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EDITORIAL COMMENT

Obesity and Cardiovascular Disease

How Can Cardiac Magnetic Resonance Help?*

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The prevalence of obesity is increasing dramatically around the world. The strong association between obesity and cardiovascular disease has drawn many investigators into attempting to better understand its complex relations with and effects on the cardiovascular system. Obesity is associated with an increased risk of developing heart failure, as well as with an overall risk of death (1). This association is mainly due to the effects of the obesity on cardiac structure and function, but is also due to the high prevalence of coexisting factors, such as coronary artery disease, hypertension, sleep-disordered breathing, and diabetes mellitus (2). Cardiac magnetic resonance (MR) imaging is now a well-

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recognized cardiac imaging technique that can help either by accurately evaluating the cardiomyopathy attributed to chronic volume overload, or by analyzing the complex mechanisms contributing to structural and functional changes in the heart and arteries in obesity. The high degree of precision in its measures of cardiac function and the practically unique approach it offers to analysis of new mechanisms interfering with such function (aortic stiffness, fatty infiltration of the heart, and fat diffusion in whole body), makes cardiac MR—and will make it increasingly in future—a preferred method in the evaluation of treatments of obesity. A nice example of what can be achieved by MR to evaluate intervention in a small cohort of obese subjects is proposed by Rider et al. (3) in this issue of the *Journal*. They demonstrated a beneficial effect of significant weight loss in the absence of additional identifiable cardiac risk factors on ventricular structure, myocardial relaxation, and aortic elastic function, in the absence of obscuring effects of weight loss on obesity-related comorbidities.

Concerning left ventricular (LV) remodeling, their study shows, as have many previous papers using echocardiography, that LV mass was increased in obese subjects compared with that in controls, even if the values they found in obese subjects were within the range of normal values previously obtained in large series of asymptomatic subjects (4,5). This increase in mass in obese subjects was most probably the result of ventricular adaptation to a chronic increase in stroke volume, which was also seen to be significant. The reduction in LV mass after weight loss was associated with a decrease in visceral fat mass and hyperleptinemia. However, as body mass index and end-diastolic volume (EDV) were independent predictors of LV mass regression on multivariate analysis, the authors emphasize that volumetric and load changes have a greater influence on LV mass regression than hormonal changes. Furthermore, although significantly higher in obese patients than in controls (0.89 ± 0.16 g/ml vs. 0.75 ± 0.17 g/ml), the concentricity index (LV mass to EDV ratio [g/ml]) has to be considered as normal. In the Dallas study, a population-based sample in which 2,633 subjects underwent cardiac MR imaging to measure LV structure, and electron beam computed tomography to measure coronary artery calcium, the first quartile of concentricity was found to be from 0.7 to 1.31 g/ml in women (and very similar results in men), and this group of subjects were found to be at low risk for having coronary artery calcium, whereas higher quartiles were associated with coronary artery calcium (6). At such levels of LV mass and concentricity, patients have also been found to be without significant decrease in regional function using very sensitive tagging techniques (7), and at low risk of having coronary artery disease, stroke, or heart failure (5) in 2 different studies by investigators from MESA (Multi-Ethnic Study of Atherosclerosis). Thus, the LV remodeling results of the present study show that a small increase in LV mass and concentricity, appropriate to increase in body size and stroke volume, can be detected by cardiac MR in obese patients compared with controls, when obesity is uncomplicated (i.e., absence of hypertension, diabetes, coronary artery disease, and so forth). Furthermore, significant but small changes in such remodeling can also be detected after significant weight loss, mainly because of the decrease in the chronic volume overload.

The second result of the study shows that peak filling rate (PFR [ml/s]) normalized by EDV (PFR/EDV [s^{-1}]) was found to be decreased and associated with longer time to peak filling rate (TPFR [ms]) in obese patients compared with controls, suggesting a significant decrease in diastolic function. However, the analysis of this result remains difficult, and it must be interpreted with caution. The authors have chosen a quantitative approach to wall kinesis during rapid diastolic filling after manually contouring endocardial borders of small axis cine images, to analyze the

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diastolic LV function. Before being applied in a small number of cardiac MR imaging and electron beam computed tomography studies, this approach has been initially described in radionuclide angiography, which provides volume changes relative to EDV, with volume measurements expressed as counts automatically estimated throughout the cardiac cycle by using a temporal resolution close to 50 ms (close to what has been done here in MR imaging). However, PFR alone, determined as the maximal slope (max dv/dt) of volume-time curve during the rapid filling, has been found to be highly dependent of the size of the LV cavity and of the stroke volume. By indexing PFR to the EDV (PFR/EDV), this results in an index of rapid filling, which by definition is mainly dependent on the preload. This technique is, therefore, not ideal for study of the diastolic function of a cardiomyopathy because of chronic volumetric overload.

In my own analysis, differences observed between obese subjects and controls, or changes after weight loss, are more likely to be due to differences in preload condition than to real modification in the diastolic function. Furthermore, when manual tracing is used to determine the slope during rapid filling, small errors or changes in tracing can lead to huge variations in the slope determination and TPFR determinates, which may partly explain large differences in normal values with high SD (from 3.2 $\pm$ 0.4 to 4.6 $\pm$ 8 for the PFR/EDV [s^{-1}]) (8). Totally automated border detection, which can now be obtained in cardiac MR imaging (9), should be applied at higher temporal resolution, given that 5 to 10 ms can be obtained, to get early LV filling kinesis information from endocardial borders with more confidence.

However, by using direct measurement of myocardial properties and less load-dependent indexes with tissue Doppler, Wong et al. (10) have studied both the systolic and diastolic function of 142 obese patients after excluding subjects with coronary artery disease, hypertension, and diabetes. They have shown that overweight subjects without overt heart disease have subclinical changes in LV function even after adjustment for mean arterial pressure and LV mass. Strain imaging in cardiac MR has been also widely studied during systole in a large number of asymptomatic subjects (7), but there are still problems in dealing with diastole using such techniques because tags are not well analyzed far from the R-wave, and because noisy myocardial velocity mappings are still obtained (because of difficulties in managing Maxwell and eddy current effects at low-velocity encoding). Diastolic function is still the weak link in cardiac MR, but images are still improving and myocardial properties during diastole should be better analyzed in the near future in complementarity with load-dependent conventional measures of mitral inflow velocities in a very similar way to what can be done using Doppler today. Some very promising preliminary cardiac MR imaging work has been initiated (11) and also applied to obese subjects with diabetes (12) by the Leiden group, but needs to be further validated and confirmed.

The last very interesting results presented by Rider et al. (3) suggested a very strong relation between aortic stiffness and inflammation. Obese subjects had a lower distensibility at the level of the descending thoracic aorta (4.2 $\pm$ 1.4 mm $Hg^{-1} \times 10^{-3}$ vs. 5.7 $\pm$ 1.9 mm $Hg^{-1} \times 10^{-3}$; $p = 0.002$) and the abdominal aorta (5.1 $\pm$ 1.8 vs. 7.4 $\pm$ 2.6, $p = 0.001$), but not at the level of the ascending aorta. But after weight loss, they observed a significant increase in aortic distensibility at all 3 levels, with the greatest improvement seen in the abdominal aorta (where the load in atheroma is supposed to be higher), whereas no improvement in such distensibility was observed in cases of continued obesity. This improvement in aortic function is likely to be related to the decrease in visceral and subcutaneous fat, resulting in reduction of both hyperleptinemia (−40%) and C-reactive protein (−63%) These 2 mediators have previously been described as being strongly related to aortic stiffness (13,14). The cholesterol profile was unchanged after weight loss, and thus cannot be a contributing factor. It is now well accepted that adipose tissue is a source of inflammatory mediators, which may stiffen the large arteries by a number of different mechanisms (15). A high level of C-reactive protein may simply act as a marker of vascular damage, but when associated with low aortic distensibility should reflect the residual interaction, which could be reduced or suppressed by a significant weight loss. Interestingly, aortic distensibility estimated by MR imaging should be now considered as a surrogate measure of arterial stiffness, and correlates with C-reactive protein and hyperleptinemia in apparently healthy obese subjects even in the absence of associated comorbidities. This work also showed that these likely interactions should be nonuniformly distributed over the different segments of the aorta.

Two final cardiac MR imaging tools, which have been recently described in the *Journal*, should also be very useful in future researches on obesity. The first concerns quantification of the accumulation of intramyocellular triglycerides in the heart by a novel spectroscopy technique (12). The second is a very exciting and novel method of quantifying myocardial T1 mapping after gadolinium injection to estimate interstitial myocardial fibrosis (16). Both techniques should be very valuable in the study of obesity, since recent animal studies have suggested that excess fatty acids help to destroy cardiac myocytes by increasing triglyceride content and the rate of apoptosis (17).

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