Chronic Heart Failure

I. Quality of Life

H. Viefhues W. Schoene R. Rychlik (Eds.)

II. Nitrate Therapy

A. Kimchi B. S. Lewis M. Weiss (Eds.)

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Introduction

A. Schneeweiss

Although the syndrome of congestive heart failure has been recognized many years ago, the approach for its evaluation and treatment has until recently, been partial and 'fragmentary'. Various aspects of the disease have been treated according to the evaluation tools and therapeutic measures available at each period. This approach resulted in some of the greatest achievements in the management of heart failure but also left many aspects neglected and also resulted in several paradoxes.

Examples of the achievements and limitations of the 'fragmentary' approach are the use of diuretics and hemodynamic measurements. The development of diuretics has provided us with an important tool for helping patients whose predominant problem was edema. The success of diuretics masked the fact that their use may often be hemodynamically unsound and that they may reduce cardiac output. Only many years after their introduction has the use of diuretics found its appropriate place.

Hemodynamic monitoring has gone via the same path. The great contribution of continuous bedside hemodynamic measurements to understanding heart failure resulted in over-usage by many clinicians, who found themselves treating hemodynamic charts rather than patients. It took almost a decade to realize that hemodynamic improvement, even in the chronic setting, does not necessarily mean symptomatic improvement or an increase in exercise capacity.

In recent years the complexity of the heart failure syndrome has been better realized and a more rational, multifactorial approach to its evaluation and management has been developed. End-points of therapy concentrate on the patient and not on parameters that are convenient to measure. Survival and exercise capacity are two important and easily evaluated end-points of treatment. An equally important goal, but more difficult to measure, is quality of life. The first part of the following presentation concerns mainly quality of life. The second part concentrates on therapy and particularly on the use of nitrates for heart failure patients. An important aspect in this topic is early prevention of the post-infarction changes in the left ventricle, leading to heart failure. Nitrates have been found effective in preventing these changes.

The material of this part is based mainly on presentations given at the first international meeting on heart failure. My colleagues and I appreciate the initiative of the Chairmen, Profs. Lewis and Kimchi, who provided that stage for our presentation.

I. Quality of Life

The Pathophysiological Basis, Clinical Presentation, and Therapy of Chronic Heart Failure

M. Böhm and E. Erdmann

Heart failure is characterized by the inability to deliver the volume of blood required by the organism due to a reduction in cardiac pumping performance. This limitation affects all the organs of the organism and results in symptoms typical of heart failure. These symptoms are caused either by reduced blood supply to the organs or by congestion upstream of the right or left ventricle, also referred to as "low output failure." In contrast, there are also forms of heart failure with a high cardiac output ("high output failure"). This less common form of heart failure is found in reduced afterload (e.g., in sepsis) or metabolic disorders such as hyperthyroidism, anemia, beriberi, Paget's disease or arteriovenous fistulas. Heart failure occurs in these cases as a consequence of inadequate elevation in cardiac output in response to increased peripheral demand. Furthermore, in both forms of heart failure compensatory reactions take place which in themselves lead to further pathological changes in the heart and other organs, and can thus exacerbate the basic disease and its symptoms. In the following sections, the fundamentals of cardiac muscle contraction, the regulation of contractile force by the sympathetic nervous system, and the specific cardiac changes which result from heart failure will be discussed. In addition, the causes of heart failure, its diagnosis, and the possibilities for drug therapy will be described. Instrumental and surgical therapeutic procedures will not be dealt with.

The Molecular Basis of Cardiac Muscle Contraction

The myocardial cell contracts upon electrical stimulation. The electrical stimulus is propagated along the cell membrane and the invaginations of the sarcolemma (the so-called transverse tubular or T system). Depolarization of the cell membrane opens voltage-dependent calcium channels, which leads to an increase in the slow inward calcium current [20]. The calcium ions which pass into the cell release further calcium from intracellular stores of the sarcoplasmic reticulum [13]. The calcium entering the cell from outside acts as a calcium trigger, whereas the calcium released from the intracellular stores mainly contributes to myocardial contraction.

Muscular contraction is described in terms of Huxley's theory of sliding filaments [17]. This theory rests on the interaction of thick (myosin, molecular weight approximately 500000) and thin (actin, molecular weight approxi-

mately 45000) myofilaments. The parallel axis arrangement of the myofilaments (sarcomeres), each of which forms an approximately 1-μm-thick myofibril, is illustrated in Fig. 1. Muscle contraction is based on shortening of a large number of serially arranged sarcomeres. This process is activated by the binding of free calcium to troponin C, a regulatory subunit of the contractile apparatus [17]. Shortening, i.e., contraction, is caused by the displacement of the myosin and actin filaments relative to one another. This is brought about by the so-called cross-bridges. The heads of the myosin molecule or cross-projections connect the actin molecule to the myosin filament (Fig. 2). On contraction, a narrowing of the angle between the myosin neck and the myosin

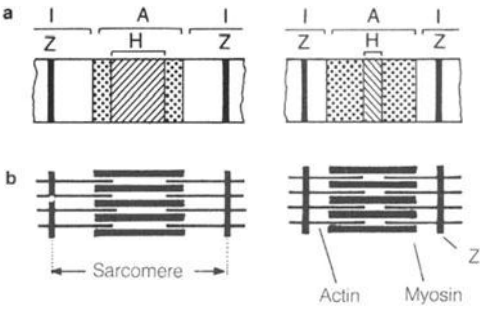

Fig. 1 a, b. Structure of the contractile apparatus of the heart, at rest *(left)*, and contracted *(right)*. In a myofibril there are about 1000 myosin molecules which are surrounded by around 2000 thinner actin molecules (**b**). The myosin molecules are attached to the Z line. The central portions of the sarcomere, which contain the thick myosin filaments with or without actin, appear under the light microscope as A bands (anisotropic picture). The lateral components which contain only actin are seen as I bands. The appearance of the central, actin-free H zone depends on the contractile condition of the myofibril. Microscopically, this molecular structure produces the typical picture of striated cardiac and skeletal muscle. (Modified from [28])

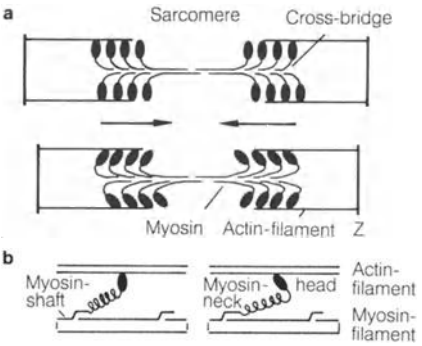

Fig. 2 a, b. Mechanism of the formation of cross-bridges in Mammalian hearts. **a** Myosin heads bind the myosin molecule to the actin filament. **b** Shortening of the muscle upon contraction occurs through a narrowing of the angle between the myosin head and myosin neck with a rapidly repeating binding and release of the cross-bridges from the actin molecule. (Modified from [28])

head occurs. Rapidly repeated binding and releasing of the myosin heads by the actin filament enable shortening of the muscle to take place [26].

The force of contraction is determined by the concentration of intracellular calcium available and the calcium sensitivity of the contractile proteins. Therefore, an increase in the force of contraction largely depends on increasing the inward flow of calcium and thus raising the intracellular calcium concentration [30]. This can be achieved either pharmacologically or through the physiological regulatory processes of the sympathetic nervous system. Upon exertion, the contractile force of the heart is augmented by activation of the sympathetic nervous system. Cardiac contractility is stimulated by sympathetic nerves and by the release of catecholamines from the adrenal medulla, kidneys, skeletal muscle, etc. The catecholamines released (norepinephrine and epinephrine) are able to activate membrane-based adenylate cyclase by binding to β-adrenoceptors in the myocardial cell membrane. Adenylate cyclase is an enzyme that, upon activation, forms increased quantities of cyclic adenosine monophosphate (cAMP) from ATP. The cAMP then activates cAMP-dependent protein kinase. This enzyme phosphorylates the sarcolemmal calcium channel, which leads to an elevation of the slow inward flow of calcium into the cell, and thereby to an increase in contractile force by facilitated calcium-induced calcium telease [27]. In diastole, about 88% of the calcium is transported back into the intracellular calcium store (sarcoplasmic reticulum) by a transport protein (phospholambam) in the membrane of the sarcoplasmic reticulum. Phospholambam can also be phosphorylated cAMP-dependently, a process which contributes to its enhanced activity during stimulation of β-adrenoceptors and leads to accelerated calcium uptake into the sarcoplasmic reticulum during diastole. The result is a more rapid relaxation of the cardiac muscle [34]. In addition to the reuptake of calcium into the sarcoplasmic reticulum mediated by phospholambam, there is also a sodium-calcium exchange mechanism which contributes to the elimination of calcium from the cytosol during diastole [19]. These mechanisms can be utilized in the treatment of heart failure with positive inotropic drugs (substances which augment contractile force; see below).

Etiology of Chronic Heart Failure

The most common cause of chronic heart failure is a decline in myocardial contractility as a consequence of long-term pressure or volume overload of one or both ventricles (arterial hypertension, recurrent pulmonary embolism, valvular defects) or dilated cardiomyopathy as a result of myocarditis. A further important cause is heart coronary disease, which causes a reduction in the oxygen supply to the myocardium. In addition to coronary heart disease, chronic anemia, hypoxemia due to pulmonary disease, hyperthyroidism, and direct impairment of myocardial contractility or a decline in the elasticity of the heart (e.g., myocardial inflammation, cardiomyopathy, amyloidosis, dys- or paraproteinemia, toxins, negative inotropically active drugs) can also be of

significance. Bradycardial and tachycardial dysrhythmias can also result in impairment of cardiac pumping ability and, through a reduction in cardiac output, can lead to the typical symptoms of heart failure. Normally, however, several of the above-mentioned basic diseases are present simultaneously, and their cumulative effects on the failing heart can cause acute deterioration and exacerbate the course of the disease by creating a vicious circle [32]. In this respect, the basis for successful treatment of heart failure would be to eliminate the underlying disorder responsible for the reduction in pumping function. Unfortunately, this is only rarely possible.

In principle, the pathogenesis of myocardial failure can be divided into myocardial mechanical and cell physiological aspects. Mechanically, changes in preload, afterload, contractility or heart rate can lead to acute pump failure. Changes in preload and afterload are mostly a consequence of pressure overload. The possible causes can be summarized as follows:

1. *Changes in the preload:* Abnormal volume conditions (e.g., hypervolemia, aortic incompetence, mitral incompetence, reduced venous supply)
2. *Changes in the afterload:* Abnormal pressure conditions (e.g., hypertension, cor pulmonale, arteriolar vasodilatation)
3. *Changes in contractility:* Ischemic heart disease, dilated cardiomyopathy drugs or toxins with negative inotropic action
4. *Changes in heart rate:* As a result of bradycardial and tachycardial dysrhythmia (below and above the so-called critical heart rate)

The cell physiological aspect refers to the influence of noxious substances on subcellular structures, such as:

1. Effect on cell membrane-based receptors for hormones and drugs (e.g., thyroid hormones, somatotropic hormone, β-adrenoapter antagonists, cardiac glycosides)
2. Effect on passive cell membrane permeability for ions(e.g., antiarrhythmic drugs such as lidocaine, anticholinergics, calcium antagonists, uremic toxins, nickel, saponin, various snake venoms, bee or wasp venoms)
3. Effect on active ion transport (e.g. cardiac glycosides, lithium, potassium)
4. Changes in sarcoplasmic reticulum function (e.g., through reduction in extracellular calcium concentration, after blockade of oxidative phosphorylation, after release of membrane damaging lysosomal enzymes, membrane damage due to snake venoms)
5. Oxidative phosphorylation disturbances (O_2 deficiency, cobalt, lead, thallium, CN/CO/halothane)
6. Effects on regulatory and contractile proteins. Changes in the sarcomeres (e.g., increase in preload), abnormal fibril growth (e.g., hypertrophic cardiomyopathy, obstructive cardiomyopathy)
7. Reduction in calcium-dependent ATPase activity (e.g., acidosis, cobalt, etc.)
8. Damage to the lysosomes with release of lysosomal enzymes (lead, snake venoms, viruses)