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Pivotal Role of Excess Intra-abdominal Adipose in the Pathogenesis of Metabolic/Obese HFpEF

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A major advance in HFpEF occurred in 2013 when Dr. Walter Paulus proposed the inflammation model of HFpEF pathogenesis. There is now a large and growing body of evidence to support this paradigm. Circulating biomarkers of inflammation are elevated in HFpEF and correlate with disease severity, symptoms, objective measures of physical and cardiac function, and clinical events.(1) During 9-year follow-up in a large population-based study, IL-6, tumor necrosis factor-α, and CRP were strong, independent predictors of incident HFpEF, but not HFrEF.(1) Inflammation biomarker levels are reduced following interventions that improve outcomes in HFpEF.(2)

There are multiple pathways by which Inflammation promotes HFpEF.(1) However, the most fundamental mechanisms are likely microvascular and mitochondrial dysfunction. HFpEF patients have severe capillary rarefaction in cardiac and skeletal muscle, and measures of microvascular dysfunction correlate with multiple adverse outcomes.(3) HFpEF patients also have reduced mitochondrial content and multiple abnormalities in mitochondrial function which also correlate with adverse outcomes. These 2 abnormalities impair tissue perfusion (oxygen delivery) and oxygen utilization (aerobic metabolism) which are critical to organ and tissue function.

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From where do the inflammatory molecules originate? A recent elegant study showed that the inflammatory markers in HFpEF enter the myocardium via the coronary sinus, and their concentrations are correlated with NTproBNP, indicating that they originate primarily from outside the heart. Dr. Paulus inferred the inflammation was caused by the multiple comorbidities, including obesity, that accompany HFpEF and which drive the majority of clinical events. A plethora of evidence now indicate that excess adipose tissue likely plays the over-arching, pivotal role in the development, progression, and adverse outcomes in HFpEF.(4) In the US, >80% of HFpEF patients are overweight/obese, twice the general population, and the HFpEF population-attributable risk from overweight/obesity is similar to that of hypertension. Excess adiopose strongly promotes inflammation, hypertension, insulin resistance, and dyslipidemia, and impairs diastolic, systolic, arterial, skeletal muscle, and physical function. Increased BMI is an independent predictor of incident HFpEF, and in established HFpEF independently predicts more severe: symptoms; exercise intolerance; cardiac dysfunction; and elevations in exercise pulmonary wedge pressures. The highest levels of BMI are associated with worse prognosis, including death. Reducing excess adipose tissue via bariatric surgery prevents development of HF.(2) In established HFpEF, reducing excess adipose via dietary caloric restriction improves symptoms, exercise capacity, and quality-of-life, and is associated with reduced inflammation.(2)

Is some fat worse than others? Adipose tissue is highly heterogeneous. Its location, density, and composition determine its local and systemic effects, including metabolic, endocrine and inflammatory, its mechanical effects, and its overall health impact. For instance, subcutaneous adipose tissue has modest adverse metabolic/systemic effects and correlation with cardiovascular outcomes. In contrast, abdominal visceral (intra-abdominal) adipose tissue (VAT) has profound metabolic/systemic effects and in clinical studies, including of HFpEF, is a strong, independent predictor of adverse outcomes.

Multiple lines of evidence suggest that among the various fat depots, VAT plays the most pivotal role in the development, pathophysiology, and adverse outcomes of metabolic/obese HFpEF.(3) VAT is intensely pro-inflammatory and metabolically active, and produces an array of inflammatory, oxidative, endocrine, vaso-active and angiogenic substances(3). VAT impairs insulin sensitivity and lipid regulation, increases blood pressure, and is key mediator of metabolic syndrome. Patients with metabolic syndrome have >50% more VAT than those without it. Further, non-obese persons with increased VAT are at high risk, and obese persons with normal VAT are at normal to low risk for metabolic syndrome. VAT is a strong, independent predictor of diabetes and incident CVD, stronger than BMI and total body adipose.

Excess VAT predicts key outcomes in HFpEF as well as their improvement with interventions. A recent study used DEXA to quantify total adipose and MRI to quantify regional fat depots in obese HFpEF, and also measured peak exercise VO_2, an objective measure of exercise intolerance in chronic HFpEF that correlates with their reduced quality-of-life.(3) VAT was a strong independent predictor of peak VO_2, independent of total adipose and stronger than for other fat depots. In a trial of dietary weight reduction in obese HFpEF, reduced VAT was the strongest predictor of the large improvement in peak VO_2 and quality-of-life. In the TOPCAT trial, where 73% of patients had abdominal obesity,

abdominal obesity was an independent predictor (HR 1.5) of all-cause, cardiovascular, and non-cardiovascular mortality.

The single piece of missing evidence regarding the role of VAT in HFpEF has been whether VAT specifically and independently predicts incident HFpEF. In this issue of the Journal, Rao and colleagues fill this key gap with an important study from the Multi-ethnic Study of Atherosclerosis (MESA), a population-based, longitudinal follow-up study that includes relatively deep phenotyping of individuals, careful follow-up, and formal adjudication of events. BMI, waist-hip ratio, and CT scans were performed in 1,806 participants. During 11-year follow-up, they found that all three measures of adiposity were significant, independent predictors of hospitalized HFpEF, but VAT (HR 2.24; CI1.44–3.49) was much stronger than BMI or waist-hip ratio, which had similar hazard ratios. These relationships remained significant even after adjusting for NTproBNP. Subcutaneous fat was not a predictor of HFpEF.

Rao found that none of the adiposity measures predicted HFrEF. These results are in accord with Savji who showed that increased BMI predicts HFpEF, particularly in women, but not HFrEF, and a study by Kalogeropoulos that showed that inflammation biomarkers predict development of HFpEF but not HFrEF.(1)

These results from Rao provide the final link to confirm the Paulus paradigm for HFpEF, capping the data from others discussed above that provide: the source of the inflammation (excess VAT); the specific mechanisms whereby excess VAT produces inflammation and metabolic dysregulation; and the final pathways by which these likely cause HFpEF (microvascular and mitochondrial dysfunction).

What is the genesis of the excess VAT? While sustained excess caloric intake is the primary contributor to obesity and excess VAT, a less recognized factor, cortisol, is an key contributor by disproportionately promoting deposition of VAT. Cortisol is elaborated in response to stress, illness, and co-morbidities. This results in catabolism of skeletal muscle tissue, conversion to adipose, and preferential deposition in the abdomen.(4) This has 3 broad, adverse consequences. 1) Even small amounts of excess VAT rapidly exert significant adverse systemic effects which progress and worsen over time. A large amount of VAT can essentially function as an independent organ. 2) Loss of skeletal muscle promotes and worsens exercise intolerance, a hallmark of chronic HFpEF. 3) Along with the liver, skeletal muscle is the key organ helping regulate insulin sensitivity. As skeletal muscle is lost and VAT accumulates, insulin dysregulation develops and progesses, resulting in metabolic syndrome and often overt diabetes. An accelerated version of this scenario is observed when patients are treated with high-dose, prolonged steroids; there is relatively rapid development of muscle wasting, abdominal obesity, insulin resistance/diabetes, and hypertension.

The adverse effects of even a small excess of VAT may help explain the late life increase in HFpEF among women. After menopause, women gain on average 2.5kg, mostly as adipose, which is disproportionately deposited as VAT, producing the array of adverse consequences discussed above and promoting HFpEF. Estrogen replacement therapy prevents this increase in VAT.

Excess VAT can contribute to HFpEF even when patients aren't obese and have normal BMI. For example, in contrast to Western populations, most Eastern Asian HFpEF patients are normal weight or even underweight.(5) However, for any given BMI, Asian populations have a significantly higher percentage of VAT compared to white populations, and this appears to account for their much higher prevalence of diabetes. In asymptomatic Asians with normal EF and relatively low BMI, larger waist circumference is associated with unfavorable LV remodeling, impaired diastolic function and worse global myocardial deformation.(4) These cross-ethnic observations further support the concept that excess VAT plays a key contributory role in HFpEF, and highlight the limitations of BMI as surrogate for body composition.

The central role of excess VAT in HFpEF has important therapeutic implications. Maintaining normal weight and body composition can prevent HFpEF, and removing excess VAT via bariatric surgery or diet can improve established HFpEF.(2) Can interventions disproportionately reduce VAT? In a study of dietary weight loss in obese women, where there was a 10% reduction in overall weight, there was a 35% reduction in VAT. In a study where pioglitazone was added to diet and exercise, pioglitazone nearly doubled the amount of VAT that was lost. Trials are planned or underway to examine whether agents aimed at reducing systemic inflammation can benefit HFpEF. It could be that targeting the source of the inflammation (VAT) may be more effective than trying to mitigate the resulting inflammation. The systemic inflammation / VAT hypothesis may also help explain why trials to date have been negative, since they selected agents that were effective in HFrEF, which is not driven by inflammation/VAT, and were focused narrowly on potential cardiac mechanisms rather than broader systemic effects. Since the 2 interventions shown to date to improve HFpEF, exercise and dietary weight loss, both reduce VAT, future studies targeting excess VAT and its numerous adverse consequences may prove more fruitful.

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Biography

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