Chapter 1
Pathophysiology of Heart Failure: Back to Basics

Gilles W. De Keulenaer, Vincent Segers, and Dirk L. Brutsaert

Abstract Basic mechanisms of chronic heart failure are reviewed. A central theme that cuts all the way through this review is that chronic heart failure is a problem of failing complexity, rather than a problem of the failure of a single unit (e.g., cell type) or processes (e.g., contractility). A brief paragraph introducing this central concept will precede the main text of this chapter.

Next, a definition of heart failure will be formulated, and the most common etiologies and symptoms of heart failure in clinical cardiology summarized. The progressive nature of chronic heart failure will then be described and its driving forces analyzed. Finally, indices of cardiac performance and heart failure will be summarized and placed into a conceptual frame. The chapter will end by scrutinizing the mechanisms of diastolic dysfunction and by formulating some future trends of heart failure research.

1 Introduction

Heart failure is a progressive clinical syndrome for which various definitions and pathophysiologic mechanisms have been proposed. Although cardiac pump dysfunction is an inherent pathophysiological mechanism of heart failure, many extracardiac dysfunctions contribute, especially when heart failure becomes chronic. Accordingly, in this multifactorial syndrome it is difficult to pinpoint the central pathophysiological mechanism. This complicates the introduction in heart failure of therapeutic strategies and of taxonomy, the latter being apparently attractive given the remarkable variability of how this syndrome clinically presents.

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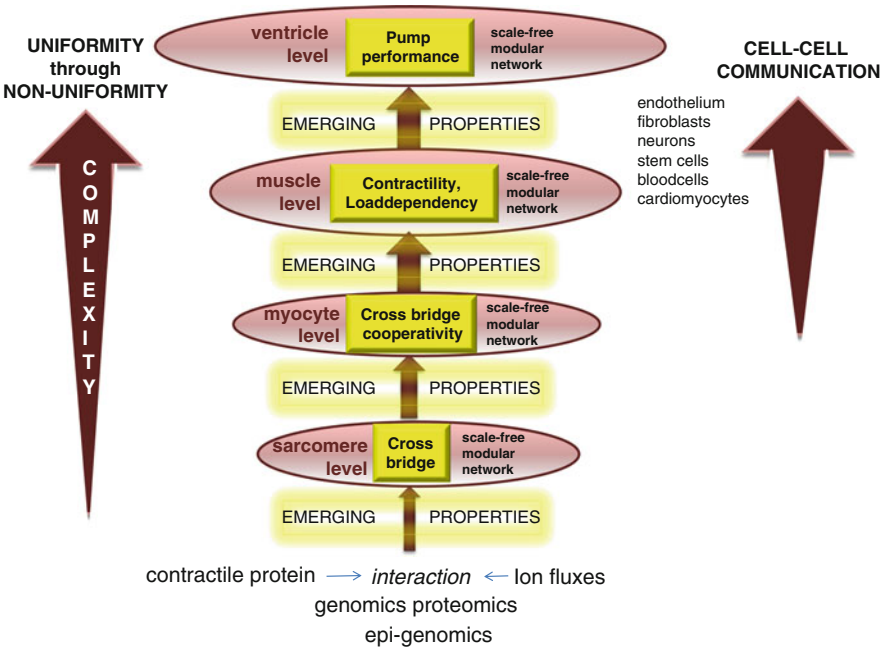

Fig. 1.1 The ventricle is a dissipative structure with emerging properties. Analogous to a dissipative structure, the heart grows as an ordered, self-organizing, optimizing pump, or super-system, through fluctuations, interactions and coherence of adjacent subsystems at each higher hierarchic scale, ranging from the subcellular modular networks (available through systems biology research) up to modular networks at the organ level and beyond. At each scale, emerging properties are added

Nevertheless, one may wonder what, if any, could be the central pathophysiologic aspect of heart failure? Could it be the maladaptive autoregulatory response upon ventricular dysfunction, involving hormones and paracrine factors, and the consecutive process of ventricular remodeling? Or should one perhaps look at lower structural/functional scales, e.g., impairment of cardiac muscle mechanical performance due either to failing excitation-contraction-relaxation coupling, or to disturbed cross-bridge cycling? Alternatively, could it be the repercussion of left ventricular dysfunction on the periphery including atria, the pulmonary circulation, the right ventricle, the kidneys, and skeletal muscles? Which of these phenomena is the most crucial, pernicious, irreversible?

These questions have no single answer as heart failure is the failure of a complex system; failure of a complex system cannot be reduced to the failure of a single process. The ventricle itself is a complex system, which means that its properties follow the scientific rules of complexity. These rules are characterized by mathematic phenomena like nonlinearity and self-organization, which provide the ventricle with all the properties of a "dissipative structure" [1–3]. This means that the ventricle behaves as a dynamic and self-organizing structure with emerging properties at each higher hierarchical scale of performance (Fig. 1.1).

From this perspective, *ventricular dysfunction and the heart failure syndrome are problems of failing complexity rather than the sum of failures of one or more components of the cardiovascular system*.

Application of scientific principles of "complex system behavior and failure" to the syndrome of chronic heart failure is unfortunately only in its infancy [4]. Heart failure is often described and subdivided from within a narrow oversimplified perspective, i.e., a single gene or gene product, a single cell type (e.g., the cardiomyocyte), a single parameter (e.g., left ventricular ejection fraction (LVEF)), a single functional aspect (e.g., contractility, filling), a single organ (e.g., the heart). In the next chapter, we discuss the pathophysiology of chronic heart failure avoiding the bias to such a narrow perspective. We also address some future perspectives and the need of introducing complex systems biology in the analysis of chronic heart failure.

2 Main Text

2.1 Definition and Pathophysiology of Heart Failure

Heart failure is a complex clinical syndrome characterized by fatigue and tissue congestion related to cardiac pump dysfunction. Cardiac pump dysfunction in heart failure may either impart impaired ventricular filling (predominantly diastolic pump dysfunction/failure) or impaired ventricular output (predominantly systolic pump dysfunction/failure), but it almost always consists of a combination of both impairments. There is currently insufficient evidence to subdivide heart failure in pathophysiological entities based on whether a diastolic or systolic impairment dominates, although this issue is currently still under debate [1, 5]. Subdivision of heart failure in distinct entities based on systolic/diastolic function ("systolic" and "diastolic" heart failure) is complicated by the fact that systolic and diastolic dysfunction nearly always coexist, that ventricular contraction and relaxation are physiologically coupled, and that there is no single criterion to precisely define a systolic or diastolic heart failure sub-entity. Most if not all heart failure indices show mere quantitative variations along the wide spectrum between predominantly concentric ("diastolic" heart failure) and eccentric ("systolic" heart failure) hypertrophy, and often follow a continuous linear relation when plotted against the patient's corresponding LVEF (Fig. 1.2) [6–9]. Cut-off values of these indices to introduce distinct heart failure sub-entities have been arbitrary. Hence, the connotations "diastolic" and "systolic" heart failure, or heart failure with a preserved (HFPEF) or reduced ejection fraction (HFREF), may have practical advantages in daily clinical medicine, but lack a conceptual basis.

Accordingly, heart failure emerges as a heterogeneous, but undividable spectrum of numerous overlapping phenotypes. Hence, at least from a pathophysiological

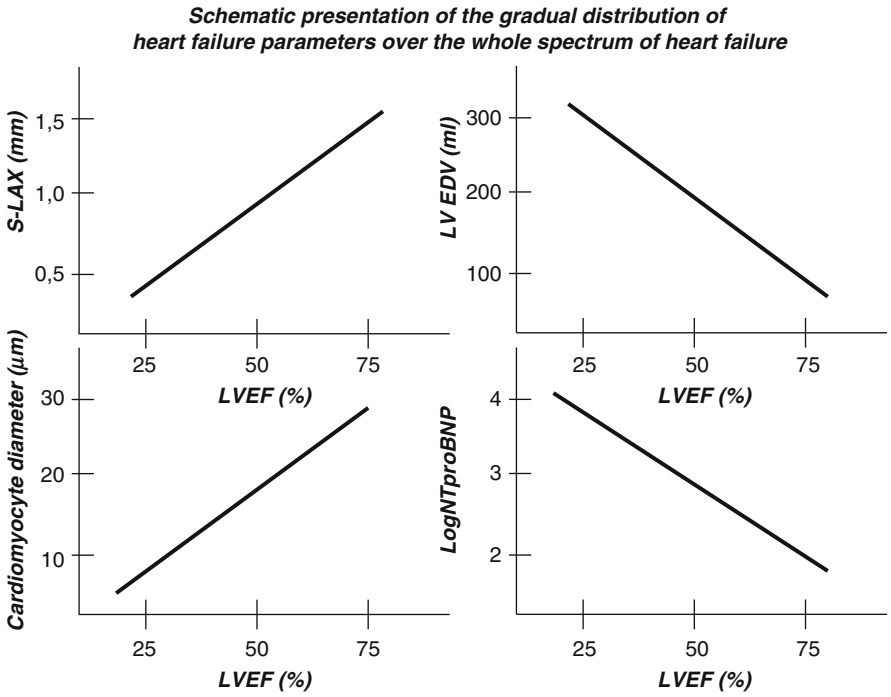

Fig. 1.2 Schematic presentation of the gradual distribution of heart failure parameters of the whole spectrum of disease. Opposite to a binary view on heart failure, most parameters of heart failure do not cluster in two groups ("low" and "high") when plotted against left ventricular ejection fraction (LVEF). Instead, they follow an uninterrupted linear relation over the whole spectrum of the syndrome (from low to high LVEF). *S-LAX* systolic long axis displacement of the mitral annulus, *LV EDV* left ventricular end diastolic volume, *LogNTproBNP* logarithm of the serum concentration of N-terminal brain natriuretic peptide. See text for references

perspective, it is artificial to subdivide heart failure in distinct disease entities. Heart failure's heterogeneity (e.g., forward and backward failure, systolic and diastolic failure, right and left ventricular failure) may, however, be accompanied by wide variations in prognosis and clinical responses to therapeutic (pharmacological and non-pharmacological) interventions. Thus, in daily clinical practice, medical management of heart failure should be individualized based on the specific phenotypic characteristics of the patient and the stage of the syndrome.

Key Points

- From a pathophysiological perspective chronic heart failure emerges as a heterogeneous, but individable spectrum of overlapping phenotypes.
- Surviving heart failure phenotypes in 2 or more so-called "disease entities" such as "HFNEF" and "HFPEF," "systolic" and "diastolic" heart failure, or "isch-

Table 1.1 Causes of heart failure

1. Cardiomyopathies
   (a) Ischemic heart disease (infarction, stunning, hibernation)
   (b) Genetic cardiomyopathy (dilated and hypertrophic)
   (c) Infectious/inflammatory cardiomyopathy
   (d) Metabolic cardiomyopathy (e.g., obesity, diabetes)
   (e) Toxic cardiomyopathy (e.g., cancer drugs)
   (f) Infiltrative cardiomyopathy (e.g., amyloidosis)
2. Myocardial overload
   (a) Pressure overload (e.g., hypertension, aortic stenosis)
   (b) Volume overload (e.g., mitral/aortic regurgitation)
3. Pericardial diseases
   (a) Constrictive pericarditis
   (b) Pericardial effusions (tamponade)
4. Electrical abnormalities
   (a) Dyssynchrony
   (b) Bradycardias
   (c) Tachycardias

emic" and "non-ischemic" cardiomyopathy may have some clinical advantages in current clinical medicine, but this should be done carefully, and should never dominate pathophysiological research.

2.2 Etiology of Heart Failure

Heart failure may be the end stage of all forms of cardiovascular disease, and of many different risk factors, contributing to the heterogeneity of the syndrome. The causes of cardiac dysfunction leading to heart failure may be subdivided into whether they directly affect myocardial or ventricular function (e.g., ischemia, toxicity, gene dysfunction, metabolic dysfunction) or place an abnormal load on the myocardium (volume of pressure overload), resulting in impairment of ventricular function (Table 1.1). In most instances, the mechanisms of progression from cardiac insult to cardiac dysfunction and finally to the full-blown syndrome of heart failure are not well understood. *These mechanisms clearly surpass the structural and functional changes of the left ventricle and also involve a complex interaction of neuroendocrine, vascular, and other noncardiac processes*. Importantly, most currently available therapies of chronic heart failure target neuroendocrine and vascular processes, rather than the structural and functional changes of the ventricle per se. The complexity of pathophysiological processes in chronic heart failure seems common to most if not all causes of heart failure and contributes to the progressive character of the syndrome, to advancing symptoms and to premature death.

Key Point

- A list of etiological factors of heart failure in clinical cardiology is provided.

2.3 Symptoms of Heart Failure and Causes of Death

The major signs and symptoms of chronic heart failure are fatigue, exercise intolerance, breathlessness, and tissue edema. They may remain absent for a long period during disease development despite dysfunction of the heart first as a muscular and even as a hemodynamic pump. Once they develop, they may be present in different degrees and combinations. Consistent with the complexity of the heart failure syndrome, the origin of these signs and symptoms cannot linearly be explained by a single mechanism, although they somehow originate from dysfunction of the heart. Symptoms and signs of heart failure are the result of a combination of both cardiac and extra-cardiac dysfunctions of chronic heart failure.

Fatigue, particularly during exercise, is a common presenting symptom of chronic heart failure. It is often difficult to distinguish from breathlessness. The mechanism of fatigue is complex and poorly understood [10]; it clearly surpasses failure of the left ventricle as a hemodynamic pump (as it correlates poorly with LVEF). Impaired cardiac chronotropic reserve [11], muscle blood flow, deficient endothelial function [12], and disordered skeletal muscle structure and function have been involved [13].

Breathlessness is equally complex and poorly understood. It also surpasses mechanisms related to dysfunction of the ventricle as a muscular and hemodynamic pump; some studies showed correlations with left ventricular diastolic function, whereas other didn't [14]. Other heart failure-related, but extra-cardiac mechanisms, likely play a role including an exaggerated ventilatory response to exercise, resulting in an abnormally steep VE/VCO2 slope [15].

Tissue edema is related to the retention of salt and water in the kidneys, which on its turn is related to the activation of the renin-angiotensin-aldosteron system (RAAS), rather than to intrinsic dysfunction of the kidneys. To what extent RAAS activation is related to reduction in renal blood flow is, however, unclear.

Key Point

- Symptoms and signs of heart failure are not explained by dysfunction of a single process, but are the result of a complex interplay of mechanisms, both cardiac and extra-cardiac.

2.4 Progression of Chronic Heart Failure: Pathophysiology and Therapeutic Targets

The progressive nature of chronic heart failure has been the subject of intense research. Usually, its progression is explained by the vicious circle paradigm in which

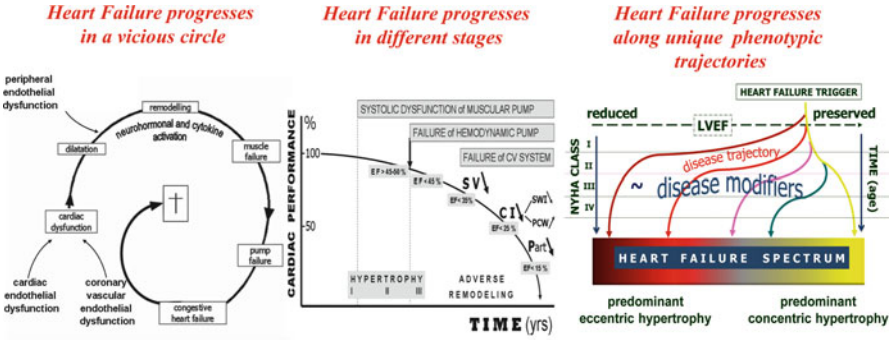

Fig. 1.3 Heart failure is a progressive disease. Each of the figures highlights a different aspect of the progression. In the vicious circle paradigm of heart failure (*left*), the pernicious, progressive, and irreversible character is emphasized as propelled by endothelial dysfunction, (mal) adaptive activation of neurohormones and cytokines. In the *middle* figure, the progressive nature of heart failure is equally emphasized, but focus is on the consecutive stages of failing cardiac performance, i.e., failure of the heart first as a muscular suction pump, then as a hemodynamic compression pump and finally of the whole cardiovascular system, with drop in stroke volume (SV), cardiac index (CI), and eventually of arterial blood pressure (Part). The spectrum paradigm of heart failure (*right*) visualizes how during heart failure progression each patient follows a unique disease trajectory. The trajectories depend on the relative contribution of the patient's traits and comorbidities (coined disease modifiers), are thus patient-specific, and hence create a spectrum of phenotypes throughout the entire population of heart failure patients

driving forces including hemodynamic disturbances, neurohormones, cytokines, and endothelial activation/dysfunction lead to successive failure of the heart as a muscular pump and hemodynamic pump, finally of the whole circulatory system. Within these progression, each patient follows its unique disease trajectory, in which LVEF remains preserved or gradually drops while symptoms develop (Fig. 1.3).

Hemodynamic disturbances. Ventricular pressure and volume overload (either directly related to the cause of heart failure, or indirectly induced by renal sodium/water retention and neurohormone-mediated vasoconstriction of arterioles) undoubtedly contribute to the progress of ventricular remodeling and heart failure, at least partly through effects of Laplace's law on ventricular wall stress. Therapeutic interventions aimed at reducing hemodynamic disturbances in heart failure (positive inotropes, diuretics, vasodilators) may reduce symptoms of heart failure. Their effects on mortality due to heart failure have, however, been disappointing [16–18].

Neurohormonal activation. Increased activity of the RAAS and of the symptathetic nervous system as well as activation of a wide variety of circulating and tissue hormonal systems are characteristic of the heart failure syndrome. These systems contribute importantly to the progression of ventricular remodeling and heart failure.

Therapeutic interventions aimed at reducing the activity of these systems (angiotensin converting enzyme inhibitors, angiotensin type I receptor antagonists, beta-1 receptor antagonists, and aldosterone receptor antagonists) have systematically reduced symptoms and mortality of heart failure, sometimes despite (temporarily) exacerbating the concomitant hemodynamic disturbances [19–22].

Cytokine activation. Cytokines are cell products released in response to tissue injury and inflammation. Increased serum concentrations of several cytokines have been shown in heart failure, including various interleukins (IL-6, IL-33, etc.) and tumor necrosis factor alfa (TNFα). Cytokines have been postulated to contribute to ventricular remodeling, but also to skeletal muscle wasting and cachexia. Therapeutic interventions directly targeting the effects of cytokines in heart failure have, however, not resulted in improved outcomes [23].

Endothelial activation/dysfunction. The endothelium in heart and vessels releases a number of local factors, both in rest and in response to a variety of stimuli, that exert effects on contractility, relaxation, passive stiffness, electrophysiology, survival and growth of cardiac and vascular cells [24]. In heart failure, the release of some of these factors is impaired, like nitric oxide, whereas the release of others is increased, like endothelin-1. Therapeutic interventions directly restoring the activity of one or more of these endothelial factors in heart failure have not yet resulted in a long-term survival benefit. There are promising preliminary data, however, with a recently discovered endothelial factor, neuregulin-1, which exerts cardioprotective and cardioregenerative effects [25]. Long-term studies still have to be performed.

Left ventricular remodeling. Although surpassing cardiac abnormalities, one of the key features of the heart failure syndrome is the pernicious process of cardiac remodeling (Fig. 1.4). This process is characterized by a progressive change in shape, volume, and muscle mass of the left ventricle, often accompanied by changes in shape and volume of the left atrium. Although ventricular remodeling is often assigned to be either eccentric (when left ventricular end diastolic volume increases) or concentric (when left ventricular walls thicken), eccentric and concentric remodeling often coexist, indicating that heart failure cannot be dichotomized into two distinct disease entities based on the ventricle's type of remodeling and its pathological architecture. *Ventricular dilatation* during cardiac remodeling has a potential hemodynamic advantage by preserving stroke volume without increasing contractility, but the disadvantage of this process is that it also augments ventricular wall stress (as defined by Laplace's law). Increased wall stress increases myocardial oxygen consumption and reprograms myocardial gene expression. *Ventricular wall thickening* has the advantage or normalizing wall stress when overcoming pressure overload, but it has the disadvantage of disturbing the relation between myocytes and microcapillaries [26]. Hence, ideally for a long term survival of chronic heart failure, a balanced spectrum of remodeling may be essential.

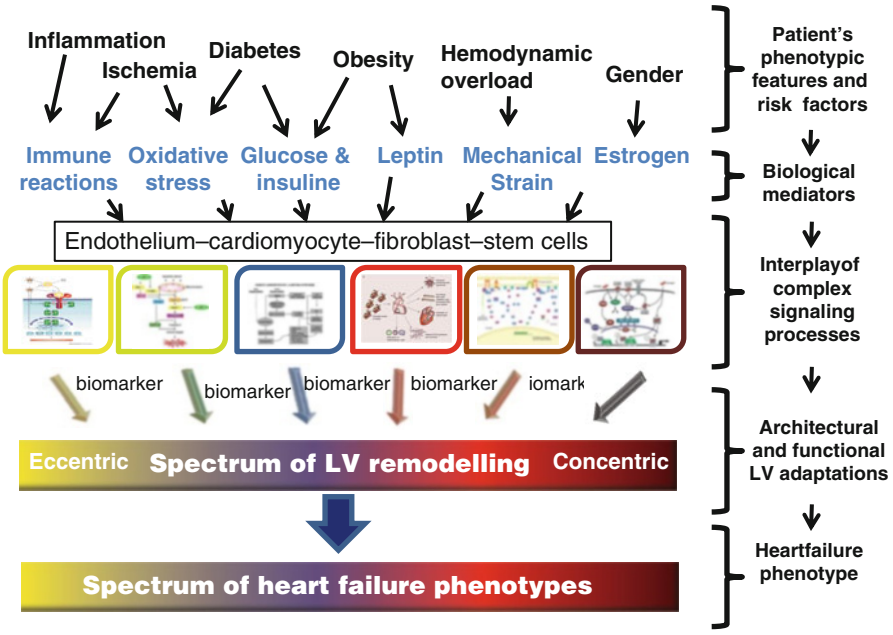

Fig. 1.4 Left ventricular remodeling results in a spectrum of cardiac phenotypes. Left ventricular remodeling is the result of an interplay of many complex processes in cardiac cells (endothelial cells, cardiomyocytes, fibroblasts, …). These processes are dependent on many mediators (reactive oxygen species, hyperglycemia, neurohormones, mechanical strain, sex hormones, etc.) whose contribution is dependent on the patient's phenotype and risk factors (e.g., gender, diabetes, coronary failure, and body mass index). Some mediators promote concentric remodeling (e.g., estrogens, leptin) whereas other promote eccentric remodeling (ischemia; inflammation, etc.). The relative contribution of each of the processes is unique for each patient, leading to a spectrum of cardiac phenotypes when a large group of patients is considered

Ventricular remodeling is the result of multiple interacting complex signaling processes, the contribution of which is linked to the patient's biological traits and comorbidities. Some of these signaling processes are linked to coronary failure, myocardial infection, or type 1 diabetes mellitus; these promote predominantly eccentric remodeling. Others, such as type 2 diabetes mellitus, obesity, hypertension, and female gender, instead tend to promote concentric remodeling [27–32]. The complex signaling processes triggered by each of the disease modifiers separately (or of their mediators, such as leptin, ischemia, hyperinsulinemia, and estrogen) are under intense investigation. In vivo, these complex signaling processes merge in qualitative and quantitative combinations, specific for each patient and leading to a spectrum of overlapping profiles of ventricular remodeling.

The cellular and subcellular processes during cardiac remodeling are extremely complex. Changes occur at the level of individual cardiomyocytes, fibroblasts, endothelial cells, purkinje fibers and cardiac stem cells, and also the communication

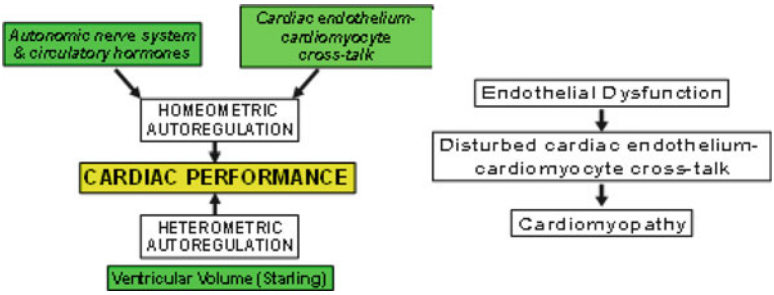

Fig. 1.5 Autoregulatory control systems of the heart. Cardiac endothelium-cardiomyocyte cross-talk is part of the autoregulatory control systems of the heart, together with the neurohormonal system and the Starling mechanism. Accordingly, cardiac endothelium dysfunction may lead to cardiomyopathy and heart failure. This relative simple concept has recently been underscored by the unexpected cardiac side effect induced by trastuzumab, an inhibitory antibody of the receptor tyrosine kinase ErbB2, which mediates cellular effects of the cardiac endothelium-derived factor neuregulin-1. Inhibition of the cardiac actions of neuregulin-1 with trastuzumab leads to left ventricular dysfunction and heart failure, which is reversible upon interrupting treatment with trastuzumab

between these cells, one of the crucial autoregulatory mechanisms of ventricular function is affected (Fig. 1.5) [33]. *Cardiomyocytes* undergo growth and apoptosis and receptor-signaling pathways of numerous hormonal and paracrine growth and survival factors (such as angiotensin II, endothelin-1, interleukin-6, IGF-1, and neuregulin-1) in the myocytes are activated. Essential myocyte functions like excitation-contraction-relaxation coupling [34] and adrenergic responsiveness [35] are disturbed. *Fibroblast* collagen synthesis is activated, but the release of enzymes for collagen degradation is also increased. Angiogenesis, controlled by *endothelial cells*, becomes impaired in the failing heart, contributing to maladaptive hypertrophy and transition to failure [26].

Cardiomyocyte renewal. The classical view on myocardial turnover and regeneration has been that cardiomyocytes are terminally differentiated cells and that no new cardiomyocytes are formed during adult life. This classical view has been challenged by recent data showing that new myocytes are formed during adulthood, both during normal aging and after myocardial injury. However, renewal of cardiomyocytes either by stem cells or cardiomyocyte division seems to be insufficient to repair myocardium and prevent heart failure after myocardial infarction. Stem cell biology has only recently been incorporated into the study of heart failure, and evidence of stem cell dysfunction as a part of heart failure pathophysiology is mounting. Development and progression of heart failure could be due in part to failure of cardiac stem cells; strategies that are focused on stem cell dysfunction might become available as a therapy in the future [36].

Key Points

- Chronic heart failure has a progressive nature, the mechanisms of which are still under investigation. Its driving forces provide therapeutic targets.

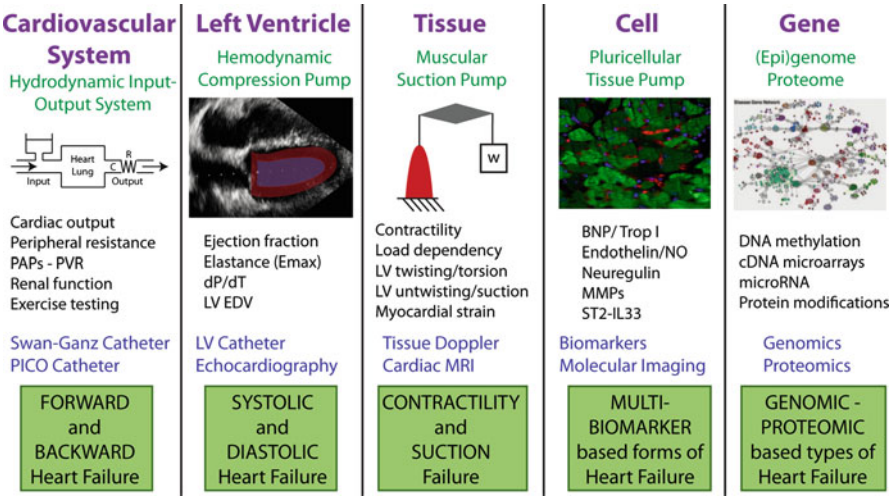

Fig. 1.6 Conceptual approaches to cardiac performance. The ventricle can be considered as part of a hydraulic input–output system with the ventricle as a *black box* (organism panel), as a hemodynamic compression pump with the cardiomyocytes as a *black box* (organ panel), as a muscular suction pump with the non-cardiomyocytes as a *black box* (tissue panel), as a pluricellular tissue pump with genes and proteins as *black box* (cell panel) or as the product of the individual's genome, epigenome, and proteome (gene panel). Within each panel-specific approach to cardiac performance, different phenotypes of heart failure can be proposed (forward and backward failure, systolic and diastolic heart failure, contractility and suction failure, multi-biomarker-based forms of heart failure, and perhaps in the future genomic-proteomic-based types of heart failure). While recording variables of cardiac function, they should be placed in their correct conceptual frame. *LV EDV* left ventricular end diastolic volume; *LA* left atrium, *BNP* brain natriuretic peptide, *TGF* tissue growth factor, *CRP* C-reactive protein, *MMP* matrix metallo-proteinase, *Tn-I* troponin-I, *SNP* single nucleotide polymorphism, *GWAS* genome wide association study

- Progression of heart failure is accompanied by structural and functional changes of the heart ("ventricular remodeling"), which result from multiple and interacting signaling processes.

2.5 *How to Measure Cardiac Performance in Heart Failure and Characterize the Syndrome?*

Diagnosis and follow-up of heart failure requires assessment of cardiac performance. Cardiac performance can be assessed at many different levels of the heart's functional complexity (Fig. 1.6), providing many possible performance indices and heart failure variables. Variables of heart failure may fit in a general circulatory context, like blood pressure and peripheral/pulmonary vascular resistance, which often receive large attention in the clinical setting of acute cardiac failure and

circulatory shock. They do not reliably reflect the function of the pump, however, since they can be normal in advanced stages of pump dysfunction.

Parameters of pump function may reflect the function of the left ventricle (LV) as a *hemodynamic pump* (e.g., LVEF and LV end systolic elastance) or they may reflect the function of the LV as a *muscular pump* (e.g., myocardial segment strain, (un) twisting velocities). This differentiation is important since in some stages/phenotypes of heart failure hemodynamic pump parameters are still preserved, giving the false impression that LV function is normal, despite severe dysfunction of the muscular properties of the ventricle (e.g., in the setting of HFPEF, or in the setting of "low gradient aortic valve stenosis and a normal LVEF"). Next, serum biomarkers such as serum natriuretic peptides, metallo-proteinases, endothelin-1, and neuregulin-1 are indices of heart failure reflecting (secretory) processes of myocardial cells. Biomarkers usually are very sensitive parameters of heart failure, increased in early stages of LV dysfunction, even when LVEF is still normal. Finally, expression levels of mRNA's and micro-RNA's, to be quantified in isolated myocardial tissue or in serum, reflect DNA activities of cardiac cells and may used in the diagnosis or staging of heart failure, although this is still experimental to date.

Recording these variables of cardiac performance and heart failure gives a reliable picture of the severity and the stage of the disease in an individual patient. For example, measuring increased levels of serum natriuretic peptides, reduced left ventricular untwisting velocities but a normal LVEF indicates that heart failure has progressed up to the stage of dysfunction of the muscular pump, but that performance of the heart at a higher hierarchic level is still intact (often due to activation of compensatory processes which optimize the function of the hemodynamic pump, despite dysfunction of the heart at the level of the cardiac muscle and lower levels of complexity).

Interestingly, within each hierarchic level of cardiac dysfunction, different "clinical phenotypes" of the heart failure syndrome can be identified, which refers to with the above mentioned clinical heterogeneity of the syndrome. For example, when heart failure has progressed up to the most severe stage, i.e., failure of the heart as a hydrodynamic input–output system, it may clinically present as *forward or backward heart failure*. Similarly, when heart failure has progressed up to the level of the hemodynamic pump clinical phenotypes of predominant *systolic or diastolic heart failure* may be differentiated. Currently, there are attempts to define heart failure subtypes based on a *multi-biomarker panel*. None of these "phenotypes" of heart failure should be viewed as a distinct disease entity. They are mere variant clinical presentations in a spectrum of heterogeneous phenotypes, to which therapeutic interventions should be tailored.

Key Point

- All indices of cardiac performance and failure fall within a specific conceptual approach to cardiac performance.

2.6 Diastolic Dysfunction

Most if not all forms of heart failure, independently of LVEF, display a certain degree of diastolic dysfunction. In fact, in many clinical condition, i.p. ischemic heart disease and hypertrophic cardiomyopathy, relaxation and filling abnormalities occur long before contraction and ejection abnormalities.

Although often subject of misinterpretation, at least from the perspective of the heart as muscular pump, "true" diastole of the ventricle only starts after early rapid ventricular filling, and hence encompasses diastasis and the atrial contraction phase. Pressure fall during isovolumic relaxation in the pump (that fully completes at end systolic volumes) and the increase in pump volume during early rapid filling are strictu sensu still part of the contraction-relaxation cycle of the ventricular muscular "systole." Diastolic failure then refers to a disease process that shifts the end portion of the pressure–volume diagram inappropriately upward so that LV filling pressures are increased dysproportionally to the magnitude of LV dilatation (Fig. 1.7). The causes of such a shift can be subdivided into (Table 1.2):

1. Decrease in ventricular diastolic compliance (i.e., true diastolic failure)
2. Slow ventricular systolic relaxation (i.e., diastolic failure secondary to impaired systolic function of the muscular pump)
3. Inappropriate tachycardia (e.g., transient atrial fibrillation, supraventricular tachy-arrythmias) (i.e., diastolic failure secondary to inappropriate abbreviation of diastolic duration)
4. A combination of a, b, and c, as is usually the case.

Causes of impaired relaxation and/or compliance can be divided into (1) Factors intrinsic to the cardiomyocyte, (2) factors within the extracellular matrix (ECM) that surrounds the cardiomyocytes, and (3) factors that activate the production of neurohormones and paracrine substances.

Cardiomyocyte. Elements and processes intrinsic to the cardiomyocyte contributing to diastolic (dys)function have been summarized in Table 1.2. In general they relate to processes responsible for calcium removal from the myocyte cytosol (calcium homeostasis), to processes involved in cross-bridge detachment and to cytoskeletal functional elements. Changes in any of the processes and elements can lead to abnormalities in both active relaxation and passive stiffness.

1. *Calcium homeostasis*. Abnormal activity of SERCA2 has been implicated in the impaired relaxation in heart failure. SERCA2 activity declines in LV hypertrophy and heart failure by reduced gene and protein expression and by reduced phosphorylation of its inhibitory modulatory protein phospholamban (PLB) [37–40]. Conversely, experimental gene transfer with SERCA2a or a negative PLB mutant improves relaxation [41, 42]. It is as yet unclear at which stages of chronic heart failure SERCA2 activity becomes affected [43]. By all means, impaired SERCA2 activity is certainly not specific for HFPEF, as it will become more pronounced when global pump performance is reduced [37].

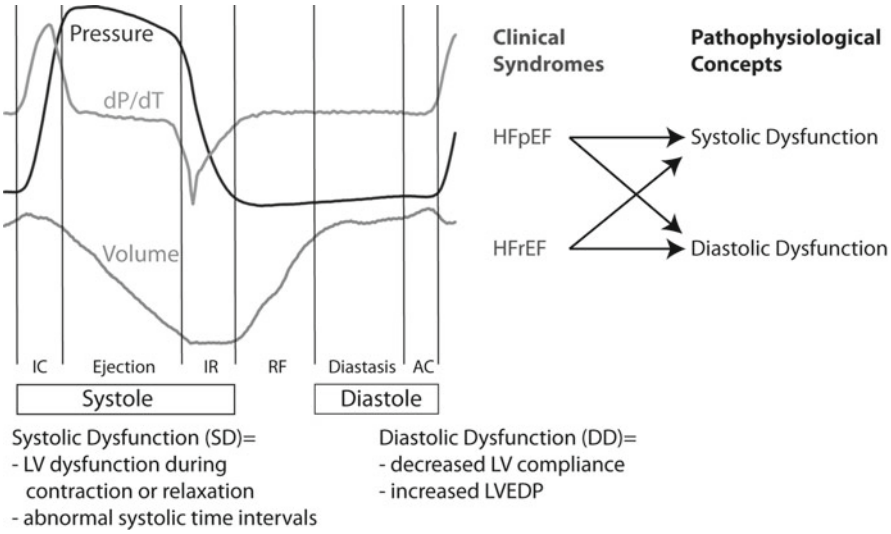

Fig. 1.7 Subdivision of the cardiac cycle from the perspective of the heart as a muscular pump. Taking into account that the heart is a muscle, "true" diastole of the ventricle only starts after early rapid ventricular filling, and hence encompasses diastasis and the atrial contraction phase. At normal rest heart rates, diastole usually lasts for approximately 50 % of the total time duration of the cardiac cycle. Pressure fall during isovolumic relaxation in the pump (that fully completes at end systolic volumes) and the increase in pump volume during early rapid filling are strictu sensu still part of the contraction-relaxation cycle of the ventricular muscular "systole." Diastolic failure then refers to a disease process that shifts the end portion of the pressure–volume diagram inappropriately upward so that LV filling pressures are increased disproportionally to the magnitude of LV dilatation

Table 1.2 Mechanisms of diastolic dysfunction

Mechanisms of diastolic dysfunction

Inappropriate tachycardia	Impaired Load Dependence of Relaxation	Ventriculo-Arterial stiffening
Intermittent atrial fibrillation; atrial tachyarrhythmias	**- Excessive Load** ▪ pressure-volume overload **- Impaired Inactivation** ▪ calcium homeostasis ✓ calcium overload ✓ calcium transport (sarcolemma, SR) ✓ modifying proteins (phospholamban, calmodulin) ▪ myofilaments ✓ Tn-C calcium binding ✓ Tn-I phosphorylation ✓ myofilament calcium sensitivity ✓ Myosin Binding Protein C ▪ energetics ✓ ADP/ATP ratio ✓ ADP and Pi concentration **- Excessive Non-uniformity of load or inactivation in space or time** **- Abnormal activity of RAAS, OS, ANP/BNP, cardiac endothelial system**	**INTRACARDIAC:** ***Hypertrophy*** **- Cytoskeletal abnormalities** ▪ microtubules (tubulin) ▪ intermediates filaments (desmin) ▪ **Increased N2B/N2BA titin** ▪ Nebuline **- Extracellular matrix** ▪ fibrillar collagen ▪ basement membrane proteins ▪ proteoglycans ▪ MMP/TIMP **- Abnormal activity of cardiac endothelial system (especially NO)** **EXTRACARDIAL:** ***Arterial Stiffening*** (reflected waves)

2. *Cross-bridge detachments*. Impaired relaxation and increased ventricular stiffness may result from slow or incomplete cross-bridge detachment.

   Abnormal cross-bridge detachment may result from reduced cAMP or cGMP-mediated phosphorylation of troponin-I, which increases calcium sensitivity of the myofibrils to calcium. Relaxation may also be impaired by alterations in the thick myofilaments as observed in genetic animal models [44], but whether this contributes to the development of relaxation disturbances in human heart failure is, however, still unknown.

   Cross-bridge detachment can also be disturbed by perturbations in loading (preload and afterload). Enhanced preload delays onset and rate of relaxation, an effect that may become particularly relevant during beta-adrenergic stimulation as the lusitropic effects of adrenergic stimulation in tachycardia may become blocked by this mechanism [45, 46]. Effects of loading on the timing and rate of relaxation are complex, and dependent on the timing of load [47, 48]. The importance of inappropriate loading has been reemphasized in studies demonstrating abnormal ventricular–arterial interaction due to a disproportionate cardiovascular stiffening in patient with HFPEF. Stiffening-induced imbalances of the ventricular–arterial load may exacerbate systemic afterload, i.e., arterial impedance and reflected waves, and hence affect onset and rate of LV relaxation [49].
3. *Cytoskeletal abnormalities*. Proteins within the sarcomere, other than the myofibrils that generate active force, contribute substantially to the stiffness of the cardiac muscle over the normal range of the sarcomere length (<2.2 μm). These molecules include titin, tubulin, and desmin, but most of the elastic force of the sarcomere is thought to reside in titin [50]. Interestingly, titin is subject of intense regulation, including isoform switching, calcium binding and phosphorylation, indicating that myocardial resting tension can be dynamically regulated.

   The two titin isoforms (N2B and N2BA) differ substantially in length and stiffness, with the N2B isoform being small and stiff. The distribution of these isoforms differs among species, heart chambers and disease states, and seems to track the corresponding variations in diastolic muscle stiffness [51]. Recent observations indicate that phosphorylation of titin may reverse the increased stiffness of cardiomyocytes in heart failure [52].

ECM. Changes in the structures within the ECM can also affect diastolic function (Fig. 1.2). The myocardial ECM is composed of three important constituents: (1) fibrillar protein, such as collagen type I, type III and elastin; (2) proteoglycans; and (3) basement membrane protein such as collagen type IV, laminin and fibronectin. It has been hypothesized that the most important component within the ECM that contributes to the development of diastolic dysfunction is fibrillar collagen (amount, geometry, distribution (especially as perimysial fibers), degree of cross-linking, ratio of collagen type I to III) [52–54]. Collagen synthesis is altered by load, both preload and afterload, by neurohormonal activation (e.g., the renin-angiotensin-aldosteron system- or RAAS—and the sympathic nervous systems), and by growth factors. Collagen degradation is under the control of proteolytic enzymes including

matrix metallo-proteinases. Any change in the regulatory processes affecting collagen degradation and synthesis can thus alter diastolic function.

Several studies have made correlations between modifications of the collagen network and diastolic muscle stiffness, but usually with rather extreme collagen modifications only [54–56]. A direct linkage between fibrosis and stiffness is thus still controversial, especially since in some other studies, correlations between the amount of fibrosis and muscle stiffness was lacking. Hence, whether these inconsistencies point towards a role for the posttranslational structure of collagen rather than the amount of collagen, or instead indicate that titin plays a more important role than ECM in general, is still subject of debate [57].

Neurohormonal and cardiac endothelial activation. Both acutely and chronically, neurohormonal and cardiac endothelial activation and/or inhibition have been shown to alter diastolic function. Chronic activation of the RAAS has been shown to increase ECM fibrillar collagen. Inhibition of the RAAS prevents or reverses this increase. Generally but not consistently, these changes have been shown to affect ventricular stiffness. Acute activation of the cardiac endothelial system has been shown to alter relaxation and stiffness [58], most likely through the release of nitric oxide.

Key Points

- Diastolic dysfunction originates from a dysfunction at the level of cardiomyocytes, at the level of the ECM, or at the level of neurohormonal or paracrine systems.

3 Future Trends

Insights into the complex signaling cascades underlying ventricular remodeling and heart failure progression are rapidly expanding. Large-scale quantitative analyses of gene expression, including cDNA microarrays and proteomic analyses, have contributed to this progress. Interestingly, with each newly described cascade, novel biomarkers, and molecular targets for therapy emerge. There is a current trend to characterize and manage heart failure patients by the measurement of 1 or multiple biomarkers [59]. In clinical trials, this blind multimarker strategy may provide clinically useful and refreshing information. It surpasses patient selection based on LVEF alone. Moreover, it may personalize heart failure management and help to optimize current heart failure guidelines.

On the other hand, one may seriously question where this linear approach will eventually lead. It may be feared that adding still more biomarkers and other disease parameters in heart failure will never end, will add even more complexity and result in a reductionist search for perfection, and will fail to relaunch conceptual thinking about heart failure. Perhaps the time has come to envisage nonlinear integrative approaches already introduced in other fields of the life sciences that encounter

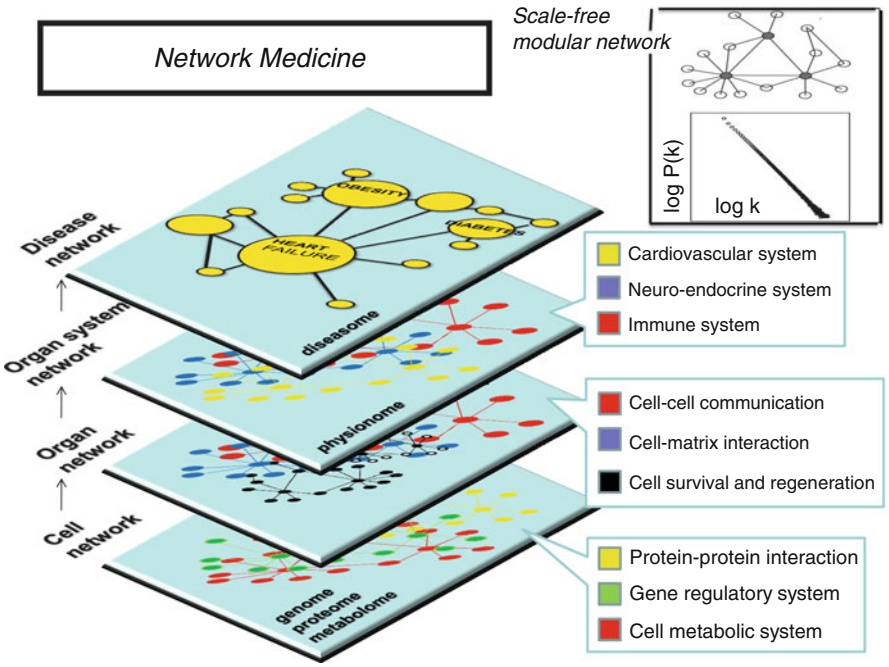

Fig. 1.8 Systems biology approach to medicine creates network medicine. Hypothetical scheme of network medicine with focus on the cardiovascular system and chronic heart failure. Biosciences are in transition from reductionist sciences to integrative sciences, i.e., a systems approach to biology. In this conceptually novel approach, physiology is not the result of traditional linear processes of structural and functional components (identified by genomic, proteomic, metabolomic sciences), but emerges from the interaction of scale-free modular biological networks composed by these components. Modular networks emerge at many different levels such as genes, transcripts, proteins, metabolites, organelles, cells, organs, and organ system

similar limits of reductionism and seek understanding from a myriad of validated bits of data [60].

Accordingly, life sciences, including heart failure sciences, encounter the limits inherent to linear reductionist approaches. Systems approaches to the complexity of the cardiovascular system are beginning to close this gap [4]. Systems biology seeks to provide a framework for the manner in which structural and functional components (as identified by, e.g., cDNA microarrays and proteomic analyses) interact in self-organizing modular biological networks. Networks, rather than the components themselves, create physiology and disease. Each node in a network represents a component (e.g., a gene, a transcript), and interconnecting nodes describe a typical architecture that is imposed by biological evolution and selection. Modular biological networks and clusters of interacting networks have been demonstrated to occur at different levels such as genes, transcripts, and proteins, but they probably also emerge at higher hierarchical levels, such as metabolites, organelles, cells, organs, and organ systems (Fig. 1.8). At each level, a network obtains new properties that

are not predicted from the properties of the network at the lower level, referring to the aforementioned concept of emerging properties in a dissipative structure introduced by Prigogine and Strengers [3]. Hence, a network perspective to biology defines a disease as the failure of biological networks or as the failure to obtain a next-level emerging property. Accordingly, systems biology is not replacing but is complementing reductionist sciences. It provides a framework for analyzing the manner in which structures of biological networks relate to function. This process is a prerequisite to understanding complex diseases or a syndrome like heart failure.

Integrating systems biology into the study of the complexity of heart failure is timely. Many questions still need to be addressed, however. What are the crucial biological networks (in the network of networks) of cardiac function and heart failure, and where are the vulnerable hubs that can destabilize networks? Can a network perspective to heart failure provide novel biological (organ-specific) fingerprints of failure that allow prediction of a patient's risk, early disease development, or disease stage? How do these fingerprints relate to the current growing list of heart failure biomarkers? Can systems biology help to define novel surrogate end points for clinical trials? How can a network, if associated with a disease, be targeted pharmacologically? How does this relate to the growing list of targets now emerging from reductionist sciences?

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