Myocardial fat content refers to the storage of triglyceride droplets within cardiomyocytes. In addition, the heart and arteries are surrounded by layers of adipose tissue, exerting vasocrine and paracrine control of the subtending tissues. The rapid development of the field of noninvasive imaging has made it possible to quantify ectopic fat masses and contents with an increasing degree of accuracy. Myocardial triglyceride stores are increased in obesity, impaired glucose tolerance, and type 2 diabetes. The role of intramyocardial triglyceride accumulation in the pathogenesis of left ventricular (LV) dysfunction remains unclear. Increased triglyceride content is associated with states of fatty acid overload to the heart, saturating the oxidative capacity. It may initially serve as a fatty acid sink to circumscribe the formation of toxic lipid species and subsequently foster cardiac damage. Epicardial and perivascular fat depots may exert a protective role by serving as an internal pool for triglycerides. It may also provide a fatty acid sink to limit cardiac lipid accumulation. When triglyceride content increases, it may also contribute to intramyocardial fat deposition. Epicardial and perivascular fat depots may also provide an alternative source of fatty acids for the heart. However, the extent to which these fat depots are utilized by the heart remains unclear. It is possible that the heart may utilize these fat depots to a greater extent in conditions of increased fatty acid supply, such as obesity and type 2 diabetes.

**DEFINITIONS**—Myocardial fat content refers to the storage of triglyceride droplets within cardiomyocytes, which can be measured in humans by use of proton magnetic resonance spectroscopy (1H-MRS) (1). In addition, the heart and vessels are surrounded by layers of adipose tissue, which is a complex organ composed of adipocytes, stromal cells, macrophages, and a neuronal network, all nourished by a rich microcirculation. The layers surrounding the heart include intra- and extrapericardial fat. Their thicknesses and volumes can be quantified by echocardiography and computed tomography or magnetic resonance imaging, respectively (2–4). Intra-pericardial fat is in direct contact with the surface of the myocardium and coronary vessels, with no separation by a physical fascia. Thus, the diffusion of secreted molecules and the migration of cells between these adjacent structures may occur. This adherent fat layer has been defined as epicardial (between myocardium and visceral pericardium), whereas the term pericardial fat has been variably used to identify fat between myocardium and pericardium, which may include adipose tissue in the space between visceral and parietal pericardium, or just external but attached to the parietal pericardium. Perivascular fat surrounds arteries and arterioles. The epicardial fat layer originates embryologically from mesothelial cells migrating from the septum transversum and hence obtains its vascular supply from the coronary arteries. The term extrapericardial (or intrathoracic or paracardial) defines thoracic adipose tissue external to the pericardial pericardium. It originates from primitive thoracic mesenchymal cells and thus derives its blood supply from noncoronary sources (5).

**FAT INSIDE THE HEART**—Studies with 1H-MRS show that the heart possesses an endogenous triglyceride depot of ≥1.0% organ mass in healthy lean individuals (1), which increases with age. In healthy subjects, short-term caloric restriction and starvation provoked a dose-dependent increase in myocardial triglyceride content and decrease in diastolic function (6). Instead, high-fat diets of short duration, resulting in greatly increased plasma lipid concentrations and a decline in diastolic function, had no influence on myocardial triglyceride content (6). These studies suggest that circulating free fatty acids (which are elevated in starvation) participate in the regulation of intramyocardial fat depots, and that the latter have rapid adaptive (i.e., buffering) capacities. In the physiologically aging male heart, myocardial triglyceride content increased in association with the age-related decline in diastolic function (7). Nonobese women with normal glucose tolerance have significantly less myocardial fat content, in inverse relationship with circulating adiponectin levels, compared with healthy men of similar age (8).

**Obesity, diabetes, and metabolic syndrome**

We and others have recently documented that cardiac steatosis is a hallmark of obesity and type 2 diabetes (1,8,9), representing a potentially remarkable endogenous source of cytosolic fatty acids. Myocardial triglyceride stores in these diseases are increased on average by two- to fourfold compared with those in control individuals (8). Cardiac adiposity is associated with greater LV mass and work, suppressed septal wall thickening, and impaired diastolic function. We observed a relationship with sex, which...
may play a part in lowering the risk of cardiovascular disease in nondiabetic women. Notably, chronic hyperglycemia can cancel these sex-related differences, which may to some extent explain the loss of a cardioprotective status in women developing diabetes (8).

**Metabolic intervention**

In patients with type 2 diabetes, the response to short-term caloric restriction, leading to an elevation in fatty acid levels, promoted an accumulation of myocardial triglycerides that was associated with a decline in LV diastolic function, as in healthy individuals. These effects were not observed when the rise in fatty acid levels was pharmacologically prevented, thus underscoring the causal role of an extramyocardial supply of fatty acids in modulating the cardiac lipid pool (10). Conversely, the prolongation of a very-low-calorie diet for 6–16 weeks reduced myocardial fat content in nondiabetic obese and in type 2 diabetic patients (11,12). This finding was accompanied by a decline in LV mass and work (12) and by an improvement in diastolic function (11). In one study (13), a study of 78 diabetic men assigned to pioglitazone or metformin or placebo for 24 weeks, neither drug changed cardiac triglyceride content, despite a decrease in
cardiac work by metformin and an improvement in LV diastolic function by pioglitazone.

**Does cardiac steatosis play a role in heart disease in humans?**

Though diastolic dysfunction and a fatty heart are usually concomitant findings in metabolic disorders, they may (11,13) or may not (6,14) be simultaneously induced or reversed by metabolic intervention, and their changes are not always correlated (6,14). In cross-sectional evaluations (9), multivariable analysis models documented that the individual contribution of myocardial fat content in explaining the observed diastolic dysfunction in type 2 diabetic patients was modest, and its correlations with the ratio of early (E) and late (atrial, A) ventricular filling velocity (E/A) and E peak deceleration was not consistently observed (15), suggesting that other unmeasured pathologic processes, coexisting in the hearts of patients with diabetes or obesity may be more directly responsible for the dysfunction.

It is important to underline that the level of circulating fatty acids has been one main correlate of human myocardial triglyceride content. The sequence of events following fatty acid overload to the heart is summarized in Fig. 1A, showing primary hyperactivation of β-oxidation, as seen in human obesity and diabetes, leading to excess formation of reactive oxygen species (ROS) (16), and resulting in modulation of sarco(endo)plasmic reticulum Ca2+-ATPase, which is an early contributor of diastolic dysfunction in the insulin-resistant myocardium (16) and of myocardial fibrosis and hypertrophy. In mouse lines overexpressing long-chain acyl-CoA synthetase in the heart (17), LV dysfunction occurs in parallel with an overstimulation of oxidation and ROS and ceramide formation, although cardiac steatosis and hypertrophy are concomitantly present.

The independent role of triglyceride accumulation in the pathogenesis of disease remains elusive because the transgenic overexpression of the triglyceride-synthesizing enzyme diacylglycerol acyltransferase 1 (DGAT1) in the heart results in a physiologic hypertrophy, serving a cytoprotective function, especially in lipid overload states (18). Accordingly, in cultured cells (19) exposed to an excess of palmitic acid, this fatty acid is poorly incorporated into triglycerides and causes apoptosis, and unsaturated fatty acids rescue palmitate-induced apoptosis by channeling palmitate into triglyceride pools. In the nonischemic failing compared with normal human heart, cardiac triglyceride content was either reduced (20) or unchanged in subjects without obesity or diabetes (21), and myocardial fatty acid oxidation was activated in obese and diabetic patients with cardiac steatosis.

Taken together, these studies make it reasonable to speculate that increased triglyceride content is a consequence of fatty acid overload to the heart, progressing more rapidly after saturation of the oxidative capacity. Under these circumstances, triglyceride accumulation may be seen as a maladaptive defense response, initially serving as a fatty acid sink to circumscribe the formation of toxic lipid
### Table 1—Studies on epicardial and perivascular fat versus CAD prediction or staging

| Ref. | Sampling technique(s) | Number of patients (specific features) | Evaluation of CAD | Relationship vs. epicardial or perivascular fat | Adjusted for risk factors and/or adiposity |
|------|-----------------------|----------------------------------------|-------------------|-----------------------------------------------|------------------------------------------|
| (2)  | Computerized tomography + invasive angiography | 251 | presence of CAD severity | YES | yes/yes |
| (40) | Echocardiography + invasive angiography | 139 | presence of CAD degree + no. stenoses | NO | n.a. |
| (42) | Echocardiography + invasive angiography | 203 | presence of CAD severity (Gensini score) | YES | yes/yes |
| (30) | Echocardiography | 527 | presence of CAD degree of stenosis unstable angina | YES | yes/yes |
| (45) | Computerized tomography | 190 | presence of CAD degree + no. stenoses coronary calcium score calcium × cut-off | YES | no/yes |
| (52) | Computerized tomography (healthy women) | 573 | coronary calcium score | YES | n.d./no |
| (49) | Computerized tomography (mixed ethnicity) | 159 | calcified plaques (+/) coronary calcium score | YES | yes/yes |
| (50) | Computerized tomography | 150 | prevalence of CAD calcium × cut-off | YES | n.d. |
| (47) | Computerized tomography | 128 *whole BMI range ^BMI <27 kg/m<sup>2</sup> | no. stenoses coronary calcium score NO*/YES^ | n.d. in the low BMI category |
| (39) | Computerized tomography | 2,726 (with arterial disease) | infrarenal aortic diameter | YES | yes/n.a. |
| (32) | Computerized tomography | 1,155 (clinical CVD excluded) | coronary calcium score aortic calcium score | YES | yes/yes |
| (43) | Computerized tomography | 264/286 (22 excluded) | presence of CAD no. plaques + no. segments atherosclerosis score plaque composition | YES | n.d./n.d. |
| (44) | Computerized tomography | 1,267 (9.7% with CVD) | prevalence of CVD prevalent CHD prevalent infarction prevalent stroke | YES | n.d./no |
| (48) | Computerized tomography | 1,119 (147 events) (mixed ethnicity) | incident CVD vs. EAT measured at postvisit | YES | yes/yes |
| (41) | Echocardiography + invasive angiography | 150 | presence of CAD no. single vs. multivessel Gensini score | YES | yes/n.d. |
| (22) | Echocardiography + carotid ultrasound | 459 (hypertensive patients) | carotid wall IMT carotid stiffness | YES | yes/no |
| (28) | Computerized tomography + invasive angiography | 71 | stenosis score atheromatosis score history of ACS total coronary occlusion | YES | yes/yes |
species, and eventually undergoing peroxidation and saturation, thereby fostering the build-up of fatty acid intermediates in the cytoplasm and functional damage to the heart. The available studies do not imply causality but suggest that accumulation of myocardial triglyceride may be at least an indirect marker of early cardiac dysfunction in selected stages of disease progression.

**FAT AROUND THE HEART AND VESSELS**—The heart, coronaries, and virtually all arteries are surrounded by a significant amount of adipose tissue. The thickness of epicardial fat at the level of the right ventricle free wall is normally <7 mm in healthy lean individuals (3,22). The distribution of fat thicknesses among different locations of the myocardium demonstrates a spread of values between 15 and 1 mm. Fat volumes around the heart correlate with advancing age (8,23), and they are larger in men than in women (8,23). Ethnicity is another potential confounder in epicardial fat studies, since this adipose depot is larger in Caucasians, followed by Asians, blacks, and Hispanics (23).

Fat around vessels and the heart may serve a supportive, mechanical purpose, attenuating vascular tension and torsion, participating in vessel remodeling, and being a vasocrine and paracrine source of cytokines, substrates, and adipokines (Fig. 1B). The rates of fatty acid incorporation and release are higher in the cardiac than in other adipose depots, and lipogenesis is stimulated by insulin only in this fat depot. Cardiac and perivascular adipose tissue may act as local energy supplier and/or as a buffer against toxic levels of free fatty acids in the myocardium and in the arterial circulation (24). The vasocrine action on nutritive tissue flow has been involved in modulating substrate fluxes to organs. Adiponectin and adipocyte-derived relaxing factors are released by perivascular fat to decrease contractile responses to vasoconstrictive agents, thus exerting a protective antihypertensive function via the control of endothelium-dependent (modulation of the nitric oxide-to-endothelin-1 ratio) and independent mechanisms (cell hyperpolarization, and production of ROS, hydrogen peroxide) (25,26). Moreover, resident macrophages can increase the release of the anti-inflammatory cytokine interleukin (IL)-10 (27).

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**Table 1—Continued**

| Ref. | Sampling technique(s) | Number of patients (specific features) | Evaluation of CAD | Relationship vs. epi- or pericardial or perivascular fat | Adjusted for risk factors and/or adiposity |
|------|-----------------------|----------------------------------------|------------------|---------------------------------------------|----------------------------------------|
| (55) | Echocardiography + invasive angiography | 68 (only women, chest pain, CVD excluded) | coronary flow reserve | YES | yes/n.d. |
| (51) | Computerized tomography | 1,067 (clinical CVD excluded) | coronary calcium score, thoracic aorta calcium, abdominal aorta calcium | YES | yes/yes, no/yes, yes/yes |
| (54) | Computerized + positron emission tomography | 161 successful of 292 (cancer patients) | FDG uptake in LAD vs. EAT vs. calcium score | YES | yes/yes |
| (37) | Computerized tomography + carotid ultrasound | 5,770 (mixed ethnicity) | carotid stiffness, IMT, coronary calcium score | YES | yes/yes |
| (38) | Computerized tomography + carotid ultrasound | 996 | IMT common carotid artery, internal carotid artery | YES | no, yes in men |
| (33) | Computerized tomography | 311 (coronary segments for plaques and fat volume) | presence of CAD, plaque burden | YES | yes/yes |
| (46) | Computerized tomography | 171 (suspected CAD) | presence of CAD, stenotic plaque (+/- calcif. vs. mix vs. noncalcif. plaque) | YES | no, NO |
| (23) | Computerized tomography | 214 (mixed ethnicity) | a) calcif. vs. no plaque, b) mixed vs. noncalcif., a) vs. b) calcium score, severity of stenoses | NO | YES/yes |

Studies include patients referred to imaging for known or suspected CAD, with few exceptions given in parentheses. The last column shows whether the relationships are maintained after adjustment for cardiovascular risk factors or (†) alternative indices of adiposity, namely BMI (in a majority of studies) or waist or amount of visceral fat. ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; calcif., calcification; EAT, epicardial adipose tissue; FDG, 18F-fluorodeoxyglucose; IMT, intima-media thickness; LAD, left anterior descending coronary artery; n.a., not applicable; n.d., indicates that the confounding variables have not been measured, or that they have been measured but not included in a multivariate regression model investigating the target relationship; noncalcif., noncalcified.
Cardiac and vascular adiposity

Obesity, diabetes, and metabolic syndrome
A positive relationship has been established between the amount of fat surrounding the heart and vessels and several components of the metabolic syndrome. Iacobellis and Willens (3) showed associations with insulin resistance, central adiposity, and clinical parameters of cardiovascular risk, including LDL cholesterol and blood pressure, together with inverse relationships with adiponectin levels. Epicardial and pericoronary fat volumes gradually increased with the number of metabolic syndrome components (4,28), and pericardial fat showed a progressive increment from lean to obese individuals with normal glucose tolerance, to those with impaired glucose tolerance, and those with type 2 diabetes (8). Conversely, in overweight children, epicardial fat was a good indicator of visceral fat, but not an independent predictor of the metabolic syndrome (29). Epicardial fat thickness was associated with C-reactive protein (30) and with proatherogenic and proinflammatory adipokines (3). However, the Framingham Offspring study, screening for 15 biomarkers of inflammation and oxidative stress, demonstrated that intrathoracic but not pericardial fat was independently associated with C-reactive protein and urinary isoprostanes, after adjustment for other adiposity indexes (31), and that visceral adipose tissue was a stronger correlate of most metabolic risk factors (32). Instead, other authors (33) reported that the thickness rather than the volume of epicardial fat was an independent predictor of metabolic syndrome and C-reactive protein levels, also when accounting for intrathoracic and visceral fat depots.

In brief, most studies show relationships between epicardial/perivascular adiposity and metabolic and inflammatory markers, though some suggest that these correlations may be at least partly mediated by the confounding association existing between extra- and intrapericardial and visceral abdominal fat volumes.

Metabolic intervention
A 6-month very-low-calorie diet program (3) decreased epicardial fat thickness relatively more than other fat depots, and the observed changes in LV mass and diastolic function were more strongly correlated with epicardial fat changes than with those of other adiposity indices. A 12-week exercise training program in obese men (34) resulted in a greater percent reduction in epicardial fat thickness than in waist and BMI, and the change was independently related with those in systolic blood pressure and insulin sensitivity. Conversely, a 24-week study comparing the effects of pioglitazone and metformin treatment in type 2 diabetic patients (35) showed an increase in pericardial fat volume in pioglitazone-treated patients, in spite of an improvement in diastolic function, leading the authors to question the notion of a causal relationship between pericardial fat volume and LV dysfunction.

The lack of a contextual measurement of intracardiac triglycerides, which are strongly correlated with epicardial fat volume, diastolic dysfunction, and cardiac mass in patients with diabetes or obesity, may limit the mechanistic interpretation of these findings.

Does adjacent adipose tissue have a role in cardiac mechanical dysfunction?
We documented that the entire mass (intra- and extrapericardial) of fat surrounding the heart ranges on average from 100 g (in healthy lean individuals) to 400 g (in type 2 diabetic patients), extending to values of 800–900 g in some patients (8). This magnitude may pose a noticeable mechanical burden on cardiac expansion. It was associated (though not independently) with cardiac remodelling and mass, peripheral vascular resistance, and lower ejection fraction and cardiac output. Pathology and in vivo imaging studies suggest that during the hypertrophic process, pericardial fat and cardiac mass increase in parallel. Results of the Framingham study (36) showed that the association was not independent of, or stronger than, that of other proxy measures of visceral adiposity. An important exception was left atrial dimension in men, extending the previous evidence of an association between epicardial fat thickness and atria enlargement or impairment in diastolic filling in morbidly obese subjects (3).

Overall, the above studies indicate that the systemic effects of obesity on cardiac structure and function may outweigh the local pathogenic effects of pericardial fat. Conversely, the latter may directly affect LV diastolic filling and consequently induce atrial enlargement.

Does adjacent adipose tissue have a role in cardiovascular disease?
Table 1 summarizes studies conducted to explore relationships between cardiac and perivascular fat and CAD. Vascular aging and subclinical atherosclerosis, as revealed by carotid stiffness and intima-media thickness, were related to epicardial fat thickness better than waist circumference in hypertensive patients (22). In the Multi-Ethnic Study of Atherosclerosis the association with carotid stiffness, but not intima-media thickness persisted after adjusting for cardiovascular risk factors (37,38). In the Second Manifestations of ARTerial Disease (SMART) study (39), intra-abdominal fat accumulation was associated with larger infrarenal aortic diameters in patients with clinically evident arterial disease.

Atherosclerotic lesions are absent in segments of coronary arteries lacking pericardial fat, such as intramyocardial bridges, as compared to intraepicardial portions of the main coronary artery in both humans and animals (5). A host of noninvasive imaging studies—with one exception (40)—have shown that patients with CAD have greater depots of adipose tissue within the pericardium and around arteries compared with healthy individuals. However, the existence of a progressive association relating the amount of pericardial fat with the severity of atherosclerosis, evaluated as number of stenotic vessels and/or degree of obstruction (23,41–43), total coronary occlusion (28), stable versus unstable angina (30), or prevalent myocardial infarction (44) was reported in some but not in other studies (40,45–47) or was found only in selected subgroups (47). A recent report (48) suggested that pericardial fat is a better predictor of incident CAD than are more general measures of adiposity, but cardiac adiposity was determined at follow-up and not at baseline.

The extent of vessel wall or plaque calcification has been used as an additional index of severity of disease. In subjects free from clinical CAD, pericardial fat was independently associated with vascular calcification (32,49,50), and the relationship was consistent between sexes and groups of different ethnicity (49). Thoracic aortic fat was associated with abdominal aortic and coronary artery calcification (51). In healthy postmenopausal women (52), pericoronary fat thickness was related to calcification in respective coronaries. Instead, in patients with CAD the relationship was not progressive (45), or was found...
only in subjects with normal BMI (47). As suggested, the presence of mere calcification could represent an advanced but stable phase of atherosclerosis, and pericardial fat may be more strongly associated with an active process as proven by the presence of noncalcified plaques. This association was observed in one retrospective (23), but not in three subsequent studies (43,46,53).

It is important to keep in mind that the number of coronary stenoses and size of plaque/obstruction may not be optimal predictors of cardiovascular events or the best guidance for management, and that the paracrine and vaso-crine nature of the interaction between fat and myocardium or arteries is most likely mediated by functional rather than anatomical outcomes, including active inflammation, vascular overtone, and tissue ischemia. The uptake of 18F-fluorodeoxyglucose in the left anterior descending coronary artery, measured with positron emission tomography as a marker of plaque inflammation and vulnerability, was correlated with CAD, calcified plaque burden, and pericardial fat volume (54). The assessment of coronary flow to identify ischemic regions in women complaining of chest pain (55) demonstrated that epicardial fat thickness was the only independent inverse predictor of coronary flow reserve, as opposed to traditional risk factors for atherosclerosis. Our findings extend this observation to patients of both sexes with and without CAD showing that only those with a severe impairment in coronary vasodilatation have a significant increase in intrapericardial fat.

Mechanisms

Epicardial and perivascular fat depots are important mechanical guides of contracting organs and vessels, and critical regulators of substrate fluxes to subtending organs because they store or release fatty acids with great flexibility to fulfill the energy needs of arterial walls and heart muscle and to avoid lipotoxicity. Their protective vasocrine function is likely mediated by adiponectin and unidentified relaxing factors. In metabolic and cardiovascular disease states, these fat tissues expand, becoming hypoxic and dysfunctional (25,56) and recruiting phagocytic cells (57). The changes in adipocyte size and increase in the infiltration of macrophages and T cells (57) reduce the production of protective in favor of detrimental adipocytokines such as leptin, resistin, IL-6, tumor necrosis factor-α, or IL-17. These molecules can reach the myocardial tissue and vessel walls by direct diffusion or by traveling in adventitial neovascularization, and it has been recently shown that epicardial adipose tissue can partially contribute to adiponectin levels in the coronary circulation (3). Thus, inflammation may propagate to the underlying arterial walls, and alter the balance between vascular nitric oxide, endothelin-1, and superoxide production, promoting vasconstriction (26). Samples of pericardial fat from CAD patients showed increased mRNA and protein levels of chemokine and inflammatory cytokines relative to subcutaneous fat (58), and lower expression of adiponectin relative to that in patients without CAD. Perivascular adipose tissue can stimulate smooth muscle cell proliferation via release of hydrosoluble protein growth factor(s) and contribute to the progression of atherosclerosis (59). Large and inflamed adipocytes display insulin resistance and greater release of fatty acids, likely overflowing toward the myocardium, thereby increasing cardiac work and oxygen consumption and supplementing cardiac steatosis. In fact, pericardial and myocardial adiposities are strongly correlated (8). In response to the reduced vascular density and hypoxia in obesity, macrophages may express platelet-derived growth factor in adipose tissue to facilitate capillary formation (56). This process and mediators may extend to the vessel wall of arteries adjacent to the adipose depot. Plaque neangiogenesis is associated closely with plaque progression and intra-plaque hemorrhage, and is predominantly thought to arise from the adventitia vasa vasa thoracis (60). This complex series of events is summarized in Fig. 1B.

CONCLUSIONS—Cardiac adi-posity was characterized in the 19th century, including the distinction between surface and intracellular fat, its association with obesity and coronary obstruction, and its dual protective or hazardous roles. Subsequently, cardiac damage was thought to be caused by inflammation; more recently this was supplanted by the idea that coronary obstruction is the central pathogenetic mechanism of cardiovascular disease. Current advancements in technology and knowledge indicate that adiposity, inflammation, and arterial obstruction are simultaneously operative in modulating tissue ischemia and plaque vulnerability. In this interaction, adipose tissue and intracellular triglycerides may shift from being protective to being detrimental, depending on their residual substrate buffering capacity and inflammatory status. The magnitude of adiposity appears as a relative index in these complex dynamics, but its determination alone may be insufficient to predict its functional impact on the vulnerability of adjacent tissues. The complementary use of molecularfunctional imaging to depict substrate oxidation, active inflammation, and organ perfusion can aid in this assessment.

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