A Review of the Roles and Limitations of Noninvasive Imaging Methods for Investigating Cardiovascular Disease in Individuals with Obesity

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Body weight has increased worldwide, characterizing a pandemic of overweight and obesity. Obesity is associated with several risk factors for cardiovascular disease. However, the association between increased body weight and cardiovascular disease is independent of the presence of classical cardiovascular disease risk factors. The direct effects of excessive fat tissue on the heart can cause a specific obesity-related cardiomyopathy in the absence of hypertension, coronary heart disease, and other structural heart diseases. Hemodynamic and structural changes contribute to obesity cardiomyopathy. The changes culminate in diastolic dysfunction, and eventually systolic dysfunction and heart failure. Several cellular cardiac changes have been described in obesity. Patients with obesity often present symptoms such as dyspnea, fatigue, lower limb edema, and chest pain. Noninvasive imaging techniques are important in assessing cardiovascular risk and evaluating symptoms. However, excess adiposity may be challenging for cardiac imaging interpretation and diagnostic accuracy. This review aims to discuss the current roles and limitations of noninvasive imaging diagnostic methods for investigating cardiovascular disease in individuals with obesity. The methods discussed include electrocardiography, echocardiography, 2-dimensional speckle tracking echocardiography, real-time 3-dimensional echocardiography, transesophageal echocardiography, computed tomography and coronary computed tomography angiography, cardiovascular magnetic resonance, stress tests ergometry, stress echocardiography, transesophageal echocardiography with pharmacological stress, stress computed tomography, stress cardiac magnetic resonance, single-photon emission computerized tomography myocardial perfusion imaging, and positron emission tomography. Although the appropriate choice of tests depends on the knowledge of methods and their limitations, patient management should be tailored according to clinical evaluation and technique availability.

Keywords: Cardiac Imaging Techniques • Electrocardiography • Exercise Test • Heart Diseases • Obesity

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Background

Obesity is characterized by fat accumulation caused by an imbalance between calorie ingestion and energetic expenditure [1]. Obesity is often classified according to body mass index (BMI) values, calculated as body weight (in kilograms) divided by height squared (in meters) [2]. Class I obesity is defined as a BMI from 30.0 to 34.9 kg/m², class II as a BMI from 35.0 to 39.9 kg/m², and class III as a BMI ≥40 kg/m², also called extreme obesity [3].

The combination of sedentarism and a high-energy dense diet results in an obesogenic environment, which leads to the epidemic of obesity observed in several countries [1]. In fact, obesity has become a major public health issue worldwide. Its prevalence has increased in developed and developing countries [3]. According to the World Health Organization, 1.9 billion adults were classified as overweight and 650 million individuals as obese in 2016 [4].

Patients with obesity have worse quality of life and life expectancy than individuals without obesity. Obesity is the most prevalent risk factor for cardiovascular disease. The association between increased body weight and cardiovascular disease is independent of the presence of classic cardiovascular disease risk factors, such as systemic arterial hypertension, dyslipidemia, diabetes mellitus, and obstructive sleep apnea [5].

Several studies have pointed to the occurrence of specific obesity-related cardiomyopathy, which is not related to arterial hypertension, coronary artery disease, or other structural heart diseases [3]. Several hemodynamic and structural changes contribute to the development of obesity cardiomyopathy [6,7]. Individuals with obesity usually have increased blood volume, stroke volume, cardiac output, and left ventricular (LV) wall stress, which decreases LV compliance, increases LV filling pressures, and induces LV dilation and hypertrophy [3,8]. The obesity-related LV phenotype can present as concentric remodeling and eccentric or concentric hypertrophy [9]. These changes culminate in diastolic dysfunction and eventually systolic dysfunction and heart failure [3,10,11]. The left atrium (LA) is commonly enlarged in obesity [3]. In fact, obesity, arterial hypertension, and aging are the major determinants for LA enlargement [12].

Obesity-associated cellular cardiac changes are characterized by myocyte hypertrophy and apoptosis, myocardial fibrosis and oxidative stress, autophagy/mitophagy abnormalities, endoplasmic reticulum stress, impaired coronary flow reserve, microvascular alterations, and endothelial dysfunction [3]. Furthermore, obesity-induced alterations in myocyte calcium homeostasis induce mitochondrial dysfunction and contractility impairment, and changed lipophagy is associated with myocardial lipid accumulation [3]. These cellular alterations have been observed often in several models of heart failure [13-17]. Systemic abnormalities, such as subclinical adipose tissue-induced inflammation, insulin resistance and hyperinsulinemia, and sympathetic nervous system and renin-angiotensin-aldosterone system activation, are involved in obesity-induced cardiac changes [3,18-22].

Obesity has been associated with cardiac arrhythmias and sudden death [23-25]. LV hypertrophy, subclinical systolic dysfunction, and diastolic dysfunction contribute to a high propensity to cardiac arrhythmia. LV hypertrophy increases the risk of ventricular ectopy and prolongation of QT and corrected QT (QTC) intervals, which is an independent predictor of cardiovascular mortality [23]. Autonomic nervous system dysfunction with increased sympathetic nervous system activity and reduced vagal tone plays a role in cardiac arrhythmia [23]. Sudden death is more frequent in patients with class III obesity than in the general population [24]. Factors other than cardiac structural derangements and prolonged repolarization are also involved in sudden death; these include mitochondrial dysfunction, oxidative stress, abnormal cardiac conduction, ion channel dysfunction, and intracellular sodium and calcium changes [25]. Pro-arrhythmic effects of dysregulated branched chain amino acid metabolism can also contribute to sudden death in obesity [25].

Noninvasive imaging techniques are important for evaluating symptoms in the general population. Furthermore, by detecting some alterations, such as myocardial hypertrophy and coronary calcification, imaging tests allow clinicians to determine risk factors for developing clinical cardiovascular disease. However, excess adiposity can be challenging to cardiac imaging interpretation and diagnostic accuracy in individuals with obesity [26-29]. This review aimed to discuss the current roles and limitations of noninvasive imaging methods for investigating cardiac disease in individuals with obesity. The methods discussed include electrocardiography, echocardiography, 2-dimensional speckle tracking echocardiography (2D-STE), real-time 3-dimensional echocardiography (RT3DE), transesophageal echocardiography (TEE), computed tomography (CT) and coronary CT angiography, cardiovascular magnetic resonance (MR), and the stress tests ergometry, stress echocardiography, TEE with pharmacological stress, stress CT, stress cardiac MR, single-photon emission computerized tomography (SPECT) myocardial perfusion, and positron emission tomography (PET).

Electrocardiography

Several abnormalities are often observed in individuals with obesity. Diaphragm elevation caused by increased abdominal...
adiposity can anatomically deviate the heart to a more horizontal position [30,31]. Leftward shift of P, QRS, and T axes, low QRS voltage, reduced T wave height, mainly in leads I, II, III, aVF, and aVL, and increased QT and QTC intervals are commonly found in individuals with obesity. Kurisu et al [31] observed that an increased BMI is associated with a leftward shift of QRS axis, and increased R wave in leads I and aVL, with a decrease in leads II, III, and aVF. In precordial leads V4 and V5, QRS height was paradoxically lower in individuals with obesity than in those with average body weight. The increase in epicardial and subcutaneous fat tissue works as electrical isolation, reducing electrical wave heights in peripheral and precordial leads. Therefore, the Sokolow-Lyon index (sum of S wave in V1 and R wave in V5 or V6 amplitudes greater than 35 mm) tends to be lower in individuals with obesity than in those with average weight [31]. Consequently, the electrocardiogram presents low sensitivity for diagnosing left and right ventricular hypertrophy in patients with obesity [32]. The Cornell criteria (sum of R wave in aVL and S wave in V3 amplitudes higher than 20 mm in women and 28 mm in men) has been considered more useful than the Sokolow-Lyon index for detecting LV hypertrophy in obesity.

Increased QTC interval and/or QT or QTc dispersion has been observed in individuals with obesity, which suggests a relationship between obesity and delayed ventricular repolarization [23,33]. By evaluating 50 individuals with a BMI ≥40 kg/m² and no other cardiovascular disease risk factor, Mukerji et al [33] observed that an increased QTC interval was associated with increased LV mass in echocardiogram and hemodynamic load condition. The study was important because it showed the influence of obesity alone in increasing hemodynamic load, LV mass, and QTC interval. Prolongation of the QT and QTC interval can be caused by increased sympathetic activity, which also reduces heart rate variability and increases the risk of cardiac arrhythmia [30].

Cross-sectional studies have shown a strong relationship between obesity and atrial fibrillation. Electroanatomic remodeling of the atria with LA dilation and fibrosis and low voltage areas and conduction velocity slowing are involved in the genesis of atrial fibrillation [34].

**Echocardiography**

The echocardiogram is a fundamental examination for evaluating cardiac structure and function. It is a widely available noninvasive and low-cost method that produces valuable information. However, obesity has a negative impact on image quality due to signal attenuation affecting the capacity of echocardiography in detecting LV thickness, function, and global and regional motion [26,35]. The use of ultrasound-enhancing agents, particularly in class III obesity, can improve LV and LA endocardial border definitions [36]. Additionally, cardiac chamber sizes should be evaluated with caution, as indexation of chamber sizes to body size can result in an erroneous diagnosis [35].

The American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend indexing LA size to body surface area (BSA), considering a threshold of 34 mL/m² as the reference value [27,37]. However, as BSA derives from body height and weight, indexing LA volume to BSA can underestimate an LA increase in individuals with obesity [12,27,38]. Stritzke et al [12] evaluated the association of obesity and hypertension with LA volume over 10 years in 1212 individuals. LA volume was indexed by body height, and LA enlargement was defined as LA/body height ≥35.7 and ≥33.7 mL/m in men and women, respectively. The prevalence of LA enlargement was lower when LA volume was indexed by BSA in individuals with obesity. As LA size is an important component in evaluating diastolic function, Singh et al [27] recommend that BSA can be used to initially index LA size. If LA size is increased, LV diastolic function should be assessed. When LA size indexed to BSA is normal in patients with obesity, then indexation to height should be applied, in accordance with the European Society of Cardiology hypertension guideline [39].

Indexation of LV mass is also a matter of concern. The American Society of Echocardiography and the European Association of Cardiovascular Imaging [27,37] recommend that, despite the advantages of indexing LV mass to height, indexing of LV mass to BSA should be used for detecting LV hypertrophy in all individuals. On the other hand, European Society of Cardiology guidelines for managing arterial hypertension recommend height-based indexing to diagnose LV hypertrophy (LV mass/height in m²/²) in individuals with overweight and obesity, with cutoff values of 47 g/m² for women and 50 g/m² for men [39].

Owing to the higher stroke volume or aortic flow rate, obesity can further increase pressure gradients in individuals with dynamic or fixed LV outflow obstruction, as observed in hypertrophic cardiomyopathy and aortic stenosis, respectively [35]. In the last 10 years, epicardial fat, located between the myocardium and the visceral layer of pericardium, has gained increased interest in the scientific community [35]. Epicardial fat, which is increased in obesity, presents most of the characteristics of other visceral depots, such as the release of hormones, cytokines, and chemokines, and local inflammation [40]. The thickness of epicardial fat is related to the occurrence and severity of coronary artery disease, atrial fibrillation, and cardiac remodeling [35]. Echocardiography can be used to measure epicardial fat thickness; however, total fat tissue volume can only be assessed by CT or MR imaging.
2-Dimensional Speckle Tracking Echocardiography

More recently, 2D-STE has been introduced in clinical practice to detect early cardiac wall-motion abnormalities and ejection fraction reduction, particularly in subclinical LV dysfunction [41]. Strain characterizes the alteration in length of a myocardial segment, and strain rate refers to the strain change per time unit [41]. 2D-STE uses computed algorithms to evaluate alterations in the mobility of acoustic speckle markers through the myocardial spatial orientations of longitudinal, circumferential, and radial planes. Then, strain and deformation variables are quantitatively calculated [41]. A high resolution is needed to measure strain rate [42]. The main contributor to longitudinal strain is the endocardium. Being located far from the epicardial coronary arteries, the endocardium is highly sensitive to ischemia and different insults; therefore, longitudinal strain is an early and robust indicator of LV dysfunction [41,42]. On the other hand, abnormalities in radial and circumferential strain occur later in myocardial injury and present low reproducibility [41].

Using global longitudinal strain, it was possible to show that adults with class III obesity present systolic dysfunction detected only by the strain technique [43]. On the other hand, the use of LA strain in overweight and obesity decreased the number of individuals with indeterminate diastolic function by reclassifying them as having normal diastolic function [44]. Therefore, additional studies are needed to better understand early markers of LA and LV function in obesity.

Real-Time 3-Dimensional Echocardiography

RT3DE ultrasound allows evaluation of heart spatial structure and the measurement of any cardiac chamber in real time. By using sophisticated software, the technique provides curves relating volume and time, which can be used to evaluate LV dyssynchrony [45]. RT3DE presents higher accuracy and reproducibility than 2-dimensional echocardiography for assessing LA and LV volumes and LV ejection fraction [46,47]. The use of RT3DE allowed early identification of increased LA volume and impaired LA function, which were considered early markers of subclinical heart dysfunction in individuals with obesity without clinical evidence of cardiovascular disease [47]. Furthermore, LA passive emptying was reduced in the obesity group, suggesting changed function of LA conduit [47].

Transeosophageal Echocardiography

TEE is a valuable technique due to its high imaging quality, mainly in individuals with class III obesity, who may have poor acoustic windows in transthoracic echocardiography [35]. Although it is usually safe, there are concerns about TEE applicability in individuals with obesity, particularly the risk of hypoxia and aspiration. TEE safety and efficacy were evaluated in 341 individuals with a BMI ≥27.5 kg/m² and 323 subjects with a BMI <27.5 kg/m² [48]. Despite a higher frequency (6.7%) of desaturation in a severely obese subgroup and 2 cases of major complications in the higher BMI group, no significant differences were observed in minor complications between individuals with high and low BMI. Therefore, TEE is currently considered safe in individuals with obesity.

CT and Coronary CT Angiography

Noncontrast CT has been employed to detect coronary artery calcification. CT scanning yields a reliable coronary calcium score at a low radiation dose and low cost to infer the presence of coronary artery disease [49,50]. Several authors have reported the high predictive power of the coronary calcium score for major adverse cardiac events [51,52].

Although calcium in coronary arteries is a component of atherosclerosis, not all coronary plaques contain calcium. Therefore, coronary CT angiography has been used to provide additional information, such as the type and risk of all plaques. It is considered the best technique to drive coronary artery disease prophylaxis with a strong negative predictive power [53-55].

In individuals with obesity, coronary CT angiography has been performed for coronary artery disease diagnosis and primary prophylaxis [55-57]. However, coronary image quality can be poor, and table weight limits can prevent its use in individuals with extreme obesity [53]. Despite new protocols and equipment to improve image quality and coronary artery visualization, the clinical relevance of intermediate degree stenosis, particularly when involving distal coronary arteries, is still a matter of concern.

Noncontrast CT is also useful in assessing epicardial and left atrial fat, which have been correlated with atrial fibrillation [23].

Cardiovascular MR

MR is a safe, radiation- and iodinated contrast medium–free technique for evaluating cardiac structure and function with good images and spatial resolution [28,58]. A disadvantage is its low availability. MR also allows assessment of fat tissue, myocardial fibrosis and edema, coronary artery patency, and myocardial ischemia and viability [59]. Currently, MR has been used to investigate coronary plaque characteristics and inflammation [60]. Although excessive body weight can reduce
image resolution, MR is probably the least obesity-compromised technique for evaluating the heart [59].

**Stress Tests**

Stress tests have been used to increase oxygen consumption and blood flow demand and induce coronary artery irregularities and impaired myocardial contractility in individuals with coronary artery obstruction.

**Ergometric Test**

Stress electrocardiogram can have several limitations in individuals with obesity, such as artefacts caused by the excessive adipose tissue, which can affect test sensitivity and specificity. Additionally, the inability to reach maximal or submaximal heart rate due to general deconditioning and low physical capacity can underestimate inducible ischemia [61]. Therefore, pharmacological stress tests associated with noninvasive cardiac imaging modalities have been used more frequently in clinical practice.

**Stress Echocardiography**

Pharmacological stress echocardiogram with dobutamine is a highly available radiation-free method with no body-weight limitation [29]. However, poor acoustic windows can reduce its usefulness in obesity. As previously discussed, the acoustic window can be improved by using contrast. The technique has mostly been used to identify myocardial ischemia by assessing ejection fraction and wall motion in different coronary territories during dobutamine infusion [29]. The images are usually acquired at basal condition and peak dobutamine infusion [35].

**TEE with Pharmacological Stress**

Stress TEE with dobutamine has been used to improve cardiac images in extreme obesity. The protocol is similar to that used in stress echocardiogram with dobutamine. The safety of stress TEE to assess myocardial ischemia has been reported in small studies [35].

**Stress CT**

Pharmacological stress has been used in combination with CT to improve visualization of obstructive coronary plaques. However, exposure to iodinated contrast and ionizing radiation can limit its use [62].

**Stress Cardiac MR**

Stress cardiac MR is an accurate method for detecting myocardial ischemia, with a positive test suggesting that patients are at a high risk of developing myocardial infarction. However, a normal stress MR result is related to low event probability [59,63]. Myocardial stress can be induced by vasodilators or drugs that increase myocardial oxygen consumption, such as dobutamine [64]. Vasodilators increase coronary flow in normal arteries with a small or no increase in stenosis arteries, therefore resulting in flow irregularities. The most commonly used vasodilators are dipyridamole, adenosine, and regadenoson [64]. The Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) trial showed that MR under adenosine-induced stress is accurate in detecting myocardial ischemia in individuals without obesity [65]. Stress cardiac MR was also effective in determining cardiac prognosis in individuals with obesity with suspected myocardial ischemia [66].

**SPECT Myocardial Perfusion Imaging**

SPECT myocardial perfusion imaging has often been used in individuals with obesity for evaluating coronary artery disease [67]. The technique is performed under stressor protocols (64). Obesity may reduce test specificity due to excess soft-tissue-induced attenuation of radioactivity and extracardiac activity, producing artifactual appearance of myocardial perfusion defects and poor signal-to-noise ratios for SPECT images [68,69]. Attenuation induced by excess adipose tissue can be corrected, and this issue has been addressed in previous studies [26]. However, it is not always simple to distinguish alterations caused by decreased myocardial perfusion from artefact of attenuation [26]. By using different positioning of the individuals, it was possible to decrease attenuation artifacts caused by elevated body weights [70]. One advantage of the method is that new SPECT equipment acquired a higher range for body weight of 246 kg [26]. The dose of radiation is also a matter of concern, as it is calculated considering the ideal body weight of an adult; dose adjustments are imprecise and limited by the higher dose allowed by the International Commission on Radiological Protection [26].

**Positron Emission Tomography**

PET is often performed under stressor protocols to evaluate myocardial viability. PET is highly feasible for the general population and presents some advantages in individuals with obesity [71]. These include a better spatial resolution and corrected attenuation, resulting in diagnostic accuracy with low false-positive results [64,72]. An advantage of the SPECT technique is a higher sensitivity to the tracers used in myocardial perfusion scintigraphy, giving it a particular advantage in the obese population [64,71]. PET using rubidium-82 has been considered the best noninvasive method for diagnostic evaluation of obese individuals with suspected coronary artery disease [64,72]. In a multicentric trial with 7061 patients, Chow et al showed that pharmacologic rubidium-82 PET had a prognostic
value independent of BMI with better accuracy than SPECT in the obese population [72].

Conclusions

Individuals with obesity are at increased risk of developing coronary artery disease and myocardial dysfunction. Traditional cardiovascular image assessment is limited by excess adipose tissue. To properly choose diagnostic methods, it is important to know the advantages and limitations of each method. Despite all the available cardiovascular image techniques, patient management must be tailored according to clinical evaluation and methods availability.

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