CONTINUING EDUCATION PROGRAM: FOCUS...

$T_2^*-$weighted perfusion MRI

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Abstract
$T_2^*-$weighted perfusion MRI is based on the so-called "first passage" approach: the modifications in the $T_2^*$-weighted MRI signal are followed during the first passage of a bolus of contrast agent. The pixel-by-pixel analysis of the curves is used to obtain parametric maps (time of arrival, time of the peak, mean transit time, relative volume and blood flow). Further analysis, with deconvolution by arterial input function (concentration of contrast agent in the blood), helps improve the quantification. It is possible to pre-inject a small dose of contrast agent to limit the impact of the extravasation of the contrast agent.

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Perfusion imaging includes a great many methods. In fact, the perfusion may be characterized by a great many parameters. In addition, these parameters may be obtained in several ways. In this article, the authors deal with perfusion MR imaging and, more particularly, the methods based on $T_2^*$-weighted variations.

Generalities

Parameters characteristic of perfusion

The three main physiological quantities characterizing the perfusion and accessible with $T_2^*$-weighted perfusion MRI are:
• the tissue blood volume or blood volume fraction. In general, the blood volume is expressed in mL of blood per 100 g (or 100 mL) of tissue (mL/100 g). The blood volume fraction, corresponding to the relationship between the blood volume (in mL) and the tissue volume (in mL) is expressed in %;

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the tissue blood flow or volume of blood circulating in a voxel per unit of time. In general, it is expressed in mL of blood per 100 g (or 100 mL) of tissue and for 1 min (mL/100 g/min);

2. the mean transit time (MTT); the blood volume and blood flow in a voxel are mathematically related through the value of the MTT (central volume theorem).

Contrast agent

T₂*-weighted perfusion imaging is based on the use of a tracer, a paramagnetic contrast agent, injected in the blood circulation. A tracer should act like the element to be characterized — in general plasma. It should be detectable by the imaging method and should not disturb the circulation of the blood [low volume injected, no arterial overpressure at the time of injection, no interaction between the tracer and the components in the blood (inert molecule), etc.]. A tracer does not allow for the overall characterization of the blood: plasma and erythrocytes take up different volume fractions and circulate at different speeds. In perfusion imaging, the terms "tracer" and "contrast agent" are used indifferently.

To obtain perfusion imaging, a non-diffusible tracer is necessary, that is, a tracer that does not cross the walls of the vessels. In general, the ability of a tracer to extravasate depends on its size, which can be determined by the molecular weight (in Da) or by the apparent molecular size (in nm) still called hydrodynamic diameter, its hydrophilic or lipophilic nature or its electrical charge. Of course, the same contrast agent may extravasate in one organ and not in another (for example, a Gd chelate does not extravasate in the brain but does so in the muscle).

Voxel model

A voxel model is used for the first passage method. It comprises a single arterial input and a single venous output. The input and the output are connected by a network comprising a great many capillaries.

At time t, the concentrations in tracer at the arterial input and the venous output are represented by Cₐ(t) and Cᵥ(t), respectively. The mean concentration in tracer is noted in the voxel Cvoxel(t). This model does not apply to all tissues (the liver comprises two vascular inputs).

The blood flow, F, at the arterial input, should be the same as the blood flow at the venous output (if not, the blood will accumulate in the voxel).

Between arterial input and the venous output, the blood has a set of possible pathways that are characterized by different lengths. Tracer molecules reaching the arterial input at the same time will require different times to cross this voxel. This distribution of transit times is an important characteristic of the microvascular network of the voxel.

Perfusion imaging methods

Dynamic methods and steady-state methods

Two approaches are used to obtain information about the perfusion. Either images are obtained on a regular basis during the passage of the contrast product in the zone of interest ("dynamic" approach), or an image is obtained before and after the injection of a contrast product ("steady-state" approach). The dynamic approach is used in almost all cases, in the absence of contrast agents that are adapted for and authorized in man. In addition, the dynamic method provides the most information.

The so-called "first passage" method

First passage information

The method consists of measuring variations in signal during the first passage of a non-diffusible contrast agent. This principle was introduced in 1824 by Hering as the "indicator dilution method" [1].

To understand the first passage concept, it is necessary to imagine the circulation of the blood in the body as a set of loops that go from the heart to an organ. When a contrast product is injected in the vein of an arm, the product reaches the heart, crosses the lungs and returns to the heart before exiting by the aorta. All the organs or parts of the body receive the contrast product by their arteries. The concentration of the arterial input will be approximately the same in each organ. The contrast product crosses each organ — this is the first passage — before returning to the heart. The return of the tracer to the heart via the different loops occurs in disorder, as the time taken by the tracer to complete a loop is variable. A second passage of the bolus of the tracer is sometimes visible in the organs, before the contrast product is diluted in the entire blood circulation. This second passage may be visible before the end of the first passage (as is the case in the brain, for example).

In the first passage experiment, we assume that we only measure the first passage (no recirculation). To come close to it, the injection of product has to be as brief as possible. Since, in practice, recirculation occurs (the circulation of blood is fortunately a closed circuit), it is necessary to extract the first passage data during the analysis. For this, the data measured is adjusted by the derivative of the gamma function (empirical discovery [2]):

\[ C_{\text{voxel}}(t) = K(t-t_0)^\alpha \exp\left[-(t-t_0)^\beta\right] \]  (1)

where \( K \), \( \alpha \) and \( \beta \) are parameters without biological significance and where \( t_0 \) represents the time of arrival of the tracer at the voxel. The equation (1) adjusted to the data represents the first passage for each pixel. Now that we have extracted the first passage information, we will see how to extract the relative and then quantitative perfusion characteristics.

"Qualitative" analysis

It is fairly direct to obtain a value for the blood volume fraction in the voxel. The mean concentration in tracer in the voxel, \( C_{\text{voxel}}(t) \), equals [3]:

\[ C_{\text{voxel}}(t) = \nu_p C_p(t) \]  (2)

where \( C_p(t) \) represents the mean concentration in tracer in the plasma of the voxel and \( \nu_p \) the volume fraction of the plasma in the voxel. Note that the form of \( C_p(t) \) and \( C_p(t) \) is not the same due to the distribution of transit times in the voxel. Nevertheless, in view of the principle of conservation...
of matter, and given that the tracer is not diffusible, the total quantity of tracer that passes through the artery should pass through the blood of the voxel. This equality of quantity is represented by:

\[
\int_{0}^{\infty} C_p(t) (F dt) = \int_{0}^{\infty} C_a(t) (F dt)
\]

(3)

In this equation, \(F dt\) represents the elementary volume of blood and \(C(t) F dt\) represents an elementary volume of tracer. By using equations (2) and (3), it is now possible to calculate \(V_p\):

\[
V_p = \frac{\int_{0}^{\infty} C_{\text{voxel}}(t) dt}{\int_{0}^{\infty} C_a(t) dt} = \frac{\text{Area under the curve } C_{\text{voxel}}(t)}{\text{Area under the curve } C_a(t)}
\]

(4)

Assuming that \(C_a(t)\) — the arterial input function — is the same for all of the voxels in the organ considered, we note that \(V_p\) is proportional to the area under the curve "concentration in contrast agent in the voxel as a function of time". To obtain a quantitative value for \(V_p\), it is necessary to also quantitatively determine the values of \(C_{\text{voxel}}(t)\) and \(C_a(t)\) (see further down). If we only have absolute pixel-by-pixel values of \(C_{\text{voxel}}(t)\), it is still possible to obtain a map of the relative plasma volume fractions. This highly useful map is used to calculate a relationship between the plasma volume fraction measured in a region of interest and that measured in a reference region.

Analysis of the first passage curve thereby allows for an estimate — at least a relative estimate — of \(V_p\). However, it is possible to go farther. On the basis of the first passage curve, it's also possible to obtain information about the MTT of the plasma in the voxel. The microvascular network of the model voxel may be described by the distribution of its transit times. The fraction of the tracer molecules with a transit time \(t\) to cross the voxel is noted as \(h(t)\). The sum of the fractions of molecules with a transit time through the voxel ranging from \(0\) to infinity is necessarily \(1\) (that is, all of the molecules). This is noted as:

\[
\int_{0}^{\infty} h(t) dt = 1
\]

(5)

It is therefore possible to mathematically define the MTT as the mean value of the distribution \(h(t)\):

\[
\text{MTT} = \frac{\int_{0}^{\infty} t h(t) dt}{\int_{0}^{\infty} h(t) dt} - t
\]

(6)

In practice, the relative value of the MTT is obtained from \(C_{\text{voxel}}(t)\) by calculating:

\[
\text{MTT} = \frac{\int_{0}^{\infty} t C_{\text{voxel}}(t) dt}{\int_{0}^{\infty} C_{\text{voxel}}(t) dt} - t_0
\]

(7)

where \(t_0\) is the time for the arrival of the tracer in the voxel [refer to equation (1)].

Now that we have the values for the relative blood volume and MTT, let’s see how to obtain a value for the relative blood flow \(F\) from the first passage curve. If \(h(t)\) is the fraction of molecules that take a time \(t\) to cross the voxel, then \(t h(t)\) is the fraction of the blood volume \((t F\) is a volume fraction) that takes time \(t\) to cross the voxel. From equation (6), we thereby obtain [4]:

\[
V_p = F \int_{0}^{\infty} t h(t) dt = F \times \text{MTT}
\]

(8)

The relationship between is called the central volume theorem. It allows for an estimate of \(F\).

Quantitative analysis

To obtain the quantitative values of \(V_p\) and \(F\), we determine the quantity of tracer that remains in the voxel following the instantaneous input of tracer:

\[
R(t) = 1 - \int_{0}^{t} h(t) dt
\]

(9)

The \(R(t)\) function is called the residue function. \(R(0) = 1\): at \(t = 0\), nothing has left the voxel (the time of arrival is considered to be zero here), then the value of \(R(t)\) decreases as the tracer leaves the voxel. Using equations (9) and (10), the concentration in tracer in the voxel may now be calculated:

\[
C_{\text{voxel}}(t) = F C_a(t) \otimes R(t) = F \int_{0}^{t} C_a(\tau) R(t - \tau) d\tau
\]

(10)

Equation (10) indicates that, to quantitatively obtain \(F\) and \(V_p\), a deconvolution of \(C_{\text{voxel}}(t)\) is required by \(C_a(t)\), which means estimating the residue function. This process is complex. Certain approaches use a model function for the residue function [5]. This deconvolution also has to be rendered insensitive to the value of the arrival time, \(t_0\) [6]. If this is not the case, the variations in arrival time result in variations in the estimates of the perfusion parameters.

The steady-state approach

With non-diffusible tracers and slow clearance (long plasma half-life), it is possible to obtain an estimate of the blood volume and an approach to the mean diameter of the vessels in the voxel by means of MRI. This approach is MRI-specific, since it is in part based on the fact that the MRI signal is sensitive to the diffusion of water [7]. This steady-state
approach has the advantage of producing maps with exceptional spatial resolution that are easy to quantify [8].

Link between MRI signal and contrast agent

Effects of contrast agents on the MRI signal

The contrast agents used in clinical MRI are not directly detectable, as opposed to other means of imaging. Their presence is detected indirectly through the effects that they induce on the MRI signal of water. The effects of relaxivity and susceptibility are distinguished.

Effects of relaxivity

The MRI contrast agents catalyze the relaxation phenomena: in the presence of contrast agent, the longitudinal relaxations—characterized by $R_1 = 1/T_1$ —and transverse relaxations—characterized by $R_2 = 1/T_2$ —occur more quickly ($R_1$ and $R_2$ increase). This increase linearly depends on the concentration:

$$R_1 = R_{1,0} + r_1 [Gd]$$  \hspace{1cm} (11a)

$$R_2 = R_{2,0} + r_2 [Gd]$$  \hspace{1cm} (11b)

where $R_{1,0}$ and $R_{2,0}$ represent the speed of relaxation in the absence of contrast agent and are characteristics that depend on the contrast agent, the magnetic field and the temperature. [Gd] represents the concentration in contrast agent.

If the contrast agent is intravascular (non-diffusible), then the $T_1$ and $T_2$ of the blood are reduced. However, due to the exchange of water occurring through the walls of the vessels, $T_1$ and $T_2$ of the extravascular space may also be slightly reduced, while the contrast agent has not penetrated in the interstitial space.

Effects of magnetic susceptibility

All of the bodies magnetize when placed in a magnetic field. The intensity of this magnetization is characterized by the magnetic susceptibility of the body. Thereby, a contrast agent has a magnetic susceptibility: gadolinium chelate (Gd) are paramagnetic, the particles of iron oxide are superparamagnetic. Without contrast agent, the magnetization of the blood differs from that of the surrounding tissue. The presence of a contrast agent in the vessels considerably reinforces this difference in the magnetization between the intravascular and extravascular compartments. Between these two compartments, there is a variable gradient in magnetic field. The variation in the heterogeneity of the intensity of the magnetic field in the voxel leads to a variation in the $T_2^*$ of the voxel.

First passage monitoring

Gd is the contrast agent most often used. The molecular weight is about 5000 Da (variable according to the manufacturer). The presence of contrast agent simultaneously induces effects on $T_1$, $T_2$ and $T_2^*$. $T_2^*$-weighted sequences are almost only used, although certain tests have been carried out with $T_2$-weighted sequences and more recently $T_1$-weighted sequences (in particular with spiral imaging that allows for very short echo times, thereby being little sensitive to variations in $T_2^*$). The choice to employ the $T_2^*$ effect is based on two main reasons:

- the effect is approximately independent of the size of the vessels (which is not the case for the effect on $T_2$ [9]);
- the $T_2^*$ effect results in higher variations in signal than the $T_2$ or $T_1$ effects.

Measurement of the tracer concentration in the voxel

Different studies have analyzed the relationship between the concentration of contrast agent in the voxel and the variation in relaxation speed (noted $R_2^* = 1/T_2^*$). It is generally accepted that [9]:

$$C_{\text{voxel}}(t) \propto R_2^*(t) - R_{2,0} = \Delta R_2^*(t)$$  \hspace{1cm} (12)

where $R_{2,0}$ represents the speed of relaxation of the base line (in the absence of Gd). If a gradient echo is repeatedly acquired — for example with an echo planar sequence (EPI) — during the passage of the bolus, for each pixel it is possible to calculate:

$$\Delta R_2^*(t) = \frac{1}{TE} \ln \left( \frac{S(t)}{S_0} \right)$$  \hspace{1cm} (13)

where $TE$ represents the echo time, $S_0$ the signal of the base line (average of several measurements) and $S(t)$ the signal as a function of time. By analyzing the shift in time of each pixel (that is, $\Delta R_2^*(t)$), we obtain parametric maps.

Measurement of the arterial input function

The relationship between signal of the voxel and concentration in contrast agent does not apply to the signal coming from the vessels. In fact, if the concentration in contrast agent is too high, the linear relationship provided by the equation (12) is no longer valid [10,11]. However, for voxels located near an artery in the magnetic field gradient between vessels and surrounding tissue, we observe a linear relationship between the tracer concentration in the artery and (\Delta R_2^*) [12]. Therefore, these voxels have to be used in order to obtain an estimate of the arterial input function.

Conclusion

The $T_2^*$-weighted perfusion MRI is based on the dynamic characterization of the first passage of an exogenous contrast agent.

Although the theoretical basis of this method has been well established, the quantification of the parameters remains difficult. In fact, the effects of relaxivity and susceptibility related to the presence of the contrast agent in a compartment are complex. More generally, a standard acquisition protocol, or recognized processing software is not available (even if the different manufacturers propose software solutions), which also raises problems. Recently, Willats and Calamante proposed a strategy for the processing of $T_2^*$-weighted perfusion data in order to standardize the practice [13].

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The author declares that he has no conflicts of interest concerning this article.

References


