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EDITORIAL COMMENT

Understanding HFpEF With Obesity

Will Pigs Come to the Rescue?*

David A. Kass, MD

The clinical syndrome we now call heart failure (HF) with preserved ejection fraction (HFpEF) affects over one-half of all HF patients globally and confers substantial morbidity and mortality. However, unlike HF with a depressed ventricular function (e.g., a low ejection fraction [EF]), HFpEF currently has no specific targeted effective therapy. HFpEF was first identified in the 1970s in patients with ischemic heart disease, but without infarction, a normal-range EF, and HF symptoms. Soon after, it became more synonymous with hypertensive, hypertrophic heart disease, and the cause was thought to be diastolic dysfunction. Preclinical models in rats (and more recently mice) and some larger mammals used hypertension as the main pathobiological trigger. Among common approaches were genetics (e.g., spontaneously hypertensive rat), with salt-volume loading (Dahl salt-sensitive rat), renal vascular hypertension, or aortic constriction. In these models, the left ventricle (LV) developed adaptive concentric LV hypertrophy (LVH) and diastolic dysfunction.

Insights from these "HFpEF" models certainly enhanced understanding of hypertrophic, hypertensive heart disease, and if that was all that was a stake, we might have had the problem solved. But HFpEF was always more than that. Human studies found abnormal cardiac-vascular stiffening and interactions, chronotropic incompetence, pulmonary hypertension, renal disease, and skeletal muscle dysfunction. HFpEF was truly transformed, however, by its intersection with an obesity and metabolic syndrome pandemic. Today, most HFpEF patients have marked visceral adiposity, many with Class II or higher levels of obesity, (e.g., BMI >35 kg/m^2), and insulin resistance with or without type II diabetes. In the meantime, HFpEF clinical trials generally enroll patients with systolic blood pressures of 125 to 135 mm Hg, and LVH is often mild or absent. Obesity worsens HFpEF outcomes and affects pulmonary and right ventricular function, and multiple biomarkers for inflammatory signaling and metabolic disease (1). Beyond these integrated effects, obesity also changes myocardial transcriptomics and predicts worse sarcomere contractility of right ventricular myocytes (2). At Johns Hopkins Hospital, where one of the few focused HFpEF clinics has been established, our patients have a median body mass index of 40 kg/m^2 (only 25% are below 33 kg/m^2), and 70% have diabetes. Similar data are appearing throughout the United States, which has among the highest obesity rates in the world, and also in Europe and Asia. This is HFpEF in 2020, and preclinical models should incorporate this as a major feature.

Animal models of obesity have long coexisted with those for hypertension and LVH, and used to study metabolic syndrome. Although rat and mouse models remain a mainstay, larger mammals are also used, most notably the pig. Pigs develop obesity with visceral adiposity when fed a high-fat diet (HFD), and their cardiovascular and metabolic features are quite similar to humans. Unlike rodents, however, in which brown fat plays a major role in fat homeostasis, pigs have negligible postnatal brown fat as found in humans. However, a HFD alone does not generate HFpEF, but must be combined with other stimuli to yield the symptoms and indicia of the clinical syndrome. Several groups have attempted such

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From the Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

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combinations, using Ossabaw, Landrou, or Yorkshire/Landrou pigs fed an HFD or Western diet (high fat/cholesterol + high fructose corn syrup) combined with pressure overload. Several models came close (3,4), inducing marked metabolic syndrome, obesity with compensated LVH, and depending upon the study's specific analyses, tissue fibrosis, oxidant stress, renal disease, vascular defects molecular signaling abnormalities, and other features. Neither these nor other porcine models have shown HF with exertional disability. Importantly, they also had not yielded hearts with elevated LV end-diastolic pressures, a defining feature of most humans with HFpEF. LV end-diastolic pressure is instead similar to control animals but at smaller heart volumes, increasing calculated passive stiffness.

In this issue of *JACC: Basic to Translational Science*, Sharp et al. (5) have added another variation on a (HFpEF-pig) theme. Their data share features and limitations of prior versions while moving the ball forward as well. They employed the Göttingen minipig, long used for obesity studies, administering a Western diet and DOCA-salt pressure/volume stress. The individual components are not new, but their combination in this animal is novel. As with earlier efforts, the new pig model develops marked dyslipidemia and insulin resistance, and a weight gain of ~40%. However, it has much more hypertension than prior renditions (systolic pressure of ~170 mm Hg), more reminiscent of hypertensive rat models, and correspondingly, ventricular mass more than doubles. As a likely consequence, diastolic pressure is elevated to 20 mm Hg. The model also produces fibrosis in liver, kidney, and heart, and endothelial dysfunction. Overall, it requires 5 months to generate.

The investigators deserve substantial credit for undertaking this task and developing a large mammalian HFpEF model that reflects many components of what is found in humans. The characterizations are clear, and many of the abnormalities are striking. In particular, the extent of obesity, metabolic defects, and impaired vascular function are relevant, and achieving this in a larger mammal should facilitate multiorgan analysis. That said, the study and model has limitations. Although they produced greater diastolic pressure, this occurred with levels of hypertension and LVH that are rarely observed in HFpEF patients today. Despite this, there is no evidence presented of pulmonary congestion, although pre- and post-capillary pulmonary hypertension was found, nor of volume overload or its associated biomarkers (e.g., N-terminal pro-B-type natriuretic peptide [NT-proBNP] as employed in human trials). Myocardial LV atrial natriuretic peptide and BNP expression are not different, though there is large variance. A key study limitation is the small number of animals studied (3 control animals, 5 with the model), which led to many measurements being insufficiently powered to obtain meaningful statistics. This is a problem with large animal models generally, because although they may arguably get us closer to the human, they are also expensive, complex to maintain, and without substantial resources, the number of studies and interventions that can be tested are limited. In this respect, they are unlikely to be widely used, but they may provide late-stage testing platforms before human trials.

There are rodent alternatives that combine hemodynamic stress and LVH with metabolic syndrome/obesity. The ZSF1 rat is an example. It is a genetic cross between the Zucker diabetic fatty rat and the spontaneously hypertensive obese rat and leptin-receptor-deficient rat. It develops LVH, obesity, diastolic dysfunction, fibrosis, and many other indicia of HFpEF. Another recent entry is a mouse fed a HFD and administered L-NAME to block nitric oxide synthase signaling and generate hypertension. More and more labs are merging components of hemodynamic stress—usually associated with a pressure load and diet-induced obesity. Although useful for mechanistic dissection, mice have their disadvantages, given differences in fat homeostasis, sex differences with females often being less affected (contrary to humans where females remain a majority of HFpEF patients), and strain dependences.

New federal-level phenomic initiatives targeting human HFpEF and the growing realization that this is a truly major unmet medical need has recently put this syndrome on center stage. Since 2004, there are just over 2,800 published papers retrievable using HFpEF as a keyword, and growth is exponential and no longer dominated by reviews (a good sign). The field has long been stymied by a lack of relevant animal models, and HFpEF's constellation of multiorgan dysfunction sustained over many decades admittedly makes it hard to mimic. That does not mean we should not try. An often-heard statement is that such and such a model, although not truly HFpEF, still is relevant because it reflects key aspects. OK, but this only goes so far. Given the prominence of

obesity these days, models lacking combined metabolic and cardiovascular phenotypes are like making onion soup with the broth, but no onions. It's soup, but some things are essential. Efforts like those by Sharp et al. (5) are important and, with a bit more tweaking, should provide a valuable testing platform. In the meantime, new molecular and cellular data from humans are appearing, and these should provide the backdrop to robustly test preclinical models and see which is really coming closest.

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ADDRESS FOR CORRESPONDENCE: Dr. David A. Kass, Division of Cardiology, Johns Hopkins University School of Medicine, Ross Research Building, Room 858, 720 Rutland Avenue, Baltimore, Maryland 21205, USA. E-mail: dkass@jhmi.edu; Twitter: @dkassjhu.

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