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EDITORIAL COMMENT

Repetitive Acute Hemodynamic Load

Progression From Systolic Decompensation to Cellular/Extracellular Compensation to Diastolic Decompensation*

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The development of myocardial cellular and extracellular changes that result in abnormal left ventricular (LV) structure and diastolic dysfunction are fundamental to the development of heart failure with preserved ejection fraction (HFpEF) (1). These changes in LV structure and function result from abnormal hemodynamic and metabolic load that occur with comorbid diseases (e.g., hypertension, diabetes, ischemia, and obesity) that are antecedent to the development of HFpEF (2). However, as many as 40% of patients with HFpEF studied in randomized clinical trials do not have LV structural changes (e.g., frank LV chamber hypertrophy) (3). In addition, patients with HFpEF remain symptomatic, with significant abnormalities in diastolic function at rest and during exercise, even when hemodynamic and metabolic load have been normalized by appropriate medical management. These facts raise several questions. Do increased loads need to be persistent (or chronic) to cause HFpEF? What cellular and extracellular changes are present in HFpEF in the absence of chamber hypertrophy that explain the presence of diastolic dysfunction? Are load-induced cellular and extracellular changes compensatory or decompensatory?

The translational studies presented by Weil et al. (4) in this issue of *JACC: Basic to Translational Science* provide novel data and important insights that help to address these questions. In their study, Weil et al. performed 2-h infusions of phenylephrine (PE) daily for 2 weeks in adult pigs with doses sufficient to raise systolic blood pressure (SBP) to 190 to 200 mm Hg.

SEE PAGE 527

The hemodynamic, structural, and functional responses to the PE infusion changed significantly over time and essentially converted from systolic decompensation to diastolic decompensation (**Figure 1**). This change in response to PE infusion was caused by alterations in cellular and extracellular structures. At baseline, 60-min PE infusion caused increased SBP, LV end-diastolic pressure (EDP), end-diastolic volume (EDV), end-systolic volume (ESV), and decreased EF (**Figure 1C**). Sixty minutes after cessation of PE infusion, SBP and LVEDP returned to normal; however, LVEDV and LVESV remained higher, and EF was still decreased. These acute changes were accompanied by myocyte injury, manifest as significant cardiac troponin I (cTNI) release and cellular apoptosis. By contrast, after 2 weeks of repetitive 2-h PE infusions, while 60-min PE infusion led to similar increases in SBP and LVEDP, no significant changes in EDV, ESV, or EF were observed (**Figure 1D**). This differential change in response was associated with a marked reduction in LV diastolic ventricular compliance (steeper end-diastolic pressure–volume relationship), concentric LV remodeling without chamber hypertrophy, cardiomyocyte hypertrophy, and a marked interstitial fibrosis as evidenced by an

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increase in collagen volume fraction. The associated myocyte injury was also blunted, with significantly less cTNI release. The investigators proposed these structural and functional changes provided a protective effect against PE-induced myocardial injury. The resultant changes in cellular and extracellular structure and function in this porcine model of repetitive PE infusion have direct application to, and are comparable with, the changes seen in patients with hypertensive heart disease–induced HFpEF.

HEMODYNAMIC LOAD: DECOMPENSATION TO COMPENSATION TO DECOMPENSATION

Hemodynamic load is one of the fundamental determinants of myocardial structure and function. PE infusion causes changes in both preload and afterload. As defined by the Law of Laplace, LV chamber preload is calculated as: end-diastolic wall stress = LVEDP × LVEDV/LVED wall thickness; and afterload is calculated as: end-systolic wall stress = LVESP × LVESV/LVES wall thickness. Therefore, the PE resultant acute (within the first few minutes) changes in EDV and EDP (increased preload) and ESV and ESP (increased afterload) cause alterations in the LV pressure–volume relations (LVPVRs) as shown in **Figures 1A and 1B**, respectively.

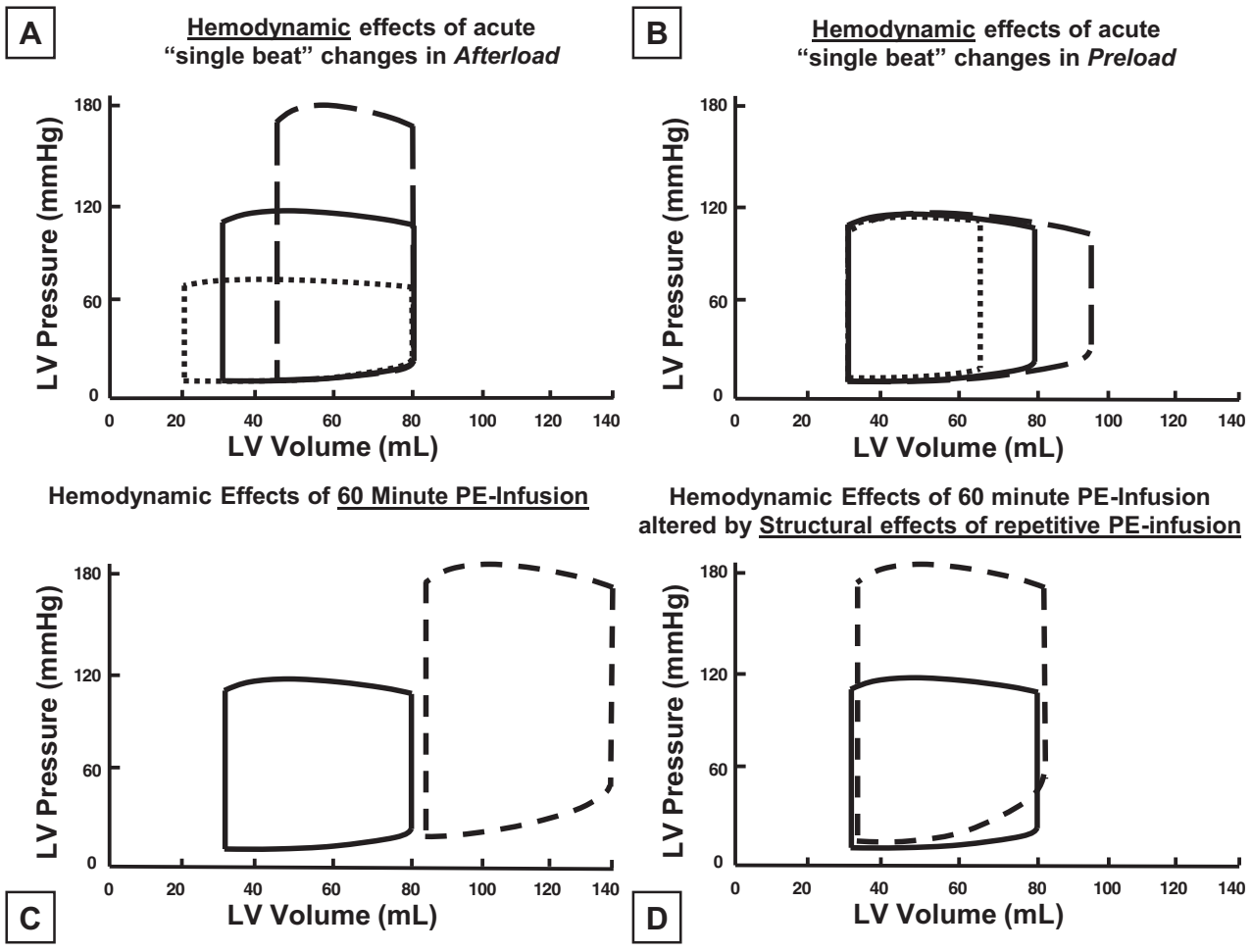
However, 60 min of PE infusion alters the LVPVR beyond that expected from acute changes in preload and afterload (5). Both heterometric (length-dependent) and homeometric (length-independent) autoregulation are activated during 60 min of PE infusion and result in an increase in developed pressure, caused by an increase in length-dependent myofilament calcium sensitivity (Frank-Starling mechanism) and a length-independent increase in the calcium transient amplitude (Anrep effect). These forms of autoregulation represent the direct effects of 60 min of hemodynamic load on molecular and/or cellular signaling (1,2) and activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). In addition, PE infusion may result in "creep," a myocardial length increase that occurs at a constant load, and stunning (as proposed by the investigators). All of these effects of PE may be responsible for the change in the LVPVR (shown in **Figure 1C**) and based on the data presented in Weil et al. (4).

Sixty minutes of PE resulted in a reduced EF, cTNI release, and apoptosis; this represents decompensated systolic function. However, the repetitive application of PE infusion and the hemodynamic, neurohumoral, and signaling changes that occurred with each infusion served as a direct stimulus to produce cardiomyocyte hypertrophy and LV concentric remodeling. In part, these changes served to compensate systolic function. By contrast, chronic activation of SNS and RAAS also led to cardiomyocyte loss through apoptosis and necrosis. In addition, hemodynamic, neurohumoral, and signaling changed the constitutive material properties of the cardiomyocyte that reduced cellular distensibility and increased myocardial stiffness. Finally, hemodynamic, neurohumoral, and signaling resulted in interstitial fibrosis that further contributed to increased myocardial and LV diastolic chamber stiffness. These changes in diastolic stiffness prevented PE-induced increases in LVEDV and preserved EF but did so at the cost of decompensated abnormal diastolic function (**Figure 1D**). Therefore, although hemodynamic load played a central role, it was the resultant neurohumoral activation and molecular signaling that were responsible for the chronic structural changes that resulted from repetitive PE infusion. Thus, when increased preload, afterload, heterometric, and homeometric autoregulation were applied (through PE infusion) in the presence of these structural changes, systolic performance was compensated at the cost of diastolic decompensation (**Figure 1D**).

CLINICAL INSIGHTS

The antecedent and/or comorbid disease processes that lead to the development of HFpEF and its characteristic structural and functional remodeling are generally viewed as imposing a constant, steady-state increase on hemodynamic and/or metabolic load. However, they are not constant or in a steady state. Hypertension-induced increases in afterload vary from hour to hour and day to day based on sleep and/or wake cycles, activity and/or exercise, emotional stress, medication half-life, and patient compliance with pharmacological and non-pharmacological management. The same applies to glucose management in diabetes. The control of each of these hemodynamic and metabolic loads also affects neurohumoral activation and molecular signaling, which, in turn, will have intrinsic variability. Therefore, the effects of the repetitive PE infusion provide an increased understanding of the pathophysiological mechanisms that result in the clinical syndrome of HFpEF. In addition, these data provide an understanding of the progressive structural and functional changes at the cellular and

FIGURE 1 Effects of Changes in Hemodynamic Load on the LVPVR



(A) Hemodynamic effects of acute, isolated, single-beat changes in afterload on the left ventricular pressure–volume relationship (LVPVR). Images represent idealized schematic drawings. **Solid line** = controls; **dashed line** = acute, isolated, single beat increase in afterload; **dotted line** = acute, isolated, single beat decrease in afterload. **(B)** Hemodynamic effects of acute isolated, single beat changes in preload on the LVPVR. Images represent idealized schematic drawings. **Solid line** = controls; **dashed line** = acute, isolated single beat increase in preload; **dotted line** = acute, isolated, single beat decrease in preload. **(C)** Hemodynamic effects of 60-min phenylephrine (PE) infusion induced changes in afterload and preload, as well as activation of both heterometric and homeometric autoregulation on LVPVR at baseline before repetitive daily PE infusions. Sixty minutes of PE infusion caused reversible increases in LV systolic and diastolic pressure, but sustained increases in LV end-diastolic and end-systolic volume and decreased ejection fraction (EF); there was evidence of decompensated systolic function. **Solid line** = controls; **dashed line** = effects on LVPVR of PE infusion. Images represent idealized schematic drawings derived from data from study by Weil et al (4). **(D)** Hemodynamic and structural effects of repetitive PE infusion on the LVPVR. After 2 weeks of repetitive PE infusions, the effects of a 60-min PE infusion–induced changes in hemodynamic load (increased afterload and preload, as well as activation of both heterometric and homeometric autoregulation) were superimposed on cellular and extracellular structural remodeling. The observed changes in LV diastolic stiffness prevented PE-induced increases in LVEDV and preserved EF but did so at the cost of increased LV diastolic PVR, decreased LV distensability, and decompensated diastolic function. **Solid line** = controls; **dashed line** = effects on LVPVR of PE infusion. Images represent idealized schematic drawings derived from data from the study of Weil et al. (4).

extracellular level that result in rest and exercise diastolic dysfunction, increased LV diastolic stiffness, and clinical presentation of heart failure in patients with HFpEF.

The data presented by Weil et al (4) present the 2-sided coin of compensatory and/or decompensatory changes in structure and function. In response to increased hemodynamic load, the cellular and/or extracellular changes in structure and/or function preserve systolic properties but degrade diastolic properties. The model presented in Weil et al. (4) results in many of the characteristics common in the

clinical syndrome of HFpEF; after the phenotype is established, these characteristics should be amenable to testing novel management schemes that reverse fibrosis and normalize cardiomyocyte structure and function.

CONCLUSIONS

The study by Weil et al. (4) provides important insights into the pathophysiological mechanisms underlying the development of clinical HFpEF and provides a porcine translational model that should be useful in further studies that examine novel therapeutic approaches to manage patients with HFpEF.

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