

## ON MY MIND



# What Exactly Is Cardiometabolic HFpEF: A Phenotype or an Endotype?

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**W**hen heart failure with preserved ejection fraction (HFpEF) was first described as a syndrome in the 1980s, it was envisioned as a hypertrophic disorder caused by uncontrolled hypertension. However, coincident with the global epidemic of obesity, we have witnessed a global epidemic of HFpEF. Currently, among patients in clinical trials of HFpEF, ~50% to 60% have a body mass index  $\geq 30$  kg/m<sup>2</sup>, and >90% have central obesity, as reflected by a waist-to-height ratio of  $\geq 0.5$ .<sup>1</sup> These estimates are impressive, since many large-scale trials specifically excluded patients with a body mass index >45 to 50 kg/m<sup>2</sup>.

ventricular-vascular stiffness. These patients had clinical features of the metabolic syndrome, that is, abdominal obesity, hypertension, hyperglycemia and insulin resistance, and lipid abnormalities. Because of this linkage, the authors coined the term cardiometabolic HFpEF. Cardiometabolic HFpEF thus emerged as a potential clinical phenotype, representing an expansion of obesity-related HFpEF. The authors identified visceral adiposity as the defining mechanism, but they did not offer specific criteria that would allow for the identification of cardiometabolic HFpEF in the clinical setting.

## INTRODUCTION OF CARDIOMETABOLIC HFPEF AS A CONCEPT

In 2017, Obokata et al<sup>2</sup> identified patients with a body mass index  $\geq 30$  kg/m<sup>2</sup> as representing a distinct phenotype of HFpEF. They reported that, in patients who had HFpEF and obesity, body mass index was a primary determinant of left ventricular filling pressures, which were elevated to a degree greater than reflected in the circulating levels of natriuretic peptides. The investigators suggested that an expansion of adipose tissue around the heart might encroach on the pericardial space in some individuals, leading to the hemodynamic features of pericardial constraint.

In 2019, Obokata et al<sup>3</sup> noted that many patients with HFpEF who did not fulfill criteria for obesity nevertheless had excess body fat, which was associated with low grade systemic inflammation and

## CHARACTERIZATION OF CARDIOMETABOLIC HFPEF AS AN ANIMAL MODEL ENDOTYPE

In 2021, Schiattarella et al<sup>4,5</sup> recognized that the most clinically relevant animal models of HFpEF depended on dietary nutrient excess as the critical trigger. A high-fat diet is the essential component of experimental combinatorial approaches, with disease progression accelerated by neurohormonal or biological stressors,<sup>6,7</sup> ultimately producing HFpEF with myocardial lipid overload, metabolic dysfunction, and systemic inflammation.<sup>7</sup> This model differed dramatically from that produced by transverse aortic constriction, which produced hypertrophy in the short-term but with rapid evolution into a dilated cardiomyopathy.<sup>8</sup> In contrast, in clinical practice, adiposity-related HFpEF rarely evolved into systolic dysfunction during long-term follow-up.<sup>9</sup>

**Key Words:** adiposity ■ heart failure ■ myocardium ■ nutrients ■ stroke volume

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Schiattarella et al<sup>7</sup> labeled the HFpEF model induced by a high-fat diet and characterized by cardiac steatosis and metabolic abnormalities as cardiometabolic HFpEF. However, the term referred to an experimental endotype rather than a clinical phenotype. The term endotype refers to a biological pathway by which a disorder is produced, whereas the term phenotype refers to a defined collection of clinical features that can be measured in patients. Subsequent studies confirmed that dietary nutrient excess in mice produced the metabolic and inflammatory derangements of HFpEF.<sup>6,7</sup> Some drew analogies between nonalcoholic steatohepatitis and cardiometabolic HFpEF,<sup>10</sup> suggesting that nutrient overload might produce steatosis simultaneously in different organs.<sup>11</sup>

## EFFORTS TO TRANSLATE AN ENDOTYPE BACK INTO A PHENOTYPE

Impressed by the apparent clinical heterogeneity of HFpEF, some investigators have utilized unsupervised cluster analysis to define subgroupings of HFpEF.<sup>12</sup> Phenomapping is a mathematical partitioning technique in which central tendencies are used to coerce patients into clusters. Advocates of this approach recognize its limitations, that is, phenomapping does not yield replicable clusters and may not reflect a biological reality.<sup>13</sup> Furthermore, since the clusters are not defined by boundaries, they do not yield criteria that allow individual patients to be assigned to a specific subgroup. In fact, obesity was a feature of most proposed clusters, but central and visceral adiposity were not typically assessed in these analyses.<sup>14,15</sup>

Despite these difficulties, some authors<sup>14–16</sup> sought to use phenomapping to move the animal model endotype into clinical practice, and they proposed cardiometabolic HFpEF as a distinct phenotype that was closely linked to obesity, insulin resistance, type 2 diabetes and systemic inflammation. However, no specific criteria were proposed to identify cardiometabolic HFpEF in clinical practice, and several aspects of the metabolic syndrome—for example, hypertriglyceridemia or low HDL cholesterol—are more

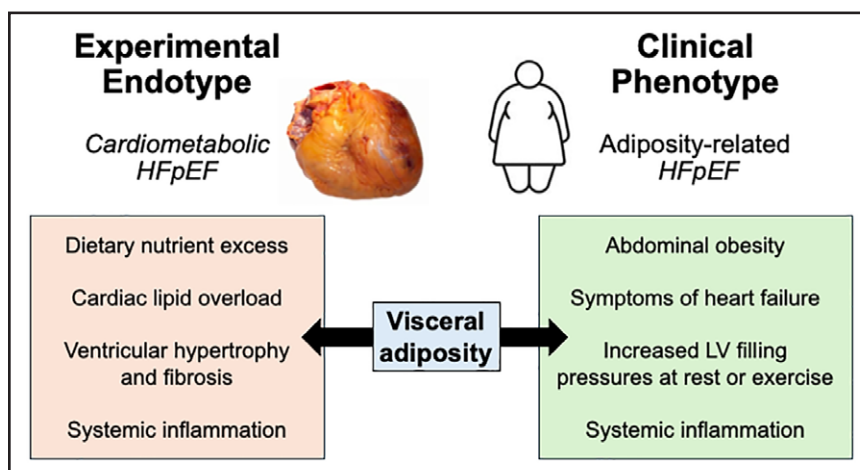
aligned with coronary artery disease than with HFpEF. Of the criteria that define the metabolic syndrome, visceral adiposity and abdominal obesity provide the closest link with HFpEF.<sup>17–19</sup>

Yet, in proposing the transition of an endotype into a phenotype, these investigators recapitulated the original proposal of Obokata et al,<sup>3</sup> who suggested that cardiometabolic HFpEF represented an expansion of the concept of obesity-related HFpEF to include nonobese patients with HFpEF who had visceral adiposity. Visceral adiposity not only predicts the occurrence of HFpEF in the general population,<sup>17</sup> but the degree of adipose tissue expansion is related to the hemodynamic and clinical severity of HFpEF.<sup>18</sup> Patients with the most marked adiposity before treatment show the most marked benefit from treatment with sodium-glucose cotransporter 2 inhibitors, mineralocorticoid receptor antagonists, angiotensin receptor neprilysin inhibitors and glucagon-like peptide 1 receptor agonists.<sup>19</sup>

## SUMMARY AND CONCLUSIONS

The experimental endotype of cardiometabolic HFpEF appears to correspond precisely to a clinical phenotype characterized by an expansion of visceral fat, particularly fat surrounding and residing within the myocardium. Visceral adiposity is the primary feature that defines the presence of the metabolic syndrome, including its focus on central obesity, hypertension, and insulin resistance,<sup>20</sup> and visceral adiposity was the central feature of cardiometabolic HFpEF when it was originally proposed as a clinical phenotype 6 years ago.<sup>3</sup>

Therefore, we propose that the term cardiometabolic HFpEF be used to refer only to the experimental endotype produced by dietary nutrient excess and cardiac lipid overload. In the clinical setting, we propose the term adiposity-related HFpEF to represent the corresponding clinical phenotype, identified by the presence of abdominal obesity or by imaging of visceral (ie, cardiac, hepatic, and mesenteric) fat depots (Figure). Whether regarded as an



**Figure.** Distinctions between the experimental endotype of cardiometabolic heart failure with preserved ejection fraction (HFpEF) and the clinical phenotype of adiposity-mediated HFpEF.

endotype or phenotype, this characterization is currently the dominant presentation of HFpEF in clinical practice and represents the defining feature of most patients who have been enrolled in large-scale HFpEF trials.

## ARTICLE INFORMATION

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