Causes and Pathophysiology of Heart Failure with Preserved Ejection Fraction

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KEYWORDS

• Heart failure with preserved ejection fraction • Ventricular-arterial uncoupling • Exercise intolerance • Comorbidities • Myocardial stiffness

KEY POINTS

- The pathophysiology of heart failure with preserved ejection fraction (HFPEF) is driven by interactions among age-dependent and gender-dependent characteristics of ventricular-arterial coupling and various predisposing comorbidities and risk factors.
- Ventricular diastolic dysfunction is central in the pathogenesis of HFPEF caused by an increased ventricular stiffness and is responsible for limited exercise tolerance.
- At tissue, cellular, and molecular levels, concentric myocardial hypertrophy, alterations in extracellular matrix and fibrosis, expressional changes, and posttranslational modifications of titin leading to increased cardiomyocyte passive stiffness ($F_{passive}$) as well as perturbations of intracellular Ca^{2+} handling have been implicated.
- Further phenotyping of patients with HFPEF and preclinical studies in animal models of HFPEF may bring further insights into the pathogenesis of the complex syndrome of HFPEF.

INTRODUCTION

Clinical experience of the last 2 decades has shown that the prognosis of heart failure (HF) has improved when the ejection fraction (EF) is reduced (HFREF), but not when the EF is preserved (HFPEF). A distinction between the pathophysiologic background for these syndromes is also supported by their pathomorphologic phenotypes: mainly eccentric left ventricular (LV) remodeling in HFREF versus concentric remodeling in HFPEF.[1–3] Nevertheless, diverse patterns of ventricular remodeling in patients with HFPEF were also shown mirroring the clinical and pathophysiologic heterogeneity of this syndrome. These findings suggest that although concentric LV remodeling is common among patients with HFPEF, many of them show normal LV dimensions or may even have an eccentric pattern.[4]

The typical patient with HFPEF is an elderly woman with a clinical history of systolic hypertension (HT), diabetes mellitus (DM), and obesity.[5] One of the initial signs of HFPEF is decreased exercise tolerance during physical stress.[6] Further progression leads to the appearance of clinical

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symptoms at rest: dyspnea, fatigue, coughing, and lung crepitation caused by pulmonary congestion, often accompanied by paroxysmal attacks of acute HF episodes with pulmonary edema.[7] In addition, patients with HFPEF are vulnerable to small changes in volume regulation, resulting in severe hypotension or hypertensive crisis.[8]

HFPEF: A SYNDROME OF DERANGED VENTRICULAR-ARTERIAL COUPLING

Interaction Between the Heart and Vasculature Is the Achilles Heel of the Cardiovascular System

HFPEF is increasingly recognized as a disease of abnormal ventricular-arterial coupling in association with decreased exercise tolerance.[9] To understand the main pathologic pathways leading to this exercise intolerance, basic issues of hemodynamic coupling between the heart and the vasculature should be reviewed under physiologic and pathologic conditions.

The term of ventricular-arterial coupling refers to an interaction between the heart and the vascular system, because the stroke volume (SV) from the LV is transferred toward the vascular tree.[10] Ideal coupling provides optimal working efficiency for the cardiovascular system in several ways. On the one hand, good ventricular-arterial coupling maintains continuous blood flow without exaggerated fluctuations in blood pressure (BP) and hence it protects peripheral organs. On the other hand, an optimal ventricular-arterial coupling allows the mobilization of cardiovascular reserve mechanisms during conditions of increased metabolic demands.[11]

To investigate the relationship between the heart and the vascular system, it is necessary to include indices characterizing ventricular and vascular properties within the same framework. One of the models allowing this type of analysis operates with LV end-systolic elastance (E_{es}) and arterial elastance (E_a), both derived from the LV pressure-volume (P-V) relationship of the cardiac cycle (Fig. 1A).[12] Ventricular function can be

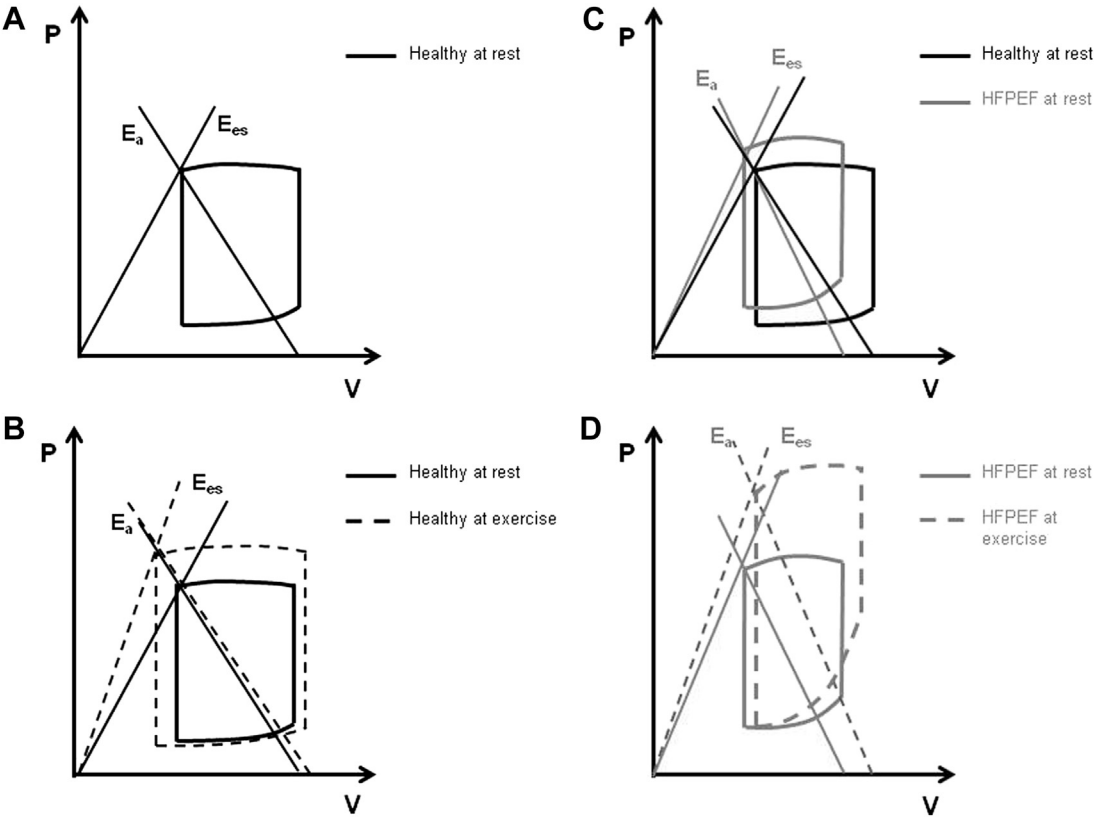

Fig. 1. LV P-V relationships in healthy individuals and patients with HFPEF. (*A*) Ventricular contractility, E_{es} (ie, the slope of the LV end-systolic P-V relationship) and the E_a (ie, the negative slope of the line through the end-systolic and end-diastolic P-V points of LV P-V relations) in healthy individuals at rest. Under normal conditions E_{es} is increased during exercise (*B*). HFPEF is associated with increased baseline E_{es} values at rest (caused by increased LV stiffness) and with increased LV end-diastolic pressure (LVEDP) (*C*). Dynamic exercise results in augmented increases in arterial BP caused by increased ventricular and arterial stiffness in patients with HFPEF (*D*).