Contrast magnetic resonance imaging for cardiovascular measurements

an vitro study

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Contrast magnetic resonance imaging for cardiovascular measurements:
an in-vitro study

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Abstract

The measurement of cardiac output, ejection fraction, and pulmonary blood volume provides valuable information about the overall efficiency of the cardiovascular system. Most of the available indicator dilution techniques for the assessment of these parameters are very invasive. However, recent studies have demonstrated that non-invasive cardiovascular quantifications by indicator dilution methods are possible by means of imaging techniques such as contrast echocardiography. The purpose of this study is to prove that the same indicator dilution principles that are used in ultrasound imaging are also applicable in contrast magnetic resonance imaging for cardiac quantifications. A paramagnetic contrast agent bolus is injected peripherally and detected in the central circulation by a magnetic resonance imaging (MRI) scanner. For this application, the first requirement is the establishment of the relationship between contrast agent concentration and measured signal intensity. As part of this research, in-vitro calibration experiments in static conditions were done using a 1.5T MRI system at the Catharina Hospital Eindhoven. Several sequences were used in order to calculate the relationship between contrast concentration and signal intensity. Since the ultimate goal is an application in dynamic conditions, due to the presence of flow, only the fastest MRI sequences are considered. The results demonstrate that sequences with positive enhancement show a linear relationship (correlation coefficient equal to 0.97) for concentrations of gadolinium lower than a specific upper bound. This upper bound varies among the different adopted sequences. The best results correspond to the calibration curve that shows the largest linear range. Based on these results, future study should involve in-vitro calibration experiments in dynamic conditions, where increased complications are expected due to the presence of flow.
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1 Introduction

The assessment of cardiovascular parameters, such as cardiac output (CO), ejection fraction (EF), and pulmonary blood volume (PBV), has fundamental importance in the clinical diagnosis because it provides information about the overall efficiency of the cardiovascular system. These cardiovascular parameters are explained in chapter 2.

Most of the indicator dilution techniques used for cardiovascular quantification are very invasive or do not provide a simultaneous and accurate measurement of all the parameters of interest. However, contrast imaging techniques might solve these inconveniences and permit a minimally invasive measurement. An overview of the most common techniques that are available for quantification of CO, EF, and PBV is presented in chapter 3.

This study aims to prove that contrast imaging methods and principles, which were applied for instance in a recent research on contrast echocardiography [22], are also applicable in the context of contrast magnetic resonance imaging. Magnetic resonance imaging (MRI) is a non-invasive diagnostic technique, which uses resonance properties of hydrogen protons, to construct high contrast pictures of the inside of the human body. An extended overview of MRI is provided is chapter 4.

Contrast MRI techniques make use of paramagnetic contrast agents, such as gadolinium compounds, which are injected in blood. The immediate effect is the signal enhancement in the desired anatomical region, e.g., the heart. Chapter 5 describes the contrast agents that are used in MRI and explains their effects on the detected MRI signal.

In order to determine the desired cardiovascular parameters by means of the mentioned principles [22], it is necessary to obtain the indicator dilution curve (IDC) of the injected contrast agent in a specific region of interest (ROI) of the image. To this end, the relationship between contrast concentration and measured gray levels in the image must be established. Therefore, in-vitro calibration experiments must be done both in static conditions and subsequently in a dynamic setting in which the complexity is expected to increase due to the presence of flow. In this thesis the static calibration experiments are carried out. Chapter 6 presents the results of the static calibration experimentation.
2 Clinical parameters

The heart is a muscular organ that pumps blood through the circulatory system in order to carry oxygen to the cells of the human body. It consists of four chambers (Fig. 2.1): the two upper atria, and the two lower ventricles. The left and the right atrium (LA and RA) are filled by blood coming respectively from the pulmonary veins and the vena cava, while the left and the right ventricle (LV and RV) pump blood into the aorta and the pulmonary artery respectively. The LA and the LV are connected by the mitral valve, while the RA and the RV are connected by the tricuspid valve.

![Figure 2.1: Scheme of the heart and the circulatory system.](image)

The ventricle cycle is divided in two phases: diastole and systole. Diastole is the expansion of the ventricle due to the blood filling, and systole is the contraction due to the blood ejection. During diastole the mitral (or tricuspid) valve is opened and blood flows from the atrium into the ventricle. During systole the
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valve is closed, and blood is pushed through the aortic valve or pulmonary valve into the aorta or the pulmonary artery, respectively.

There are two circulatory systems, i.e., the systemic circulation, which brings oxygen to all the body, and the pulmonary circulation, which passes through the lungs where the gas exchange takes place.

The overall efficiency of the heart and the circulatory system is usually characterized by some main parameters:

- The pulse rate (PR), which is the number of cardiac cycles per minute.
- The cardiac output (CO), which is the blood flow through the aorta outtrack.
- The ejection fraction (EF), which is the percent volume variation of the ventricles.
- The pulmonary blood volume (PBV), which is the blood volume in the pulmonary circulation.

2.1 Cardiac Output

The CO is the volume of blood that is ejected by the left ventricle into the aorta expressed in liters per minute. Due to the cyclic contraction-expansion of the ventricles, the CO is a periodic function of time. However, it is often represented by a single value, which is a measure of the average flow. The CO is related to the ventricular volume variations during the cardiac cycle. If $V_{ed}$ is the end-diastolic volume and $V_{es}$ is the end-systolic volume, then the stroke volume (SV), which is the volume of blood ejected from the ventricle to the artery in one cardiac cycle, equals the difference $V_{ed} - V_{es}$. Therefore, the CO can be defined as given in Eq. 2.1.

$$CO = SV \cdot PR$$

2.2 Ejection Fraction

The EF is a measure of the efficiency of the myocardial contraction. If the end diastolic and the end systolic ventricular volumes are measured, the percent EF is defined as given in Eq. 2.2.

\[ \text{This is true only if we assume that there is no regurgitation (valve insufficiency).} \]
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\[
EF \% = \frac{V_{ed} - V_{es}}{V_{ed}} \cdot 100
\]  

(2.2)

In case of insufficiency of the mitral valve, the EF is the sum of the forward EF (FEF), which is due to the blood volume that is ejected into the aorta, and the regurgitant EF (REF), which is due to the blood volume that is ejected back into the LA.

### 2.3 Pulmonary Blood Volume

Blood volumes measurements are important parameters to evaluate the cardiac preload and the symmetry of the cardiac efficiency. In particular, the pulmonary blood volume (PBV) is the blood volume between the pulmonary artery and the LA, the central blood volume (CBV) is the blood volume between the pulmonary artery and the LV, and the intra-thoracic blood volume is the blood volume between the RA and the LV.
3 Indicator Dilution Methods

Indicator dilution methods are based on the dilution of a small amount of indicator (an easily and accurately measurable substance) that is injected into the bloodstream (hence the name indicator dilution). Vascular indicators are used in applications using the indicator dilution technique, however, many indicator (also referred to as contrast agents) types exist [30–32]. Several physiological parameters can be determined by measuring the indicator concentration downstream, a certain distance away from the injection site.

The path from the injection point to the measurement site downstream should have no branches through which the indicator could (partially) disappear. Specific requirements for vascular indicators are: it should not be absorbed by tissues, it should be non-toxic, and it should be cleared in a natural way after a while (after the measurement) [33]. There are many different types of indicators, all employed in different applications: chemicals, inert gases, radioactive isotopes, dyes (dye dilution), and heat (thermodilution).

3.1 History

Indicator-or tracer-dilution methods have been used in circulatory studies for a long time. They are being used for measuring blood flow, volume of distribution, translocation across barriers, etc. For a comprehensive history of indicator dilution methods refer to [34].

Hering, professor at the Royal Veterinary School in Stuttgart, introduced the indicator dilution method to measure hemodynamic properties, e.g., the blood circulation velocity. Between 1824 and 1826 he carried out experiments in horses, which he published in 1829. At that time he thought he had measured velocity, whereas he had measured the appearance time of the indicator.

In 1890, 65 years later, G.N. Steward published an abstract in which he described his application of Hering's method to measure the appearance time, using NaCl as indicator. By measuring the conductivity of the samples, he found that there was not only a delay, but also a dispersion of the indicator. In 1897, Steward suggested that the indicator dilution technique could be used to measure blood flow.

It took 30 years more before Steward's idea was picked up, using the indicator dilution curves to calculate flow. Furthermore, his idea suggested that the area under the curve had something to do with the flow. From the late 1920's until
the 1940's William F. Hamilton was the dominant figure in the indicator dilution field. He used the Hering-Steward technique and a dye (a soluble colorant, used to provide contrast in the different tissues and organs) as indicator. Hamilton also recognised that Stewart's calculation was only valid if no tracer recirculation was present in the indicator dilution curve.

In 1950 Zierler et al. began using the indicator dilution theory to measure blood flow and volume in the forearm of a man [35]. This research led to the insight that the first-passage indicator dilution curve (without recirculation) is a result of its input (an instantaneous injection) and the impulse response \( h(t) \). \( h(t) \) is basically the function that describes the path between the injection and detection site.

### 3.2 Theory

This section describes the theory of measuring three clinical parameters of interest, namely: \( \text{CO} \), \( \text{EF} \), and \( \text{PBV} \). Before going into detail, Fig. 3.1 shows a general form of an indicator dilution curve (IDC).

An IDC is a graphical representation of the contrast agent concentration versus time \(-C(t)\) measured downstream– as a result of a contrast agent injection upstream, while a certain flow \( \Phi(t) \) is present between the injection and detection point (Fig. 3.1). The CO is assumed to be a time continuous flow.

For a detailed derivation of the formulae given in the next sections, see [22, pp. 8–31].

#### 3.2.1 Cardiac Output

The indicator dilution theory assumes that the indicator in uniformly diffused into an unknown volume \( V \), and the injected mass \( m \) of the indicator is known. Only then the unknown volume can be determined. By combining the equations 
\[
\Phi(t) = \frac{dV(t)}{dt} \quad \text{and} \quad C(t) = \frac{dm}{dV},
\]
where \( \Phi(t) \), \( V(t) \), \( m \), and \( C(t) \) are the instantaneous flow, the volume of the carrier, the mass of the tracer, and the tracer concentration at time \( t \), respectively, Eq. 3.1 can be derived.

\[
\Phi(t) = \frac{dV(t)}{dt} = \frac{1}{C(t)} \frac{dm}{dt} \tag{3.1}
\]

14 Indicator Dilution Methods
Two main techniques make use of Eq. 3.1, one uses a continuous tracer infusion, and the other one uses a rapid tracer injection. These techniques are discussed in section 3.3.1.

### 3.2.2 Ejection Fraction

The indicator dilution theory for EF measurements is based on a mathematical interpretation of the IDC. Notice that the forward ejection fraction (FEF, which is the EF minus the regurgitant ejection fraction (REF)) is being measured, and that the indicator must be rapidly injected into the ventricle.

![Mono-compartment model for LV EF simulation.](image)
A ventricle can be modelled as a mono-compartment system, as shown in Fig. 3.2. The indicator is injected during the diastolic phase; after the \(n\)th end-diastole, the contrast concentration is given as \(C_n\) and equals the indicator mass \(m\) in the ventricle divided by \(V_{ed}\). The next systole, part of the mass \((\Delta m)\) is ejected out of the ventricle, and the concentration at the \((n+1)\)th end-diastole drops to \(C_{n+1}\), as given in Eq. 3.2.

\[
C_{n+1} = \frac{m - \Delta m}{V_{ed}} = C_n \cdot \left(1 - \frac{V_{eq} - V_{es}}{V_{ed}}\right)
\]

(3.2)

Combining Eq. 3.2 with Eq. 2.2, yields Eq. 3.3.

\[
EF\% = \left(1 - \frac{C_{n+1}}{C_n}\right) \cdot 100
\]

(3.3)

The left ventricle (LV) can be well approximated by a single monocompartment model, whose impulse response equals an exponential function. The IDC \(C(t)\) after a rapid contrast injection during diastole can be represented as given in Eq. 3.4, where \(C_0\) is the concentration after an instantaneous indicator injection into the compartment after time \(t = 0\), and \(\tau\) is the time constant of the system [36].

\[
C(t) = C_0 \cdot e^{\frac{-t}{\tau}}
\]

(3.4)

If the model in Eq. 3.4 is used to fit the IDC, Eq. 3.3 can be expressed as given in Eq. 3.5.

\[
EF = 1 - \frac{C_{n+1}}{C_n} = 1 - \frac{e^{\frac{-\Delta t}{\tau}}}{e^{\frac{-t}{\tau}}} = 1 - e^{\frac{-\Delta t}{\tau}}
\]

(3.5)

The time interval \(\Delta t\) is the cardiac period \(\Delta t = \frac{60}{PR}\) seconds. With this technique there is no need for triggering the end-diastolic time, and only the cardiac period \(\Delta t\) is required.
3.2.3 Pulmonary Blood Volume

The measurement of volumes by means of the indicator dilution theory is based on the mean transit time (MTT), which is the average time the indicator needs to go from the injection to the detection site. When the CO is known, the volume between the injection and detection site can be calculated according to Eq. 3.6.

\[ V = MTT \cdot CO \]  

(3.6)

3.3 Indicator dilution techniques

3.3.1 Classic indicator dilution techniques

Continuous tracer infusion

These techniques use large amounts of contrast, so the indicator (contrast agent) must be absolutely inert, harmless, and not toxic [22][33]. Two indicators dilution techniques satisfy these requirements, namely oxygen (O₂), which is used in the Fick technique, and heat, which is used in the continuous thermodilution technique.

Fick Technique. This technique makes use of two indicator concentration measurement sites, one (site a) before the injection point, and one (site b) after the injection point. Assuming constant concentrations \( C_a \) and \( C_b \), and a stationary flow \( \Phi_a = \Phi_b = \frac{dV}{dt} \), Eq. 3.7 can be derived.

\[ \Phi = \frac{dm}{dt} \frac{1}{C_b - C_a} \]  

(3.7)

The clue to this technique lies in the indicator (O₂) injection; oxygen is namely injected by the lungs themselves. \( C_a \) and \( C_b \) are the venous and the arterial oxygen concentrations, and are measured in the pulmonary artery and an arm artery, respectively. The mass of the injected tracer (oxygen) is measured with a spirometer [33].

Warm (continuous) Thermodilution Technique. This technique uses heat as an indicator. The injected heat can easily be cleared through the blood vessel walls, so that the distance between the injection and sampling site should be as short as possible. An electric heater (resistor) continuously generates heat that is absorbed
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by the blood and thus injected into the right atrium (RA), while the temperature is measured by a thermistor in the pulmonary artery (PA). The flow (CO) can be calculated using Eq. 3.8, where \( q \) is the heat (in Watt, comparable with the term \( \frac{dm}{dt} \)), \( T_b - T_a \) the temperature difference (in Kelvin, comparable with the term \( C_b - C_a \)), \( c_b \) the specific heat of the blood (in \( J \cdot kg^{-1} \cdot K^{-1} \)), and \( \rho_b \) the density of the blood (in \( kg \cdot m^3 \)).

\[
\Phi = \frac{q}{c_b \rho_b (T_b - T_a)}
\]  

(3.8)

The advantage of continuous tracer infusion techniques is the possibility of continuous CO monitoring.

**Rapid injection of the tracer**

Rapid tracer injection techniques perform the injection of a small bolus of indicator. Therefore, due to the small amount, the constraints on the nature of the tracer are less restrictive.

The basic principle of these methods relates to Eq. 3.1. However, in this context \( C(t) \) is not constant. The indicator is rapidly injected into a fluid-dynamic system (Fig. 3.1) where a carrier fluid (e.g., blood) is flowing, and the IDC is measured in a different site. The IDC contains all the information to estimate the flow, whose value is derived from Eq. 3.1 by an integration over time as shown in Eq. 3.9. The flow is assumed to be constant, so that \( \Phi \) can be moved out of the integration. The resulting formula, referred to as Stewart-Hamilton equation, provides the measurement of the mean flow \( \Phi \).

\[
\int_0^\infty \Phi C(t) dt = \Phi \int_0^\infty C(t) dt = \int_0^\infty \frac{dm}{dt} dt = \int_0^\infty m = \Phi \int_0^\infty C(t) dt
\]  

(3.9)

Since the circulatory system is a closed system, the contrast recirculates. As a consequence, the tail of the IDC is masked by the rises due to the contrast recirculation (Fig. 3.3). In addition, depending on the measurement technique, the IDC is often very noisy. Therefore, a model is necessary to fit the IDC and estimate the integral of Eq. 3.9.
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Figure 3.3: The continuous line shows the theoretical IDC (first passage of the indicator) while the crosses represent the measured IDC.

All the IDC methods are based on the following assumptions, which also cause measurement errors.

- The blood flow is constant during the measurement (about one minute).
- There is an instantaneous and uniform mixing of the tracer.
- The injection is so fast and can be modelled by a dirac impulse.
- The loss of indicator is either absent or known.

The use of different indicators leads to different sensors and techniques. The most common techniques are cold thermodilution, dye dilution, and lithium dilution.

**Cold Thermodilution.** This technique uses either cold dextrose or saline (blood-isotonic solution, 0.9% NaCl) as an indicator. A Swan-Ganz catheter is inserted via a central vein through the right atrium and ventricle so that its tip lies in the pulmonary artery (Fig. 3.4). It is carried in the right position by the dragging force of the flowing blood thanks to a doughnut-shaped air-filled balloon on the tip of the catheter. The cold solution is injected rapidly through a port of the catheter that ends at a side hole into the right atrium. The cold solution mixes with blood into the right atrium and ventricle before passing through the pulmonary artery, where the temperature decrease is sensed by a thermistor on the side of the catheter. The CO is then calculated from the temperature-time curve.
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Figure 3.4: Swan-Ganz catheter for cold thermodilution. The IDC is measured by the temperature fall.

With the same interpretation of heat and temperature that is used in Eq. 3.8, Eq. 3.9 can be written as in Eq. 3.10, where $q$ is the total injected heat expressed in Joule and $\Delta T$ is the temperature fall expressed in Kelvin ($c_b$ and $\rho_b$ are the same as in Eq. 3.8).

$$\Phi = \frac{q}{c_b \rho_b \int_{t_0}^{\infty} \Delta T(t)dt} \quad (3.10)$$

Dye Dilution. This technique makes use of a colored dye such as indocyanine green, usually referred to as cardiogreen. Using the principle of absorption photometry, the concentration of cardiogreen, which is usually injected into the pulmonary artery, can be detected by the light absorption peak at the wavelength of 805nm.

In the past, blood samples had to be drawn by a catheter placed in the femoral or brachial artery and analyzed by an external photometry device. Nowadays, the use of optical fibers allows in-situ measurements.

Once the system is calibrated, meaning that the peak absorption is related to the concentration $C(t)$ of the dye, the flow is directly given by Eq. 3.9.

Lithium Dilution. Lithium is a fluid that can be injected and detected by a specific sensor. The sensor consists of a lithium-selective electrode in a flow-through cell.

---

2 Placed at the site of origin, in order to observe the process sample in an unmodified state.
The transducer measures a voltage $E$ that is logarithmically related to the lithium concentration according to the Nerst equation (Eq. 3.11), where $C_{\text{ext}}$ and $C_{\text{int}}$ are the external and the internal (with respect to the membrane) lithium ionic concentrations, $R$ is the gas constant (8.314 $J\cdot mol^{-1}\cdot K^{-1}$), $T$ is the absolute temperature, $F$ is the Faraday constant (96485 $C\cdot mol^{-1}$), and $n$ is the valence of the ions, which for lithium ions ($Li^+$) is 1.

$$E = \frac{RT \ln(C_{\text{ext}})}{nF \ln(C_{\text{int}})} \quad (3.11)$$

The sensor is connected to a three-way tap on the arterial line and a small peristaltic pump draws blood with a flow of 4.5ml/min.

After calibration, the lithium concentration is determined and a lithium IDC is generated. The time integral of the measured IDC is used as given in Eq. 3.9 for the CO assessment.

3.3.2 Contrast Imaging Techniques

Several medical imaging technologies (nuclear, magnetic resonance, and ultrasound imaging) can be used in combination with a suitable contrast for IDC measurements. These contrast imaging techniques are minimally invasive\(^3\), and permit the simultaneous measurement of several IDCs from different sites in the central circulation.

Radionuclide Techniques for Nuclear Imaging (PET and SPECT). In these techniques a small amount of radioisotopes, referred to as radiopharmaceuticals, is peripherally injected. The radioactive decay of radioisotopes leads to the emission of $\alpha$ and $\beta$ particles as well as $\gamma$- and $x$-radiation. Hence, the detection of the indicator is performed by radioactivity measurements in a photon counter referred to as gamma camera. The information detected and recorded by these scanners is analyzed and processed to generate images. In these images the concentration of the radiopharmaceuticals can be derived from the average video density in a fixed ROI, so that an IDC can be obtained.

Contrast Magnetic Resonance Imaging Technique. In this technique a bolus of a paramagnetic contrast agent, such as gadolinium, is injected in order to selectively alter the magnetic resonance image intensity of a particular anatomical region.

\(^3\) Catheterization is not required. Only a peripheral intravenous injection of the indicator is needed.
Therefore, the gadolinium concentration $C(t)$ can be calculated from the signal intensity in a fixed ROI.

**Contrast Ultrasound Imaging Technique.** In this technique a bolus of ultrasound contrast agent (UCA) is injected into a peripheral vein. UCA are micro-bubbles of gas that reflect ultrasounds and are easily detected by an ultrasound transducer. An IDC can be measured in a specific ROI in the images produced by an ultrasound scanner.

### 3.3.3 Comparison between the available techniques

Nowadays, what is considered the gold standard technique for CO measurements is the thermodilution, especially the cold one, which also allows a simultaneous RV EF estimate. Still common in the clinical practice is the dye-dilution method, especially after the introduction of optical fibers. The Fick method procedure is more complicated, since it requires the use of both a spirometer and a gas analyzer. The use of lithium dilution is spreading due to the less invasive approach. The indicator dilution methods can be easily performed in the operating room during surgery and in the intensive care unit. The main disadvantage is the use of catheterization, which brings several risks and complications.

There is no unique approach for the simultaneous measurement of CO, LV EF, RV EF, and blood volumes (ITBV, CBV, and PBV). Different techniques must be used, which make the measurement a complex and slow procedure. Moreover, accurate measurements of CO and especially blood volumes require catheterization, resulting in very invasive applications. Also the measurement of FEF requires catheterization, as well as the assessment of RV EF, whose geometrical assessment is rather complex.

In this context, contrast imaging techniques might permit the simultaneous and minimally invasive measurement of CO, LV EF, RV EF, and blood volumes (ITBV, CBV, and PBV). The measurements are based on the hemodynamics, therefore, they are directly related to the cardiac efficiency.

Radionuclide techniques are not applicable to patients under surgery or intensive care as well as to patients in special conditions (e.g., pregnant or breast feeding women). That is not the case in ultrasound and magnetic resonance imaging, since the contrast agents used in these techniques are safe. Another disadvantage of radionuclide techniques can be the low spatial resolution of the acquired images (between 4 and 5 mm). On the other hand, ultrasound and magnetic resonance imaging produce high spatial resolution images (between 1 and 2 mm), which makes them suitable techniques to perform the desirable measurements.
4 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a non-invasive imaging technique that is used primarily in medical settings to produce images of the inside of the human body. It gives excellent contrast between soft tissues and high spatial resolution (between 1 and 2mm) in every direction [24].

Felix Bloch and Edward Purcell discovered the magnetic resonance phenomenon independently in 1946. In the beginning, MRI was developed and used for chemical and physical molecular analysis. Because of this, MRI was earlier referred to as Nuclear Magnetic Resonance (NMR). In 1971, Raymond Damadian showed that the nuclear magnetic relaxation times of tissues and tumors differed. This motivated scientists to consider magnetic resonance for the detection of disease. In the beginning of the 70’s, Paul Lauterbur discovered the possibility of creating a two-dimensional picture by introducing gradients in the magnetic field [26]. Independently, also Peter Mansfield utilized gradients in the magnetic field in order to show more precisely the differences in the resonance.

MRI is now a routine method within medical diagnostics for many diseases. It has replaced several invasive methods of examination and reduced the risk and discomfort for many patients.

4.1 MRI principles

Magnetic resonance imaging is based on the phenomenon of nuclear magnetic resonance, which is the resonance of atomic nuclei [20]. Hydrogen is the most abundant element in the human body (63%) in its association in water molecules. A hydrogen atom consists of a proton nucleus and a single electron. Each hydrogen nucleus shows an angular moment\(^4\) \(\vec{J}\), generally referred to as spin, which is due to the nucleus rotation around its own axis. Since the nucleus has electric charge and is rotating, a magnetic field is generated around it and represented by the magnetic dipole moment\(^5\) \(\vec{\mu}\) [17]. Therefore, a nucleus can be considered as a small magnet with separate poles (Fig. 4.1).

\(^4\) All nuclei with odd atomic weights and/or odd atomic numbers, such as the hydrogen nucleus, which has one proton, possess an angular momentum.

\(^5\) In the general case, for a current loop, the magnetic moment is \(\vec{\mu} = S \vec{I} \hat{n}\), where \(S\) is the loop surface, \(\vec{I}\) is the electrical current and \(\hat{n}\) is the normal vector with respect to \(S\).
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Figure 4.1: Nuclei with spin (\( J \)) have a characteristic magnetic moment (\( \vec{\mu} \)), and are regarded as microscopic magnets.

The magnetic moment is parallel and proportional to the spin angular moment by a physical constant, the gyromagnetic ratio \( \gamma \), which is a proton property characterized by quantum mechanics, and is equal to \( 2.675 \times 10^8 \text{ rad} \cdot \text{s}^{-1} \cdot \text{T}^{-1} \). Thus, the relationship between the spin angular moment and the magnetic moment is given as in Eq. 4.1.

\[
\vec{\mu} = \gamma \cdot \vec{J}
\]  

(4.1)

The spinning protons, which have both angular and magnetic moment, possess a specific spin quantum number that characterizes their orientations and corresponding energy levels. In absence of an external magnetic field, the direction of the magnetic moments of spinning protons is completely random. When a large number of such protons are placed in an external magnetic field of magnitude \( B_0 \), applied in the z direction, they tend to align themselves in the direction of the field. According to the quantum theory\(^6\), only two orientations of the nuclear magnetic moment relative to the field direction are possible: parallel (pointing up) and antiparallel (pointing down) (Fig. 4.2).

\(^{6}\) The quantum theory constrains the nuclear magnetic energy states so that only certain energy levels are permitted.
Figure 4.2: Magnetic moments of spinning protons without (a) and with (b) the presence of an external magnetic field. \( \theta \) is the angle between the direction of the magnetic moment and the external magnetic field.

These two states correspond to two allowed energy levels. The parallel orientation corresponds to a lower energy level. At equilibrium, the number of protons at the lower energy level exceeds that at the higher level. This leads to a net magnetization \( \vec{M} \) in the direction of the field, which is the vectorial sum of all the magnetic moments of the nuclei in the object considered, and is referred to as longitudinal magnetization (Fig. 4.3).

Figure 4.3: Development of net magnetization \( \vec{M} = \sum \vec{\mu}_i \) by slight preference for magnetic moments to align parallel to the external magnetic field.

According to classical mechanics, the magnetic moment experiences a torque \( \vec{\tau} \) from the external magnetic field, which is equal to the rate of change of its angular momentum, and is given by the equation of motion for isolated spins in Eq. 4.2.
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\[
\vec{\tau} = \frac{d\vec{J}}{dt} = \vec{\mu} \times \vec{B}_0 \tag{4.2}
\]

Combining Eq. 4.1 and Eq. 4.2, Eq. 4.3 can be derived.

\[
\frac{d\vec{\mu}}{dt} = \gamma \vec{\mu} \times \vec{B}_0 \tag{4.3}
\]

As a result, the magnetic moment precesses around the axis of the external magnetic field (Fig. 4.4) at a special frequency referred to as Larmor frequency. The relationship between the Larmor frequency and the applied magnetic field is the solution of Eq. 4.3 (see Appendix A), and is given as in Eq. 4.4.

\[
f_L = \left(\frac{\gamma}{2\pi}\right)B_0 \tag{4.4}
\]

\(\frac{\gamma}{2\pi}\) is equal to 42.58 \(\cdot\) 10^6 Hz/T in the case of protons. This is the frequency on which the nuclei can receive the RF energy to change their states and exhibit nuclear magnetic resonance. According to quantum theory, the energy required to produce the transition between the two states of different energy is given as in Eq. 4.5, where \(h\) is the Planck's constant equals to 6.6 \(\cdot\) 10^{-34} J \cdot s.

\[
E = h \cdot f_L \tag{4.5}
\]

Figure 4.4: Precession of a nuclear spin about the external magnetic field applied in the z direction.
If an additional alternating field $B_1$, aligned along the x-axis and rotating about the z-axis with frequency equal to the Larmor frequency, is applied, then the spin system absorbs energy. Thus, the population at the upper energy level increases while that of the lower level decreases. This is referred to as resonant process. As a result, the net magnetization vector $\vec{M}$ is no longer in the direction of the external magnetic field, and it starts moving away from the z-direction. The net magnetization vector is flipped of a certain angle $\theta$ determined by Eq. 4.6 which relates $\theta$ to the field strength $B_1$ and duration ($\Delta t$) of the applied RF pulse.

$$\theta = \gamma B_1 \Delta t \quad (4.6)$$

An RF energy pulse required to rotate the net magnetization into the transverse plane is referred to as 90-degree pulse. If enough energy is supplied, the net vector can be completely flipped over with a 180-degree clockwise shift in the opposite direction with respect to the external magnetic field. Once the RF pulse is finished, the net magnetization vector returns to its original equilibrium state through a process of relaxation. The previously absorbed energy is emitted at the same precession frequency and can be detected as an electrical signal. The transient response MR signal of a spin system after a RF pulse excitation is referred to as free induction decay (FID) signal. The electrical signal is detected by a receiver coil (see section 4.6), and the induced voltage can be derived applying the principle of reciprocity and the Faraday law\(^7\) as given in Eq. 4.7 and Eq. 4.8 [17].

$$\Phi = \int_{\text{object}} \vec{B}(\vec{r}) \cdot \vec{M}(\vec{r}) \, d\vec{r} \quad (4.7)$$

$$V(t) = -\frac{\partial \Phi}{\partial t} = -\frac{\partial}{\partial t} \int_{\text{object}} \vec{B}(\vec{r}) \cdot \vec{M}(\vec{r}, t) \, d\vec{r} \quad (4.8)$$

$\vec{B}$ is the magnetic field generated by the coil at location $\vec{r}$ and $\Phi$ is the magnetic flux through the coil. As the $M_z$ component varies much slower than the $M_{xy}$ component, it can be neglected, and the resulting expression is given as in Eq. 4.9.

$$V(t) = -\int_{\text{object}} \vec{B}_{xy} \cdot \frac{d}{dt} \left[ \vec{M}_{xy}(r, t) \right] d\vec{r} \quad (4.9)$$

\(^7\) The Faraday law of induction states that a time-varying magnetic flux through a conducting loop induces in the coil an electromagnetic force (or voltage) that is equal to the rate at which the magnetic flux changes through the coil.
4.2 Magnetic relaxation

Relaxation expresses the recovery toward equilibrium of nuclear dipoles that have been disturbed by RF excitations [20]. The time-dependent behavior of the net magnetization vector $\vec{M}$ in the presence of an applied magnetic field $B_1$ is described by the Bloch equation as given as in Eq. 4.10, where $M_0^0$ is the equilibrium value for $\vec{M}$ in the presence of $B_0$ only [17]. $T_1$ and $T_2$ are, respectively, the longitudinal and transverse relaxation times. They are relaxation parameters unique to each tissue.

$$\frac{d\vec{M}}{dt} = \gamma \vec{M} \times \vec{B} - \frac{M_x \vec{i} + M_y \vec{j} + (M_z - M_0^0) \vec{k}}{T_2} - \frac{(M_z - M_0^0) \vec{k}}{T_1}$$

Eq 4.10 can be split into Eq. 4.11, Eq. 4.12, and Eq. 4.13 for the different coordinates.

$$\frac{dM_x}{dt} = \gamma M_x B_0 - \frac{M_x}{T_2}$$

$$\frac{dM_y}{dt} = -\gamma M_y B_0 - \frac{M_y}{T_2}$$

$$\frac{dM_z}{dt} = \frac{M_0^0 - M_z}{T_1}$$

Finally, the solutions of the Bloch equation (Eq. 4.10) are given in Eq. 4.14 and Eq. 4.15, which represent the time dependent behavior of the magnetization vector in the transverse and in the longitudinal plane, respectively.

$$M_x(t) = M_0 e^{\frac{-t}{T_2}} \cos(\gamma B_0 t)$$

$$M_y(t) = -M_0 e^{\frac{-t}{T_2}} \sin(\gamma B_0 t)$$

$$M_z(t) = M_0 \left(1 - e^{\frac{-t}{T_1}}\right)$$

An important parameter in MRI is the spin density $\rho$. The spin density is proportional to the effective number of hydrogen nuclei per unit volume contributing to the signal from each voxel of the object [20]. Thus, the constant...
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$M_0$ in Eq. 4.14 and Eq. 4.15 is proportional to $\rho$ [17][24][39]. $\rho$ can be used together with $T_1$ and $T_2$ to distinguish different tissues.

4.2.1 $T_1$ relaxation

Longitudinal or spin-lattice relaxation time $T_1$ refers to the amount of time that the tissue magnetization takes to return to its equilibrium state in the longitudinal direction of the external magnetic field after excitation with a RF pulse [16][18][20]. The energy that is absorbed by the magnetic spins from the RF pulse is transferred back to the environment or lattice during the relaxation process.

At equilibrium, the net magnetization vector lies along the direction of the external magnetic field and is referred to as the equilibrium magnetization $M_0$. In this configuration, the longitudinal component of magnetization $M_z$ equals $M_0$ and there is no transverse magnetization. It is possible to change the net magnetization by exposing the nuclear spin system to energy with frequency equal to the energy difference between the spin states (Eq. 4.5). If enough energy is transferred to the system, it is possible to saturate the spin system and make $M_z$ equal to zero. This is the case of a 90-degree pulse (Fig. 4.5). The time constant that describes how $M_z$ returns to its equilibrium value is the spin lattice relaxation time $T_1$. The description of this behavior as a function of time is derived from the Bloch equation (Eq. 4.10) and is given as in Eq. 4.15.

![Figure 4.5: Longitudinal relaxation curve after applying a 90-degree pulse.](image)

Since there is an exchange of energy between protons and environment, $T_1$ relaxation times depend on the nature of the surrounding molecules. For instance, the magnetization associated with lipids relaxes faster than that associated with pure water or much larger molecules, such as proteins. Moreover, also the magnetic field magnitude has influence on the $T_1$ relaxation time. In general, $T_1$ increases with the field magnitude for most tissues.

4.2 Magnetic relaxation
4.2.2 $T_2$ relaxation

The second relaxivity property of tissue is the transverse or spin-spin relaxation, referred to as $T_2$ relaxation. In this relaxation process the magnetic moments of the spins turn out of phase as a result of their mutual interaction [16][18][20]. Each of the spins experiences a slightly different magnetic field and rotates at its own Larmor frequency, leading to loss of spin phase coherence (dephasing). As a result, the transverse magnetization $M_{xy}$ decays and, therefore, returns to its equilibrium state. The longer the elapsed time, the larger the phase difference and the transverse magnetization decrease are (Fig. 4.6).

![Figure 4.6: Progressive spin dephasing and decreasing net transverse magnetization (horizontal arrows below the circles) after the creation of transverse magnetization by the excitation pulse.](image)

The time constant that describes this process is the relaxation time $T_2$. The transverse magnetization after a RF excitation pulse (Fig. 4.7) is derived from Bloch equation (Eq. 4.10), and is described as a function of time as given in Eq. 4.14.

![Figure 4.7: Transversal relaxation curve after applying a 90-degree pulse.](image)

Unlike the $T_1$ relaxation, no energy is transferred from the nuclei to the environment during the $T_2$ relaxation. Nuclei in the excited and ground state may exchange energy with each other. However, in biological tissues the main contribution to $T_2$ relaxation comes from the relatively static magnetic field of
neighboring protons. Thus, large molecules, which tend to reorient more slowly than small molecules, promote $T_2$ relaxation and have shorter $T_2$ times. The magnetic field strength influences $T_2$ much less than $T_1$.

In conclusion, each tissue has a characteristic $T_2$ relaxation time that is not directly dependent on the magnetic field magnitude and is referred to as the decay of the transverse magnetization. However, the actual rate of signal decay is more rapid than predicted based on $T_2$ (Fig. 4.8). The actual observed transverse relaxation time, referred to as $T_2^*$, is affected by local magnetic field inhomogeneities, which cause the precessional rates of the individual spins to differ from each other and dephase.

![Figure 4.8: The actual signal decay from $T_2^*$ relaxation time (gray) is faster than that from $T_2$ (black).](image-url)
4.3 Spatial localization

The measured MR signal does not contain localization information. Therefore, in order to reconstruct an image, it is necessary to make a spatial encoding [20]. Since the precession frequency is proportional to the magnetic field magnitude, if an additional magnetic field gradient $\tilde{G}$ is superimposed on the static external magnetic field, the spatial locations within the object can be encoded with localized precession frequencies. Magnetic field gradients are applied in the three orthogonal axes at different times allowing three-dimensional location of the signals' origins. Frequency and phase-based spatial encoding techniques with different gradient methods are used to access the spatial locations within the object being imaged.

a) Slice selection. Firstly, images slices are excited selectively by applying a slice select gradient during application of the radio frequency pulse.

b) Frequency encoding. If an imaging gradient is applied along one axis of an image selected slice while the MR signal is being measured, the source of MR signals in one dimension can be localized.

c) Phase encoding. The second in-plane axis of the image is localized by phase encoding, which involves mapping the location of the sources of MR signals based on differences among their phases at readout. The phase encoding gradient is established by applying a single brief magnetic field pulse perpendicular to the axes of slice selection and frequency encoding. This pulse causes precessional frequencies to vary momentarily along this axis. Once the phase encoding gradient pulse has ended, the precessional frequencies are once again uniform, but the phase changes persist. Therefore, the signal acquired during echo readout contains phase differences caused by the phase encoding gradient. The phase encoding gradient must be applied repeatedly at different strengths to locate the source of MR signals along the phase encoding axis. The variation of the phase-encoding gradient is necessary to fill the different rows of the $\kappa$ space (see section 4.4) and, as a result, the $\kappa$ space trajectory.

The whole procedure (Fig. 4.9) for a spin echo (SE) sequence (see section 4.5.1) starts with the slice selection gradient, which spreads out the Larmor frequency over a broad range so that the frequencies contained in the RF pulse

---

8 A magnetic field gradient is a magnetic field that increases linearly in strength along a particular direction ($x$, $y$ or $z$). The strength of a gradient refers to the rate at which its magnetic field changes with distance.
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Affect only a slice. The phase-encoding gradient is pulsed briefly after the first RF excitation pulse has been turned off, making the Larmor frequency depend on spatial position along the phase-encoding direction. Afterward, magnetization components everywhere in the slice regain the same Larmor frequency, but the phase depends on their position along the phase-encoding direction. Spatial information in the phase-encoding direction can be resolved if many separate MR signals are collected. The amplitude of the phase-encoding gradient for each signal is decreased systematically. Each of these signals is measured while the frequency-encoding gradient is active, which creates a distribution of Larmor frequencies along the frequency-encoding direction. A first frequency-encoding gradient is necessary for the MR signal to form during the middle of the second one. As Fig. 4.9 shows, a SE sequence uses two RF excitation pulses to generate the MR signal; this will be explained in section 4.5.

\[
S(t) = \int \frac{d}{dt} M_0(\mathbf{r}) e^{-\gamma t} e^{-i(\mathbf{B}_0 + \mathbf{G} \cdot \mathbf{r}) \mathbf{r} \cdot dt} \approx \int \frac{d}{dt} \rho(\mathbf{r}) e^{-\gamma t} e^{-i(\mathbf{B}_0 + \mathbf{G} \cdot \mathbf{r}) \mathbf{r} \cdot dt} = e^{-\gamma t} \int \rho(\mathbf{r}) e^{-i(\mathbf{B}_0 + \mathbf{G} \cdot \mathbf{r}) \mathbf{r} \cdot d\mathbf{r}}
\]

(4.16)

The exponential \( \gamma (\mathbf{B}_0 + \mathbf{G} \cdot \mathbf{r}) \) represents the precession angular frequency at the location \( \mathbf{r} \). The derivative can be approximated by a coefficient (constant)
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\[ e^{-\frac{\pi}{2} r B_0} \] of the integral, as \( \tilde{G} \cdot \tilde{r} \) and \( \frac{-1}{T_2} \) are negligible. After demodulation (i.e., removal of the carrier signal \( e^{-iyB_0 t} \) by a mixer), and assuming relaxation effect to be negligible (i.e., removal of \( e^{\gamma T_2^*} \) factor) Eq. 4.16 can be written as given in Eq. 4.17.

\[ S(t) \propto \int \rho(\tilde{r}) e^{-i\gamma (\tilde{G} \cdot \tilde{r})} d\tilde{r} \]  

(4.17)
4.4 **K-space and image reconstruction**

The κ space represents the placement of raw frequency data collected through the pulse sequences in a multi-dimensional space in which an image is to be reconstructed [17]. Thus, making a variable substitution (Eq. 4.18), the MR signal expression (Eq. 4.17) can be written as a κ space signal as in Eq. 4.19.

\[
\vec{\kappa} = \frac{\gamma t G}{2\pi} \tag{4.18}
\]

\[
S(\vec{\kappa}) = \int_{\text{object}} \rho(\vec{r}) e^{-i2\pi\vec{\kappa}\cdot\vec{r}} d\vec{r} \tag{4.19}
\]

Note that the κ space signal is in the form of a multi-dimensional Fourier transform for a limited set of points. If we focus on a selected slice (\(G_z\)), the two κ space coordinates of these points define the sampling trajectory in frequency domain (Fig. 4.10), which in the two-dimensional case is defined by either Eq. 4.20 or Eq. 4.21.

\[
\begin{align*}
  k_x &= \frac{\gamma}{2\pi} G_x t \\
  k_y &= \frac{\gamma}{2\pi} G_y t \\
  k_x &= k \cos \phi \\
  k_y &= k \sin \phi
\end{align*} \tag{4.20}
\]

\[
\begin{align*}
  k_x &= k \cos \phi \\
  k_y &= k \sin \phi
\end{align*} \tag{4.21}
\]

**Figure 4.10:** κ space sampling trajectory of a frequency encoded FID signal.

Denoting the image function by \(I(x, y)\), the two dimensional Fourier transform is given as in equation Eq. 4.22, which shows the same structure as Eq.
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Therefore, Eq. 4.19 can be used to reconstruct \( I(x, y) \), i.e., \( \rho(x, y) \), by an inverse Fourier transform.

\[
S(k_x, k_y) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} I(x, y) e^{-i 2\pi (k_x x + k_y y)} \, dx \, dy \quad (4.22)
\]

It is necessary to generate sufficient data to cover the \( \kappa \) space. A conventional strategy to cover the \( \kappa \) space is to generate a set of "identical" signals using repetitive excitations, and then encode each properly so that the \( \kappa \) space will be covered with multiple lines. There are two different imaging methods to implement this strategy, referred to as phase encoding and Random transform (or back-projection). The former uses the excitation sequence explained in section 4.3, resulting in a rectilinear sampling of the \( \kappa \) space (Fig. 4.11 a) in which in each row resolve the frequency-encoding direction, and the data samples in the columns are responsible for spatial information along the phase encoding direction. The latter uses another excitation sequence in which the spatial information is encoded in the spin echo signals by two-dimensional frequency encoding. Thus, the frequency encoding gradients, applied in the x and y direction, vary from one excitation to another, resulting in a radial covering of the \( \kappa \) space (Fig. 4.11 b).

![Figure 4.11: \( \kappa \) space coverage with phase encoding (a) and Random transform (b) method](image)

As a result, there are two ways of sampling the \( \kappa \) space signals. In the rectilinear sampling case, it is assumed that the object is bounded by a rectangle of widths \( W_x \) and \( W_y \) (Fig. 4.12 a). Therefore, the sampling requirements according to the Nyquist theorem\(^9\) are given as in Eq. 4.23.

---

\(^9\) The Nyquist theorem states that the sampling frequency must be greater (or equal) than twice the bandwidth of the input signal in order to be able to reconstruct the original signal perfectly from the sampled version.
\[
\Delta k_x \leq \frac{1}{W_x} \quad \Delta k_y \leq \frac{1}{W_y}
\]  

(4.23)

Figure 4.12: The object being imaged (a), and rectilinear sampling of \( K \) space (b).

Since the frequency encoding is used along the \( x \) direction and the phase encoding is used along the \( y \) direction, Eq. 4.24 can be derived from Eq. 4.20.

\[
\begin{aligned}
\Delta k_x &= \frac{\gamma}{2\pi} G_x \Delta t \\
\Delta k_y &= \frac{\gamma}{2\pi} \Delta G_y T_{pe}
\end{aligned}
\]  

(4.24)

\( \Delta t \) is the sampling time interval, \( \Delta G_y \) is the phase encoding gradient step size, and \( T_{pe} \) is the phase encoding interval. Therefore, substituting Eq. 4.24 in Eq. 4.23, the requirements on the data acquisition parameters are given as in Eq. 4.25.

\[
\begin{aligned}
\Delta t &\leq \frac{2\pi}{\gamma G_x W_x} \\
\Delta G_y &\leq \frac{2\pi}{\gamma T_{pe} W_y}
\end{aligned}
\]  

(4.25)

In the polar sampling case, it is necessary to assume space limitedness and frequency limitedness\(^{10}\). Considering that the object is bounded by a circle of

\(^{10}\) This is only an approximation since a function cannot be both space and frequency limited at the same time.
radius $R_x$ (Fig. 4.13 a), the requirements on the data acquisition parameters, that satisfy the Nyquist theorem, are finally given as in Eq. 4.26.

![Figure 4.13: The object being imaged (a), and polar sampling of the $\kappa$ space (b).](image)

$$
\begin{align*}
\Delta t & \leq \frac{\pi}{\gamma \sqrt{G_x^2 + G_y^2 R_x}} \\
\Delta \phi & \leq \frac{2\pi}{2([2\pi R_x R_y] + 1) + 1}
\end{align*}
$$

Depending on how spatial information is encoded, the image reconstruction technique is different. If the $\kappa$ space is sampled rectilinearly, the image reconstruction is made by taking the inverse Fourier transform of the $\kappa$ space data. Since the 2-D $\kappa$ space consists of discrete samples, an inverse 2-D discrete Fourier transformation\(^{11}\) (DFT) is used to reconstruct the 2-D MR image of the selected slice. In contrast, in the case of polar sampling, the image reconstruction is made by taking the inverse Random transform (or back-projection) of the $\kappa$ space data.

\(^{11}\) The DFT is defined as a mathematical series, with the number of terms equal to the number of data samples. The terms in the series are summed to calculate the luminance of one pixel of the MR image.
There are various techniques for acquiring MR images [20] depending on the RF pulses and the magnetic field gradients used to generate the MR signal. Characteristics and timing of the RF pulses and magnetic field gradients are referred to as pulse sequences. The pulse sequence must be repeated several times. This repetition is used to fill the $K$ space for a 2D MR image. Moreover, a first sequence is usually executed for several seconds to allow the longitudinal magnetization to reach a steady state.

Apart from FID signals, another useful form of MR signals are the echoes, whose formation is explained in section 4.5.1. A feature distinguishing an echo signal from a FID signal is the "two-sidedness" of the former, one side of which is generated during the rephasing of the transverse magnetization, and the other side during its following dephasing period (Fig.4.14) [17].

The time between repeated RF excitations pulses is referred to as repetition time TR. Under steady conditions, the longitudinal magnetization recovers approximately to a fraction of its equilibrium value between RF pulses. Longer values of TR allow more $T_1$ relaxation to occur, and this property can be exploited to adjust the contrast between tissues with different $T_1$. The time for data acquisition is the product of TR and the number of pulse-sequence repetitions.

The time between the application of the RF excitation and the formation of the echo, taken from the center of the RF pulse to the center of the echo, is the echo time TE. The amplitude of the transverse magnetization at the echo peak depends
on TE and $T_2$ of the tissue, as TE is prolonged the transverse magnetization becomes weaker. Adjusting TE influences the contrast between tissues that have different $T_2$.

The timing parameters TE and TR, unlike the intrinsic parameters $T_1$, $T_2$, and spin density ($\rho$), do not depend on the tissues properties, and, therefore, they can be directly modified by the operator in order to obtain different contrast MR images. Thereby, an image whose contrast is predominantly generated by differences in $T_1$ of the tissues is referred to as a $T_1$ weighted image. Similarly, for $T_2$ and $\rho$ the images are referred to as $T_2$ weighted and spin density-weighted images. In general, $T_1$ weighted images are obtained with short TRs and TEs, $T_2$ weighted images with long TRs and TEs, and spin density weighted images with long TR and short TE.

The description of the most typical pulse sequences is explained in the next paragraphs [20].

4.5.1 Spin echo sequence

The most common used pulse sequence in clinical MRI is the spin echo (SE) pulse sequence. The pattern of the basic pulse sequence is the same from one repetition to the next, except for changes in the strength of the phase-encoding gradient. Fig. 4.15 shows the timing pattern of RF excitation pulses, the magnetic gradient used to select a particular planar section (the slice selection gradient), the gradients used to resolve the signals from all voxels within the selected section (the phase encoding and frequency encoding gradients), and the measurement of RF signal from the patient on each sequence repetition.

![Figure 4.15: Spin echo sequence](image)

In the SE sequence, the 180-degree pulse is applied after the 90-degree pulse in order to rephase the transverse magnetization (Fig. 4.16), which had begun
to dephase after the 90-degree pulse due to spin-spin interactions and magnetic field inhomogeneities. Thus, the 180-degree pulse reverses the direction of all transverse magnetization, making the relaxation, which occurs between the initial 90-degree RF pulse and signal echo, immune to fixed magnetic field inhomogeneities. As a result, the transverse relaxation measured in SE sequences is related entirely to $T_2$ relaxation effects, i.e., the irreversible dephasing of transverse magnetization resulting from spin-spin interactions.

![Figure 4.16:](image)

**Figure 4.16:** The partly dephased transverse magnetization is turned into mirror-image positions by a 180-degree RF pulse that tips the magnetization about the y axis (a). The fastest precessing spins ($F$) catch up with those precessing more slowly ($S$), leading to rephasing (b).

Fig. 4.15 shows how the slice selection gradient is turned on only when slice-selection RF pulses are applied into the patient. The phase encoding gradient is turned on, to a different strength for each repetition of the basic sequence, sometime between signal excitation and signal measurement. The signal from the patient is measured by receiver coils during the total sampling time ($T_s$) while the frequency encoding gradient is turned on.

The SE signal amplitude for a voxel with tissue parameters $T_1$, $T_2$, and $\rho$ is derived from Bloch equation (Eq. 4.10), and is given as in Eq. 4.27.

$$S_{SE} = \rho \left[ 1 - 2e^{-\frac{(TR-TE)}{T_1}} + e^{-\frac{-TR}{T_1}} \cdot e^{-\frac{TE}{T_2}} \right]$$  (4.27)

### 4.5.2 Inversion recovery sequence

The inversion recovery (IR) sequence is commonly used in MRI and consists of an inverting 180-pulse, a 90-degree pulse, and a rephasing 180-degree pulse. The timing pattern of these pulses, the gradients used for section selection and voxel resolution within the selected section, and signal measurement are shown in Fig. 4.17.
The expression for the signal in IR imaging for a voxel with tissue parameters $T_1$, $T_2$, and $\rho$ is derived from Bloch equation (Eq. 4.10), and is given as in Eq. 4.28.

$$S_{IR} = \rho \cdot \left[ 1 - 2e^{-\frac{TR}{T_1}} + 2e^{-\frac{(TR+TE)}{T_1}} - e^{-\frac{TR}{T_1}} \right] \cdot e^{-\frac{TE}{T_1}} \quad (4.28)$$

4.5.3 Gradient echo sequence

Gradient-echo imaging techniques provide methods of accumulating images in much shorter total times than conventional pulse sequences. In the gradient-echo pulse sequence (Fig. 4.18) the RF excitation pulse tilts the magnetization by a flip angle $\theta$, which is typically between $0^\circ$ and $90^\circ$. Without using the 180-degree pulse, another form to generate an echo makes use of time-varying gradient magnetic fields. Thus, a negative frequency encoding gradient is turned on, and, as a result, spins start to lose phase coherence. However, if a positive gradient of the same strength is applied, the transverse magnetization components gradually rephase, resulting in an echo at time $TE$, referred to as gradient echo. As in SE imaging, the basic gradient echo pulse sequence must be repeated a large number of times (e.g., 128, 192, or 256, depending on the desired spatial resolution in the phase encoding direction), each repetition with a different degree of phase encoding so that a sufficient number of phase encoding “views” is collected to form an image.

---

12 A gradient echo is an echo created by reapplication of a magnetic gradient instead of a 180-degree pulse.
In gradient-echo imaging, formation of an echo by gradient reversal does not eliminate the dephasing effects of magnetic field inhomogeneities. Therefore, the signal decay between the initial 0-degree pulse and gradient echo depends on T2 relaxation plus relaxation caused by magnetic field inhomogeneities, and is governed by T2* relaxation time.

4.5.4 Fast gradient echo sequences

In fast gradient echo or fast field echo (FFE) imaging, the gradient echo sequence (Fig. 4.18) is applied with very short TR values (TR << T2). As a result, the system reaches a dynamic equilibrium\(^{13}\), referred to as steady state, after a time of the order of T1. Based on how transverse magnetization is handled after each excitation, these methods are conveniently grouped into two classes: spoiled steady state imaging methods and unspoiled steady state imaging methods. Methods in the first class establish a steady-state longitudinal magnetization, but destroy or “spoil” any residual transverse magnetization before a new RF pulse is applied. Methods in the second allow both the longitudinal and transverse components to reach a dynamic equilibrium state.

In spoiled steady state imaging the transverse magnetization generated by a pulse has not been completely dephased when the next pulse is applied, since TR << T2. This residual transverse magnetization is destroyed using various spoiling methods before a new pulse is applied.

The acquire images are mainly T1 weighted, since transverse magnetization, carrying T2 information, is suppressed [19].

---

\(^{13}\) The dynamic equilibrium state means that before each excitation the same magnetization situation exists.
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The expression for the signal in spoiled steady state imaging for a voxel with tissue parameters $T_1$, $T_2$, and $\rho$ is derived from Bloch equation (Eq. 4.10), and is given as in Eq. 4.29.

$$S_{GE\,\text{spoiled}} = \rho \cdot \left[ \frac{1 - e^{-\frac{TR}{T_1}}}{1 - \cos \theta \cdot e^{-\frac{TR}{T_1}}} \right] \cdot \sin \theta \cdot e^{-\frac{TE}{T_2}}$$

The term $e^{-\frac{TE}{T_2}}$ is due to the delay between the excitation pulse and the echo, so there is still a minimal contribution of $T_2$. The flip angle $\theta$ is typically between $0^\circ$ and $90^\circ$.

There are different spoiled steady state FFE sequences with acronyms such as $T_1$-FFE, FLASH, and SPGR, depending on the MR scanner brand.

In unspoiled steady state imaging $TR$ is on the order of $T_2$, and no attempt is made to spoil the transverse magnetization, so both the longitudinal and transverse magnetization will reach a steady state.

The expression for the signal in unspoiled steady state imaging for a voxel with tissue parameters $T_1$, $T_2$, and $\rho$ is derived from Bloch equation (Eq. 4.10), and is given as in Eq. 4.30.

$$S_{GE\,\text{unspoiled}} = \rho \cdot \frac{1 - e^{-\frac{TR}{T_1}}}{1 - e^{-\frac{TR}{T_1}} - \left( e^{-\frac{TR}{T_2}} - e^{-\frac{TR}{T_2}} \right) \cdot \cos \theta}$$

There are different steady state FFE sequences with acronyms such as N-FFE, FAST, GRASS, and FISP.

4.5.5 Fast spin echo sequence

In fast spin echo (FSE) or turbo spin echo (TSE) imaging, multiple echoes are generated following a single excitation pulse and multiple rephasing 180-degree pulses, accompanied by the slice selection gradient pulses (Fig. 4.19). The phase encoding gradient pulse that precedes each echo has a different value.
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Figure 4.19: Fast spin echo pulse sequence showing multiple signals generated after a single excitation pulse and multiple rephasing pulses, in the same draw as RF excitations.

The parameter TSE factor is the number of echoes acquired after each excitation.

4.5.6 Echo planar sequence

Echo planar imaging (EPI) techniques involve acquiring multiple gradient echoes per excitation. The most familiar version of such a multiecho technique is that in which all the gradients echoes used to form an image are obtained after a single excitation pulse. This can be accomplished by oscillating the frequency encoding gradient rapidly, so that numerous echoes are generated. Successive weak phase encoding gradient pulses are applied prior to each signal measurement to change the amount of phase encoding of signals during acquisition (Fig. 4.20). Unlike with other techniques, the magnitude of the phase encoding gradient pulse is not changed. In fact, the phase encoding of each repetition is additive.

Figure 4.20: EPI sequence showing multiple signals generated after a single excitation pulse in the same draw as RF excitations.
The parameter EPI factor is used to specify the number of k-space profiles collected per excitation. For example, an EPI factor of 64 means a measurement time 64 times faster than a normal gradient echo sequence.
4.6 Instrumentation

The stationary external magnetic field for MR imaging of the human body is provided by a large superconducting magnet with a typical strength of 0.5T to 1.5T. A diagnostic quality imaging system requires a magnet with good field homogeneity [16].

Generally, three orthogonal gradient coils are used to provide gradient magnetic fields. Though the gradient coils generate magnetic fields in the $z$-direction, they provide software-controlled displacements in the $x$-, $y$- and $z$-directions (Fig. 4.21).

During the nuclear excitation phase, an RF coil (see Appendix C) with electronic circuitry is used to transmit time-varying RF pulses. The same RF coil with computerized programming and switching control is used for receiving the radio frequency emissions during the nuclear relaxation phase. The FID signal is recorded in the RF coil at a selected radio frequency. The computerized control of electronic circuitry allows the programming of the RF coil to transmit and receive specific RF pulses as required by the selected pulse sequence for image reconstruction. The RF transmitter section includes a wave synthesizer, RF modulator, RF amplifier and a coupler that couples the RF signal to the RF coil. The RF receiver section uses the coupler to switch the signal from the RF coil to an assembly of pre-amplifiers and demodulators. The received FID signal is then sent to an analog-to-digital converter for recording the data in digital format.

It must be taken into account, components that are sensitive to magnetic fields, such as the computer and magnetic data storage media, must be kept at safe distance from the main magnet. As a result, the MRI acquisition system must be surrounded by a Faraday’s cage to isolate the magnetic fields from the surroundings departments and devices in the hospital.
Figure 4.22: Simplified block diagram of a representative MR system.
4.7 Motion and Flow

The flow of blood is a particular case of motion in a patient that causes artifacts in the MRI acquisition (Fig. 4.23) [17][18][19][20]. To minimize these artifacts, their mechanism must be known.

![Figure 4.23: Cross-sectional image of the lower abdomen with motion artifacts.](image)

The most evident effect of flow is the spatial shift. Since a point source located at $x = 0$ at the same time of excitation pulse will be shifted to $x = v \cdot TE$ (where $v$ is the velocity component) during detection. Therefore, the resulting image reflects the location of the object at the echo time TE. In case of flowing blood\(^{14}\) in SE sequences during systole, the 180-degree pulse do not hit the spins that were excited by the 90-degree pulse, since the blood has moved out of the excited slice when the 180-degree pulse is applied. Therefore, the signal from blood during systole is almost zero. During diastole, however, the signal is higher because the blood velocity is low. Thus, the blood gives a varying signal in the phase-encoded direction, depending on the cardiac phase in which the profiles are measured. These signal variations will give rise to ghosts in the phase encoding direction (Fig. 4.25). This artifact can be avoided by applying ECG triggering so that all profiles are measured during the same cardiac phase at low flow.

Another important effect of flow is the phase shift. The velocity component of spinning nuclei along the direction of the magnetic field gradient induces a proportional phase shift in the transverse magnetization. Any changes in the velocity component causes dispersion in the phase shifts. Thus, movement during the application of the gradient pulses used for spatial encoding makes the phase of the magnetization different from what it would be without motion (Fig. 4.24).

\(^{14}\) This is only valid for ventricles and arteries, not for atria and veins.
These phase shifts, induced by motion during TE, result in phase-encoding errors and leads to unequal signal losses.

When blood protons in a voxel are all moving at the same velocity, they undergo identical phase shifts. If the protons in a voxel have identical velocities, the net intensity of the MR signal is strong, but there are motion-induced phase shifts that cause artifacts along the phase encoding axis of the image. When protons in a voxel move at different velocities, however, there are several phase shifts in the voxel. Thus, the coherence of the magnetization and the resulting signal intensity are reduced, referred as intravoxel phase dispersion.

If the velocity varies from one acquisition to another, the changes in the phase of the magnetization disrupt the Fourier-transform relationship between the $\kappa$ space and the MR image. However it affects only the phase-encoding direction (modulation of phase-encoding direction of the $\kappa$ space). Thus, motion induced phase-encoding errors manifest as artifacts along the phase-encoding axis regardless of the direction of the motion. These artifacts manifest as altered signal intensity, often accompanied by reduced signal intensity of the moving structure itself. If motion is entirely random, the location of the misrepresented signal intensity in the image varies randomly, and the artifacts are smeared along the phase-encoding axis. However, artifacts from periodic motion, referred to as ghost artifacts (replicas of something in the image) (Fig. 4.25), are more coherent and are located at regular intervals along the phase-encoding axis. Ghosts arise from velocity changes during different TE intervals.
The phase shifts that result from motion, during and between the application of imaging gradients, can be reduced by configuring a gradient waveform to make its first\textsuperscript{15} and possibly higher moments vanish at TE. This procedure is referred to as gradient moment nulling (GMN), and its implementation involves the addition of one or more pulses to the gradient waveform before the echo is sampled.

Phase sensitivity due to the flow is inherent in MR signal generation and is exploited in MR imaging for conventional flow measurements by means of appropriate pulse sequences. The phase-sensitive methods for conventional flow measurement do not provide accurate imaging and assessment of in-flow. When a specific slice or volume under flow is imaged through repeated pulse sequences, the phase sensitivity causes a loss in the signal, but, at the same time, the in-flow of fresh nuclei leads to an increase in the signal intensity. In fact, they have not been excited earlier and, as a result, have the full longitudinal magnetization. In in-flow sensitive or time-of-flight (TOF) methods, longitudinal magnetization is exploited making the signal insensitive to flow-induced phase shifts transverse magnetization. The ability of measuring specific in-flow in predetermined directions leads to MR angiography.

\textsuperscript{15} The gradient's first moment is that one produced by constant velocity motion.
5 Contrast Agents in MRI

A chemical contrast agent is a substance that is introduced into the body to change the contrast between tissues. In MRI, this is made by means of altering the relaxation times $T_1$ and $T_2$ of tissue [19][20].

5.1 Mechanism and relaxivity theory

All materials placed in a magnetic field affect that field by the magnetic susceptibility $\chi$. This inherent property gives the ratio between the magnetization $\vec{M}$ (net magnetic dipole moment per unit volume in the material) and the external magnetic field strength $\vec{H}$, which is given as in Eq. 5.1.

$$\vec{M} = \chi \vec{H}$$  \hspace{1cm} (5.1)

Thus, the relationship between the total magnetic field in the material $\vec{B}$ and the external magnetic field strength $\vec{H}$ is given as in Eq. 5.2.

$$\vec{B} = \mu \vec{H}$$  \hspace{1cm} (5.2)

$\mu$ is the permeability of the material (likewise $\mu_0$, which is the permeability of free space), and is related to the susceptibility as given in Eq. 5.3.

$$\mu = \mu_0 \cdot (1 + \chi)$$  \hspace{1cm} (5.3)

As a result, the total magnetic field in the material $\vec{B}$ can be written as in Eq. 5.4.

$$\vec{B} = \mu_0 \cdot (\vec{H} + \vec{M})$$  \hspace{1cm} (5.4)

Paramagnetic substances have a very large net positive magnetic susceptibility, which represents the ability to become magnetized in an external magnetic field. The presence of unpaired electrons in the paramagnetic ion is a mandatory component to induce a change in the $T_1$ and $T_2$ relaxation rates of water protons, leading to variations in tissue. Therefore, the magnetic dipole moment created by the unpaired electrons can enhance the relaxation rates of water protons, either by direct interaction with the water protons or by its local magnetic field influence. The relaxivity contributions of a paramagnetic ion are highly dependent
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on its spin state, so that a paramagnetic ion with the highest spin quantum number\textsuperscript{16} is desirable. The gadolinium ion (Gd\textsuperscript{3+}) of the lanthanide metal group has a high spin quantum number, which makes it a good relaxivity contrast agent [20]. Other ions that have been considered as potential MR contrast agents include Fe\textsuperscript{3+}, Dy\textsuperscript{3+}, and Mn\textsuperscript{2+}. Although a high spin quantum number is theoretically desirable, it is not the only factor that determines whether an MR contrast agent is efficacious. In addition, a contrast agent must have low toxicity and high stability during infusion.

### 5.2 Different contrast agents

The use of paramagnetic contrast agents to improve the diagnostic specificity of MRI examinations has expanded rapidly in the last two decades. Various formulations of the paramagnetic materials Gd, Dy, Mn and Fe are currently being developed. To minimize their inherent toxicity, these metal ions are chelated with low molecular weight ligands like diethylene-triaminepenta-acetic acid (DTPA), DTPA-bismethylamide (DTPA-BMA), and tetraazacyclododecane tetra-acetic acid meglumine (DOTA). The most commonly used paramagnetic metal ion is gadolinium, which is complexed with various ligands, as mentioned before, and acts as positive $T_1$ relaxation agent\textsuperscript{17}[20].

Extracellular MRI contrast agents are characterized by their pharmacokinetic behaviour. After intravenous administration, these compounds rapidly diffuse out of the vasculature into the extracellular space. The easy and fast contrast diffusion out of the circulation leads to a short half-life and rapid excretion, usually via the kidneys. After intravenous injection in human, for example, Gd-DTPA rapidly undergoes intravascular distribution and diffusion into the extracellular space. The early distribution phase is complete within a few minutes (10 min), and the elimination phase has a half-life of about 1,5 hours [12][20]. This clearance rate from the circulation implies that the contrast-enhanced phase of the MRI examination is relatively short.

Gadopentate dimeglumine (Gd-DTPA or Magnevist\textsuperscript{®} [Berlex Laboratories]) was the first extracellular gadolinium chelate developed for clinical

\textsuperscript{16}The spin quantum number is the property of all nuclei related to the largest measurable component of the nuclear angular momentum. The relaxivity contributions of a paramagnetic ion are highly dependent on its spin state. If $S$ denotes the spin quantum number of the total electron spin of the paramagnetic ion, then the relaxation rate is proportional to $S \cdot (S + 1)$.

\textsuperscript{17}A positive relaxation agent increases the MR signal intensity.
use. It was approved for use in the United States by the Food and Drug Administration (FDA) in 1988 [20].

Unlike extracellular MRI contrast agents, which distribute non-specifically throughout the plasma and interstitial space of the body, blood-pool contrast agents (BPCAs) can remain largely in the vasculature throughout the period of an MRI examination. Several different solutions to make effective BPCAs are currently being developed, including polymeric and dendrimeric complexes of Gd\(^{3+}\), low molecular weight Gd\(^{3+}\) complexes that reversibly bind to serum proteins, and ultra-small iron oxide particles [11].

### 5.3 Concentration, relaxation times and signal intensity

Contrast-agent enhancement is based on alteration of the two relaxivity parameters and can be categorized according to the shortening it imparts on either \(T_1\) or \(T_2\). Shortening of \(T_1\) is the result of dipole–dipole interactions, which occur when the frequency of time-varying magnetic fields produced by contrast agents (as a result of molecular rotation and tumbling) is similar to the resonance (Larmor) frequency of protons. Increases in local magnetic field inhomogeneities enhance dephasing of non-stationary protons, resulting in decreased \(T_2\) or \(T_2^*\). A contrast agent that predominantly affects \(T_1\) relaxation is referred to as a **positive relaxation agent** because the enhanced shortening of \(T_1\) relaxation results in increased signal intensity on a \(T_1\)-weighted image. By comparison, a contrast agent that predominantly affects \(T_2\) or \(T_2^*\) relaxation is referred to as a **negative relaxation agent** [20]. In fact, reduced \(T_2^*\) results in decreased signal intensity on a \(T_2\)-weighted image.

The presence of a paramagnetic ion influences the relaxation properties of nearby protons, leading to \(T_1\) and \(T_2^*\) reduction, depending on the concentration of the paramagnetic contrast agent. This influence on the \(T_1\) and \(T_2^*\) values of tissue can be formalized as given in Eq. 5.5 and Eq. 5.6 respectively [3][5][8][13][19].

\[
\begin{align*}
T_1^{-1}(observed) &= T_1^{-1} + R_1 \cdot C \\
T_2^{-2}(observed) &= T_2^{-2} + R_2 \cdot C
\end{align*}
\]  

(5.5)  

(5.6)

\(R_1\) is the relaxivity of the contrast agent (longitudinal and transverse) and \(C\) is its concentration.

The gadolinium chelates enhance \(T_1\) relaxivity and thereby result in visible contrast enhancement on \(T_1\)-weighted pulse sequences with short TRs and TEs. Although these agents primarily affect \(T_1\) relaxation rates, producing positive
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Contrast enhancement, their effect is biphasic, since at very high concentrations they also show T2* effects and negative contrast enhancement, even on T1-weighted pulse sequences.

The signal intensity decrease due to increasing concentrations of paramagnetic ion species, on the basis of T2* effects, is usually unrecognizable with most used doses. However, when the contrast agent resides in the vascular space (e.g., brain tissue perfusion), the disturbance of the homogeneity of the local magnetic field is large and the reduction of T2* can be the dominating effect. The loss of the NMR signal is due to the appearance of small regions of high and low magnetic susceptibility when the contrast agent is heterogeneously distributed within voxels of an image. The magnetic susceptibility differences affect the local resonance frequency by modifying the magnetic field experienced by nearby water protons. This can affect MR images in three ways [2].

First, by increasing the diversity of magnetic fields within a voxel, variations in magnetic susceptibility lead to dephasing on spins within a voxel resulting in an increase in water resonance linewidth (spreading of Larmor frequencies). This results in decreased MR signal intensity from pulse sequences, such as gradient echoes, which do not fully reestablish phase coherence loss due to static inhomogeneities. The signal decrease that is seen in these circumstances is commonly referred to as susceptibility induced T2 shortening.

Second, in these same pulse sequences, the variations in magnetic field can lead to a net displacement in the resonance frequency throughout a whole voxel. This in turn results in phase shifts that are seen with phase sensitive imaging techniques, such as phase mapping or “zebra” techniques. In both cases, the effect (signal loss or phase shift) increases with greater echo times.

Third, in pulse sequences with complete rephasing of static inhomogeneities (e.g., spin echoes), an increase in resonance linewidth or shift in resonance frequency will not directly lead to signal loss or phase distortions. However, if the echo time is sufficient to allow substantial diffusion of water through an area with a different magnetic field during the TE period, then the magnetic field variations become a dynamic phenomenon in the reference frame of the spin. Under these conditions the requirement for spin echo rephasing is violated. This leads to spin dephasing and hence to signal loss on spin echo images as well. Although this effect can be less pronounced than on gradient echo images, with sufficient TE the signal attenuation can be quite significant.

Therefore, susceptibility-gradient induced signal attenuation is an indirect consequence of tissue perfusion. This effect can be seen on both rapid spin echo and gradient echo imaging using conventional imaging techniques. Rapid imaging
techniques are especially suited for imaging of phenomena due to the high temporal resolution needed to characterize the passage of these agents through the vascular space.

Since the observed MR signal loss is larger than predicted by classical relaxation, several theoretical models have been proposed to account for it.

The first class of models assumes a rapid movement of the water spins across the regions of heterogeneous field, and can be considered a fast exchange model analogous to those developed in relaxation theory. This leads to analytic expressions for measured $T_2$ relaxation rates. The assumptions of this model are likely to be met in cases where the size of the high susceptibility regions is small, or where water diffusion rates are high.

The second class of models can be considered the opposite extreme, where the water spins can only be assumed to be in a small region of the heterogeneous magnetic field distribution during the echo time. In this "slow exchange" case, the magnetic field experienced by the spins can be considered as approaching a linear field gradient. By modeling the distribution of such linear gradients through space, expressions for the behavior of the transverse magnetization can be derived. The conditions of this model are likely to be satisfied in cases where the regions of heterogeneous magnetic field are large, or the diffusion coefficient of water is small. In the case where water exchange is neither obviously fast nor slow (the so-called "intermediate exchange" regime), simplified analytic expressions for relaxation behavior are difficult to derive. For this reason, "intermediate exchange" models use Monte Carlo techniques to explicitly follow spins through heterogeneous field distributions. In their simplest form, these techniques have been applied to predict the distribution of field strengths, and hence static line shapes within tissues. In more challenging applications, these techniques have modeled not only static, but also dynamic (diffusion related) spin dephasing.

### 5.4 Pulse sequences and imaging techniques

The type of MR pulse sequence used to generate a clinical MR image and its associated parameters affects the visualization of contrast from tissues. The ultimate goal in optimizing MR scanning technique for contrast-agent visualization is to suppress the contrast from unchanged tissue parameters and accentuate the contrast on the basis of the parameter that is altered by the contrast agent. This requires knowledge of the mechanism of contrast-agent enhancement, the MR pulse technique being used to measure that parameter, and how the operator-dependent parameters can be adjusted to optimize the enhancement of the adopted contrast agent.
The positive T₁ enhancement effects of the gadolinium contrast agents are well visualized with T₁-weighted spin-echo imaging and T₁-weighted gradient-echo imaging techniques [20]. These pulse sequences have been previously explained in section 4.5.1 and 4.5.3.

Conventional spin-echo imaging remains the mainstay of MR pulse sequences used with MR contrast agents. This approach can provide images with T₁, T₂, and spin-density information. During the same long-TR interval used to produce a T₂-weighted image, a second image can be obtained with a short or intermediate TE (resulting in a second image with spin-density or intermediate T₂ weighting). One of the major disadvantages of conventional spin-echo imaging, when used to produce T₂-weighted scans, is the long imaging time. Imaging time is directly proportional to TR, which, for a typical T₂-weighted pulse sequence, is usually from 2 to 3 seconds long.

The gradient-echo imaging offers an alternative approach with substantially reduced imaging time and RF power deposition. T₁, T₂ and spin density weighted images can be generated by a change of the operator-dependent parameters of flip angle θ, TR, and TE. One of the major disadvantages of this technique is that susceptibility effects become prominent. This enhanced magnetic susceptibility effect can be exploited to advantage for contrast agent visualization.

However, there are other techniques that have been developed more recently and can show contrast enhancement.

A recent innovation is fast, or turbo, spin-echo imaging, which permits T₂-weighted scans to be acquired in a much reduced scan time. In this approach, multiple echoes are acquired with different phase encoding during each TR interval (see section 4.5.4). Images with both proton density- and T₂-weighted information can be obtained in a time that ranges from one-fourth to one-sixteenth with respect to that required for conventional spin-echo techniques. Since the images are generated by multiple TE data measurements, which are then averaged together for an effective TE image, the image contrast is different from that of a conventional spin-echo sequence. For example, the MR signal from fat is more intense on a T₂-weighted image, reflecting the brighter signal that fat produces on short-TE images.

Echo-planar imaging (EPI) is an ultrafast MR technique (see section 4.5.5) which can provide high-quality images that are free of motion artifact and provide high proton density-, T₁-, and T₂-weighted contrast. One of the primary advantages of EPI, when used in conjunction with contrast infusion, is that it can provide information regarding physiological information previously inaccessible to
MRI. Tissue perfusion can be assessed with high spatial resolution. During controlled bolus injection of a susceptibility contrast agent, such as gadolinium, ultrafast imaging techniques are applied with rapid sequential image acquisition. Decreases in brain signal intensity on these MR images are related to the presence of the susceptibility agent, which functions as a negative contrast-enhancement agent. The change in intensity of the MR signal is directly related to the concentration of the contrast agent, thus yielding data on tissue perfusion.

Techniques using magnetization transfer (MT) have been introduced last years in clinical MRI. MT results from excitations of protons in macromolecules that do not contribute directly to signal intensity in MR images. However, this excitation affects magnetization of water protons bound to these macromolecules. Macromolecular protons have a much broader range of resonant frequencies than those in free water. Therefore, RF pulses with larger or smaller frequencies than the resonant frequency of water protons, can excite macromolecular protons and saturate their magnetization. This saturated magnetization is then transferred from the macromolecular protons to the surrounding water protons, affecting the MR signal of the water protons.

The application of MT with spin-echo imaging can improve the enhancement effect produced by a gadolinium chelate in the brain. The result is a shortening of T1, with lower overall available magnetization and signal intensity. In theory, enhancement with gadolinium chelates is not mediated by macromolecular interactions and thus is not suppressed by the application of MT. Accordingly, MT pulses preferentially suppress the signal from background tissue, improving the conspicuity of gadolinium-enhanced regions. This can lead to improved visualization of abnormal contrast enhancement at a standard dose.
6 Calibration

Several in-vitro calibration experiments were made in order to obtain the relationship between contrast agent concentration and MR signal intensity.

6.1 Gadoteridol

The specific contrast agent used in the calibration was Gadoteridol (Gd-HP-DO3A or ProHance® [Bracco ALTANA]). Gadoteridol is a non-ionic extracellular contrast agent for MRI, with a low molecular weight complex of gadolinium. It is in the form of a sterile solution for intravenous injection. The FDA approved the clinical use of Gadoteridol in the United States in 1992 for a dose range of 0.1 to 0.3 mmol/kg [20] soon after that it has been approved by regulatory authorities in Japan and many European countries. Partly because of the ring nature of the chelate, Gd-HP-DO3A is more stable both in vitro and in vivo than either Gd-DTPA or Gd-DTPA-BMA.

The pharmacokinetics of intravenously administered gadoteridol in normal subjects conforms to a two compartment open model with mean distribution and elimination half-lives (reported as mean ± SD) of about 0.20 ± 0.04 hours and 1.57 ± 0.08 hours, respectively. Gadoteridol is exclusively eliminated in the urine with 94.4 ± 4.8% (mean ± SD) of the dose excreted within 24 hours post injection. There is no detectable biotransformation or decomposition of gadoteridol. The renal and plasma clearance rates (1.41 ± 0.33 $ml\ min^{-1}\ Kg^{-1}$ and 1.50 ± 0.35 $ml\ min^{-1}\ Kg^{-1}$, respectively) of gadoteridol are essentially identical, indicating no alteration in elimination kinetics during passage through the kidneys and that the drug is essentially cleared through the kidney.

Gadoteridol is a positive relaxation agent (see section 5.3) since it decreases T1 relaxation times. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

The published and standardized values [28][29] for the relaxivity parameters of Gadoteridol are $r_1 = 3.7 ± 0.1\ mM^{-1}\ s^{-1}$ and $r_2 = 5.5 ± 0.1\ mM^{-1}\ s^{-1}$. 

6.1 Gadoteridol
6.2 Static experiments

6.2.1 First experiment

A solution of Gadoteridol (0.5mol/L) was diluted in water in twenty-four tubes of 16mm of diameter and 10cm of length, with different concentrations varying between 0 and 50mmol/L: twenty-one concentrations from 0 to 5mmol/L in steps of 0.25mmol/L, and three very high concentrations of 10, 15 and 25mmol/L (Fig. 6.1). The experiment was performed at room temperature on a clinical 1.5T MR system (Gyroscan Intera, software release 10.3, Philips Medical Systems, Best, The Netherlands) with Mastergradients (maximum amplitude 30mT/m). A Cardiac Sense coil was used as the receiver.

![Figure 6.1: Scheme of the corresponding concentrations (mmol/L) in the MR image.](image)

![Figure 6.2: MR image of the twenty-four tubes with the different concentrations of Gadoteridol.](image)
Several pulse sequences with different settings were tested, and the acquired MR images (Fig. 6.2) were recorded in TIF and JPEG format. The TIF images, which are not compressed, were analyzed with LabView® (National Instruments) software in order to measure the gray level values for the different concentrations in a specific region of interest (ROI).

Mean values and standard deviations of the gray levels from different images with the same pulse sequence and setting were calculated for each concentration. All the resulting data are plotted in a graph. In order to show more clearly the relationship between concentration and signal intensity, the very high concentrations (10, 15 and 20mmol/L) are not included in the graph. The signal intensity for these values is almost zero.

The results show that the sequences with positive contrast enhancement are more suitable to find a linear relationship between concentration and signal intensity. It must be taken into account that the final purpose is the application of the sequences in dynamic and flow conditions. Therefore, only the results of the fastest sequences are reported below.

- **3D Nodes T1 FFE**

Fast Field Echo (FFE) sequence with T1 contrast enhancement, TR = 9.2ms, TE = 4.60ms, flip angle = 15°, FOV = 400mm, matrix scan reconstruction = 400x512, and ten slices of thickness = 6mm.
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Figure 6.3: Graph of signal intensity as a function of gadolinium concentration for 3D Nodes T1 FFE.

Fig. 6.3 shows that the signal intensity increases with contrast concentration up to 1.5mmol/L. Below this threshold, the correlation coefficient between concentration and signal intensity is 0.99. Therefore, with this acquisition technique, the contrast concentration is linearly related to the measured signal intensity for concentrations ≤ 1.5mmol/L. From this value, the signal intensity varies significantly and decreases for very high concentrations (≥ 4.75mmol/L). The average of the standard deviations in the linear range for the different measurements is 6.9. It is appreciated that there is an uncommon dip in the graph at 2.5mmol/L, which also appears in the other sequences used. The cause could be that the receiver coil did not surround and include all the tubes (Fig. 6.1).

- **Perfusion EPI**

Fast Field Echo (FFE) sequence with T1 contrast enhancement and Echo Planar Imaging (EPI) fast imaging mode, EPI factor = 15, TR = 17ms, TE = 8.10ms, flip angle = 8.20°, FOV = 300mm, matrix scan reconstruction = 64x128, and five slices of thickness = 3.5mm.
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Figure 6.4: Graph of signal intensity as a function of gadolinium concentration for Perfusion EPI.

Fig. 6.4 does not show a very clear relationship between contrast concentration and signal intensity in any range. The reason could be that the MR images recorded with this acquisition technique are too small (128x128) to obtain a precise signal intensity value. It is also appreciated the uncommon dip at 2.5mmol/L.

6.2.2 Second experiment

A second experiment was made with the same sequences as the first experiment. However, this time the total coverage of the tubes with the receiver coil was ensured. Moreover, three more fast sequences with different parameters, which could be useful for a dynamic experiment, were tested.

Solution of Gadoteridol (0.5mol/L) was diluted in water in seventeen tubes (16mm of diameter and 10cm of length) with different concentrations varying between 0 and 4mmol/L in steps of 0.25mmol/L. The experiment was performed at
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room temperature by means of the same clinical 1.5T MR system (Gyroscan Intera, software release 10.3, Philips Medical Systems, Best, The Netherlands) with Mastergradients (maximum amplitude 30mT/m). Two Sense Flex L coils (20cm of diameter), placed on the bottom and on the top of all the tubes, were used.

Figure 6.5: MR image of the seventeen tubes containing different concentrations of Gadoteridol. The tubes are arranged with increasing Gadoteridol concentration. The bottom row contains the tubes with the lowest concentrations and the top row contains the tubes with the highest concentrations. Within each row, the concentrations increase from left to right.

Five pulse sequences with different settings were used, and the acquired MR images (Fig. 6.5) were recorded in TIF and JPEG format. The TIF images were analyzed with LabView® (National Instruments) software to measure the signal intensity (gray level values) for the different concentrations in a specific ROI.

Mean values and standard deviations of the gray levels from the different images, made with the same pulse sequence and setting, were calculated for every concentration. The resulting data are plotted in a graph.

The hypothesis made on the reason for the dip at 2.5mmol/L in the first experiment is here confirmed. In fact, due to the complete coil surrounding the dip does not appear anymore in the measurements.

- **3D Nodes T1 FFE**

Fast Field Echo (FFE) sequence with T1 contrast enhancement, TR = 9.2ms, TE = 4.60ms, flip angle = 15°, FOV = 410mm, matrix scan reconstruction = 400x512, and ten slices of thickness = 6mm.
Fig. 6.6 shows that the signal intensity increases with the contrast concentration up to 2.5mmol/L. The correlation coefficient between concentration and signal intensity up to 1.25mmol/L is 0.97. Beyond this concentration the signal intensity starts to saturate, and, eventually, to decrease. Therefore, with this acquisition technique, the contrast concentration is linearly related to the measured signal intensity for concentrations ≤ 1.25mmol/L. The average of the standard deviations in the linear range for the different measurements is 24.3.

- **Perfusion EPI**

Fast Field Echo (FFE) sequence with T1 contrast enhancement and Echo Planar Imaging (EPI) fast imaging mode, EPI factor = 15, TR = 17ms, TE = 8.10ms, flip angle = 8.20°, FOV = 300mm, matrix scan reconstruction = 64x128, and five slices of thickness = 3.5mm.
Fig. 6.7 does not show a very clear relationship between contrast concentration and signal intensity in any range. In fact, the signal intensity varies in a very short range of values. The reason could be that the MR images recorded with this acquisition technique are too small (128x128) to obtain a precise signal intensity values.

- **Spoiled FFE (T1-FFE)**

  Fast Field Echo (FFE) sequence, TR = 6ms, TE = 1.76ms, flip angle = 80°, FOV = 240mm, matrix scan reconstruction = 256x512, and one slice of thickness = 5mm.
Fig. 6.8 shows that the signal intensity increases very fast with contrast concentration up to 2.5 mmol/L. The correlation coefficient between the concentration and the signal intensity up to 1 mmol/L is 0.92, and then the signal intensity starts to saturate. Therefore, with this acquisition technique, the contrast concentration is linearly related to the measured signal intensity for concentrations ≤ 1 mmol/L.

- **FLASH**

Fast Field Echo (FFE) sequence, TR = 250 ms, TE = 1.05 ms, flip angle = 80°, FOV = 430 mm, matrix scan reconstruction = 192x512, and six slice of thickness = 10 mm.
Fig. 6.9 shows that the signal intensity increases with contrast concentration up to 2.5mmol/L. The correlation coefficient between the concentration and the signal intensity up to 1mmol/L is 0.97. Beyond this concentration the signal intensity starts to saturate, and, eventually to decrease. Therefore, with this acquisition technique, the contrast concentration is linearly related to the measured signal intensity for concentrations ≤ 1mmol/L. The average of the standard deviations in the linear range for the different measurements is 10.7.

- **FAST**

Fast Field Echo (FFE) sequence, TR = 7.4ms, TE = 2.1ms, flip angle = 100°, FOV = 230mm, matrix scan reconstruction = 128x256, and one slice of thickness = 5mm.
Fig. 6.10 does not show a very clear relationship between signal intensity and concentration of Gadoteridol because the signal intensity varies in a very limited range.
7 Conclusion

The assessment of CO, EF, and PBV is very important for the diagnosis of circulatory system diseases. Unfortunately, some of these measurements, such as PBV, require the use of very invasive indicator dilution techniques. However, recent studies on contrast echocardiography have demonstrated that contrast imaging techniques permit efficient non-invasive cardiovascular quantifications.

This study aims to prove the applicability in contrast magnetic resonance imaging of the same indicator dilution principles used in ultrasound imaging for cardiac quantifications. Therefore, a bolus of gadolinium CA should be injected in a peripheral vein and detected in the central circulation by an MRI scanner in order to measure an IDC. To this end, a fundamental step concerns the establishment of the relationship between CA concentration and measured signal intensity (calibration).

The results from the calibration experiments in static conditions have proved a linear relationship between signal intensity and concentration of Gadoteridol for T1 positive enhancement. This linear relation holds in a low CA concentration interval. This range is suitable for an in-vivo application, and varies among the different MRI sequences that we tested. Those sequences in which the calibration curve does not show an early saturation are more suitable for the final application in patients. Moreover, only the fastest sequences will be suitable for an in-vivo application due to the flow conditions. Therefore, considering all these requirements, the 3D Nodes T1 FFE sequence results the best option for the future in-vivo measurements. The calibration curve for this sequence shows a linear relationship (correlation coefficient 0.97) from 0 to 1.25mmol/L. Beyond this value the signal intensity starts to saturate, and, eventually, to decrease.

In conclusion, this thesis shows that, in principle, the same methods applied for the assessment of cardiovascular parameters in contrast echocardiography can also be applied in contrast MRI, once the calibration techniques and settings that are explained in this report are used.
8 Appendix A

Eq. 4.3 can be represented as in Fig. A.1 and written as in Eq. A.1. Because of the constraints of Eq. 4.3, rotation is the only possible motion of the magnetic moment.

\[ \vec{\omega} \times \vec{r} = \gamma \vec{\mu} \times \vec{B}_0 \]  \hspace{1cm} (A.1)

![Figure A.1: Precession of a nuclear spin about the external magnetic field applied in the z direction.](image)

Fig. A.1 shows that \( \vec{r} \) can be written as \( \mu \sin \theta \hat{r} \). Therefore, replacing \( \vec{r} \) and making Eq. A.1 scalar, Eq. A.2 can be derived.

\[ \omega \mu \sin(\theta) \sin \left( \frac{\pi}{2} \right) \hat{v} = \gamma \mu B_0 \sin(\theta) \hat{v} \] \hspace{1cm} (A.2)

After simplification, Eq. A.2 is equal to Eq. A.3, which is the solution of Eq. 4.3 and can be written as in Eq. 4.4.

\[ \omega = \gamma B_0 \] \hspace{1cm} (A.3)
9 Appendix B

Referring to Eq. 4.9, \( \overline{B}_{xy} \) and \( \overline{M}_{xy} \) can be written as in Eq. B.1 and Eq. B.2 respectively.

\[
\overline{B}_{xy} = (B(r) \cos \theta, B(r) \sin \theta) = B(r) e^{i\theta} \quad (B.1)
\]

\[
\overline{M}_{xy} = (M_{xy}(r) \cos \varphi, -M_{xy}(r) \sin \varphi) \cdot e^{-\frac{t}{T_2}} = M_0(r) e^{-\frac{t}{T_2}} e^{-i\varphi} \quad (B.2)
\]

The term \( e^{-\frac{t}{T_2}} \) derives from the transverse magnetization (Eq. 4.14), and \( \varphi \) is equal to \( \gamma (B_0 + \vec{G} \cdot \vec{r}) t \), which represents the precession angular frequency multiplied by the time \( t \). Since vectors \( \overline{B}_{xy} \) and \( \overline{M}_{xy} \) have been defined as complex numbers (Eq. B.1, Eq. B.2), their scalar product can be written as the real part of the product of complex numbers, after conjugating one of them. Therefore, substituting Eq. B.1 and Eq. B.2 in Eq. 4.9, Eq. B.3 is derived. The real part can go out of the integral because the derivative and the integral are linear operators.

\[
V(t) = - \int_{\text{object}} \text{Re} \left[ \frac{d}{dt} B(\vec{r}) M_0(\vec{r}) e^{-\frac{t}{T_2}} e^{-i(\vartheta + \varphi)} \right] d\vec{r} =
\]

\[
= -\text{Re} \left[ -i \gamma B_0 - i \gamma \vec{G} \cdot \vec{r} - \frac{1}{T_2} \right] \int_{\text{object}} B(\vec{r}) M_0(\vec{r}) e^{-\frac{t}{T_2}} e^{-i(\vartheta + \varphi)} d\vec{r} \quad (B.3)
\]

Since \(-i \gamma \vec{G} \cdot \vec{r}\) and \(-\frac{1}{T_2}\) are negligible, after demodulation (i.e., removal of the carrier signal \( e^{-i\vartheta t} \)), Eq. B.3 is approximated by Eq. B.4.

\[
V(t) \approx \text{Re} \left[ \gamma B_0 \int_{\text{object}} B(\vec{r}) M_0(\vec{r}) e^{-\frac{t}{T_2}} e^{-i(\vartheta + \varphi)} d\vec{r} \right] \equiv \text{Re}[S(t)] \quad (B.4)
\]

If a quadrature component \( \text{Im}[S(t)] \) is generated and added to Eq. B.4, (for instance by using a second perpendicular detection coil, or generating in the demodulation mixer a \( \frac{\pi}{2} \) phase shifted version of the signal) the detected signal can be expressed as \( S(t) \) in complex domain. The signal \( S(t) \) can be written as in
Contrast magnetic resonance imaging for cardiovascular measurements: an in-vitro study.

Eq. B.5, assuming a homogeneous reception field within the object volume ($B(\vec{r})$ constant) and neglecting all the linear coefficients.

\[ S(t) = \text{Re}[S(t)] + i \cdot \text{Im}[S(t)] \approx \int_{\text{object}} M_0(\vec{r}) e^{i \frac{t}{T_1}} e^{-i \omega G \cdot \vec{r} t} d\vec{r} \]  

(B.5)
10 Appendix C

The relation between an electric current and the magnetic field generated by it, is given by the Biot Savart’s law, and is given as in Eq. C.1.

\[
\frac{dB}{dt} = \frac{\mu_0 I}{4\pi r^3} \times d\vec{l}
\]  

(C.1)

where \( I \) is the electric current, \( d\vec{l} \) describes the length and the direction of the current element considered, \( \vec{r} \) is the vector between the current element \( d\vec{l} \) and the position where the magnetic field is measured. By integrating over all current elements, the magnetic field can be found as a function of the overall current geometry. In the case of a RF coil, which in its simplest form is a circle (Fig. C.1), the generated magnetic field by along the line through the center of the circle and perpendicular to the plane of the coil is given as in Eq. C.2.

\[
B_y = I \frac{\mu_0 R^2}{2(R^2 + y^2)^{3/2}}
\]  

(C.2)

Figure C.1: Magnetic field generated by a current loop.
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11 Bibliography


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# 12 List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BPCA</td>
<td>Blood Pool Contrast Agent</td>
</tr>
<tr>
<td>CA</td>
<td>Contrast Agent</td>
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<tr>
<td>CBV</td>
<td>Central Blood Volume</td>
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<tr>
<td>CO</td>
<td>Cardiac Output</td>
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<tr>
<td>DFT</td>
<td>Digital Fourier Transform</td>
</tr>
<tr>
<td>DOTA</td>
<td>Tetraazacyclododecane tetra-acetic acid meglumine</td>
</tr>
<tr>
<td>DTPA</td>
<td>Diethylene-triaminepenta-acetic acid</td>
</tr>
<tr>
<td>DTPA-BMA</td>
<td>Diethylene-triaminepentacetic-acid-bismethylamide</td>
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<td>ECG</td>
<td>ElectroCardioGram</td>
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<tr>
<td>EF</td>
<td>Ejection Fraction</td>
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<td>Echo Planar Imaging</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FEF</td>
<td>Forward Ejection Fraction</td>
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<tr>
<td>FLASH</td>
<td>Fast Low Angle SHot</td>
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<td>FFE</td>
<td>Fast Field Echo</td>
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<td>FID</td>
<td>Free Induction Decay</td>
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<td>Fast Imaging with Steady Precession</td>
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<td>FOV</td>
<td>Field Of View</td>
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<td>GMN</td>
<td>Gradient Moment Nulling</td>
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<tr>
<td>GRASS</td>
<td>Gradient Recalled Acquisition of Steady State</td>
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<td>IDC</td>
<td>Indicator Dilution Curve</td>
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<td>IR</td>
<td>Inversion Recovery</td>
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<td>ITBV</td>
<td>Intra-Thoracic Blood Volume</td>
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<td>LV</td>
<td>Left Ventricle</td>
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<td>MR</td>
<td>Magnetic Resonance</td>
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<td>Mean Transient Time</td>
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<td>SPECT</td>
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<th>Abbreviation</th>
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<td>SPoiled GRadient</td>
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<tr>
<td>TE</td>
<td>Echo Time</td>
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<td>TOF</td>
<td>Time Of Flight</td>
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<td>TR</td>
<td>Repetition Time</td>
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<td>Turbo Spin Echo</td>
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