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EDITORIAL COMMENT

Nutrient Intake and Exercise Capacity in Heart Failure With Preserved Ejection Fraction

Doughnut Assume it Is Only About Diastolic Function*

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Heart failure with preserved ejection fraction (HFpEF) is already at epidemic proportions, and the prevalence is growing as associated comorbidities become more common (1). One of the strongest population-attributable risk factors for incident HFpEF is obesity (2), and weight loss has been proposed as an effective treatment and preventive strategy for HFpEF. Thus far, studies have focused on weight loss through surgery (3) or caloric restriction (4), both of which appear to benefit patients with HFpEF. Comparatively little attention has been paid to whether specific dietary components may also affect the HFpEF syndrome. Given that humans with HFpEF (5) and proposed HFpEF animal models (6) have significant metabolic dysfunction, this seems highly likely.

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In this context and in this issue of *JACC: Basic to Translational Science*, Carbone et al. (7) present the thought-provoking results of their translational study investigating the relationship between dietary patterns and factors related to HFpEF. Using data from a single 24-h dietary recall, they find that unsaturated fatty acids (UFAs) are positively and simple carbohydrates negatively correlated with peak oxygen consumption (VO_2) from treadmill cardiopulmonary exercise (CPX) testing in patients with HFpEF. They complement this work with an animal study in which they demonstrate that CD-1 mice consuming an excess of saturated fatty acids (SFAs) or sugars develop evidence of left ventricular diastolic dysfunction, and conversely that mice consuming high levels of UFAs have less diastolic dysfunction. They propose that the murine results support the human findings.

The authors should be congratulated on exploring an important topic that has not been extensively investigated in human HFpEF. Although young and able to perform maximal treadmill VO_2, the patients with HFpEF in this study were morbidly obese and predominantly women, and had multiple comorbidities. The cardinal manifestation of HFpEF is exercise intolerance, and treadmill CPX testing represents the quantitative gold standard to assess this issue. The CPX tests in this study were carefully conducted, and despite objectively determined maximum effort patients with HFpEF were substantially limited below predicted VO_2. Accordingly, although likely early in the disease course, this HFpEF cohort is reasonably representative of clinical practice. The murine feeding studies were also well described and carefully conducted. Although not conducted in an experimental model of HFpEF per se, the observations support the concepts that UFA intake can modify body weight, despite similar calorie intake, and that both SFA and sugar intake can adversely affect cardiac function.

Although well acknowledged by the authors, the dietary assessment used in this study has important methodological limitations. Human diets vary

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tremendously from day to day and the best way to capture long-term intake is by collecting multiple 24-h recalls or by using a food frequency questionnaire (8). Using a single 24-h recall to estimate habitual nutrient intake carries the risk of introducing both systematic and random errors of assessment (9). Regardless of that limitation, the authors still observed statistically significant associations in the hypothesized direction. Because of measurement error and the small sample size, the associations could be highly attenuated. The possibility exists that the true effects of UFA and excess sugar consumption are larger than seen in this study.

It is important to note that UFAs include monounsaturated fatty acids and polyunsaturated fatty acids, either omega-3 or -6. Therefore, they comprise a heterogeneous group of fatty acids with diverse functions. Although it is generally accepted that increasing UFA intake has an overall beneficial effect on cardiovascular health, there are still many unknowns in the way different fatty acids affect outcomes and what are the best substitutions to achieve healthy diets. A recent Cochrane review concluded that replacing SFAs with polyunsaturated fatty acids decreases the risk of cardiovascular disease, but that the effect of replacing SFAs with monounsaturated fatty acids was less clear and less well studied (10). Additionally, the food sources of monounsaturated fatty acids vary substantially depending on the overall dietary pattern. In the context of a Mediterranean diet, most monounsaturated fatty acids are plant derived, coming from olive oil, whereas in a Western dietary pattern, the main source of monounsaturated fatty acids are animal derived. Therefore, the downstream effects of these fatty acids may be significantly modulated by dietary pattern. Larger studies with more comprehensive dietary collection will be needed to disentangle these complexities.

Additional challenges in interpreting this study are the cross-sectional association between dietary assessment and CPX testing, and the difficulty in adjusting for other known predictors of VO_2 due to the small sample size. In older adults, the strongest predictors of peak VO_2 and its decrease over time are age and gender (11). In turn, the impact of age and gender on the decline in VO_2 over time are substantially mediated by fat-free mass and habitual physical activity (12). The authors correctly point out that diets rich in UFAs have previously been associated with increased fat-free mass, as seen in this study's body composition analysis and confirmed in the murine feeding study. However, because lifestyle protective factors tend to cluster together (13), patients with HFpEF who consume healthier diets also may engage in more habitual physical activity and maintain more fat-free mass over time. Future studies on this topic will need to account for this important potential confounder.

The authors are appropriately careful not to assign causation of reduced VO_2 to dietary intake in the human study, and do not overemphasize the diastolic function aspect of the animal study. It is now generally accepted that HFpEF is not a disease solely of ventricular diastolic function, but rather a heterogeneous syndrome with multisystem deficiencies in cardiovascular and noncardiovascular reserve (14). Recent studies suggest that reduced peak VO_2 in HFpEF relates to impaired skeletal muscle metabolism as much or more than cardiac function (5,15). We agree with the authors that their results, as well as those from large cohort studies (16,17) and small interventional pilots (18), support the concept of targeted dietary intervention studies in HFpEF. These should be coupled with ongoing experimental work to understand the metabolic consequences of specific dietary components. Preferably, such studies would be conducted in animal models that reflect the metabolic disarray and multisystem dysfunction of human HFpEF (6). We believe that studying the effect of interventions likely to have broad-based metabolic impact holds great promise in clarifying the pathophysiology, and ultimately the treatment, of HFpEF.

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