CARDIAC IMAGING

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1. INTRODUCTION

Cardiovascular diseases (CVDs), the group of disorders of the heart and blood vessels, are one of the main causes of death. According to the World Health Organization, (WHO) almost 30% of deaths in the entire world are because of CVDs (29.3% in 2002) (1). In the United States, as reported by the American Heart Association, cardiovascular diseases are the leading cause of mortality, having accounted for 38.0% of all deaths in 2002 (2). In that year, Coronary Heart Disease, which includes acute myocardial infarction, other acute ischemic (coronary) heart disease, angina pectoris, atherosclerotic cardiovascular disease, and all other forms of heart disease, caused one of every five deaths, being the single largest killer of males and females in the United States. It is also important to consider that, very often, people who die of a coronary attack have no previous symptoms. Therefore, a need exists for accurate diagnosis of cardiac diseases, together with an early screening for cardiac pathologies, both as minimally invasive as possible. Cardiac imaging provides tools for this CVD diagnosis and screening, emphasizing early diagnosis and patient follow-up.

Cardiac imaging constitutes a significant technological challenge because the heart has an intricate 3-D shape, and a fast and complex periodic movement. Several noninvasive imaging techniques exist that provide qualitative and quantitative information about the state of the heart and great vessels. Continuous improvement in the spatial and temporal resolution of these imaging techniques, as well as their increasing potential to visualize not only anatomy, but also function and metabolism, make cardiac imaging a powerful tool for clinical diagnosis. This tool also allows the assessment of different disease stages, which is essential in therapy evaluation and the follow-up of cardiac diseases.

One of the most important technological challenges for cardiac imaging is that the heart is the fastest moving organ in the human body, requiring an acquisition frame rate of at least 10 images per second (and for some applications much higher). Detection of subtle changes for early diagnosis of diseases poses additional acquisition requirements and frequently several imaging modalities have to be considered.

As an example, the steps in the progression of coronary heart disease (CHD), one of the most prevalent and serious cardiac diseases, can be followed:

- First, a **partial obstruction of a cardiac artery occurs**. Sometimes it can be compensated for by collateral flow, so that at rest the flow is normal, whereas during stress, lack of irrigation appears (a low myocardial flow reserve exists).
- Regional lack of **perfusion** is the next step in the progression. A lack of sufficient oxygen supply produces an increase in anaerobic metabolism. Consequently, the myocardium can either reduce its activity to decrease its nutrient consumption (hibernating myocardium), or try to maintain the function, but this risks partial necrosis.
- Regional **movement abnormalities** are produced when some parts of the myocardium are either in hibernation or necrotic. These abnormalities first appear in diastole, and also in systole when they are more severe.
- **Global abnormalities** constitute the next step. As the disease progresses, the abnormalities are not only regional, they also affect the global activity of the heart. A reduction in its pumping capacity occurs (ejection fraction, cardiac output), and the infarcted myocardial regions produce detectable abnormalities on an electrocardiogram (ECG).

As can be seen, when the disease progresses, it is more easily detected, as more effects and more evidence exist. Cardiac imaging tries to achieve an early detection of the disease, as soon as the first signs appear. The focus of cardiac imaging is therefore the identification of subtle and local changes in perfusion or metabolism, or slight changes in regional movement. The diagnosis of CHD should proceed by following the disease chain:

- Functional abnormalities: changes in ECG (at rest or during stress tests), decrease of ejection fraction [measured by 2-D echocardiography, more recently by more accurate 3-D echocardiography and magnetic resonance imaging (MRI)].
- Movement abnormalities: visualized by echocardiography, and more recently and also more accurately with tissue Doppler imaging, MRI including tagged-magnetic resonance imaging (tagged-MRI) and strain measurements.
- Perfusion abnormalities: traditionally detected using nuclear medicine—single photon emission computed tomography (SPECT)—more recently with MRI or even ultrasound (US), in both cases with contrast agents.
- Arterial obstruction: detected using angiography and catheters, including intravascular ultrasound (IVUS) and, more recently, with fast computed tomography (CT).

As outlined in this example, many different observations and imaging modalities intervene in the accurate diagnosis of cardiac diseases. In this article, the main cardiac function descriptors will first be overviewed and, second, the main cardiac imaging modalities will be described, with special emphasis on applications and examples.

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2. DESCRIPTORS OF CARDIAC FUNCTION

The heart is a complex organ composed of different tissues and structures (3). Its function is to pump the blood to the rest of the body and the pulmonary circulation. Therefore, the most important functional parts in the heart are the cardiac muscle or myocardium, the atrio-ventricular and arterial valves, and the coronary arteries that provide proper nutrients to the heart muscle. The following subsections will describe the main parameters that regulate both the morphology and function of the myocardium, and the cardiac valves and coronary arteries. These descriptors are also the most relevant clinical parameters. It should be noted that, in order to obtain some of these parameters, image analysis or postprocessing techniques may be required (see Refs. 4–6 for a review).

2.1. Myocardial Function and Morphology

The myocardium is responsible for the correct pump function of the heart. Different cardiac diseases alter its morphology and function.

2.1.1. Myocardial Morphology. Some cardiac diseases modify the myocardial morphology, leading to increased thickness of the myocardium or enlarged ventricular volume. The most common indexes to assess these changes are the following:

- *Left Ventricle* (*LV*) *volume* is defined as the enclosed volume within the endocardium of the LV. It is a basic parameter to derive other left ventricular indexes. It is usually measured either at end-diastole or end-systole.
- *LV mass* is defined as the myocardial mass of the LV and is calculated as the difference between the volumes enclosed by the ventricle epicardial and endocardial surfaces, multiplied by the relative density of cardiac muscle.
- *Right Ventricle* (*RV*) *volume and mass* are defined by similar parameters.

These parameters can be obtained with most imaging modalities, although with different accuracy. In general, 2-D modalities (echocardiography, angiography) have to assume a simplified geometry (an ellipsoid) of the left ventricle, whereas more accurate measures can be obtained with tomographic modalities (MRI, CT). The complex geometry of the right ventricle always requires tomographic techniques.

2.1.2. Myocardial Global Function (2-D/3-D). Myocardial global function refers to the capacity of the heart to perform correctly as a blood pump. Late stages of cardiac diseases are frequently characterized by an important degradation of the cardiac global function. The main clinical indexes of global function are:

- *Stroke volume* (SV): the volume of blood ejected by a ventricle per heartbeat. It is calculated as the difference between end-diastolic and end-systolic volumes. In normal conditions, the stroke volumes of both ventricles are nearly equal.
- *Ejection fraction* (EF): the ratio of the ventricular stroke volume to the end- diastolic volume. It is an excellent predictor for assessing the alteration of global ventricular function. Typical values of ejection fraction at rest are 55% to 65%.
- *Cardiac output* (CO): total volume of blood pumped by the left ventricle in liters per minute. It is computed as the SV multiplied by the heart rate. Typical normal value in adults is 5 L/min.

2.1.3. Myocardial Regional Function. Assessment of the function of different myocardial regions or segments is very important in evaluating the severity of several cardiac diseases at an early stage. Subtle local motion or perfusion abnormalities may indicate, for example, the presence of ischemia because of coronary occlusion. Enhanced regional function assessment is one of the main areas of focus in new cardiac imaging modalities and postprocessing tools. Myocardial segmental function can be analyzed by examining motion and perfusion patterns, and it is an important key in determining myocardial viability after ischemia.

2.1.3.1. Motion and Deformation. Myocardial segmental motion and contraction is an important indication of proper segmental function. Commonly, myocardial movement is assessed visually using different imaging modalities (mainly ultrasound and MRI). Objective evaluation is also pursued by quantifying motion and contraction, and normally uses postprocessing techniques (such as optic flow, wall-tracking, landmark-tracking).

- *Motion analysis:* Regional motion can be assessed either visually or by quantifying parameters such as regional mean velocity and regional mean displacement. Intramyocardial motion can also be studied, dividing the myocardium into different layers.
- *Wall thickening:* The most common parameter used to assess radial contraction is wall thickening. Wall thickening is the difference between end-diastole and end-systole myocardial width.
- *Strain analysis:* Strain is a parameter defined in continuum mechanics that represents the deformation of an object with respect to its original shape. In the case of the myocardium, it indicates the active contraction of each region, allowing its differentiation from passive movement caused by the contraction of neighboring regions. Depending on the measurement technique and the imaging modality used, the deformation is studied in only one dimension, or by using a strain sensor in two or three dimensions.

2.1.3.2. Perfusion. Regional myocardial perfusion represents tissue irrigation by blood flow. It is a good indicator of the capacity of coronary arteries to respond to myocardial work and oxygen demand. The regional study of myocardial perfusion helps to determine if re-

duced blood flow exists because of partial or total coronary occlusion, and how the myocardial tissue responds to the decrease of flow.

It is important to study perfusion, not only under normal conditions, but also during stress, because in abnormal conditions the coronary vessels can be capable of providing blood at rest (possibly through collateral vessels), but are not able to respond to increased demands for oxygen. Stress can be produced by exercise, but is usually induced with a coronary vasodilator such as dipyridamole or adenosine.

Different imaging modalities allow the acquisition of quantitative measurements of segmental myocardial perfusion (mainly nuclear imaging, but also echocardiography or MRI with contrast agents).

2.1.3.3. Viability. After an ischemic event, it is very important to determine whether (and where) the cellular tissue is viable and could recover, or is infarcted. Regional viability is commonly assessed by observing the segmental perfusion, and metabolism together with its motion and contraction. Viability assessment determines whether myocardial reperfusion therapy or revascularization surgery is indicated. Different reversible and irreversible situations may occur.

- *Viable tissue:* Hibernating myocardial regions (segments with low contraction and perfusion) are metabolically active and can benefit from coronary revascularization, whereas stunned myocardium (low contractility and normal perfusion) do not always need reperfusion and usually recover by themselves.
- *Nonviable tissue:* Scarred myocardium shows contractility and perfusion defects even at rest and cannot recover.

Myocardial viability is an important topic in cardiac imaging and several techniques [mainly nuclear imaging, but also echocardiography and MRI (7)] have been proposed recently for its evaluation.

2.2. Valvular Function

The function of cardiac valves, both atrioventricular valves and outflow tract valves (pulmonary and aortic), is to lead the blood flow in one direction and avoid retrograde flow. Valvular dysfunction may induce severe changes in global cardiac function. The most common valvular problems are stenosis and regurgitation.

- *Valvular stenosis* is the narrowing of a valve, usually caused by limitation of the valve cusp motion. It produces an increased pressure gradient and flow rate across the valve. These two parameters can be measured to assess the severity of the stenosis, indicating whether valve replacement is appropriate.
- *Valvular regurgitation or insufficiency* results from the valve leaflets not completely sealing when the valve is closed, so that regurgitation of blood occurs (retrograde flow). Retrograde flow velocity is normally measured to assess the severity of the regurgitation.

Valvular function can be noninvasively assessed with imaging techniques based on ultrasound or MRI that can measure blood velocity or flow.

2.3. Coronary Arteries Assessment

Coronary artery disease has its origin in the atherosclerosis of one or several coronary arteries. Atherosclerotic processes narrow the arterial lumen, thereby restricting blood supply. Accurate assessment of the physiological severity of coronary stenoses is very important in determining whether a pharmacological or a mechanical treatment is indicated. It can be verified measuring the coronary flow reserve and assessing the state of the plaque.

- *Coronary flow reserve* is defined as the ratio of maximal to resting coronary blood flow. Maximal coronary flow is normally induced by exercise or with a coronary vasodilator such as dipyridamole or adenosine. Coronary flow reserve is normally greater than 3.0. It can be evaluated with nuclear imaging positron emission tomography (PET) and MRI.
- *Plaque assessment* is important because the presence of plaques in the arteries produces narrowing of the vessels and, most importantly, the danger of their sudden rupture, which would release their lipid content potentially creating a thrombus (artery obstruction). It is estimated that nearly 70% of unexpected heart attacks are related to plaque rupture. Evaluating the risk of a plaque rupture is still a challenge for cardiac imaging attempting to characterize its thin fibrous cap. The artery lumen can be studied by angiography, but the plaque cap is thinner than 100 μm, which places it beyond current noninvasive imaging resolution. However, invasive intravascular ultrasound (IVUS) can be applied. Research into CT and MRI for this purpose seems promising.

3. CARDIAC IMAGING MODALITIES

In the past decades, medical imaging has rapidly evolved and its application to the assessment of heart physiology and pathology has been enormous. Each medical image modality is based on different physical properties that can be related to specific anatomical or functional features of the heart The following sections provide a brief overview of the different cardiac imaging modalities, placing a special emphasis on how cardiac function descriptors are assessed by taking into account the accuracy and limitations of each modality.

3.1. X-ray Angiography

Static chest x-ray films do not provide detailed anatomical or functional information about the heart, as the difference in the x-ray absorption between the blood and the heart walls is small. x-ray imaging alone does not show

the structures of the heart or the anatomy of the coronary artery tree that supplies blood to the heart muscle. Additional problems are the presence of ribs that create additional contrasts on the image, plus the fact that chest x-ray is only a projective image. For these reasons, only gross information about the great vessels and the size of cardiac chambers can be obtained.

The x-ray absorption difference between blood and surrounding tissue can be increased by injecting contrast agents. In **Cine angiography,** proposed initially in 1966, a radio-opaque dye is injected via a catheter[1] directly into the structures to be visualized, while the patient is exposed to x-rays. As the dye fills the heart chambers or the vessels, delineation of heart and vessel anatomy can be obtained, as well as moving images of the ventricular contraction.

The information obtained is 2-D, although usually two projections at different angles are acquired to get a representation of the whole heart anatomy and to resolve potential vessel overlaps. Simplified assumptions (such as the ellipsoidal shape of the left ventricle) make it possible to compute volumetric information and derive parameters such as the ejection fraction.

This modality is usually good at anatomic delineation of lesions (Fig. 1), but much less satisfactory in determining their severity and the degree of hemodynamic disturbance that they have produced. It has been considered the gold standard for coronary artery assessment to depict luminal changes secondary to atherosclerotic disease. However, catheterization is costly, requires patient hospitalization, and has a risk of complications. For these reasons, and considering that up to 70% of vessels with critical (60% to 90% diameter reduction) stenoses are underestimated angiographically, alternative noninvasive imaging techniques are preferred.

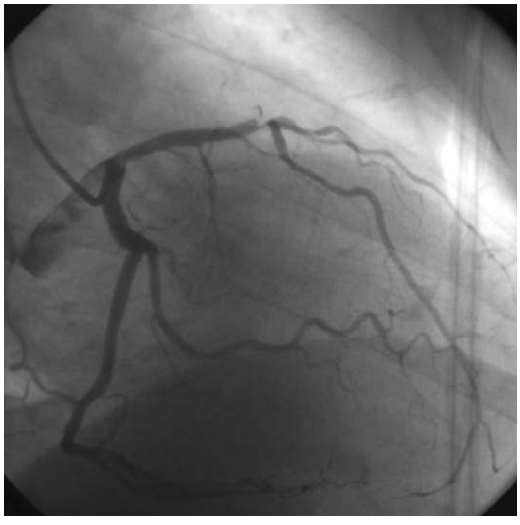

Figure 1. Left coronary x-ray angiography, showing a severe lesion in the left anterior descending coronary artery.

3.2. Echocardiography

Echocardiography, or ultrasound imaging of the heart, shows the anatomy and movement of cardiac and intracardiac structures in a completely noninvasive way. Ultrasound was used in medicine soon after the development of sonar principles around the 1940s. In 1953, Edler and Hertz produced the first moving images of the beating heart. Echocardiography, being portable, widely available, noninvasive, and requiring relatively inexpensive equipment, soon became an important tool in cardiac diagnosis. Now, it is a modality well established in clinical practice, showing cardiac anatomy and function in real time, both in rest and under stress.

Two echocardiographic acquisition modes are widely available: M-mode and 2-D B-mode. M-mode (motion mode) is a useful acquisition technique to explore moving objects providing a convenient representation of localized motion. This acquisition mode explores continuously the object along a single fixed scan line. The acquired data is displayed as a 2-D image, with depth in the vertical axis and time in the horizontal one (Fig. 2). Its main advantage is that the temporal resolution is very high in comparison with 2-D echocardiographic sequences; however, it only provides information about the region explored by the scan line. Even with this restriction, the method is widely used in practice to assess valvular and myocardial function. It is often employed in combination with Doppler techniques, providing a very good representation to extract quantitative measurements in time.

2.0 B-Mode imaging displays an anatomical section of the heart by sweeping the object along a series of angles (Fig. 2). This acquisition can be continuously repeated to obtain an image sequence, showing movement in real time. Myocardial and valvular function can be therefore assessed simultaneously, taking into account the different myocardial segments, valvular leaflets, and Doppler measurements.

In the last decade, important technological achievements have improved the quality of conventional echocardiographic images. Harmonic imaging constitutes one of these developments. It is based on nonlinear ultrasound-tissue interaction. As a result, the fundamental frequency of the transmitted ultrasound is resolved in multiple frequency components. Nonlinear effects occur, especially at the boundary between different tissues, and they are mainly represented at the second harmonic of the fundamental frequency. Selecting these frequencies in the received signal clearly improves image quality and contrast resolution of tissues.

Complementary techniques have multiplied the possibilities of echocardiography. In the following sections, the most relevant advanced echocardiographic techniques are reviewed.

[1]Catheterization involves the threading of a thin plastic tube from an artery in the leg or arm through the arterial system and into the coronary arteries of the heart where pressure readings are made and radio-opaque dye can be injected.

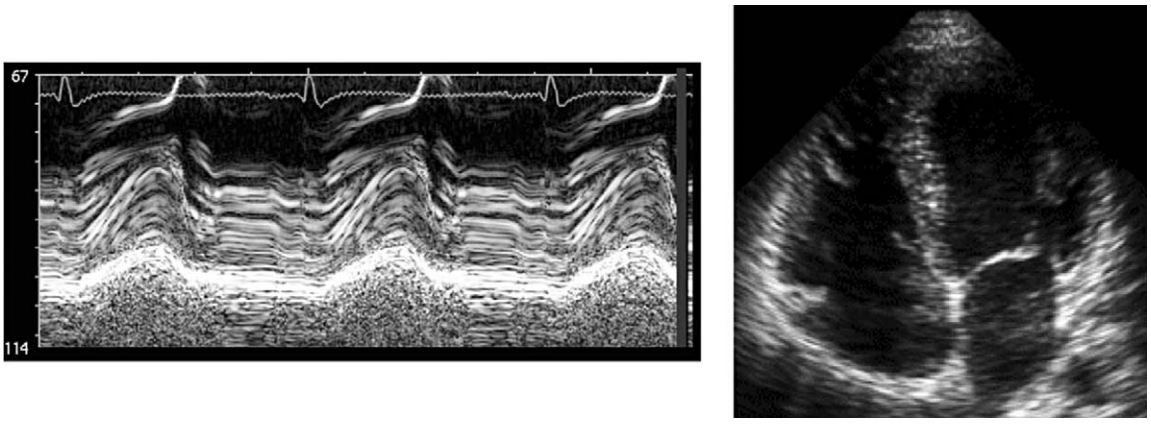

Figure 2. Echocardiography images. (*Left*) M-mode. (*Right*) B-mode image from a four-chamber sequence, at end-systole (video available at *http://www.die.upm.es/im/videos*). Courtesy of Hospital G.U. Gregorio Marañón (Madrid, Spain).

3.2.1. Doppler Techniques. Doppler principles have made it possible to measure the speed of the blood and tissues inside the body, by recording the shift in frequency caused by the reflection from a moving target (8). Doppler measurements were first acquired using two independent piezoelectric crystals, one continuously transmitting and the other continuously receiving, measuring all the velocities along the beam. This technique is the so-called continuous wave (CW) Doppler. Its main advantage is that high velocities can be measured; however, is not spatially selective. This last disadvantage is overcome with pulsed wave (PW) Doppler. In this case, short ultrasound pulses are transmitted with a pulse repetition frequency (PRF). The depth of the volume to be explored can be selected by modifying the time the receptor is active. The main limitation of this technique is that velocities higher than a threshold (one-half of PRF) cannot be measured and produce aliasing.

These techniques have produced two different echocardiographic modalities: color Doppler echocardiography and tissue Doppler imaging. In both cases, the velocity component of either the blood or the tissue in the beam direction is measured. In the case of the heart, both signals are present and they can be differentiated because they have different features: Tissue moves slower than blood, whereas tissue echo has more amplitude than the signal reflected from the blood. Filtering the echo signal can separate the tissue Doppler signal (lower frequencies) and the blood Doppler signal (higher Doppler frequencies)(9).

3.2.1.1. Color Doppler Echocardiography. Color Doppler echocardiography measures the blood flow magnitude, and presents this information codified in color over a 2-D anatomic image (color flow mapping) (Fig. 3). Bluish colors usually represent motion away from the transducer and reddish colors represent motion toward the transducer. This technique is very well established in the clinical routine to evaluate valvular stenosis and insufficiencies. Turbulent flow is clearly detected in regions with an increase in the **Doppler** frequency shifts variance.

3.2.1.2. Tissue Doppler Imaging (TDI). TDI, in contrast, represents the velocity of heart walls, filtering out the signal from the fast-moving blood. This technique allows quantification of heart wall motion and objective analysis of myocardial dysfunctions (9). For example, it has been proven that myocardial velocity gradient is decreased in the presence of ischemia (10). This technique also provides a way to perform objective stress echocardiography, a great advantage because, normally, stress studies are evaluated visually with high interobserver disagreement (7).

Strain rate and strain measurements can be obtained from TDI, providing a new imaging modality that assesses active myocardial contraction. Strain rate is obtained as the spatial gradient of myocardial velocities and the strain as the temporal integral of the strain rate (11).

The main drawback of Doppler techniques is that only one component of all these parameters is measured: the component on the US beam direction. New techniques processing conventional echocardiography attempt to avoid this problem in order to obtain bidimensional displacement and strain (12,13).

3.2.2. Contrast Echocardiography (MCE). Contrast echocardiography is the combination of echocardiographic imaging techniques with contrast agents specifically designed to be visualized through ultrasound (Fig. 4). These contrast agents consist of the dilution of gas microbubbles that amplify the reflected signal (14). The amplification is because of the oscillation or rupture of the microbubbles when they are insonated. Contrast is delivered through intravenous injection and it is confined to the vascular space. The contrast enhances the signal from the blood so it can be used to enhance Doppler studies. Another important application is endocardial border enhancement in stress and myocardial motion assessment studies.

The most interesting application of contrast echocardiography is in the quantification of myocardial perfusion. Recently, several different studies have revealed its potential to determine the degree of irrigation in the presence of coronary artery disease (14). In order to identify

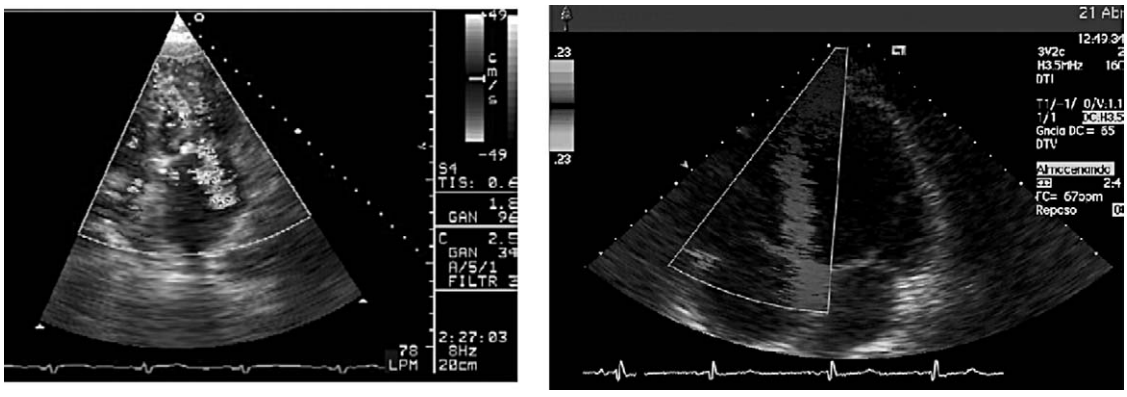

Figure 3. *Left*. Color Doppler image of a mild to moderate mitral regurgitation. The image shows an abnormal turbulent jet from the left ventricle into the left atrium systole. Image courtesy of Hospital Dr. Negrín (Gran Canaria, Spain). *Right*. Tissue Doppler image of a four–chamber view of a healthy subject during systole. Image courtesy of Hospital G. U. Gregorio Marañón (Madrid, Spain).

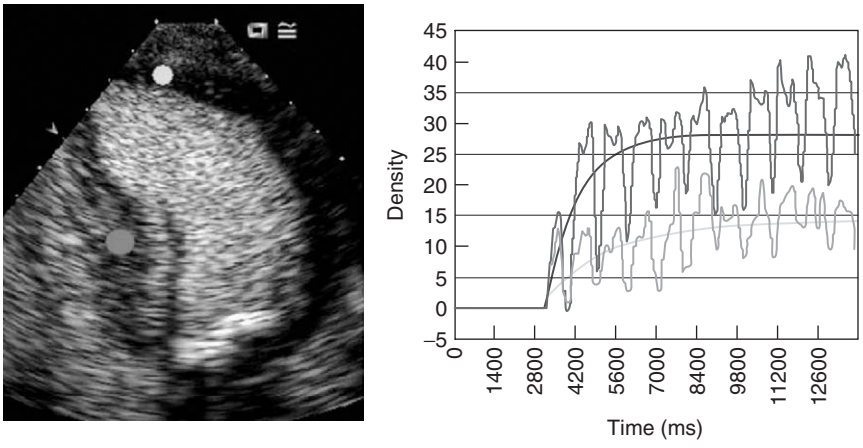

Figure 4. Myocardial perfusion imaging. The blood pool is bright because it is full of contrast medium. On the *right*, time perfusion curves of two different regions with normal (*red*) and abnormal (*green*) perfusion patterns.

subtle changes in the ischemic process, specific quantification tools are required.

3.2.3. Transesophageal Echocardiography (TEE). One of the limiting factors of conventional echocardiography is the presence of attenuating tissues in the interface between the US transducer and the heart, allowing only certain ultrasound transducer positions and directions (US windows) to be possible. To overcome this problem, **transesophageal echocardiography** has been proposed, providing high-quality images including color flow at the expense of being partially invasive. A specifically designed transducer is placed in the esophagus very close to the heart, avoiding attenuating tissue. Its main application is the assessment of valvular function, and valvular, interventricular, and interatrial prosthesis status.

3.2.4. 3-D Echocardiography. 3-D echocardiography is a relatively new development in US that allows 3-D visualization of the complete heart structure. Different acquisition schemes have been proposed. 3-D multiplane transthoracic or transesophageal echocardiography consists of acquiring several planes of the heart with a known relative position. The whole cardiac cycle is acquired at each plane position. Volume through time is reconstructed by taking all the acquired planes at each temporal position. An offline system to reconstruct and process the data is usually required. Recently, another acquisition scheme has been proposed using a 3-D US transducer made up of 3000 piezoelectric crystals that acquires a 3-D volume in real time without reconstruction requirements (Fig. 5). Manipulation of the volume, biplane, and full-volume acquisition are included in the echographer.

3-D echocardiography has been used to compute LV volume and mass more accurately and to perform wall motion analysis, taking into account the three spatial dimensions and avoiding the typical 2-D errors, such as out of plane motion.

3.2.5. Other US Techniques. Other US related techniques include intravascular ultrasound (IVUS). In this case, an ultrasound transducer of very high frequency (20—40 MHz) is located at the end of a catheter to image the vascular lumina and vascular walls (Fig. 6). This

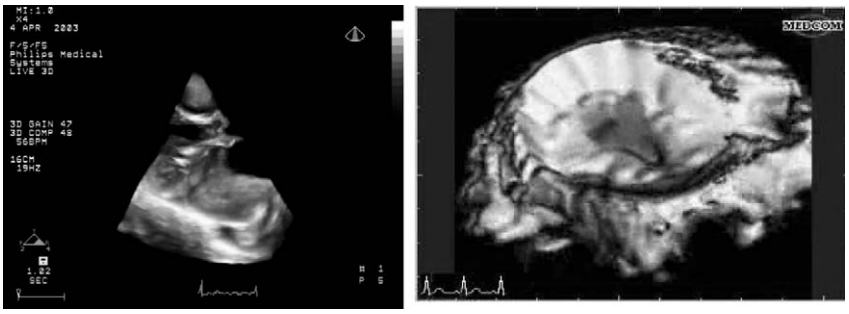

Figure 5. 3-D echocardiography. *Left*. Aortic and mitral valve volume acquired using a 3-D real-time system. Image courtesy of Royal Philips Electronics (Eindhoven, The Netherlands). *Right*. 3-D volume of an atrioventricular valve with the color flow superimposed, acquired using a multiplane acquisition scheme. Image courtesy of MedCom GmbH (Darmstadt, Germany). Videos available at *http://www.die.upm.es/im/videos*.

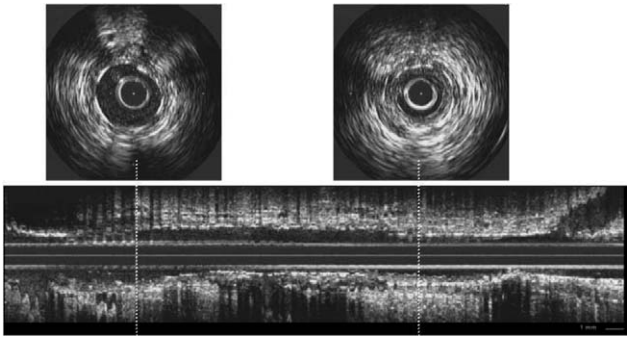

Figure 6. IVUS imaging. 2-D longitudinal view of a coronary artery treated with a stent (*bottom*) and transverse views showing the metal struts of the stent (*left*) and the restenosis of the stent in a distal segment (*right*). Images courtesy of Hospital Dr. Negrín (Gran Canaria, Spain).

technique can be used to assess stent placement and results of percutaneous transluminal angioplasty (PTA), which refers to all surgical methods used to treat vessel occlusion and narrowing, both in the short-and long-term (restenosis assessment). It is currently the benchmark for assessment of coronary atherosclerotic plaques and their components.

Another interesting technique is the so-called elastography that has recently been applied in combination with IVUS to measure the stiffness of the arterial wall. Elastography measures strain using speckle tracking techniques when the tissue is under known compression. Differences in compression of an arterial wall may be obtained from the differences in systemic blood pressure, or inflating an intravascular balloon.

3.3. Nuclear Imaging

Nuclear imaging, also called isotope imaging, is based on the detection of an injected radio-labeled drug that is taken up by the perfused heart. Normally ^{201}Tl or ^{99m}Tc are used. ^{201}Tl is a potassium analog that is actively transported into myocytes by their cell membrane if it is functionally active, and whose kinetic features are directly proportional to tissue blood flow: normal tissue has more rapid uptake and washout than underperfused, viable tissue (7). Recently, red cells tagged with ^{99m}Tc (^{99m}Tc sestamibi) are also being used.

Two acquisition techniques are possible: first-pass and gated equilibrium studies. In the former, the first passage of an injected radio-label bolus through the heart and great vessels is imaged in two dimensions. In gated equilibrium studies, the tracer is mixed with the blood pool to assess function during the cardiac cycle. ECG-gated images of the moving heart can be obtained by accumulating gamma-counts over several minutes and assigning the counts to specific heart views along the ECG cycle.

3.3.1. SPECT (Single Photon Emission Computed Tomography). Although planar (projection) images have been used, presently most studies are tomographic 3-D reconstructions obtained with a rotating gamma camera: SPECT imaging (Fig. 7).

In clinical practice, images are obtained at rest and during pharmacological or exercise stress. Examination at rest shows myocardial areas that are inactive, whereas examination during pharmacological or exercise stress shows areas where perfusion is reduced and becomes inadequate during high demand. Presently, SPECT imaging is a well-established, clinically useful technique for studying myocardial perfusion in cases of ischemia, for assessing myocardial viability, and for diagnosing coronary artery disease.

However, SPECT has some limitations, such as the artifacts that may develop from its nonuniform attenuation, especially when it is used for women and obese patients.

3.3.2. PET (Positron Emission Tomography). PET is another radionuclide imaging technique that uses different short-lived radionuclides that decay producing positrons. These positrons interact with nearby electrons, producing two annihilation photons. These photons can be efficiently detected by opposing detectors, resulting in a technique that is more sensitive than SPECT and is also less susceptible to attenuation. Although its higher cost has meant that PET has had limited use in cardiology until now, it can quantify regional myocardial metabolism and perfusion. Metabolism is measured by the uptake of ^{18}F-FDG, an analogue of glucose that is transported into cells and trapped. Perfusion is assessed with ^{13}N-ammonia, ^{15}O-H_2O, and ^{82}Rb, and is able to quantify coronary artery disease and myocardial blood flow (7,15). PET can also accurately identify myocardial viability with ^{18}F-FDG: Although nonviable myocardium has both decreased blood

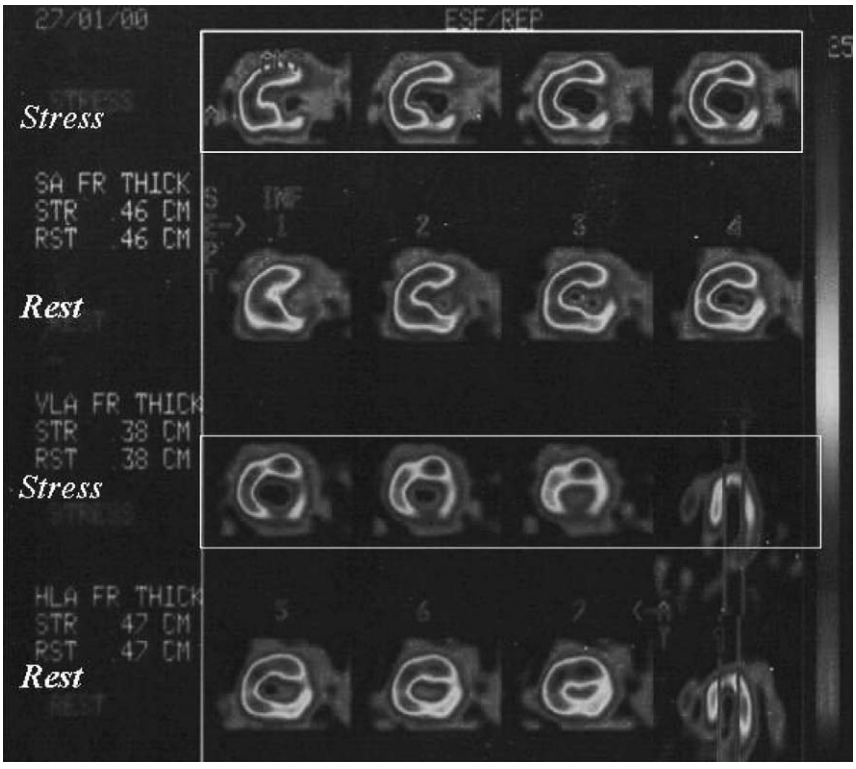

Figure 7. SPECT study showing different views of the heart after radioisotope administration. The images show the reversible changes under stress that recover at rest, suggesting the presence of ischemia.

flow and glucose uptake, viable myocardium has normal glucose uptake and either reduced blood flow at rest or decreased perfusion reserve under stress (7).

PET is a technique with potentially better resolution than SPECT. In PET, attenuation can be compensated for, although the resolution can still be degraded by respiratory and cardiac wall movement. Emerging techniques like PET-CT combine PET and CT in a single scanner. Their use is two-fold. First, CT can be used for attenuation correction. Second, as both techniques are complementary, the information provided by CT about anatomy, coronary angiography, and plaque characterization can be complemented with the perfusion and metabolism information provided by PET.

3.3.3. Molecular-Imaging. Molecular imaging can be defined as the *in vivo* characterization of biological processes at the cellular and molecular level. It can be achieved with different imaging modalities, mostly PET and SPECT, but also MRI and US, and even others, such as biofluorescence or bioluminiscence. Molecular imaging has received increasing attention in recent years because imaging the distribution of targeted molecules allows the tracking of biochemical processes before their physiological consequences appear. In the cardiovascular system, several applications for molecular imaging exist, from which two key examples are presented here: imaging of angiogenesis and imaging of apoptosis (16).

Angiogenesis, the formation of new capillaries from existing microvessels, occurs when ischemia or hypoxia exist in a tissue, and in other situations, such as inflammation. It is a complex phenomenon involving the interaction of several factors, one of these being the altered expression of vascular endothelial growth factor (VEGF) receptors. The expression of VEGF is induced by hypoxia, indicating that it is a key natural mediator of angiogenesis in response to ischemia. VEGF can be labeled with ^{111}In and it is preferentially retained by ischemic muscle in experimental studies (17), so imaging its distribution with SPECT, complemented with perfusion imaging (^{99m}Tc-sestamibi) in dual-isotope acquisitions, could assess hypoxic stress within viable tissue (6,18).

Apoptosis, programmed cell death, occurs in association with CVD. In patients with myocardial infarction undergoing reperfusion therapy, SPECT with ^{99m}Tc-labeled annexin-V (a protein with high affinity for a molecule expressed on the membrane of cells undergoing apoptosis) can show the accumulation of the tracer at the site of infarct better than ^{99m}Tc-sestamibi (19). It has also been proposed as an early, noninvasive technique for tracking heart transplant rejection (20).

3.4. Cardiac Magnetic Resonance (CMR)

Magnetic resonance imaging is a nonionizing modality that produces very good imaging of soft tissues. It can produce detailed high-resolution 3-D images of the heart's chambers and large vessels without interference from adjacent bone or air, in arbitrary imaging planes (e.g., long-and short-axis views) (Fig. 8). Its high contrast discrimination between blood and myocardium avoids the need for contrast agents. ECG-gated images of the moving heart (around 20—30 images per cardiac cycle) can be obtained and, presently, the acquisition of a single slice along the cardiac cycle can be fast enough for patients to hold their breath during the procedure, so

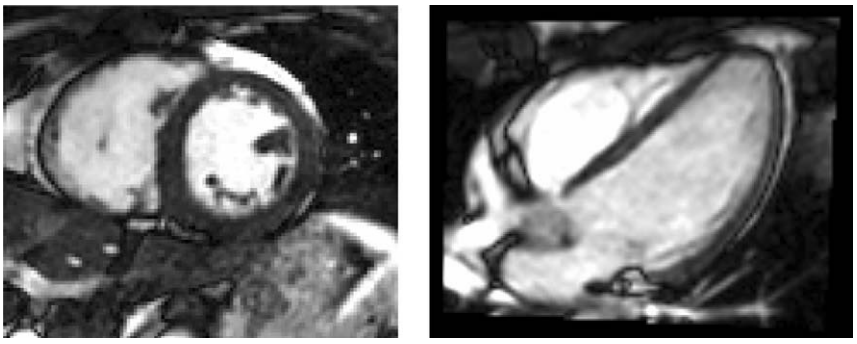

Figure 8. Short axis (*left*) and long axis (*right*) MRI CINE sequences. Videos available at *http://www.die.upm.es/im/videos*. Images courtesy of Hospital G. U. Gregorio Marañón (Madrid, Spain).

that artifacts caused by breathing movement are avoided in 2-D acquisitions. In volumetric acquisitions, misalignments between slices are still produced because of changes in heart position in different apneas.

The high contrast and good resolution of MRI ensure that functional information can also be obtained. Volumes can be obtained with good accuracy (avoiding the simplifying assumptions typical of 2-D imaging) by integrating the area from contiguous slices. In this way, the derived parameters, including ejection fraction,, stroke volume, and wall-thickening, can also be computed accurately. MRI can also be used to obtain additional information, such as tissue or blood motion and perfusion.

3.4.1. Tissue, and Blood Motion. MRI is a modality that is also very adequate for measuring blood flow and tissue motion, acquiring truly functional images. This capacity is not only because of the acquisition of sequences of images with good tissue contrast, but also because of the possibility to use different acquisation techniques. Some motion analysis techniques specific for MRI are phase-contrast MRI and tagged-MRI.

Phase-contrast MRI (PC-MRI) uses the sensitivity of the MR phase to motion and was originally developed to quantify blood motion. This technique uses a velocity-encoding magnetic field gradient that can quantify the velocity of tissue or blood flow in the direction of the gradient. Protons flowing along that direction acquire a phase shift proportional to their velocity. Acquiring two images with different velocity-encoding gradients and subtracting one from the other produces a difference image proportional to the motion in one direction (21).

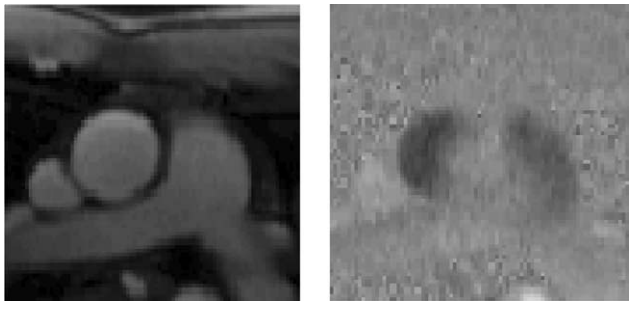

Figure 9. Modulus (*left*) and phase (right) images of a phase-contrast MR study of the output track of the aorta. Videos available at *http://www.die.upm.es/im/videos*.

Three orthogonal measurements (plus a reference one) can show the velocity in any direction. Traditionally, phase-contrast images show blood flow as different levels of gray (Fig. 9). Appropriate postprocessing software can quantify blood velocity through a vessel section or a valve, locating possible regurgitant flows or assessing valvular stenosis. Recently, this technique has also been proposed to quantify tissue motion (especially the myocardial strain tensor), after the myocardial displacement obtained from PC-MRI (21,22).

Tagged-MRI uses specific sequences (e.g., spatial modulation of magnetization; SPAMM) to create two orthogonal sets of parallel planes of magnetic saturation, which appear as a pattern of dark lines or *tags* (23,24) (Fig. 10). Tracking these tags over time by image postprocessing algorithms is equivalent to tracking the material points on the tissue (myocardium), providing information on tissue deformation. Analysis of these images usually involves three steps: segmentation of the myocardium (endocardium and epicardium); detection of tag intersection points in each slice and time frame; and fitting a motion field to the tags detected (21). Although normally used as 2-D, 3-D extensions (or 4-D [3-D plus time]) have also been proposed (25).

Harmonic phase imaging (HARP) has been proposed as a technique to detect tag locations and to track motion without the need of segmentation (21,26). This technique obtains the motion information from the spectral peaks, which correspond to the tagging spatial modulation, in the frequency domain.

In all these techniques, acquisition speed is a key factor. To avoid respiratory motion, the whole acquisition should be acquired in a single breath-hold. In the past, hardware improvements (mainly increased gradients) have made possible faster and faster acquisition protocols. However, fast switching of even larger magnetic gradients could be limited by physiological constraints. An alternative is the introduction of parallel acquisitions, using arrays of simultaneously operating receiver coils in what is called SENSE (sensitivity encoding) (27), achieving considerable reductions in acquisition time without sacrificing spatial resolution.

3.4.2. Perfusion. Contrast agents based on gadolinium, such as Gd-diethylenetriamine penta-acetic acid (Gd-DTPA), allow myocardial perfusion assessment with MRI (28). After an intravenous bolus injection of Gd-DTPA,

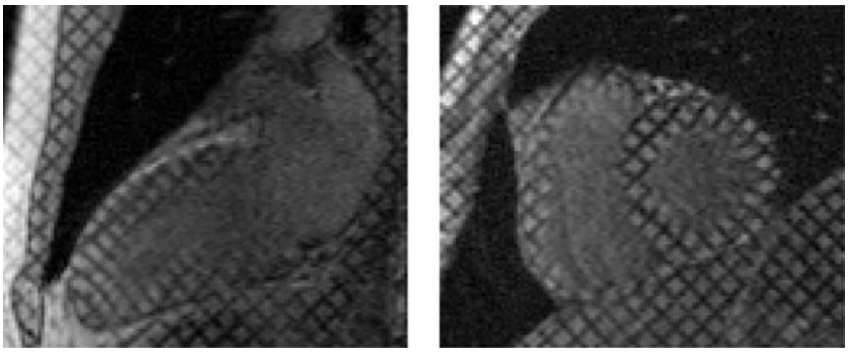

Figure 10. Long axis (*left*) and short axis (*right*) tagged-MR images of the heart. Images courtesy of Clínica Creu Blanca (Barcelona, Spain).

images of the heart are acquired rapidly to observe the first-pass of the bolus. Regions with normal perfusion show rapid and uniform image enhancement during the passage of Gd-DTPA, whereas regions with a perfusion defect enhance more slowly. This technique was not in clinical use until fast acquisition sequences became possible, as its practical use requires simultaneously having good spatial and temporal resolution, and multislice coverage of the whole heart. Imaging the whole heart during the passage of the bolus is still a challenge, where parallel imaging techniques could again be useful.

Gadolinium-enhanced images have also been proposed to detect coronary artery stenosis with high accuracy.

Recently, **gadolinium delayed enhancement** (DE) has also been proposed to identify infarcted or scarred myocardium. The strategy is again to use an intravenous Gd-DTPA bolus injection, but to acquire the images after at least 5 min after contrast injection. In normal tissue, the Gd-DTPA, which remains extracellular, has been cleared away after that time, but in necrotic myocytes, because of the cellular membrane breakdown, it is kept longer, providing brighter images (7). Then this different enhancement pattern is a clinically useful index of myocardial viability.

3.5. Computed Tomography (CT)

Computed tomography, or the process of creating cross-sectional images of x-ray attenuation through a patient's body, has a good capacity for delineating anatomy with high spatial resolution. Its role in cardiac imaging started with the development of very fast acquisition techniques (scan times in fractions of a second), mainly electron beam CT (EBCT) and multidetector CT (MDCT), also called multislice CT (MSCT).

EBCT improves acquisition times by avoiding moving parts in the scanner. Instead of a rotating x-ray source, it uses an electron beam that is electromagnetically focused on large tungsten targets surrounding the patient. A rotating fan-beam of x-ray photons can thus be produced, achieving scan times as fast as 50 ms for a single slice, which, in practice, freeze the heart movement. EBCT acquisition of overlapping sections of coronary arteries using iodinated contrast agents is able to locate some vessel anomalies, for example, it can detect significant stenoses. 3-D reconstruction by specialized software can also help to identify and localize these alterations, and currently does so with better resolution than MRI.

EBCT is also used in the detection and quantification of artery calcification (calcium deposits in the arteries), providing a calcium score, which is an indication of the volume and density of calcification, related to the risk of coronary arterial narrowing.

MDCT scanners have also appeared in the last few years, making possible the simultaneous acquisition of several slices. Large detection width in the axial direction, with a wider x-ray beam, can achieve good spatial resolution with a reduced patient dose. Currently 16-, 32-, and even 64-slice scanners are available, which implies not only technical requirements, but also new reconstruction algorithms adequate for this 3-D cone-beam geometry [traditional 2-D fanbeam reconstruction produces visible artifacts if more than 4 slices are used (29)].

Thus, ECG-gated CT scans in a single breath-hold with submillimeter section thickness collimation and rotation times in the order of 300–500 ms are possible (30), suggesting scan times of around 5–10 heartbeats and making it possible to acquire high-resolution 3-D images of the heart and great vessels. Specific software tools provide automatic segmentation of the arteries and visualization of the longitudinal and transversal sections (Fig. 11). The increased resolution makes it possible to better detect and characterize stenosis and plaque in arteries. However, high-risk plaques (that could rupture suddenly) very often do not produce significant stenoses, nor are they calcified, but instead filled with fat and inflammatory cells with a thin fibrous cap (31). The current challenge is to detect non-invasively these vulnerable plaques, and several imaging modalities could be needed.

4. CONCLUSIONS

In the last decades, medical imaging in general, and cardiac imaging specifically, have experienced a tremendous evolution. The first steps were mainly concerned with visualizing the state of the heart anatomy. Soon, both valvular and myocardial function could be analyzed, visualizing the anatomy in movement. Later advances have been related to visualizing and quantifying myocardial perfusion and metabolism. The main challenge, already partially achieved, is to be able to detect subtle changes in the coronary arteries and in the myocardium to

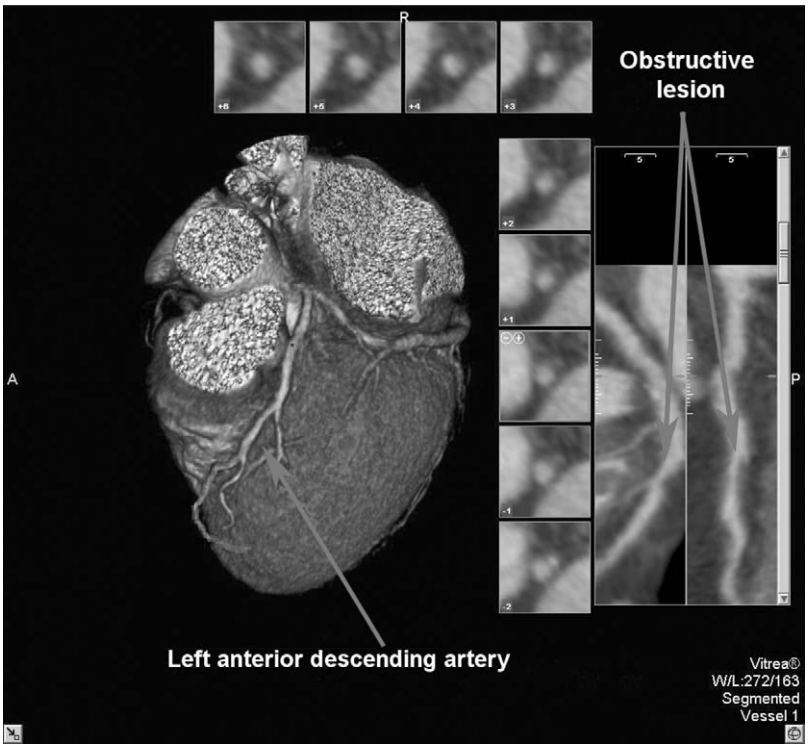

Figure 11. Left anterior descending coronary automatic segmentation. The transverse and longitudinal sections of the artery are visualized to characterize an existing lesion. Image courtesy of Dr. M. A. García-Fernández.

Table 1. Comparison of the Relative Strengths of Different Current Imaging Modalities for the Evaluation of Cardiac Anatomy, Function, Perfusion, and Metabolism

	x-ray angiography	US	Nuclear imaging	MRI	CT
Anatomy	+	+ +	−	+ + +	+ + +
Function	+	+ + +	+ +	+ + +	+
Perfusion	−	+ +	+ + +	+ +	−
Metabolism	−	−	+ + +	+	−

contribute to an early diagnosis of disease and to an accurate follow-up of treatment. The currently available imaging modalities are all needed because they are complementary, showing different features of the heart and vessels.

Table 1 summarizes the ability of each imaging technique to show anatomy, function, perfusion, or metabolism. X-ray angiography continues to be the method of reference to assess coronary artery disease, although noninvasive methods such as MDCT are receiving increasing interest. Ultrasound goes on being a widely available and useful technique to image the heart, providing good myocardial and valvular function assessment, and recently also myocardial perfusion. Its main limitation, however, is the low quality of the images. Nuclear techniques are the reference in the study of myocardial perfusion and metabolism with the main disadvantage of their spatial and temporal resolutions. MRI is now an established technique to assess myocardial function, perfusion, and predominantly viability, and therefore its clinical use is continuously increasing. One of the most promising and emerging techniques is MDCT, which provides a fast way of assessing coronary heart disease.

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