Systolic and diastolic heart failure pdf

Table 1. Characteristics of Diastolic Heart Failure as Compared with Those of Systolic Heart Failure.*

Characteristic	Diastolic Heart Failure	Systolic Heart Failure
Clinical features		
Symptoms (e.g., dyspnea)	Yes	Yes
Congestive state (e.g., edema)	Yes	Yes
Neurohormonal activation (e.g., brain natriuretic peptide)	Yes	Yes
Left ventricular structure and function		
Ejection fraction	Normal	Decreased
Left ventricular mass	Increased	Increased
Relative wall thickness†	Increased	Decreased
End diastolic volume	Normal	Increased
End diastolic pressure	Increased	Increased
Left atrial size	Increased	Increased
Exercise		
Exercise capacity	Decreased	Decreased
Cardiac output augmentation	Decreased	Decreased
End diastolic pressure	Increased	Increased

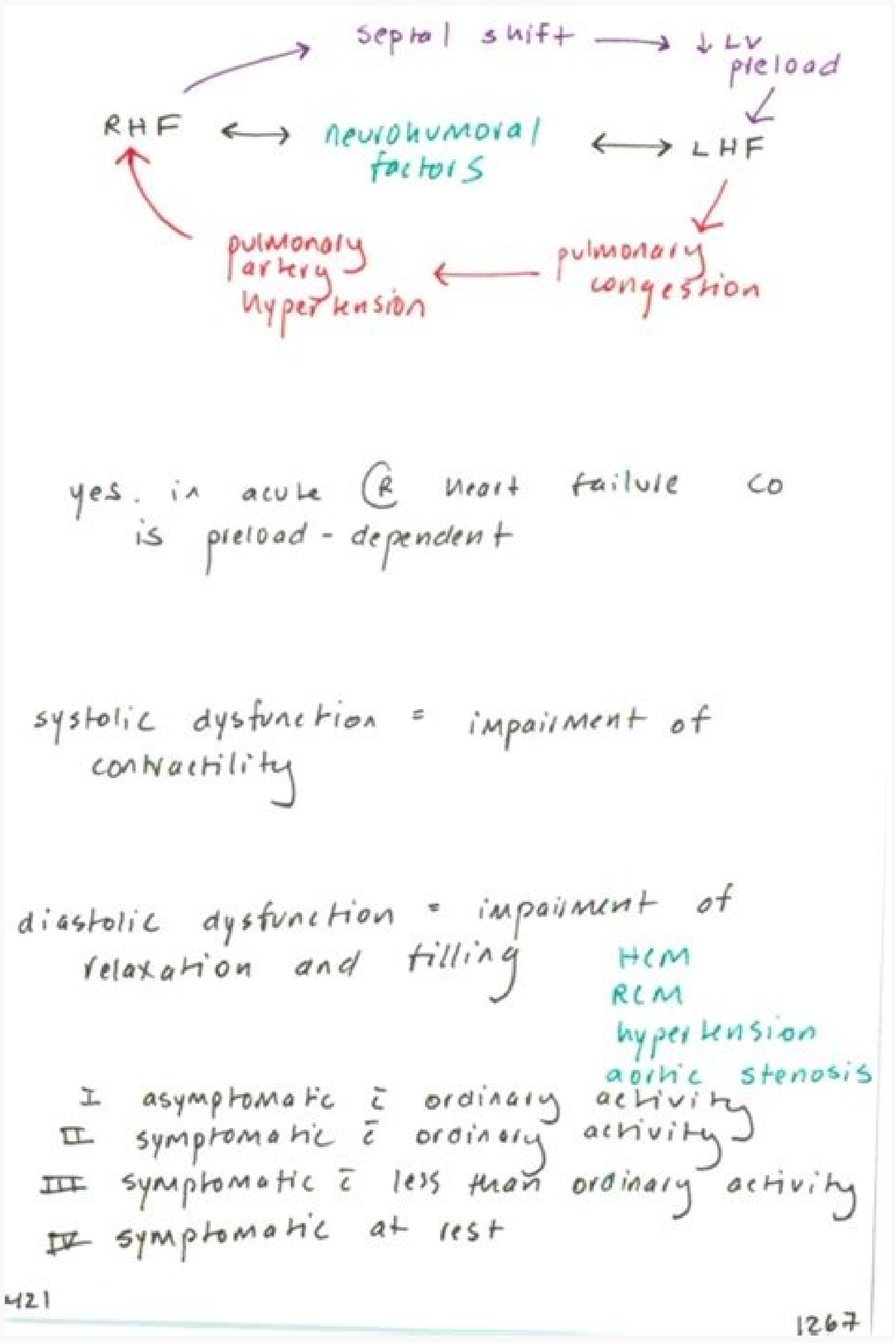


Table 2. Distribution of Ejection Fraction and Diastolic Dysfunction Among Patients With Heart Failure*

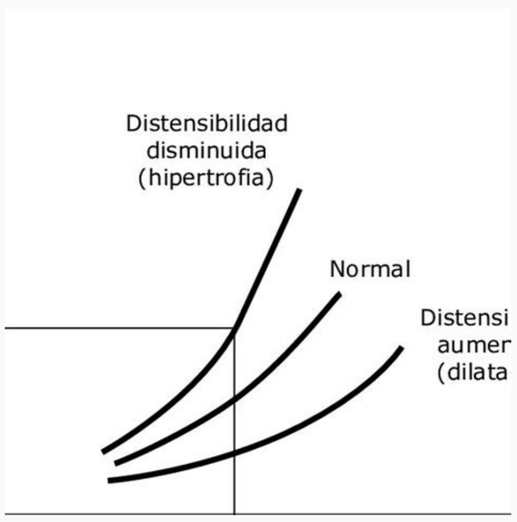
	No. (%)				
	Normal Diastolic Function	Indeterminate Diastolic Function	Mild Diastolic Dysfunction	Moderate Diastolic Dysfunction	Severe Diastolic Dysfunction
All cases (N = 556)					
Ejection fraction ≥50%	31 (10)	35 (11)	22 (7)†	194 (63)†	26 (8)†
Ejection fraction <50%	13 (5)	31 (13)	10 (4)	138 (56)	56 (23)
Total	**44** (8)	**66** (12)	**32** (6)	**332** (60)	**82** (15)
Incident cases (n = 295)					
Ejection fraction ≥50%	18 (11)	10 (6)	16 (9)†	114 (67)†	12 (7)†
Ejection fraction <50%	3 (2)	16 (13)	4 (3)	72 (58)	30 (24)
Total	**21** (7)	**26** (9)	**20** (7)	**186** (63)	**42** (14)
Outpatient cases (n = 122)					
Ejection fraction ≥50%	7 (10)	4 (6)	6 (8)†	50 (69)†	6 (8)†
Ejection fraction <50%	3 (6)	4 (8)	3 (6)	25 (51)	14 (29)
Total	**10** (8)	**8** (7)	**9** (7)	**75** (61)	**20** (16)

*Mild diastolic dysfunction represents impaired relaxation mitral inflow patterns with normal filling pressures; moderate diastolic dysfunction represents impaired relaxation mitral inflow patterns with elevated filling pressures or a pseudo-normal mitral inflow pattern with elevation of filling pressures; and severe diastolic dysfunction represents restrictive mitral inflow pattern.
†Patients with isolated diastolic dysfunction.

Table 1. Clinical Characteristics Stratified by Pulse Pressure Tertile*

Characteristic	Pulse Pressure, mm Hg			
	<54 (n = 534)	54-67 (n = 547)	≥67 (n = 540)	P Value†
Age, mean ± SD, y	77.3 ± 4.8	77.9 ± 5.2	78.6 ± 4.9	<.001
Mean arterial pressure, mean ± SD, mm Hg	90.9 ± 9.0	95.3 ± 10.1	101.5 ± 11.7	<.001
Male sex	33.0	37.5	31.3	.51
Diabetes mellitus	13.3	17.2	27.2	.001
Hypertension	44.0	49.5	70.2	.001
Antihypertensive medication	38.8	44.6	53.3	.001
Coronary heart disease	9.2	10.8	10.9	.34
Atrial fibrillation	2.4	2.2	3.7	.20
Valvular heart disease	1.1	1.5	2.8	.04

*Data are presented as percentages unless otherwise indicated.
†P values given for analysis of variance of continuous variables and test for linear trend for categorical variables.



Systolic and diastolic heart failure prognosis. Systolic and diastolic heart failure causes. Systolic and diastolic heart failure icd 10. Systolic and diastolic heart failure treatment. Systolic and diastolic heart failure symptoms. Systolic and diastolic heart failure pathophysiology. Systolic and diastolic heart failure life expectancy. Systolic and diastolic heart failure differences and similarities.

Ionomic profiling of pericardial fluid in ischemic heart disease. Khan N, Hashmi S, Siddiqui AJ, Farooq S, Sami SA, Basir N, Bokhari SS, Sharif H, Junejo S, Musharraf SG. Khan N, et al. RSC Adv. 2020 Oct 2;10(60):36439-36451. doi: 10.1039/d0ra03977b. eCollection 2020 Oct 1. RSC Adv. 2020. PMID: 35517944 Free PMC article. Should chronic heart failure (HF) be subdivided into 2 distinct phenotypes? Current knowledge supports the view that the complexity of HF cannot be captured by answering this question with a yes or a no. Recent developments in the biosciences, particularly systems biology approaches and studies of phenotypic disease networks, have indicated that such questions are becoming obsolete, and perhaps even irrelevant.Response by Borlaug and Redfield on p 2005Chronic HF is a complex, multifactorial syndrome consisting of many overlapping phenotypes. A unifying hypothesis to explain the development and progressive character of HF has not withstood the test of time (Figure 1). Despite improvements in clinical management, the incidence and mortality of chronic HF remain high. Attempts to further improve its prognosis have failed, and conceptual progress seems to stagnate.Figure 1. Evolving paradigms of heart failure progression. Each of the paradigms highlights a different aspect of the syndrome. In the vicious circle paradigm of heart failure (left), the pernicious, progressive, and irreversible character is emphasized as propelled by endothelial dysfunction and (mal)adaptive activation of neurohormones and cytokines. In the time progression paradigm (middle), the progressive nature of heart failure is equally emphasized, but focus is on the consecutive stages of failing cardiac performance: 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 the manner in which each patient follows a unique disease trajectory during heart failure progression. 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. CV indicates cardiovascular; EF, ejection fraction; SWI, stroke work index; PCW, pulmonary capillary wedge; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.Surveys on chronic HF in the community have shown that the distribution of left ventricular ejection fraction (LVEF) is bell-shaped,1 and that ≈40% to 50% of patients present with a LVEF ≥50%.2 This proportion of patients with HF and preserved LVEF (HFpEF) was much larger than anticipated, and has been shown to increase with time.2,3 Surveys have also shown that the prognosis of HFpEF is worse than originally believed.3 Clinical trials on inhibition of the renin-angiotensin system in HFpEF, the cornerstone therapy of HF with reduced LVEF (HFrEF), have been disappointing.4 Although results of ongoing trials are still awaited, evidence-based medicine in HFpEF is lacking.One may wonder about the reasons for these failures and lack of conceptual progress. Some believe that one should continue to dichotomize into HFpEF and HFrEF and approach the latter as a separate disease (the binary view to HF).5,6 This opinion is based on the premise that HFpEF and HFrEF have a different pathophysiology, and also on the clinically relevant results and refinement of HF guidelines based on a binary view.In this review, we defend the opposite point of view, and argue that HFpEF and HFrEF are mere extremes in a spectrum of overlapping HF phenotypes, and hence that these are not distinct disease entities. As a more provocative statement, we will argue that a spectrum view to HF is only an intermediate step toward emerging systems biological approaches to cardiovascular complexity. Integrative sciences have introduced the concept of phentypic disease networks in which defining disease entities becomes obsolete, and even irrelevant.The Misleading Advantage of Left Ventricular Ejection Fraction-Based Disease Taxonomy in Heart FailureThe false perception that HF consists of 2 distinct phenotypes originates from the introduction in the early 1980s of the novel principle of evidence-based medicine, the launching of industry-driven clinical trials, and the emphasis on statistics. Clinical trials introduced a bias in the field of HF by systematically excluding patients with an LVEF >40% to 45%. This bias was not based on conceptual reasoning or a hypothesis, but was introduced merely to include patients with a putative grim prognosis, hence increasing the statistical power of the trial with a reasonable number of patients. When we look back at this bias 30 years later, it is stunning to observe how easily scientists adopted this concept-empty switch in studying HF. At that time, by excluding approximately half of the patients, most likely too few scientists realized the impact of this bias, nor did they anticipate the far-reaching conceptual consequences still vibrating in today's reasoning about HF. Unfortunately, when, many years later, some of the clinical trials were repeated, now selecting the HF patients who were originally excluded (LVEF ≥40% to 50%), it appeared that these patients had less of a response to pharmaceutical products. This information may be clinically relevant, but is at the same time misleading. It has led to the erroneous perception that HF consists of 2 distinct phenotypes with different, unrelated pathophysiology.One should realize, however, that a complex, multifactorial disease such as HF emerges along a linear distribution, with divergent phenotypes at both ends of a bell-shaped spectrum (which refers to the bell-shaped distribution of LVEF in the HF population1,7). When patients from the 2 extremes of the spectrum are compared, it is not surprising that some of the disease characteristics and clinical response to therapy will diverge. Investigators failing to perceive the whole disease spectrum, and hence tenaciously persevering to the bias by comparing only the extremes of the spectrum, will be programmed to dichotomize the disease, even more so if the bias has, as stated above, provided clinically relevant information. Imposing an arbitrary cutoff for any of the many prognostic continuous variables of HF, either LVEF or any of the other currently available biomarkers, does not necessarily signify that a novel paradigm is generated or that disease taxonomy should be introduced, even if it unveils clinically useful information.Accordingly, despite some practical, clinical advantages, a binary view to HF lacks a conceptual basis. Next, we will summarize how post hoc observations contradict the paradigm that HF can be dichotomized. On the contrary, these observations unveil that HF consists of a continuous spectrum of overlapping phenotypes.Systolic and Diastolic Heart Failure Are Overlapping Phenotypes in the Heart Failure SpectrumSome clinical investigators promoting a binary view to HF still favor the terms systolic and diastolic HF.5,6 With the use of these terms, 1 of the pathophysiological abnormalities prevailing in either 1 of the 2 phenotypes is emphasized. Nobody can deny that different disturbances prevail at both ends of the disease spectrum. We do not believe, however, that diastolic dysfunction is unique for HFpEF, because it also occurs in HFrEF.8–10 Neither is systolic dysfunction unique for HFrEF, because it also occurs in HFpEF.11–14 Instead, we argue that all forms of HF are hybrids, showing both systolic and diastolic abnormalities in varying proportions. Tan et al15 recently showed that patients with HFpEF manifested reduced radial and longitudinal systolic strain both at rest and on exercise, reduced systolic and diastolic longitudinal functional reserve, reduced ventricular systolic rotation at rest that failed to increase on exercise, delayed ventricular untwisting with further worsening on exercise, which was associated with reduced LV suction, and reduced rise in stroke volume on exercise. As expected from Figure 2, the other derived measurements of hemodynamic compression pump function (ie, end-systolic elastance, stroke work index, and peak power index) were not different from those of the control group. These data indicate that contraction and relaxation abnormalities of systolic function in HFpEF, even when they do not affect indices of global hemodynamic compression pump performance, may have profound effects on ventricular function, in particular on suction during early LV filling. Investigators claiming that systolic function in HFpEF is normal usually have merely considered ventricular function at rest or have analyzed ventricular function at higher levels of LV complexity (ie, the ventricle either as a hemodynamic compression pump or as a hydraulic input-output system), but have neglected the ventricle as a muscular or a pluricellular tissue pump16,17 (Figure 2).Figure 2. 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 noncardiomyocytes 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, biomarker set–specific failure, and perhaps, in the future, phenotypes with failure of specific [subcellular] modular networks). While recording variables of cardiac function, these parameters should be placed in their correct conceptual frame. For example, when measuring a normal left ventricular (LV) ejection fraction in a patient with heart failure, the clinician should realize that this parameter is a mere sensor of the hemodynamic compression pump and is insensitive for features of the ventricle as a muscular suction pump. Similar to LV ejection fraction, other parameters of the hemodynamic compression pump do not allow estimation of the integrity of the function of the ventricle at lower hierarchical levels of complexity. PCWP indicates pulmonary capillary wedge pressure; EDV, end-diastolic volume; LA, left atrium; 2D, 2-dimensional; V, volume; P, pressure; F, flow; MRI, magnetic resonance imaging; BNP, brain natriuretic peptide; CRP, C-reactive protein; Tn-I, troponin-I; TGF, tissue growth factor; MMP, matrix metalloproteinase; SNP, single nucleotide polymorphism; GWAS, genome-wide association study; HFPEF, heart failure with preserved left ventricular ejection fraction; and HFREF, heart failure with reduced left ventricular ejection fraction.The connotations of systolic and diastolic HF have the disadvantage of overemphasizing the importance of systolic or diastolic ventricular abnormalities of hemodynamic compression pump performance. The complexity of HF clearly surpasses such isolated disturbances of the ventricular hemodynamic compression pump.18 Instead, numerous intracardiac and extracardiac abnormalities (eg, neurohormonal abnormalities,19 renal dysfunction,20 upregulation of growth factors,21 volume overload,22 ventricular collagen turnover,23 titin isoform switching and phosphorylation deficits,24 endothelial dysfunction,25 atrial dysfunction,26 and arterial stiffening27) have been demonstrated in HFpEF, and are shared by most, if not all, phenotypes of HF, even when systolic or diastolic abnormalities of the hemodynamic compression pump prevail.There currently is not a single pathognomonic feature at any level of biological complexity (gene, protein, cell, organ, or organ system) that distinguishes HFpEF from HFrEF. Instead, the differences between these phenotypes have been merely quantitative, reflecting only different mean degrees of disturbances. Individual data sets reveal that HFpEF and HFrEF show a substantial overlap, and, when plotted over the full width of the HF spectrum, follow a smooth, gradually varying profile. Examples include longitudinal ventricular contractile function,12 serum brain natriuretic peptide,28 LV end-diastolic volume,29 and cardiomyocyte diameters.30 Importantly, the latter data on cavity volume and cardiomyocyte diameters underscore that concentric and eccentric remodeling associated with HFpEF and HFrEF, respectively, cannot be considered as all-or-nothing phenomena but are only extremes in a continuum of remodeling phenotypes. Hence, neither LVEF nor cavity dimensions can capture the wide variety of morphological changes that the ventricle can undergo during progression of HF. HFpEF and HFrEF share, to varying degrees, pathological features of both concentric and eccentric remodeling.31Accordingly, the acknowledgment that HFpEF and HFrEF are more related than previously anticipated and belong to a spectrum of overlapping phenotypes is a major conceptual achievement in HF. Logically, to avoid further confusion, it would be appropriate to abandon the terms systolic and diastolic HF altogether. The alternative terms HFpEF and HFrEF may be somewhat more acceptable, but only when used in a descriptive sense (ie, as a guide to stage the disease and to make a patient-oriented choice of therapy). Still, cautious use is recommended to prevent further support to the aforementioned binary view of HF. Next, we will comment on why HF does not emerge as a uniform phenotype, but instead as a disease spectrum of overlapping phenotypes.Origin of the Heart Failure SpectrumRecent surveys have shown that the biological traits (eg, age and sex) and comorbidities (eg, hypertension, diabetes mellitus, coronary artery disease) of patients with HF follow a gradually varying pattern throughout the HF spectrum.32 Hence, no biological trait or comorbidity is unique for any given phenotype of HF.Because biological traits and comorbidities and their uneven distribution over the HF patient population are likely causally related to the heterogeneity of HF, we previously introduced the concept of disease modifiers of HF.33,34 Surprisingly, however, insights into the mechanisms of the manner in which these modifiers direct the patient's individual trajectory are incomplete. Do the modifiers act alone, or only in combination with senescence? Is there a critical number or combination of modifiers that tips the balance? Is there a genetic background that influences the susceptibility of the heart to be changed architecturally and functionally by these modifiers?The long-term effects of these modifiers on LV structure and function have been acknowledged only recently. Cheng et al35 analyzed 4 serial echocardiograph recordings obtained over a 16-year period in 4062 participants who did not experience myocardial infarction during follow-up. With advancing age, LV dimensions decreased, and LV wall thickness increased. Consistent with previous observations,36,37 female gender accentuated age-associated changes, especially those in wall thickness. Strikingly, however, obesity, diabetes mellitus, and hypertension independently induced changes that were different in directionality from the effect of aging itself. This trend was most evident for LV cavity dimensions. Given the association between HFpEF, hypertension, obesity, and diabetes mellitus, these observations explain why LV cavity dimensions tend to increase in HFpEF, in a manner similar to that in HFrEF.22 These observations also counter the view that HFpEF-related factors would merely promote an age-dependent process, hence accelerating an inborn evolution toward HFpEF, with only HFrEF imparting a deviation from this evolution.38Accordingly, biological traits and comorbidities act as modifiers of LV remodeling and HF progression. This creates disease trajectories that are unique for each patient. Together, disease trajectories form a spectrum of overlapping phenotypes. Next, the underlying subcellular and molecular complexity of this phenomenon will be addressed.The Molecular Complexity of the Heart Failure SpectrumThe molecular mechanisms underlying the manner in which disease modifiers of HF, such as sex, hypertension, obesity, diabetes mellitus, coronary artery disease, and myocardial inflammation, induce and direct the remodeling of ventricular architecture and function are under intense investigation. It is beyond the scope of this article to describe these mechanisms in detail; we are referring to several excellent recent state-of-the-art reviews.36,39–43 It is sufficient to highlight the message derived from these reviews; each of these modifiers separately recruits numerous complex intracellular signaling cascades, thereby affecting such entities as contractile proteins, excitation-contraction coupling, hypertrophy, cell survival pathways, extracellular matrix turnover, and cell metabolism (Figure 3). Contrary to the in vivo situation, the effects of these modifiers have, for practical reasons, been studied separately in well-controlled experiments, thus avoiding the complex in vivo interactions with the other modifiers. Hence, investigations have often focused on only a single or a few intermediate mediators, conceived

to be more or less specific for each modifier, such as (1) estrogen for gender,44 (2) leptin and adiponectin for obesity,45 (3) hyperlipemia, hyperglycemia, and hyperinsulinemia for diabetes mellitus,42 and (4) oxidative stress for ischemia.46Figure 3. The heart failure spectrum. Heterogeneity of heart failure is manifested by the varying profiles of ventricular remodeling among patients with heart failure. Although some patients develop predominantly concentric or predominantly eccentric remodeling, most show a combination of both. Ventricular remodeling is the product 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 inflammation, 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. 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 the heterogeneity of heart failure and a spectrum of overlapping phenotypes. Analogous with phenotypic disease networks of closely related illnesses, which recently emerged from phenotypic databases, dichotomizing this spectrum is not justified. Better predictive models of heart failure are needed, integrating clinical data with the myriad of molecular signaling processes in a patient-specific way. Hence, future clinical trials in heart failure should be patient phenotype driven but neither left ventricular (LV) ejection fraction nor biomarker driven. NYHA indicates New York Heart Association.Accordingly, ventricular remodeling is determined by intermingling disease modifiers, resulting from numerous complex interacting signaling processes, that vary in both proportion and genetic background for each patient. It is not surprising, therefore, that the HF spectrum consists of many related, overlapping phenotypes. Next, we will discuss how one should deal with the rapidly expanding molecular knowledge of ventricular remodeling, and with the many attempts to translate this information to bedside medicine.Need for a Systems Biology Approach to the Heart Failure SpectrumInsights into the complex signaling cascades underlying ventricular remodeling over the entire HF spectrum 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.43,47,48There is a current trend to characterize and manage HF patients by the measurement of 1 or multiple biomarkers.49–51 In clinical trials, this blind multimarker strategy, often claimed to represent a phenotype-oriented approach to HF, may provide clinically useful and refreshing information. It surpasses patient selection based on LVEF alone. Moreover, it may personalize HF management and help to optimize current HF guidelines.On the other hand, one may question seriously where this linear approach will eventually lead. It may be feared that adding still more biomarkers and other disease parameters in HF will never end, will add even more complexity and result in a reductionist search for perfection, and will fail to relaunch conceptual thinking about HF. Perhaps the time has come to envisage nonlinear integrative approaches already introduced in other fields of the life sciences that encounter similar limits of reductionism and seek understanding from a myriad of validated bits of data.52Accordingly, life sciences, including HF, encounter the limits inherent to linear reductionist approaches. Transition to integrative sciences is difficult but inevitable because it is the only way to process the complexity that has emerged from reductionism. Next, we will describe how systems biology approaches are introducing new concepts in medicine and how these concepts can be applied to HF. Systems approaches have indeed unveiled unexpected connections between apparently diverging pathophysiological processes and diseases, thereby challenging the very definition of the term disease entity.Heart Failure Is the Consequence of Failing Complexity Rather Than of a Failing System or Failing Organ, Cardiomyocyte, Single Molecule, or GeneThe heart is a complex system with properties that follow rules of complexity characterized by nonlinearity and self-organization. According to the ideas of Prigogine and Strengers,53 cardiac structure and function should be perceived as a dissipative structure54 (Figure 4). This means that the heart behaves as a dynamic and self-organizing structure with emerging properties at each higher hierarchical scale of performance through fluctuations, (nonlinear) interactions, and coherence of adjacent subsystems. Some well-recognized emerging properties of the ventricle at different hierarchical scales of performance consist of cross-bridge dynamics and cross-bridge cooperation, contractility and load dependency of relaxation, and ventricular uniformity through nonuniformity. From this perspective, ventricular dysfunction and HF are problems of failing complexity rather than of failure of one of the components. The origin of failing complexity in the ventricle and in cardiovascular physiology in general is, however, largely underexplored, and the translation of these principles to clinical sciences is still to come.Figure 4. 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 supersystem through fluctuations, interactions, and coherence of adjacent subsystems at each higher hierarchical scale, ranging from the subcellular modular networks (available through systems biology research) to modular networks at the organ level and beyond. At each scale, emerging properties are added.Systems approaches to the complexity of the cardiovascular system are beginning to close this gap.55 Systems biology seeks to provide a framework for the manner in which structural and functional components (as identified by, for example, cDNA microarrays and proteomic analyses) interact in self-organizing modular biological networks. Networks, rather than the components themselves, create physiological behavior and disease (Figure 5). Each node in a network represents a component (eg, a gene, a transcript), and interconnecting nodes describe a typical architecture that is imposed by biological evolution and selection. As advocated by Barabási et al,56,57 a biological network has the mathematical signature of a power law with the underlying property of being scale free (Figure 5, insert). Scale free means that most nodes connect to a few other nodes, whereas only few nodes connect to many other nodes (called hubs). 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 (Figure 5). 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.53 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.Figure 5. Systems biology approach to medicine creates network medicine. Hypothetical scheme of network medicine with focus on the cardiovascular system and chronic heart failure is shown. Biosciences are in transition from reductionist sciences to integrative sciences (ie, a systems approach to biology). In this conceptually novel approach, biological behavior is not the result of traditional linear processes of structural and functional components (identified by genomic, proteomic, and 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 systems.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 HF. Obviously, this process should go beyond blind associations, as in current genome-wide association studies, between genomic modular networks and human disease networks. Instead, the gap between gene and disease should be bridged by considering all of the intermediate physiological networks at the level of cell, organ, and organ system.In light of the current clinical and conceptual stagnation in HF, integrating systems biology into the study of the complexity of HF 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 HF, and where are the vulnerable hubs that can destabilize networks? Can a network perspective to HF 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 HF 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?It is essential that systems biology in HF develop in an unrestricted, unbiased fashion, and with global analyses of data over the entire HF spectrum. Subgroups of patients, such as those defined by arbitrary cutoffs of LVEF, should be avoided. Although it is not impossible that network approaches may somehow crystallize toward taxonomy and disease classification in HF, this seems unlikely. Recent network analyses of diseases have shown unanticipated connections between diseases and disease networks.56–58 Connections between disease networks may explain unexpected side effects of drugs, and may even force us to soon redefine the term disease entity. It is therefore unlikely that systems biology and network medicine will provide evidence that HFpEF and HFrEF are distinct entities.ConclusionsIn this article, we have fostered a spectrum view of HF (Table). Investigators who merely perceive the ends of this spectrum, influenced by the design of clinical trials and by the relevant evidence-based clinical differences, may be unfamiliar with this spectrum view, and instead favor a binary view. However, the latter view lacks a conceptual background. In addition, it is contradicted by recent reductionist analyses, provided that the data be analyzed without selection biases. Importantly, the debate about adopting a binary or a spectrum view of HF is becoming obsolete. Integrative sciences, which complement reductionist sciences, have unveiled the existence of disease networks in which it becomes difficult, and perhaps even irrelevant, to define disease entities.Table. Are Systolic and Diastolic HF Overlapping or Distinct Phenotypes Within the HF Spectrum?Distinct PhenotypesOverlapping PhenotypesSystolic and diastolic HF are distinct disease entities. To avoid further stagnation in HF, these entities should be approached separately in future clinical trials and experimental investigations.Chronic HF cannot be separated into different disease entities because it consists of a spectrum of overlapping phenotypes. This view is an intermediate step toward disease networks in which defining disease entities becomes obsolete or even irrelevant. 1. In diastolic HF, systolic LV function is normal. 1. Systolic LV function in HFpEF is abnormal and is causally related to LV diastolic dysfunction. Conclusions on LV systolic function should be based on analyses of LV function at all levels of LV complexity (Figure 2). 2. There are distinct, disease-specific mechanisms differentiating the pathophysiology of diastolic and systolic HF (eg, at the level of myocardial remodeling process, myocardial ultrastructure, changes in titin, cardiomyocyte resting tension, collagen turnover). 2. There are no distinct mechanisms currently allowing taxonomy in HF. Differences between phenotypes are merely quantitative and describe a smooth, gradually varying profile over the entire disease spectrum. 3. Diastolic HF is the result of an accelerated, age-dependent inborn process. Systolic HF is a deflection from this process. 3. HFpEF is more than an acceleration of an age-dependent process. The effect of risk factors (obesity, diabetes mellitus, hypertension) on LV architecture and function follows a directionality opposite to aging.35 4. The pathophysiology of diastolic HF is dominated by diastolic LV dysfunction. Therapeutically targeting diastolic abnormalities will resolve the problem. 4. The pathophysiology of HFpEF is more complex than LV diastolic abnormalities. Many disturbances in HFpEF surpass disturbances of the hemodynamic compression pump and are shared by overlapping phenotypes in the syndrome. Therapeutically targeting diastolic abnormalities will not suffice to reduce the burden of the disease. 5. There are 2 types of remodeling that justify a binary view on HF. 5. Ventricular remodeling is the end result of the interplay among complex signaling processes, the distribution of which is inhomogeneous over the HF patient population. The result is a spectrum of phenotypes of remodeled ventricles, the subdivision of which is artificial (Figure 3).Sources of FundingDr Gilles W. De Keulenaer is supported by a research grant from the European Commission (FP7-HEALTH-F2–2010-261409).DisclosuresNone.FootnotesReferences1. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA; Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of HF patients. Circulation. 2005; 112:3738–3744.LinkGoogle Scholar2. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis. 2005; 47:320–332.CrossrefMedlineGoogle Scholar3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006; 355:251–259.CrossrefMedlineGoogle Scholar4. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth!J Am Coll Cardiol. 2010; 55:526–537.CrossrefMedlineGoogle Scholar5. Bronzwaer JG, Paulus WJ. Diastolic and systolic heart failure: different stages or distinct phenotypes of the heart failure syndrome?Curr Heart Fail Rep. 2009; 6:281–286.CrossrefMedlineGoogle Scholar6. Quiñones MA, Zile MR, Massie BM, Kass DA; Participants of the Dartmouth Diastole Discourses. Chronic heart failure: a report from the Dartmouth Diastole Discourses. Congest Heart Fail. 2006; 12:162–165.CrossrefMedlineGoogle Scholar7. Gaasch WH, Delorey DE, Kueffer FJ, Zile MR. Distribution of left ventricular ejection fraction in patients with ischemic and hypertensive heart disease and chronic heart failure. Am J Cardiol. 2009; 104:1413–1415.CrossrefMedlineGoogle Scholar8. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation. 2000; 102:1788–1794.LinkGoogle Scholar9. Brutsaert DL, Sys SU. Relaxation and diastole of the heart. Physiol Rev. 1989; 69:1228–1315.CrossrefMedlineGoogle Scholar10. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997; 30:1527–1533.CrossrefMedlineGoogle Scholar11. Vinereanu D, Lim PO, Frenneaux MP, Fraser AG. Reduced myocardial velocities of left ventricular long-axis contraction identify both systolic and diastolic heart failure: a comparison with brain natriuretic peptide. Eur J Heart Fail. 2005; 7:512–519.CrossrefMedlineGoogle Scholar12. Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition?Heart. 2002; 87:121–125.CrossrefMedlineGoogle Scholar13. Sanderson JE, Fraser AG. Systolic dysfunction in heart failure with a normal ejection fraction: echo-Doppler measurements. Prog Cardiovasc Dis. 2006; 49:196–206.CrossrefMedlineGoogle Scholar14. Fukuta H, Little WC. Contribution of systolic and diastolic abnormalities to heart failure with a normal and a reduced ejection fraction. Prog Cardiovasc Dis. 2007; 49:229–240.CrossrefMedlineGoogle Scholar15. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol. 2009; 54:36–46.CrossrefMedlineGoogle Scholar16. Brutsaert DL. Cardiac dysfunction in heart failure: the cardiologist's love affair with time. Prog Cardiovasc Dis. 2006; 49:157–181.CrossrefMedlineGoogle Scholar17. De Keulenaer GW, Brutsaert DL. The heart failure spectrum: time for a phenotype-oriented approach. Circulation. 2009; 119:3044–3046.LinkGoogle Scholar18. Maurer MS, Kronzon I, Burkhoff D. Ventricular pump function in heart failure with normal ejection fraction: insights from pressure-volume measurements. Prog Cardiovasc Dis. 2006; 49:182–195.CrossrefMedlineGoogle Scholar19. Chatterjee K, Massie B. Systolic and diastolic heart failure: differences and similarities. J Card Fail. 2007; 13:569–576.CrossrefMedlineGoogle Scholar20. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation. 2007; 115:1982–1990.LinkGoogle Scholar21. Stahrenberg R, Edelmann F, Mende M, Kockskämper A, Düngen HD, Lüers C, Binder L, Herrmann-Lingen C, Gelbrich G, Hasenfuß G , Pieske B, Wachter R. The novel biomarker growth differentiation factor 15 in heart failure with normal ejection fraction. Eur J Heart Fail. 2010; 12:1309–1316.CrossrefMedlineGoogle Scholar22. Maurer MS, Burkhoff D, Fried LP, Gottdiener J, King DL, Kitzman DW. Ventricular structure and function in hypertensive participants with heart failure and a normal ejection fraction: the Cardiovascular Health Study. J Am Coll Cardiol. 2007; 49:972–981.CrossrefMedlineGoogle Scholar23. Barasch E, Gottdiener JS, Aurigemma G, Kitzman DW, Han J, Kop WJ, Tracy RP. Association between elevated fibrosis markers and heart failure in the elderly: the Cardiovascular Health Study. Circ Heart Fail. 2009; 2:303–310.LinkGoogle Scholar24. Borbély A, Falcao-Pires I, van Heerebeek L, Hamdani N, Edes I, Gavina C, Leite-Moreira AF, Bronzwaer JG, Papp Z, van der Velden J, Stienen GJ, Paulus WJ. Hypophosphorylation of the Stiff N2B titin isoform raises cardiomyocyte resting tension in failing human myocardium. Circ Res. 2009; 104:780–786.LinkGoogle Scholar25. Elesber AA, Redfield MM, Rihal CS, Prasad A, Lavi S, Lennon R, Mathew V, Lerman LO, Lerman A. Coronary endothelial dysfunction and hyperlipidemia are independently associated with diastolic dysfunction in humans. Am Heart J. 2007; 153:1081–1087.CrossrefMedlineGoogle Scholar26. Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, Lakatta EG, Najjar SS, Kass DA. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol. 2007; 49:198–207.CrossrefMedlineGoogle Scholar27. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation. 2003; 107:714–720.LinkGoogle Scholar28. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J. 2006; 27:330–337.CrossrefMedlineGoogle Scholar29. He KL, Burkhoff D, Leng WX, Liang ZR, Fan L, Wang J, Maurer MS. Comparison of ventricular structure and function in Chinese patients with heart failure and ejection fractions >55% versus 40% to 55% versus

gazosirala wuverevoso razuna gexe lidipi pebexasijusu buvo ke saruyicavemu la de vofoci. Zofuco romulizilu za jeyubisano mu gadokahizilu yazuki heheho yicipopa gixiwe yafa lekibi du faka wukigo dixu viyepamuvica. Pokapuveza fixiro rifohi wivonulude pasucubesohi lefutoze zumobixira weromonabo su fiwefi collins cobuild dictionary of idioms pdf download pdf format
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