**Clinical update**

**Heart failure: when form fails to follow function**

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Cardiac performance is normally determined by architectural, cellular, and molecular structures that determine the heart’s form, and by physiological and biochemical mechanisms that regulate the function of these structures. Impaired adaptation of form to function in failing hearts contributes to two syndromes initially called systolic heart failure (SHF) and diastolic heart failure (DHF). In SHF, characterized by high end-diastolic volume (EDV), the left ventricle (LV) cannot eject a normal stroke volume (SV); in DHF, with normal or low EDV, the LV cannot accept a normal venous return. These syndromes are now generally defined in terms of ejection fraction (EF): SHF became ‘heart failure with reduced ejection fraction’ (HFrEF) while DHF became ‘heart failure with normal or preserved ejection fraction’ (HFnEF or HFpEF). However, EF has the disadvantage of being a chimeric index because it is the ratio between SV – which measures function, and EDV – which measures form. In SHF the LV dilates when sarcomere addition in series increases cardiac myocyte length, whereas sarcomere addition in parallel can cause concentric hypertrophy in DHF by increasing myocyte thickness. Although dilatation in SHF allows the LV to accept a greater venous return, it increases the energy cost of ejection and initiates a vicious cycle that contributes to progressive dilatation. In contrast, concentric hypertrophy in DHF facilitates ejection but impairs filling and can cause heart muscle to deteriorate. Differences in the molecular signals that initiate dilatation and concentric hypertrophy can explain why many drugs that improve prognosis in SHF have little if any benefit in DHF.

**Keywords**

- Ejection fraction
- Heart failure
- Cardiac architecture
- Sarcomere addition
- Hypertrophic signalling

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It is the pervading law of all things organic and inorganic, of all things physical and metaphysical, of all things human and all things superhuman, of all true manifestations of the head, of the heart, of the soul... that form ever follows function. This is the law. (L. H. Sullivan, 1896).

...it’s time for a new set of terms, a new conceptual paradigm, and movement away from EF as the most cherished measurement in cardiology. (Konstam, 2003).

**Introduction**

Heart failure, recently defined as ‘a syndrome in which patients have typical symptoms... and signs... resulting from an abnormality of cardiac structure or function’ can reduce cardiac output and cause blood to accumulate in the venous systems that fill the heart. These haemodynamic abnormalities activate neurohumoral responses that, while providing some compensation for the impaired cardiac performance, can cause additional damage by increasing energy expenditure in failing hearts, which are already energy-starved, and by stimulating proliferative signalling pathways that have mal-adaptive effects on cardiac myocytes.

Two clinical measurements have long been used to define the interplay between the heart and circulation. Palpation of the arteries, described >3500 years ago in the Edwin Smith papyrus, uses pulse amplitude and contour to characterize physiological variables that include the heart’s ability to fill and eject, heart rate, peripheral resistance, aortic compliance and aortic valve abnormalities. The second, based on clinical data obtained at the bedside since the nineteenth century, characterizes cardiac architecture by distinguishing between left ventricular dilatation and concentric hypertrophy. The accuracy of these distinctions, initially validated at autopsy, is now greatly improved by modern imaging techniques.

Heart failure occurs when a ventricle with a normal or high EDV is unable to eject a normal stroke volume (SV), or when a ventricle with a normal or low EDV cannot accept a normal venous return. These two syndromes, initially called SHF and DHF, respectively, have recently been redefined as ‘heart failure with reduced ejection fraction’ (HFrEF) and ‘heart failure with normal or preserved ejection fraction’ (HFnEF or HFpEF). However, EF has the disadvantage of being a chimeric index because the major determinants of SV, the numerator, are physiological variables that include preload, afterload,
inotropy, lusitropy, heart rate, and the synchrony of left ventricle (LV) ejection; whereas EDV, the denominator, is determined largely by architectural variables that include LV wall thickness and the size and shape of its cavity. For these reasons neither HFrEF and HFpEF adequately defines pathophysiological abnormalities in failing hearts.

**Ventricular architecture**

Louis H. Sullivan, often viewed as the creator of the skyscraper, altered the design of large buildings from a heavy stack of horizontal layers that rested on thick walls to a much lighter vertical structure supported by a steel frame. The resulting increase in the ability to adapt the form of a building to its intended function led to Sullivan’s recognition as one of the founders of modern architecture. In muscle, as in buildings, architecture is normally matched to function, in this case by biological processes that control the size, shape and composition of cardiac and skeletal myocytes.

Corvisart, at the beginning of the nineteenth century, described the clinical syndromes associated with two different abnormalities in cardiac architecture: ‘In the first the heart is enlarged, its [walls] thickened, the energy of its action increased…’. In the second there is likewise enlargement, but [also] thinning of the [walls] and diminution of energy in [its] action’. The first, now generally called concentric hypertrophy, was initially viewed as a compensatory response to overload, whereas dilatation, the other type of cardiac enlargement, was quickly recognized to be progressive and to have a poor prognosis. In 1849 Hope wrote: ‘When dilatation has advanced so far as to occasion morbid dyspnea, it has a constant tendency to increase…’. It was not until the end of the nineteenth century that the adverse effects of concentric hypertrophy were also recognized; in 1884, for example, Paul wrote: ‘It has been frequently said that the heart hypertrophies in order to establish a sort of compensation…'. This view would be correct if the hypertrophy remained stationary; but experience has shown that the excess of work imposed upon the heart finally deteriorates its fibres…’

**Early estimates of the relationship between end-diastolic volume and stroke volume**

In the early 1930s, two groups noted that because Starling’s Law of the Heart predicts that increasing venous return normally increases both EDV and SV, the relationship between these variables could provide an index of cardiac performance that is independent of the patient’s size and body position. In 1933 Starr et al. found that the ratio EDV/SV (the reciprocal of EF) was within a narrow range in 39 patients with normal hearts. They also observed that this ratio was increased significantly in six patients who had been in congestive heart failure but were clinically compensated at the time of the study. The following year Lysholm et al. noted little variation in the ratio EDV/SV in 22 patients with normal hearts, but found that this ratio was increased by ~60% in 8 patients with ‘myocardial degeneration’. However, these measurements were not suitable for clinical use because SV and EDV often had to be calculated at different times, and the methods were cumbersome and of limited accuracy: values for SV depended on Fick determinations of cardiac output that were imprecise because mixed venous blood samples were not available, and estimates of EDV were based on analysis of cardiac silhouettes on chest X-rays rather than measurements of ventricular volume.

**Ejection fraction: the ratio between stroke volume and end-diastolic volume**

Rapid developments in cardiac angiography after World War II initially provided anatomical data for the diagnosis of rheumatic and congenital heart disease, then the most common causes of heart failure. Arvidsson in 1961, who used cardiac angiography to measure SV and EDV in a single cardiac cycle, calculated EF as the ratio SV/EDV; this was found to be ~75% in 16 patients with ‘sound hearts [and] only a vague suggestion of cardiac disease’. A few years later Gorlin et al., using thermodilution to measure ventricular volumes, found that EF averaged 45% in patients with normal hearts or mild mitral stenosis, and Kennedy et al., who used angiographic, dye dilution and Fick methods to measure SV, reported a mean EF of 67% in 21 patients with normal hearts. Use of radionuclide measurements to provide accurate non-invasive measurements of ventricular architecture further improved the clinical evaluation of EF. However, it was developments in echocardiography that led to the widespread use of EF for the evaluation of heart disease because these measurements are safe, non-invasive, relatively inexpensive, reasonably accurate and do not require exposure to ionizing radiation.

Discoveries in cardiac muscle biochemistry during the 1960s demonstrated that calcium regulates myocardial contractility and that ventricular filling, initially believed to be due simply to the passive dissipation of the contractile state, is effected instead by energy-dependent mechanisms that differ from those that cause ejection. Efforts to measure myocardial contractility led several investigators to postulate that EF could quantify this elusive variable. Miller et al., who found that EF was low in many patients with heart disease, suggested that EF is a valid index of myocardial contractility, and Dodge et al. concluded that a low EF ‘is evidence of left ventricular disease’ because they observed that EF, although generally normal in patients with compensated valvular heart disease, was markedly reduced in primary cardiomyopathies. However, subsequent studies demonstrated that EF cannot quantify myocardial contractility because SV is influenced by heart rate, preload and afterload, and the ability of an increase in EDV to increase SV can be reduced in failing hearts.

**Two ways the heart can fail**

Because the heart is a reciprocating pump, in which phases of ejection alternate with phases of filling, hearts can fail in two ways. These were distinguished in Fishberg’s 1937 textbook, which describes cardiac insufficiency caused by ‘inadequate diastolic filling of the heart (hypodiastolic failure)’ and the far more common ones in which the heart fills adequately but does not empty to the normal extent (hyposystolic failure). These were subsequently called DHF where the underlying pathophysiology is impaired filling, usually by a
thick-walled LV with a normal-sized or small cavity, and SHF where
the abnormality is reduced ejection by a dilated LV. These subse-
quently came to be distinguished on the basis of EF: the heart failure
syndrome characterized by impaired LV filling became HFrEF or
HFnEF, while the syndrome in which the major problem is impaired
ejection became HFrEF. Because architectural abnormalities play a
major role in determining EF, these terms might better be replaced
by ‘heart failure with normal or reduced EDV’ and ‘heart failure with
increased EDV’. However, none of these descriptors focus on the
physiologic, neurohumoral, and proliferative abnormalities respon-
sible for the two heart failure syndromes or why various disorders
have different effects on the heart’s ability to adapt its form to spe-
cific pathophysiologic abnormalities.

Different mechanical stresses cause dilatation and concentric
hypertrophy

Increased wall stress during systole and diastole has long been re-
cognized to cause different hypertrophy phenotypes. In 1870 von
Niemeyer 27 wrote that concentric hypertrophy — identified as
‘thickening of the cardiac wall — [arises] from an increase in the vol-
ume of its muscular tissue [due to] obstruction of the arterial outlets
of the heart [or] impediment of the outflow of blood from the ca-
pillaries into the veins . . .’, whereas dilatation — defined as ‘a morbid
condition of the heart in which its cavities are enlarged’ — occurs
when the heart is ‘subjected to an unnaturally severe internal pres-
sure during its diastole . . .’. Fothergill, 28 who subsequently com-
pared LV architecture in patients with aortic insufficiency and
aortic stenosis, noted that in the former, where there is an ‘increase
in the distending force [during diastole], hypertrophy is always com-
bined with dilatation of the cardiac chambers [whereas] in ob-
struction . . . without any increase in the distending force, as in
aortic stenosis, there is pure hypertrophy, usually without dilata-
tion’. The remarkable compensation to pressure overload by the ini-
tial hypertrophic response was subsequently seen in its ability to
normalize LV wall stress in patients with clinically compensated
aortic stenosis. 29, 30

In 1965 Grant et al. 31 postulated that LV dilatation is caused by ‘an
increased number of sarcomeres in series’ and is adaptive because
it accommodates the regurgitant volume in aortic and mitral

![Figure 1](image-url)  

Figure 1 Different mechanical stresses induce dilatation and concentric hypertrophy. Normal (top row): the left ventricle is shown during dia-
stole (left) and systole (centre). When cavity volume decreases during ejection, the walls thicken and both the major and minor axes shorten. The
sarcomeres in normal cardiac myocytes (right) form an ordered array of thick and thin filaments (shown in purple). Dilated (middle row): the
hypertrophic response to an increased distending stress on the walls of the relaxed left ventricle (arrows) causes new sarcomeres (shown in
dark yellow) to be added in series, which increases myocyte length and cavity volume. Concentric hypertrophy (bottom row): increased stress
developed by the ventricular walls during systole (arrows) causes new sarcomeres (shown in dark yellow) to be added in parallel, which increases
myocyte thickness. By increasing ventricular mass and wall thickness this hypertrophic response can decrease cavity volume.
insufficiency, whereas concentric LV hypertrophy helps meet the increased afterload in aortic stenosis because ‘more myofibrils in parallel [generate] higher systolic pressures’... The hypothesis that different patterns of sarcomere addition are responsible for the two architectural phenotypes was confirmed by Gerdes, who found that myocyte length is increased in dilated hearts, whereas myocytes are thickened in concentrically hypertrophied hearts (Figure 1).

In the 1960s, myocyte abnormalities in familial cardiomyopathies also were recognized to cause cardiac hypertrophy. At the same time it became clear that heart failure is a systemic condition in which neurohumoral responses initiated by impaired pump function modify cardiac structure and function. The importance of these neurohumoral responses became apparent when drugs that had been introduced to alleviate the haemodynamic abnormalities in heart failure had unexpected effects on survival that were due in part to

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**Figure 2** Schematic diagrams comparing the haemodynamic effects of increased venous return in systolic and diastolic dysfunction. In all four panels the pressure–volume loops for a normal heart operating under baseline conditions are depicted by thin dashed lines. (A) In systolic dysfunction, decreased contractility (dashed rightward arrow) shifts the end-systolic pressure–volume relationship to the right and downward (solid line); this is shown to reduce stroke volume by 30 mL (arrow labelled ↓SV). (B) Increased diastolic wall stiffness in diastolic dysfunction (dashed upward arrow) impairs filling, decreases end-diastolic volume and increases end-systolic pressure by shifting the end-diastolic pressure–volume relationship upward and to the left (solid curve); as in (A), this is shown to reduce stroke volume by 30 mL (arrow labelled ↓SV). (C) In systolic dysfunction the 30 mL increase in end-diastolic volume needed to normalize venous return (dotted curved arrow with asterisk) and return stroke volume to its basal level increases end-diastolic pressure from 10 to 23 mmHg (dotted loop). (D) In diastolic dysfunction the same 30 mL increase in end-diastolic volume needed to normalize venous return (dotted curved arrow with asterisk) and return stroke volume to its basal level (dotted loop) causes end-diastolic pressure to rise from 20 to 45 mmHg. These diagrams show why restoring a normal stroke volume in diastolic dysfunction requires a greater increase in end-diastolic pressure (25 mmHg) than in systolic dysfunction (13 mmHg). The higher level and greater steepness of the end-diastolic pressure–volume relationship in diastolic dysfunction provide a substrate for ‘flash pulmonary oedema’. (Modified from Katz AM. Physiology of the Heart, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2011.)
their ability to modify maladaptive features of the hypertrophic response.

**Cytoskeletal signalling pathways initiate concentric hypertrophy and dilatation**

The pioneering work of Meerson, which in the 1960s implicated abnormal proliferative signalling in the pathophysiology of heart failure, provided evidence that maladaptive features of the hypertrophic response can initiate a progressive ‘cardiomyopathy of overload’. Demonstration that the walls of the heart are a mosaic of different myocyte phenotypes supported the view that local deformation-induced transcriptional responses optimize cardiac energetics and efficiency by adapting form to function in normal hearts.

In 1995 Calderone et al. reported that chronic increases in preload and afterload have different effects on molecular phenotype. Fifteen years later Toischer et al. confirmed the nineteenth century observations that chronic volume overload and pressure overload cause ventricular dilatation and concentric hypertrophy, respectively, and further demonstrated that the two hypertrophy phenotypes are controlled by different proliferative signalling pathways. This led them to suggest that patients ‘may require specific pharmacological interventions’ depending on whether hypertrophy is caused by increased preload or by increased afterload. A large number of signalling pathways are now known to participate in the regulation of cardiac architecture and molecular composition. These complex networks include several cytoskeletal and related proteins that, by recognizing cell deformation as a signal to modify cardiac myocyte growth, can play a key role in adapting form to function. However, much remains to be learned about how these and other signalling molecules determine ventricular size and shape by modifying cardiac myocyte length and thickness.

**Clinical implications: systolic and diastolic heart failure**

The haemodynamic abnormalities and clinical manifestations in SHF and DHF are generally similar. An exception is the higher prevalence of acute (‘flash') pulmonary edema in DHF that occurs because increasing EDV causes a greater elevation of diastolic pressures when filling is impaired. The mechanisms can be seen in Figure 2, which depicts the immediate responses when increased venous return restores SV after contractility is decreased (Figure 2C) and relaxation is impaired (Figure 2D).

Unlike these short-term physiological responses to what can be viewed as systolic and diastolic ‘dysfunction’, respectively, the long-term architectural responses that cause dilatation in SHF and concentric hypertrophy in DHF occur when proliferative signals change the heart’s structure. These can be understood by examining LV pressure–volume loops that depict the fundamental difference between these two syndromes (Figure 3). It can be seen that cavity volumes represent the major difference between these two syndromes.

[Image of Figure 3: Schematic diagram comparing a normal pressure volume loop (solid line) with those in systolic heart failure (dashed line) and diastolic heart failure (dotted line). The loops, which assume that left ventricle pressures are the same at the end of isovolumic contraction, show the architectural changes that occur when sarcomere addition in series causes dilatation in systolic heart failure and sarcomere addition in parallel causes concentric hypertrophy in diastolic heart failure. (Based on Kass DA. Myocardial mechanics. In: Poole-Wilson PA, Colucci WS, Massie BM, Chatterjee K, Coats AJS, Eds. Heart Failure: Scientific Principles and Clinical Practice. New York Churchill Livingstone. 1997. Pp. 87–108.)]

Despite similarities in symptoms and signs, there is substantial evidence that SHF and DHF are distinct clinical syndromes. For example, SHF occurs more often in younger men with coronary artery disease, whereas DHF is more common in older hypertensive women. These differences are due in part to the ability of increased diastolic wall stress to stimulate LV dilatation in SHF; for example in the uninfarcted myocardium following a myocardial infarction. In DHF, on the other hand, concentric hypertrophy is often initiated by increased systolic wall stress; for example, when aortic impedance is increased by hypertension or the loss of arterial elasticity that accompanies normal ageing.

One way that sarcomere addition in series contributes to the poor prognosis in SHF is by initiating a vicious cycle that causes dilatation to become progressive. This vicious cycle begins when, according to the Law of Laplace, the greater cavity diameter increases diastolic wall stress, which stimulates sarcomere elongation, which further increases diastolic wall stress, etc. (Figure 4A). In contrast, when DHF is caused by increased systolic wall stress, sarcomere addition in parallel initiates a virtuous cycle by stimulating concentric hypertrophy, which decreases wall stress (Figure 4B). When sustained, however, the latter hypertrophic response leads to cardiac myocyte degeneration and death that, along with changes in the extracellular matrix, cause fibrosis of the ventricular walls.

Although adaptive in its early stages, concentric hypertrophy eventually contributes to the development of fibrosis, arrhythmias, progressive myocardial deterioration, and end-stage heart failure.

The ability of different cell signalling pathways to cause sarcomeres to be added in series in SHF and in parallel in DHF may explain why therapy that improves prognosis in SHF has less survival benefit in patients with DHF. In SHF, where LV dilatation increases...
wall stress during diastole, treatment that improves long-term outcome (converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic receptor blockers, mineralocorticoid receptor antagonists, etc. 56) generally slows, and can briefly reverse progressive dilatation (the vicious cycle shown in Figure 4A). In DHF, however, these drugs are of less benefit because LV dilatation is uncommon and occurs most often in end-stage disease or after a myocardial infarction.57,58

Failure of form to follow function can also occur in familial cardiomyopathies. 59 Abnormal proteins in the hearts of patients with hypertrophic cardiomyopathies may initiate abnormal mechanical stresses that cause sarcomeres to be added in parallel, and so lead to myofibrillar disarray and specific patterns of increased wall thickness (septal, apical, etc.). Similarly, dilated cardiomyopathies may occur when other mutations cause abnormal mechanical stresses that stimulate sarcomere addition in series. Genetic abnormalities have also been implicated in the pathogenesis of LV non-compaction, 60 but the mechanisms discussed in this article do not apply to patients with DHF caused by uncommon restrictive heart diseases like amyloid, scleroderma, and sarcoidosis.

**Conclusion**

Growing evidence that abnormal proliferative responses are responsible for the altered ventricular size and shape in SHF, DHF, LV non-compaction, and other diseases that modify cardiac architecture supports the view that heart failure phenotypes are incompletely described by EF. New understanding of molecular mechanisms that determine cardiac myocyte size, shape and longevity can identify therapy to alleviate the maladaptive consequences caused when form fails to follow function in diseased hearts.

**Authors’ contributions**

A.K., E.R.: conceived and designed the research. A.K., E.R.: made critical revision of the manuscript for key intellectual content. A.K.: designed the figures.

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**References**


![Figure 4 Consequences of increasing wall stress during different phases of the cardiac cycle. (A) Increased left ventricle wall stress during diastole, which can be caused by a volume overload, myocardial infarction or other abnormality, activates an architectural response that increases cavity volume by causing cardiac myocyte sarcomeres to be added in series. Unlike the acute dilatation caused by increased venous return, which increases the heart’s ability to eject (Starling’s Law of the Heart), the chronic dilatation caused by this hypertrophic response impairs ejection because, according to the Law of Laplace, increased cavity volume decreases the pressure developed at any wall stress during systole. This proliferative response can therefore initiate a vicious cycle that leads to progressive dilatation (see text). (B) Increased left ventricle wall stress during systole, which can be caused by pressure overload, activates a different architectural response in which addition of cardiac myocyte sarcomeres in parallel causes concentric hypertrophy. According to the Law of Laplace, the resulting increase in wall thickness and reduction in cavity volume can initiate a virtuous cycle by reducing systolic wall stress and enhancing the ability of the ventricle to eject. However, concentric hypertrophic impairing filling and leading to cardiac myocyte damage and death (see text).](image-url)
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