The Heart Failure Spectrum: Time for a Phenotype-Oriented Approach
Gilles W. De Keulenaer and Dirk L. Brutsaert

*Circulation* 2009;119;3044-3046; originally published online Jun 8, 2009;
DOI: 10.1161/CIRCULATIONAHA.109.870006

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/cgi/content/full/119/24/3044

Subscriptions: Information about subscribing to Circulation is online at http://circ.ahajournals.org/subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail: journalpermissions@lww.com

Reprints: Information about reprints can be found online at http://www.lww.com/reprints
The Heart Failure Spectrum
Time for a Phenotype-Oriented Approach
Gilles W. De Keulenaer, MD, PhD; Dirk L. Brutsaert, MD, PhD

Chronic heart failure (HF) occurs at any level of left ventricular ejection fraction (LVEF). Mostly driven by clinical trial design, HF has nevertheless been dichotomized according to LVEF as HF with preserved ejection fraction (HFPEF) or HF with reduced ejection fraction (HFREF). During the ongoing discussion on the pathophysiology of HF, some researchers have focused on differences whereas others have focused on the overlap between HFPEF and HFREF. These discussions have received great attention especially because recent clinical trials have shown an unexplained resistance to therapy (especially to renin-angiotensin-aldosterone system inhibition) in HFPEF. With no alternative therapies available, medical progress in HFPEF is stagnating.

The current issue of Circulation contains a report on clinical characteristics and risk factors in patients with incident HF among Framingham Heart Study participants. Incident HF was classified as either HFREF when LVEF was ≤45% or as HFPEF when LVEF was >45%. HFPEF accounted for 41% of the inclusions. Female gender, elevated systolic blood pressure, and atrial fibrillation enhanced the odds to be classified as HFPEF whereas prior myocardial infarction and left bundle branch block reduced these odds. Among preonset HF patient characteristics, only female gender increased the odds of developing HFPEF instead of HFREF. These data are largely consistent with previous surveys on patient characteristics in HF and add information to this syndrome’s phenotypic diversity.

As stated in the article, the investigators’ rationale to subdivide patient records into 2 groups, according to an a priori cutoff value of LVEF of 45%, was based on a prior evaluation showing that mortality risk increased linearly for LVEF <45%. Inconsistently in this study, however, survival data did not differ between HFREF and HFPEF, which puts into question the original rationale for subdividing HF patients according to LVEF. An in-depth discussion of the rationale to subdivide HF in a bimodal fashion based on LVEF is warranted.

Figure 1. Analyzing symptomatic HF populations over a wide range of LVEF reveals a continuous spectrum of diseases or disease stages rather than separate disease entities. A, Unimodal distribution of LVEF among 7599 patients enrolled in the CHARM program. B, Distribution of systolic function of longitudinal axis fibers. S-LAX indicates systolic mitral annular amplitude by M-mode) measured by Yip and coworkers (unpublished image kindly provided by J.E. Sanderson). C, Distribution of cardiomyocyte diameters in 49 HF patients with either reduced or preserved LVEF, as measured by Van Heerebeeck et al. (unpublished image kindly provided by A. Borbely). D, Distribution of clinical patient characteristics in 4 large HF cohorts with different LVEF cutoffs. The continuous distribution of functional, morphological, and clinical variables shown in this figure should encourage epidemiologists, clinicians, and basic scientists to look for (dys)continuities of other variables (such as genetic factors, titin isoforms, and serum markers) in HF as well. Many of these data may already be available but remain hidden in the biased dichotomized HF approach.

Large registries have established that the distribution of LVEF in HF is unimodal. Any cutoff for LVEF to subdivide HF into 2 hypothetically distinct entities is thus arbitrary. Moreover, as illustrated in Figure 1D, previous estimates have suggested that incidences of phenotypic characteristics...
of HF patients such as gender, hypertension, and diabetes mellitus change gradually, not abruptly, over the wide LVEF range.5–8 Similarly, measures of ventricular function, including contractile function of longitudinal fibers3 and cardiomyocyte diameter,4 do not show abrupt changes at any level of LVEF, but they cover a gradual and continuous spectrum over the whole range of LVEF. Similarly, serum fibrosis markers are upregulated in both HFPEF and HFREF with values that do not differ in both cases.9 Accordingly, in-depth analyses of HF over the whole range of LVEF do not provide data to support the hypothesis that separate disease entities (HFPEF and HFREF) would exist. Instead, as depicted in Figure 1, there is much more evidence for a continuous HF spectrum of overlapping, strongly related disease phenotypes.

An additional rationale for some to subdivide HF into 2 entities is based on the false premise that LVEF is a reliable parameter for systolic function. Recent studies have shown, however, that systolic LV function can be markedly impaired even when LVEF is normal. This observation should be a reminder that LVEF is a mere index of global ventricular pump performance,10,11 blind to many mechanical ventricular abnormalities in heart failure, such as dysfunction of longitudinal subendocardial muscle fibers; twisting, untwisting, and suction abnormalities; disturbed nonuniformities of strain; or abnormal paracrine cross-talk in the pluricellular ventricular tissue pump12 (Figure 2). Hence, although LVEF is a powerful prognostic parameter—when decreased—and useful in daily clinical practice to obtain a first impression of global ventricular pump performance during disease staging, it is largely inadequate to provide a platform for subdividing HF into 2 entities or to introduce de novo pathophysiological concepts. Arbitrarily subdividing HF into 2 entities on the basis of LVEF alone is counterproductive. A fresh look, beginning by minimizing the emphasis on LVEF, is urgently needed.

If not from the perspective of LVEF, how then should we approach HF in clinical trials and pathophysiological studies? We advocate an approach from a patient-tailored (ie, phenotype-oriented) view. Now that surveys such as the Framingham Heart Study in this issue of Circulation have established that distinct patient characteristics (including female gender, hypertension, absence of myocardial ischemia, and perhaps diabetes mellitus) act as disease modifiers, promoting a preserved ejection fraction (ie, protecting the heart from dilating), future bench and bedside HF studies should focus on these disease modifiers. For example, is the combination...
of female gender, hypertension, and a nonischemic pathogenesis a predictor of reduced clinical benefit to candesartan in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial independently of LVEF? Future clinical trials should be designed and statistically powered to answer these questions. Applying such a phenotype-oriented approach may induce a paradigm shift in understanding the heterogeneous progression of chronic HF and hopefully inject new life into the stagnating field of HFPEF.

If not from the perspective of LVEF, how should we approach ventricular function? As depicted in Figure 2, the heart can be conceptually approached as a hydrodynamic input-output system, a hemodynamic compression pump, a muscular pump, or a pluricellular tissue pump. The heart’s performance at each of these levels of complexity is reflected by specific parameters, as shown in the Figure 1. The clinical usefulness of any of these parameters depends on the clinical situation or the pathophysiological stage of the disease (circulatory shock versus exertional dyspnea). None of these parameters, however, provides a platform to dichotomize the pathophysiology of HF. Let us not overestimate LVEF, because it is not worth it.

Disclosures
None.

References

Key Words: Editorials heart failure ventricular ejection fraction models, cardiovascular risk factors