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PATHOPHYSIOLOGY OF THE LEFT HEART FAILURE

Methodical Support

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CONTENT

LIST OF ABBREVIATIONS

1. A – atrial wave
2. Ang II – angiotensine II
3. ADP – adenosine diphosphate
4. ATP – adenosine triphosphate
5. ATPase – adenosine triphosphatase
6. CO – cardiac output
7. cAMP – cyclic adenosine monophosphate
8. DHF – diastolic heart failure
9. E – mitral wave
10. ECM – extracellular matrix
11. EDP – end diastolic pressure
12. EDV – end diastolic volume
13. EF – ejection fraction
14. ET – ejection time
15. ET-1 – endothelin 1
16. F_{max} – maximal force of contraction
17. HF – heart failure
18. h – ventricular wall thickness
19. ICT – izovolumetric contraction time
20. IL – interleukin
21. IP3 – inositol phosphate
22. IRT – izovolumetric relaxation time
23. LV – left ventricle
24. LVEDP – left ventricular end diastolic pressure
25. LVHF – left ventricular heart failure
26. MMPs – matrix metalloproteinases
27. P – ventricular pressure
28. r – ventricular chamber radius
29. RAAS – renin-angiotensin-aldostenone system
30. ROS – reactive oxygen species
31. RV – right ventricle
32. SERCA – sarco-endoplasmic reticulum calcium-ATPase
33. SHF – systolic heart failure
34. SR – sarcoplasmic reticulum
35. SSF – systolic shortening fraction
36. SV – systolic volume
37. TGF β – transforming growth factor beta
38. TNC – troponin-C
39. TNF-α – tumor necrosis factor alpha
40. V_{max} – maximal velocity of contraction

PREFACE

This methodical support represents a synthesis of the most important conceptual data concerning the pathophysiology of left heart failure. It underlines the pathogenic significance of the crucial mechanisms involved in the appearance and exacerbation of both patterns of heart failure: systolic and diastolic. The reader of this work will understand better why and how both systolic end systolic and end diastolic volumes of left ventricle in systolic heart failure increase both in conditions of compromised inotropic response. Likewise, mechanisms leading to lusitropic dysfunction that contributes to stroke volume and cardiac output decreasing despite the preservation of the ejection fraction are emphasized. It is noteworthy, the explanation of cornerstone mechanisms is illustrated by synoptic and comprehensive schemes showing how the classical cardiac laws are realized in a failed heart: length-force relation (Starling's mechanism), velocity-force relation (Sonnenblick's mechanism), frequency-force relation (Bowditch's mechanism). The role of myocardial hypertrophy and fibrosis in diastolic and systolic disorders is discussed on cellular and molecular levels with identification of the factors triggering the left ventricle pump function worsening.

On the other hand, the principle functional and circulating markers and predictors of heart failure are related with specification of their pathophysiological significance. The presence of a common interface between inflammatory response, neuroendocrine activation, collagen turnover disturbance, melusin expression and macroergic phosphates lack is depicted in the pathogenesis of heart failure exacerbation.

The contemporary concepts regarding the pathophysiology of stunning and hibernating myocardium as an aftermath of ischemic impact are treated as well.

These viewpoints, taken together, will contribute to better understanding of real mechanisms of heart failure.

This work could be useful for students studying systemic pathophysiology in the 3rd year, for students studying clinical pathophysiology in the 4th year, and residents as well.

1. GENERAL NOTIONS

Heart failure (HF) is a heterogenous clinical syndrome common for many cardiovascular disorders which is manifested by ventricular incapacity to pump sufficient blood matching peripheral oxygen and metabolic peripheral needs.

In developed countries the overall prevalence of HF in the adult population is 2%, and its rate is rising with age, and it affects 6–10% of people over age 65. Although the relative incidence of HF is lower in women than in men, women constitute at least one-half of HF cases because of their longer life expectancy.

According to the affected side of the heart the following forms of HF are distinguished:

– left HF, which is due to the left ventricle (LV) inability to pump enough blood in the systemic circuit, and is manifested by blood congestion in the pulmonary system;

– right HF, which results from the right ventricle (RV) inability to pump enough blood in the pulmonary circuit, and is manifested by blood congestion in the systemic circulation.

The International Right Heart Foundation Working Group adopted a comprehensive definition of RHF: "A clinical syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to suboptimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures – at rest or with exercise". The right HF can be isolated or might be a consequence of left ventricular dysfunction associated with pulmonary congestion.

According to the predominant dysfunction of diastole or systole the following patterns of LVHF are distinguished:

1. Diastolic heart failure (DHF).
2. Systolic heart failure (SHF).

At a certain phase of evolution the DHF could demonstrate signs of systolic dysfunction and *vice versa*: DHF encompasses signs of diastolic abnormalities.

The key repercussion of both DHF and SHF is a progressive decreasing of cardiac output (CO) leading to oxygen delivery impairment. Alteration of preload and/or afterload represents the main precondition of pump dysfunction beginning.

Evolution of heart failure means also an involvement of local and generalized compensatory mechanisms aiming a clear target: from one hand to confine the

progression of pump function inability, and on the other hand to improve the peripheral circulation in order to alleviate tissue oxygen supply.

In this regard it should be noted that myocardial structural, metabolic and functional changes of failed heart are summarized in the entity of cardiac remodeling attributed to both contractile cardiomyocyte and extracellular matrix.

2. SYSTOLIC HEART FAILURE (SHF)

SHF is a type of heart failure manifested by incapacity of the left ventricle to develop an adequate intraventricular pressure during the systole necessary for ensuring a cardiac output for a normal supply of peripheral tissues with oxygen. The cardinal sign of SHF is not only reduction of cardiac output (like diastolic heart failure), but a decline of ejection fraction of the LV (EF < 40%).

The most important pathogenical factors leading to SHF are myocardial ischemia (e.g. ischemic heart disease) associated with progressing energy depletion, contractile cardiomyocytes loss (e.g. myocardial necrosis and marked apoptosis) and disorders in the signal transduction regulating cardiac excitation-contraction coupling. The last appears as a common mechanism of different patterns of SHF.

Excitation-contraction coupling represents a phenomenon whereby the action potential triggers the cardiomyocytes to contract. When a cardiac cell is depolarized calcium ions enter the cell during phase 2 of the action potential through L-type calcium channels located on the sarcolemma (fig. 1).

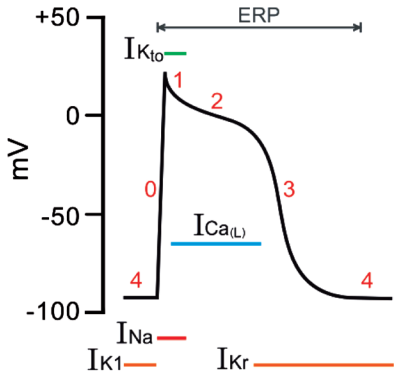


Figure 1. Phases of action potential of the contractile cardiomyocyte (non-pacemaker)

Phase 0 is caused by a transient increase in fast Na^+ – channel conductance (potassium channels are closed in this time). Phase 1 – an initial repolarization that is caused by the opening of a special type of transient outward K^+ channel producing a short-lived, hyperpolarizing outward K^+ current (I_{Kto}). Phase 2 (plateau) is due to calcium entering $I_{Ca(L)}$ through long-lasting (L-type) calcium channels that open up when the membrane potential depolarizes to

about –40 mV. This plateau phase prolongs the action potential duration and distinguishes cardiac action potentials from the much shorter action potentials found in nerves and skeletal muscle. Phase 3 – repolarization (K ion efflux inactivating Ca channels). Phase 4 – resting membrane potential.

The entered in cardiomyocyte calcium triggers a subsequent release of calcium that is stored in the sarcoplasmic reticulum (SR) through special calcium-release channels named as ryanodine receptors. Calcium released by the SR increases the intracellular calcium concentration from about 10^{-7} to 10^{-5} M. The free calcium binds to troponin-C (TN-C) that is part of the regulatory complex attached to the thin filaments. When calcium binds to the TN-C, this induces a conformational change in the regulatory complex such that troponin-I (TN-I) exposes a site on the actin molecule that is able to bind to the myosin ATPase located on the myosin head. This binding results in ATP hydrolysis that supplies energy for a conformational change to occur in the actin-myosin complex (fig. 2).

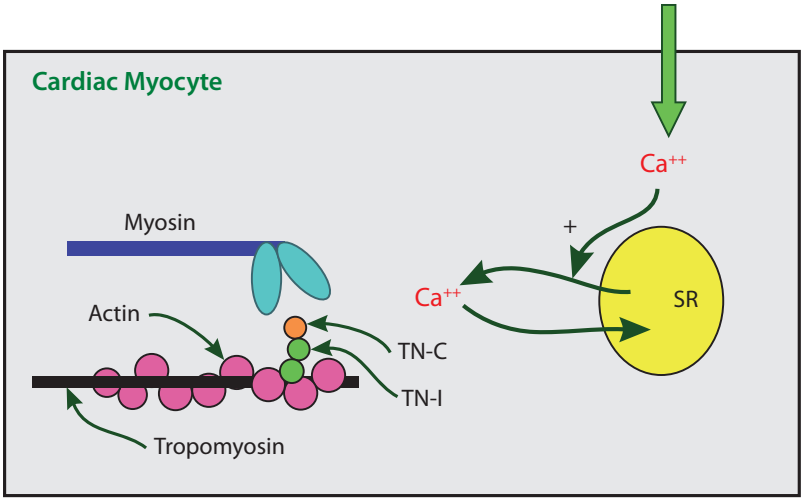


Figure 2. Cardiac myofilaments. Myosin (thick filament) containts two heads having ATPase activity. Thin filament is made up of actin, tropomyosin, and troponin (TN). TN-C binds Ca^{++} released by the sarcoplasmic reticulum (SR). TN-I inhibits actin-myosin binding until Ca^{++} binds to TN-C

The result of these changes is a movement between the myosin heads and the actin, such that the actin and myosin filaments slide past each other thereby shortening the sarcomere length (fig. 3).

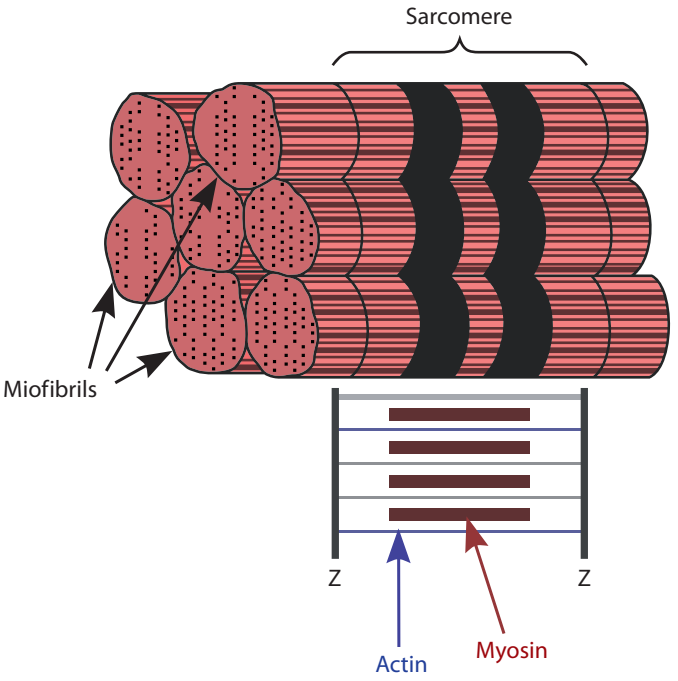


Figure 3. Cardiac myocyte composed of myofibrils, each of which contain's myofilaments. The sarcomere lie's between two Z-lines

Cardiac myocyte is a specialized muscle cell that is approximately 25 μ in diameter and about 100 μ in length. The cardiac myocyte is composed of bundles of myofibrils that contain myofilaments. The myofibrils have distinct, repeating microanatomical units, termed sarcomeres, which represent the basic contractile units of the myocyte. A sarcomere is defined as the region of myofilament structures between two Z-lines. The distance between Z-lines (i.e., sarcomere length) ranges from about 1.6 to 2.2 μ in human hearts. The sarcomere is composed of thick and thin filaments – myosin and actin, respectively. Chemical and physical interactions between the actin and myosin cause the sarcomere length to shorten, and therefore the myocyte to contract during the process of excitation-contraction coupling. The interactions between actin and myosin serve as the basis for the sliding filament theory of muscle contraction.

Myosin is a protein having a molecular weight of approximately 470,000 daltons. There are about 300 molecules of myosin per thick filament. Each myosin contains two heads that are the site of the myosin ATPase, an enzyme that hydrolyzes ATP required for actin and myosin cross bridge formation. These heads interact with a binding site on actin.

At the end of phase 2, calcium entry into the cell slows and calcium is sequestered by the SR by an ATP-dependent calcium pump (SERCA, sarco-endoplasmic reticulum calcium-ATPase), thus lowering the cytosolic calcium concentration and removing calcium from the TN-C. To a quantitatively smaller extent, cytosolic calcium is transported out of the cell by the sodium-calcium-exchange pump. The reduced intracellular calcium induces a conformational change in the troponin complex leading, once again, to TN-I inhibition of the actin binding site. At the end of the cycle, a new ATP binds to the myosin head, displacing the ADP, and the initial sarcomere length is restored.

Mechanisms that enhance the concentration of cytosolic calcium increase the amount of hydrolyzed ATP and the force generated by the actin and myosin interactions, as well as the velocity of shortening. Physiologically, cytosolic calcium concentrations are influenced primarily by beta-adrenoreceptor-coupled mechanisms. Beta-adrenergic stimulation, as occurs when sympathetic nerves are activated, increases cAMP which in turn activates protein kinase to increase in calcium entry into the cell through L-type calcium channels. Activation of the inositol phosphate (IP_3) signal transduction pathway also can stimulate the release of calcium by the SR through IP_3 receptors located on the SR. Furthermore, activation of the cAMP-dependent protein kinase phosphorylates a protein (phospholamban) on the SR that normally inhibits calcium uptake. This disinhibition of phospholamban leads to an increased rate of calcium uptake by the SR. Therefore, beta-adrenergic stimulation increases the force and shortening velocity of contraction (i.e., positive inotropy), and increases the rate of relaxation (i.e., positive lusitropy).

In systolic heart failure one or more mechanisms responsible for calcium control and actin-myosin formation availability can be impaired.

Firstly, it is the mechanism of altered feasibility of beta-adrenergic dependent fashion of L-type calcium channel activation. In heart failure, even in an early phase an increased activity of sympatho-adrenergic system is established. This phenomenon leads to beta-adrenergic receptors down regulation.

Secondly, decreased number or activity of ryonide receptor of sarcoplasmic reticulum can lead to lowered sequestration of calcium into sarcopalsma during the phase 2 of action potential. As result the systolic calcium pool does not reach a level needed for an adequate actin-myosin bridges formation.

Thirdly, reduced responsiveness of troponin C to calcium action that can alter the TrI functioning and decrease number of actin-myosin links.

Fourthly, mismatching cooperation between TrC and TrI resulting in a failed discovery of actin fields for myosin heads.

Fifthly, decreased of ATP amount that confines the actin and myosin filaments interaction.

Sixthly, decreased expression of phospholamban or decreased activity of its phosphorylation by cAMP dependent mechanism can overactivate SERCA2α leading to premature calcium evacuation detrimentally to actin-myosin interaction.

Intrinsic myocardial contractility loss is a pattern of decreased inotropic response to natural agents like catecholamines, endothelin 1 and angiotensin II. It is a very important loop of HF pathogenesis as a preconditioning of blood congestion in the pulmonary circle does to left ventricle pump function disability. The major predictor of pump dysfunction is progressive diminution of ejection fraction. More than that, decreased myocardial contraction is a precondition of left ventricle dilatation and worsening of heart failure. Cardiac cavity dilatation is considered as a sign of end stage HF.

How can dilatation develop in systolic dysfunction?

Decreased myocardial contraction leads to progressive elevation of LV end systolic volume. Gradual increase of end systolic volume leads to the increase of LV end diastolic volume, but both stroke volume and ejection fraction remain below normal level. Likewise, the LV shortening fraction is decreased.

However, increased end diastolic volume measured as increased ventricular end-diastolic pressure or pulmonary capillary wedge pressure associated with incomplete ventricular emptying means a rise of preload. It could be an important compensatory event because it activates the Frank-Starling mechanism in order to maintain stroke volume despite the loss of myocardium inotropy. Indeed, for a certain time Frank-Starling mechanism including might blunt the slope of pump function decline because this myogenic mechanism is the most efficient endeavor in conditions of energy depletion.

Note that in patients with systolic dysfunction myocardial diastolic disorders often occur mainly due to energy lack. If preload does not rise, the decline in stroke volume would be even greater for a given loss of inotropy.

Nevertheless, earlier or later the failure heart will trigger a phenomenon of ventricular remodeling with a pattern of dilation.

Both contractile performance decrease and intrinsic inotropy loss are changing in ventricular pressure-volume relation. They are manifested by decreasing the slope of the end-systolic pressure in response to the end diastolic volume elevation ratio (fig. 4).

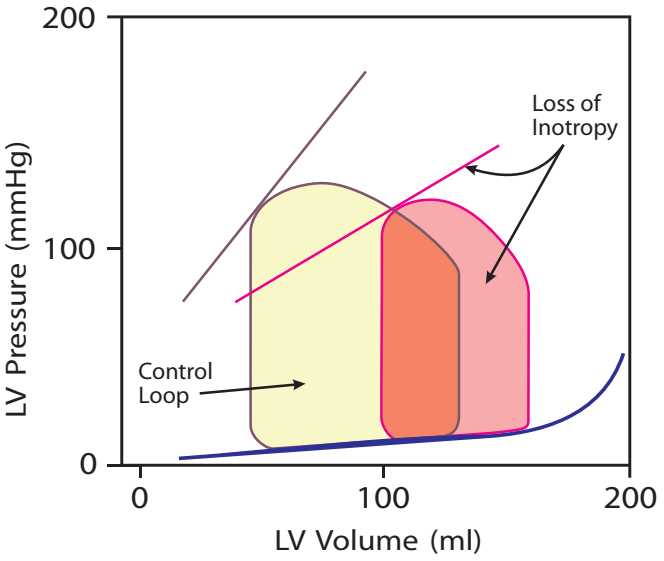


Figure 4. Effects of acute left ventricular failure (loss of inotropy) on left ventricular pressure-volume loop. Heart rate unchanged

Thus, the efficiency of Starling mechanism is decreased and the stroke volume (shown as a width of the pressure-volume loop) falls despite the increase of end diastolic volume. As the stroke volume decreases and the end-diastolic volume increases, there is a substantial reduction in ejection fraction.

It is noteworthy, systolic heart failure is always accompanied by decreased ejection fraction because myocardial inotropy loss compromises the functional worth of Frank-Starling mechanism.

A decrease in inotropy shifts the Frank-Starling curve downward (point A to B in the figure 5). This causes the stroke volume (SV) to decrease and the left ventricular end diastolic pressure (LVEDP) and end diastolic volume to increase. The change in stroke volume is the primary response, whereas the change in left ventricular end diastolic pressure is a secondary response to the change in pumping parameter. If inotropy is increased (such as occurs during exercise), the Frank-Starling curve shifts up and to the left (point A to C in the figure 5), resulting in an increase in stroke volume and a decrease in left ventricular end diastolic pressure.

Once a Frank-Starling curve shifts in response to an altered inotropic state, changes in ventricular filling will alter stroke volume by moving either up or down the new Frank-Starling curve.

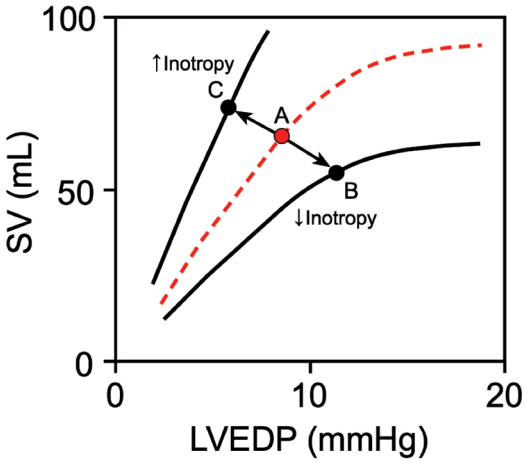


Figure 5. Role of myocardium inotropy role in Frank-Starling mechanism (pattern of SV and LVEDP relation)

The decreased myocardium inotropy as a key mechanism of systolic dysfunction has serious consequences of quality of Sonnenblic mechanism or force-velocity relation. It refers to myocardial shortening velocity dependence on afterload level and provides insight as to why a loss of contractility causes a reduction in stroke volume. A loss of inotropy results in a decrease in the shortening velocity of cardiac fibers. Because there is only a finite period of time available for ejection, a reduced velocity of ejection results in less blood ejected per stroke. The residual volume of blood within the ventricle is increased (increased end-systolic volume) because less blood is ejected.

The classical study describing the force-velocity relationship for cardiac muscle using cat papillary muscles was published by Edmund Sonnenblick in 1962. We all experience this, for example, when we lift heavy versus light objects. The heavier the object that we lift, the slower our muscles contract. In summary, there is an inverse relationship between shortening velocity and afterload (fig. 6).

If the inotropic state of the cardiac fiber is increased, there is a parallel shift in the force-velocity curve such that there is an increase in both V_{max} and in maximal isometric force (F_{max}) (fig. 7).

The increase in velocity at any given preload results from the increased inotropy enhancing force generation by the actin and myosin filaments, and increasing the rate of cross bridge turnover. The increase in V_{max} is particularly noteworthy because V_{max} represents the intrinsic capability of a muscle fiber to generate force independent of load.

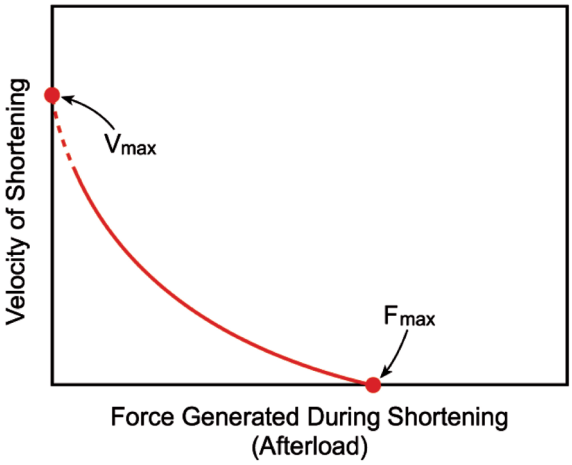


Figure 6. Sonnenblick's mechanism: relation between velocity and force Changes in inotropy alter the force-velocity relationship

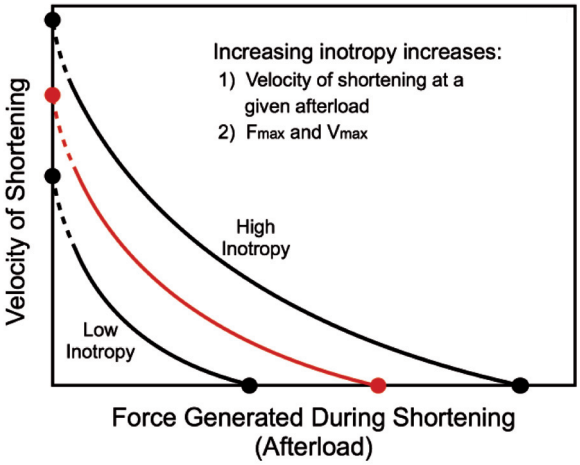


Figure 7. Inotorpy influence on velocity-force relation

Changes in inotropy produce significant changes in ejection fraction.

EF (%) is calculated as stroke volume divided by end-diastolic volume. It is commonly used as a clinical index to assess the inotropic state of the heart. In heart failure, for example, there often is a decrease in inotropy that leads to a fall in stroke volume as well as an increase in preload, thereby decreasing EF.

Changes in inotropic state are particularly important during exercise. Increases in inotropic state help to maintain stroke volume at high heart rates and elevated arterial pressures. Increased heart rate alone decreases stroke volume

because of reduced time for diastolic filling, which decreases end-diastolic volume. Elevated arterial pressure during exercise increases afterload on the heart, which tends to reduce stroke volume.

When the inotropic state increases at the same time, the end-systolic volume decreases so that the stroke volume can be maintained and allowed to increase despite reduced time for ventricular filling and elevated arterial pressure.

Thus, the reduced inotropy in SHF is an opportune condition for decrease of myocardial shortening velocity which results in the increased time of isovolumetric contraction. On the other hand, the ejection time increases respectively. As a consequence stroke volume falls and end systolic volume rises. Increasing of the end systolic volume leads to pleload level elevation which likewise needs including of velocity-force relation (fig. 8).

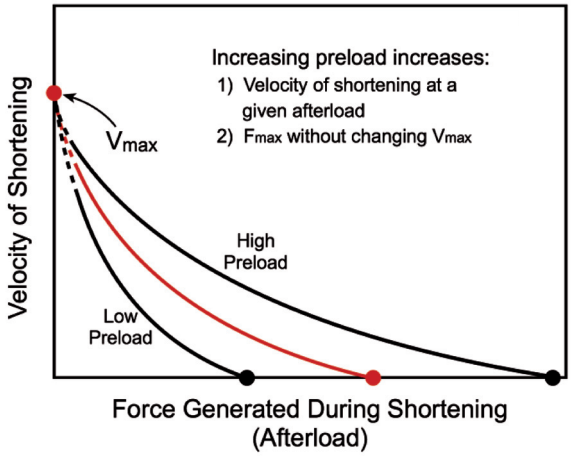


Figure 8. Preload effect in the force-velocity relationship

According to Sonnenblick phenomenon increased preload leads to acceleration of isovolumetric contraction, and to increased myocardium shortening velocity. Impaired inotropy does not ensure a normal pump functioning, and as a result the repercussion end diastolic volume begins to rise.

Hence, conceptually SHF should be viewed as a loop of functional consequences of central hemodynamics triggered by unable inotropic capacity of the worn-out myocardium resulting in the end diastolic volume increase followed by the end diastolic volume elevation, stroke volume decrease and finally ejection fraction decline.

The most important mechanism regulating inotropy is the autonomic system and neuroendocrine activity. Sympathetic nerves play a prominent role in ventricular and atrial inotropic regulation, while parasympathetic nerves (vagal

efferents) have a significant negative inotropic effect in the atria but only a small effect in the ventricles.

The most important cardiac effect is attributed to norepinephrine which markedly increases shortening velocity at the same afterload lever (fig. 9).

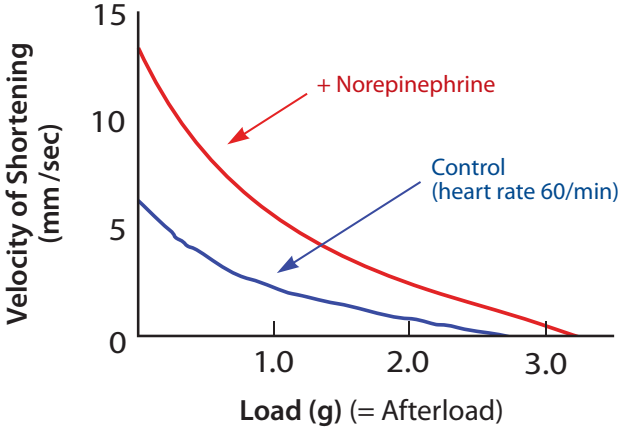


Figure 9. Velocity force relation under norepinephrine action

Under certain conditions (e.g., exercise, stress and anxiety), high levels of circulating epinephrine augment sympathetic adrenergic effects.

In the human heart, an abrupt increase in afterload can cause an increase in inotropy (so called the Anrep effect).

The Anrep effect is observed when a sudden increase in afterload on the heart causes an increase in ventricular inotropy. The phenomenon is observed in denervated hearts and isolated cardiac muscle, as well as in intact hearts; therefore, it represents an intrinsic change in inotropy. A sudden increase in aortic pressure, for example, causes a rapid increase in left ventricular end-diastolic volume. This leads to an initial increase in the contractile force of the ventricle through the Frank-Starling mechanism. If the increased afterload is maintained for 10-15 minutes, the force of contraction increases further, and in the intact heart, the end-diastolic volume begins to decrease.

The functional significance of the Anrep effect is that the increased inotropy partially compensates for the increased end-systolic volume and decreased stroke volume caused by the increase in afterload. Without this mechanism, increases in afterload would cause greater reductions in stroke volume than what is normally observed. The mechanisms responsible for the initial response and the delayed response appear to be different. The initial increase in contractile force (Frank-Starling mechanism) is largely due to increased troponin C sensitivity to calcium. The delayed response likely involves several mechanisms that promote increased release of calcium by the sarcoplasmic reticulum.

An increase in heart rate also stimulates inotropy (Bowditch effect or frequency-dependent inotropy) due to accumulation of intracellular calcium via the sodium-calcium exchanger.

Systolic heart failure is accompanied by the impairment of both velocity-force relation and frequency-force relation, and they are relied on myocardial inotropy disorders.

A recent European definition of HF is as: "Heart failure is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiological circulation. The syndrome of heart failure is characterized by symptoms such as breathlessness and fatigue, and signs such as fluid retention."

Systolic heart failure is the most important pattern of HF leading to blood congestion in the pulmonary circle (increased arterial pulmonary pressure and pulmonary capillary wedge pressure) producing disorders in gaseous exchange, a patophysiological support of dyspnea.

Pulmonary edema is a condition associated with increased loss of fluid from the pulmonary capillaries into the pulmonary interstitium and alveoli.

Pulmonary edema of cardiac origin most commonly results from an increase in pulmonary capillary pressure caused by an elevation of left atrial pressure (pulmonary capillary wedge pressure) associated with left systolic ventricular failure. Pulmonary hypertension can also lead to elevated capillary pressures and pulmonary edema.

When the right ventricle becomes unable to pump adequately blood in the pulmonary system with increased arterial pressure a blood congestion begins in the circulatory pool of vena cava inferior manifested by peripheral edema. The last is boosted by increased activity of rennin-angiotensin-aldosteron system causing fluid retention in the organism.

The Ang II effects are versatile and point important targets of circulatory homeostasis: vasoconstriction, sympathetic activation, myocardial hypertrophy, fibroblast activation, extracellular matrix growing, increase of free oxygen radicals production, expression of inflammatory cytokines, etc.

Increased neuroendocrine activity leads to myocardium hypertrophy as a pattern of heart remodeling. Volume overload triggers excentric hypertrophy development. Prolongation of myocytes by serial apposition of sarcomeres might insure a rise of velocity and extent of shortening with an unchanged tension.

Pressure overload conduces to concentric hypertrophy. Thickening of myocytes by parallel apposition of sarcomeres increases tension with an unchanged extent of shortening.

Hypertrophy is a condition of decreased ratio capillaries/cardiomyocytes and myocardium ischemization detrimentally to energy synthesis.

3. DIASTOLIC HEART FAILURE

Diastolic heart failure is a pattern of HF manifested by diastolic relaxation impairment. As contractility capacity is not altered for a certain time ejection fraction (EG) of the left ventricle remains normal. Therefore DHF is defined as HF with preserved EF (> 45%). The incidence of DHF with preserved EF increases with age due to the related diastolic disorders of the myocardium. In younger patients the primary diastolic dysfunction is a result of 2 major causes:

1. Alteration of the active diastole (lusitropy) due to calcium homeostasis and calcium turnover impairment.
2. Alteration of the passive diastole due to diastolic compliance loss because of myocardial hypertrophy and/or fibrosis.

Both causes lead to the left ventricle filling abatement resulting in a decrease of systolic volume. Thus, in DHF with isolated or predominant diastolic dysfunction the stroke volume is lowered and consequently cardiac output also decreases. So, despite preserving the EF diastolic dysfunction is a cause of heart failure because due to cardiac output fall the oxygen delivery to peripheral tissues is compromissed.

Normaly diastole has a duration of about 2/3 from the cardiac circle and consists of 2 components: active and passive which form together 5 phases:

(1) protodiastole, (2) isovolumic relaxation, (3) rapid filling, (4) diastasis and (5) atrial kick.

Isovolumic relaxation (0.03-0.06 sec) is considered as an active phase of diastole being strongly energy dependent. As this phase is produced in isovolumic conditions (aortic and mitral valves are closed – no LV filling) the intraventricular pressure rapidly falls and induces an adequate gradient for ventricular filling.

The used energy for isovolumic relaxation stemed mainly from glucose oxidation is necessary for calium elimination in sarcoplasmic reticulum by specific calcium ATPase pump (SERCA2a) and respective actin-myosin binds decoupling. Therefore all causes leading to energy lack are responsible for isovolumic relaxation impairment. Among them are noteworthy myocardial ischemia (coronary artery diseases), metabolic and endocrine disorders such as diabetes mellitus, metabolic syndrome, hypothyroidism etc.

SERCA2a expression enhancement is a promising tool for calcium elimination during diastole. This process is controlled by phospholamban in an indirect manner. Hence, the last factor expression increase in DHF is a cause of

SERCA2a activity and expression diminution that leads to calcium excessive accumulation in the cardiomyocyte. Finally, calcium excess can be extended to mitochondria while these organels are able to store Ca in cases of cation accumulation in the sarcoplasma. However, mitochondrial calcium store has negative outcomes because it induces oxidation-phosphorilation decoupling and energy decline. On the other hand, oxidative stress activation due to increased reactive oxygen species formation alters the calcium metabolism and ATP formation.

It is considered that calcium heart homeostasis abnormality is an early predictor of diastolic heart feailure. It is chiefly a result of ATP depletion, ischemia and both SERCA2a low expression and amount. Importantly to underline, that an incipient mechanisms of calcium excess is increased myofibril sensitivity to cation.

In patients with ischemic heart disease the diastolic dysfunction is the first manifestation and the first cause of HF. However, quite rapidly diastolic dysfunction if followed by systolic derangements due to inotropy impairment.

Even a decreased myocardial contractility can ensure a normal ejection fraction because the stroke volume is reduced. Therefore, in ischemic heart disease the heart failure for a certain long time is characterized by DHF pattern with a preserved EF appraisal. When energy deficiency due to myocardial ischemia impairs myocardium systole diastolic dysfunction is accompanied by systolic dysfunction. As consequence a mixed or combined heart failure develops.

The early functional sign of DHF is decreased isovolumic relaxation velocity and slope of the intraventricular diastolic pressure fall. It chiefly regards to isovolumic relaxation phase disturbance.

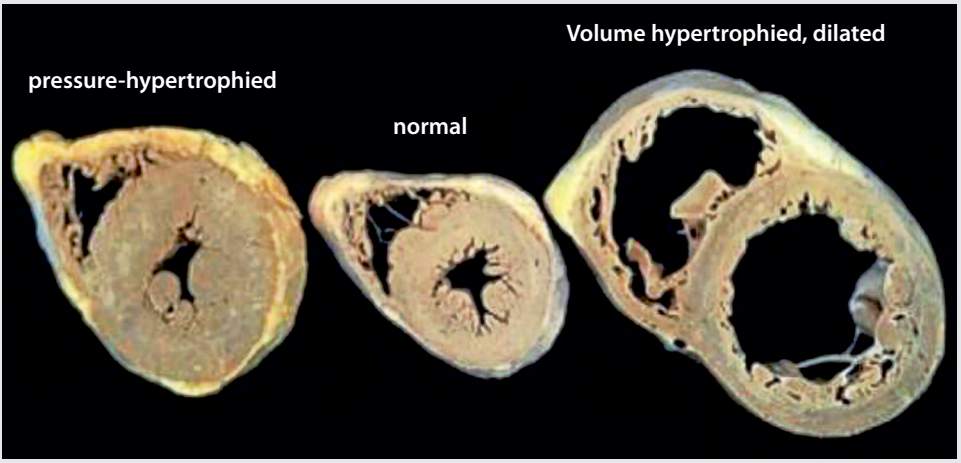
Passive diastole is a functional entity of the ventricular filling (3^{rd} and 4^{th} phases) followed after isovolumic relaxation when both the atrial and mitral valves open. It is correlated with myocardial distensibility of stiffness or so called diastolic compliance. This property is ensured by an adequate ration between cardiomyocyte size and space of myocardium interstitium. The last can increase due to excessive collagen synthesis or necrotic myocardium replacement by collagen (process of scaring).

Thus, myocardial hypertrophy and fibrosis are 2 major causes affecting diastole, primary passive relaxation. They are inherent to patients with arterial hypertension and patients with post-infarction sclerosis or fibrosis.

A hypertensive patient demonstrates a prime diastolic dysfunction resulting in DHF manifested by normal EF and decreased stroke volume even the contractile

capacity is raised. A patient with myocardial infarction with increased diastolic stiffness has in 40-50% cases a pattern of DHF.

In case of arterial hypertension or aortic stenosis myocardial hypertrophy might develop in 2 distinct patterns: concentric or eccentric (fig. 11).



Left ventricular hypertrophy with and without dilation, viewed in transverse heart sections. Compared with a normal heart (*center of figure*), the pressure-hypertrophied hearts (*left*) have increased mass and a thick left ventricular wall, while the hypertrophied, dilated heart (*right*) has increased mass and a normal wall thickness.

Figure 11. Three macro-patterns of myocardium (from left to right): concentric hypertrophy, normal and eccentric hypertrophy

In diastolic dysfunction the most important role is referred to concentric hypertrophy because in parallel located myofibrils from one hand, myocardium thickness increase , and, from the other hand, the left ventricle cavity decrease.

In the pattern of eccentric hypertrophy myofibrils in series arranged do not change the ventricular cavity, but due to increased stiffness confine the myocardial compliance.

In concentric hypertrophied myocardium the end diastolic volume decreases correlatively to left ventricle diameter diminution. In this situation the Frank-Starling law efficiency is poor. However, the contraction ability of hypertrophied myocardium is boosted, a fact which leads to more active systolic ejection of the blood. As result the end systolic volume also increases, but finally the stroke volume is reduced despite the ejection fraction is normal.

In eccentric hypertrophy of myocardium the end diastolic volume is reduced lesser because increased diastolic stiffness. Therefore the stroke volume diminution is not so marked like in concentric hypertrophy.

Most of this elastic force is now thought to reside in the macromolecule titin, whereas contributions of microtubules (tubulin) and intermediate filaments (desmin) appear < 10% at operating sarcomere lengths.

Titin is expressed as varying isoforms that impart different mechanical properties, and this likely plays a role in altering passive stiffness in failing hearts. Titin can also be post-translationally modified by Ca^{2+} (even in the diastolic range) and by phosphorylation, blurring notions of passive versus active tone.

Diastolic tension is produced not only by titin extension but also by titin–actin interaction through disk Z, and this can be inhibited in a calcium-dependent manner by S100A1, a calcium-binding protein abundantly present in the myocardium (fig. 12).

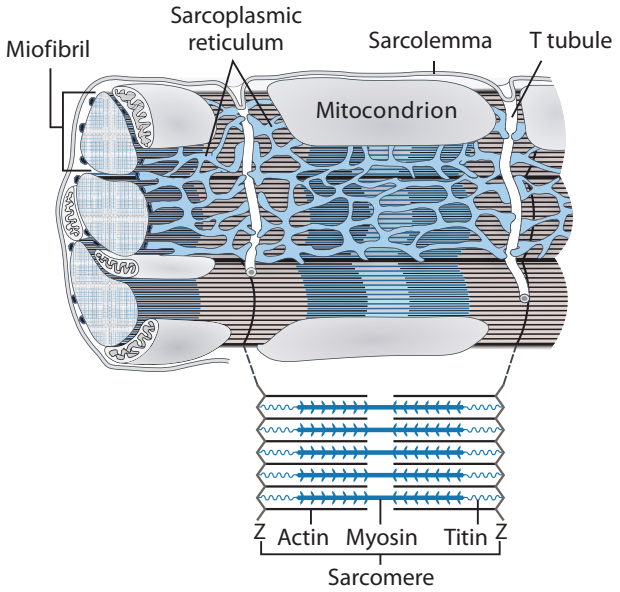


Figure 12. Titin assembly in the sarcomere

Direct consequences due to myocardial hypertrophy:

→ Wall stress is often increased in heart failure due to either ventricular dilatation or the need to generate high systolic pressures to overcome excessive afterload.

→ Wall stress is estimated from *La Place's relationship*, in which the wall stress (σ) is proportional to ventricular pressure (P) and ventricular chamber radius (r), and inversely proportional to ventricular wall thickness (h):

$$\sigma = \frac{P \times r}{2h}$$

→ In response to a sustained increase in pressure and chamber radius, hypertrophy of the ventricular myocytes is stimulated.

→ The increased mass of muscle fibers serves to maintain contractile force and counteract the elevated ventricular wall stress.

→ Eventually, the chamber may dilate out of proportion to wall thickness, resulting in excessive hemodynamic burden on the contractile units, rapid deterioration of ventricular function and worsening of symptomatology.

→ Lowering wall stress as a way to slow the remodeling process is a common therapeutic target.

The lusitropic effect in a hypertrophied heart might be augmented in a state of hyperthyroidism because T3 hormone positively regulates the expression of Ca-ATP-ase of sarcoplasmic reticulum (SERCA2a). In patients with hypothyroidism, inversely, the isovolumic relaxation is markedly delayed and they as a rule often have early signs of diastolic heart failure.

Pathophysiologically, the pressure-volume relation is considered to be the most important mechanism of left ventricle filling in DHF.

In patients with diastolic dysfunction (e.g. due to excessive interstitial fibrosis), but without myocardial hypertrophy the pump function decline could develop faster because of length-force relation impairment and decreased ejection pressure (fig. 13). This phenomenon is usually a way of progressive increasing of end systolic pressure.

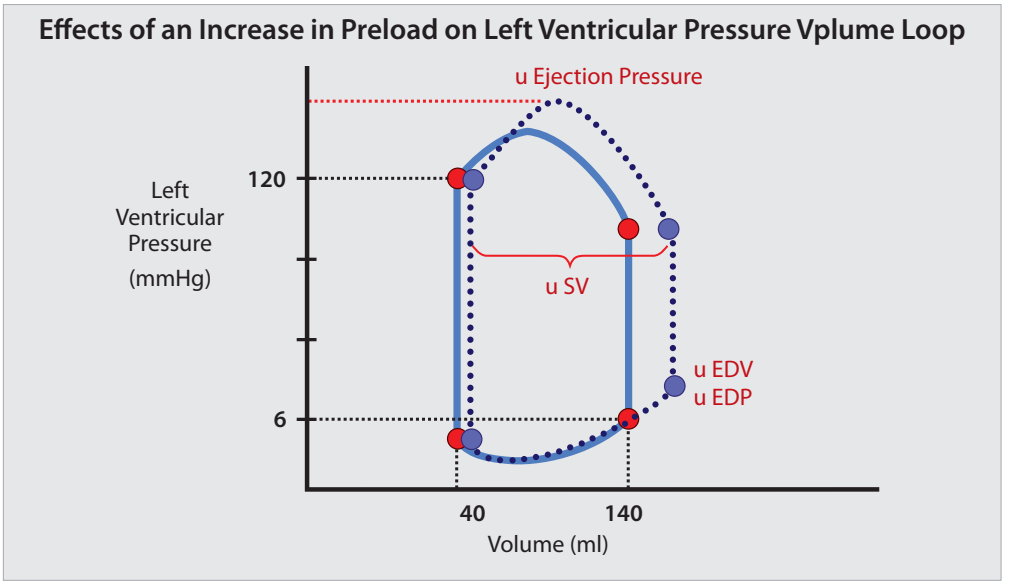


Figure 13. Dependence of ejection pressure on end diastolic volume and pressure

The decrease of ventricular filling leads to a lower intraventricular systolic pressure, and to a risk of ejection fraction reducing. Respectively, DHF begins to be associated with systolic heart failure.

Shifting to right and down of the length-force relation curve is a precondition of heart maladaptation to increased afterload (fig. 14).

Peripheral resistance rising claims a bigger contractile power and it could be realized mainly y 2 mechanisms: (1) increase of inotropy and (2) Frank-Starling mechanism involvement.

It is remarkable that inotropy stimulation by catecholamines is associated with lusitropy activation. Therefore an adequate response of the heart to afterload increasing is possible in conditions of a reliable diastole.

In patients with DHF but with myocardium hypertrophy the inefficiency of Frank-Starling mechanism is compensated by increased contractile force and inotropy of myocardium for a certain time .

Note that catecholamines are involved not only in inotropy stimulation, but also in energy depletion and diastolic relaxation perturbation.

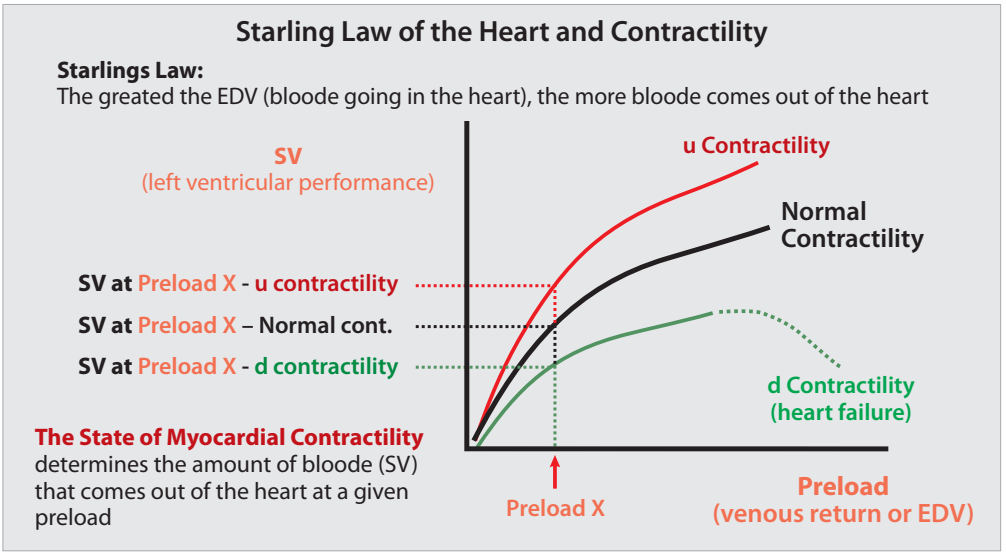


Figure 14. Relation between different preload levels and myocardium contractility

Afterload elevation is the most difficult effort for the heart. A reducing of afterload level does not need an increase of end diastolic volume and a high level of intraventricular pressure respectively (fig. 15). In contrast, high afterload can be achieved optimally via activation of diastole, that is provided by Frank-Starling mechanism.

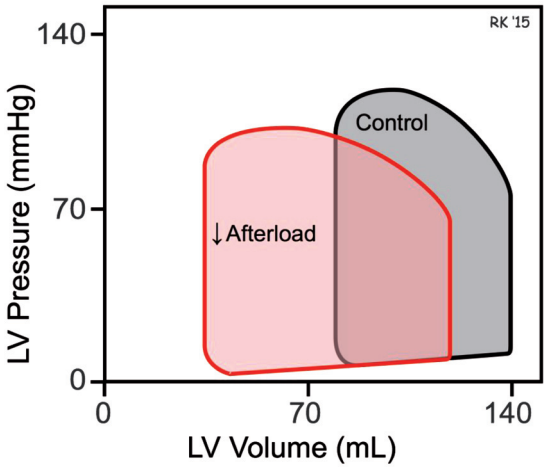


Figure 15. Afterload level and end diastolic volume relation

Cardiac fibrosis. Extracellular matrix (ECM) is estimated as an important component of myocardium playing a certain role in both cardiac muscle contraction and relaxation. The protein element of ECM is fibrillar collagen which has different elasticity property due to its type. Type I collagen is the most abundant protein of ECM (≈ 70%), but in the same time it is the most compliant. Type III collagen is less quantitatively (< 28%) with high stiffening capacity. Physical properties of the myocardium are strongly dependent on ESM, and evidently influence LV filling and diastole potency. The amount of synthesized collagen as well as the ratio between complain type I collagen and rigid collagen type III represent a factor determining the quality of lusitropic function of the heart. Normally fibrilalr collagen type I is more abundant and constitutes around 70% of ECM proteins. Excessive collagen deposition between cardiomyocytes affects the diastolic recoil of the heart and impairs (especially type III) left ventricle filling. The collagen network of the heart consists of epimysial, perimysial, and endomysial components, around which muscle fibers are oriented. The LV develops a negative diastolic pressure (suction) when coiled perimysial fibers release the energy stored during systolic compression; this contributes to diastolic filling that is not entirely passive. Microdisarray and macrodisarray of these components, especially of perimysial fibers, are implicated in the pathogenesis of diastolic dysfunction.

Among many neuroendocrine factors stimulating cardiac fibrosis, angiotensin II (Ang II) has the strongest effect. It has been proven that Ang II administration in mouse for 1 week period using a technique of continuous octapeptide infusion increased the myocardial space of fibrosis by 78%. This

phenomenon was associated with increased left ventricle end diastolic pressure by 52% and clearly demonstrates the role of renin-angiotensin-aldostenone system (RAAS) in DHF pathogenesis.

The incidence of DHF increases by aging (maximum level at the age of over 75) in parallel with RAAS activity elevation.

Myocardial fibrosis considered as one of factors leading to myocardium remodeling and heart failure. ECM increases together with myocardium hypertrophy, cardiomyocyte loss (due to apoptosis, oncosis, autophagy or micronecrosis) and metabolic disorders (e.g. type II diabetes mellitus) and it has a contributory role in the heart failure evolution.

Extracellular matrix deposition and fibrosis formation occur through the action of cardiac fibroblasts. In the setting of pathological stress, fibroblasts proliferate and differentiate into myofibroblasts, thereby gaining the capacity to contract and secrete collagen I, collagen III, and fibronectin. Proliferation and activation of these cells, the most abundant cell type in the myocardium, derive from a variety of sources, including resident fibroblasts, adult epicardial cells undergoing endothelial-to-mesenchymal transition, and circulating, collagen-secreting bone marrow – derived cells. Scar formation after myocardial infarction arises from replacement fibrosis in which regions of myocyte dropout are replaced by scar. In contrast, fibrosis arising during hypertension-induced pressure overload and in remote regions after myocardial infarction is reactive (perivascular or interstitial), leading to decreased compliance and diminished oxygen diffusion capacity. Both individual myofibroblasts and collagenous septa within the LV facilitate and propagate the arrhythmic phenotype of the remodeled heart.

Cardiac fibrosis is an independent and predictive risk factor for heart failure in both ischemic and nonischemic cardiomyopathy. Recent data show that cardiac fibrosis, long held to be irreversible, may regress under certain circumstances. Some evidence suggests that the modulation of cardiac fibrosis alters the arrhythmic phenotype in patients with heart disease. To date, no therapeutic strategy has been developed to specifically target fibrosis in the heart. Cardiac fibroblasts are unique and phenotypically distinct from fibroblasts isolated from other tissues (as reviewed elsewhere); they also display phenotypic heterogeneity within the heart itself. In addition, the precise phenotypes of fibroblasts from normal, injured, and failing hearts are ill-defined, and mechanisms underlying the transition from normal wound healing to maladaptive fibrotic remodeling remain unresolved. Interestingly, the abundance of newly formed, thin collagen fibers increases in the remote region of infarcted heart but decreases with time in the infarct zone, suggesting collagen maturation in the infarct zone. Furthermore, neurohormonal inhibition leads to an increase

in scar maturation while diminishing remote, reactive fibrosis. Because infarct-associated scar is necessary to prevent ventricular rupture, it may be advantageous to target new collagen fiber formation to allow scar maturation. Regardless of these challenges, there is reason to believe that therapies focusing on cardiac fibrosis may prove salutary in the treatment of ventricular remodeling. Some therapies in current use may target, at least in part, cardiac fibroblasts. Specifically, angiotensin II provokes cardiac fibroblast proliferation and net accumulation of collagen in vitro and cardiac fibrosis in vivo. Interestingly, the expression of angiotensin II receptors in cardiac fibroblasts exceeds that in cardiac myocytes, and angiotensin receptor blockers appear to have antifibrotic actions. In patients with hypertensive heart disease, losartan reduced cardiac fibrosis and serum collagen markers. In addition, treatment with statins resulted in reduced fibrosis and reduced collagen synthesis. Small-molecule inhibitors of histone deacetylases attenuate fibrosis in a preclinical model of pressure overload via mechanisms involving transcriptional silencing of the gene coding for connective tissue growth factor. The size, shape, and thickness of the extracellular matrix are important determinants of the architecture of the intact ventricles and thereby their pumping function. The ECM can be thought of as a scaffolding, or internal skeleton, of the ventricles. Remodeling of the ECM occurs with replacement fibrosis following myocardial infarction, a process that has been referred to as a "morphologic footprint of earlier myocardial necrosis". Myocardial necrosis enhances the release of growth factors in the connective tissue, which results in the formation of new fibroblasts. When this process is inadequate, such as after infarction, there is thinning of the ventricular wall, possible ventricular aneurysm formation, and further impairment of LV pump function. The increased synthesis of ECM enhances myocardial stiffness in pressure overload hypertrophy and reduces the rate of ventricular relaxation (and filling) as well as contraction (emptying). Fibrosis can be stimulated by long-term activation of the renin-angiotensin-aldosterone system, especially by aldosterone.

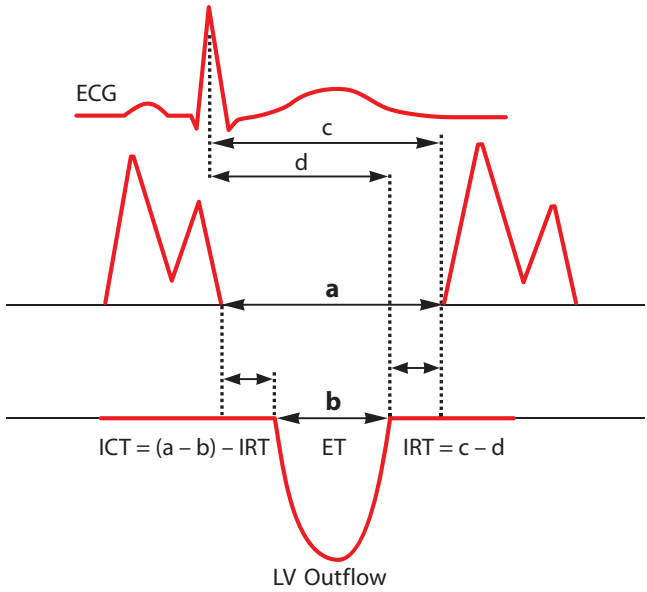
Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes involved in the degradation of the ECM. Their activity can be inhibited by a group of proteins termed tissue inhibitors of MMP. The myocardial fibrosis consequent to myocardial infarction and pressure-load hypertrophy may be associated with changes in ECM degradation resulting from an imbalance between MMPs and tissue inhibitors of MMPs, favoring the latter, and causing excessive fibrosis. Conversely, overexpression of MMPs may play an important role in ventricular remodeling in patients with dilated cardiomyopathy as well as in patients with ventricular volume overload states such as valvular regurgitation. Both imbalances can affect hemodynamics adversely.

4. PREDICTORS OF DIASTOLIC HEART FAILURE

All markers having prediction value up on diastolic relaxation abnormality belong to: (1) functional, (2) morphological, and (3) metabolic or circulatory indices.

- Among are the most important the functional predictors to echocardiographic indices. In this regard Tei index is considered as an earliest functional parameter indicating lusitropic function derangements.

It comprises a relation between the time of isovolumic relaxation, isovolumic contraction and the time of blood ejection during the systole (fig. 16).



$$\textbf{TEI INDEX} = \frac{\mathbf{a - b}}{\mathbf{b}} = \frac{\mathbf{(ICT + IRT)}}{\mathbf{ET}}$$

Figure 16. Tei index checking (ICT – isovolumetric contraction time; IRT – isovolumetric relaxation time; ET – ejection time)

Its elevation (> 0.49) means diastolic disorders before other functional indices change, and generally is due to isovolumetric phases disturbances of cardiac circle. Next functional indices are: mitral wave E (early LV filling, normal value < 0.9 cm/sec) and atrial wave A (the last third of LV filling, normal value < 0.7 cm/sec).

A global functional index showing LV capacity of filling is end-diastolic pressure and end-diastolic volume.

● The most important morphological markers of DHF are represented usually by: (1) myocardium concentric hypertrophy; (2) myocardium fibrosis; (3) myocardium inflammation; (4) myocardium sclerosis; (5) LV geometric remodeling. All these predictors are very difficult assaying and need special invasive and non-invasive methods. Therefore the best practical application of these markers become possible when the multi-marker panel is used.

● Circulatory predictors of DHF: the significance of multi-marker panel.

The central marker with authentic predictor value is attributed to galactin 3. It is a protein belonging to the lectin family which increases in the blood in patients with DHF accompanied with increased fibrosis. Circulatory level of galactin 3 is positively correlated with fibroblast activity and lusitropy disorders. On the other hand, galactin 3 is negatively correlated with isovolumic relaxation velocity. Its diagnostic value is especially recognized in patients with arterial pressure which do not represent signs of heart failure, but are candidates to DHF.

Furthermore, galactin 3 might be an important mediator and promoting factor of myocardium fibrosis because it is required for transforming growth factor (TGF)-β mediated myofibroblast activation and matrix production.

Galactin 3 is expressed in activated macrophages, with binding sites localized to the myocardial extracellular matrix and cardiac fibroblasts, where it induces fibroblast proliferation, collagen deposition, and ventricular dysfunction.

It should be noted that galectin 3 is an indicator not only of myocardial fibrosis, but also other fibrotic conditions, including liver cirrhosis and pulmonary fibrosis, all of which could increase risk of overall mortality.

Another circulating marker and predictor of myocardial fibrosis and risk of DHF evolution is ST2, a member of the IL-1 receptor family. It exists in 2 forms, a transmembrane receptor (ST2L) as well as a soluble decoy receptor (ST2).

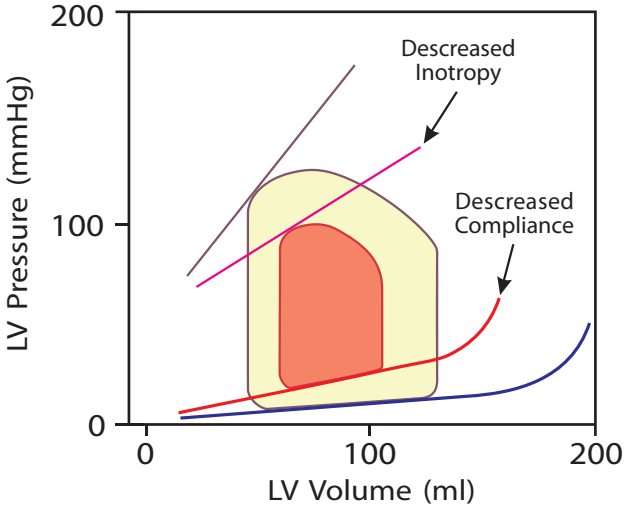
The ligand of ST2L is interleukin-33, which is involved in reducing fibrosis and hypertrophy in mechanically strained tissues. In in vitro and in vivo models, ST2L transduces the effects of interleukin-33, whereas the excess soluble ST2 leads to cardiac fibrosis and ventricular diastolic dysfunction.

For a stronger prediction of diastolic dysfunction and DHF developing both markers galactin 3 and ST2 should be estimated together.

5. COMBINED SYSTOLIC AND DIASTOLIC HEART FAILURE

It is not uncommon in chronic heart failure to have a combination of both systolic and diastolic dysfunction. Therefore, the slope of the end-systolic pressure-volume relationship is decreased and the slope of the passive filling curve (reciprocal of compliance) is increased in the ventricular pressure-volume loop shown to the right (fig. 17).

When this occurs, there is a dramatic reduction in stroke volume (width of pressure-volume loop) because the end-systolic volume is increased and end-diastolic volume is decreased. Both ejection fraction and stroke work are also decreased.



Effects of a combination of systolic dysfunction (decreased inotropy) and diastolic dysfunction (decreased compliance) on left ventricular pressure-volume loop. Heart rate and systemic vascular resistance are unchanged.

Figure 17. Pressure-volume relation in combined SHF and DHF

The changes shown in the figure assume that the heart rate and systemic vascular resistance are both unchanged; however, in patients both of these parameters will likely be increased because of reflex sympathetic activation.

This combination of systolic and diastolic dysfunction, coupled with compensatory volume expansion, can lead to very high end-diastolic pressures that can cause pulmonary congestion and edema, as well as systemic edema and ascites (particularly when the right ventricle is in failure).

6. FACTORS LEADING TO HEART FAILURE WORSENING

Heart failure worsening depends on a series of intrinsic and extrinsic factors often being in an interdependent relation. The pattern of the so called *"circus vicious"* is too conspicuously relevant in the model of heart failure.

The most important factors able to interfere in the HF worsening are:

1. Post-infarct ventricular remodeling.
2. Neurohormoral activation.
3. Boosting of inflammatory response.
4. Decrease of melusin expression.
5. Stunned and hibernated myocardium.

Myocardium remodeling is a term initially proposed in 1990 by E.Braunwald and J.Pfeffer in order to depict a pattern of structural changes of myocardium after acute myocardial infarction. Later, remodeling became an entity encompassing a versatile metabolic, structural and functional changes associating and influencing heart failure.

Myocardium remodeling begins after any harmful action which provokes finally modification of the myocardial geometry.

Myocardial infarction is the most severe myocardial impact resulting in a lost of certain space of contractile cardiac muscle, and as consequence both systole and diastole are impaired. The future of myocardial recovery tightly depends on quality of remodeling which in fact is correlating with necrosis size. Post-infarct remodeling is a predictor of heart failure, and for this reason it assumes a negative prognostic value. It refers mainly to necrotic zone, low-viable myocardium and myocardium entirely keeping contractile capacity.

In this regard it should be noted:

- Activation of fibroblasts in order to synthesize collagen for necrotic tissue substitution. This process starts just after a few hours after infarction, lasts around 3-4 months and is counteracted by activation of extracellular matrix metalloproteinases, a process triggered by free oxygen radicals and inflammation mediators.
- Myocardial ischemia persisting even after revascularization impairs contractility and a special precondition named as stunning is developed and hibernating myocardium develops when ischemia is managed or is improved but remains beneath adequate level.

• Hypertrophy of vital myocardium in order to compensate the lost contractile capacity due to necrosis.

Conceptually post-infarction remodeling can represent: (1) a balanced phenomenon between fibrosis and symmetric hypertrophy such as facilitating the functional recovery after infarction, and is named *adaptive remodeling*; or (2) a limited fibrosis and asymmetric hypertrophy such as worsening HF evolution, and is named *pathological remodeling*.

The pathological remodeling is assayed functionally when the main parameters of diastolic relaxation become worse. An elevation of end diastolic volume or end diastolic pressure of more than 20% in comparison with the initial value is considered as a functional pattern of pathological remodeling.

Lowered collagen synthesis is an opportune condition of left ventricle cavity dilation and therefore the end diastolic volume progressively elevates.

Asymmetric hypertrophy is a condition of myocardial contractile capacity weakening manifested chiefly by a decline of maximal isovolumic contraction velocity and ejection time increase. As a result the end-systolic volume increases, but the both stroke volume and ejection fraction decrease.

Accordingly, heart failure based on a pathological post-infarction remodeling is always a combined HF because the both functional patterns are impaired: systolic contraction and diastolic relaxation.

Functionally, post-infarct remodeling is viewed as a specific type of left ventricular remodeling that is a consequence of an increase in both preload and afterload causing an enlargement of ventricular chamber and a hypertrophy of normal myocardium. The increase in preload is sustained by the phenomenon of infarct expansion, which is an enlargement of infarct scar. This causes a regional increase in the ventricular volume subtended by the expanded infarcted myocardial wall. In infarcted myocardium, ventricular contraction is not symmetrical, because the necrotic segments have lost their contractility.

It is noteworthy, cardiomyocytes modify their transcriptional activity during remodeling, reactivating the expression of fetal genes that are normally silenced during adult life. These include genes encoded for structural heart proteins, which allow for the lengthening of cardiomyocytes through the addition of new sarcomeres in series. Myofibrils undergo a qualitative alteration, because cardiomyocytes reduce the synthesis of isoform α of myosin heavy chain (α-MHC) to increase the production of isoform β (β-MHC). This change is associated not only with a reduced energetic requirement for the cardiac muscle, but also with a reduced contractility of sarcomeres. The force generated by each contractile unit is further decreased by the reduction in the mean number of myofibrils per sarcomere.

There are two types of causes of remodelling: mechanical and biochemical. While mechanical causes are an increase in both preload and afterload, biochemical causes are linked to the production of soluble mediators capable of promoting ventricular remodeling. For example, angiotensin II and aldosterone stimulate cardiac hypertrophy and fibrosis, and an increase in catecholamines helps to maintain a normal cardiac output in front of the contractile dysfunction of infarcted segments. Many other soluble factors are produced by cardiac cells in response to various types of potential damage, for example, ischemia-reperfusion injury or mechanical strain. This explains the link between mechanical and biochemical causes of post-infarct remodeling.

Chronic volume overload and increased adrenergic tone promote metalloproteinases activity. These proteolytic enzymes break down collagen cross-links, thus weakening the myocardial wall and worsening the ventricular chamber dilatation. MMP-9 probably is the most important metalloproteinase involved in ventricular remodeling. It has been suggested that collagen degradation during post-infarct remodeling is due to an imbalance between the activity of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases.

Survived cardiomyocytes become hypertrophic in response to integrin-mediated mechanotransduction and soluble factors produced during myocardial stress: angiotensin II and endothelin-1.

Heart failure always is associated with neurohormonal activation manifested mainly by the elevation of circulating levels of catecholamines, angiotensin II, aldosteron and endothelin 1. Their harmful action on cardiovascular homeostasis means:

- energy depletion, a process mediated by increase of calcium influx in the cardiomyocyte:
- oxidative stress overactivation due to stimulation of free oxygen radicals production;
- stimulation of hypertrophy and fibrosis processes;
- triggering of cell apoptosis;
- boosting of pro-inflammation cytokines expression.

Systemic inflammation is activated in the early phase of heart failure and is progressing during HF worsening. The natural trigger of inflammation is IL-1beta whose expression is induced by inflammasome (a complex of intracellular proteins). The last could be activated by free oxygen radicals, and another inherent repercussion is activation of caspase 1. Therefore inflammation activation is accompanied by cell apoptosis.

IL-1beat stimulates the expression of IL-6 and TNF-alpha.

TNF-alpha triggers a lot of events referred to heart failure pathogenesis, such as contractile depression, cell apoptosis, oxidative stress activation, peripheral and coronary vascular remodeling.

Melusin role in heart failure worsening is linked to triggering of ventricular cavity dilation and abrupt impairment of diastolic function. Melusin is a part of the heat shock protein 90 machinery and acts as a molecular chaperone in controlling cardiomyocyte survival and adaptive hypertrophy signaling pathways in the heart in response to different stress conditions thereby interaction with carcoplasmic domain of integrin-beta1, a membrane receptor that connects the intracellular cytoskeleton with the extracellular matrix, allowing muscle cells to respond to mechanical stimuli.

Melusin protects cardiomyocytes from apoptosis and induces a compensatory hypertrophic response in several pathological conditions. Therefore, selective delivery of the melusin gene in heart may represent a new promising gene-therapy approach for different cardiac pathologies.

The protective role of melusin in the heart is strictly related to the cardiac response to stress stimuli. Upon mechanical stretching, the heart activates a compensatory hypertrophic response, causing an increase in the thickness of the left ventricle wall that preserves contractility. However, if the stimulus becomes chronic, the heart undergoes a pathological evolution from adaptive hypertrophy to dilated cardiomyopathy with loss of contractile function, known as maladaptive remodeling. Melusin expression levels increase in left ventricles in the first week of pressure overload, during the induction of the compensatory hypertrophic response. Mechanical stress induces in the heart the activation of specific signal transduction pathways and the release of neurohumoral mediators acting on cardiomyocytes, fibroblasts and endothelial cells, regulating the heart's response to stress. The balance between these signals may direct the overall cardiac response to a compensatory or to a maladaptive remodeling.

In patients with heart failure expression of melusin positively correlates with ejection fraction value. Decreased melusin expression rapidly leads to cardiac dilation and to a marked ejection fraction fall.

Stunned and hibernated myocardium represents 2 distinct functional patterns of myocardium linked to post-ischemic statement or chronic persisting ischemia. When ischemia is severe and prolonged, it causes myocyte death and results in loss of contractile function and tissue infarction. In cases of less severe ischemia, some myocytes remain viable but have depressed contractile function. G.R.Heyndrickx described first the phenomenon of prolonged depression of regional function after a reversible episode of ischemia in dogs and later this

was called *myocardial stunning*. Functional recovery of the myocardium after a certain time of ischemia (not too long) is delayed.

When ischemia is prolonged, the cardyomyocytes have depressed contractile function, but they remain viable – *hibernating myocardium*. It has a conspicuous benefit because it needs less oxygen due to decreased metabolic activity (hibernation effect).

Thus, myocardiac stunning means a delayed myocardial functional recovery after an episode of ischemia (fig. 18. B), and hibernating underlines a functionally depressed myocardium in chronic ischemia (fig. 18. C).

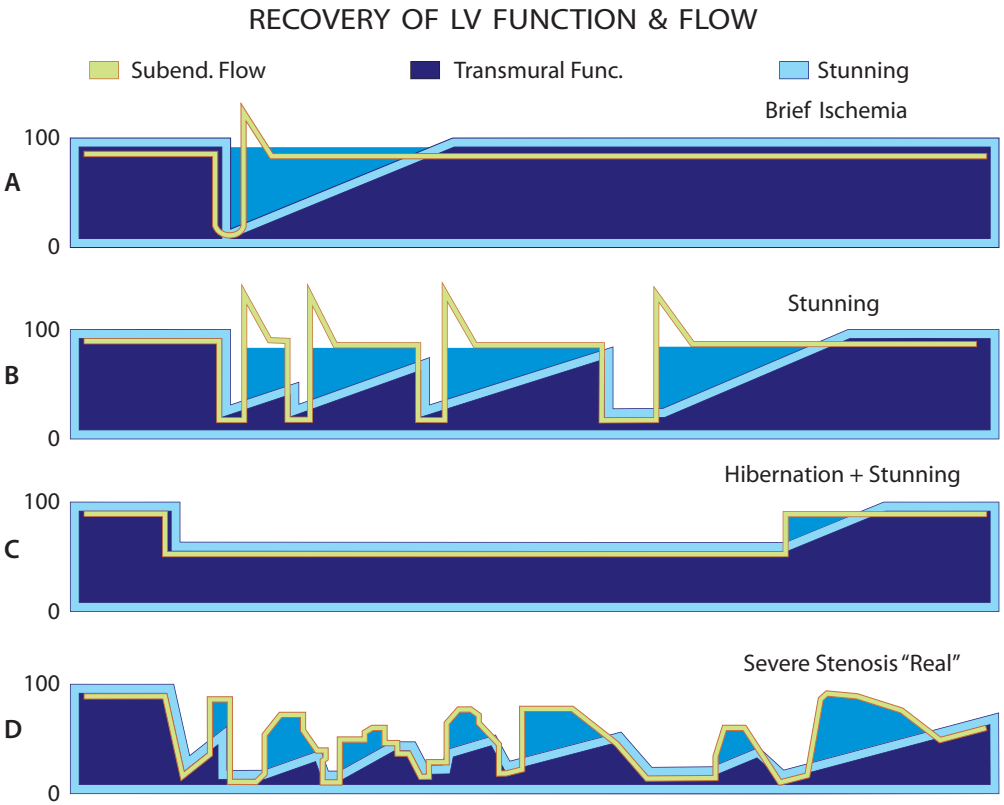


Figure 18. Interaction between ischemia period and myocardial function recovery in both stunning and hibernating myocardium

An ischemic but non-infarcted myocardium can exist in a state of hibernation without cell death. It is suggested that hibernating myocardium is a state of persistently impaired myocardial and left ventricular function at rest due to reduced coronary blood flow that can be partially or completely restored to normal either by improving blood flow or by reducing oxygen demand.

It is considered that stunning and hibernating myocardium are the processes by which the myocardium adapts to reduced myocardial oxygen supply to maintain cellular integrity.

There are two major hypotheses for myocardial stunning: (1) an oxygen-free radical hypothesis and (2) calcium overload hypothesis.

Postischemic dysfunction may be due to cytotoxic oxygen-derived free radicals (i.e. hydroxyl radicals, superoxide anions) that are thought to be generated during occlusion or, upon reperfusion. Such radicals cause lipid peroxidation, altering their function and structure.

Brief ischemia followed by reperfusion damages Ca^{2+}-pump and ion channels of the sarcoplasmic reticulum. This results in the electromechanical uncoupling of energy generation from contraction that characterizes myocardial stunning. Calcium accumulates in the cell at the time of reperfusion and that is followed by a partial failure of normal beat-to-beat calcium cycling, which perhaps occurs at the level of the sarcoplasmic reticulum. This mechanism is proposed to account for contractile dysfunction.

Hibernating myocardium is characterized by the following: (1) episodic and/or chronically reduced blood flow, which is directly responsible for the decrease in the myocardial contractile function; (2) tissue ischemia and resultant remodeling without necrosis, which causes prioritization of metabolic process in the myocardial cell relative to contractile function; (3) residual contractile reserve in response to inotropic stimulation (in at least half of clinical cases); (4) recovery of contractile function after successful revascularization.

The most important pathological findings are:

1. A progressive loss of contractile protein (sarcomere) occurs without a loss of cell volume. The depletion of sarcomeres is most prominent near the perinuclear region but may extend to the entire cell.

2. Numerous small mitochondria can be found in the areas adjacent to the glycogen-rich perinuclear zone.

3. Nuclear heterochromatin is evenly distributed in the nucleoplasm.

4. A substantial loss of sarcoplasmic reticulum occurs. The sarcoplasmic reticulum loses T-tubules and becomes disorganized.

5. Primitive cytoskeleton proteins, including titin and cardiotin, have increased expression in the hibernating myocytes cells. The expression of primitive proteins suggests the occurrence of dedifferentiation of myocytes. Cell dedifferentiation is reversible after restoration of blood flow with revascularization. It is not clearly known whether cell death occurs by means of apoptosis or necrosis.

Circulatory level of endothelin 1 (ET-1) plays a certain role in the hibernating myocardium pathogenesis because this oligopeptide is recognized as the strongest vasoconstriction agent provoking thus cardiac ischemia. This effect is mediated by receptor type A placed on smooth muscular cell. Noteworthy, the ET-1 is stoked in special granules surrounded the zone of hibernating myocardium. Neuroendocrine activation (e.g. sympathetic and RAAS system activation) leads to granule discharging and to a rapid ET-1 rise in the myocardium compromising hence the cardiac functioning. Maintenance of high ET-1 levels impairs the hibernating myocardium functioning recovery after revascularization (to note that functional rehabilitation after the ischemia settling could be partial or complete). Likewise it is important the fact that ET-1 causes a negative inotropic effect in heart failure as well as a diastolic relaxation disorder. Extracardiac ET-1 production also can be a serious factor leading to hibernating myocardium, especially in patients with arterial hypertension and endothelium alteration. In the ischemia-reperfusion syndrome plasma ET-1 level elevates not only during coronary constriction, but also after coronary flow restoration perhaps due to action of reactive oxygen species. It has been demonstrated that Ang II stimulates both cardiac and extracardiac synthesis of ET-1.

Hibernating myocardium is a functional heart pattern inducing cardiac cell apoptosis due to boosting of reactive oxygen species (ROS) release and inflammation markers expression.

The main ROS effects in hibernating myocardium and HF in general follow as: (1) caspase activation; (2) endonuclease activation; (3) mitochondrial phosphorilation diminution; (4) lysosomal enzymes activation; (5) SERCA2α inhibition.

Inflammation cytokines are intensively expressed in hibernating myocardium and might sustain functional cardiac depression due to stimulation of beta heavy myosin chain.

The shifting of alpha heavy myosin chain to beta isoform is considered as a maladaptive response of heart failure. Persistent expression of beta heavy myosin chain in hibernating myocardium could be a precondition of incomplete cardiac function recovery after revascularization.

Modifications in thick filament protein content and performance are thought to underlie contraction-relaxation dysfunction in human heart failure associated with reduced expression of ATPase due to reducing of alpha heavy myosin chain from approximately 5-10% in normal myocardium to 2-3% in hibernating myocardium and to less than 2% in failing myocardium.

The replacement of alpha- by beta- heavy myosin chain (possessing slower actomyosin enzymatic kinetics) may underlie to a significant degree the reduced myocardial shortening velocity and reduced relaxation function in human heart failure.

Phosphorylation of the myofilament proteins myosin regulatory light chain and troponin-I are both reduced in heart failure and collectively result in an elevated myofilament sensitivity to calcium activation, which inhibits relaxation function.

Recent studies in animal models of heart failure and human failing myocardium converge and indicate that sarcomeric dysfunction, including altered maximum force development, calcium sensitivity, and increased passive stiffness, largely originates from altered protein phosphorylation, caused by neurohumoral-induced alterations in the kinase-phosphatase balance inside the cardiomyocytes.

A proven contemporary concept corroborates the fact of misbalance between two isoforms of the biggest sarcomer protein – titin: the N2B, more rigid and the isoform N2BA, more compliant in the hibernating myocardium. The prevalence expression of the first, N2B is a mechanism of diastolic dysfunction and Frank-Starling mechanism inefficiency. Likewise, decreasing of the titin phosphorolation can be a cause of cardiac contractility depression.

As conclusion: the knowing of the real cellular and molecular mechanisms of heart failure should be a reliable support for searching of new circulating markers and predictors of both systolic and diastolic heart failure patterns.

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