Association guidelines give aspirin a class I indication for use in patients with chronic stable angina (level of evidence A) (3). This recommendation, however, has been interpreted to embrace a myriad of aspirin formulations: various salts, polymer-coated in rapid-release (compressed, soluble), buffered, and enteric-coated preparations, which may influence the bioavailability of the preparation (4). We recently evaluated the effect of low-dose enteric-coated aspirin preparations on platelet COX-1 in both healthy volunteers and patients with stable CAD. Low-dose enteric-coated aspirin failed to inhibit platelet cyclooxygenase in some individuals. Specifically younger, heavier patients and those with a history of prior myocardial infarction were less likely to have an adequate response (5).

Not withstanding the initial uncontrolled studies, we agree that the jury is still out on the clinical relevance of aspirin resistance. However, it is not an unreasonable goal that a drug has its intended pharmacological effect. In the case of aspirin, near complete inhibition of platelet cyclooxygenase is most likely to be achieved with the correct preparation and dose.

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**THE EMPEROR’S NEW CLOTHES ARE LOOSE: LOWER BODY MASS INDEX, NOT CALORIE RESTRICTION, ACCOUNTS FOR IMPROVED DIASTOLIC FUNCTION**

A recent study in JACC (1) concludes that diastolic function is improved in individuals on long-term calorie restriction (CR) compared to those eating a “Western diet.” We would like to point out that other studies demonstrate a correlation between diastolic dysfunction and body mass index (BMI) as an independent factor. In the study by Fontana et al. (1), control subjects eating a Western diet had an average BMI of 27 kg/m²; the CR adherents had a BMI of 25 kg/m². Mortality and morbidity rise significantly above a BMI of 22 kg/m², and a BMI of 25 kg/m² is (generously) considered by U.S. Department of Agriculture panelists as the upper limit of normal weight. Therefore, a BMI of 27 kg/m² is well within the category of overweight. An average male height 5 ft 9 inches with a BMI of 20 kg/m² weighs 135 lbs. If his BMI is 27 kg/m², he weighs 35% more at 182 lbs, a 47-lb difference!

In a study of the effect of isolated obesity on diastolic function Pascual et al. (2), state: “Subclinal left ventricular diastolic dysfunction is present in all grades of isolated obesity, correlates with BMI, and is associated with increased systolic function in the early stages of obesity.” In that study, a BMI between 25 and 29.9 kg/m² was classed as “slight obesity.” Another study (3) states: “Diastolic function was negatively correlated with age, BMI, systolic blood pressure, diastolic blood pressure and left ventricular mass index.”

In addition, control subjects had 26% body fat, and the CR subjects had 9.3%. Obesity is known to raise tumor necrosis factor-alpha and other pro-inflammatory cytokines (4). Long-term inflammatory effects may change ventricular elasticity, but the observed difference may be due more to the large difference in body fat and BMI than to the CR versus Western diets. It is probable that the difference in diastolic function attributed to CR is at least...
partly due to the secondary effect of being thin, and not the direct result of the CR diet.

Finally, the small number of adherents to a CR life-style speaks to the difficulty in depriving oneself every day of preferred type and amounts of food. We hypothesize (5) that alternate-day calorie restriction, in which one eats less and more than needed to maintain body weight on alternating days, will provide the same health benefits as daily CR; it is a much more agreeable way of living, and it appears to have a profound effect on cardiac function (6).

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REPLY

We appreciate the views expressed by Dr. Johnson and colleagues regarding our recent study (1) concerning caloric restriction (CR) and diastolic function (DF). We agree that in large population studies, diastolic dysfunction, body mass index (BMI), and adiposity are correlated. It would be ideal to have a BMI and body-fat–matched control group that is healthy and not calorie restricted. However, it is self-evident that such a control group is not readily available. It would be extremely difficult to find healthy individuals, other than extreme endurance athletes, who have a BMI <20 kg/m² who are not calorie restricted. Individuals with a BMI <20 kg/m² who are not endurance athletes or calorie restricted are generally in ill-health and frail or heavy smokers. Endurance exercise training causes major cardiovascular adaptations, so athletes are also not an appropriate control group. The control group in our study consisted of individuals typical of the U.S. population, as 78.2% of the men and 68.1% of the women older than 40 years are overweight or obese in the U.S. (2).

In our study (1) we provided evidence that, in humans, long-term CR with optimal nutrition (at least 100% of the recommended daily intake for each nutrient) results in very low levels of inflammation, as demonstrated by low serum C-reactive protein and tumor necrosis factor-alpha concentration, and reduced left ventricular stiffness, indicated by the lower model-based image processing–derived chamber stiffness parameter $\kappa$ and viscoelastic chamber constant $c$. We also found that CR is associated with low serum concentrations of transforming growth factor-beta, a powerful pro-fibrotic molecule that plays a role in regulating the myocardial composition of the extracellular matrix, thus potentially having salutary effects on $\kappa$ and $c$ (3).

In contrast, individuals who are very thin owing to chronic diseases generally have elevated levels of systemic inflammation and have diastolic dysfunction despite a low BMI (4–6). For the group considered, long-term CR is the cause, and the coexistent low BMI is one effect. Conversely, we are not aware of any mechanism by which a low BMI, as an independent variable, can improve DF. The improved DF observed is mediated by other CR effects, such as lowering blood pressure and decreasing the levels of inflammatory cytokines, hormones, and growth factors that may reduce fibrosis, increase compliance, and improve cardiac efficiency.

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Implications and Controversies of Recent Hypertension Trials

Williams has written a comprehensive and thought-provoking review of the recent hypertension literature (1). One of his major contentions is an iteration of the hypothesis that achieving better cardiovascular outcomes depends on more aggressive blood pressure (BP) control and not on the specific choice of antihypertensive