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# Assessment of cardiovascular impairment in obese patients: Limitations and troubleshooting of available imaging tools

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ABSTRACT

The prevalence and severity of obesity have increased over recent decades, reaching worldwide epidemics. Obesity is associated to coronary artery disease and other risk factors, including hypertension, heart failure and atrial fibrillation, which are all increased in the setting of obesity. Several noninvasive cardiac imaging modalities, such as echocardiography, cardiac computed tomography, magnetic resonance and cardiac gated single-photon emission computed tomography, are available in assessing coronary artery disease and myocardial dysfunction. Yet, in patients with excess adiposity the diagnostic accuracy of these techniques may be limited due to some issues. In this review, we analyze challenges and possibilities to find the optimal cardiac imaging approach to obese population.



## Evaluación de la insuficiencia cardiovascular en pacientes obesos: limitaciones y resolución de problemas de las técnicas de imagen disponibles

*Palabras clave:*
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RESUMEN

La prevalencia y la severidad de la obesidad se han incrementado en las últimas décadas, alcanzando el grado de epidemia a nivel mundial. La obesidad se asocia a enfermedades arteriales coronarias y otros factores de riesgo, incluyendo hipertensión, insuficiencia cardiaca y fibrilación auricular, que se incrementan en los casos de obesidad. Se dispone de diversas técnicas de imagen cardiaca no invasivas, tales como ecocardiografía, tomografía computarizada cardiaca, resonancia magnética y tomografía computarizada de emisión de fotón único cardiaca, para evaluar las enfermedades arteriales coronarias y la disfunción miocárdica. Sin embargo, en pacientes con exceso de adiposidad, la precisión diagnóstica de estas técnicas puede verse limitada debido a diversas cuestiones. En esta revisión analizamos las dificultades y las posibilidades de encontrar la técnica de imagen óptima en la población obesa.



## Obesity and cardiovascular risk

World Health Organization has declared the global obesity epidemic a worldwide public health crisis. Excess adiposity is associated with several comorbidities such as type 2 diabetes mellitus, coronary artery disease (CAD), heart failure, atrial fibrillation, respiratory complications, malignancies, osteoarthritis and spinal degeneration.[1] Obesity is not only a risk factor for cardiovascular disease independently on age, dyslipidemia, smoking, diabetes and hypertension[2] but it also contributes in developing traditional cardiovascular risk factors.[3] Obesity can be measured by several methods, including body mass index (BMI), waist circumference and waist-to-hip ratio. Body weight indexed to height to measure the BMI is a commonly used index of overweight and obesity. An adult is considered of normal weight when the BMI is 18.5 to 24 kg/m$^2$, overweight when the BMI is 25.0 to 29.9 kg/m$^2$, and obese when the BMI is $\geq$30.0 kg/m$^2$. Men and women with waist circumference values $\leq$102 cm and $\leq$88 cm, respectively, are considered normal, whereas men and women with waist circumference values >102 and >88 cm, respectively, are considered pathological.[4]

Fat is involved in insulin resistance, up regulation of sympathetic nervous system and down regulation of β-adrenergic receptors, producing and releasing several biomolecules.[5] Endocrine activity of adipose tissue leads to elevated adipokine levels, higher oxidative stress and disorders of haemostatic and fibrinolytic systems involved in endothelial dysfunction and atherosclerosis.[6] Fat distribution plays a key role in developing CAD: patients with visceral obesity have been found to have higher levels of proinflammatory adipokines including tumor necrosis factor alpha, interleukin 6, monocyte chemoattractant protein-1, resistin,

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leptin and C-reactive protein.[7] Epicardial adipose tissue (EAT) is the visceral fat depot of the heart and represents a source of bioactive molecules. Because of its proximity to the myocardium and absence of fascial boundaries, EAT directly influences myocardial homeostasis through vasocrine and paracrine mechanisms. Indeed, abnormalities of EAT secretory properties are implicated in the development of pathological conditions, including coronary atherosclerosis, left ventricular (LV) hypertrophy, LV diastolic dysfunction and aortic stenosis.

Not only the severity of obesity and fat distribution show a crucial role in cardiovascular impairment but also its onset. A longer duration of overall and abdominal obesity beginning in young adulthood is associated with increased coronary calcium artery score (CAC) and its 10-year progression through middle age independent on the degree of adiposity. This information may help understanding the consequences of a greater prevalence and cumulative exposure to excess adiposity over the life course as a result of the obesity epidemic suggesting that preventing or at least delaying the onset of obesity in young adulthood may substantially reduce the risk of coronary atherosclerosis and limit its progression later in life.[8] Several patterns play a key role. Among these, gender and substrate metabolism are crucial. In particular, imaging of young woman with excess adiposity by using $^{11}$C-acetate and $^{11}$C-palmitate, has showed that an increase in BMI is associated with a shift in myocardial substrate metabolism toward greater fatty acids use. In contrast with women, men show a greater insulin resistance pathway suggesting interplay between gender and obesity.[9]

Body weight is also directly related to the development of heart failure (HF). The mechanism responsible for this association is still under investigation. Increased volume overload induces dilatation of the left ventricle leading to diastolic dysfunction. Increased volume after load causes LV eccentric hypertrophy leading to systolic dysfunction while increased volume overload induces LV dilatation leading to diastolic dysfunction.[1] Excess adiposity also has a direct effect on the myocardium triggering cardiac adaptation and remodeling. This latter mechanism is still poorly explained. Unexpectedly, it has been observed that obesity is associated with improved survival once the diagnosis of HF is established.[10]

It has been recently demonstrated that individuals who were overweight or obese before HF development have lower mortality once they have HF compared with normal BMI individuals. Therefore, weight loss due to advanced HF may not completely explain the protective effect of higher BMI in HF patients[11] Indeed, the most recent HF guidelines by the American College of Cardiology/American Heart Association do not specifically recommend weight reduction in obese patients with HF.[12] The obesity paradox has been also observed in CAD.[13] Data from large acute coronary syndrome trials such as the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY)[14] have shown an independent inverse correlation between BMI and overall mortality. Several mechanisms could explain this paradox in patients with cardiovascular disease. However, the underlying pathophysiology of the obesity paradox has not been completely clarified. In the first place, obese subjects are considered to be at high risk for cardiovascular disease, and they may be screened and treated earlier in the time course of disease, modifying the natural history of their status compared with normal weight patients (lead time bias).[15] The increased cardiac output and myocardial demands, in combination with the higher prevalence of endothelial dysfunction, may cause overweight and obese patients to be diagnosed with HF at an earlier stage of the disease than patients in lower BMI categories.[16] High cardiac output and expanded blood volume also trigger hypertension in obese patients, even in presence of lower systemic vascular resistance, compared with normal weight patients. In the overall population, higher systemic resistance leads to worst outcome of hypertensive cardiovascular disease. Therefore the comparatively low values in obese may translate into a better outcome in this population.[16]

BMI itself has been disputed as the optimal measurement to use for assessing health risk associated with obesity. Other measures, such as waist-to-hip ratio and visceral fat measurement, described above, may better identify patients with higher cardiovascular risk among overweight individuals. Indeed, it has been shown that BMI is a poor discriminator of cardiovascular heart disease risk in women compared with men despite a worse metabolic profile in those with increased BMI.[17] Nevertheless, diagnosis and risk stratification of cardiovascular impairment in obese population are crucial to identify those subjects who might benefit from straight therapeutic strategies.

## Cardiac imaging tools

A number of noninvasive cardiac imaging modalities are available to assessing CAD and myocardial dysfunction in the overall population.[18] Stress echocardiography is a powerful method used for the diagnosis and risk stratification of patients with suspected or established CAD, for evaluating HF and determining the extent of hibernating myocardium. Cardiac gated single-photon emission computed tomography (SPECT) boasts great value for combined evaluation of LV function and geometry, myocardial perfusion and viability.[19] Cardiac imaging whit $^{123}$I-meta-iodobenzylguanidine (MIBG) allows the assessment of myocardial sympathetic innervation.[20] Cardiac positron emission tomography (PET) imaging with novel flow tracers looks to be a potential alternative to SPECT in selected populations, such as obese subjects, due to its higher spatial resolution, accurate attenuation correction, quantitative capabilities allowing myocardial blood flow and coronary flow reserve measurements with high accuracy.[21] The assessment of coronary circulatory function with PET demonstrated that increased body weight is independently associated with abnormal coronary circulatory function suggesting that mediators directly released from the adipose tissue may be involved in the regulation of coronary vasomotor function and thus in the initiation and development of CAD.[22] Computed tomography (CT), CT coronary angiography and magnetic resonance (MR) imaging evaluate myocardial impairment mainly at morphological level.[18] Cardiac CT has the ability to provide calcium burden information with high negative predictive value and CAC scoring is useful to identify subclinical atherosclerosis.[23] Measurement of CAC is also reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk, while CT coronary angiography has great spatial resolution in depiction of coronary artery stenosis. Interestingly, obesity is associated with the progression of CAC among individuals considered to be at lower risk for CAD suggesting that interventions aimed at the primary prevention of obesity may help to retard the development and progression of CAC.[24] Cardiac MR, with fast sequences protocols, steady-state free-precession method for cine imaging and coronary angiography, represents a unique modality capable to define cardiac function and anatomy, myocardial perfusion and myocardial scar. Shah et al.[25] first reported on the feasibility and usefulness of vasodilator stress cardiac MR perfusion imaging for the prognostic assessment of obese subjects, and found a strong association of inducible ischemia with major adverse cardiac events, whereas patients with neither ischemia nor late gadolinium enhancement had a very low annual rate (0.6%) of events. However, all cardiac imaging techniques have some limitations in special patient categories, such as obese subjects.