total mass and h/R and mass/volume ratios (Fig. 12).

Figure 12.



	NORMAL	PRESSURE OVERLOAD	VOLUME OVERLOAD
LV PRESSURE (mmHg)	117±7/10±1	226±6*/23±3*	138±7/23±2*
LVMI (gm/m^2)	71±8	206±17*	196±17*
LV WALL THICKNESS (mm)	8.2±.6	15.2±.9*	10.6±.5*
h/R	.34±.03	.56±.05*	.33±.02
σ_m (10^3 dynes/cm²) PEAK SYSTOLIC	151±4	161±24	175±7
END DIASTOLIC	17±2	23±3	41±3*

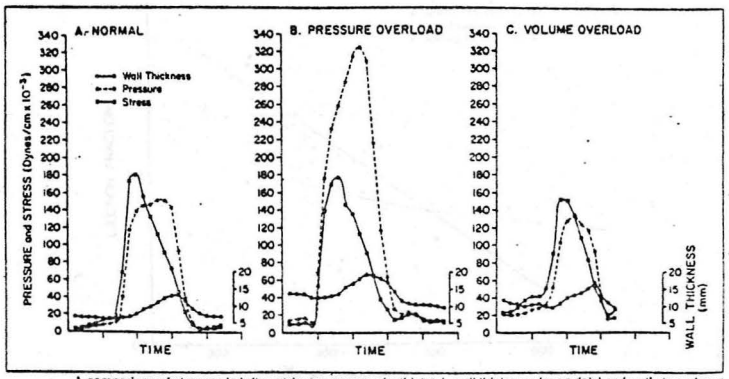
*p<.01

Left ventricular (LV) pressure, left ventricular mass index (LVMI), wall thickness, ratio of wall thickness to radius (h:R) at end diastole, and meridional left ventricular wall stress (σ_m) in patients with normal hearts compared to those with chronic left ventricular pressure-overload or volume-overload. Only patients with chronic left ventricular pressure- or volume-overload who were well compensated and had no depression of systolic function (left ventricular ejection fraction) were included.

From Grossman et al. (1975).

However, peak systolic wall stress is similar in normal subjects and in patients with compensated pressure or volume overload (Fig. 13).

Figure 13.



A comparison of changes in left ventricular pressure (solid dots), wall thickness (open dots) and wall stress (open squares) throughout the cardiac cycle for representative normal, pressure-overloaded, and volume-overloaded left ventricles. In the pressure-overloaded ventricle (B), the markedly elevated systolic pressure is exactly counterbalanced by increased wall thickness, with the result that wall stress remains normal. In the volume-overloaded ventricle (C), peak systolic stress is normal but end-diastolic stress is increased.

From Grossman et al. (1975).

Myocardial performance, normalized with respect to weight or volume initially remains within normal limits in hypertrophy caused by moderate, gradually applied stress. Peak systolic wall stress is also normal. This classifies the hypertrophy as physiologically appropriate. At least in some patients, hypertrophy eventually fails to keep up with the increased load. Wall stress becomes chronically high and pathological hypertrophy develops with depressed myocardial function and progressive pump failure. At this stage the depression of contractile performance is irreversible.

Grossman (1980) has recently reviewed the difficulties that are encountered when attempts are made to separate physiological from pathological hypertrophy. Such a separation is important not only for theoretical reasons but also holds the solution to a crucial clinical problem, i.e. the proper timing of corrective surgery in valvular (and some forms of congenital) heart disease, particularly in lesions with volume overload such as mitral or aortic regurgitation.

It is essential to take loading conditions into account when evaluating contractile performance in patients with pressure overload. Figure 14 shows the relationship between ejection fraction and mean systolic wall stress in a series of patients with aortic stenosis and varying degrees of clinical severity.

Figure 14.

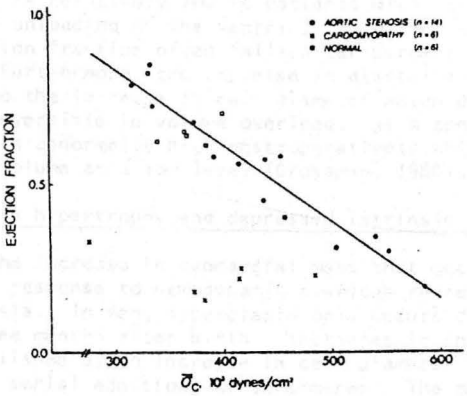


Figure 14. Relationship between LV ejection fraction and mean systolic stress ($\bar{\sigma}$). Values for 14 patients with aortic stenosis and varying degrees of heart failure are plotted together with values from normal subjects and patients with congestive cardiomyopathy.

From Gunther and Grossman (1979).

EF was strongly, linearly, and negatively related to wall stress and varied from 0.19 to 0.85. However, the patients all fell on the same regression line that applies to normal subjects whereas patients with cardiomyopathy consistently fell below this line. Thus, the depressed pump performance in patients with aortic stenosis may be viewed as being caused by an inadequate amount of hypertrophy rather than by a depression of intrinsic myocardial contractile state (Grossman, 1980). This view is consistent with the generally favorable results of corrective surgery with marked post-operative improvement in pump function after relief of the pressure overload. A true depression of intrinsic contractile state is often seen after long-standing severe pressure overload. Cellular damage may occur either as a direct consequence of the overload or be caused by ischemia.

In contrast, patients with chronic volume overload and depressed myocardial function according to simple conventional measurements, e.g. ejection fraction, often do poorly after surgical correction. This has usually been attributed to an irreversible depression of intrinsic contractile performance but may at least partially reflect persistently abnormal and irreversible loading conditions. Systolic wall stress is relatively low in patients with uncorrected mitral regurgitation due to unloading of the ventricle into the left atrium against a low pressure. Ejection fraction often falls after surgery when the mitral valve becomes competent. Furthermore, the increase in diastolic volume and fiber length (as opposed to the increase in cell diameter which dominates in pressure overload) may be irreversible in volume overload. As a consequence, systolic wall stress may remain abnormally high post-operatively which will keep ejection fraction and stroke volume at a low level (Grossman, 1980).

Cellular mechanisms in hypertrophy and depressed intrinsic contractile state.

Hypertrophy. The increase in myocardial mass that occurs both during normal growth and in response to hemodynamic overload represents hypertrophy rather than hyperplasia. In man, hyperplasia only occurs during fetal life and during the first three months after birth. Increases in chamber size and wall thickness are accomplished by an increase in cell diameter by parallel addition of myofibrils and by serial additions of sarcomeres. The mechanisms that induce hypertrophy are still unknown but are generally thought to be under hemodynamic or mechanical rather than hormonal control (Grossman, 1980; Zelis et al., 1981).

The progression of structural and ultrastructural changes during hypertrophy is often assumed to follow a pattern originally described by Meerson. There is an initial stage of adaptation, characterized by transient breakdown of myocardial cells. This is followed by a period of compensated hypertrophy with normal function. A final stage of degeneration features disruption of cellular and subcellular structures, loss of myofibrils and increased collagen content, and interstitial fibrosis (Ferrans, 1983). The structural changes that occur during the early stages vary with the stimulus but their functional significance is largely unknown. The correlations between the morphological abnormalities and the depressed systolic function and increased stiffness during the final stage of hypertrophy are obvious. The initial stage with cellular damage is probably present only in acute and massive hemodynamic overload, e.g. primarily in experimentally induced pressure overload.

Contractile state. The cellular basis for Starling's law until recently thought to be Huxley's sliding filament theory according to which the force of contraction is proportional to the degree of overlap between actin and myosin filaments. Force development is then greatest at a sarcomere length of about 2.2μ. This mechanism would explain both the ascending and descending limb of the Starling curve (Sonnenblick and Skelton, 1974). However, sarcomere length is not increased beyond 2.2μ in dilatation and failure due to chronic volume overload (Sagawa, 1978) and other studies have failed to demonstrate a well defined optimal sarcomere length (Pollack et al., 1978). The increase in developed tension that occurs with increasing fiber length is at least partially

linked to an increased activation of sarcomeres by calcium ions (Fabiato and Fabiato, 1975; Maughan et al., 1979).

Willerson (1983) and Tilton et al. (1983) have recently reviewed the biochemical determinants of the depressed contractile state in CHF with pathological hypertrophy. Contractile dysfunction may be caused by abnormalities in any of three different areas: (1) Myocardial energy utilization, (2) Mitochondrial membrane function, and, (3) Excitation - contraction coupling.

Several groups have linked the depressed function to a depressed myosin ATPase activity, perhaps related to a change in myosin isoenzyme distributions. It is not yet known whether the decreased myosin ATPase activity is a cause or consequence of failure. Changes in mitochondrial respiration and calcium kinetics occur but their significance is unknown. Other abnormalities affecting intracellular calcium transport at the level of the sarcolemma and the sarcoplasmic reticulum have also been described but, again, it is not known whether these changes are primary or secondary.

Relationship between cardiac pump function and the peripheral circulation.

The preceding section has demonstrated that cardiac pump performance is dependent on intrinsic myocardial contractile state but also greatly affected by loading conditions, i.e. preload and afterload. It follows that the pump performance under normal conditions as well as in failure will be influenced by the state of the peripheral vasculature.

There is no simple approach to the analysis of the coupling between the heart and the circulation. Recent efforts (Ross, 1976; Weber et al., 1982) have been based on Guyton's methods (Guyton, 1963) of describing the balance between overall cardiac function and the state of the peripheral circulation. Cardiac output and venous return are viewed as functions of right atrial pressure. The characteristics of the cardiac and the venous function curve and their intersection define a given circulatory state.

Similar concepts can also be applied to the coupling of the heart to the arterial and venous circulations. On the arterial side, fiber shortening, stroke volume, and cardiac output are inversely proportional (Fig. 15) to afterload, expressed as the resistance to ejection offered by peak or mean systolic arterial pressure. A failing heart produces a subnormal cardiac output against any given afterload. Arterial loading conditions are characterized by a positive and linear relationship between cardiac output and arterial pressure. The slope of this relationship, which is equal to the ratio pressure/flow, represents peripheral resistance. In the absence of reflex regulation, any increase in cardiac output will produce an increase in blood pressure that is larger in CHF than under normal conditions. Therefore, persisting vasoconstriction will limit the benefits that can be achieved by improving contractile state.

Figure 15.

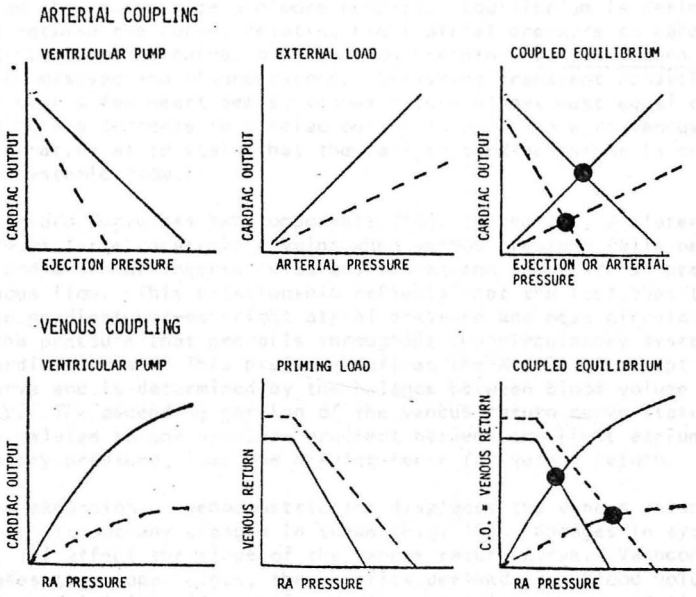


Figure 15. Functional coupling of the heart to the arterial and venous circulation. Solid lines represent normal conditions, dashed lines CHF. For further explanation, see text.

Adapted from Weber et al. (1982).

It may also be argued that pressure is an inadequate measure of afterload. Pressure is the product of resistance and flow. This approach is strictly valid only for systems with a steady, non-pulsatile flow. A pulsatile flow requires the use of impedance rather than resistance, i.e. measurements of the ratio pressure/flow over a range of frequencies combined with an estimate of any phase shift between pressure and flow. Measurement of impedance requires high fidelity pressure and flow tracings and Fourier analysis. Under normal conditions, most of the total impedance is accounted for by the pressure/flow ratio at the basic frequency of oscillation of the system, i.e. heart rate, and impedance is not materially different from resistance. Increased stiffness of the arterial system, which is a feature of CHF, is likely to increase the contribution of the high-frequency terms and impedance will differ significantly from resistance. However, the clinical value of impedance measurements is still undetermined.

Conditions on the venous side are more complex. Equilibrium is defined by the intersection between the curves relating right atrial pressure to cardiac output (the original Starling curve) and to venous return. Venous return is a term that is often misused and misunderstood. Excluding transient conditions that may persist over a few heart beats, venous return always must equal cardiac output. To attribute a decrease in cardiac output to a decrease in venous return is as informative as to state that the fall in cardiac output is caused by a decrease in systemic flow.

The venous return curve has two components (Fig. 15 and 16), a plateau that reflects collapse of large capacitance veins when venous pressure falls below a critical limit, and a linear inverse relationship between right atrial pressure and systemic venous flow. This relationship reflects that the fact that the X-axis measures the gradient between right atrial pressure and mean circulatory pressure, i.e. the pressure that prevails throughout the circulatory system shortly after cardiac arrest. This pressure defines the X-axis intercept of the venous return curve and is determined by the balance between blood volume and vascular capacity. The ascending portion of the venous return curve states that flow is linearly related to the pressure gradient between the right atrium and the mean circulatory pressure, i.e. the driving force for venous return.

Blood volume expansion or venoconstriction displaces the venous return curve to the right without any changes in shape (Fig. 16). Changes in systemic resistance (Fig. 16) affect the slope of the venous return curve. Vasoconstriction decreases the slope. Thus, the benefits derived from blood volume expansion in CHF are minimized if associated with systemic vasoconstriction (Fig. 15).

Figure 16.

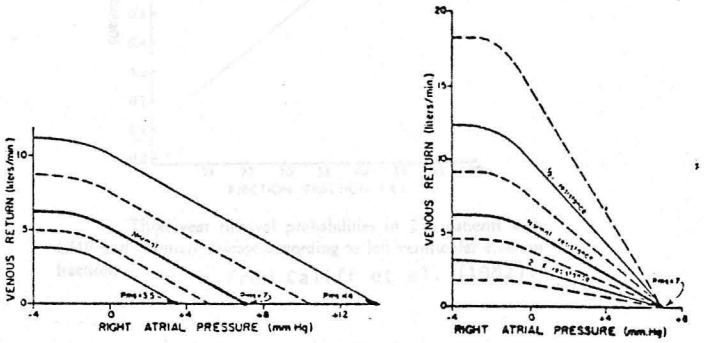


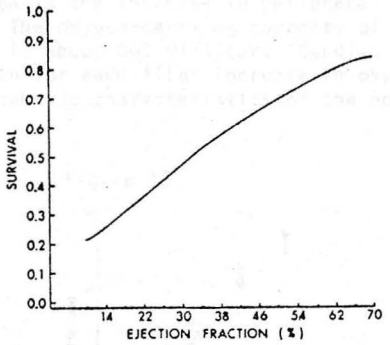
Figure 16. Effect of changes in systemic resistance (right) and in effective blood volume (left) on venous return.

From Guyton (1963).

This analysis emphasizes further the crucial role of systemic resistance in CHF. The increased systemic resistance and increased afterload depress stroke volume and cardiac output. The potential effect of inotropic agents is minimized unless combined with vasodilatation. Systemic vasodilatation also has favorable effects on venous return. This means that the classification of vasodilator agents as affecting primarily the venous or the arterial system at least to some extent is artificial. An agent with a primary arterial *in vitro* effects will also significantly alter the function of the venous system.

The close coupling between the heart and the periphery may explain why descriptors of cardiac function that are highly sensitive to loading conditions (and consequently poor descriptors of intrinsic myocardial contractile state) are powerful predictors of prognosis, e.g. ejection fraction (Fig. 17).

Figure 17.



Three-year survival probabilities in 236 patients with CHF and coronary disease according to left ventricular ejection fraction. From Califf et al. (1982).

Califf et al. (1982) have described a strong relationship between ejection fraction and survival in patients with ischemic heart disease. Preoperative ejection fraction also predicts long-term prognosis (Forman et al. (1980)) following valve replacement in patients with aortic regurgitation but not aortic stenosis.

A low ejection fraction expresses the combined effects of deteriorating contractile state, increasing afterload, and decreasing preload reserve. Similarly, pressure/volume ratios determined during exercise (Corbett et al., 1981) measure manifest rather than intrinsic contractile state. However, failure of the myocardium to respond normally to endogenous beta-adrenergic stimulation and any development of exercise-induced ischemia are factors that are likely to have an adverse effect on the prognosis.

Cardiovascular response to exercise in normal subjects and in patients with CHF.

The essence of the present therapeutic approach to heart failure is to regulate preload and afterload to minimize symptoms and signs of congestion and to maximize cardiac output and tissue perfusion. Exercise places greater demands on the cardiovascular system than other physiological conditions. Many patients with significantly depressed myocardial function are symptomatic only during exercise. An understanding of the mechanisms that regulate the cardiovascular response to exercise is therefore a prerequisite for a rational approach to the treatment of chronic CHF.

Normal response.

The outstanding feature of the normal cardiovascular response to dynamic exercise is an increase in cardiac output and rate of oxygen transport that matches on a one-to-one basis the increase in peripheral oxygen demand and systemic oxygen uptake. The oxygen-carrying capacity of arterial blood at normal hemoglobin levels is about 200 ml/liter. Cardiac output increases by approximately 5 liters/min for each liter increase in oxygen uptake (Fig. 18). Other hemodynamic and metabolic characteristics of the normal response are shown in Figure 19.

Figure 18.

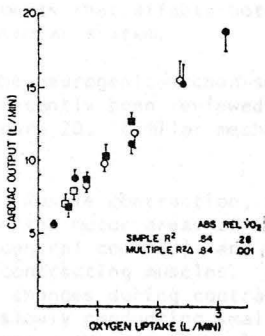
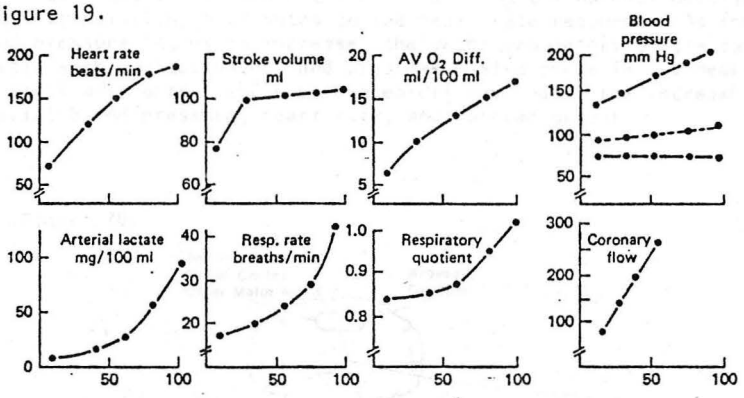


Figure 18. Relationship between oxygen uptake and cardiac output during different forms of dynamic exercise. Symbols as in Figure 21. Cardiac output (l/min) = 4.5 + 4.8 · $\dot{V}O_2$ where $\dot{V}O_2$ is oxygen uptake in l/min.

From Blomqvist et al. (1981).

Figure 19.



Principal features of cardiovascular, respiratory, and metabolic responses to exercise. Data points represent sitting rest, three levels of submaximal exercise, and maximal exercise. Values are plotted against relative load, that is, actual oxygen uptake as percentage of maximal oxygen uptake. Blood pressure data represent systolic, mean, and diastolic brachial artery pressures. Coronary flow measurements are given as milliliters per minute per 100 g cardiac muscle.

From Blomqvist (1979).

The increase in metabolic rate and demand for oxygen transport is satisfied by a complex set of adjustments that affects both the central and peripheral components of the cardiovascular system.

Reflex regulation. The neurogenic mechanisms that govern the cardiovascular response to exercise have recently been reviewed by Shepherd et al. (1981). A summary is presented in Figure 20. Similar mechanisms operate during static and dynamic exercise.

With onset of skeletal muscle contraction, signals are received by the cardiovascular centers from the motor areas of the brain where the voluntary contraction is initiated (central command), and from receptors which sense the degree of activity of the contracting muscles. Receptors in the muscles are stimulated by the chemical changes during contraction. The afferent impulses reach the spinal cord via slowly conducting small medullated (group III or Aσ) and nonmedullated fibers (group IV or C-fibers) and ascend in the spinothalamic tract to the cardiovascular centers in the brain. As a result of these inputs to the cardiovascular centers, the vagal activity to the heart decreases and the heart rate increases. The increased sympathetic noradrenergic outflow leads to increased cardiac contractility, increased tone of the splanchnic, renal, and other resistance vessels, constriction of the splanchnic capacitance vessels,

and release of catecholamines, mainly epinephrine, from the adrenal medulla. Beta-adrenergic stimulation contributes to the heart rate response. As the arterial blood pressure begins to increase, the mechanoreceptors of the carotid sinus and aortic arch are activated, and presumably also those in the heart subserved by vagal afferents. These baroreceptors may modify the increase in systolic arterial blood pressure, heart rate, and cardiac output.

Figure 20.

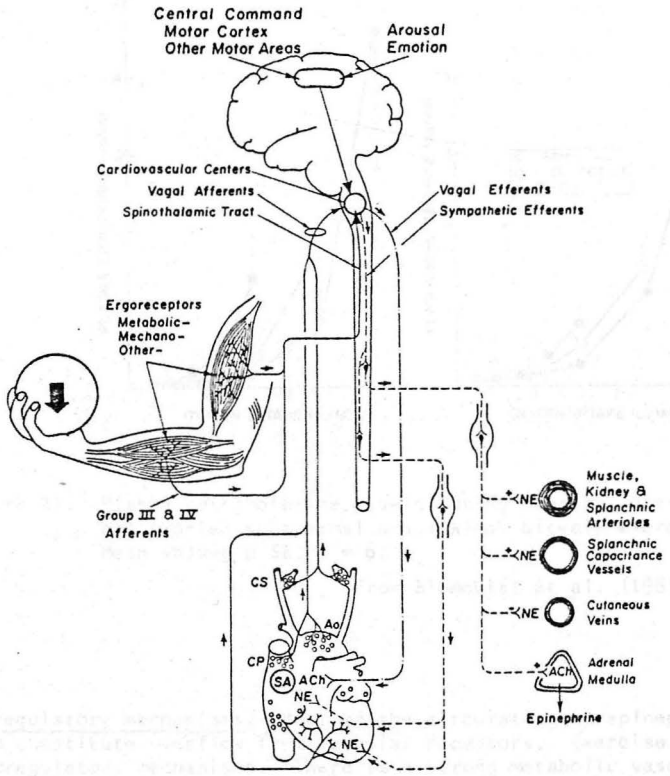


Figure 20. Neurogenic mechanisms involved in the cardiovascular response to exercise. See text for details.

From Shepherd et al. (1981).

The activation of the sympathetic nervous system is manifest as elevated plasma catecholamines (Fig. 21). The magnitude of the increase is related to relative intensity of work (actual oxygen uptake as a fraction of the individual's maximum) and to absolute oxygen uptake (Blomqvist et al., 1981; Lewis et al., 1983).

Figure 21.

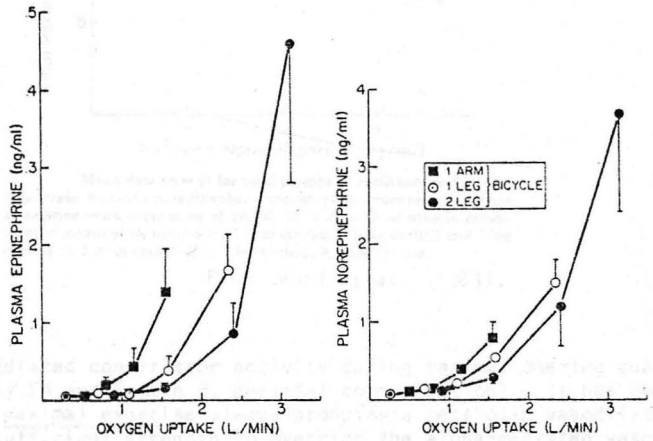
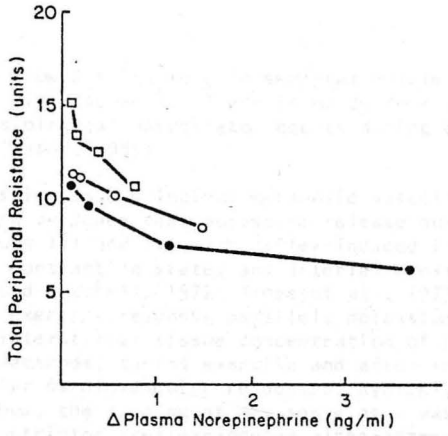


Figure 21. Plasma catecholamine levels during one-arm, one-leg, and two-leg submaximal and maximal bicycle exercise. Mean values ± SE, N = 6.

From Blomqvist et al. (1981).

Vasoregulatory mechanisms. Most of the circulating norepinephrine is thought to constitute overflow from vascular receptors. Exercise also activates local vasoregulatory mechanisms. There is a strong metabolic vasodilator drive. In a young normal subject, the transition from rest to maximal exercise is typically associated with a 3-fold reduction in systemic resistance. Thus, at the systemic level the metabolic vasodilator activity overrides the neurogenic vasoconstrictor drive. Systemic resistance is minimal under conditions when the neurogenic constrictor drive is maximal (Fig. 22), i.e. during maximal exercise involving both legs. Metabolic stimuli during submaximal exercise do not completely abolish the effects of the alpha-mediated vasoconstrictor drive in blood vessels supplying working muscle (Remensnyder et al., 1962), but there is no

Figure 22.



Mean data (n = 6) for total peripheral resistance as function of increase in plasma norepinephrine concentration from rest to exercise at relative work intensities of 25, 50, 75, and 100% of muscle group-specific maximal O_2 uptake for 1-arm cranking, 1-leg cycling and 2-leg cycling. □, 1-Arm cranking; ○, 1-leg cycling; ●, 2-leg cycling.

From Lewis et al. (1983).

evidence for alpha-mediated constrictor activity during maximal one-leg quadriceps exercise (Gaffney FA and Saltin B, personal communication). It has been widely accepted that maximal exercise always produces a metabolic vasodilator activity that is of sufficient strength to override the alpha-mediated vasoconstriction. However, studies in normal subjects have clearly demonstrated that there is significant residual vasoconstrictor activity also during maximal exercise if it involves large muscle groups and requires rates of oxygen uptake and transport that equal or exceed maximal systemic capacity. Leg blood flow and conductance decrease when two-leg exercise is combined with arm exercise and when the maximally active muscle mass increases from one leg to two legs (Clausen et al., 1973; Saltin et al., 1976; Klausen et al., 1982). This adjustment is analogous to the vasoregulation in CHF, i.e. a systemic flow that is inadequate relative to metabolic demands is redistributed to provide optimal perfusion.

Olsson (1981) has recently reviewed the regulation of blood flow in skeletal muscle. In his generalized control system, the primary error signal is muscle activity rather than oxygen use and local pO_2. Carbon dioxide and potassium fit the role as principal vasodilator agents better than other agents. They have release rates proportional to the contractile activity and the magnitude of exercise-induced concentration changes is consistent with a physiologically important role. Neither can explain all features of the exercise response but these agents, combined with decreases in pO_2 and increases in osmolarity, markedly reinforce each other's vasodilatory effects. Adenosine is an important

regulator of coronary flow but its role in skeletal muscle may be limited to conditions associated with ischemia. There is no current support for prostaglandins as major physiological vasodilator agents during exercise (Korner, 1975; Johnson, 1975; Olsson, 1981).

The role of potassium as a principal metabolic vasodilator agent is intriguing. There is strong evidence that potassium release during exercise activates muscle afferents (Groups III and IV) with reflex-induced increases in heart rate, cardiac output, contractile state, and arterial pressure (Wildenthal et al., 1968; McCloskey and Mitchell, 1972; Tibes et al., 1977). The time course of the cardiovascular exercise response parallels potassium release (Saltin et al., 1981). Similar interstitial tissue concentration of potassium (as measured with a ion-specific electrode) during exercise and after intraarterial potassium infusion produce similar cardiovascular responses (Rybicki, Mitchell et al., work in progress). Thus, the same agent may serve as a vasodilator (local effects) and a vasoconstrictor (reflex-induced alpha-adrenergic stimulation).

The combined effects of the local vasodilator and systemic vasoconstrictor drives is a redistribution of cardiac output (Fig. 23).

Figure 23.

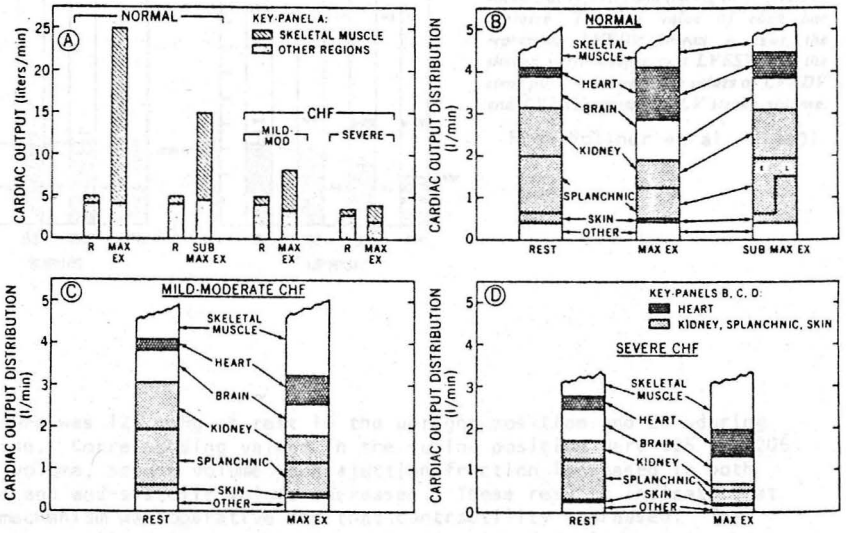


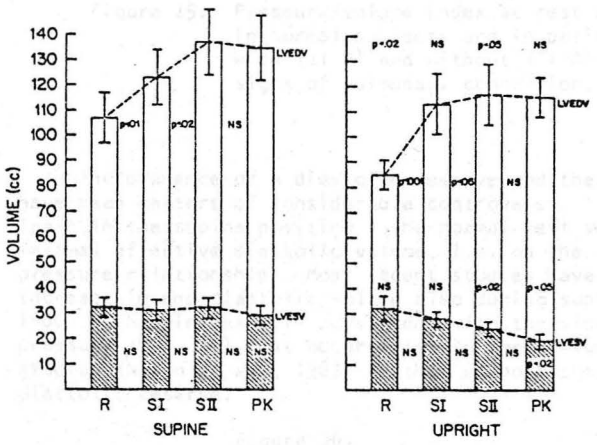
Fig. 1. Regional distribution of the cardiac output at rest (R) and during exercise (EX) in normal subjects and patients with congestive heart failure (CHF). These data are estimates from limited quantitative data in humans and supplemented by directional changes in regional blood flow from animal studies. (A) Total cardiac output and its distribution to skeletal muscle (crosshatched) and all other regions (light stipple). (B, C, and D) The distribution of blood flow to the circulations exclusive of skeletal muscle. Attention is called to blood flow to the heart (double crosshatch) and to the circulations rich in alpha receptors (kidney, skin, splanchnic) (heavy stipple) by the pattern of shading (key in D). MAX-EX, maximum exercise; SUB MAX EX, submaximal exercise at 50%–60% of maximum. E, the distribution of cardiac output to the splanchnic and cutaneous circulations early during submaximal exercise in normals; L the late response.

From Zelis and Flaim (1982).

The fraction going to skeletal muscle increases markedly during exercise. Virtually the total increase in cardiac output is directed to the working muscles. Total flow to tissues other than active skeletal muscle remains constant but there is a redistribution within these regions. There is increased flow to the myocardium and - as in severe CHF at rest - decreased flow in the renal, splanchnic and cutaneous circulations. Cerebral flow remains constant. Regional variations in the density of post-ganglionic alpha-receptors and basal vascular tone as well as differential distribution of signals in efferent sympathetic nerves account for these regional flow differences (Zelis and Flaim, 1982).

Cardiac performance during exercise. The normal exercise response of the left ventricle is illustrated in Figure 24.

Figure 24.



Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and stroke volume at rest (R) and during three levels of exercise. The top value of each bar represents LVEDV (mean ± SEM), the shaded portion represents LVESV, and the clear portion between the values of LVEDV and LVESV represents LV stroke volume.

From Poliner et al. (1980).

Systolic pressure was 125 mmHg at rest in the upright position and 204 during maximal exercise. Corresponding values in the supine position were 125 and 206. End-diastolic volume, stroke volume, and ejection fraction increased in both body positions and end-systolic volume decreased. These results indicate that the Starling mechanism was operative and that contractility increased. The decrease in end-systolic volume and increase in ejection fraction and stroke volume at a time when systolic blood pressure increased is evidence for enhanced contractility that is also manifest as a marked increase in the end-systolic pressure/volume ratio (Fig. 25).

Figure 25.

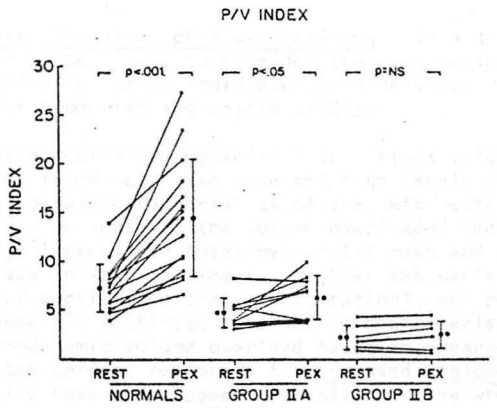


Figure 25. Pressure/volume index at rest and during maximal exercise in normal subjects and in patients with aortic regurgitation with (II B) and without (II A) symptoms, cardiomegaly, and signs of pulmonary congestion.

From Dehmer et al. (1981).

The presence of a diastolic reserve and the role of the Starling mechanism have been matters of considerable controversy. It has been suggested that - at least in the supine position - the normal left ventricle operates at or near its maximal effective diastolic volume, i.e. on the steep portion of the volume-pressure relationship. Most recent studies have shown an exercise-induced increase in end-diastolic volume also during supine exercise (Poliner et al., 1980). This increase is consistent with the significant rise in end-diastolic pressure (Fig. 26) that occurs also in normal subjects. Echocardiographic studies (Nixon et al., 1983) further support the presence of a significant diastolic reserve.

Figure 26.

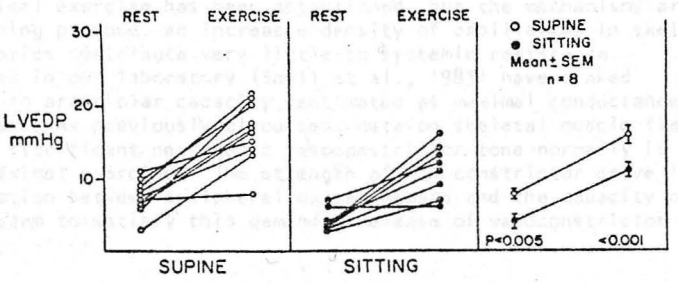


Figure 26. Left ventricular end-diastolic pressure (LVEDP) in the supine and sitting positions at rest and during exercise.

From Thadani and Parker (1978).

Cardiovascular adaptations after physical training. In a discussion of the pathophysiology of CHF it is pertinent to consider the cardiovascular adaptations induced by physical training in normal individuals. A detailed review has recently been published by Blomqvist and Saltin (1983).

High levels of physical activity impose an intermittent volume overload, combined with markedly increased metabolic rate and high levels of sympathetic stimulation. The morphological characteristics of the left ventricle of a marathon runner are similar to those of the volume overloaded ventricle illustrated in Figure 12, i.e. a large increase in total myocardial mass and chamber size with only a modest increase in wall thickness. Neither the early stages of volume overload (caused by aortic or mitral regurgitation), nor physical training produces significant changes in intrinsic contractile characteristics. Both physical training and hemodynamic volume overload cause an expansion of total blood volume. However, the cardiac responses to increased preload are different. Patients with CHF generally have a decreased diastolic reserve whereas one of the principal adaptations to physical training is an increase in the ability to utilize the Starling mechanism. In a sedentary individual blood volume expansion of 1-1.5 liters produces a large increase in central venous pressure but no change in maximal stroke volume or maximal cardiac output. A fit individual with large basal stroke volume is able to achieve an even larger maximal stroke volume and cardiac output after volume expansion. It is not known whether this difference is caused by altered diastolic properties of the myocardium or is related to pericardial effects on cardiac diastolic compliance.

There is a striking difference between the afterload effects of CHF and physical training. CHF is characterized by vasoconstriction and physical fitness by an increased capacity for vasodilatation. The average young normal subject is likely to have a maximal oxygen uptake of 3 liters/min and a maximal cardiac output of 20 liters/min. Corresponding values in a champion endurance athlete may reach, respectively, 6 and 40 liters/min. Yet, arterial pressures during maximal exercise are similar in both, and consequently, the athlete's systemic vascular resistance is only half as large as that of the average individual. The reduction in systemic resistance is a prerequisite for the increase in cardiac output.

A strong inverse relationship between oxygen uptake and systemic vascular resistance during maximal exercise has been established, but the mechanisms are poorly defined. Training produces an increased density of capillaries in skeletal muscle but the capillaries contribute very little to systemic resistance. However, recent studies in our laboratory (Snell et al., 1983) have linked maximal oxygen uptake to arteriolar capacity, estimated as maximal conductance after ischemic exercise. As previously discussed, data on skeletal muscle flow strongly suggest that significant neurogenic vasoconstrictor tone normally is present also during maximal exercise. The strength of the constrictor drive is a function of the relation between peripheral oxygen demand and the capacity of the cardiovascular system to satisfy this demand. Release of vasoconstrictor

activity and increased arteriolar capacity are crucial training-induced adaptations, but the potential for vasodilatation cannot be effectively utilized unless there is a simultaneous improvement in cardiac pump performance. The key to a better understanding of the cardiovascular effects of training is likely to be a better definition of how the local vasodilatory and central vasoconstrictor mechanisms interact. The mechanisms that operate at the cellular level are unknown.

Response to exercise in CHF.

The normal one-to-one relationship between oxygen demand and oxygen transport is disrupted in severe CHF. Patients with mild lesions are able to compensate for a depressed stroke volume by relative tachycardia. Cardiac output remains within normal limits at submaximal levels of exercise whereas maximal cardiac output and oxygen uptake are depressed in proportion to the decrease in stroke volume (Fig. 27). In severe CHF, a more prominent reduction in stroke volume combines with regulatory abnormalities, including an attenuated heart rate response, to produce a subnormal cardiac output (Fig. 28).

Figure 27.

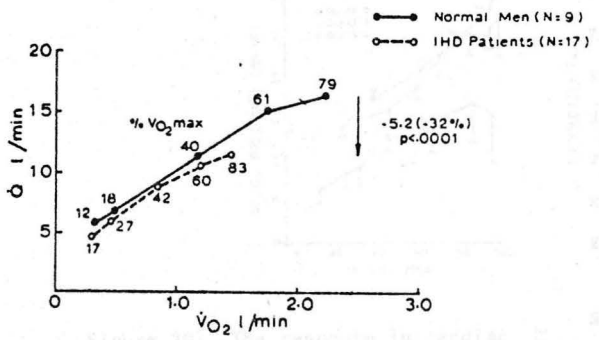


Figure 27. The relationship of cardiac output ($\dot{Q}$, L/min) to oxygen consumption ($\dot{V}O_2$, L/min) in normal men and in patients with ischemic heart disease.

From Bruce et al. (1973).

Figure 28.

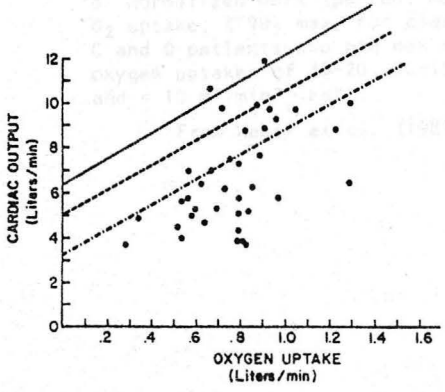


Figure 28. The relationship of cardiac output to oxygen uptake during bicycle exercise after myocardial infarction. Dashed line: relationship in normal subjects; outer lines; two standard deviations. Closed circles: data points from the patients.

Data from Wohl et al. (1977).

Other features of the exercise response in CHF are illustrated in Figure 29.

Figure 29.

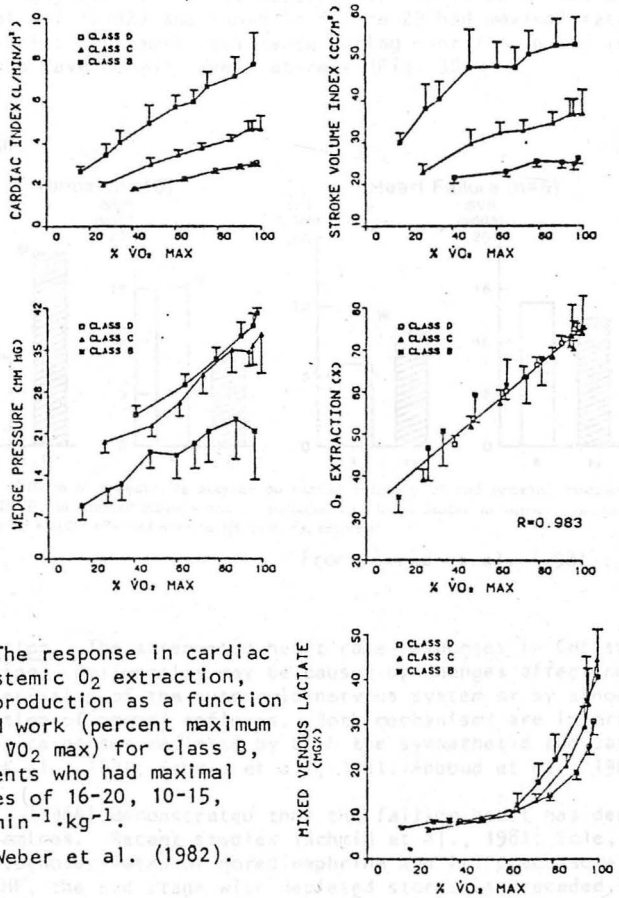
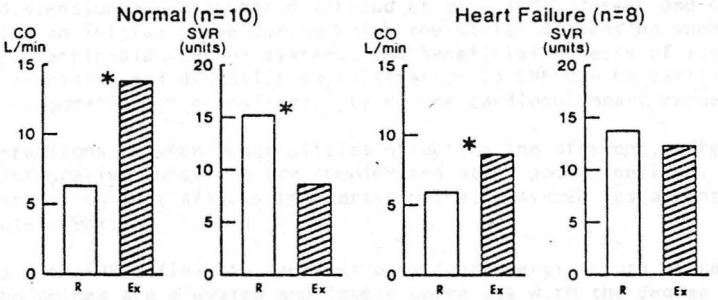


Figure 29. The response in cardiac function, systemic O_2 extraction, and lactate production as a function of normalized work (percent maximum O_2 uptake, % $\dot{V}O_2$ max) for class B, C and D patients who had maximal oxygen uptakes of 16-20, 10-15, and < 10 $ml \cdot min^{-1} \cdot kg^{-1}$.

From Weber et al. (1982).

Patients with severe failure have not only a low stroke volume at rest but are also unable to achieve the normal exercise-induced increase above resting levels. Filling pressures are elevated at rest and increase steeply during exercise, particularly in patients with severe CHF. However, irrespective of the degree of failure, patients retain a normal ability to extract the available oxygen. The heart rate response to exercise and other forms of stress, e.g. changes in posture, is blunted (Goldstein et al., 1975). Maximal heart rate in normal middle-aged subjects is 170-180 beats/min. The three groups of patients studied by Weber et al. (1982) and shown in Figure 29 had maximal rates of 158, 154, and 140 beats/min. Systemic resistance during exercise in CHF remains high even in patients who have normal levels at rest (Fig. 30).

Figure 30.



Effects of dynamic leg exercise on cardiac output (CO) and systemic vascular resistance (SVR) in normal subjects and in patients with heart failure in supine position. *Significant ($P < 0.05$) effect of exercise (R, rest; Ex, exercise).

From Abboud et al. (1981).

Reflex regulation. The attenuated heart rate responses in CHF suggest autonomic dysfunction. Dysfunction may be caused by changes affecting the basic functional characteristics of the autonomic nervous system or by abnormal patterns of activation of normal reflexes. Both mechanisms are important in CHF and they affect the responses mediated by both the sympathetic and parasympathetic systems (Eckberg et al., 1971; Schmid et al., 1981; Abboud et al., 1981).

Chidsey et al. (1964) demonstrated that the failing heart has depleted stores of catecholamines. Recent studies (Schmid et al., 1981; Sole, 1982) have revealed abnormal turnover rates of norepinephrine and its precursors. At least in some forms of CHF, the end stage with depleted stores is preceded by increased turnover rates of norepinephrine (which serve as an indicator of overall sympathetic activity). Turnover rates may remain high even in the depleted stage and

approach maximal rates of synthesis under basal conditions. This leaves little or no sympathetic reserve and may account for the apparent paradox of beneficial effects of long-term treatment with beta-adrenergic blocking agents in some patients with severe cardiomyopathy (Swedberg et al., 1980).

Chronically increased levels of adrenergic activity could be expected to cause down-regulation with decreased density of the adrenergic receptors. However, studies of responses to exogenous adrenergic agonists reveal no consistent pattern. Tilton et al. (1983) have recently reviewed receptor characteristics in CHF. They concluded that end-stage CHF is associated with abnormal receptor density and responsiveness but that it is uncertain whether similar dysfunction occurs also during the early stages of CHF.

The manner in which normal neurogenic control mechanisms may affect the cardiovascular regulation in various forms of CHF was discussed briefly in the introduction. Studies of specific receptor systems indicate that reflex often is modified in CHF. Cardiovascular, renal, and hormonal effects of atrial and ventricular distension are attenuated (Abboud et al., 1981; Zucker and Gilmore, 1981) following an initial phase during which the atrial distension suppresses the renin-angiotensin-aldosterone system. The beneficial effects of sodium restriction, diuresis, and digitalis administration in CHF can be partially explained by restoration of normal activity of the cardiopulmonary receptors.

The interactions between abnormalities affecting the afferent, efferent, and central integrative functions are complex and still poorly defined. At least the dysfunction that affects the parasympathetic system has a central component (Sole, 1982).

Patients with CHF definitely manifest a hyperadrenergic state at rest. Plasma catecholamines are elevated and levels correlate with the degree of failure and ventricular dysfunction (Markham et al., paper in print). An early paper by Chidsey et al. (1962) also established the concept that the response to exercise is hyperadrenergic. Plasma norepinephrine levels in CHF are markedly elevated at intensities of exercise that produce little change in normal subjects. However, the rate of release of norepinephrine is determined by relative (per cent of individual maximum) rather than absolute work load as shown in Figure 31. Oxygen uptakes during exercise at 2-4 X resting levels correspond to loads well below 50% of maximal capacity in normal subjects but are maximal in patients with severe CHF.

Figure 31.

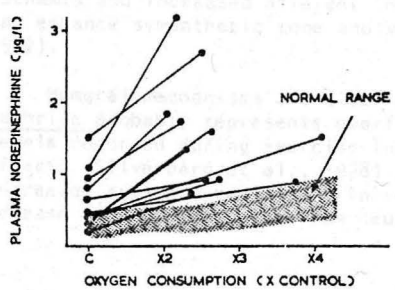


Figure 31. Changes in plasma norepinephrine during exercise in congestive heart failure. Oxygen consumption during the exercise period is expressed in multiples of the resting oxygen consumption. (C= control or resting values.) The normal range is represented by the stippled area.

From Chidsey et al. (1962).

Markham et al. showed that patients with advanced CHF actually have subnormal catecholamine levels during maximal exercise. Furthermore, they found strong correlations between exercise capacity and the magnitude of the increase in norepinephrine and heart rate above resting levels. Their data (presented in Table 3) suggest that patients with severe CHF have an attenuated rather than an excessive adrenergic response to exercise. The combination of high resting and low maximal levels of norepinephrine is consistent with Sole's (1982) concept - based on norepinephrine kinetics in the failing heart - of a diminished sympathetic reserve.

Table 3. Plasma catecholamines (ng/ml) and heart rate (beats/min) at rest sitting and during maximal upright exercise in patients with severe CHF (n=16) and in normal subjects (n=6). Data from Markham et al. (paper in print) and Lewis et al. (1983).

		Epinephrine	Norepinephrine	Heart Rate
Rest	CHF	0.07	0.75	90
	Normals	0.04	0.38	80
Exercise	CHF	0.16	1.92	136
	Normals	0.46	3.67	194
Ratio Exercise/Rest	CHF	2.4	2.6	1.5
	Normals	11.5	9.7	2.4

Vasoregulatory mechanisms. Several mechanisms contribute to the vasoconstriction in CHF. Skeletal muscle vascular resistance, which is a major determinant of systemic resistance during exercise, is influenced by at least three major factors, all of which may be modified by the presence of CHF: (1) neurohumoral vasoconstrictor activity, (2) metabolic vasodilator activity, and (3) basal physical properties of the arterial system.

Increased α_1-stimulation is the principal neurohumoral factor. Neurogenic vasoconstrictor responses to exercise are normally buffered by vasodilator stimuli originating in arterial baroreceptors and atrial receptors but these reflexes are blunted in CHF (Abboud et al., 1982). Relative skeletal muscle ischemia and increased afferent impulse traffic from metabolic muscle receptors may enhance sympathetic tone and vasoconstrictor drive in CHF (Zelis and Flaim, 1982).

Humoral mechanisms are also important. Most of the circulating norepinephrine probably represents overflow from vascular receptors but the high levels recorded during exercise in many patients with CHF may have hormonal effects (Silverberg et al., 1978). Angiotensin contributes significantly to the increased systemic resistance in several ways, including facilitation of the release of norepinephrine from neurovascular junctions. Salt and water retention

is promoted by renal vasoconstriction and activation of the renin-angiotensin-aldosterone system. Several studies (Zelis and Flaim, 1982) suggest that the abnormal sodium and water balance in CHF increases the stiffness of the arterial system and effectively limits the degree of vasodilatation that can be achieved by local release of metabolic vasodilators. Hyperemic limb flow as measured after arterial occlusion at rest is reduced in CHF and does not increase after alpha-blockade. Diuretics enhance and mineralocorticoids reduce conductance. Recent clinical data also suggest that treatment with diuretics improves hemodynamics and exercise capacity primarily by reducing afterload (Wilson et al., 1981).

Little or no thought has been given to the possibility that the metabolic vasodilator activity may be impaired in CHF because of mechanisms other than increased vascular stiffness. However, the rate of release of metabolic vasodilator agents may be proportional to the level of contractile activity and energy transformation in skeletal muscle (Olsson, 1981) which is reduced in CHF. Potassium concentrations in the femoral vein during submaximal and maximal treadmill exercise are strongly and linearly related to oxygen uptake. Maximal release rates are higher after training (Saltin et al., 1968). Potassium may not be the only or even the principal metabolic vasodilator but may at least be regarded as an indicator of the strength of the vasodilator activity.

The low levels of metabolic activity during exercise in patients with CHF may also affect neurogenic control mechanisms. Many aspects of the hemodynamic, neuroendocrine, and metabolic responses to 2-leg exercise in patients with CHF are similar to the responses to exercise with a much smaller active muscle mass in normal subjects, e.g. one-arm cranking (Blomqvist et al., 1981; Lewis et al., 1983). Systemic resistance remains high and the heart rate during maximal exercise is more than 50 beats/min below the normal level during maximal treadmill or 2-leg bicycle exercise. These findings are consistent with reduced levels of metabolic vasodilator activity and afferent impulse traffic from skeletal muscle receptors relative to exercise involving a larger muscle mass.

There is little direct evidence to support the conventional concept (Zelis and Flaim, 1982) that skeletal muscle ischemia during exercise in CHF produces increased afferent traffic from metabolic skeletal muscle receptors and thereby activates neurogenic vasoconstrictor mechanisms. Blood lactate levels during exercise in CHF follow a pattern analogous to that of the plasma catecholamines. Lactate levels are high when related to absolute work load and oxygen uptake but normal or low in relation to the relative intensity of work. Levels during maximal exercise are subnormal, particularly in patients with severe CHF (Weber et al., 1982; Wilson and Ferraro, 1983). Blood lactate levels are imperfect measures of the rate of anaerobic metabolism in muscle but the combination of low lactates and low oxygen uptake suggest that the impulse flow from the metabolic receptors is reduced rather than increased in CHF. A reduced impulse flow may combine with the abnormalities in neurotransmittor metabolism and receptor function to limit further the heart rate response to exercise. A negative feed-back system with subnormal heart rate and metabolic vasodilator responses may operate when a low capacity for oxygen transport makes the patient unable to support exercise at normal rates of energy turnover.

Cardiac function. There is general agreement that the degree of functional impairment in CHF (determined from measurements of maximal oxygen uptake) cannot be predicted from data characterizing hemodynamics and ventricular function at rest (Franciosa et al., 1981). Markham et al. (paper in print) were also unable to demonstrate any significant correlation between exercise capacity and any of several measurements of ventricular performance during exercise. Table 4 provides a summary of their results and corresponding data from normal subjects.

Table 4. Left ventricular volumes and ejection fraction at rest sitting and during maximal upright bicycle exercise in patients with severe CHF (n=16) and in normal subjects (n=7). Radionuclide ventriculography data from Markham et al. (paper in print) and Poliner et al. (1980).

		EDVI	ESVI	SVI	EF
Rest	CHF	125	99	27	.27
	Normals	46	17	30	.72
Exercise	CHF	130	101	29	.24
	Normals	64	10	54	.91
Ratio Exercise/Rest	CHF	1.04	1.02	1.07	0.89
	Normals	1.39	0.59	1.80	1.38

EDVI and ESVI = end-systolic and end-diastolic volume indices, SVI = stroke volume index, EF = ejection fraction.

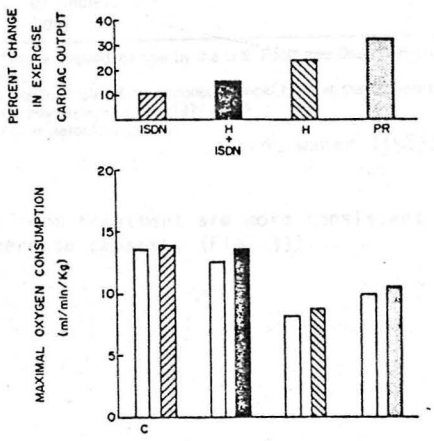
Similar results have been presented by Higginbotham et al. (1983). The main feature of the patient data is the lack of functional reserve. The normal subjects show a significant enhancement of contractile performance and a utilization of the Starling mechanism whereas there is little or no change from rest to exercise in any of the parameters characterizing the patient group. It is not surprising that under these circumstances the magnitude of the heart rate response becomes the principal determinant of exercise capacity. However, the apparent lack of exercise-induced changes in ventricular function may have been overemphasized by the technical limitations inherent in radionuclide ventriculography of large hearts with severely depressed function (Firth et al., 1982).

Patients with lesser degrees of failure (Fig. 25) are likely to show larger changes in ventricular performance during exercise but a relative lack of diastolic reserve and inability to respond to sympathetic stimulation with enhanced contractility is still evident (Dehmer et al., 1981). Univariate correlations between indices of ventricular function and exercise capacity are poor also in moderately severe CHF. This should not be surprising. One would expect to find differences with respect to ventricular performance between groups of patients with different degrees of severity of CHF according to clinical criteria. Such differences are also present (Fig. 25). However, exercise

capacity is strongly related to cardiac output, i.e. the product of stroke volume and heart rate. A patient with poor contractile performance may still achieve a relatively high cardiac output if (1) systemic resistance is relatively low, (2) the end-diastolic volume is large, and, (3) the heart rate response is adequate.

Effects of vasodilators and inotropic agents on exercise capacity in CHF. It has been well established that short-term treatment with vasodilator and inotropic agents often improves cardiac output and reduces elevated filling pressures without affecting maximal oxygen uptake or exercise capacity (Fig. 32).

Figure 32.



Short-term effects of vasodilators on exercise hemodynamics and exercise capacity in patients with left ventricular failure. C, control; H, hydralazine; ISDN, isosorbide dinitrate; PR, prazosin.

Data from 5 studies, compiled by Franciosa (1982).

The increased flow is directed to regions other than active skeletal muscle and the systemic A-V O_2 difference decreases (Franciosa, 1982). It is not clear to what extent the mode of action of the agent determines the effect on exercise performance (Franciosa, 1982; Packer and Jemtel, 1982; Weber et al., 1981; Weber, 1983), i.e. direct-acting vs. receptor-dependent vasodilators, β_1 specific vs. other inotropic agents (Table 5).

Table 5.

EFFECTIVENESS OF VARIOUS PHARMACOLOGIC THERAPIES: RESPONSE IN AEROBIC CAPACITY

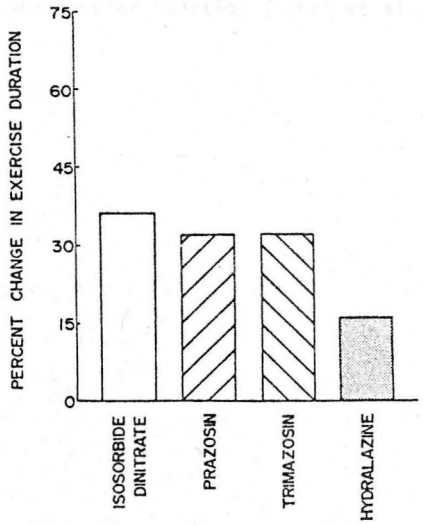
Drug	N	% AC Increase
Hydralazine (nonspecific vasodilator)	19	0% in 19 of 19
Trimazosin* (α_1-receptor antagonist)	27	20% in 23 of 27
Pirbuterol* (β-receptor agonist)	16	0% in 16 of 16
Amrinone* (inotropic agent of unclear action)	16	27% in 16 of 16

* Not approved for use by the U.S. Food and Drug Administration.
Data from placebo-controlled clinical trials at the University of Pennsylvania Hospital, 1977–1982.
AC = aerobic capacity.

From Weber (1983).

The effects of long-term treatment are more consistent with improvements of both hemodynamics and exercise capacity (Fig. 33).

Figure 33.



Long-term effects of vasodilators versus placebo on exercise capacity in patients with left ventricular failure.

Data from 7 studies, compiled by Franciosa (1982).

The systemic A-V O_2 difference is wider than in the untreated conditions or after acute administration of the drug which implies an improved distribution of flow (Franciosa, 1982; Packer and Jemtel, 1982; Weber et al., 1981; Weber, 1983). The delayed onset of the beneficial effects suggests that secondary adaptations are important. Such adaptations may at least partially be related to an increased physical activity after the initiation of treatment and represent a training effect. Other potential explanations include (1) improved renal perfusion which causes (a) decreased renin-angiotensin activity, (b) a diuresis with decreased salt and water content and decreased stiffness of the arteriolar walls (which improves the responsiveness to metabolic vasodilator agents), and decreased interstitial edema with improved capillary exchange, (2) decreased pulmonary congestion with decreased shortness of breath and improved gas exchange.

Role of physical training in CHF. Exercise therapy in patients with severe CHF may at first thought seem as irrational as treatment with beta-blocking agents. There are, however, reasons to believe that a carefully controlled exercise training program may be beneficial in some patients with CHF. As previously stated, increased capacity to vasodilate is one of the principal effects of physical training in normal subjects. Both the decrease in systemic resistance and the improved oxygen extraction after training in normal subjects are due to a relative increase in blood flow to active muscle, produced by a combination of an increased maximal vascular conductance, increased metabolic vasodilator drive, and decreased residual neurogenic vasoconstrictor activity. Training may well produce similar adaptations in CHF.

There is only limited clinical experience but the results are generally favorable. Carefully conducted programs appear to be safe and effective in terms of improving exercise capacity and symptoms. Vasoregulatory mechanisms have not been studied but the available results are consistent with an improvement due to peripheral and regulatory adaptations rather than to any primary changes in ventricular function (Letac et al., 1978; Lee et al., 1979; Conn et al., 1982).

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