Fatty degeneration of the human heart was first reported by the French cardiologist Corvisart more 200 years ago in 1806, while the first distinction of epicardial/pericardial fat from intramyocardial fat was made by the German physician scientist Virchow in 1858. Interest in these observations and their cardiovascular consequences continue to grow as techniques for noninvasive assessment of pericardial and intramyocardial fat improve. The amount of fat stored in nonadipocyte tissue (liver and muscle) is usually minimal and tightly regulated; however, recent studies have reported cardiac steatosis in human metabolic diseases such as obesity, diabetes mellitus, and metabolic syndrome. Mahmod et al., in this issue of Circulation: Cardiovascular Imaging, compared 39 subjects with symptomatic (64%) and asymptomatic severe aortic stenosis (AS) to 20 healthy controls and found increased myocardial fat in patients with AS. Using 1H-magnetic resonance (MR) spectroscopy, the authors measured myocardial triglyceride content (MTC) and reported that patients with symptomatic AS had the highest level of MTC as compared with asymptomatic patients and healthy control subjects. MTC values correlated inversely with regional myocardial function using circumferential and longitudinal strain obtained by myocardial tagging methods, with a gradation between the control, asymptomatic AS, and symptomatic AS groups. The authors were able to show a modest correlation of MTC with myocyte lipid content on biopsy samples of a subgroup of patients who underwent surgery ($r = 0.66; P = 0.036$). Most importantly, the authors demonstrated near complete reversal of myocardial steatosis and circumferential (but not longitudinal) myocardial systolic dysfunction in the first year after aortic valve replacement (AVR) surgery. These findings were not significantly correlated to the patients' metabolic status and seem to be specific to the degree of hypertrophic state as they are dose dependent; increasing with symptomatic AS, and reversible when treated with AVR.

Substitution of interstitial tissue by fat in the left ventricle (LV), thus, the term lipomatous metaplasia (LM), is indeed common in pathological cardiac conditions beyond metabolic diseases. In a large pathology study, 68% of patients with ischemic heart disease, 37% with chronic valvulopathy, 26% with idiopathic dilated cardiomyopathy, 15% with Chagas disease, and 55% of those with aneurysmal walls had LM finding on pathological examination. Research in chronic animal models revealed similar findings, with fat deposition noted in rabbits with reperfused myocardial infarction followed longitudinally for the equivalent of 8 human years. The lipid accumulation in diseased hearts seems to result from a return to a fetal transcription program in cardiac myocytes in response to stress. This programmatic switch favors glucose metabolism in myocytes as opposed to free fatty acid metabolism under normal physiological conditions. This lipid accumulation process may be worsened with metabolic syndrome and lead to more significant myocardial dysfunction. Marfella et al. examined LV histological specimens in patients with severe AS undergoing AVR with and without metabolic syndrome, and only found vacuolated myocytes and very elevated triglycerol levels in patients with severe AS with metabolic syndrome compared with patients lacking metabolic syndrome. The degree of AS, LV mass, and LV dimensions were not significantly different in these 2 groups of patients, but of note, the patients with metabolic syndrome had reduced LV ejection fraction (EF).

With the advancement of imaging technologies, metabolic alterations of the myocardium are detectable noninvasively with several techniques. Intramyocardial fat was found by multidetector computed tomography (using Hounsfield units) in 68% of 53 patients who had myocardial infarction, mostly in the subendocardial layer and generally in infarcts $>3$ years old. Intramyocardial macroscopic fat is also present in 5% of subjects without known cardiac disease using multidetector computed tomography. Using specific MRI fat and water separation pulse sequences to detect fat, 12.9% of 124 patients with dilated cardiomyopathy were found to have fat...
deposition.\textsuperscript{13} Patients with LM had an increased indexed LV end-diastolic volume, a reduced LVEF, and a greater volume of late gadolinium enhancement as compared with the patients without LM.\textsuperscript{13} Lücke and colleagues\textsuperscript{14} used a simplified protocol that detected the fat chemical shift artifact on steady state free precession cine images (the main workhorse sequence of cardiac magnetic resonance), and detected the presence of LM in 11% of 315 patients with chronic ischemic heart disease. In extreme cases of metabolic syndrome, patients with generalized lipodystrophy had a dramatically increased MTC and left ventricular hypertrophy.\textsuperscript{15} Among the different techniques, MTC allows the best quantification of myocardial fat content but also requires the most specialized software and expertise.\textsuperscript{16,17}

Given its advantages, is \textsuperscript{1}H-magnetic resonance spectroscopy with MTC measurement ready for broader clinical use? Within the same laboratory, the myocardial triglyceride levels measured by \textsuperscript{1}H-magnetic resonance spectroscopy are highly reproducible over time.\textsuperscript{18} However, comparing the results from different laboratories can be difficult. Mahmood et al\textsuperscript{19} used a Siemens 3 T Trio MR system (Erlangen, Germany) and reported MTC values of 0.89±0.42% in symptomatic AS, 0.75±0.36% in asymptomatic AS, and 0.45±0.17% in controls. The generalized lipodystrophy study cited earlier used a 1.5 T Gyroscan Intera MR system (Philips Medical Systems, Best, The Netherlands) and reported MTC values of 0.89±0.42% in symptomatic AS, and 0.6±0.2% in control subjects and varied from 0.6±0.2% to 0.89±0.42% in the diseased subjects. These results demonstrate how normal subjects in one laboratory may correspond well with biopsy-proven fibrosis. However, no data are available from post-AVR patients to provide additional insights into this question.

In summary, fatty heart is common in metabolic diseases and is present in many other cardiac disorders. Noninvasive cardiac fat imaging, especially \textsuperscript{1}H-magnetic resonance spectroscopy techniques, provides for quantitative assessment of myocardial fat content and opens a wide path for important potential applications. For example, it is presently uncertain whether reversing metabolic dysregulation with a substrate use strategy or by genetic reprogramming would also reverse the myocardial fat-associated myocardial dysfunction. As with many topics in medicine, lessons from history often guide our way. The possession of constructive doubt, as Morgagni suggests, is emblematic of many of our research strategies. Characterizing and quantifying myocardial fat is the first step in recognizing what we do not know, and lays the groundwork for discovering its metabolic and functional importance.

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None.

References


Disclosures

None.

References


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