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The use of magnetic resonance in myocardial ischaemia

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Abstract. Despite the efforts that have been made at an international level to identify and control cardiovascular risk factors, cardiopathies and, in particular, coronary artery disease (CAD), remain the principal cause of death in Europe and the United States. These data confirm the importance and necessity of non-invasive, reliable diagnostic imaging of early CAD. Coronary angiography is still the hinge, around which all instrumental and laboratory investigations turn, for cardiac ischaemia today. Indeed, it still holds the role of "gold standard" for the study of the coronary arterial lumina, particularly the smaller vessels due to their complex spatial geometry and because of cardiac motion. At present, with the exception of the study of the coronary arterial lumen, MR is a non-invasive examination, already capable of supplying precise global and regional function, the evaluation of the intra-cardiac flow, myocardial perfusion and the overall viability of the heart. (www.actabiomedica.it)

Key words: Myocardial ischaemia, MRI, myocardial viability

Introduction

Due to it's vast clinical and epidemiological relevance in the general population, in terms of incidence/prevalence and morbidity/mortality, cardiac ischaemia is the object of investigation by the international scientific community.

Despite the efforts that have been made to identify and control cardiovascular risk factors, cardiomyopathies and, in particular, coronary artery disease (CAD), remain the principal cause of death in Europe and in the United States.

One out of every five deaths in Europe in 1998 was correlated to CAD, and, every year, about 1.1 million American citizens and 300,000 German citizens are struck by heart attacks, with a 40% mortality rate. Moreover, half of these subjects die without ever having been hospitalized (1).

These data confirm the importance and necessity of a non-invasive, reliable diagnostic and preventive imaging of early CAD.

Coronary angiography is still the hinge around which all instrumental and laboratory investigations turn for cardiac ischaemia today. Indeed, it remains the "gold standard" for the study of the coronary artery lumen, especially for the smaller cardiac vessels due to their dimensions and to the difficulty in the reconstruction that derives from the complex spatial geometry and consensual movement during the cardiac cycle, in particular in the presence of an accelerated cardiac frequency.

However, coronary angiography, which is invasive and with the possibility of serious complications, including allergic reactions to the iodated contrast medium, contrast nephropathy, haemorrhage or dissection of the coronaries, is not able to provide information about cardiac morphology or cardiac metabolism.

For this reason a progressive series of technologies can caming the non-invasive study of the heart, such as magnetic resonance imaging (MRI) and computed tomography (CT) have been applied. Looking at these advances the possibility that coronary angiography will be utilized more for therapeutic applications, such as stent application , thrombolysis etc., rathes than for diagnostic purposes, is predicable.

In fact, nowadays, angiography has been widely substituted by MRI and computed tomography in the study of great vessels and peripheral vasculature; consequently, the more invasive technique for large and peripheral vessels is almost exclusively performed during surgery.

Without going into detail as to the respective potentials of CT and MRI for coronary vasculature evaluation it must be said that these methods provide high quality imaging that encourages their use in study of coronary circulation.

Indeed, CT and MRI are now able to supply solutions to the limits that imaging once had:

- high contrast resolution that allows for the study (with CT) of structures with similar densities (e.g. vessel walls and myocardial muscular tissue);
- a high spatial resolution that allows for the imaging of the smaller vessels;
- a high temporal resolution that offers the possibility of synchronizing with ECG so as to record the movement of epicardial vessels.

It is sufficient to take a look at the coronary angiographic image obtained with the use of multidetector CT (fig. 1) and image resolutions from machines with 1.5 T field strength, to be able to affirm that the CT and MRI will most likely take over the role of diagnostic cardiac imaging in the near future.

The use of MRI for of coronary artery evaluation is currently going through an important developmental phase (fig. 2) even if, when compared to CT, it is plausible to presume that its scientific validation and application in routine clinical settings will need more time to become well established.

With the exception of the study coronary arterial lumen, MRI is a non-invasive technique that is already able of supplying an accurate assessment of global and regional function, the evaluation of the intra-cardiac blood flow, myocardial perfusion and viability.

This fact, together with the intrinsic characteristics of the MRI (i.e. high contrast resolution, excellent

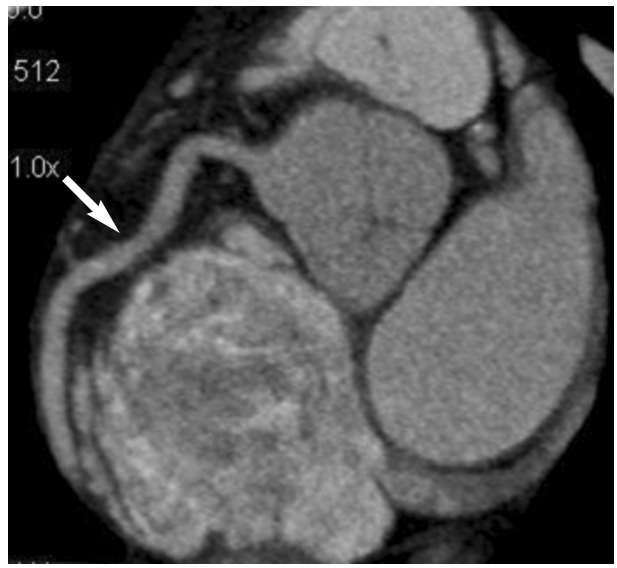

Figure 1. Coronarographic image obtained with a 64 row CT scan (MIP). Good visualization of right coronary artery (arrow).

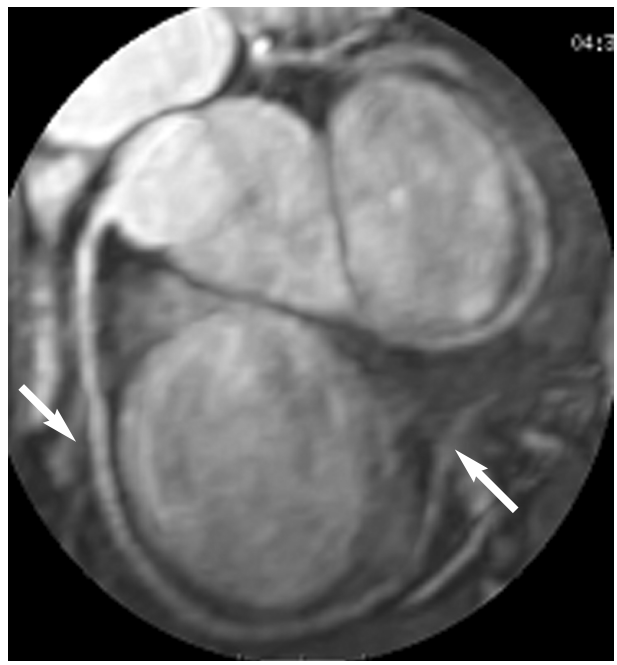

Figure 2. MRI 3D FIESTA fat-sat without administration of contrast medium. Panoramic view of right coronary artery (arrows). (Courtesy of General Electric healthcare)

spatial resolution, multiplanar acquisition, absence of ionizing radiation, high safety margin of paramagnetic contrast medium (c.m.) that can be administered to renal-impaired patients) could become the "new gold standard" for imaging cardiac ischaemia.

Myocardial ischaemia

The term Cardiopathic Ischaemia (C.I.) defines a large spectrum of diseases with different aetiologies, such as unstable angina, stable angina, angina variant, acute myocardial infarction, and silent ischaemia, all of which have a common factor i.e. the mismatch between coronary blood flow supply and myocardial oxygen demand.

This complex physiopathology, which is the basis of cardiopathic ischaemia, results in vascular damage that leads to a permanent or temporary reduction in coronary blood flow which is, more often than not, caused by arteriosclerosis.

Myocardial ischaemia induces a metabolic, electrical or mechanical alteration.

Due to the intrinsic nature of the morphologic and functional parameters that need to be evaluated during the diagnostic course of cardiopathic ischaemia, it has become even more necessary to use a series of evaluation techniques and the integration of the data obtained for prognostic/therapeutic value.

Since its introduction in cardiovascular imaging, MRI has distinguished itself, thanks to its resolution characteristics and its ability to image in multiple planes. Therefore, MRI is taking on an ever more important role in the diagnostics of C.I.

It is worth noting the use of MRI in American Emergency Rooms for chest pain in suspected cases of coronary ischaemia, a problem that has a huge clinical epidemiological impact, yet it still represents challenge with the most common diagnostic methods available for application in this field (2, 3).

MRI principles in cardiology

MRI represents an exceptional technique used in the morphological imaging of the heart. The main advantages lie in the high contrast resolution (grey scale) as well as in the multiplanar and panoramic views that it offers.

High contrast resolution is an important factor in imaging the myocardial tissues, the adipose components, and the pericardium, making it not only possible to identify the smallest pericardial effusion, but also to differentiate its characteristics. The multiplanarity of cardiac MRI allows for an optimum evaluation of the cardiac chambers and anatomic structures. The panoramic advantages of the MRI, compared to those of echocardiography, permit an accurate evaluation of the left and right atria, the ventricles, the endocardium, and the pericardium.

Black blood sequences enable the definition of the endocardiac borders (fig. 3); the intra-cavitary blood flow is devoid of signal, thus delineating endocardiac borders.

Cardiac synchronization is a must for all morphological sequences, so as to eliminate any possible artefacts caused by cardiac motion, which, if present, significantly degrade the image quality.

Manufacturers of MRI scanners have dedicated a great deal of effort in producing efficient and reliable

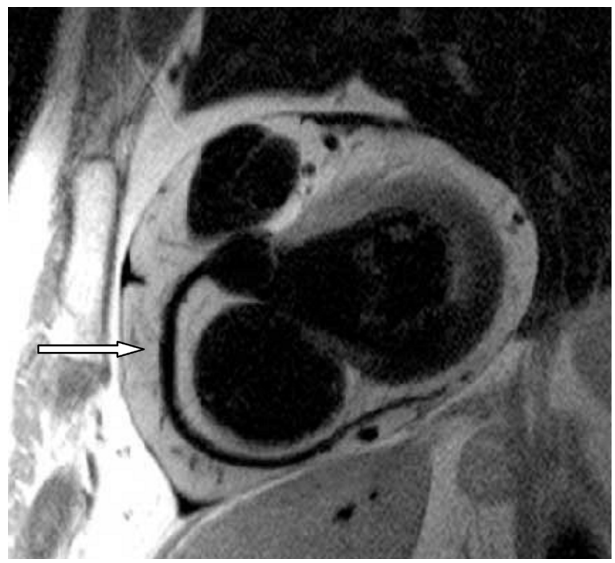

Figure 3. Black blood image in short axis view without administration of contrast medium. This sequence for a good spatial resolution and CTN ratio allows excellent visualization of parietal pericardium, epicardic and endocardic profiles and right coronary artery (arrow)

triggering, and have developed approaches for accurate reconstruction of the cardiac cycle for cine-sequences and high quality static images.

Cardiac synchronization is used in most cases of cardiac MRI. This is done by means of an electrocardiogram in telemetry, so that the heart may be imaged through the various phases of its functional cycle.

The images may be acquired and correlated directly to the cardiac synchronization during the sequence, known as prospective gating, or indirectly at the end of the sequence, known as retrospective gating. When spin-echo sequences are used, the acquisition takes place in a multi-layer, multi-phase modality, as the number of layers for a TR is in proportion to the R-R internal on the ECG, each will be in a different temporal and spatial position. The use of a fast sequence and a short TR allows for the acquisition of a mono-layer, multi-phase modality.

All the functional phases, seen in rapid succession through a cine-loop, will be documented for each layer. However, the presence of even the most common arrhythmia such as bigeminy during the course of multiple images acquired in a cardiac cycle, deteriorates the signal /noise relationship. Even the "traditional" techniques in fast-cine or spin-echo (SE) give poor quality results under these circumstances. The presence of such a disorder in the cardiac rhythm (like atrial fibrillation) makes the examination difficult, as it is observed with the gated SPECT (G-SPECT) (4, 5). Nowadays, modern equipment and state of the art technologies, have supplied mechanisms that are able to pin-point and discard extrasystoles.

Given that the most common indications for the cardiac MRI are congenital heart disease, ischaemic cardiomyopathies, cardiomyopathies, myocardial pathologies, vulvopathies, and cardiac masses, it is easy to understand the importance of having not only information regarding morphology, but also regarding the functional status, and, therefore information on contractility evaluation.

Cine MRI and myocardial tagging are the two principal techniques used for the study of the myocardial contractility. Cine MRI is an essential phase in the study of the heart. It involves the acquisition of numerous images of one layer in the various phases of the cardiac cycle and presents them in rapid succession (cine-loop), so as to allow for an evaluation of the cardiac kinetics and dynamics of the blood flow.

Gradient echo (GE) sequences are usually used, known as fast low angle shots (FLASH) on gradient-recalled acquisition in the steady state (GRASS) with a re-focus of the spin of the laminar blood flow, with shortened acquisition times if reduced flip angles (30 degrees) and short TR (20-30 ms) and TE (4-17ms) are used.

The images are characterized by the high blood signal (white) that very well defines the internal profile of the cardiac wall (grey). The examination is carried out with 5–10 mm thick slices, acquired in perpendicular or parallel planes to the septum (long axis and short axis).

Once the images of the contiguous slices in the various cardiac phases of the cycle have been acquired, it is possible to calculate the ventricular end systolic and end diastolic volumes, by summing up the volumes obtained, layer by layer, and multiplying the chamber area (region of interest) by the slice thickness, on end systolic and end diastolic frames.

Short axis images are usually used for this, since they minimize the partial volume effect, and, therefore that of calculation, which starts from the base of the heart, corresponding to the atrio-ventricular valve up to the apex.

When acquiring images during a brief breath-hold (12-20 secs), care must be taken to ensure that the position of the diaphragm is consistent so as to obtain acquisition from the level. Moreover, it must not be forgotten that numerous well distributed phases have to be acquired throughout the whole cycle. Repetition times (RT) must also be taken into consideration, which, in turn, depend on cardiac frequency.

Numerous studies reported in literature have demonstrated that there is absolute accuracy when using cine MRI for the evaluation of the ventricular and kinetic regional geometry (measurement of the diastolic thickness of the myocardium, calculation of the systolic thickening, evidence of the paradoxical and dyskinetic movements) (6).

One way in which the kinetics of myocardium contractility can be studied is the tagging (fig. 4) of cine MRI, which is done by means of radio-frequency (RF) impulses and pre-saturation, that allow for the

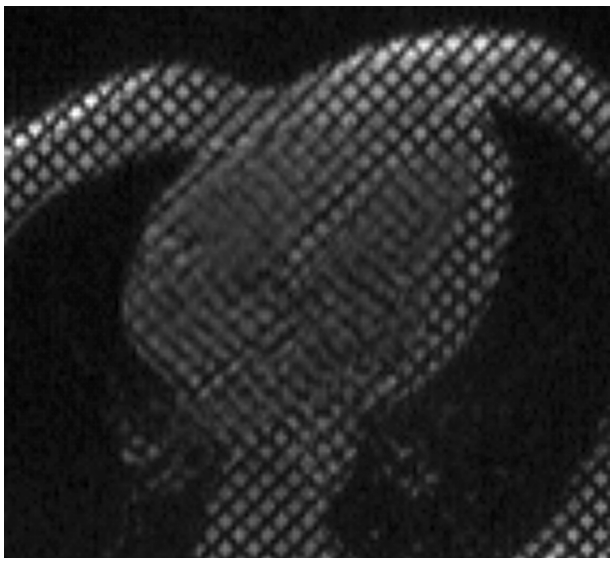

Figure 4. Tagging in 4 chambers: a strong tool for the study of myocardic contraction

marking of the myocardial tissue prior to image acquisition (7).

The selective RF impulses are applied in the presence of linear magnetic fields, thus changing the protonic magnetization in one or more areas of the tissue.

The protons, having been excited, retain the memory of the RF impulse for a certain period of time, dependent on the relaxation time (T1) of the tissue.

Site, number, thickness and intensity of the signal of the saturated area will vary depending on the RF impulse and the direction of the magnetic field gradient. The saturations may be radial or may weave to form a grid. Changes in the saturation are identified by cine MRI.

Tagging is a non-invasive way to evaluate myocardial motion (both normal and pathological): translateral in the direction of the long axis, rotatory, torsion of the circumferential fibres (5).

An agreement has been made between the hospital staff who operate with the machinery and the company the technicians, that the stationary magnetic field for the study of the heart must be at least 1.5 Tesla. With the improvement of the characteristics of the electronic components and receiving coils, the old concept that when magnetic field strength increases, artifacts also increase, is no longer acceptable. Moreover, the optimization of the signal/noise ratio with high magnetic fields has appreciably shortened image acquisition time appreciably and has allowed the set up of ultra-fast sequences, in which extremely high quality images are obtained during relatively short (12-18 secs) breath holds.

Other essential technical characteristics improve signal/noise ratio, and in turn make for a shorter imaging time, such as gradients that give high standard performances (at least 40-50 T/m) and phased-array surface receiving coils.

The technology is aided by post-processing workstations that enable the user to enhance the diagnostic images with the precise quantitative information, making cardiac MRI competitive with other available investigational methods.

These technical advances have refined cardiac MRI and have made the modality more flexible, presuming that exams will be performed by *highly qualified and skilled operators* who dedicate themselves full time to cardiovascular MRI.

Techniques for Studying Cardiac Volumes and Calculating Mass

MRI may be used to obtain images of the heart in any plane. In this way standard scans can be used to obtain reproducible examinations and to visualize and interpret the normal cardiac anatomy correctly, along with its possible variants and to recognize the presence of any artefacts on the images. The scan planes may be orientated with normal cardiac anatomy to obtain longitudinal, horizontal and short axis images, or along the larger body axes to obtain axial, sagittal and coronal images.

The latter are used for panoramic imaging, offering a whole evaluation of the mediastinal cavity. These planes are used to study the relationships between adjacent structures, such as the trachea, bronchi, large vessels and the oesophagus.

The optimum slice thickness, whatever the orientation of the scan, is between 8-10mm.

A axial scan image is orientated along the vertical axis, parallel to the interventricular septum, between the centre of the mitral valve and the apex of the heart. This type of scan provides a "two chamber" image that

is useful in the evaluation of the ventricle, apex of the anterior walls and the diaphragm, the atrio-ventricular valve and in the evaluation of the cranio-caudal dimensions of the atrium. It is also used to calculate the Ejection Fraction (EF) and volume, that are evaluated using the area length method (Fig 5 a, b, c, d).

In the long horizontal axis images, the scan plane is perpendicular to the interventricular septum. An image obtained along the long vertical axis, provides a "4 chamber" image, useful for the evaluation of the apical region of the interventricular septum, of the free ventricular walls, and of the atrio-ventricular valves.

The volumes and ejection fractions of the chambers may also be calculated with this axis, according to the 2D technique.

The short axis images are obtained through planes that are orthogonal to the longitudinal or horizontal axis, orthogonal to the interventricular septum, with contiguous sections included in the valvular plane (base of the ventricles) to the apex.

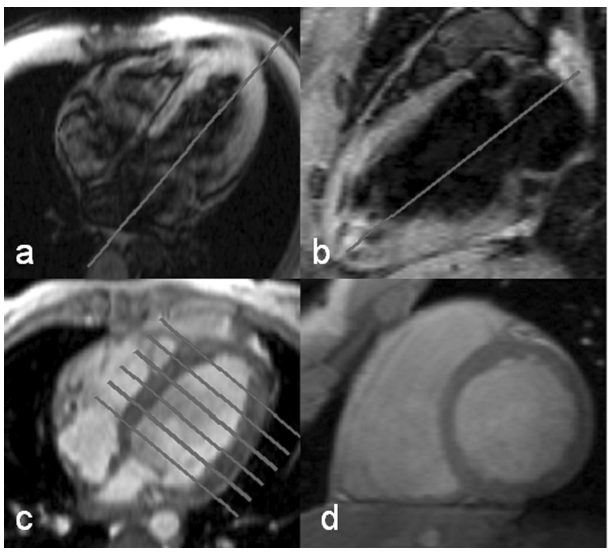

Figure 5. (a-b-c-d): MRI scout images; a) orientation of scan plane on axial view from mitral valve to cardiac apex to obtain longitudinal long axis view; b) Longitudinal long axis view is a scan plane for the horizontal long axis view (4 chambers view) from mitral valve to cardiac apex; c) Horizontal long axis view (cine FLASH 2D); orientation of the scan plane perpendicular to the long axis view to obtain contiguous short axis views (thickness 8 or 10 mm) from mitral valve to cardiac apex. d) Short axis view (cine FLASH 2D)

Cardiac MRI offers the possibility of obtaining contiguous short axial images of the heart of a known thickness with excellent contrast between the different anatomic structures. Short axial sequences are carried out using black blood, cine sequence and tagging techniques. If the MRI does not foresee the 3D evaluation of the cardiac mass and volume, which can be exclusively obtained with short axis in cine that include the whole volume of the ventricles, then at least 3 scan planes should be carried out: base line (or submitralic), medium (or trans-papillary) and apical (Fig. 6).

These allow the evaluation of the ventricle walls, the atrial structures, the aortic bulb, and the pulmonary artery cone.

Three-dimensional reconstruction of the cine images in short axis allows a quantitative, highly accurate measurement of the cardiac mass, which couldn't be performed to this degree of accuracy with prior imaging techniques; end systolic and diastolic volumes for the left and right ventricle and the ejection fraction can also be calculated (Fig. 7). The accuracy of the measurements that can be obtained with MRI is based on the excellent natural contrast between the blood and heart, now further enhanced by steady state sequences (True FISP, FIESTA) (8).

High contrast allows easier identification of the endocardial and epicardial borders. This facilitates the application of image processing algorithms that automatically recognize these borders; although today the measurements are manually made, eventually this may be automated.

Cardiac MRI interpretation has high reproducibility in the intra- and inter observer measurements; it must not be forgotten that other methods, such as the echocardiograph, have a reproducibility of the quantitative measurements of 13-21% (9).

Precision and high reproducibility have made cardiac MRI the reference method for determining cardiac mass and ventricular volume in numerous studies, particularly for the study of the right side of the heart, which is difficult to evaluate in echocardiography.

In addition, cardiac MRI represents the only reproducible method able to verify the presence of all diagnostic criteria present in an arrythomogenic dy-

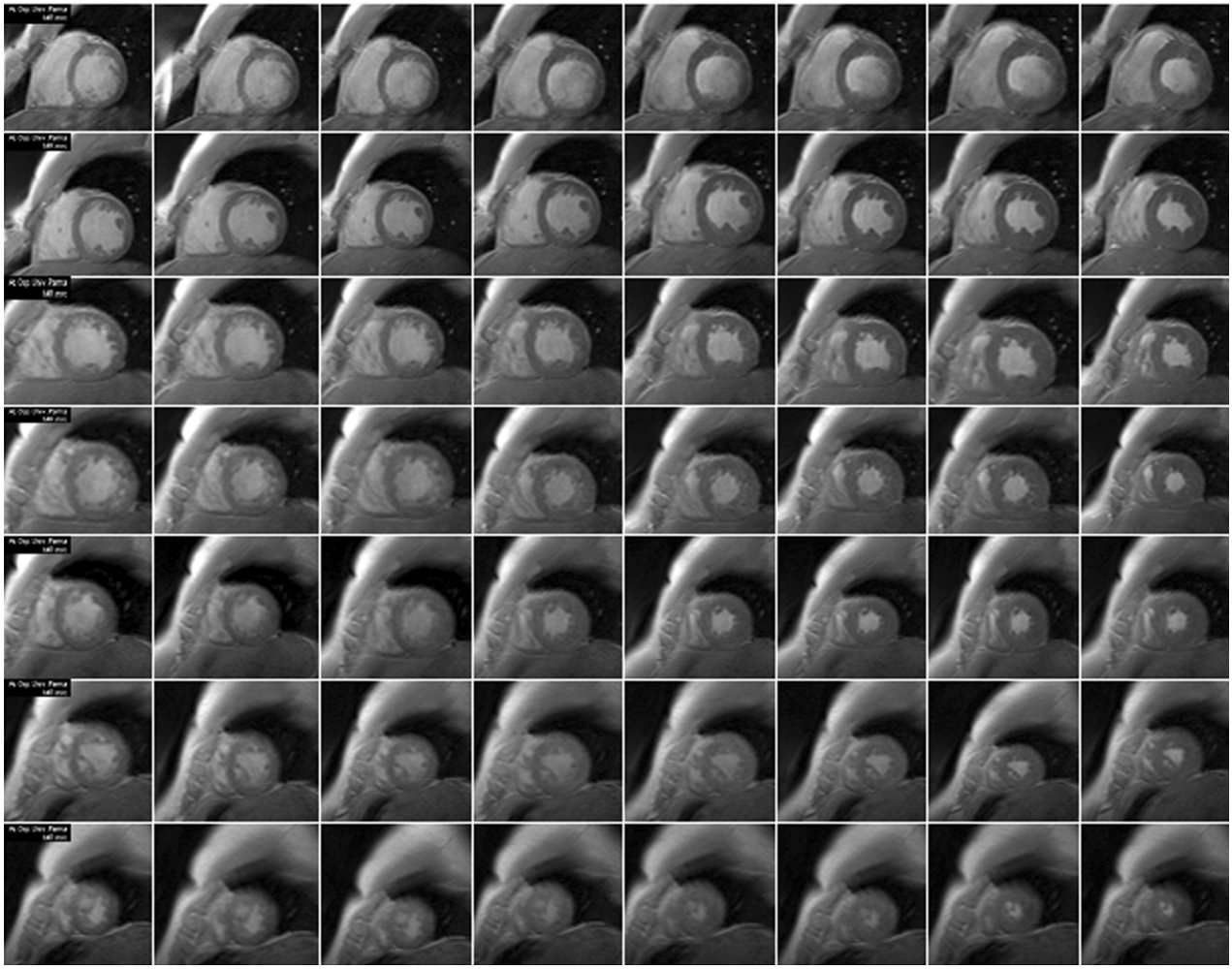

Figure 6. Short axis views cine FLASH 2D of a complete cardiac cycle, from base to apex of the heart.

splasia of the right ventricle, such as the dimensions of the right ventricle, the presence of localized asynergy at the level of the free wall and the area with fibroadipose infiltration (10).

Evaluation of Regional Kinetics

Since an ischaemic insult inevitably results in a compromise of regional contractility, this has been one of the indirect parameters used in the diagnosis of ischaemia for many years.

This is why the echocardiograph has been of extraordinary success both in clinical and research terms. State of the art technology has brought echographic equipment to excellent levels of efficiency that provide high quality images in 90% of the cases.

Despite the excellent quality of the cardiac MR images, with cine images and myocardial tagging, it only plays a marginal role in the clinical evaluation of the regional ventricular function. This is due to a variety of factors: the MRI equipment is often occupied, due to overuse, the ultrasound is "less complex" than the MRI for most operators, and echography is less costly. However, at the same time, attention has been turned towards the cardiac stress MRI (primarily with dobutamine), for superior image quality and choice of imaging, allowing for a more accurate dia-

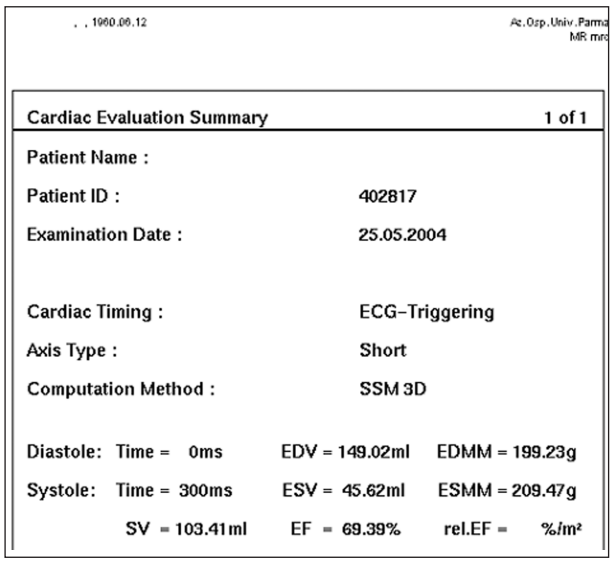

Figure 7. Report of the 3D post-processing. Cardiac volume, cardiac mass and ejection fraction are displayed.

gnosis. This is particularly true when dealing with asynergies of ischaemic nature in regions that are difficult to explore, as in the case of inferior and/or inferior-lateral walls (4).

Unfortunately, what may be gained on the one hand in terms of diagnostic accuracy, is lost on the other, in terms of organizational hitches, with difficult access to the MRI equipment. There is also the question of safety that arises with the use of ischaemia-inducing and pro-arrhythmic drugs such as dobutamine.

However, this scenario could rapidly change if the tagging of images were no longer used for qualitative evaluation and were to become a routine practice for quantitative evaluation.

It goes without saying that when the evaluation of the regional function is automatically and quantitively carried out, it reduces diagnostic uncertainties connected with the interpretative capacities of the operator. Moreover, the numeric evaluation is richer in information and the examination is highly reproducible.

The possibility of using cine MRI and myocardial tagging is extremely reassuring for the study of the myocardial contractibility as they are the only examinations that allow for the evaluation of the myocardial contractibility and its torsion and translational mechanisms.

These examinations not only provide accurate information regarding the global function but also give details of systolic thickening, both at baseline and under pharmacological stress and, therefore allow for the study of the geometry and kinetics of the complications of acute and chronic myocardial infarction.

Myocardial Perfusion

Myocardial perfusion imaging is becoming more and more common and has been the subject of recent clinical trials. It has always had an important role due to its potential support for the revascularization techniques, covering, thrombolysis, angioplasty, minimally-invasive surgery, trans-myocardial laser revascularization and even genetic therapy.

Therefore, the need of information arises, not only concerning coronary vessel conditions, but also the micro-circulation and myocardial perfusion (11).

Cardiac scintigraphy has allowed visualization of myocardial perfusion, initially with the planar imaging, followed by SPECT, and now PET; it is common practice to use cardiac scintigraphy in the study of a presumed ischaemic cardiomyopathy.

However, nuclear medicine shoes intrinsic limitations, such as only modest spatial resolution. Moreover, it is difficult to meet the demands for examinations, due to the limited sites offering the exam.

This is why researchers and pharmaceutical companies turned their attention towards alternative methods, and, in particular, towards MRI, which allows myocardial perfusion evaluation (12,13).

Further more MRI supplies advantages that are peculiar to its methodology and is capable of acquiring a series of consecutive images (between 60-80) throughout the entire cardiac cycle, using ultra fast sequences, usually in 3-7 scans oriented along the short axis during the first pass of a bolus of paramagnetic contrast medium injected into a peripheral vein (fig. 8).

This technique can now be superimposed on that of the SPECT and PET used in nuclear medicine (14).

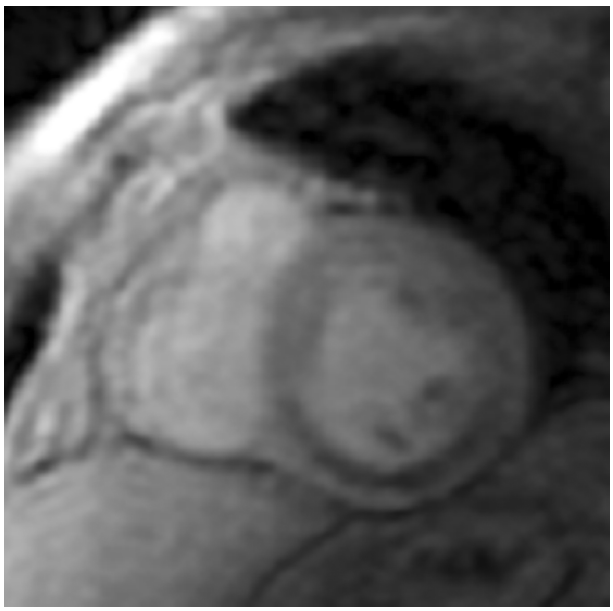

Figure 8. MRI short axis view; first pass of contrast medium. A band of ipointensity in the inferior wall of the left ventricle (arrow) is related to sub-endocardic deficit of enhancement (ischaemic area)

Myocardial perfusion may be semi-quantitatively evaluated, revealing areas of relative hypo-perfusion.

This evaluation is, of course, carried out both at baseline and under pharmacological stress (e.g. dobutamine), capable of inducing a maldistribution of the blood flow.

A *quantitative evaluation* of the absolute values of myocardial perfusion seems to be more complicated. Therefore a *time intensity curve* should be applied in order to obtain this value, by means of a videointensometric measurement of the myocardium, the principles of the marking theory (Fig. 9).

However, presently, this clashes with the pharmacokinetic characteristics of the available markers and the dynamic response of the signal, compared to the local concentrations of the contrast medium.

Indeed, the low molecular weight of the chelating agents in the gadolinium commercially available today induce a multi-compartmental distribution both at an intravascular and interstitial level, which, in turn, reflects in a "pollution" of the signal, revealing perfusion abnormalities as well as myocardial disease; higher molecular weight contrast agents are limited to the intravascular space.

These contrast mediums are at present at an advanced stage of clinical development, and the econo-

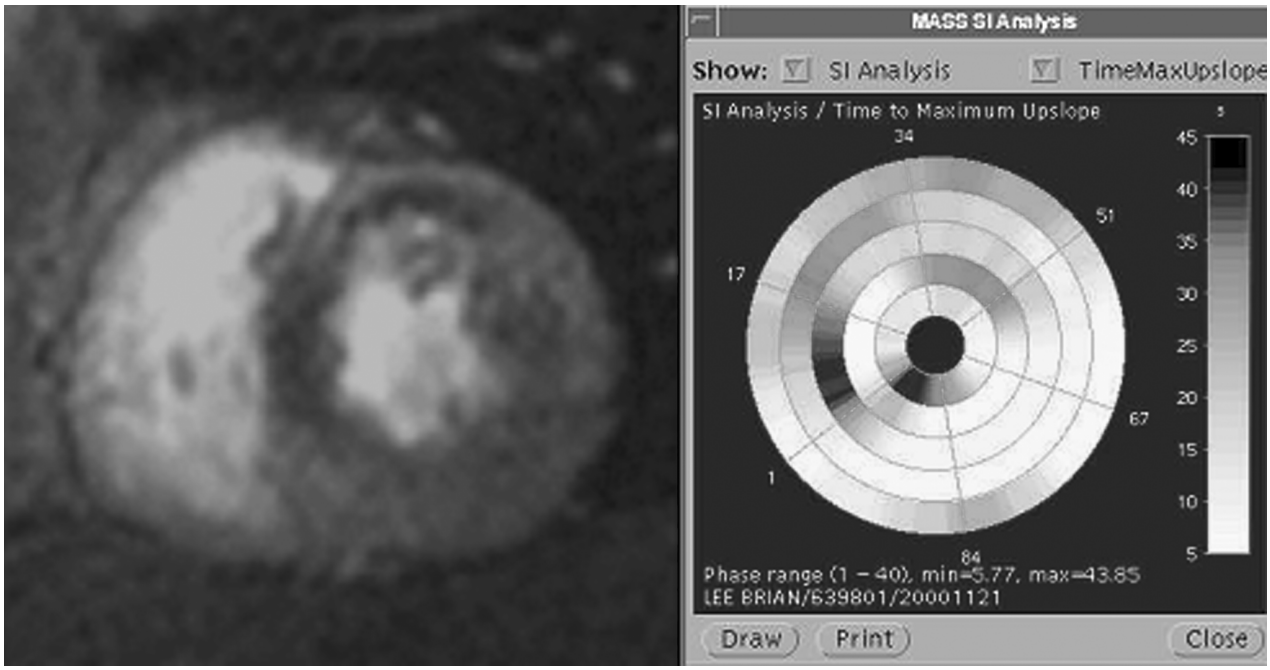

Figure 9. (a-b): Quantitative evaluation of cardiac perfusion. Ischaemia isolated of interventricular septum. a) Low septum perfusion during the first pass of contrast medium (arrow). b) Bull's eye show the same report (dark color).

mical interest shown in this field leaves hope for a rapid commercialization.

However, while it seems that some kind of solution may be found for this question, the possibility to quantitatively measure remains dubious, given that the correspondence between local concentration of the contrast medium and the signal generated does not seem to be linear, thus making difficult the application of the adopted principles with radioactive markers.

Despite this, studies carried out on animal models imply that acceptable approximations may overcome this intrinsic limit (13).

Another question which still remains, although it is moving along the lines towards a solution, but cannot be ignored, is the evaluation of the images themselves.

Once acquired, the images must be carefully scrutinized so as to identify the hypoperfused areas.

There are two available methodological approaches:

1) an evaluation in cine of the images to be carried out by an operator with pertinent expertise in the identification of the hypoperfusion based on the relative reduced increase of the signal;
2) the generation of a time-intensity curve in the single zones and the comparison of the flow-dependant indexes of their measurability.

The first approach is entirely based on the experience/expertise of the operator and, therefore, while increasing the variability of the method, at the same time it makes it easily applicable.

The generation of the *time intensity curve* depends on accurate semi-automatic and automatic post processing programmes. Although such programmes are now coming out on the market, they have a great deal of difficulty in dealing with the enormous quantity of data to be processed and are, at present, mainly the prerogative of small niche ultra - specialized centers.

In other words, post processing is at the start of an ever increasing developmental phase which is a vital part of the diagnostic process, a necessary compendium if the expert eye of the operator is "substituted".

The evaluation of myocardial perfusion by means of MRI, has begun its clinical course.

Viability, Delayed Enhancement and Infarcted Myocardium

The possibility of evaluating the myocardial viability in patients with known ischaemic cardiopathy is of important clinical relevance.

In fact, one of the strongest predictors of long term survival is the entity of the contractile dysfunction of the left ventricle (LV). However, this dysfunction does not necessarily mean that necrosis will follow and a collagenous scar will develop; this may also be recognized in the presence of a viable tissue that is temporarily malfunctioning, after ischaemic reperfusion or chronic hypoperfusion.

According to the terms commonly used by cardiologists, the viable myocardium is usually identified as *"stunned" or "hibernating"*. The condition of *stunning,* is a condition in which there is a metabolic and contractile alteration due to a prolonged ischaemic event with an adequate restoration of the coronary blood flow at rest. The term *hibernated,* means that the myocardial tissue in which the coronary flow is chronically reduced (but over a critical threshold that maintains cellular survival) is associated with a reduction in the contractile function.

As the two conditions do not exclude one another, repeated episodes of ischaemia that provoke myocardial stunning, in the presence of a reduced myocardial blood flow, may lead to a state of myocardial hibernation (15).

The study of the myocardial viability is aimed at the verification of the presence of viable myocardium, to give a topographic description, evaluate the extent and pathophysiological characteristics, such as the contractile reserve and inducibility with the correct stimulus. The reason why such an effort must be applied to diagnostics is that this tissue may recover to normal contractibility after coronary revascularization, but, above all, because its presence has important prognostic consequences if revascularization does not take place. However, the prognostic significance is far from easy, as it varies on the basis of the presence of global or regional dysfunction of the left ventricle, the evaluation period (acute or progressive infarcted myocardium), and the extension of the infarction (6, (16)

There are various methods that may be utilized in

the evaluation of viable tissue, such as nuclear-medicine and echocardiography with isotope stimulus, but cardiac MRI seems to offer a more accurate definition, through the study of delayed enhancement after the intravascular administration of contrast medium (delayed-contrast enhancement, DE- MRI).

The use of a Gradient Echo sequence with parameters particularly sensitive to the accumulation of the contrast medium, allows the mapping of the cardiac tissue and the identification of any necrotic tissue.

Necrotic tissue has an altered enhancement kinetics, in particular a delayed washout of the deposited gadolinium-chelate.

When the results obtained with this method were compared to those obtained with PET, they were very similar (17). It has recently been demonstrated that the zones of altered contrast enhancement correspond precisely to the necrotic tissue, as the tissue conserves correct kinetics of the marker, and the distinction between necrotic and viable tissue is possible (18).

No delayed uptake of the contrast agent can be observed when the myocardium is viable, and there is no reduction in the wall thickness. Only a segmental alteration of the myocardial contractibility can be observed. The viable myocardium observed at MRI is clearly shown at MRI control at about 40 days (1).

Long term follow up that shows the disappearance of focal contractile dysfunction is indicative of stunning. While on the other hand, the wall motion abnormality is more an indication of the presence of a hibernated myocardium, a condition which is reversible after the restoration of the coronary perfusion after coronary by-pass (19).

The delayed acquisition of the image after the administration of a contrast agent allows for a clear distinction of the infarcted tissue from surrounding tissue. This technique has an excellent noise/contrast ratio, much more so than other sequences.

Indeed, the use of the DE-MRI technique with GE T1 weighted sequences after the administration of gadolinium shows the nonviable tissue as hyperintense areas.

The acquisition is made 15-20 minutes after the administration of 0.1- 0.2 mmol/kg of contrast agent, revealing the secondary fibrotic substitution after ischaemic injury.

The mechanism involved in the accumulation of the contrast medium in the necrotic tissue is not yet completely clear.

Various mechanisms have been hypothesized:

- an accumulation of the paramagnetic contrast agent in the large interstitial spaces present in necrotic tissues;
- a slow washout of the contrast medium in the necrotic tissues;
- contrast bound to the proteins within the necrotic tissues.

Kim et al were the first to evaluate the behaviour of contrast enhancement in acute/chronic infarction and in severe, but transient ischaemic injury in animal models (20).

In his study the animals were examined by MRI and the data obtained supplied not only information regarding the delayed enhancement but also morphological data and ventricular kinetics through the use of cine – MRI.

The results of the DE-MRI in hearts removed from dogs were compared to the histo-pathological TTC stained sample slices. A strong correlation was observed between the location, spatial extent of the area in which there was a delayed enhancement of the contrast agent, and the infarcted area.

This connection excluded the possible interpretation that the hyperintensity was present not only in the part of the myocardium that had become necrotic post infarction, but also in the reversibly injured area adjacent to the necrotic zone. However, hyperenhancement occurs not only in regions of cellular necrosis but also in a border zone of injured but viable myocytes surrounding the acute infarct in the first 24 hours; partial–volume effects may also play a role in the overestimation of infarct size (20) (Table 1).

Indeed, the observation that the spatial extent of the scar, and thus the hyperintensity, at 8 weeks was smaller than the spatial extension of the myocardium that had gone into necrosis at 3 days after the ischemic event, could have been interpreted in this way.

In reality, the temporal changes in hyperintensity may be explained by the reduction in the infarcted area that normally occurs between the 4th and 8th week, therefore the study concluded by saying that *the de-*

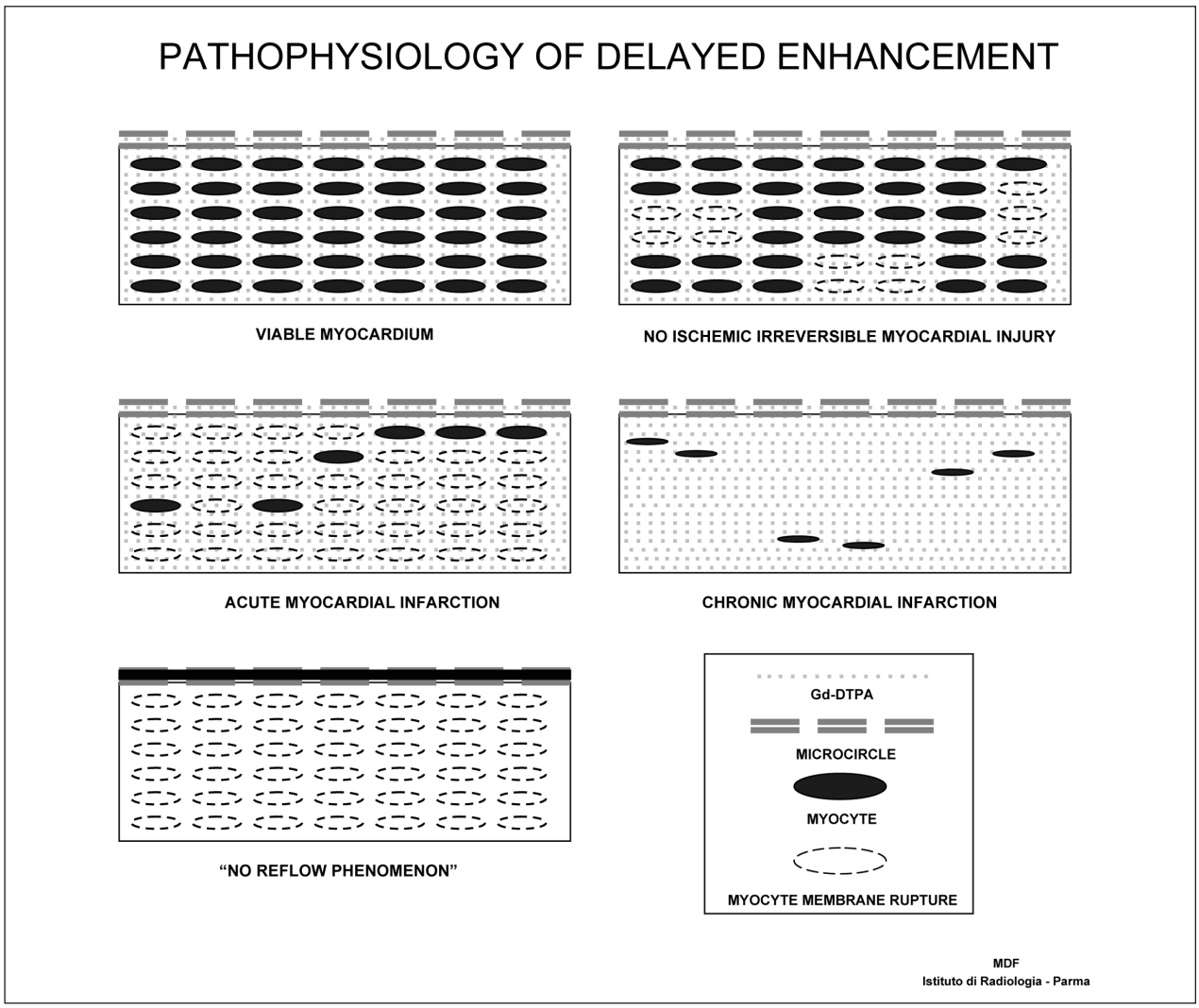

Table 1. Schematic drawing (capillary and tissue) of the distribution volume of an extracellular contrast agent in normal (A), acute myocardial infarcted (B) and chronic infarcted myocardium (C)

layed uptake of the contrast agent takes place only in the regions with irreversible ischemic injury (20).

On the basis of these findings, the trials that followed, both in animal models and in humans, showed that the hyperintensity of a segment or a myocardial region is a predictive parameter of the functional recovery of myocardial injury (21).

It is therefore, essential to have a clear picture/evaluation of the transmural extent of the hyperintensity at MRI study since a strict correlation between the extent of recovery of the contractile function and the transmural extent of the collagenous scar.

Thanks to the spatial resolution and tissue identification that it offers, the DE-MRI is able to quantify the area of viable myocardium and to delimit the nonviable regions (22).

The presence of a myocardial infarct is accompanied by a prolonged relaxation time in the T1, T2 weighted and STIR sequences with a consequent increase in the signal intensity in the affected area; these variations in the relaxation times at the myocardium site of the infarct can already be observed in vivo *3-6 hours after coronary occlusion and up to 20 days thereafter (20).*

Apart from the intrinsic variations in signal intensity, the presence of a recent myocardial infarct is associated with alterations in the contractibility and may slow down the intra-cavitary flow surrounding the infarcted area, which assumes a characteristic high signal intensity in spin-echo images.

The diagnostic accuracy of the MRI, which is greatly enhanced by the addition of paramagnetic contrast medium, allows not only for the identification of the infracted area but also a quantitative evaluation of the area. This is demonstrated by the close correlation observed for enzymatic and autopsy measurements (21), based on the altered local bio-distribution of the contrast agent i.e. the wash-in washout , in the infarcted area, where an increase in signal is produced in the T1 delayed acquisitions (5-15 mins. after the i.v. administration of GD-TPA), (fig 10 a-b) (23).

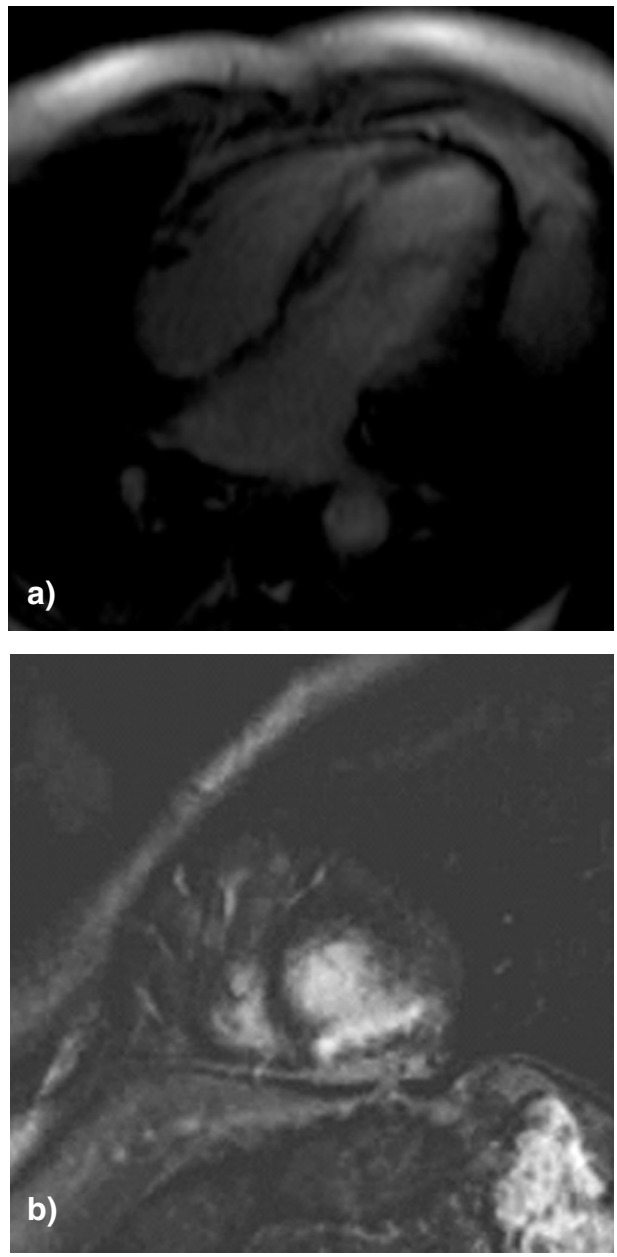

Figure 10. (a-b): Delayed enhancement. a) 4 chamber view shows transmural late enhancement in the cardiac septum (arrow) due to focal necrosis. b) MRI short axis view: subendocardic late enhancement in the inferior wall of the left ventricle

A Comparison Between MRI and Other Conventional Methods for the study of Myocardial Ischaemia.

Today, MRI offers evident advantages over other more consolidated methods for the study of myocardial ischaemia.

This is particularly true for nuclear-medicine, given that the MRI offers a superior spatial resolution, allowing for an optimal distinction of the subendocardial perfusion alterations, with a diagnostic accuracy that is superior to both PET and myocardial scintigraphy (24).

MRI is able to detect myocardial infarcts confined to the subendocardium and therefore, of limited transmural extent (25).

Imaging times are greatly reduced by MRI, both in the evaluation of the ischaemia and viability, with the added advantage of not using ionizing radiation, a fact that should not be underestimated.

When MRI is compared to echocardiography, the most evident advantage is observed when dealing with perfusion, where echography following contrast administration still has many limitations, such as the presence of artifacts at the lateral wall of the left ventricle (26).

There is still little data available to date that compares stress echography with dobutamine and delayed MRI enhancement, even if recent data has tended to indicate MRI as having an advantage.

In the case of an unclear echocardiographic examination, from a morphological point of view, MRI allows for an objective diagnosis of any post-infarct

ventricular aneurysm and/or the possibility, of enhancing the contrast between the mural thrombus formation and the surrounding structures (23).

Moreover, recent MRI studies have demonstrated a strong correlation between the transmural extension of the hyperintensity and the recovery of the contractile function after coronary revascularization. Indeed, the probability of recovery progressively reduces with the increase in transmural delayed hyperintensity.

This is the reason why MRI using the DE-MRI technique, has an advantage over other investigational tools, when carrying out predictive investigations concerning myocardial dysfunction recovery in patients after revascularization (27).

Albeit that the question of the high cost involved in the employment of this technique remains to be overcome, if the prospective of avoiding useless invasive examinations is taken into account, this seems to be a way to a solution.

Conclusions

Cardiac MRI offers a variety of techniques to evaluate myocardial viability in patients with acute or chronic myocardial infarction through the assessment of global and regional cardiac function, of delayed enhancement, of myocardial response to low dose dobutamine, and through the visualization of infarct size as well its transmural extent.

Larger clinical trials and its use in routine clinical care have to show its value in patient care.

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