JACC: HEART FAILURE
VOL. 5, NO. 11, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jchf.2017.09.009

Structural and Functional Phenotyping of the Failing Heart

Is the Left Ventricular Ejection Fraction Obsolete?

Michael R. Bristow, MD, PhD,[a] David P. Kao, MD,[a] Khadijah K. Breathett, MD,[b] Natasha L. Altman, MD,[a] John Gorcsan III, MD,[c] Edward A. Gill, MD,[a] Brian D. Lowes, MD, PhD,[d] Edward M. Gilbert, MD,[e] Robert A. Quaife, MD,[a] Douglas L. Mann, MD[c]

ABSTRACT

Diagnosis, prognosis, treatment, and development of new therapies for diseases or syndromes depend on a reliable means of identifying phenotypes associated with distinct predictive probabilities for these various objectives. Left ventricular ejection fraction (LVEF) provides the current basis for combined functional and structural phenotyping in heart failure by classifying patients as those with heart failure with reduced ejection fraction (HFrEF) and those with heart failure with preserved ejection fraction (HFpEF). Recently the utility of LVEF as the major phenotypic determinant of heart failure has been challenged based on its load dependency and measurement variability. We review the history of the development and adoption of LVEF as a critical measurement of LV function and structure and demonstrate that, in chronic heart failure, load dependency is not an important practical issue, and we provide hemodynamic and molecular biomarker evidence that LVEF is superior or equal to more unwieldy methods of identifying phenotypes of ventricular remodeling. We conclude that, because it reliably measures both left ventricular function and structure, LVEF remains the best current method of assessing pathologic remodeling in heart failure in both individual clinical and multicenter group settings. Because of the present and future importance of left ventricular phenotyping in heart failure, LVEF should be measured by using the most accurate technology and methodologic refinements available, and improved characterization methods should continue to be sought. (J Am Coll Cardiol HF 2017;5:772–81) © 2017 by the American College of Cardiology Foundation.

Heart failure remains a major health care problem, affecting 6.5 million adults in the United States (1). Although progress has been made in developing effective drug and device therapies, the pace of new development has slowed (2). The beneficial therapies that have been developed, encompassing 8 drug and 2 device classes, have been based on clinical trials using the major inclusion criterion of a reduced left ventricular ejection fraction (LVEF), typically ≤0.40, which defines the heart failure with reduced ejection fraction (HFrEF) phenotype. In contrast, entry criteria that have included a relatively preserved LVEF, so-called HF with preserved EF (HFpEF), have been uniformly unsuccessful. Thus LVEF is able to successfully identify heart failure therapeutic phenotypes.

Recently Konstam and Abboud (3) argued that the LVEF has "exhausted its usefulness as a presumed

From the [a]Division of Cardiology, Department of Medicine, University of Colorado Anschutz Medical Campus, School of Medicine, Aurora, Colorado; [b]Division of Cardiology, Department of Medicine, University of Arizona, Tucson, Arizona; [c]Division of Cardiology, Department of Medicine, Washington University Medical School, St. Louis, Missouri; [d]Division of Cardiology, Department of Medicine, School of Medicine, University of Nebraska Medical Center, Omaha, Nebraska; and the [e]Division of Cardiology, Department of Medicine, School of Medicine, University of Utah Medical Center, Salt Lake City, Utah. Supported by U.S. National Heart, Lung, and Blood Institute (NHLBI) grant 1R01HL48013 to Drs. Bristow and Lowes; NHLBI grant 2R01 HL48013 to Drs. Bristow, Lowes, Gilbert, Kao, and Quaife; American Heart Association Heart Failure grant SFRN 16SFRN31420008 to Drs. Bristow, Altman, Breathett, Kao, Gill, and Gilbert; NHLBI grant 1K08HL125725 to Dr. Kao; NHLBI grants R01 HL73017 and R01 HL089543 to Dr. Mann. Dr. Bristow is an officer and director of ARCA biopharma; and sponsor of the drug referred to in Online Reference 14. Dr. Quaife has received imaging equipment support from Phillips Corp. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 18, 2017; revised manuscript received September 4, 2017, accepted September 10, 2017.

marker of contractility and a means of categorizing cardiomyopathies. In fact, the latter practice has stymied advances in pathophysiological understanding and therapeutics." Their argument centers on the limitations of EF as a measurement of intrinsic ventricular contractile performance, primarily because of its load dependency. Based on this argument, could the LVEF-based method of classifying heart failure be limiting progress in the development of new therapeutic approaches, which ideally would be based on some other phenotypic classification? The answer to this question depends on the validity of the LVEF measurement for estimating fundamental ventricular myocardial pathophysiologic abnormalities underpinning heart failure, on its utility in identifying distinct heart failure phenotypes amenable to specific therapeutic approaches, and on the utility and availability of alternative methods of phenotyping the failing heart. We address these issues by reviewing historical work on LVEF, defining what is specifically measured by LVEF, and providing original data for the relationship between LVEF and other hemodynamic measurements as well as molecular changes in the failing human heart.

HISTORICAL EMERGENCE OF THE EJECTION FRACTION CONCEPT

The concept of ventricular EF was a byproduct of the development of methods to reliably measure stroke volume (SV), which if done angiographically requires accurate measurements of ventricular volumes (4). In their classic paper measuring left ventricular volumes of normally functioning mammalian hearts with 67-fold variation in heart weight (dogs to horses), Holt et al (4) noted that cardiac output, ventricular and SVs increased with body and heart weights, but the residual and ejected fractions of ventricular end diastolic volume remained constant from the smallest to the largest animals investigated. In other words, in the absence of pathophysiologic perturbation, the fraction of end diastolic volume ejected in systole is tightly regulated across mammalian species. The term ejection fraction was first used by Kennedy et al. (5) to describe the ejected component of ventricular volume, measured as: [SV/end-diastolic volume]. Sonnenblick (6) was the first to relate EF to sarcomere shortening, the basis for LVEF as a measurement of contractile function.

LVEF MEASURES THE 2 MAJOR CHARACTERISTICS OF PATHOLOGIC ECCENTRIC REMODELING

The most common ventricular myocardial disease process causing heart failure in patients <75 years age (7) is eccentric pathologic hypertrophy characterized by increased LV volumes and mass with no or little increase in wall thickness (8–11). Although heart failure-associated eccentric remodeling is usually described in anatomical terms (8–11), it also includes progressive contractile dysfunction (12–14) and gene expression changes associated with both hypertrophy and decreased contractility (15,16). Eccentric hypertrophy is associated with increased ventricular end diastolic and systolic volumes but also includes chamber geometric changes, with the LV transitioning from a prolate ellipse to a more spherical shape (15). These remodeling changes (**Figure 1**) can occur in both the right and left ventricles.

In the formulaic definition EF = SV/end diastolic volume (EDV), the numerator (SV) is a measurement of contractile function, whereas the denominator (EDV) estimates the degree of chamber dilation due to eccentric hypertrophy. Stroke volume is the result of [EDV − end-systolic volume (ESV)], which means that SV is related to the degree that ESV, an excellent measurement of intrinsic contractile function (17), is altered relative to EDV. Accordingly, the LVEF ratio combines elements of systolic function and eccentric hypertrophic remodeling in a single measurement.

DOES LVEF RELIABLY MEASURE CONTRACTILE FUNCTION? In order to provide contemporary hemodynamic and molecular data for an examination of the hypothesis that LVEF reliably measures contractile function and eccentric hypertrophy, we report results from 2 longitudinal clinical studies in which hemodynamics and septal ventricular myocardial gene expression were measured before and after left ventricular reverse remodeling produced by β-blockade (Online Methods).

Figure 2A shows left ventricular volume and LVEF measurements in 32 nonischemic dilated cardiomyopathy (DCM) patients treated for 3 or 12 months with β-blocking agents (18,19), which, in two-thirds of the patients was associated with the reverse remodeling changes shown in **Figure 1**. The same relationships at baseline prior to the administration of β-blocking agents are given in Online Figure 1. As shown in **Figure 2A**, across a wide range of LVEFs (0.14 to 0.62; median: 0.43 expressed as absolute percentage in **Figure 2**), LVEF is inversely related to indexed EDV (EDVI) ($r = -0.81$; $p < 0.0001$) but is unrelated to SVI ($r = 0.11$). SVI is weakly ($r = 0.51$) related to EDVI (**Figure 2A**) and, as previously reported in coronary artery disease patients without heart failure (20),

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

EDVI = end diastolic volume index

ESVI = end systolic volume index

HFmrEF = heart failure with mid-range left ventricular ejection fraction

HFpEF = heart failure with preserved left ventricular ejection fraction

HFrEF = heart failure with reduced left ventricular ejection fraction

LVEF = left ventricular ejection fraction

PWP = pulmonary wedge pressure (mean)

RNV = radionuclide ventriculography

SVI = stroke volume index (in reference to body surface area)