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Reclassifying Heart Failure: Predominantly Subendocardial, Subepicardial, and Transmural

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> "Everything should be made as simple as possible, but not more so."
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> —Albert Einstein

Heart failure remains a major public health burden in the United States. Approximately 5 million people sustain chronic heart failure, and 500,000 new patients are diagnosed with heart failure every year [1,2]. Timely recognition, classification, and grading of heart failure require a robust and practical algorithm. Whereas the classification by the World Health Organization has focused primarily on the etiologic and pathogenetic factors [3], the recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for chronic heart failure [4] emphasize the development and progression of disease (Table 1). The classification based on the clinical manifestations has customarily described heart failure by the left ventricular ejection fraction (LVEF) in two distinct forms: (1) diastolic heart failure or (2) heart failure with preserved LV function and systolic heart failure. Such classification is somewhat reminiscent of the distinction between backward and forward cardiac failure emphasized in the mid-twentieth century. A broader look at the heart failure population suggests that such demarcation is artificial because heart failure consists of a continuous spectrum wherein systolic and diastolic abnormalities are inseparable [6–9].

This review proposes a framework for describing heart failure using a combination of symptoms and patterns of aberrant myocardial mechanics that are discerned through noninvasive cardiac imaging techniques. We believe this approach can identify cohorts of patients with similar presentations, prognosis, and response to therapeutic interventions. One can classify the pathophysiology of heart failure into three broad subgroups: (1) heart failure with predominant subendocardial dysfunction, (2) heart failure with predominant subepicardial dysfunction, and (3) heart failure with transmural dysfunction (Table 2). This classification scheme corresponds to the structural and functional subunits of the left ventricle that govern the normal ejection and suction performance of a beating heart. The counterdirectional right- and left-handed helical myofiber geometry of the subendocardial and subepicardial regions support two fundamental forms of muscle action that work in close rhythmic balance [10–13]. To better describe this continuum of action, we use the structural analogy of natural vortex patterns [10]. The inside core of vortex swirls inwards and downwards, gathering implosive suction energy by centripetal action. The outer core expels and disburses energy upwards and outwards simultaneously by centrifugal action. For example, stirring cream in a cup of coffee leaves an inward swirl with aggregation and dissolution in the center while an outward expansion and separation occurs in an opposite direction. The suction and expulsion processes of a vortex motion occur in different regions yet are interlinked. The diastolic and systolic performance of the LV depends on the functional integrity of the subendocardial and subepicardial regions but is coupled

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Table 1
Progression of cardiomyopathy

At risk for cardiomyopathy or heart failure (no structural disease)	Asymptomatic cardiomyopathy (structural heart disease)	Symptomatic cardiomyopathy
Stage A[a]	Stage B[a]	Stage C and stage D[a]
Stage 1[b]	Stage 2[b]	Stage 3[b]
Normal subendocardial and subepicardial function	Subendocardial, subepicardial, or transmural dysfunction	Subendocardial, subepicardial, or transmural dysfunction

[a] American College of Cardiology/American Heart Association diagnosis and management of chronic heart failure in the adult [4].

[b] Heart Failure Society of America definition, classification, and staging of adult cardiomyopathies: proposal for revision [5].

synergistically. If the subendocardial region is affected, the outcome predominantly affects the suction performance, although ejection is still maintained with compensation offered from the outer subepicardial region. If compensation is not possible due to concomitant dysfunction of the subepicardial region, expulsion dynamics are reduced and the LV dilates.

Noninvasive techniques such as MRI and echocardiography are useful for understanding LV longitudinal and circumferential dynamics in clinical settings. Observational data regarding the utility of characterizing transmural mechanics in clinical settings are rapidly accumulating.

Heart failure with predominant subendocardial dysfunction

Most progressive myocardial diseases, including coronary ischemia, have been shown to cause subendocardial dysfunction. This dysfunction results in an early preferential involvement of longitudinal LV mechanics [14]. The timing of contraction-relaxation crossover is the most vulnerable period of myofiber mechanics [15,16]. In early stages, ventricular relaxation either regionally or globally becomes abnormally slow and impaired with a progressive delay in the timing of onset of relaxation. The epicardial function which governs the circumferential strain and twist mechanics of the LV remains either normal or shows an exaggerated compensation. Compensatory features such as myocardial hypertrophy of the subepicardial region attempt to reduce subendocardial stress, thereby preserving the global LVEF [17]. Interestingly, hearts undergoing regression of cardiac hypertrophy show marked apoptosis within the subepicardial region, which supports the hypothesis that changes within the subepicardial region in hypertrophied heart may, indeed, reflect a compensatory mechanism [18].

Progressive remodeling of the subepicardium and loss of cardiac muscle resilience by fibrosis result in gradual loss of early diastolic longitudinal relaxation and a delay in LV untwisting. These changes are accompanied by elevation of LV filling pressures and the appearance of varying grades of diastolic dysfunction. This stage manifests clinically as heart failure with preserved systolic function.

Heart failure with predominant subepicardial dysfunction

Predominant subepicardial myofiber dysfunction has been shown to manifest with loss of

Table 2
Classification of cardiac mechanics in heart failure

Functional impairment	Longitudinal mechanics	Circumferential mechanics	Torsional mechanics	Global EF	Diastolic filling pressures	Clinical syndrome
Predominant subendocardial dysfunction	Impaired	Preserved	Preserved	Preserved	Elevated	Diastolic HF/ HENEF
Predominant subepicardial dysfunction	Preserved	Impaired	Impaired	Preserved	Elevated	Diastolic HF, HENEF
Transmural dysfunction	Impaired	Impaired	Impaired	Impaired	Elevated	Systolic HF

Abbreviations: EF, ejection fraction; HF, heart failure; HFNEF, heart failure and normal ejection fraction.