Kanal's MR Physics:

Clinical MRI, MRA and MRS; Understanding and Applying

Vail 2020 MR Physics Course

Overview and Objectives

- Discuss gadolinium-based MR contrast agent use, including mechanism of action, distribution, time versus concentration considerations, and the clinical impact and benefits of higher relaxivity agents.

- Identify numerous MR imaging artifacts, how to recognize them, and how to decrease or eliminate them.

- Describe the unique advantages and clinical applicability of utilizing such MR pulse sequences as inversion recovery (including FLAIR and STIR), diffusion weighted imaging, perfusion weighted imaging, and MR spectroscopy.

- Identify various types of MR angiographic sequences and their specific advantages, limitations, and artifacts.

- Introduce the concepts underlying MR spectroscopy and spectroscopic imaging and demonstrate how these are clinically applied in routine patient care settings.

Who Should Attend

This is a unique, highly focused and concentrated MR course developed by Dr. Kanal, and is designed for radiologists, neurologists, cardiologists, physicists, technologists, industry specialists, and others who seek to understand how MR imaging works and how to clinically apply it.

CME Accreditation and Designation

In support of improving patient care, the University of Pittsburgh is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME) and the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians

The University of Pittsburgh School of Medicine designates this live activity for a maximum of 20.75 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Other health care professionals

Other health care professionals will receive a certificate of attendance confirming the number of contact hours commensurate with the extent of participation in this activity.

Faculty Listing

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Faculty Disclosure

All individuals in a position to control the content of this educational activity including members of the planning committee, speakers, presenters, authors, and/or content reviewers have disclosed all relevant financial relationships with any proprietary entity producing, marketing, re-selling, or distributing health care goods or services, used on, or consumed by, patients.

The following relevant financial relationships were disclosed:

Emanuel Kanal, MD is a consultant for Bracco Diagnostics, GE Healthcare and Medtronic.

No other planners, members of the planning committee, speakers, presenters, authors, content reviewers and/or anyone else in a position to control the content of this educational activity have relevant financial relationships to disclose.

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Vail 2020 MR Physics Course

Course Schedule:

Sunday:

Welcome	4:15 PM
• Basic MR Imaging Review – Part 1- T1, T2, relative proton density (RPD)	4:30 PM – 6:00 PM
BREAK	6:00 PM - 6:10 PM
• Basic MR Imaging Review – Part 2 - TR, TE, Computer Simulation Review	6:10 PM - 7:00 PM
End of Session	7:00 PM

Monday:

• Review of gradient echo MR imaging: The role of TR, Flip Angle	7:00 AM - 8:20 AM
BREAK	8:20 AM - 8:30 AM
• Review of gradient echo MR imaging: TE vs. T2*, how to successfully Achieve T1, T2*, and or proton density weighting	8:30 AM - 9:30 AM
• Question and Answer Session	9:30 AM -9:45 AM
End of Session	9:45 AM
SKI BREAK	
• Inversion Recovery Imaging and its Variants, Parts 1 & 2	4:30 PM - 5:30 PM
BREAK	5:30 PM - 5:40 PM
• Inversion Recovery Imaging and its Variants, Parts 1 & 2 (cont'd)	5:40 PM - 7:00 PM
• Question and Answer Session	7:00 PM - 7:15 PM
End of Session	7:15 PM

Tuesday:

• MR Safety: Overview, MR Safety Certification and the ABMRS	7:00 AM - 7:50 AM
BREAK	7:50 AM - 8:00 AM
• GBCA Safety Update: Accumulated Intracranial Gadolinium	8:00 AM - 9:30 AM
• Question and Answer Session	9:30 AM – 9:45 AM
End of Session	9:45 AM
SKI BREAK	
• Artifacts, Part 1 Fat saturation, water saturation, chemical shift artifact, magnetization transfer imaging	4:30 PM - 5:30 PM
BREAK	5:30 PM - 5:40 PM
• Artifacts, Part 2 Truncation artifact, fat-water edge enhancement artifact, fat saturation failure	5:40 PM – 7:00 PM
• Question and Answer Session	7:00 PM -7:15 PM
End of Session	7:15 PM

Wednesday:

• MR Contrast Agents	7:00 AM - 7:50 AM
BREAK	7:50 AM - 8:00 AM
• High relaxivity GBCA and Associated Sequence Optimization Techniques	8:00 AM - 9:30 AM
• Question and Answer Session	9:30 AM -9:45 AM
End of Session	9:45 AM
SKI BREAK	

Vail 2020 MR Physics Course

Wednesday:

• Diffusion/Perfusion Weighted MRI: Part 1	4:30 PM - 5:30 PM
BREAK	5:30 PM - 5:40 PM
• Diffusion/Perfusion Weighted MRI: Part 2	5:40 PM – 7:00 PM
• Question and Answer Session	7:00 PM -7:15 PM
End of Session	7:15 PM

Thursday:

• Summary of Principles, Techniques and Uses of MRA	7:00 AM - 7:50 AM
BREAK	7:50 AM - 8:00 AM
• MR Spectroscopy	8:00 AM - 9:30 AM
• Question and Answer Session	9:30 AM -9:45 AM
End of Session/Course	9:45 AM

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Basic MR Imaging Background Physics:
An Introduction to T1, T2, Proton Density, TR, and TE

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Introduction:

In CT scanning and in essentially all X-ray based imaging examinations, we attempt to pass X-rays through specific tissues of the body. The greater the degree to which the traversed tissue manages to stop the passage of these X-rays, the whiter this tissue will appear on the resultant image. It is thus effectively the case that the greater the electron density of the tissue the greater it will stop the passage of X-rays and thus the whiter these tissues will appear on such images. In magnetic resonance imaging, however, how white or black or gray a tissue will appear is dependent upon multiple varied factors that all must be simultaneously considered. In a nutshell, all of magnetic resonance (MR) - be it imaging, angiography, spectroscopy, etc. - is the creation, manipulation, and ultimate detection of tissue magnetization at very specific means and times. It is thus the magnetic characteristics of the tissues being imaged, together with the effects of the manipulations that we carry out on the magnetization of these tissues, which will determine the ultimate signal intensities of the tissues being examined via MRI. It is the purpose of this introductory lecture to introduce the student to some of the most important of these factors that will determine the intensities of the imaged tissues on the final image, namely: TR, TE, T1, T2, and proton density.

Background Information:

Assume that we are dealing with a frame of reference defined by the three orthogonal axes, labeled by convention as X (anteroposterior), Y (left to right), and Z (superoinferior). Assume further that we are discussing an MR imaging system into

which we are about to place our patient where the external magnetic field of the imaging system, Bo, lies along the Z-axis. When placing a patient into the powerful magnetic field of an MR imaging system the effect of its magnetic field on the hydrogen nuclei (henceforth referred to as protons) of the various tissues of the body is to cause them to become magnetized. In other words, one can think of the (hydrogen) protons of the patient's liver as being magnetized, with a strength (magnitude) and direction to this tissue's magnetization. The tissue's magnetization can therefore be depicted as a vector, or arrow, where the strength of the magnetization is depicted by the length of the arrow/vector whose direction depicts the direction of, let's say, its north pole. The orientation of this tissue net magnetization vector (NMV) will lie along the same direction as the external magnetic field Bo to which the tissue was exposed (and which magnetized it in the first place), which, in our example, is along the Z-axis.

Relative Proton Density:

The degree to which the tissue is magnetized is dependent upon several factors. For example, the stronger the magnetic field Bo to which we expose the tissues the greater the degree to which they will be magnetized and thus the longer will be their net magnetization vectors. Further, as we are discussing hydrogen nuclei, or protons, that are being magnetized in the first place, the greater the number of protons per unit volume of tissue, the greater the amount of magnetization (per unit volume) from that tissue. Thus two tissues exposed to the same magnetic field Bo may well differ in their initial magnetization magnitudes (also referred to as their Mo values) due to inherent

differences in their relative proton densities. The tissue with a greater proton density (also known as spin density or proton spin density) will be more magnetized per unit volume of tissue, and will thus be depicted with a longer vector, than another tissue with fewer protons per unit volume (i.e., lower relative proton density (RPD)). Since we already noted above that all of MR will be the creation, manipulation, and ultimate detection of tissue magnetization, the greater the relative proton density (RPD) of the tissue the more this will contribute to that tissue's signal intensity, and the whiter it will appear on the image.

Preparatory Phase:

If we now expose this magnetized tissue to a radiofrequency oscillating magnetic field that is oscillating at a precise, particular frequency, there would be an extremely efficient transfer of energy, or resonance, between the oscillating RF magnetic field transmitter and the tissue's protons. The grossly evident effect of such an energy transfer is a nutation, or change in orientation, of the tissue's NMV away from the vertical Z axis along which it was initially oriented prior to our turning on the RF oscillating magnetic field transmitter. This nutation takes the form of a complex spiral motion down away from the vertical Z axis. To assist in depicting this motion in a simpler manner, physicists have devised what is referred to as the rotating frame of reference. This rotating frame is simply a mathematical simplification of what is actually going on in three dimensions, and allows us to more simply depict it (from a certain point of view) as a two dimensional motion. Let's return to the three

orthogonally oriented axes in our laboratory frame of reference. If we spin this frame of reference around its Z axis (like a toy jack) in the same direction and frequency at which the NMV is spiraling downward once the transmitted RF oscillating magnetic field is turned on, we will be in what we refer to as the rotating frame of reference. In this rotating frame of reference the net magnetization vectors of each tissue's protons do not appear to be spiraling at all. Rather, in the rotating frame, the effect of the transmitted RF is to begin to rotate the tissue NMV around the X axis (along which the RF is being directed), on the Z-Y plane, like the hands on the face of a clock.

It is most important to note that as far as the brief RF pulses used in practical MR imaging are concerned, we are to think of the RF as effecting a change in the direction, **but not the magnitude/strength**, of the tissue NMV. Thus the result of a brief RF pulse would be that the direction of the NMV would no longer be along the Z axis (i.e., vertical), but rather at some other position along the face of the clock that is the Z-Y plane. The exact orientation of the tissue NMV would depend on the strength and duration of the transmitted RF pulse. If this transmitted RF pulse is left on for just enough time and at the right strength to tip the tissue's NMV from the vertical, Z, axis to the horizontal, Y axis, by definition we would refer to that transmitted RF "burst" as having been a 90 degree RF pulse. Similarly, a 180 degree pulse is one where the tissue magnetization is rotated by 180 degrees around the X axis, and so on. Thus, assume that the tissue NMV was such that one unit of magnetization was oriented along the vertical, Z, axis after being placed into the magnetic field Bo. Following a single 90

degree RF pulse (transmitted at the appropriate frequency, of course) the NMV for this tissue would still have a unit length of one and would be oriented along the Y axis when this pulse is completed.

It is well known that a moving electrical charge induces a magnetic field perpendicular to the motion vector of the charge (Faraday's Law). The converse is also true; a moving/varying magnetic field will induce a voltage, or current, in a direction perpendicular to the motion vector of the magnetic field. If I set up an electrical conductor (i.e., an antenna, or receiver coil) in a plane perpendicular to the direction of motion of this moving magnetic field, I will then be able to detect electrical voltage induced within this coil. **The receiver coils used in MRI to detect the magnetization brought down to the horizontal plane are oriented in such a way that they can ONLY detect magnetic fields that are moving in the horizontal, X-Y plane.** Thus, only those tissue NMV's that have a component that is pointing along the X-Y plane are detectable by the receiver coils in our MR imaging system. Indeed, another term, then, for horizontal magnetization is signal. The greater the magnitude of horizontal magnetization the greater the measurable MR signal at that instant in time. A useful analogy might be that of a flashing police beacon; it is only detectable along a specific axis or plane. By standing over or under the beacon one might not see the flashing, coherent light signal at all. But at the appropriate orientation perpendicular to the light itself (i.e., along the plane of the light's rotation), the coherent signal of light is clearly detectable.

Note that prior to the transmitted RF being turned on, the tissue protons' NMV was oriented entirely along the Z axis. At this point the NMV is absolutely invisible to our imaging system/receiver coils, as the net component that is oriented along the X-Y plane is zero (i.e., there is no horizontal magnetization, and thus no signal to detect - yet).

We cannot measure this vertical, Z component of magnetization directly. If, however, we could find a way to tip this net magnetization vector out of the Z axis and into the horizontal X-Y plane, we would then be able to measure it directly as signal intensity. As noted above, if we expose the protons within the static external magnetic field Bo to the correct resonant frequency oscillating magnetic field (also somewhat loosely referred to as a "radio wave"), the tissue NMV will nutate away from the Z axis down towards the horizontal X-Y plane. If I transmit a 90 degree RF pulse, the NMV of each tissue will point along the Y axis (in the rotating frame) at the end of that 90 degree RF pulse. This would tip the tissue's net magnetization vector down to point along the Y axis - directly at the receiver coils. I would thus be able to detect a signal in my coils from the net magnetization vector that is now pointing along the appropriate plane/axis for detection by the receiving coils of the MR imaging system. Thus, for an RF pulse that produces a 90 degree nutation in the orientation of the NMV (for example, from along the Z axis initially to along the Y axis at the end of the RF pulse), immediately after turning off the 90 degree radiofrequency pulse the NMV points

entirely along the Y axis (in the rotating frame), with the component along the Z axis being 0.

We are now ready to embark upon a discussion of the mechanisms via which the tissue NMV will return to the Mo state in which it had been prior to our having disturbed it with the 90 degree RF pulse. It is in this section of the lecture that we will introduce and discuss the concepts of T1, T2, TR, and TE.

T1 and T2 Relaxation Times:

Before we get into lengthy discussions as to what is occurring in T1 and T2 relaxation, it may help to point out that we are able to differentiate between materials in life by differing characteristics that they may possess. For example, some things are green, some are red; our eyes can differentiate between these states. We can explain why things have different colors if we so desire, but the important thing is that even if we do not fully understand the basis for why one object is green and not, say, blue, we are still able to clearly differentiate between the colors of the two objects being discussed. Such is the case in magnetic resonance imaging, where instead of the colors of two objects, or tissues, it is the magnetic properties of these tissues that we are discussing and differentiating amongst. Some tissues may have long T1 values, while others may have short ones. Similarly, some may have long T2's, while those of other tissues may be short. Without even yet understanding what these factors are, we can already begin to understand that in MRI we are attempting to take advantage of these

inherently differing magnetic characteristics of the tissues being imaged and use that to permit us to display them in a visually contrasting way.

T1 Relaxation:

As you may recall, immediately following the 90 degree RF pulse, the effect of that pulse was to have flipped the net magnetization vector of each tissue in the slice by 90 degrees, to the point where they were now oriented along the Y axis. After turning off the 90 degree RF pulse the net magnetization vector (of each tissue) would immediately begin returning, or relaxing, towards the state that it had been in prior to our having disturbed it with the RF pulse - namely, returning to the Z axis, parallel to the B_o static magnetic field. This relaxation results in alterations in the magnitude and direction of each tissue's net magnetization vector, causing it to decrease in the Y axis and increase back into the Z axis. For the sake of clarity, let us first examine what is occurring in each of these two axes independently.

We began (Mo) with the tissue's magnetization oriented along the vertical, Z axis. The magnitude of each tissue's NMV was dependent at least in part upon the strength of the magnetic field Bo to which it was exposed as well as the relative proton density of the tissue being examined. After the 90 degree RF pulse, all of this magnetization is nutated so that it ends up pointing along the Y axis. At that point there would be no vertical magnetization whatsoever (i.e., none of the tissue's net magnetization vector would be oriented along the Z axis at that time). As time passes,

we will fully recover all of this vertical magnetization. The rate at which this vertical magnetization recovers may well differ from tissue to tissue. In fact:

The time after the 90 degree RF pulse that must pass before the tissue recovers 63% of its initial vertical magnetization is referred to as the T1 value of the tissue.

Please note therefore that T1 is a unit of time. Further, the longer the T1, the slower the rate at which that particular tissue recovers its vertical magnetization after being nutated out of the Z axis by an RF pulse. Incidentally, the T1 of a tissue is also referred to as the spin-lattice relaxation, as it occurs by the tissue (spin) giving up the excess energy that it absorbed (from the RF pulse) to the environment (lattice). Further, as the relaxation process is one that is recovering magnetization back to the Z, or longitudinal, axis, another name for T1 relaxation is also longitudinal relaxation.

(For those of you requesting extra credit, it is also fair to point out as an optional item at this point that the T1 of the tissue itself is influenced by the strength of the magnetic field to which one exposes the tissue being studied. In other words, a tissue will recover its vertical magnetization after an RF pulse more **slowly** if it is exposed to a stronger magnetic field than it would if it would have been exposed to a weaker external magnetic field Bo. We will not be discussing that anymore during this lecture, however.)

To illustrate how consistent this phenomenon is, let's say that a given tissue has a T1 value of 1 second. Thus for that tissue, one second following a 90 degree RF pulse, by definition there will be 63% of the initial vertical magnetization already recovered back along the vertical Z axis. (In other words, 37% of the initial vertical magnetization magnitude would not have yet recovered at one second following that single 90 degree RF pulse.) After another second (i.e., a total of two seconds following the single 90 degree RF pulse) an additional 63% would recover of the 37% that had not yet vertically recovered after the first second had passed. This yields a total of 63% plus (63% of 37) or 63% plus 23%, or a total of roughly 86% recovery. Thus, 86% of that tissue's initial vertical magnetization will have recovered after two such T1 time periods (in this case, two seconds) following a single 90 degree RF pulse. Similarly, after three, four, and five such T1 time periods following a single 90 degree RF pulse there will be a total of roughly 95%, 98%, and 99+% vertically recovered. For simplicity's sake, it is quite acceptable to consider magnetization that has recovered more than 99% of its initial vertical value as fully recovered vertically. As noted, this will occur at roughly five times the T1 value of any tissue following an RF pulse. In our example, in other words, it is quite acceptable to say that the tissue will have (practically speaking) fully recovered back to where it had started out by roughly five seconds after that single 90 degree RF pulse.

In reality, T1 values may differ substantially for different tissues. For example, the T1 value for white matter (at a given field strength) may be 750 milliseconds,

whereas for fat it may be 250 milliseconds and for cerebrospinal fluid (CSF) it may be 2,250 milliseconds. (The numbers used herein are for teaching and illustrative purposes only, and are not meant to represent actual values for any given tissue or field strength.) Using the explanation and reasoning illustrated in the previous paragraph, 2250 milliseconds following a single 90 degree RF pulse to which all three such tissues of white matter, CSF, and fat were exposed, fat will have its net magnetization vector fully recovered vertically (as 2250 ms is far more than five times its T1 value of 250 milliseconds). Similarly, white matter will have around 95% of its vertical magnetization already recovered vertically, as three T1 time periods will have passed for white matter since the 90 degree RF pulse. CSF, on the other hand, will only have recovered roughly 63% of its initial vertical magnetization, as it has the longest T1 (2250 ms) of these tissues being discussed. Another way of stating this is that after 2250 milliseconds following a single 90 degree RF pulse, one T1 time period will have passed for CSF, three will have passed for white matter, and many more than five will have passed for the T1 of fat.

It therefore also stands to reason that were I to examine the system very shortly after the 90 degree pulse was applied, all tissues would have vertically recovered, or relaxed, only slightly. Furthermore, were I to wait a very long time after the 90 degree pulse was given, all of the tissues that had been "knocked down" by the RF pulse would have already substantially or even fully recovered back to their initial Mo state,

with all of the net magnetization vectors for each tissue pointing fully back along the Z axis.

It is easy to see, therefore, that if I were to somehow measure the magnitude of the net magnetization vector in the Z axis at different times after applying a 90 degree pulse, I would get different values for the various tissues based on inherent differences in their vertical magnetization recovery rates - i.e., inherent T1 differences. However, if the measurement of how much vertical magnetization has already recovered is performed too early, there is little to no opportunity for the tissues to properly differentiate from one another. Similarly, if the measurement of how much vertical magnetization has already recovered is performed too late following the 90 degree RF pulse, even though they may have markedly differing T1 values, all the tissues may have essentially fully recovered back to their baseline (vertical) values, without our having any way of knowing which got there first (i.e., without any T1 information in the signal, or "image").

This is somewhat analogous to attempting to measure the cooling rate of boiling water in an open cup versus that of boiling water in an insulated container. If I pour the boiling water into both containers and then proceed to immediately measure their temperatures, both will measure 100 degrees Celsius, since neither will have had any significant opportunity to undergo cooling. Similarly, if I wait a week before performing my measurements, the water in both containers will be at room

temperature. No apparent contrast would be demonstrated despite very significant differences in their intrinsic respective cooling rates. Ideally, if I am trying to contrast the temperatures measured for the two liquids based on the cooling rates of their containers, the time that I should choose for temperature measurement should be when the greatest relative temperature difference has been achieved. From similar reasoning, I should therefore also attempt to measure this (T1-based) difference in the vertical NMV's magnitude from each tissue at a time following the RF pulse when there is the greatest difference in vertical magnetization recovered between the tissues being examined in order to maximize their difference, or contrast.

Repetition Time (TR):

You'll recall that we cannot directly measure the length of the tissue's net magnetization vectors while they are oriented along the vertical Z axis. However, we can and do succeed in measuring the net magnetization vector magnitude along the Y axis or X-Y plane. Thus, in order to measure how much of the vertical component of the NMV has recovered at any given time following a 90 degree RF pulse, we have to first do a little trick. This trick is to flip the net magnetization vector(s) at the instant that we wish to measure their lengths, back again into the horizontal, Y axis with yet another 90 degree RF pulse. Since a 90 degree RF pulse tips all vertical tissue magnetization into the horizontal (Y) axis without changing its strength (i.e., vector length), applying a second 90 degree RF pulse at a given time following the first will enable us to measure what we have already vertically recovered by that point in time when we chose to

apply this second 90 degree RF pulse. The time interval between successive 90 degree RF pulses is referred to as the Repetition Time, or TR. It can be thought of as the amount of Time that we allow for Recovery of the vertical magnetization of the tissues being studied.

Partial Saturation:

It is important to emphasize several points regarding TR at this juncture. Firstly, please note that it is an operator controllable parameter. The user (technologist/radiologist) may select whatever point in time TR that they desire (within the limitations of the MR scanner itself) to re-excite, or bring the vertical magnetization back down again to the horizontal axis to be measured. Secondly, for reasons that we will not delve into in this lecture, we actually repeat this recovering-exciting-recovering-exciting process hundreds of times in order to generate a single MR image. You can thus think of each RF pulse in this train as serving two functions: 1) To bring the vertical magnetization that has recovered to that point down to the horizontal axis so that it can be measured, and 2) To itself serve as the preparatory RF pulse or he subsequent RF pulse that will follow one TR later.

If we choose and maintain a constant TR such that every TR we again apply that same 90 degree RF pulse, the effect is that a steady state equilibrium, or "balance", is built up. In other words, at each time TR after the preceding 90 degree RF pulse there will be the exact same amount of vertical magnetization recovered and available to be

brought back down to the horizontal axis by the next 90 degree RF pulse to be measured. For example: If the T1 of a tissue is 1,000 milliseconds and we select a TR value of 1,000 milliseconds, the MR imaging system will provide another 90 degree RF pulse every 1,000 milliseconds. Since this is the same as the T1 of the tissue being studied, it therefore stands to reason (as noted in the preceding T1 discussion) that immediately prior to each and every RF pulse that will be applied, the tissue's vertical magnetization will have recovered to a point where 63% of its initial Mo vertical value (that it had had before being exposed to its first pulse) will be pointing once again back along the vertical, Z axis. The effect of the subsequent 90 degree RF pulse is then to effectively flip the recovered vertical component of the tissue's net magnetization vector back to the Y axis, thus enabling our system to measure it and simultaneously forcing the tissue to once again start over its vertical magnetization recovery process.

Magnetization that is rapidly re-pulsed (i.e., very short TR values) such that it hardly gets to vertically recover before it is again "hit" with each subsequent RF pulse is referred to as saturated. Conversely, magnetization that has either fully recovered after a previous RF pulse or has never been "hit" by an RF pulse before is referred to as unsaturated. Thus, such a pulse sequence consisting of a train of consecutive 90 degree RF pulses separated by a time period called TR is called a **partial saturation** pulse sequence, as each pulse, followed by a fixed time TR, allows for recovery of some, but not necessarily all, of its initial vertical magnetization magnitude.

The strength of the signal thus obtained (i.e., after each 90 degree RF pulse) is dependent upon how much of the original net magnetization vector has managed to recover back to the Z axis during time TR. This, in turn, is dependent upon how much time (TR) we have allowed to elapse between successive 90 degree pulses as well as the T1 relaxation rate of the tissue being imaged. It is also dependent upon the proton density of the tissue(s), since this represents the number of protons per unit volume of each of the imaged tissues that are being excited and are recovering in this fashion.

T2 Relaxation:

While all the above is going on another phenomenon is simultaneously occurring. When we flipped the net magnetization vector of the tissue(s) from the Z to the Y axis with a 90 degree RF pulse, at the instant of completion of this RF pulse there is a coherent tissue magnetization oriented along the Y axis. In other words, immediately following a 90 degree RF pulse, the magnetic moments of the individual nuclei composing the tissue's net magnetization vector are no longer in a random orientation in their precessional orbits but rather are in phase together. This results in a detectable net magnetization vector oriented along the Y axis. This yields a strong intensity signal for the receiver coils as in the analogy of the flashing police beacon discussed previously.

Let's say that at this moment, following the 90 degree RF pulse, we turn off the RF pulse and simply sit back to observe what would happen. As we know, the initial

horizontal tissue magnetization (a.k.a., signal) is high since the tissue's NMV is fully horizontally oriented immediately following the completion of the pulse. With time, we know that the tissue's NMV will return to its full vertical orientation. Thus, the initial higher signal amplitude from each tissue will decrease over time until there is no horizontal tissue magnetization component (i.e., signal) detectable anymore. The rate at which the signal from various tissues decays to zero is determined by the T2 value of that tissue. In fact,

The time after the 90 degree RF pulse that must pass before the tissue loses 63% of its initial horizontal magnetization (i.e., signal intensity) is referred to as the T2 value of the tissue.

Note once again that T2 is a unit of time. As this relaxation occurs by a coupling of spins between protons, another name for T2 decay is spin-spin relaxation. Furthermore, since we are dealing with a loss of the net magnetization vector in the X-Y, or transverse, plane, another name for T2 relaxation is also transverse relaxation.

It is important to realize that different tissues (both normal and abnormal) may likely have different T2 values. In other words, tissues may well vary in their rates and efficiencies with which they lose their horizontal magnetization phase coherence, or signal. We can thus use this T2 difference between tissues as one more factor on which we can capitalize in order to yield different signal intensities between various tissues

and thus produce image tissue contrast. Thus, the shorter the T2 value for any tissue, the more rapidly it loses signal (a.k.a. transverse magnetization), and vice versa.

For example, suppose a tissue has a T2 of 100 ms. Thus, after 100 ms (one T2 length of time for that tissue) has elapsed following the initial 90 degree pulse, only 37% of the initial net magnetization vector brought down to the horizontal plane is still pointing along the Y axis. In fact, after 200 ms (a time period equal in length to two T2 time periods for this theoretical tissue), the amount of the net magnetization vector that is still pointing along the Y axis is 37% of 37%, or 14%. Similarly, after three such T2 time periods, <5%, after 4, <2%, and after 5, <1%. We can approximate that after five T2 time periods for any tissue (500 ms in our theoretical tissue example here with a theoretical tissue T2 value of 100 ms) we will have essentially lost all of our signal, as that is how long it would take for all of the magnetization brought down to the horizontal axis (by the 90 degree RF pulse) to decay to essentially zero.

It is also true that there is another operator controllable parameter that determines the intensity of the measured signal from each tissue. The operator can select when to examine and measure just how much horizontally oriented magnetization is indeed present at that time for each tissue following an RF excitation pulse. This parameter is known as the TE of the study, which stands for the selected Time to Echo. It might help to think of the operator selectable TE as the chosen Time to Examine how much signal (coherent horizontal magnetization) is still present for each

tissue. This permits the user to take advantage of differing horizontal magnetization decay rates (i.e., T2 values) in order to attempt to measure the horizontal NMV components from each tissue when they are most different. Thus one might intentionally allow for a more extended amount of time TE before measuring the amount of signal (i.e., horizontal magnetization) that remains for two given tissues that significantly differ in their T2 values. This would permit more signal decay from the tissue whose signal decays rapidly (shorter T2) from that of the tissue whose signal decays relatively slowly (longer T2).

Thus, it is the total effects of each of these five parameters, TR, TE, T1, T2, and proton density, that will determine the ultimate signal intensities of the tissue(s) being examined.

General Discussion:

T1 values for typical tissues in the body are generally (as a ballpark figure) approximately 5 to 10 times the magnitude of T2 values for the same tissues. Thus a tissue may well have T1 and T2 values of 1000 and 100 ms, respectively.

Please note that while T1 denotes time relative to realignment of the net magnetization vector back to the Z axis, T2 deals with a dephasing in the X-Y plane resulting in a net loss of signal. For example, the longer the TR the greater the degree of vertical magnetization recovery that we will permit for the net magnetization vector of

each tissue. This will yield a stronger resultant signal per tissue from the subsequent 90 degree pulse, as more will have recovered to be available to bring down to the horizontal, signal-detectable axis with the subsequent pulse. Conversely, for a fixed TR, those tissues that have a shorter T1 will give a stronger signal, as they will have had more protons will have relaxed towards the Z axis by the time the next 90 degree pulse comes along to flip all vertical magnetization into the detectable, horizontal plane.

For T2, however, for any given selected time TR, the tissues with shorter T2 values will give less intense signals than do those having longer T2 values. This holds true since the signal (coherent horizontal magnetization) from those tissues with shorter T2 values, by definition, decays more rapidly than that from tissues with longer T2 values.

Finally, two tissues with identical T1 and T2 values may still yield different signal intensities if they differ in relative proton spin densities. In other words, the greater the net magnetization vector of a tissue, the greater the received signal. The relative proton density is one of the factors that increases the net magnetization vector of a tissue.

For partial saturation examinations, the longer the TR the greater the degree of recovery of each tissue and, therefore, the greater the resultant signal intensity from each tissue. However, with very long TR values, the difference (i.e., tissue contrast)

between the signals obtained from each of the tissues may be less as compared to that obtained with shorter TR's. This was seen with the boiling cups of water analogy noted above, where if I measure the temperature of the water in these two containers (a Styrofoam cup and a glass cup) a few minutes after pouring the boiling water into these cups, I should be able to contrast these two cups' cooling rates nicely. However, if I wait several hours before measuring the temperature of the water in these two cups, they may both measure near room temperature. I will have thus lost my ability to contrast these two cups' cooling rates by waiting too long to measure the temperature of the water in these cups. Similarly, if I wish to contrast the two tissues by virtue of differing T1 vertical magnetization recovery rates, I need to select a TR value that is appropriate to catching the magnetization of the tissues being examined as being substantially different. Such a relatively short TR (and TE) study would generate an image that would highlight T1 differences between tissues, and would be referred to as T1 weighted. If I wait too long, however (by selecting a very long TR), I will have lost my ability to differentiate signal from the imaged tissues by which would have recovered its vertical magnetization more/faster by that TR (since by then both tissues would have nearly completely recovered their vertical magnetization components). Thus, long TR studies thus effectively decrease the T1 weighting of the study.

Similarly, by decreasing the TE to near zero values, we are not providing enough time for the magnetization brought down to the horizontal plane by the 90 degree RF pulses to differentiate themselves from each other in their horizontal decays. Thus,

there is little T2 weighting with short TE studies. If more T2 weighting (i.e., differentiation between the tissues based on their rates of horizontal magnetization decay) is desired in the resultant image, we would select a longer TE for our study. This would permit more time for the tissues to decay significantly along the horizontal plane at rates that depend on the tissues' T2 values. Thus, prolonging the TE increases the T2 weighting of the study, while decreasing (drastically) the selected TE decreases the amount of T2 weighting of the study.

Combining what was stated above, to create an image with T1 weighting and little T2 weighting, we could design a partial saturation pulse sequence with a relatively short TR (to provide for the T1 weighting) and a relatively short TE (to do away with potential T2 weighting). Conversely, to create an image with T2 weighting and little T1 weighting, we could design a partial saturation pulse sequence with a relatively long TR (to provide for little T1 weighting) and a relatively long TE (to provide for T2 weighting). Finally, image contrast that might be present in studies created with long TR values (little T1 information) and short TE values (little T2 weighting) are therefore predominantly proton density weighted, where the tissues with the greatest relative proton density have the greatest signal.

Summary:

It is thus demonstrable that it is the combination of the tissue T1, T2, and relative proton density parameter values, in combination with the user selected TR and TE parameter values, that will determined the ultimate appearance and intensities of the tissues in the image. By appropriately choosing the operator selectable imaging parameters, we can optimally define when to best differentiate the signals from the imaged tissues based on their intrinsic magnetization behavioral characteristics, T1, T2, and relative proton density.

We have not yet begun to touch upon other crucial parameters that need to be selected for every MR image produced, including, among others, sequence type (e.g., inversion recovery pulse sequences and its TI parameter, gradient echo imaging (spoiled or non-spoiled) and the accompanying excitation flip angle imaging parameter, chemical specific fat saturation, fast imaging techniques, MR angiographic imaging techniques, etc.), contrast agent type, dosing, and timing administration, field of view, slice thickness, number of excitations, number of phase and frequency encoding steps, number of slices, receiver bandwidth, receiver coil type, etc. Some of these will be covered later in this course. As you are hopefully starting to appreciate, however, the more we know about the magnetic properties and behavior of the tissues being imaged, the more we will be able to "take control" of them and make them visually contrast with each other on images obtained in efficiently performed MR imaging examinations.

Modified Flip Angle Gradient Echo Magnetic Resonance Imaging

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We are by now at least somewhat used to the concepts of T1 governed longitudinal magnetization recovery and T2 (or T2*) determined transverse magnetization (a.k.a. signal) decay. For partial saturation studies the longer the TR the more the longitudinal magnetization is permitted to recover prior to the subsequent RF pulse. Similarly, the longer the TE the more we permit the transverse magnetization to decay prior to its detection. Each of these processes begins to grow or decay in one direction (longitudinal recovery or transverse decay) and continues unidirectionally in that direction. It is, unfortunately, not the same for flip angle. As we vary flip angle (keeping TR and TE constant) we find that the signal intensity for each tissue also varies, although it is now no longer unidirectional in nature. In other words, it is incorrect to assume that the signal intensity for any given tissue would increase (or decrease) if the primary excitation flip angle increases. The signal could, in fact, increase, decrease, or even remain the same, depending on the tissue being imaged and the specific flip angles from and to which we are changing. (The reason(s) behind this observation will be clarified in greater detail later in this text.) In fact, for all tissues, signal intensity will increase, peak, and then decrease as the excitation flip angle is increased from 0 degrees through to 180 degrees. The flip angle at which maximal signal intensity is obtained from any tissue in partial saturation MR imaging is defined as the Ernst angle, which is determined by the target tissue's T1 value and the selected TR with which we choose to examine it. It also therefore stands to reason that since different tissues may have unique T1 values, the Ernst angle for different target tissues may be quite different from each other. In addition, as T1 values are modified by, for

example, the administration of contrast agents to the patient, the corresponding Ernst angles for those tissues affected by the contrast agent would also be altered relative to the new T1 value of those tissues. Finally, as tissue T1 values are also field strength (Bo) dependent, Ernst angle for a given TR varies for any tissue with different static field strength MR imaging systems.

Since Ernst angles differ for varying tissue T1 values (and field strengths and TR values), one can now understand how it might therefore be possible to select the flip angle to one that best matches the Ernst angle of one of the tissues of interest. This could yield an absolute increase in the signal intensity from that target tissue while simultaneously potentiating a decrease in signal from adjacent, background tissues against which this target tissue might be contrasted. Such a technique would allow for an increased contrast-to-noise ratio (CNR), and therefore detectability, of such pathologic entities with no change in scan time. Indeed, with appropriate simultaneous modifications of multiple operator parameters such as flip angle, TR, TE, and NEX, it might be entirely possible to decrease scan time while maintaining diagnostically successful CNR for the tissues of interest.

There are several intrinsic differences between gradient and spin echo techniques. For example, the excitation flip angle is assumed to be 90 degrees in spin echo imaging, whereas it is user selectable (and quite often not 90 degrees) in gradient echo imaging. This provides a powerful contrast-controlling parameter, flip angle, that

is only clinically generally accessible in gradient echo, and not spin echo, imaging techniques. We will return to how this can be used to our advantage in controlling the tissue contrast in an image shortly.

Further, gradient echo imaging does not utilize a 180 degree pulse as its echo inducing stimulus. Thus, the power deposition into the patient (a major factor in determining patient heating secondary to MR imaging) is considerably decreased. This is especially so considering the fact that power deposition is proportional to the square of the flip angle transmitted into the patient. Thus, a 180 degree pulse deposits four times the power into the patient as does a 90 degree RF excitation pulse.

The absence of the 180 degree pulse in gradient echo imaging also results in the transverse magnetization, or signal, in such sequences decaying at a rate determined by the T2*, and not T2, of the tissues being studied. This results in gradient echo imaging being intrinsically more, or much more, sensitive to static magnetic field heterogeneity (susceptibility) induced signal loss than is spin echo imaging with otherwise comparable TE values.

Perhaps a more subtle difference between these two techniques is that gradient echo techniques are more sensitive to signal from more rapidly flowing structures, as the "echo-inducing stimulus" (i.e., the gradient reversal) is not slice specific, and thus can induce an echo in the excited flowing blood (for example) even after it has left the

plane of excitation. In spin echo imaging, on the other hand, the echo inducing stimulus is a 180 degree pulse that is transmitted in such a manner as to make it resonant to only that same slice. Thus, if the blood that had been excited (and nutated to the transverse plane) by the 90 degree pulse had managed to flow out of the imaged slice by the time the 180 degree pulse was transmitted (i.e., by time TE/2), the blood with coherent transverse magnetization would not be resonant with the echo inducing 180 degree pulse and would therefore decay by T2* time frames (and not T2). Thus, by the time TE came along ,the signal from this flowing blood would be markedly attenuated, if present at all, leaving a flow void in such rapidly moving blood. This helps to explain one reason why blood within the descending abdominal aorta may be quite intense on certain gradient echo sequences but is often quite dark or black when examined with spin echo imaging techniques.

Contrast manipulation via modification of the excitation flip angle parameter:

Most neuroradiologic pathological conditions manifest increased T1, T2, and proton density values as compared to their normal tissue of origin counterparts. It is therefore often the case that the so-called "T2-weighted" imaging sequence is the one wherein much of the diagnostic information being sought is identified. There is often also a considerable amount of contrast available based on differences in the proton density and T1 values of the tissues being examined. Varying the primary excitation flip angle, in addition to the TR and TE, allows us to selectively emphasize or de-emphasize the proton density, T1, and T2 differences between the target tissues of

interest, and is yet one more powerful parameter that can be used in the diagnostic armamentarium of the clinical MR radiologist. How this works requires some introduction and explanation, which follows:

Until now we have been dealing with partial saturation spin echo studies, where 90 degree excitation pulses are essentially always clinically utilized. In order to emphasize T1 differences between tissues, we would shorten the TR of the study. This would catch the tissues at a time where the one(s) with fast longitudinal magnetization recovery rates (i.e., short T1 tissues) would have longitudinally recovered to a significantly greater degree than would the more slowly longitudinally recovering tissues (i.e., the ones with longer T1 values). We then bring down these partially recovered magnetization vectors from these tissues to the transverse, detectable plane and sample them quickly (short TE), before there can be much of an opportunity for there to be much transverse magnetization decay from any of these tissues. The short TE would de-emphasize T2 differences between the tissues (decrease T2 weighting) while the short TR would increase T1 weighting.

To erase T1 differential information from the image we would increase the TR of the study. Thus, even with large, disparate T1 values for the tissues, the long TR of the imaging sequence permits even the slower longitudinally recovering tissue to recover a substantial amount of its longitudinal magnetization prior to the subsequent RF pulse. Thus, differences in the rates at which these tissues recovered longitudinal

magnetization (T1 differences) would no longer be apparent, as both would have been permitted, by the long TR, to substantially recover longitudinally without our being able to detect who got there first/faster. Having thus erased T1 information from the image by selecting a long TR study, we can then emphasize T2 information by allowing the tissues whose magnetization has just been brought down to the transverse plane by the subsequent RF pulse to transversely decay for awhile. If after a long TE value there is a substantial amount of signal from tissue B and little from A, we can then correctly conclude that the signal from B transversely decays more slowly than does that of A; i.e., tissue B has a longer T2 than does tissue A. If instead we wish to de-emphasize T2 information, we would drop the TE to minimal values, thus catching the transverse magnetization from these tissues before they can run a transversely decaying race. Having thereby erased T2 information by dropping the TE to very small values and having erased T1 weighting by increasing the TR to very long numbers, any tissue contrast detected in the image at that point would be secondary to difference in proton densities between the tissues being imaged.

In gradient echo imaging, however, we now have the ability to modify the RF excitation flip angle. To explain why 90 degrees is not always the flip angle that will yield the greatest signal (transverse magnetization) from every tissue, let us examine the effects of the RF pulse more closely.

Each RF pulse applied can be thought of as serving two simultaneous, yet opposing, purposes. Firstly, it brings tissue magnetization down from the longitudinal axis into the detectable, transverse plane, since in MR imaging the only magnetization that can be detected is that which is transverse (i.e., perpendicular to the Bo, static magnetic field of the imaging system). Thus, increasing the flip angle from 0 to 90 degrees results in a greater the amount of magnetization being brought down to the detectable, transverse plane. You will recall, however, that partial saturation MR imaging is accomplished not with a single RF pulse, but rather with a train of RF pulses separated by time TR. Each pulse therefore also serves to simultaneously remove magnetization from the longitudinal axis, from which it will need to recover prior to the application of the subsequent RF pulse at time TR. To illustrate the importance of these two opposing outcomes, let's consider the case of imaging two tissues, one with a short T1 (Tissue A) and the other with a long T1 (Tissue B).

Tissue A with its short T1 recovers longitudinal magnetization more rapidly than does Tissue B (by definition). Thus, at a given TR following the prior RF pulse, Tissue A will be closer to recovering full longitudinal magnetization prior to the application of each subsequent RF pulse than will be Tissue B. By the time the next RF pulse is transmitted at time TR, there will therefore be more longitudinal magnetization available for Tissue A than for Tissue B to bring down to the detectable transverse plane (and from which it will decay prior to its detection at time TE). One would therefore detect more signal (i.e., transverse magnetization) when performing large flip angle

studies from such short T1 tissues as Tissue A than from those with longer T1 values as is the case with B. The reason for this in retrospect is the fact that tissue A managed to more successfully overcome the handicap of having the RF pulse bring some/all of its magnetization out of the longitudinal axis, since it will recover it more rapidly than will Tissue B. Indeed, we can already make the generalization that the signal from short T1 tissues is not hurt as badly as it is for long T1 tissues, where substantial fractions of their longitudinal magnetization will not have recovered by the time each subsequent RF pulse is applied.

If, on the other hand, we substantially lower the RF excitation flip angle, we accomplish two things: 1) the amount of magnetization brought down to the detectable, transverse plane is decreased, but simultaneously, 2) the amount of magnetization brought out of the longitudinal axis is markedly decreased as well. We will not have "spent" so much of our (longitudinal) magnetization with each RF pulse if we choose a very low RF flip angle. Therefore, there will be much more still left in the longitudinal axis from which it will begin its longitudinal recovery immediately after each RF pulse is turned off. Therefore, the long T1 of Tissue B will not be nearly as much of a handicap now as it was if large flip angles would have been selected.

In fact, one can generalize the above as follows: The shorter the T1 of the tissue(s) being examined, or the longer the TR of the study being performed, the more one can afford to request large flip angles, since more magnetization will have longitudinally

recovered by the time each subsequent RF pulse is applied. But conversely, the longer the T1 of the tissue(s) being examined, or the shorter the TR of the study being performed, the less one can afford to request large flip angles, since less magnetization will have longitudinally recovered by the time each subsequent RF pulse is applied. Thus, the signal from long T1 tissues is selectively boosted if low flip angle studies are requested, while the signal from short T1 tissues is selectively boosted if large flip angle studies are requested.

Applying the above, it holds true that with a very low flip angle, there is little in the way of longitudinal magnetization that is pulled from the longitudinal axis with each RF pulse from which the tissue longitudinal magnetization will need to recover by the subsequent RF pulse in our pulse train. Thus, differences in the rate of longitudinal magnetization recovery (i.e., T1 differences) between tissues plays less of a role in determining signal intensity from these tissues if we do not provide much of a longitudinal magnetization "race" for these tissues to run in the first place. This is the case when very small RF flip angle studies are performed. We can therefore decrease the amount of "T1 weighting" in our image by drastically decreasing the RF excitation flip angle so as not to create significant differences between tissue longitudinal magnetization in the first place. If such a small flip angle study was performed, there would thus be little "T1 information" in the resultant images. As there is not much left to longitudinally recover after each RF pulse, it would not therefore make much difference for how long the tissues would be permitted to longitudinally recover before

applying each subsequent RF pulse. Thus, the selected TR value would play less and less of a significance role in determining tissue contrast/intensities as low and even lower RF excitation flip angles were requested. After all, why should I care how long I waited for longitudinal magnetization to recover after each pulse if I did not remove much of it from the longitudinal axis by each pulse in the first place? Thus, with very low flip angle gradient echo studies effectively erasing T1 contrast from the image, the selected TR can be considerably decreased while still preserving predominantly T2* and/or proton density weighted image contrast. In other words, we do not need to erase T1 contrast information anymore by increasing the TR values to several thousand milliseconds; we can now request, for example, a 15 degree flip angle gradient echo study with a TR of 400 or 500 ms and still successfully erase T1 information, leaving us with T2* and/or proton density weighting such as might be seen in the myelographic, bright CSF images. This is historically what provided the sudden popularity for gradient echo imaging techniques, as they permitted "myelographic-like", T2* weighting to be accomplished with much shorter TR values (and thus scan times) than had been accomplished using the typical long TR and long TE spin echo imaging that had been done prior to that point.

With larger RF flip angles requested, there is more magnetization that is being nutated out of the longitudinal axis with each pulse. There is thus more of a longitudinal "race" for the tissues being imaged to run before the next RF pulse comes along. Utilizing appropriately short TR values with these large RF flip angle studies

provides for more opportunity to observe significant differences in recovered longitudinal tissue magnetization by the time the next pulse comes along, due to T1 differences between the tissues being studied. Thus, very small flip angle studies de-emphasizes T1 contrast information (and permits shorter scan times via shorter TR myelographic-like studies), while large flip angle studies (with short TR values) potentiate T1 contrast information.

As always, T2* information (i.e., differences in rates of transverse magnetization decay) is emphasized by providing the tissues with an opportunity to run a transverse decaying race - i.e., increased TE values. If minimal TE values are requested, the signal is sampled prior to the tissues having had an opportunity to transversely decay to any significant degree. We will therefore not be able to differentiate tissues based on how quickly they lose their signal (i.e., transverse magnetization). Thus, very short (minimal) TE values decrease T2 (or T2*) weighting, whereas longer TE studies emphasize T2 (and T2*) differences and weighting.

In summary, the RF excitation flip angle is user determined in gradient echo imaging, thus enabling the operator to even more selectively emphasize (or de-emphasize) tissue/image contrast based on proton density, T1, or T2 differences between tissues of interest. Gradient and spin echoes also differ in the power deposition per unit time accompanying each, with far less patient heating occurring in gradient echo imaging. The 180 degree pulse of the spin echo technique is slice specific,

whereas the echo inducing stimulus in gradient echo imaging is a gradient reversal, which is not specific to the slice being imaged. The absence of the 180 degree pulse makes gradient echo imaging intrinsically sensitive to T1 and/or proton density and/or T2* differences between tissues, while spin echo imaging can be made sensitive to T1 and/or proton density and/or T2 tissue differences. Thus, gradient echo images will much more sensitively display foci of static magnetic field distortions as foci of decreased signal, or signal voids. Either of these imaging techniques can be clinically applied where appropriate to better answer diagnostic questions at hand.

Fast (Turbo) Spin Echo and Echo Planar Imaging Techniques

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Fast (Turbo) spin echo and echo planar imaging techniques:

Spin echo imaging sequences are performed with a specified TR and TE. The experiment is repeated N_p number of times (where N_p refers to the number of phase encoding steps examined), each time separated by time TR, each performed with a unique strength to the phase encoding gradient used. Each echo is digitized and stored in its corresponding position within k-space. As always, the convention of k-space is such that the echoes acquired with steep positive values to the phase encoding gradient amplitudes are placed in the uppermost, top rows of k-space, those with weakest phase encoding gradient amplitudes are placed in the middle rows of k-space, and those with the steep negative values to the phase encoding gradient amplitudes are placed in the lowermost, bottom rows of k-space. Every TR another unique step of the phase encoding gradient is used, and the echo so acquired is written to its corresponding position within k-space. When k-space will have been entirely filled in this manner, each row will correspond to the digitized version of each echo acquired at time TE. All echoes would have originated at the same TE values following their respective 90 degree excitation pulses but differ in that they are acquired following different, unique strengths to the phase encoding gradient, and each echo will have been acquired one TR following the prior one and prior to the next. Thus, with each pass through TR one line/row of k-space is filled. As a result of this relationship, to fully acquire an image's k-space data would require TR x N_p seconds.

In multiecho spin echo MR imaging, multiple 180 degree pulses are transmitted within each TR time period resonant with the excited slice to produce a train of echoes at various TE values for the tissues within the imaged slice. Thus, for each slice of the multislice sequence requested, multiple echoes are sampled at several TE times within each TR time period. The digitized echo from each TE is placed as a new line in the k-space that corresponds to that particular TE studied. Notice that we still only perform one step to the phase encoding gradient per TR time period, with each spin echoes at their corresponding TE times sampled following the same phase encoding gradient step. Therefore, using a TR of 2500 ms, if the strongest positive phase encoding step is used, for example, the echo acquired at TE of 20 ms following the 90 degree pulse will be recorded as line #1 in its corresponding k-space. Similarly, the next echo acquired at TE of 80 ms, for example, would also be recorded as line #1 for its k-space. Upon completion of N_p number of unique phase encoding steps, each acquired one TR following the prior one, we will have successfully filled out the k-space for TE of 20 ms as well as that of TE of 80 ms. Each of these will then be placed through a two dimensional Fourier transform to yield two separate images, one representing the signal intensity from that same slice at TR of 2500 ms and a TE of 20 ms, the other representing the signal intensity from that same slice at TR of 2500 ms and a TE of 80 ms.

In a fast, or turbo, spin echo (FSE) pulse sequence there are two basic changes from standard multiecho spin echo MR imaging. Multiple echoes are still sampled (at various TE values), but this time a new phase encoding step is performed prior to the

acquisition of each echo obtained within each TR in such FSE techniques. Furthermore, each of these echoes, acquired at various TE times, is then added as a new line within the same k-space (i.e., each will be placed within the same matrix of values upon which the Fourier transform will be performed from which to create a single image). As always, the amplitude of the phase encoding step used determines the position in k-space in which the digitized echo is recorded. Thus, with each pass through TR, we fill a number of lines or rows corresponding to the number of phase encoding steps/echoes obtained for each slice. The image may have been acquired with a specific TR value, but its data originated at various TE values. The reconstructed image is referred to as if it had been acquired with a single TE (e.g., TE of 20 ms, or TE of 100 ms), but in actuality numerous TE times were sampled and used in the reconstruction of this image. At least one MR manufacturer refers to this parameter as effective TE (TE_{ef}) to help highlight the fact that the tissue intensity information displayed in the image does not actually originate from this TE time alone.

The immediate benefit of the FSE technique is that of decreasing total scan acquisition time. For such two-dimensional Fourier Transform Fast Spin Echo technique sequences, the total scan acquisition time would therefore be given by:

$$\text{Scan Time}_{FSE} = \frac{TR \times NEX \times N_p}{\#\ \text{echoes per image per T}}$$

For example, if, instead of obtaining one echo per slice per TR, 16 echoes are acquired in that TR time period on that same slice, all preceded by a unique step to the phase encoding gradient and all are placed within the same k-space from which that single image will be calculated, the examination would require only 1/16th the total scan time to perform. Such a study will have been said to have been performed with an echo train length (ETL; a.k.a. turbo factor) of 16, since 16 echoes were acquired (with 16 unique phase encoding step values) within each TR time period per slice. One can thus think of standard spin echo imaging as fast spin echo with an echo train length of 1.

This is intrinsically similar to echo planar imaging where multiple gradient recalled echoes (for example, the entire data set needed to fill k-space and reconstruct a single image) are acquired after one RF pulse (i.e., within one free induction decay time period). Gradient echoes can be performed much more rapidly than can spin echoes, thus increasing the temporal density of echoes acquirable within a fixed time following the primary RF excitation pulse. Furthermore, the power deposition consideration of fast spin echo imaging is not a concern in echo planar imaging, as there are no 180 degree pulses used in echo induction, but rather gradient reversals which do not deposit power. Limitations of echo planar imaging, however, include the fact that as no 180 degree pulses are used there is no correction made for static magnetic field heterogeneities. Thus, by their nature echo planar sequences are T2* sensitive, and are sensitive to dephasing effects of fixed magnetic field distortions. Further, due to the acquisition of all the imaging data following a single RF pulse without the usage of 180

degree pulses, chemical shift artifact between fat and water based signal can be quite pronounced and is manifest far more in the phase encoding direction than in the frequency encoding direction more typical of the more standard spin and gradient echo imaging techniques with which we have been dealing to date.

Among the limitations of fast spin echo imaging techniques is the fact that the images so obtained are no longer necessarily representative of the tissue magnetization as it appears at a single particular combination of TR and TE. While it is still the result of magnetization at a particular TR, the slice was actually sampled at multiple varied TE times, and the resultant signals were all included within the same k-space data set from which the Fourier transform created a single image. Since the signals from each tissue will change as TE changes (since the signal is fading from each tissue via T2 decay mechanisms), there is the potential for confusing or misleading intensities in the image. This can yield varied intensities in the tissues within the image compared to what we might have expected from a more typical spin echo study performed with similar TR and "TE" values. This process of sampling various TE times and therefore signal intensities from each tissue and reconstructing a single image out of these echoes may also yield a broadening of the line spread function, resulting in a degree of blurriness in the resultant images. This is most noticeable at short effective TE values, where the intensities of the signal from the tissues are most rapidly changing. (Remember, the tissues' signal intensities are changing most rapidly initially, immediately following the RF pulse. Echoes acquired at various short TE values following this pulse will see the

greatest difference in their intensities and thus the greatest broadening of the line spread function - i.e., the greatest amount of blurriness in the images.)

This problem can be overcome, or at least partially corrected, by at least three approaches:

Firstly, examine the shape of the signal decay from any tissue at relatively long TE values. Notice how the slope of the signal decay from any tissue is quite steep at first, only to flatten out towards the end (towards the longer TE values). (Sort of like Nixon's nose, or, for the younger amongst you, a ski slope - suicidal at first, but then gentle at the bottom). Thus, fast spin echo sequences/studies performed with **long** TE values tend to sample the slice when the signal intensities for the various tissues are not as significantly changing as they would have been at shorter TE values. There is less blurring and more true reproduction of the anticipated signal intensities of the tissues in the image with such FSE studies where longer effective TE values were requested.

Furthermore, and with similar reasoning, the user can select to obtain a shorter ETL (i.e., fewer echoes per slice per TR time period). This decreases the blurriness in the resultant image due to incorporation of signals over a shorter TE time range into the same image. There is thus less of a change in signal for each tissue over this shorter TE acquisition range. If the number of echoes so acquired within each RF excitation pulse can be diminished (and the rate at which these echoes are acquired can be increased),

this can help ensure that data for any given slice is not acquired over too broad a spread of (especially short) TE values. Further, with shorter requested TE values, the range of TE times actually sampled is smaller and may thus better approximate that which would have been present at the requested TE time.

Thirdly, it can be shown that the predominant determinant of image contrast results from the signals acquired from the echoes performed with the lower amplitude phase encoding gradient strength steps (with spatial resolution information - edge sharpness - predominantly originating from the echoes acquired following the higher absolute amplitude phase encoding gradient strength steps). It is thus possible to help fast spin echo imaging acquire images that appear similar in tissue contrast to that which would be seen at conventional short TE imaging by ensuring that the lower amplitude phase encoding gradient strength steps are all performed prior to the echoes obtained at short TE values.

To illustrate this aspect of the FSE technique further, assume that the operator has requested a FSE study to be performed with a TR of 2500 ms, an effective TE of 20 ms, and an echo train length of 4. The echo acquired at TE of 20 ms will be preceded by the lowest amplitude phase encoding step. In fact, every TR, the echo acquired at a TE of 20 ms would be preceded by another unique phase encoding step of the middle quarter of k-space (since an ETL of 4 had been requested). The subsequent echo acquired, for example, at a TE of 40 ms, would be performed with a unique phase

encoding steps whose amplitude would lie within the next higher or lower 1/8th from zero to the strongest that would eventually be studied in the k-space to be filled. Each of the subsequent acquired echoes at TE of 60 ms would be performed with a unique value to the phase encoding steps which would be within the next higher or lower 1/8th of those that will eventually be traversed throughout k-space. Finally, all echoes acquired at TE time of 80 ms would be preceded with a unique step to the phase encoding gradient that would lie somewhere within the outermost 1/8th of those in this k-space (i.e., strongest positive and negative phase encoding gradient steps). Although these are at TE of 80 ms and not the requested 20 ms, the rationale is that as they are acquired with the steepest amplitudes to the phase encoding gradient, they would contribute the least to he signal intensities of the image but still contain and contribute the necessary spatial resolution data.

In order to ensure that cerebrospinal fluid (CSF) appears relatively dark on the "first echo", or long TR short TE type of image contrast, it is helpful to perform somewhat reduced TR studies to ensure that the long T1 of CSF sufficiently handicaps it to result in its being darker than white or gray matter, with their shorter T1 values.

The long TE times that are being spent on each slice by sampling numerous echoes at various TE times results in fewer slices being acquired in multislice mode than would normally have been accessible to standard spin echo studies. Thus, it is not uncommon to see FSE studies being performed with longer TR values (e.g., 3 to 6

second TR values). This would provide the simultaneous benefits of permitting the user to obtain more slices in multislice mode as well as stronger signal from long T1 tissues such as CSF.

It is also important to note that FSE imaging is intrinsically less sensitive to susceptibility induced signal loss (i.e., signal/transverse magnetization dephasing resulting from static magnetic field heterogeneities). In fact, susceptibility induced signal loss would be less noticeable at a given TE value in fast spin echo imaging than it would have been on a standard spin echo image acquired at the same TR and TE values. A gradient echo study at the same TR and TE values would of course be the most sensitive to signal loss as a result of susceptibility induced dephasing, due to the absence of any 180 degree refocusing pulses. As a result of the above, if one is intentionally searching for the presence of, e.g., parenchymal iron and is doing so by searching for foci of signal void which might accompany regions of iron deposition, the FSE technique would make it more difficult to detect such regions of signal loss. Conversely, where there is a potential imaging problem due to the presence of significant magnetic field susceptibility variations (as might be found around, for example, a metallic clip), usage of the fast spin echo imaging technique might help potentiate obtaining diagnostic information at a closer radius to the clip, or source of this inhomogeneity, than might have otherwise been possible.

One should also be aware that when using such techniques, due predominantly to J-coupling-related phenomena (and possibly with a contribution from stimulated echoes), there is a very intense signal from fat that is persistent at even relatively long values of TE. This fat-based signal can be so intense that fat pre-saturation techniques might be called for in certain circumstances to avoid this potential diagnostic pitfall from occurring.

Diffusion/Perfusion Weighted Imaging

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Diffusion Weighted Imaging:

Tissues vary in the rates in which water molecules diffuse through them. For example, water molecules diffuse rapidly in CSF, but more slowly in while matter (ADC 0.6) or gray matter (1.0). Diffusion within infarcted and acutely ischemic tissue has been demonstrated to be considerably slower than it is through normal gray/white matter. (Uncertain theory, but possibly secondary to greater intracellular water within minutes following infarction and therefore less extracellular fluid/space for diffusion to occur within => relatively restricted diffusion). This decrease in water molecule diffusion recovers and then even overshoots with time if the tissue proceeds to infarction and cell lysis. It therefore follows that if we can find a way to differentiate between areas of relatively low from high diffusion we should be able to detect and differentiate acutely ischemic tissue. DWI is more sensitive and specific for acute ischemia than is FLAIR or other T2 weighted approaches, which tend to become positive a few hours/days subsequently. These areas are often larger in volume than what had been positive initially on DWI techniques. We can create MR imaging sequences that are intrinsically sensitive to such water molecule diffusion that occurs between the excitatory RF pulse and the selected TE. Diffusion encoding gradients are applied and reversed prior to TE; for all "motionless" tissues, this yields no net result of change in the signal in the image. However, for tissues in which diffusion has occurred, diffusion that occurs along the axis of and during the time between turning on and reversing these diffusion encoding gradients produces magnetization dephasing that results in signal loss from that tissue in which the diffusion is occurring, commensurate

with the degree of diffusion that has occurred. (Conceptually this is quite similar to that which occurs during each phase of a phase contrast MR angiographic exam.) One can therefore also make the diffusion weighting sensitive to diffusion along any one, two, or all three axes. Thus, DWI is sensitive to the presence of motion itself, and can be thought of as an ultrasensitive "flow void", with signal losses from motion/diffusion of as small as a few microns in length. The degree of signal loss is sensitive to what is known as the B value of the study, such that the greater the B the greater the degree of diffusion induced signal loss for that tissue.

The imaging sequence is typically a T2 weighted or FLAIR sequence onto which have been added such diffusion encoded gradient manipulations. Therefore, the signals from the tissues on the images will be precisely that which we would have expected to see on a T2 weighted study or FLAIR study, modified by a diffusion-induced signal decrease in the various tissues in that image. The greater the B value of the diffusion weighted MR study that is performed, the greater he diffusion-based signal loss that results in those tissues in which there is diffusion. Therefore, by repeating the study at various B values, one can then generate a pixel-by-pixel map of the apparent diffusion coefficient (ADC) of the tissues in that image. (It is only referred to as an apparent diffusion coefficient and not an actual diffusion coefficient because there are other factors that can contribute to the signal loss displayed by some tissues with increasing B value other than purely the diffusion coefficient, such as gross motion/flow.) Thus an image can be generated where the intensities of the tissues in the

image are directly dependent upon the detected/calculated ADC values of each pixel/tissue in the image, such that the higher the observed ADC the brighter it will be displayed on the ADC map image.

With a relatively low B value, tissues with long T2 values may be relatively intense on these "diffusion weighted" images despite the presence of substantial amounts of diffusion in these tissues. This may be secondary to more heavy T2 weighting for these tissues at these particular imaging parameters and relatively less diffusion weighting. High intensity on so-called "diffusion weighted" images from long T2 yet high diffusion tissues is referred to as "T2 shine-through". This may be especially easily seen with long T2 tissues and relatively low B value studies. Repeating the study with higher B values should help to decrease the signal from these tissues, correctly identifying them as having high relatively diffusion coefficients. Using stronger gradient subsystems are one way that manufacturers are able to increase the B value of the study, since increasing the amplitude of the diffusion encoding gradients is one mechanism available to increase the B value of the study (as is leaving them on for longer time and waiting longer between turning them on and reversing them). Ideally, we would like to do the study at relatively short TE values to help decrease the amount of T2 shine through potential in the study. Rapid, strong gradients are a definite advantage here!

A little in the way of nomenclature is in order here. A tissue in which there is a relatively high amount of water diffusion will appear relatively dark on a strongly diffusion weighted image. On the other hand, on an ADC map image, recall that the greater the amount of diffusion exhibited by a tissue the brighter that tissue will be displayed. Therefore, for example, in the setting of an acute cerebral infarction, one might reasonably expect there to be intense signal from the acutely infarcted tissue on a T2-weighted image on which diffusion weighting with a high B value was performed - i.e., on a heavily diffusion weighted image. This results from the relatively restricted diffusion in the region of the acute infarction compared to the normal adjacent brain parenchyma. With constrained water diffusion, there is less signal loss from the acutely infarcted brain than there is from the normal adjacent brain in which diffusion based signal loss is readily observed. On an ADC map of that same brain, however, since it would map out the observed ADC values of the various tissues in that image, the lower observed ADC values of the acute infarction would result in decreased displayed signal intensity for that region of the brain relative to the more normal adjacent parenchyma.

To make matters more confusing (or more consistent, depending upon how you look at it!), we will shortly be hearing about exponential ADC maps, or eADC mapping. On such images we will once again be seeing acute infarctions appearing as regions of greater signal intensity relative to the adjacent normal brain parenchyma.

As with phase contrast MR angiography, diffusion weighting can be performed along one, two, or all three axes. In fact, diffusion weighted MRI is quite similar to phase contrast MRA without the final echo subtraction step used to generate the angiographic images.

To decrease susceptibility sensitivity, such DWI sequences are typically spin echo sequences that, to increase the efficiency of scanning, are detected via the utilization of echo planar imaging techniques. Thus, there is still quite definitely some T2* sensitivity, although of course not as much as there could have been had a pure gradient echo/EPI technique been used. To decrease this field distortion sensitivity it is most useful to be able to acquire the image data VERY rapidly and shorten the total TE times during which data acquisition is being performed. Thus once again, very strong rapid gradients are a most definite advantage to clinically practical diffusion weighted imaging.

There are other, non-ischemic etiologies that have been demonstrated to also exhibit increased signal intensity on diffusion weighted imaging sequences. These include abscesses, certain multiple sclerosis plaques, certain neoplastic tissues including especially epidermoid tumors as well as occasional meningiomas, etc., methemoglobin containing hemorrhages, proteinaceous foci such as mucous as in retention cysts, etc. However, the vast majority of these do not present a differential diagnostic difficulty for

ischemia due to their characteristic locations and/or their morphologies and or their clinical presenting histories.

Perfusion Weighted Imaging:

This is the term used to describe any MR imaging sequence that differentiates signal intensities based on relative degrees of tissue perfusion. There are numerous such perfusion weighted MR imaging sequences available, although the most common by far utilizes the rapid bolus administration of a T2* shortening MR contrast agent, such as any of the gadolinium-based MR agents that have been FDA approved for several years for neuroradiologic application. Using sequences designed to be sensitive to static magnetic field distortions/heterogeneities, one can visualize such regions as foci of signal loss with such imaging approaches as long TE gradient echo or echo planar imaging sequences. Thus, while the contrast agent is passing through the anatomy of interest, tissue that is being perfused would experience field distortion secondary to the presence of high concentrations of intravascular paramagnetic contrast material compared to the extravascular space. This would produce signal loss but only from perfused tissues. With this approach, it is possible to perform rapid repeated imaging of the same anatomy/slices and observe the changing signal intensities that would be experienced over time as the bolus of contrast material courses through the perfused tissue. Non-perfused tissue, on the other hand, would not experience this change, or would experience it over a longer time and/or with a relatively blunted response if the feeding vessel were, for example, stenotic. By continually re-imaging the

same slice(s), one can arrive at relative blood flow, relative blood volume, and mean transit time data, among other tissue characteristics that would permit an at least qualitative assessment of tissue perfusion characteristics.

It is possible and perhaps not infrequent to observe regions of perfusion relative defect which are larger than regions of abnormal signal on diffusion weighted imaging of the same anatomy. This presents an interesting picture of what may be tissue at risk for ischemic progression. This is supported by the observation that the region that is abnormal acutely on diffusion weighted imaging sequences is often smaller than that which ultimately becomes apparent as abnormal on standard MR imaging sequences such as FLAIR or T2 weighting. Thus, there might be a "penumbra at risk" at the time of the initial ischemic event which, if identified and appropriately treated sufficiently early in the evaluative process, might be potentially salvageable tissue.

It is research such as this that has made diffusion weighted imaging and perfusion weighted imaging one of the hottest topics in the MR imaging arena today.

An Introduction To Fat Saturation, Water Saturation, and Magnetization Transfer Contrast

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Background/Introduction:

Due to differences in molecular composition and structure, the electron cloud distribution surrounding various molecular configurations will differ slightly one from another. As electrons are electrically charged particles moving at rapid velocities, there are induced molecular-sized magnetic fields associated with these various molecules that tend to be distributed around these molecules in a relatively fixed, predictable, and quite unique manner. The result is that even when expose to the same external Bo magnetic field, there are slightly different magnetic fields experienced by hydrogen nuclei in, for example, water from those of hydrogen nuclei in fat molecules, which are themselves in turn different from those in other molecular structures and environments. Therefore, due to the relationship described by the Larmor equation (precessional frequency = W_0 = magnetogyric ratio x Bo), hydrogen nuclei ("protons") in water molecules have a slightly different resonant frequency from those of protons in other molecules with their peculiar and unique electron cloud and molecular-sized magnetic field distributions. (It is in fact this magnetic fingerprint, so to speak, of hydrogen based nuclei relative to its particular molecular and atomic neighbors that is the basis for hydrogen magnetic resonance spectroscopy, which detects these fine perturbations of resonant frequencies of hydrogen as it is exposed to these varying magnetic fields in the molecules of the substance(s) being studied.)

The human body has a substantial population of hydrogen nuclei that are based in fat and others based in water molecules. All the other innumerable molecular environments, or "neighborhoods", in which hydrogen nuclei may find themselves in the human body (e.g., adjacent to a nitrogen, or phosphorous, etc.) do not have a substantial concentration of any one configuration, but are rather disbursed evenly throughout innumerable other possible states and molecular "neighborhoods". The result is that there is a small background population of hydrogen nuclei exposed to a vast array of various molecular configurations and their attendant electron clouds/magnetic fields, but that there are only two populations in which hydrogen nuclei are found in substantial numbers; fat and water. Therefore, it can be inferred that all clinical hydrogen-based MR images are actually images reconstructed from signals received from essentially two populations of hydrogen nuclei: those in water (H_20) and those based in fat (with its long -CH_2 side chains).

Image Contrast Objectives:

Diagnostically successful magnetic resonance examinations provide good image contrast between target and background tissues. Indeed, the decision to manipulate TR, TE, TI, and/or flip angle values, or to use fat or water saturation options, or the decision to administer an MR contrast agent are examples of decisions that are almost always associated with or motivated by the search for improved image contrast between at least two tissues of interest being studied. Nevertheless, despite the considerable image contrast so often achievable with magnetic resonance studies, there are occasions where

image contrast may remain relatively poor despite attempts at optimizing numerous imaging and timing sequence parameters.

As image contrast is the difference between the signal intensities for a given tissue pair, it stands to reason that two tissues both displaying very low - or even both very high - signal intensities will yield low image contrast between them. Thus, an ideal situation for producing high image contrast is one where the signal intensity for one - and only one - of a given tissue pair being contrasted is quite high, while the signal for the other of these tissues would be near zero.

Image contrast objectives such as these have been clinically implemented in such imaging sequences/options as chemical specific (a.k.a., fat) saturation, short TI inversion recovery (STIR), and fluid attenuating inversion recovery (FLAIR) sequences. Here the fat or short T1 or CSF/long T1 tissue, respectively, is being targeted to have its signal nullified on the resultant image in order to generate improved contrast between one of these tissues and the target tissue against which it is being compared. For example, a bright signal from a high proton density, long T2 multiple sclerosis plaque will be more easily detected when it is adjacent to a high proton density, long T2 CSF-filled lateral ventricle if the signal from the CSF is reduced to zero. Such is the objective of FLAIR techniques when implemented in the evaluation of multiple sclerosis.

Fat (Chemical, Frequency Specific) Saturation Techniques:

Let us focus for a minute on the chemical (frequency) specific saturation techniques; when targeting fat signal, this is also known as fat saturation. As noted above, even when expose to the same external Bo magnetic field, there are slightly different magnetic fields experienced by hydrogen nuclei in water versus fat molecules. Therefore, hydrogen nuclei ("protons") in water molecules have a slightly different resonant frequency from that of protons in fat molecules. In fact, the difference in resonance frequency between fat- and water-based protons is field strength dependent, and is given as 3.5 parts per million. Applying the Larmor equation for hydrogen nuclei (whose magnetogyric ratio is 42.58 MHz/Tesla) at 1.5 Tesla, this results in 42.58 Mhz/T x 1.5 T, or roughly 224 Hertz difference in precessional, resonance frequencies between water- and fat-based hydrogen nuclei.

In a fat saturation sequence, we take advantage of this fat-water proton resonant frequency difference by transmitting a brief radiofrequency oscillating RF pulse (while no gradient magnetic fields are energized), tuned to be resonant with the frequencies of only fat-based protons and not those of water-based protons. Thus, after the application of this fat-saturating pulse, only fat-based protons find themselves resonant with the transmitted special preparatory fat saturation pulse, and therefore, only fat-based protons find their magnetic moments nutated out of the longitudinal Z axis. At this point there is coherent transverse magnetization present from only fat-based protons. This transverse fat magnetization is then destroyed (by any number of possible means), and the desired pulse sequence (e.g., partial saturation spin echo) is

then run. However, since at the onset of this pulse sequence the magnetization from fat-based protons has already been destroyed/nullified by the fat saturating pulse, only water-based magnetization from the excited tissues is available to be nutated down to the detectable transverse plane, where it will be detected at time TE. No signal from fat will be transversely available, or therefore detectable, at time TE as the fat-based magnetization can be said to have been saturated, or destroyed, by the preparatory fat saturation RF pulse that had been applied. Thus, fatty tissues will appear dark (saturated) on such a sequence, whereas other (water-based proton) tissues' signal intensities will be determined by the typical differentiating factors such as T1, T2(*), proton density, TR, TE, TI, flip angle, etc.

It is also entirely possible to target water-based proton signal for destruction instead of that of fat-based protons by simply tuning the frequency of the transmitted RF saturation pulse to the resonant frequency of water-based hydrogen instead of that of fat-based hydrogen. At 1.5 Tesla, to continue the above example, this would be a roughly 224 Hertz offset in the center frequency of the transmitted RF saturation pulse.

Magnetization Transfer Imaging/Contrast Technique:

Magnetization transfer imaging/contrast works in a manner quite similar to that described above for fat saturation. Similarly, an RF pulse tuned to be off the water resonance peak will be applied in this sequence immediately prior to each primary

excitation pulse (each TR). However, before proceeding, it would be appropriate at this point to provide some background information:

Water-based protons in and around tissues (both normal and abnormal) can be thought of as being found in one of three compartments. They may be:

1) bound to complex molecules and/or proteins within the tissues themselves. This compartment can be thought of as containing bound hydrogen nuclei.

2) within water molecules that abut these more complex molecules noted in #1, above, where these water-based hydrogens may occasionally interact with, or interchange between, themselves and the hydrogens in the bound compartment noted above. This compartment may be thought of as a boundary compartment between those within compartments 1 and 3.

3) found in and only in water molecules in the surrounding milieu, where their predominant (if not only) chemical interactions are with other water molecules. This compartment can be thought of as being that of free, or bulk, water.

The presence of hydrogen nuclei in proteins is interesting in that the molecular "neighborhood" of such proton-bound hydrogens is extremely variable. It may be near nitrogen in one location on the protein molecule, whereas another hydrogen may be near carbons, or phosphorus, or oxygen, or any number of possible variables. Each of these will therefore experience a unique magnetic field from its particular molecular

environment, and therefore its particular resonant frequency. The total population of any given bound hydrogen frequency will be relatively small, as there will not bee too many in one particular molecular environment. Thus, there will be numerous hydrogen nuclei whose resonant frequencies are almost equally distributed among various frequencies (i.e., static magnetic fields), both higher and lower than those of water- (and fat-) based protons.

Just as with fat saturation techniques, we can choose to provide a radiofrequency pulse that is not on the water (or fat) frequency range immediately prior to our selected MR imaging pulse sequence. For example, for a partial saturation spoiled gradient echo pulse sequence using a 20 degree RF pulse flip angle as its primary excitation pulse to be repeated each TR time interval, we might provide this off-resonance RF pulse immediately prior to transmitting each 20 degree RF pulse (i.e., every TR). As this pulse is off the resonant frequencies of water- (and fat-) based protons, it should have no direct effect whatsoever on the tissues being imaged. However, there is indeed an observed effect on our image. In order to explain this, it is necessary to understand that the three compartments in which hydrogen exists that was conceptually explained above are not static, fixed situations. In fact, hydrogens may exchange, or transfer, from one to another - sometimes quite readily. The rates at which hydrogens exchange from one compartment to another may be quite variable for different tissues, and is determined by numerous factors that are beyond the scope of this overview.

Nevertheless, the presence of such an exchange provides us with a unique opportunity for diagnostic imaging.

A saturating RF pulse is applied to a population of hydrogen nuclei situated at a frequency that is removed from that of the water (and fat) based protons being targeted for diagnostic imaging. Due to the exchange of protons between these compartments, however, some of these saturated protons will exchange with those of the bulk (free) water group. This latter group is the primary one being imaged in diagnostic MR imaging (in addition to the those protons that are fat-based). Thus, the greater the number of saturated protons from the bound or boundary compartment protons that exchange with the free water protons prior the our detecting a signal (echo) at time TE, the less available signal there will be for that tissue. For tissues that have little to no such proton exchange, the signal loss when using a magnetization transfer prepared pulse sequence is near zero, and the signal intensity from that tissue appears very similar to how it would have been even had the magnetization transfer (MT) pulse not been applied. Distilled water, for example, (or cerebrospinal fluid (CSF)) has essentially only a free, or bulk water compartment; its signal intensity is hardly affected, if at all, by the presence of an MT pulse. White matter, on the other hand, has rather substantial and relatively rapid exchange between protons in the bound and boundary compartments with those in the free water compartment. It therefore displays a rather substantial signal loss on sequences in which MT pulses are used relative to its intensity on similar sequences but in which such MT pulses are not applied. In fact, the

magnetization transfer ratio (MTR) is a term that is occasionally used to represent the intensity of the tissue when imaged while using an MT pulse relative to its intensity when such a pulse is not used.

There are several other factors that come into play in determining the signal intensity of the tissues imaged with MT pulses. These include the power and duration of the MT pulse, its frequency range and center, the length of time between application of the MT pulse and the primary pulse sequence excitation pulse (and echo time, TE), to name a few. Furthermore, it has been shown that especially with small frequency offsets (i.e., little difference (only a few hundred Hertz) in the transmitted frequency for the MT pulse from that of free water) another phenomenon, referred to as spin lock, comes to play as a, or the, dominant role, in determining tissue signal intensities. Nevertheless, the general rule is that the application of an MT pulse permits the operator to relatively specifically decrease/partially saturate the signal from specific tissues - while leaving that of other tissues relatively intact. This provides the potential benefit of increased contrast to noise ratio between two tissues, one of which is intense and not (substantially) affected by the MT pulse and another of which is less intense and made even darker by the MT pulse that more significantly saturates its signal. Two prime clinical examples of where this may be diagnostically useful are contrast enhanced MR imaging and time of flight magnetic resonance angiography.

For contrast enhanced MR imaging, the region of contrast enhancement is typically one where there has been disruption of the blood brain barrier. This is often associated with edematous/inflammatory reaction; i.e., increased interstitial fluid contents. The more fluid-like (e.g., free water like) the tissue the less the tissue will have its signal weakened by the presence of the MT pulse. Thus, a typical result might be that the area of contrast enhancement/blood brain barrier disruption enhances and is not significantly saturated by the MT pulse whereas the more normal background tissue against which it is being contrasted is more severely saturated by the MT pulse. This yields a greater contrast between these two tissues and potentially increased diagnostic content and/or reliability or confidence. There have been several articles in the peer reviewed literature that have suggested or demonstrated that the increased contrast to noise available with standard dose contrast administration in conjunction with the utilization of MT pulses yields similar image diagnostic content as images performed without MT pulses and with high (triple) dose intravenous contrast administration. Nevertheless, by this same reasoning it also stands to reason that the utilization of high dose intravenous contrast administration in conjunction with MT pulses should yield even greater contrast to noise than triple dose alone or single dose with MT pulses.

In a similar fashion, the objective with MR angiography (MRA) is to produce images of vascular structures/blood flow with background stationary tissue signal reduced to zero. Intravascular blood suffers almost no perceptible signal loss from the

application of MT pulses due to the high concentration of free water based protons, while adjacent tissues such as white matter may have significant signal saturation from such pulses. Thus, contrast to noise between these two tissues is increased, providing a more successful Maximum Intensity Protocol (MIP) image filtering process in the production of MR angiographic images, with darker backgrounds and typically more distal, smaller caliber, more slowly flowing vessels seen in such sequences. A significant drawback of MT time of flight (TOF) MRA is that it typically takes quite some time to apply this pulse; perhaps several dozen milliseconds. Therefore, the shortest TR that can be used increased rather substantially, so that a 25 ms TR may now be in the 50 ms range. Scan acquisition times may significantly increase for such MT TOF MRA techniques.

It should be noted that due to the technique itself there is generally excellent background stationary tissue suppression with phase contrast (PC) MR angiographic imaging. Thus, there is no real benefit from applying MT pulses to PC MRA techniques.

An Introduction To Inversion Recovery, STIR, and FLAIR MR Imaging Sequences

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Inversion Recovery pulse sequence:

The partial saturation spin echo sequence that we have been dealing with until now consists of a 90 degree pulse followed by a 180 degree pulse at time TE/2 and an echo peaking at time TE. An Inversion Recovery Spin Echo pulse sequence is the same as just described except that it begins with a 180 degree pulse that inverts all the tissue magnetization from the +Z to the -Z axis. After a user selectable time TI (Interpulse Delay or Inversion Time), a 90 degree pulse is applied to nutate the net magnetization vector of each tissue in the imaged slice (each in various stages of longitudinal magnetization recovery based on the tissue's T1 and the selected TI) into the detectable transverse plane, where (following another 180 degree pulse to produce a routine spin echo), the tissue's transverse magnetization is detected at time TE. This whole 180-90-180-echo RF train is then repeated every TR. Let's review the time intervals for the purpose of securing the nomenclature in this sequence: the time between the initial 180 degree pulse and the subsequent 90 degree pulse is referred to as the TI (interpulse delay, inversion time, etc.), the time between the 90 degree pulse and the echo is again, as always, referred to as the TE (echo time), the time between the 90 degree pulse and the subsequent 180 degree pulse is again, as always, the TE/2, and the time between repeating the entire 180-90-180-echo sequence with a new, unique strength to the phase encoding gradient is referred to as the TR (repetition time).

Such a pulse sequence tends to do especially well in optimizing tissue contrast from differences in tissue T1 recovery rates, since the initial inversion pulse provides for

the potential for even greater than usual longitudinal magnetization recovery differentiation for the tissues being examined. But in point of fact this technique is primarily used because of another reason that provides a curious benefit unique to this sequence.

The initial inversion pulse inverts all tissue magnetization to the -Z axis. As there is no coherent transverse tissue magnetization following this pulse, (i.e., tissue transverse magnetization is already at zero amplitude), it will remain at zero. Longitudinal magnetization, however, is oriented along the minus Z axis with a magnitude that is essentially the same as it had been initially (Mo) prior to the 180 degree inversion pulse. Therefore, this tissues will begin to recover their longitudinal magnetization by "climbing" up along the Z axis, at a rate that is determined by the T1 of each tissue. In other words, as time passes following the 180 degree inversion pulse, the longitudinal magnetization will decrease its negative magnitude (i.e., become progressively smaller along the -Z axis), then eventually become positive and continue to become stronger along the +Z axis until the initial magnetization state - Mo - has been restored. In order for this to occur, recognize that at some point in time following the 180 degree inversion pulse the longitudinal magnetization will pass through zero on its way to full recovery back along the +Z axis. The time at which this occurs is unique to each tissue and is dependent at least in part on the tissue T1 value. If TI is selected to specifically coincide with the time that the magnetization of a given tissue will be passing through (or near) zero, that tissue will have no longitudinal magnetization for

the 90 degree pulse to nutate to the detectable transverse plane. There will thus be no transverse magnetization, or signal, detectable (i.e., transverse) at time TE for this tissue, which will appear black in the resultant image. This TI time is referred to as that tissue's null, or bounce, point, and may be ideal for providing excellent tissue contrast for this tissue versus any other that is far from zero longitudinally speaking at that same time TI.

For tissues with a short T1, such as fat, the time TI at which its magnetization will cross zero is quite short. Thus, a short TI inversion recovery sequence would be appropriate to null the signal from fat (or any other tissue with a similarly short T1). Examples of tissues with short T1 values include fat; some highly proteinaceous fluid; tissues containing certain paramagnetic substances such as tissues that took up an administered gadolinium-containing MR contrast agent, or melanin within a melanoma; and certain (methemoglobin-containing) stages of hemorrhage. These sequences are referred to as STIR sequences (Short TI Inversion Recovery), and are actually not specific for erasing the signal for fat, but rather attenuate the signal from any short T1 tissue being studied if its T1 coincides with or approximates that of fat (such as those in the list noted above).

It is well recognized that while it is not a foolproof generalization, it is often the case that tissues with long T1 values also have long T2 values. For partial saturation sequences the long T1 and long T2 work as relatively opposing forces. A long TR is

necessary to permit the longitudinal magnetization component of that tissue to recover sufficiently prior to bringing it down to the transverse plane with the subsequent 90 degree RF pulse. With inversion recovery sequences, however, the long T1 of a tissue (I.e., its slow longitudinal magnetization recovery rate) results in more magnetization still left along the inverted Z axis if short TI values are selected. Thus, these can be combined with longer TE studies to emphasize both the long T1 nature and the long T2 nature of this same tissue, each in this case helping to contribute to the total signal detected from this tissue over that detected from short T1 and short T2 tissues. This is what is meant by the statement that is sometimes heard regarding the so-called synergistic, instead of opposing, T1 and T2 actions as far as inversion recovery sequences are concerned.

It should be noted that the receiver coils detect magnitude of transverse magnetization, and can thus "see" an identical signal intensity for a given tissue when its inverted magnetization is nutated to the detectable transverse plane or when the same tissue recovers this same amount of magnetization magnitude along the +Z axis at a later time TI. Thus, with increasing TI for any tissue, the signal would first decrease (as the inverted magnetization approaches closer and closer to zero), then bottoms out at zero (the null or bounce point), then, for even longer TI values, increases as the longitudinal magnetization progressively increases along the +Z axis from which it will be brought to the transverse plane by the subsequent 90 degree pulse and detected.

It is therefore possible that at a given time TI, one tissue with a shorter T1 may well find itself above zero (i.e., along the +Z axis) by as much as another tissue might find itself oriented inverted along the -Z axis. If these two tissues are adjacent to each other, voxels at the borders of these tissues may contain components of both such tissues within them. Thus, following the 90 degree pulse, the same amount of magnitude is brought down to the transverse plane from these two tissues but in opposing phases. These tissue signals will thus cancel each other, resulting in a black signal void along the interface of these two tissues in the image. The best way to avoid this is to change the TI values selected (or, alternatively, modifying the TR of the study which may also likely succeed in correcting for this problem).

For tissues with long T1 values, since such tissues (by definition) recover their longitudinal magnetization slowly, it will take them some time for them to reach the zero (null, bounce) point. Thus, to null the signal from these tissues, a longer TI value would need to be used. Fluids such as cerebrospinal fluid (CSF) are typical examples of tissues with such long T1 values. Such studies are therefore referred to as FLuid Attenuating Inversion Recovery (FLAIR) sequences. The rationale behind such FLAIR sequences is to "null" CSF signal while preserving that of long T2 lesions that may be adjacent to the CSF-filled ventricles or extra-axial spaces. This is accomplished by selecting long TR and long TI values appropriate to null CSF signal while simultaneously preserving signal from the lesions (with a T1 value that, while perhaps long, would not be quite as long as that for CSF). This is combined with a long

requested TE value, thereby increasing the (relative) lesion signal compared to that of the more rapidly decaying normal gray/white matter. Thus, FLAIR images are effectively heavily T2-weighted except for the signal from CSF which has been selectively "nulled".

The TI that is appropriate for nulling a given tissue is dependent upon several factors, including and especially the tissue T1 (which is itself dependent upon the static magnetic field strength Bo being used to examine the patient) and the selected TR value. Nevertheless, assuming that a very long TR value is being used (actually, assuming that roughly TR-(TI+(TE/2)) is more than four or five times the tissue T1), which is in fact commonly the case, the TI to be used is one that corresponds to the time when half of the tissues longitudinal magnetization will have recovered. This can be thought of, so to speak, as the tissues longitudinal magnetization recovery half time. This number can be demonstrated to be roughly 0.69 times the T1 of the tissue in question. Thus, if we wish to destroy all signal on an inversion recovery sequence from a tissue that has a T1 (at the selected static magnetic field to be used to image that patient) of 1,000 ms, and if we are using a very long TR of several thousand milliseconds, the appropriate TI to select would be roughly 690 ms. (The shorter the TR used the shorter would be the appropriate TI to null signal from that tissue.) Considering that tissue T1 values decrease when exposed to decreasing static magnetic field strengths, the TI that would be appropriate to null the signal from a specific tissue at a given static magnetic field

strength would decrease as the static field to which the patient is exposed decreases (assuming constant TR).

In summary: For partial saturation pulse sequences, the longer the TR the greater the degree of recovery of each tissue and, therefore, the greater the resultant signal intensity from each tissue. The longer the TE the weaker the signal detected from all tissues as they decay at a rate determined by their T2 values. With inversion recovery, however, the relationship is even more complex, since with increasing TI time the signal will first decrease in intensity, reach zero, then again increase in intensity as the net magnetization vector again increases towards the +Z axis. Therefore, the signal will be intense with very short TI values, will decrease in intensity or potentially DISAPPEAR with slightly longer values to TI, and finally increase again in intensity as the TI is increased yet further. Short T1 tissues (e.g., fat) will be erased from the image with short TI values (STIR sequences), whereas tissues with long T1 values (e.g., CSF) will disappear if long TI values are selected (FLAIR sequences). Recall that STIR sequences are not specific for fatty tissue, but rather decrease the signal from any and all tissues with T1 values similar to those of fat, whereas fat (chemical specific pre-) saturation sequences destroy signal from only true fat-based protons, regardless of the T1 of the tissues being examined.

A Summary of the Principles, Techniques, and Uses of

Magnetic Resonance Angiography

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Introduction

Over the years, the number of diagnostic sequences used in routine clinical magnetic resonance imaging (MRI) has grown geometrically. The last decade has seen the incorporation into routine clinical practice of multiecho, multislice imaging; inversion recovery and short TI inversion recovery imaging; gradient-echo modified flip angle imaging; contrast-enhanced imaging; rapid/turbo imaging; and recently, fast or turbo spin-echo imaging techniques. It has also brought the development and dissemination of magnetic resonance (MR) angiographic imaging techniques to routine clinical MRI, especially for neuroradiologic and, more recently, non-neuroradiologic applications.

There are several different MR angiographic approaches available that use markedly different techniques, each with unique advantages and disadvantages. Modifications of each of these techniques also have been developed over time. The more that is understood about these imaging techniques — their benefits, limitations, and artifacts — the more they can be applied appropriately and wisely to clinical cases.

There are two major, well-established MR angiographic techniques routinely used today. The more common is the time-of-flight (TOF) technique. The phase contrast technique, although not used as often, offers another approach to obtaining diagnostic MR angiographic images. Each can be performed using either two-

dimensional or three-dimensional Fourier transform (2D-FT, 3D-FT) data acquisition, and each is associated with numerous variations, advantages, and limitations/artifacts.

Time-of-Flight MR Angiography

The TOF MR angiographic technique capitalizes on the nature of stationary tissue to partially saturate or lose detectable signal (i.e., transverse magnetization) if pulsed rapidly and repeatedly with resonant radiofrequency (RF) power.

Placing a patient in a static (or constant) magnetic field induces a net magnetization of the hydrogen nuclei (hereafter referred to as "protons") of the patient's tissues. The north pole of the tissue's magnetization will orient along the same direction as the north pole of the static magnetic field (B_0) of the MR imager to which the patient is exposed. This tissue magnetization oriented along the same axis as B_0 cannot be detected directly. We can only detect that component of the tissue's magnetization that is oriented at right angles to B_0. Thus, to detect this magnetization, some or all of it must be oriented perpendicular to the axis of the imager's B_0.

In typical partial saturation MRI techniques, an RF oscillating magnetic field pulse (RF pulse) that is resonant with the selected slice is applied. This has the effect of tipping, or flipping, down the magnetization of the tissues within that slice (fully or partially, depending on the selected excitation flip angle) to the detectable, transverse plane, which is perpendicular to B_0. After this RF pulse is applied, the transverse

component of the tissue's magnetization becomes detectable by MRI. Transverse magnetization can be considered synonymous with signal intensity.

After detecting the tissue's transverse magnetization component at some user-selected time TE following the RF pulse, the tissue's transverse magnetization begins to decay back toward zero, while its longitudinal component parallel to B_0 rebuilds, or recovers, along the longitudinal Z axis. These decaying and recovering effects occur simultaneously, albeit at different rates. The rates at which the transverse and longitudinal magnetization components decay and recover are defined by the tissue T2 and T1 time constants, respectively. The shorter the T1 of the tissue, the more rapidly that tissue recovers its longitudinal magnetization after being tipped out of the longitudinal orientation by an RF pulse. Similarly, the shorter the T2 of the tissue, the more rapidly that tissue loses, or decays, its transverse magnetization back toward zero after being tipped into the transverse plane by an RF pulse.

At some user-defined time TR following the initial RF pulse, after a certain amount of tissue transverse magnetization decay and longitudinal magnetization recovery has occurred, the cycle is repeated by transmitting another RF pulse and detecting the tissue's transverse magnetization component at the same time TE following the RF pulse. This cycle may be repeated dozens, hundreds, or even thousands of times to gather sufficient data from which an image or image set is generated. The greater the magnitude of the transverse magnetization from a given

tissue, the whiter that tissue will be depicted on the final MR image. In other words, a tissue with a high detected signal intensity (i.e., much transverse magnetization detected at time TE after the RF pulse is applied) will appear white, whereas one with a weak signal intensity (i.e., little transverse magnetization detected) will appear as a darker region on the image.

Assuming that TR is much shorter than T1, the greater the amount of RF power that is deposited per unit of time into stationary tissue, the greater the amount of saturation (i.e., the greater the loss of detectable tissue magnetization and, therefore, signal intensity). The amount of RF power deposited into tissue per time is dependent on the frequency with which the RF pulse will be transmitted into the patient (i.e., the TR) as well as the power of each individual RF pulse (i.e., the RF pulse excitation flip angle). Thus, the more rapidly the RF pulse is repeated (i.e., the shorter the TR), the greater the saturation of the stationary tissue's magnetization. Furthermore, again assuming that TR is much shorter than T1, the greater the amount of RF power per pulse (i.e., the greater the selected excitation flip angle) the greater the degree to which the tissue magnetization and signal is reduced/saturated.

In other words, the shorter the TR, the more the signal detectable from stationary tissues can be reduced. In addition, at the very short TR values used in typical MR angiographic studies, the greater the flip angle, the more the signal detectable from stationary tissues can be reduced.

Due to the phenomenon of resonance and the manner in which MRI is performed, the RF pulse will tip, or flip, magnetization in a selected slice/slab of patient tissue and will have little or no effect on magnetization outside this slice/slab. Protons within blood vessels outside the imaged volume are not excited, or flipped, by the RF pulse. Therefore, even after the first RF pulse is applied, the magnetization of tissue protons outside of the selected excitation volume is still longitudinally oriented and not partially weakened. The result is that these as yet unaffected, nonflipped, inflowing protons, which had not yet absorbed any resonant RF power from any RF pulses, may still be fully magnetized or unsaturated. Thus, unsaturated protons outside of the imaged volume may have flowed into the slice/slab being imaged during the TR time interval. These unsaturated protons now within our slice being imaged are fully magnetized when the next RF pulse is transmitted resonant to the slice/slab being imaged. They therefore have a great deal of longitudinal magnetization available to be flipped down to the detectable transverse plane by this - and each - subsequent RF pulse.

Stationary protons within the imaged volume, on the other hand, are flipped, or excited, by the first RF pulse, and then quickly re-excited one TR later prior to their full magnetization recovery. During that brief TR time period, the stationary protons may not have had enough time to recover longitudinal magnetization. These protons,

therefore, have little magnetization that can be brought down to the detectable, transverse plane when each subsequent RF pulse is applied.

Because of the arrival of unsaturated, reinforcement protons to the imaged volume during each TR time, inflowing blood protons will selectively provide a relatively strong signal from the volume being imaged, while a relatively weaker signal will be detected from the partially saturated, background, stationary tissues whose magnetization had been weakened or partially saturated by prior exposure to resonant RF pulses. Under this scenario, the strongest signal, or the greatest amount of transverse magnetization, in each volume is detected from the inflowing protons, while the design of the study attempts to minimize signal from stationary tissue within that slice/slab.

After a set of images has been acquired, a mathematical algorithm known as a maximum intensity projection (MIP) algorithm is performed on the data set. The effect of this MIP data manipulation is essentially to retain the strongest signals from that slice/slab and discard the weaker signals. If done properly, the final displayed image will represent the strongest signals from the base, or source, images, originating from the rapidly inflowing protons, whereas the weaker signals from the stationary tissues will be discarded, thereby producing an angiographic-like record of the slice/slab. The effect of filtering the source gradient-echo image data through the MIP algorithm is to

produce the MR angiogram, which, simply stated, is a picture of the brightest pixels on the source images.

As noted above, this technique can be thought of as a gradient-echo MRI examination that can be acquired via either 2D-FT or 3D-FT methods, with the associated advantages and disadvantages of each approach. Thus, the data can be acquired rapidly with a 2D-FT technique as multiple single-slice acquisitions stacked one adjacent to the other, or over a longer period of time as a 3D manipulable slab of data that can be reformatted and displayed along any desired imaging plane.

Potential Problems

A successful TOF MR angiographic study would be one where the flowing structures within the imaged volume are visible and the stationary structures are not. This technique may therefore fail either because: 1) Stationary structures may appear bright on the final MR angiographic image and be misinterpreted as flowing structures, and/or 2) flowing structures may not appear as intense and be misinterpreted as stationary structures.

Stationary Structures Appearing Bright

Any strong signal (at the selected TR, TE, flip angle, etc.) on the source images would be incorporated into the final displayed MR angiographic image after the MIP algorithm is performed. Some stationary tissues have very short T1 values - that is,

they rapidly recover their longitudinal magnetization after an RF pulse. Despite exposure to an RF pulse one TR earlier, this rapid recovery rate might allow these tissues to recover a significant amount of longitudinal magnetization prior to the subsequent RF pulse. With a significant amount of longitudinal magnetization already recovered and available to be tipped to the detectable transverse plane when the subsequent pulse arrives, the tissue produces a strong signal.

Tissues with an especially short T1 include (among others) fat, Pantopaque®, methemoglobin, and tissues that took up a paramagnetic MR contrast agent, which shortens T1. If these tissues are located within the excited slice/slab, they might emit a strongly detectable signal at the selected scan parameters similar to the signal emitted by rapidly flowing blood protons. This short T1 stationary tissue signal may also make it through the MIP algorithm filter and remain visible in the final MR angiographic image.

For example, it is not at all uncommon for fat within the dorsum sellae or the short T1 posterior pituitary gland to appear in the final TOF MR angiographic images of the sella turcica. Additionally, a drop of Pantopaque® — an older, oil-based intrathecal contrast agent no longer used for myelography — near the tip of the basilar artery may produce a bright signal on TOF MR angiographic source images, and, therefore, the post-MIP angiographic image. A rounded, bright signal contiguous with the basilar

arterial tip may be misinterpreted as a flowing structure, such as a basilar tip aneurysm. These situations may complicate the differential diagnosis.

For these reasons, it is not uncommon to combine fat saturation techniques with TOF MR angiography (MRA) to decrease the intensity of the fatty tissues in the vicinity of the target tissues being studied. A drawback, however, of combining fat (chemical- or frequency-specific) saturation techniques with TOF MRA is that the time required to transmit a reasonably accurate fat saturation pulse increases the minimum TR achievable, thus increasing scan acquisition time.

Another example of a stationary structure appearing bright would be a short T1, methemoglobin-containing clot within, for example, a thrombosed sagittal sinus. Although not flowing, the clot may emit a strong signal on the base images obtained with TOF MRA because of its very short T1 value. Passing through the MIP filter, this bright signal may be misinterpreted as flow from a patent sagittal sinus when, in fact, the sinus may be entirely thrombosed.

Another method has been proposed and applied for decreasing the signal intensity of all tissues with short T1 values, regardless of the source of the short T1 signal. This method entails preparatory inversion pulses using a short TI to "null" the signal from all short T1 tissues. Although not yet commonly applied, this so-called multiple inversion recovery technique does hold promise.

Some types of artifacts (e.g., susceptibility artifacts) may also cause intense signal, which passes through the MIP filter and appears on the final MR angiographic image. Especially in the case of the susceptibility-induced, intense signal artifact, the signal may be curvilinear in morphology and mistaken for a true vascular structure.

Flowing Structures Not Appearing as Intense

The role of TE. Flowing blood may fail to appear as intense signal on the MR angiographic images because of the natural dephasing that occurs during time TE. Remember that an attempt is being made to detect coherent transverse magnetization from tissues whose transverse magnetization components are decaying at a rate described by the T2 or T2* time constant of the tissues. The shorter the T2* the faster this coherent transverse magnetization, or signal intensity, decreases or dephases. For flowing blood, the motion of flow itself serves to increase the processes by which the coherent tissue transverse magnetization dephases. In other words, the fact that the tissue to be detected is flowing, increases the rate at which the detectable signal disappears. Thus, to successfully sample strong signals from flowing blood, very short TE values (typically single-digit or low single-digit values) should be used. It is for this reason that selecting a longer TE value may be a major cause for flowing signal loss in MRA. Fortunately, most MR systems do not readily allow the user to arbitrarily increase the TE value of the study. In fact, the TE value used in MRA typically defaults to the shortest value technically obtainable by the system for the selected study.

Saturation flow dynamics: The roles of TR, flip angle, rate/direction of flow, slice/slab thickness (eg, excitation, or imaged, volume). There are other potential reasons why flowing signal may be invisible. Due to the nature of TOF flow-related physics, any flowing protons that remain—for whatever reason—within the excitation volume long enough to "get hit" by subsequent RF pulses will experience a weakening, or partial saturation, of their magnetization. This will, therefore, be accompanied by a decrease in detectable signal. Parameters that may be associated with flowing protons repeatedly hit by RF pulses include thicker slices/slabs, slower rates of flow, and shorter TR values, where flowing blood protons may be hit with the resonant RF energy several times before exiting from the excitation volume. Similarly, if the vessel is not perpendicular to the imaging plane but has some components that are parallel to it, the proton(s) must take a longer path within the excitation volume before exiting. The same can be said for blood flowing in a circular path within the excitation volume, such as in a giant aneurysm or arteriovenous malformation (AVM). Under such circumstances, saturation (i.e., loss of magnetization and, therefore, signal intensity) can be expected from these flowing protons as they attempt to penetrate deeper into the excitation slice/slab, since they will get hit repeatedly with resonant excitation RF pulses.

2D-FT vs 3D-FT TOF MRA

The 2D-FT TOF techniques typically image multiple thin slices. The most common technique studies one single slice at a time. When the data acquisition for that slice is entirely complete, the data are sent to be reconstructed into an image while the system begins scanning and acquiring data on another single slice, often in a location contiguous with the prior slice studied. The acquired data are passed through an MIP filter and are then stacked and reformatted for display along any desired plane. With 2D-FT, volumes that are excited by the RF pulses each TR time period tend to be substantially thinner than those excited with a 3D-FT technique. Thus, the blood protons can much more readily exit the thinner excitation volume or selected slice and wash in fresh, unsaturated spins before the "arrival" of the next RF pulse. However, current 2D-FT techniques typically do not provide slices thinner than about 1.5 mm, thus limiting the spatial resolution objectives achievable.

With 3D-FT TOF techniques, it is possible to acquire truly contiguous data without concern over patient movement between scans of adjacent slices, since information from the entire slab is excited—and induced to echo—with each RF pulse transmitted. Very thin slices can be mathematically reconstructed from these sequences, with slices of <1 mm easily achievable. Signal to noise ratios, or the smoothness of the image, tend to be improved over 2D-FT techniques.

However, 3D-FT MRA typically excites substantially thicker volumes/slabs than does 2D-FT MRA. With 3D-FT techniques, the entire slab is excited—and produces an echo—with each TR. (The individual slices that will subsequently be reconstructed and displayed are actually mathematically teased out of the data acquired.) Blood entering the excited slab between adjacent RF pulses may yield high signal at that entry location within the slab, but may fail to successfully exit the studied volume by the time the subsequent RF pulse arrives. The subsequent RF pulses will then saturate, or weaken, the signal from the flowing blood as it penetrates deeper into the excitation volume imaged. Thus it is important in 3D-FT TOF MRA that the anatomy of interest be positioned close to the entry region of the excited slab (e.g., within the lower third of the slab for imaging of a superiorly flowing vessel) and not the middle or deepest portions of the excited volume.

Role of TR

There is a greater saturation potential for flows deep in this slab compared with thinner slices/slabs (such as those used in 2D-FT scans). This saturation potential is greatest for blood that stays in the excitation volume for a long time. This can be seen, for example, with slow flowing blood (eg, veins), blood circling within a giant aneurysm or AVM, or blood flowing parallel to the imaging plane within the slice/slab. For imaging these types of flow patterns, TOF MRA may be suboptimal. Longer TR values would permit more time for the excited flowing blood to flow out of the imaged volume and for fresh, unsaturated reinforcement spins to wash in before the subsequent

RF pulse. Increasing the TR in 3D-FT TOF MRA, therefore, would yield greater depth of penetration of intense signal into the scanned volume because more time between RF pulses allows unsaturated blood to penetrate further into the excited slice/slab. However, this would be accompanied by increased signal/magnetization recovery from stationary spins, producing a potentially noisier background against which the vessels would be displayed. Furthermore, increasing TR also yields a linear increase in scan acquisition time.

Multiple Overlapping Thin-Slice Acquisitions

Another technique to overcome this saturation potential of thick-slab 3D-FT TOF MRA is to perform the examination with multiple overlapping thin-slice acquisitions (MOTSA). This technique negates the saturation effect of much of the flowing blood by decreasing the thickness of the individual slabs through which blood needs to flow in any given TR time period. To cover the length of the structure to be examined with this technique requires multiple, thinner slabs to be examined as separate acquisitions, which results in increased scan acquisition time.

Role of Flip Angle in 2D-FT and 3D-FT TOF MRA

As noted, with the ultrashort, single-digit TR values so commonly used in TOF MRA, generally, the greater the selected excitation flip angle, the more saturated, or weaker, the signals from stationary tissues. This also applies, however, to the signal

from flowing protons if they do not escape the imaged volume prior to arrival of the subsequent RF pulse.

For thicker excitation volumes, slow flowing blood, in-plane flow, and/or short very TR studies, it is possible that unsaturated blood might replace previously saturated blood protons near the entry edge of the excitation volume. However, the previously hit blood protons may then only slightly penetrate the slab before the next RF pulse. These previously hit, partially saturated protons, therefore, will appear darker as the blood vessel in which they are found penetrates to deeper portions of the excitation volume. With 3D-FT MRA, the excitation volume is relatively thick; therefore, the 3D-FT techniques are accompanied by, and are more prone to, exhibiting such saturation effects and loss of signal from flowing blood deep in the excitation volume. Because of this, it may be advantageous to decrease the excitation flip angle for 3D-FT TOF MRA to enable flowing blood to traverse more deeply into the excited volume without becoming severely saturated. The other option, noted above, is to choose a longer TR to provide more time for the blood to escape the excited volume and be replaced with fresh blood-based protons. In either case, however, performing the study with a decreased RF excitation flip angle results in the background stationary tissue also becoming brighter/less severely saturated, and may produce a grainy, more noisy, final MR angiographic image after MIP processing.

As a result of the above, for 3D-FT TOF MRA, decreasing the TR while simultaneously decreasing the RF excitation flip angle results in little change in the intensities of the flowing or stationary background tissues while decreasing overall scan acquisition times.

With a single, thin, 2D-FT slice, previously excited blood typically has little problem being replaced by the subsequent RF pulse one TR later. Therefore, large flip angles (e.g., 60° to 90°) are far more common with 2D-FT TOF MRA, while smaller flip angles (e.g., 10° to 30°) are more common with 3D-FT TOF MRA.

TONE/RAMP pulses and 3D-FT TOF MRA

Another solution to the problem of progressive saturation as the flow penetrates deeper into the excitation slab is to vary the excitation flip angle that is applied across the thickness of the excited volume so that the flip angle is progressively greater as penetration occurs deeper into the slab in terms of the direction of flow in the vessels being studied. This results in less severe saturation of the flowing blood near the edge of the slice/slab studied, and greater visibility of the vessel. The degree of background suppression/saturation would also, however, vary across the volume, as the stationary background tissues would also have been exposed to varying amounts of RF power deposition, depending on their positions within the studied slice/slab. This technique has been called TONE or RAMP imaging and it is sometimes used as an adjunct to 3D-FT TOF MRA. With the relatively thin slices typically studied sequentially with 2DFT

TOF MRA, this TONE or RAMP technique would be neither necessary nor ordinarily applied.

Magnetization Transfer

Instead of making the flowing blood brighter, another technique that has been successfully used with TOF MRA is decreasing the intensity of stationary background tissues. A magnetization transfer (MT) pulse is transmitted to decrease the signal intensity of some, especially proteinaceous, tissues, (e.g. and especially that of white matter) without significantly affecting the intensities of tissues that are more like distilled water. Thus, applying an MT pulse immediately prior to the main RF excitation pulse permits a greater degree of saturation or decrease of the signal from stationary tissue while not significantly affecting the intensity of the signal received from flowing blood-based protons. The MT pulse is transmitted before each excitation pulse, every TR. As it takes some time to transmit such a pulse, minimum attainable TR values—and therefore scan time—also increase with use of this technique.

The Role of Paramagnetic, Gadolinium-Based, Intravenous MR Contrast Agents in 3D-FT "TOF" MRA: Dynamic Contrast-Enhanced MRA

With the application of an MIP filtering algorithm, the quality of the final angiographic images may be improved by decreasing the intensity of the background stationary tissues and/or increasing the signal intensity of the flowing blood. If the

signal from the flowing blood is partially saturated, intravenous administration of a T1-shortening paramagnetic contrast agent (such as any of the gadolinium chelates) prior to performing 3D-FT TOF MRA may improve image quality. With the use of a contrast agent, even if the flowing protons experience multiple resonant RF pulses, their markedly decreased T1 values enable more magnetization recovery, and therefore signal, to be obtained from the flowing protons by time TR when the next RF pulse hits.

One limitation of this approach is that the signals of stationary tissues that take up the contrast agent will also be boosted, thus increasing the signal/noise of the background against which the vessels will be portrayed. To counteract this limitation, shorter imaging times (shorter TR values or partial k space techniques such as keyhole imaging, time averaging, subtraction techniques, etc.) may be used so that the images could be temporally resolved before the background tissues are affected by the agent. For example, the contrast agent may be administered as a bolus at the same time that the MR angiographic data are being obtained. This will provide the greatest intravascular concentration of the agent, and thus strongest vascular signal, at the time of sampling. Those background tissues that take up the agent do not have time to absorb it in significant quantities before imaging is complete; therefore, the signal from these tissues is not a problem.

Dynamic enhanced 3D-FT "TOF" MRA with rapid injection of contrast agent, alone or with continued infusion/drip techniques, can be most useful in studying slow

or in-plane flowing structures such as venous imaging, AVMs, giant aneurysms, or long segment studies of the thoracic/abdominal aorta. A drawback of dynamic enhanced imaging is that it is optimally performed only once/the first time contrast is bolused, since within a few moments after administration of contrast agent, the background tissues that take up the agent will be quite intense and may therefore appear on the MIP processed images of subsequent MRA attempts.

Subtraction techniques, such as those used in conventional angiography, are most helpful here as well. With this technique, the last image acquired before the arrival of contrast agent into the vascular tree is used as a mask to subtract from the subsequent MR angiographic images. This not only helps to decrease the effect of patient motion, but also works well in decreasing background signal intensities and increasing visualization of more subtle, slower regions of flow and smaller-caliber vessels. Subtraction techniques have been applied in the neuraxis, for example, in contrast bolus enhanced 3D-FT "TOF" MRA of AVMs, or for the body in contrast bolus enhanced 3D-FT "TOF" MRA of the renal arteries, aorta, pulmonary vasculature, and peripheral vasculature ("run off" studies).

A novel technique being proposed and studied by some MR equipment manufacturers and researchers entails continually studying the same slice(s) with a total scan time of just a few seconds per slice. The patient receives an intravascular bolus of contrast agent. When the hardware/software detects a sudden and noticeable change

in the intensity of the received signal, it triggers the image acquisition to begin. This automates the process of acquiring data during the predominantly intravascular phase of the contrast agent for the volume being studied. This technique has promise for automating the masking/subtraction technique, thus decreasing the effects of patient motion. Another approach is to simple apply a 2 cc bolus test dose of the agent and continually re-scan the same slice/slab of interest to determine the appropriate time delay between the peripheral bolus injection and the arrival of the contrast bolus to the anatomy to be studied. For such test bolus studies, it is of course important to ensure that the bolus injection rate for the test dose study is the same as that which will be eventually used for the actual bolus contrast enhanced 3D-FT "TOF" MRA study.

Spatial Presaturation Pulses

With either TOF MRA or phase contrast MRA (discussed below), it is possible to use spatial presaturation pulses. Immediately prior to the application of the RF excitation pulse of the MRA pulse sequence, an additional RF pulse is applied (with the appropriate gradients turned on) to be resonant with tissues in very specific locations in the body. For example, in axial imaging of the cervical carotid arteries with a 2D TOF technique, selection of superior presaturation pulses would excite the tissues immediately superior to the slice being studied. Intraluminal venous blood flowing caudally, which will soon flow into the slice being imaged, will become saturated. It will produce little or no signal when it enters the excited slice because it had been

spatially presaturated. Using this technique "erases" venous or arterial inflowing blood signal, depending on the direction of blood flow and the placement of spatial presaturation pulses. This technique is useful not only to decrease the degree and amount of overlapping vascular structures, but also to confirm or identify the direction of flow within any particular vascular structure.

It should be noted, however, that spatial presaturation may be less effective in the presence of intravascular, T1-shortening contrast agents, as the effect of these agents is to help these enhanced tissues recover longitudinal magnetization more rapidly. Thus, despite the presence of a recent spatial presaturation RF pulse, there may be considerable detectable magnetization present within the flowing blood by the time it reaches the imaged volume of interest.

Phase Contrast MRA

Phase contrast MRA is very different from TOF in terms of methodology and mechanism of action. With phase contrast MRA, the entire slice/slab is excited using a typical gradient-echo imaging sequence to which a unique gradient manipulation has been added. This consists of turning on (positive polarity) and then reversing (negative polarity) one of the three gradient coil sets in the system (referred to as the flow, or velocity, encoding gradient). This is then repeated but in the reverse order, that is, the

same gradient is turned on in the negative polarity first, and then reversed to the positive polarity. The results of these two echoes, or signals, are then subtracted from each other. The effect is that since all stationary tissue signals are unchanged in phase or intensity each time, subtracting one signal result from the other yields a net signal of zero. For structures that were flowing along the direction of the flow encoding gradient, however, the signal/phase is not the same the second time the sequence is repeated (in the reverse gradient energizing direction) as it was the first time; therefore, the subtraction leads to a net signal/phase for flowing structures alone.

The signal sensitivity to flow, however, exists only for that component of flow that lies parallel to the flow encoding gradient. In order for the signal to be sensitive to flow along any of the three orthogonal axes, the entire study needs to be repeated with the flow encoding gradient orthogonal to the axis first studied, and then again a third time with the flow encoding gradient oriented orthogonal to the first two flow encoding axes. Thus, the study needs to be done with flow encoding gradients energized along all three axes in order to be sensitive to flow along any axis.

All signals obtained are then filtered through an MIP algorithm as is done in TOF sequences. Further, just as with TOF MRA, phase contrast MRA can be acquired via either 2D-FT or 3D-FT methods. It should be noted that just as with TOF MRA, saturated flowing blood also yields no useful vascular signal, as all saturation dynamics also apply to this imaging sequence as well.

With phase contrast MRA, the intensity of the flowing signal is dependent on the rate of flow of the protons. A new parameter used with this sequence is the maximum velocity encoding value. This parameter allows the operator to determine the fastest rate of flow (cm/sec) in the imaged volume. If the determination of maximum velocity is correct, then the faster the flow, the more intense, or white, the signal will be from the flowing structure. If incorrect, however, and there is flow present within the excited volume that is faster than the value entered as the maximum velocity encoding variable, this flow may appear darker than does slower flow in that same image, which is referred to as velocity encoding aliasing. Thus, it is important to carefully select the maximum velocity encoding parameter. If the selected setting is too low, faster flowing structures will be displayed as darker intensities, as if they were flowing slower. If the selected setting is too high, most of the flow will be displayed as relatively low-signal intensity. To help differentiate between true flow rates and velocity aliasing in phase contrast MRA, repeated phase contrast MRA studies, each with different maximum velocity encoding settings may be helpful, for example, in evaluation of AVMs to identify and differentiate arterial feeders from more slow flowing/nidus vessels.

General Clinical Uses of MRA

In general, TOF MRA is most often used for neuroradiologic work such as in the circle of Willis, cervical carotid bifurcations, and AVM evaluation. Phase contrast MRA

can be added for clinical questions that involve slow flowing structures, (e.g., sinus thrombosis-related questions), in-plane flow, and regions of interest that have foci of bright signal/shortT1 tissues.

As noted, MT pulses in conjunction with TOF MRA have been demonstrated to be a useful addition in helping to saturate or decrease the signal from the stationary gray and white matter while not substantially affecting that from the flowing blood. Since phase contrast MRA does a superb job of decreasing stationary background tissue intensities to near-zero levels, MT pulses generally are not required or especially helpful for phase contrast MRA. With TOF MRA, MT pulses result in increased contrast-to-noise between the intraluminal flowing blood and the background brain parenchyma, and typically allow one to follow the vessels more distally within the brain and/or visualize slower flow. It should be kept in mind that it is not always the diagnostic objective to visualize smaller and/or more distal vessels. Often, as in renal artery stenosis or aneurysm evaluation in the circle of Willis, imaging is being used to look for abnormal morphology in relatively large-caliber vessels. In such cases, adding MT pulses may be of minimal use. The drawback is that it requires time to transmit an MT pulse, thus increasing the minimum usable TR to several dozen ms, which increases scan acquisition time.

For neuroradiologic applications, contrast-enhanced MRA is used for those cases in which the saturation potential is high, such as in the evaluation of AVMs, giant

aneurysms, or occasionally tight stenoses at the common carotid bifurcation. Saturation potential also may be high when 3D-FT TOF MRA studies are designed using very short TR values (eg, <5 ms) and/or very large flip angles. Studies such as these may be designed to markedly decrease scan acquisition time but may result in substantial decreases in signal from all tissues—stationary and flowing. For these types of examinations, rapid administration of a standard dose of contrast agent, timed to be predominantly intravascular at the region of interest especially when the lowest-order phase encoding steps are being acquired, can be a useful diagnostic option. This technique provides for a high concentration of the contrast agent in its first pass through the vascular tree, thus providing substantial T1 shortening of the flowing blood. With sufficiently short TE values, the T2* shortening effects that accompany this technique can be successfully negated. These studies have the benefit of producing MR angiographic images with strong signal from flowing blood, weak signal from severely saturated stationary tissue (which will not have had an opportunity to take up contrast agent), and considerable decreases in scan acquisition time.

To date, contrast-enhanced TOF MRA has proven to be the mainstay of evaluation of the renal arteries, abdominal aorta, peripheral "run-off" vascular studies, and pulmonary emboli searches. In these studies, 3D-FT TOF MRA with rapid administration of contrast agent or infusion/drip administration is a powerful combination that allows fast and accurate assessment of the intravascular morphology.

3D-FT time of flight (generally unenhanced) MRA has been found to be of substantial clinical value for aneurysm evaluation of the circle of Willis and/or posterior fossa and for evaluation of AVMs prior to therapy (e.g. gamma-knife irradiation of the nidus), where neurosurgeons may be more comfortable with MRA than they are with conventional angiography for nidus localization. Unenhanced 2DFT time of flight MRA is especially useful in the evaluation of slow flow and questions of vascular patency. Additionally, while 2DFT time of flight MRA has been used for carotid bifurcation evaluation, small ulcerations and wall irregularities are more easily missed with MRA than with conventional angiography. Further, there is still a problem of overestimation of stenosis, especially with varying TE values between different MRI systems. For these reasons 3D-FT dynamic bolus (first pass) ultrarapid scan time MRA has been used over the past few years for this evaluation and has enormously improved the reproducibility and reliability of MR imaging of this region. There have been almost concurrent significant relatively recent advances along multiple fronts, including the development of very short TE (and TR) capabilities, the introduction of reproducible and reliable MR compatible injector systems, the development of superb quality receiver coils able to cover well from the aortic arch up to and including the entire intracranial volume, and increased efficiency of filling k-space and unique and ingenious ways in determining how and when and even what parts of k space will be filled (e.g., elliptic centric k space ordering techniques). With these advances, the role of bolus contrast enhanced MR angiographic imaging in the evaluation of the carotid and

vertebral systems has markedly increased - and will continue to do so as this technology continues to permeate the installed base and MR community at large.

Unenhanced (and possibly enhanced) 3D-FT TOF MRA technique also may be useful for diagnostic confirmation of vasculitis, although the rather subtle vessel-wall irregularities that may be present with this condition are at the limits of the spatial resolution that is available with MRA today in clinically realistic scan times. Finally, bolus contrast enhanced dynamic 3D-FT MRA has been shown to be reliable and useful in the evaluation of the aorta, the peripheral vessels, especially of the lower extremities, and of the renal arteries, and has also been applied to upper extremity and pulmonary vasculature evaluations. Coronary MRA is a major focus of research. Although technically more difficult due to the inherent difficulties associated with cardiac motion and its effects on image quality, significant advances have been and continue to be made in this field.

Finally, you may be wondering why for the bolus contrast enhanced 3D-FT "TOF" MRA studies I wrote "TOF" in quotes. Well, actually, the reason for that contains substantial irony. Considering the mechanism of action of the contrast agent and its role in determining the signal intensities of the blood versus the background stationary tissues, such imaging sequences are actually, in fact, not at all time of flight dependent. In other words, they are not dependent upon the delivery, during TR, of replacement unsaturated protons to the vasculature being studied in order to detect an

intense signal from the vascular lumen. If you think about it, the reason that the vasculature being studied has intense signal is due to the exquisitely short T1 values of the intraluminal blood relative to the markedly longer T1 values of the unenhanced background tissues by/at the time the data is collected. In other words, we have come a complete circle, because these MRA images are actually nothing more than strongly T1 weighted images! It is therefore more appropriate to refer to these images as bolus contrast enhanced 3D-FT MRA and NOT time of flight MRA.

Conclusion

Rapid progress is continuing in the technology and applications of clinical MRA. The future of this technique for vascular diagnostic work is most promising and, at this point, has unlimited potential. Only time will tell what further advances are yet to be obtained in the realm of spatial and temporal resolution using more capable and powerful gradient subsystems, intravascular contrast agents, and more powerful postprocessing computing power. The development of the technology as well as the sequences (especially increased efficiency of filling k-space and unique and ingenious ways in determining how and what parts of k space will be filled and when) have already resulted in marked gains in the clinical applicability of especially contrast enhanced MRA. But as with almost any aspect of diagnostic MRI, the more that is understood about these imaging techniques and their advantages and disadvantages, the more they can be appropriately used in clinical cases.

Table I:

Factors affecting flow intensity in (unenhanced) Time of Flight MRA:

Slice/slab orientation relative to the angle of flow
Slice/slab thickness
    2D versus 3D Fourier Transform
Rate of flow
Direction of flow
Type of flow (e.g., pulsatile, laminar)

Flowing blood T1/T2*/proton density (PD)
        Presence/absence of contrast agent(s)
Stationary tissue T1/T2*/PD
    Presence/absence of contrast agent(s)
Presaturation pulse
Presence or absence of magnetization transfer pulse(s)
Presence/absence of (and order of) gradient moment nulling
TR
TE
Flip angle
Voxel volume (i.e., number of phase encoding steps, number of frequency encoding samples, slice/slab thickness, field of view, [if 3D-FT, number of slices])
NEX
Type of reconstruction technique used (e.g., MIP)

Factors affecting flow intensity in Phase Contrast MRA:

Slice/slab orientation relative to the angle of flow
Rate of flow
Direction of flow
Type of flow (e.g., pulsatile, laminar)
Maximum velocity encoding (i.e., flow encoding gradient amplitude)
Direction(s) along which velocity encoding was performed
Flowing blood T1/T2*/proton density (PD)
Presence/absence of contrast agent(s)
Stationary tissue T1/T2*/PD
Presence/absence of contrast agent(s)
Presaturation pulse
Presence/absence of (and order of) gradient moment nulling
TR
TE
Flip angle
Voxel volume (i.e., number of phase encoding steps, number of frequency encoding samples, slice/slab thickness, field of view, [if 3D-FT, number of slices])
NEX
Type of reconstruction technique used (e.g., MIP)

Table II:

TOF MRA Advantages:

Strong signal from rapidly flowing structures

Readily, easily, and reliably accomplished

Rapidly acquired

PC MRA Advantages:

High sensitivity to slower flowing blood

Can assess rate of flow via signal intensity scale (i.e., signal intensity is related to velocity; quantification data availability)

Directionally sensitive

Generally excellent background suppression

TOF MRA Disadvantages:

MIP artifacts (Bright foci, usually possessing a very short T1, appear as "flow". Typical such foci include certain stages of hemorrhage, thrombus, aneurysm, fat, pantopaque, contrast enhancement, melanoma, susceptibility artifacts, etc.)

Saturation potential (can be overcome with contrast, e.g., gadolinium)
More limited than PC-MRA for thick 2D or 3D slices/slabs
- In-plane or circular flow
- Very short TR values
- High flip angles

PC MRA Disadvantages:

Velocity encoding aliasing

Generally longer study times

Needs very strong gradient subsystem(s) to encode successfully for very slow flow

Nephrogenic Systemic Fibrosis: Past, Present, and Future

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Introduction

Since 2006, when the association of gadolinium-based contrast agents (GBCAs) with Nephrogenic Systemic Fibrosis (NSF) was first recognized, there has been a restructuring of the practices within the radiologic community, as we have attempted to identify a means of preventing the development of this disease. During the past three to four years, the radiologic community has seen certain opinions, ideas, and practices come and go in this regard. Some of our initial thoughts in this regards have proven incorrect, while others have been almost uncannily on the mark from the very beginning.

As we begin our fifth year since the connection between GBCAs and NSF was first suggested, it might prove helpful to review where had have been in our opinions and practices, where we are today, and where we are likely to go in the future as our knowledge in this regards continues to progress.

Where have we been?

Since 2006 much was published regarding the role of GBCAs and the development of NSF in patients with significant renal disease. It has been noted for quite some time that there were more NSF-related research studies than cases of NSF. However, all recognized that, rare as it is, NSF was a most serious disease with no

reliable known cure. We knew that the disease can involve the entire body, including the skin, heart, diaphragm, testes, dura, etc., but, interestingly, seemed to spare the brain parenchyma itself – as if, perhaps, the blood brain barrier played some sort of protective role… NSF seemed to almost always be – but according to some, not always – associated with a prior GBCA administration. Higher administered doses were recognized as being associated with a greater likelihood of NSF development. It was known that the disease was found in patients with severe or end stage chronic kidney disease (CKD), and that most, but not all, were dialysis patients. Initially it was thought that the disease was associated only with Omniscan, but within a year it was recognized that there were also cases associated with prior Magnevist and Optimark administration. There was a concern by some that this disease was a class association, and might be associated with any GBCA at possibly equivalent likelihoods. Others felt that the associations with Omniscan and possibly Optimark were far greater than with any of the other agents.

The American College of Radiology (ACR), through its ACR Guidance Document for Safe MR Practices: 2007, took the initiative and recommended screening patients who were at greater risk of renal disease. When significant renal disease was identified, it was recommended that reconsideration be given as to whether GBCAs were actually required at all. If it was deemed clinically desirable to

administer a GBCA to them, it was recommended to use the lowest dose absolutely required – e.g., half dose - to attain the diagnostic objective. It was recommended that Omniscan – and some felt Optimark and perhaps even Magnevist – should not be used in patients with significant renal disease, and that macrocyclics or possibly lower dose Multihance (with its higher relaxivity) be used instead in this population. It was recommended that hemodialysis patients who were administered GBCAs undergo immediate hemodialysis following the MR examination for which the GBCA had been administered, and that this be repeated daily for the next few days. In Europe and in other locations, Omniscan, Optimark, and Magnevist were outright contraindicated in patients with severe renal disease.

Hundreds of lawsuits were filed, almost all targeting the pharmaceutical firms who produced these agents.

Where are we?

It is now recognized that somewhere between 10% - 20% of all NSF cases NSF are in patients who were in acute renal failure, and not just those with CKD, at the time of GBCA administration. Further, it is also now recognized that although the

vast majority of NSF cases in CKD patients are in those with end stage renal disease (i.e., CKD stage 5), NSF can also be found in patients with CKD stage 4, and, it is now recognized, even rarely in patients with Stage 3 CKD. As the vast majority of diseases manifest bell shaped population distribution curves, it stands to reason that it would be unlikely that there would be a sharp eGFR cutoff above which the disease incidence precipitously drops to zero.

Initial reports of patients with NSF yet with no history of prior GBCA administration were followed by reports of high gadolinium levels in the tissue biopsy of these patients. Considering that prior GBCA administration history is nearly ubiquitous in NSF patients, this lent even further strength to the argument that GBCA administration was indeed necessary – but not sufficient – for the development of NSF. Whether the simultaneous presence of elevated serum phosphate, or iron, or calcium, or erythropoietin, or some combinations, or some other factors were needed for NSF to develop was not and is still not known.

Today's recommendations and practices almost universally recognize an increased risk of developing NSF in renal disease patients who receive linear GBCAs as compared to those who receive macrocyclic ones. In some areas, Magnevist has been specifically named among the linear agents as having a higher risk of NSF,

albeit not as high as that with Omniscan or Optimark. The US Food and Drug Administration (FDA), on the other hand, had chosen to treat all the (FDA-approved) GBCAs equally in this regard, and has provided a black box warning clarifying a perceived risk of developing NSF after the administration of any GBCA, with no black box content differentiation whatsoever in regards to frequency on NSF development following administration of the various GBCAs. (Their May 23, 2007 Public Health Advisory on this issue does mention that when a specific agent had been named, more cases had received Omniscan, then Magnevist, then Optimark.) The author of this manuscript is not aware of any regulatory agency or scientific/societal body in the world that has agreed with this opinion, and has even gone so far as to publish in the peer reviewed literature a commentary strongly disagreeing with the FDA's approach that attempts to suggest that the NSF-related risks among the various GBCAs is equivalent.

Today it is known that there appear to be biopsy confirmed cases of NSF developing after prior isolated administrations of Omniscan, Magnevist, or Optimark (in order of frequency) with rare or isolated case of NSF having been reported following the administration of Gadovist and (not-biopsy confirmed) Prohance, and Dotarem (unclear biopsy status). As of today, there do not appear to

be any biopsy confirmed cases of NSF reported with a history of isolated prior Multihance, Primovist/Eovist, or Vasovist/Ablavar administration.

If it is felt necessary to administer a GBCA to a patient who is perceived to be at higher risk for NSF, the vast majority of these patients at this time seem to be administered macrocyclic GBCAs (Dotarem, Gadovist, or Prohance) or lower dose Multihance, taking advantage of its higher relaxivity.

It is most important to note that there have been exceedingly few new cases of NSF diagnosed worldwide in roughly two years. This astonishing observation suggests that in less than two years since the initial association of NSF with GBCA we have managed to alter our practices sufficiently to almost eradicate this disease. This is a strong testament to the ability of the medical community to rapidly disseminate new information - which is in no small part attributable to the power of the Internet today – as well as their ability and willingness to rapidly change their practice and prescription patterns.

What has changed in the past few years that has resulted in this impressive near-eradication of new NSF cases? Polling the MR community reveals that there have been three major practice alterations since this GBCA-NSF association was first

identified. Interestingly, all three behavioral modifications undertaken by the MR community worldwide were those recommended in early 2007 in the American College of Radiology Guidance Document for Safe MR Practices: 2007. These include:

1) Prospective patient screening to determine estimated glomerular filtration rate (eGFR) calculations prior to GBCA administration.
2) Avoiding GBCA administration, or administering lower doses, to patients with significant renal disease.
3) Changing the administered GBCA brand from those perceived to be more associated with NSF to those that are perceived to be significantly less so associated.

It is not know which, or which combination, of the above has yielded this overwhelmingly successfully precipitous drop in observed new NSF cases since these modifications were clinically implemented worldwide in mid-2007. Indeed, it may specifically be the combination of these three that has resulted in this near eradication of new NSF cases.

Lawsuits that are being filed today have taken on an entirely new "flavor". As opposed to the initial battery of suits that were almost exclusively aimed at the pharmaceutical firms providing these GBCAs, today's newly filed lawsuits are now almost universally naming the radiologists and the sites who administered these agents. Since the issuance of warnings by the pharmaceutical firms and the newly issued black box warnings in all GBCA product labels in the US, the pharmaceutical firms can now clearly state that we have been warned about the risks. At this stage it would appear difficult to hold them responsible for any new NSF case that might develop. After all, it is now a recognized possible associated adverse event of which the prescribing physician must be aware in their risk benefit analysis prior to administering these agents. Therefore, should a new case of NSF result today, it is quite clear that the decision making process as to why the agent was given, how much was given, and specifically which agent did the site elect to administer, will undergo extreme scrutiny.

Finally, the European community has seen the recent recommendations for reclassification of all GBCAs, such that Omniscan, Optimark, and Magnevist would all be referred to as high-risk agents, the Macrocyclic GBCAs would be considered low risk agents, and the rest would be referred to as intermediate risk agents. The recommendations for the low risk agents and the intermediate risk

agents are virtually identical, whereas they are far more stringent for the three higher risk agents. Further, in the US, Covidien, makers/distributors of Optimark, has taken the most unusual step of spontaneously contraindicating their own agent in patients with stage 4 or 5 CKD or acute renal failure (even though the FDA has still not requested that they do so). On December 8, 2009, a public FDA Panel Meeting was convened in Gaithersburg, MD for the sole purpose of revisiting the issue of GBCA classification and labeling relative to their perceived relative risks of being associated with NSF. The conclusion of that meeting included the two panels recommending to the FDA that Omniscan be contraindicated in patients with severe or end stage chronic renal disease or acute renal failure (Optimark had already voluntarily adopted this labeling by the time this meeting was convened, as noted above), and that Magnevist labeling be reworded to in some way ensure that it was clearly relayed that it, too, was perceived to be at a higher risk for NSF association than the other GBCAs (besides for Omniscan and Optimark).

Where are we going?

Considering that the following is discussing the future, it should be clear to all that these are merely predictions, and represent no more than this author's best guesses

as to where the industry is headed. So forewarned, here are several predictions for our collective future:

1) Some have already questioned whether we need to continue screening patients. After all, they claim, there are no new cases - perhaps the disease has been eradicated! This is akin to suggesting that anti-malarials are no longer required for those traveling to high risk locales since, after all, those who have taken them in the past have not come down with the disease! Ordinarily, this suggestion would not be worthy of a response. However, considering the present financial crisis and the attempts to reign in costs, this suggestion has arisen from some otherwise quite reputable sources. It is my opinion that common sense will prevail, and that prospective patient screening for those who are about to receive GBCAs will remain a mainstay of routine radiologic practice. Perhaps we might discover new ways to screen patients or methods of verbal screening that might prove as reliable and as effective as serum eGFR determinations are today. But prospective patient screening is here to stay – as well it should be. Indeed, what we require now is the development of a reliable means for screening patients with clinically undetected acute renal failure. This population has been demonstrated to

be able to develop NSF despite the lack of prior renal disease history and even with rapid renal function recovery within a few weeks following the GBCA administration.

2) The FDA will likely accept the recommendations of the two Panels, made on December 8, 2009, and relabel Omniscan as contraindicated for stages 4 or 5 CKD or acute renal failure, and will find appropriate wording to relabel Magnevist as being perceived to be at a higher risk of NSF association than other FDA-approved GBCAs (besides for Omniscan and Optimark).

3) Reliance on "stage 3 CKD" or "30 mlmin/1.73 m2" as a sharp cutoff above which NSF cannot occur will finally be recognized as inappropriate. Nephrologists know that patients with eGFR values of 30 are quite different from those with 59 – despite both being classified as stage 3 CKD. Radiologists will recognize the need to focus not on an artificially classified "stage" but rather the measured eGFR for decision making purposes. A patient with an eGFR of 32 will not be functionally equated with one with an eGFR of 58, despite their both falling into the same artificially-created Stage 3 category of chronic kidney disease.

4) Total prior cumulative dose monitoring might be deemed warranted for patients with significant renal disease.

5) Agent selection will continue to play a major role in NSF case development. Human nature being what it is, I predict that future cases of NSF will develop after administration of agents that are perceived to be at a greater risk for the development of NSF – perhaps predominantly in patients with clinically as-of-yet unrecognized acute renal failure. The resultant well publicized lawsuits will almost certainly discourage future usage of these agents in the general population, not just those perceived to be at higher NSF associated risk.

6) Administered GBCA doses will continue to decline. While we can defend high dose administration for specific patients where subtle pathologic processes need to be accurately detected and/or quantified, much of diagnostic imaging will suffice with decreasing doses. This will be further potentiated by present and new higher relaxivity agents that produce similar levels of contrast enhancement and lesion detectability with smaller doses of administered gadolinium ion.

7) Finally, the number of lawsuits against pharmaceutical firms will decrease to zero as existent cases are settled. Physicians and sites will continue to increasingly become the targets of new lawsuits alleging malpractice in GBCA administration associated with any new NSF cases that might arise in the future. This is even more likely if NSF results

after GBCA administration in the setting of clinically unrecognized acute renal failure, or if a perceived higher risk agent is accidentally administered to a patient with known significant renal disease, or if a site chooses to stop screening patients for renal disease and administers a perceived higher risk agent to a patient with significant CKD.

To this day we still have no actual proof as to what causes NSF and the role GBCAs play in this regard. Undeniably, however, a mainstream opinion has emerged as to the relationship between GBCAs and NSF, and that is the theory of transmetallation/dissociation, the release of the gadolinium ion from its ligand molecule, and sequelae thereof. "Mainstream thinking" certainly does not constitute any sort of "proof" per se. Nevertheless, in this exceptionally litigious NSF environment (at least in the US), one would be well advised to have very clear and defendable reasons for not following commonly accepted practices and opinions should NSF develop after alternate practices were followed.

Conclusion

Many have pointed to the discovery of a relationship between GBCA administration and the development of NSF in patients with significant renal disease as a significant flaw in the drug review and approval process. Some have pointed to this event as raising and embodying a question of confidence in our drug, and indeed medical care, delivery process. That may be the case, although such a discussion would be beyond the scope of this article. What is clear, however, is that ironically, what has also been demonstrated is that at least part of the system works – and works exceedingly well and efficiently. The fact remains that within less than 24 months from a GBCA-NSF association first being postulated in the peer reviewed literature, the MR community has gotten the word out and has modified its behavior in such a manner as to reduce the incidence of new cases of the disease to nearly zero. This is indeed a rather astonishing accomplishment in its own right, and attests to the efficiency of the conferences, peer reviewed literature, and especially the internet and other avenues utilized throughout the medical community to "get the word out" and disseminate the required information faster than has ever before been possible. And that itself yields hope and indeed some modicum of confidence in our collective medical future.

We have been most fortunate to see the near disappearance of NSF just a few years after its association with GBCAs was first recognized. This almost certainly resulted form significant modifications in how the MR community has approached GBCA administration to patients with potentially significant renal disease. With intelligent continued application and refinement of these same guidelines, we may be able to proudly claim our share in helping to eradicate this rare but most serious disease.