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Paradigm and element shift in MR contrast agent applications

Peter A. Rinck

The Gadolinium Story is the permanent talk of the town: In certain people the injection of some gadolinium contrast agents can either lead to deposits of gadolinium in tissues or to severe, partly deadly side effects. I have been in the scientific gadolinium contrast agent business for more than 35 years and have summarized the history as I have witnessed it in a number of columns. The last and most factual report appeared in 2015, describing the historical course of events as clearly as one can and asking the most important question: "Gadolinium – will anybody learn from the debacle?" [1].

The entire affair has been taken over by lawyers, judges, and health administrators and meanwhile its handling has completely gone off course. The companies and people involved seem not to want to collaborate but rather to fight each other. Some people are confused, some try to evade assuming any responsibility for what they have caused and whitewash themselves, some say it's an act of God, some try to make money – while patients suffer and hardly anybody talks about them or tries to help.

The long awaited decision of the London-based European Medicines Agency (EMA) on what should happen with linear gadolinium-based MR contrast agents is many months delayed, most likely due to objections by lobbyists [*]. Meanwhile, the number of examinations with gadolinium contrast agents slowly declines and the indications are curtailed.

The odds are that there will be drastic changes in contrast agent use in the near or medium future. It seems as if manganese-based agents could replace gadolinium agents, at least for selected indications: There is an old new kid in town.

Manganese was the first element applied to enhance pathologies in MR imaging; its use was described by Paul C. Lauterbur, Maria Helena Mendonça-Dias and Andrew M. Rudin in 1978 [2]. They imaged five dogs with myocardial infarctions after injecting a manganese salt solution and were able to highlight the lesions.

Yet, gadolinium became the element of choice for MR contrast agents because of its high relaxivity and patent issues. However, it is an element foreign to the human body whereas manganese is an essential trace element.

The odds are that there will be drastic changes in contrast agent use in the near or medium future: There is an old new kid in town.

The only managnese-based agent approved and sold for clinical imaging was Teslascan (Mn-DPDP), a compound used for liver imaging. As it didn't sell for the indication it was withdrawn from the market some time ago.

In addition to imaging of the liver, manganese-enhanced MRI (MEMRI) with Mn-DPDP has a wide range of potential applications. Research is focused upon both depiction of brain damage and functional mapping of neural pathways to map brain activation independently and with higher contrast than measurements of hemodynamics in fMRI.

Contrary to gadolinium-based compounds, which are unspecific agents, manganese agents can actively track biological processes. Manganese also has an affinity for the myocardium and can act as biomarker in heart disease. It competes with calcium for entry into cardiac cells. There, its ions bind to macromolecules and influence the relaxation of cell and tissue water. Heart diseases gradually inactivate calcium transport mechanisms (due to lower metabolic activity). Thus, manganese uptake is reduced accordingly; manganese-induced changes of tissue relaxation reflect quantitatively tissue calcium homeostasis and thus myocardial viability [3, 4].

During the development of Mn-DPDP as an MR contrast agent for liver studies, it was discovered that this compound and its metabolite, manganese pyri-

doxyl ethyldiamine (Mn-PLED), also possess therapeutic properties. Mn-DPDP has been studied in cancer patients and in patients with myocardial infarctions. The contrast enhancement in MR imaging relies on the release of manganese from the chelate, the therapeutic activity depends on manganese that remains bound to DPDP or PLED.

Mn-PLED's stabilized derivate calmangafodipir [$Ca_4Mn(DPDP)_5$] has even superior therapeutic properties [5].

MEMRI of the heart is a good example of one of the few promising molecular imaging methods, because the same manganese-based compound can be used for diagnostics and treatment of, e.g., myocardial infarctions, cancer, and drug intoxication – it has *theragnostic properties* –, is inexpensive, and addresses a mass market.

■ It's not only a reshuffle of the card deck; some of the players will leave the card table and will be replaced by others. Small start-ups seem to liaise with distributors without an R&D department of their own, whereas the former big players seem to adopt a *wait and see* attitude.

*** Addendum:** On 10 March 2017, EMA, the European Medicines Agency recommended the suspension of the marketing authorisations of gadoversetamide (Optimark), gadodiamide (Omniscan) and gadopentetic acid (Magnevist, et al.), as well as gadobenic acid (MultiHance).

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Gadolinium contrast: A farewell to well-known brands

Peter A. Rinck

Nearly 30 years after it was pointed out for the first time at a scientific conference that linear gadolinium-based contrast agents could become unstable *in vivo* and release free gadolinium [1], the long-awaited assessment of the European Medicines Agency (EMA) on gadolinium-based MR contrast agents was published at the end of last week. Expected last November, it came on 10 March [2], and the outcome was slightly different than foreseen by scientists working in the field.

The decision was made and published only some days after one of the major pharmaceutical players in the gadolinium contrast agents market introduced a replacement of their disputed gadolinium contrast agent at ECR 2017 in Vienna. It is a generic that was originally developed and introduced in 1989 by a French company ... "*Honi soit qui mal y pense* – A scoundrel, who thinks badly of it."

At that time, the better binding of the gadolinium ion to the transporting chelate, i.e., the higher complex stability, was attacked as a marketing trick by the competition. Well, it was not. Once again, the transience and volatility of sales and marketing promises became very clear and upsetting. It should be embarrassing to the manufacturer(s), but they can count on the fast-moving radiological consumer market. The slogans of yesteryear to divert attention away from the company leaders' fundamentally wrong assessments are rapidly forgotten by the radiological consumers.

The slogans of yesteryear to divert attention away from the company leaders' fundamentally wrong assessments are rapidly forgotten by the radiological consumers.

It was clear that the misused and abused compounds with severe late adverse effects (nephrogenic systemic fibrosis, NSF) would have to be removed from the market; they were already tagged for withdrawal by the EMA in July 2010, described as "high risk." They included gadodiamide (Omniscan), gadopentetic acid (for instance, Magnevist, Magnegita, and Gado-MRT-ratiopharm), and gadoversetamide (Optimark).

Up to this point, the EMA recommendations are easy to understand. However, the handling of medium-risk compounds is difficult to fathom. Medium-risk compounds include gadofosveset (Vasovist, Ablavar), gadoxetic acid (Primovist, Eovist), and gadobenic acid (MultiHance), of which gadofosveset is not on the market any more.

Gadobenic acid as well as gadoxetic acid are excreted by both the kidneys and the liver, although the percentage of liver excretion is far higher for gadoxetic acid. Still, gadobenic acid is the best enhancing contrast agent on the market. As far as I am aware, there were no direct cases of NSF with gadobenic acid, but there were a small number of "confounding" cases with combinations of gadodiamide. There is no scientific or statistically based reason to damn gadobenic acid and to promote gadoxetic acid for liver examinations, as EMA has now done.

The delay in the EMA's decision and the noncommittal verdict punishes all manufacturers, though some are given an unnecessary little piece of chocolate. It does not shed a complimentary light upon EMA. EMA's suspension, described as a "precautionary approach," is a balancing act, locking the stable door after the horse has bolted, and, at the same time, trying to keep all doors open by stating:

"For those marketing authorizations recommended for suspension, the suspensions can be lifted if the respective companies provide evidence of new benefits in an identified patient group that outweigh its risks or show that their product (modified or not) does not release gadolinium significantly (dechelation) or lead to its retention in tissues."

As Paracelsus stated: "Solely the dose determines that a thing is not a poison." It stands to reason that if the radiologists using the compounds and the companies pushing off-label use at high dose would have

adhered to the recommended dose, much misery could have been prevented.

Perhaps EMA or its predecessors should have made a more thorough and probing evaluation 30 years ago. Or were the authorities and the industry too closely related?

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Spreading the news: Science and the media

Peter A. Rinck

Last year I wrote about my worries concerning the reports on scientific research published by the lay media – even by those commonly considered serious and reliable [1]. As an example, I chose the articles of two science writers in German dailies about side effects of gadolinium contrast agents. They were mixing facts and opinion in a simplistic way and making sweeping judgments.

Even for well-respected publications, facts in science or research often are of less interest than a good story. Cautiously phrased sentences summarizing the contents of "the latest scientific paper" seem not to attract readers.

The concoction of selected facts, wishful thinking, and opinion as well as negative sensationalism sells; bad news can be good news for publishers.

This can be expected from newspapers and TV, or internet media known for and dedicated to yellow journalism, but not from the leading authoritative publications.

A good tale trumps facts – one only needs an irresistible headline.

A good tale trumps facts – one only needs an irresistible headline.

It is sad when trailblazing scientific research is being distorted in this way. However, it is a far more serious issue when faulty research results are taken up by the media in a sensationalist manner, and ends up having harmful, even catastrophic consequences, for patients and the general public, possibly creating a long-lasting negative effect on medical care [2, 3].

Some science journalists have a scientific background, but this does not mean they necessarily can cover science and research for the media -- they need good writing skills and they have to be able to write in an easily understandable, uncomplicated way, be precise, and be good communicators of scientific studies and results to a large public. Few scientists or researchers without a solid journalistic background have this ability.

What makes a good journalist?

Good science journalists possess a broad mind, are good readers and listeners, and know their target audience. They do not rely barely on press releases, but verify facts, vet sources (even if they must read complete scientific papers), have the capability to see through planted stories and possible commercial or political goals, and avoid people who try to steer stories in one direction.

Thus, as outsiders, good science journalists can be more suited to uncover scientific fraud than the scientific community.

The methods of such scams are rather effective. I didn't want to use a recent example – so as not to step on the toes of people whom we meet at conferences and society meetings of our time. Let's pick a well-known 40-year-old example: the scam of Dr. Raymond Damadian's tumor detection machine.

On 21 July 1977, Lawrence K. Altman of the *New York Times* wrote:

"A New York City medical researcher announced yesterday at a news conference that he had developed 'a new technique for the nonsurgical detection of cancer anywhere in the human body.' ... after repeated questioning, Dr. Damadian said that he retracted as "not accurate" the contention that his device had diagnosed cancer anywhere in the body. …

"The manner of Dr. Damadian's announcement was rather unusual. Ordinarily, researchers report their findings at a medical conference or through scientific journal articles. Sometimes, a medical center and its researchers hold a news conference in conjunction with publication of a journal article. …

"Dr. Damadian took the unusual step of retaining [a] public relations and advertising firm which chartered a bus to bring representatives of the news media and financial institutions to Downstate Medical Center from New York [4]."

In another article in the *New York Times*, Grant Fjermedal pointed out major discrepancies between what Damadian claimed and what he had actually accomplished, "discrepancies sufficient to make him appear a fool if not a fraud [5]."

Good public relations

Negative media evaluations can still be good public relations as this famous "radiological" example for the involvement of the press and the spread of fraudulent research revealed. Scientific offenders are not necessarily cast out. Professional societies try to avoid controversies, not exposing colleagues or even friends – nor people or companies with a strong political or financial influence. The truth is being "balanced."

Damadian became famous and rich because he repeated over and over again what outstanding scientific contributions he had made – but through platforms he created and channels he controlled and partly owned. He avoided responsible media.

Commonly, the blame is put on journalists and publishers, the Murdochs of our time. Irresponsible science writing can be caused by scientific illiteracy or a lack of appropriate experience in journalists and, of course, by the newspaper publishers' understandable interest in selling their product; there are also scientific journal publishers and editors who are immodestly greedy.

There is no easy solution. The blame for misleading the public should be shouldered equally by journalists, scientists, journal editors, and research institutions. Usually the topic is swept aside. However, for some months "fake news" and "alternative truths" are the talk of the press and state administrations. It's nothing new; basically, lies and disinformation are as old as mankind.

Recognizing and fighting them is important – in particular in medicine and radiology. They have to be brought up and discussed already at medical school to expose students to the actual spectrum of medical life beyond daily hospital routine. We need analytical and critical radiologists.

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English in medicine and science – Or: English in the post-Brexit world

Peter A. Rinck

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For many people, perhaps for most who read this column, English is not their mother tongue, in other words, their first language. English is not my first language – nor my second which was Latin; English is my third language. Since I spent many years in different countries, English took over: I wrote scientific articles and books mostly in English, very few are in German or other languages.

The option of a scientific community in favor of one or the other language is only seemingly free.

The option of a scientific community in favor of one or the other language is only seemingly free; some years ago I mentioned in a column:

"The late president of France, Georges Pompidou once stated: 'We must not let the idea take hold that English is the only possible instrument for industrial, economic and scientific communication.'" [1]

He was right, in Europe, it could be Russian or German; he, of course, thought of French. He also highlighted the main feature of international English: its "global" range. He distinguished between the use of a language as a communicative instrument for securing competitive advantages – economic reasons – and the use of a language as a medium for the maintenance of identity, culture, and a distinct civilization.

Nearly one fifth of the population of the European Union speaks German as their first language. English, French, and Italian as first languages are only spoken by some 16% each. However, 47% of EU citizens claim that they speak or can speak English, 31% of them as a foreign language. Very few are able to chat away in French, Italian, German, or Russian as their third or fourth language.

Yet, there is a kind of grass-roots movement critically reflecting the use of English as a language of science – but not of business. Some of the foes of English as the universal language stress that the ubiquity of English ensures Anglo-American superiority around the world, and it is difficult to refute this argument. Although British impact is limited, US-American economic and political influence is strong.

However, the "international" or "global" English spoken abroad has lost a clear cultural identity; it has established itself as a globalized language without a distinct cultural background. Thus, the current discussion about linguistic diversity is also a sign of the globalization debate.

But is the everyday radiological world a global village? Or does the dictate to have to use English lead to cognitive impoverishment and a loss of medical identity and independence?

If you want to dance on an international stage – give talks, publish papers, apply for grants – there is no getting around English. However, teaching is more successfully done in the national languages because it allows a better understanding of contents and distinction of subtleties of a topic.

The same question holds for scientific publications. The expression of nuances is far easier in one's own language … the "radiological" or "medical" English turns into a code of limited vocabulary and stilted and artificial phrases, not only in writing, but also as spoken English. This kind of English is a relative of British, North American, South African, and Indian English, but to many "native" English speakers scientific English is a foreign language they don't understand.

On the other hand, we used to invite "native speakers" to lecture at conferences only when they spoke clear English; an English tainted by dialects from, e.g., Yorkshire, Arkansas, or India was counterproductive for conference participants with English as a second language. The best teachers were those who spoke English as a second language well and taught with a pedagogical drive. They were under-

stood by most participants who had English as a second language and there were less verbal misunderstandings. On the other hand, native speakers had comprehension problems.

Scientific or global English is distinct from such a personal, individual language: it is the global tool for business, international health care and sales – and the natural sciences. What is essential for the natural sciences and medicine, is not necessarily applicable for the humanities which live and blossom beautifully in other languages than English. For the time being, international English will remain the global business and science language. It is a simple language that can easily be used to communicate with one another and for which there is no imminent replacement.

I have experienced radiologists from the French-speaking part of Belgium talk to their colleagues from the Flemish-speaking part in English. The same holds for Switzerland. German speakers talk in English to their counterparts from Geneva or Lausanne. However, English will stay or become a second or third tier scientific or medical language in regions of the world where huge populations speak a single language of their own, e.g., in Latin America or China. Those who want to sell or teach here need to speak the local language.

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When radiologists can be useful …

Peter A. Rinck

This is a short but true story from the capital city of a good-sized country. Somewhere on the outskirts of this city, there lives a family with two little children, a boy and a girl. They have a huge garden to play in, and a two-seater electric toy car. Usually the girl drives – because she is a year older.

Some weeks ago, the boy started coughing and his nose was running. When after two days the cough hadn't disappeared, the parents took him to emergency at the next hospital.

There, the staff took an x-ray. The emergency doctor saw "a small shadow", but she told the parents that this was of no importance:

"It's a cold. After some days it will be gone."

The parents took the boy and a copy of the x-ray, and went home.

The boy continued coughing, as boys do every so often.

When after two days the cough had not disappeared the parents made a mistake. They wanted the best for their little boy; in this case they wanted the best pulmonologist in the country. They checked the list of "best doctors" and found a highly recommended expert professor; he even had a private office in their city, and they got an appointment for the next day.

They should come back in some days for further examinations: a CT, an MRI, and perhaps a biopsy.

The pulmonologist looked at the boy, then at the x-ray, and stated that most likely the boy had a lung tumor. They should come back in some days for further examinations: a CT, an MRI, and perhaps a biopsy.

The next days were pure hell for the parents. The nagging thought was that the little boy suffered from an incurable cancer; it wrecked all their hopes and plans for the family.

By the end of the week the mother met a former neighbor, a retired female radiologist, at the supermarket. Crying, she told her the story of the little boy. The radiologist said:

"That sounds strange to me. Lung cancer is extremely uncommon in children."

She accompanied the mother home and looked at the x-ray:

"That's not a tumor. That's the thymus. The child has a cold, and the x-ray is normal."

She explained to the parents what a thymus is and, that because of its variability in shape, the interpretation of x-rays of young children requires years of experience. She didn't answer the question why the pulmonologist didn't come up with the correct diagnosis.

The cough receded after some days by itself. The parents slept well again, a heavy load taken from their minds. Perhaps they have learnt a lesson. The retired radiologist was happy she could help.

This story could be a fable like Aesop's; it's a tale that contains a message. However, I am not Aesop and you have to draw your own conclusions.

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Contrast agent safety – a short and critical approach

Peter A. Rinck

Safety is one of the main factors in the development of a new contrast agent. Of course, the main goals are the improvement of tissue contrast and characterization and overall diagnostic sensitivity and specificity. But you always have to take into account biodistribution, tolerance, stability, elimination, metabolism and toxicity. Still, at the end of the process, there is no absolutely safe contrast agent.

In July, the European Medicines Agency (EMA) confirmed the restrictions on some linear gadolinium agents and the suspension of the authorizations of others. This is due to the occurrence of Nephrogenic Systemic Fibrosis (NSF) some years ago and followed the findings that gadolinium depositions were found in brain tissue although there is no evidence that gadolinium in the brain causes any harm or remains there forever.

What could it cause? Dementia? If you check the literature, gadolinium is not mentioned, aluminium is – as well as magnetic fields: "There is at least moderate evidence implicating the following risk factors [for dementia]: air pollution; aluminium; silicon; selenium; pesticides; vitamin D deficiency; and electric and magnetic fields."[1] Choose whatever pleases you.

Even with all NSF cases considered and included, the overall incidence of adverse reactions with MR contrast agents is approximately 0.2% and they are mostly mild; the risk of death is lower than one case in one million patients. On the other hand, the overall incidence of adverse reactions with iodinated x-ray contrast agents is between 3% and 15%; again, these are mostly mild reactions; yet the risk of death is estimated with ten in one million patients.

Concerning the incorporation of components of contrast agents, x-ray agents are also on place one. Just to mention one complication: There are numerous reports and scientific papers about the incorporation of iodine into thyroid glands of adult and infant/children patients [2, 3]. Iodinated contrast media application increases the risk of thyroid dysfunction in pediatric patients. It is recommended that those at risk of developing iodine-induced thyroid symptoms should be closely monitored after receiving iodinated contrast media. In infants, the deposit of huge doses of iodine in the thyroid might lead to disturbances in brain development.

The overall risk of death after injection of MR contrast agents is lower than one case in one million patients – that one of iodinated x-ray contrast agents ten in one million patients.

What is the optimum strategy?

The best safety approach towards contrast agents is – as with all drugs – not to use them. One should think at least twice whether contrast agents (or different drugs) are of advantage for the patient in a particular case where you want to use them and, if so, apply them at the given doses and recommendations.

NSF is an iatrogenic disease and seems to have disappeared after the users obeyed the recommended rules. However, hysteria has been whipped up by hundreds of irrelevant and incompetent papers and articles. Only few physicians dealing with the MR contrast agent topic behaved reasonably and took a realistic approach to the problem.

In the meantime, the whole disaster has been cleaned up although a lot of dirt has just been swept under the carpet and stays hidden there.

However, let's face it: there won't be any way around gadolinium-based contrast agents in MR diagnostics in the near future. At present, there is no replacement by a different class of unspecific, global contrast agents for the wide range of indications gadolinium-containing agents are needed for.

Moreover, nearly all superparamagnetic iron oxides both for intravenous and for oral use have disap-

peared from the market; they were withdrawn or, after the preclinical stage, never launched.

The seemingly only contrast agent of this kind still in clinical evaluation is ferumoxtran-10. It is claimed to detect early-stage cancer metastases in lymph nodes in patients with progressive prostate cancer [4]. Apparently a German company will try to bring ferumoxtran-10 back the Central European markets; the same company seems to also move into marketing a manganese compound. However, both already approved agents are aimed at niche applications.

Lessons of the debacle

In an earlier column I asked: "Gadolinium – will anybody learn from the debacle?" The answer is: Apparently not.

Gadolinium contrast agents were used off-label for high-dose MR angiography, which basically caused the NSF disaster [5]. Nowadays, there is a subtle suggestion moving around to use ferumoxytol for MR lymphography. Ferumoxytol is an iron replacement product for patients with anemia.

Of course, physicians are allowed a certain leeway to employ techniques and pharmaceuticals "off label" without approval of the health authorites, but as I wrote in an earlier column about gadolinium agents: "It stands to reason that if the radiologists using the compounds and the companies pushing off-label use at high dose would have adhered to the recommended dose, much misery could have been prevented."

The U.S. Food and Drug Administration (FDA) has already acted preventively and strengthened an existing warning that serious, potentially fatal allergic reactions can occur with the anemia drug Feraheme (ferumoxytol) [6]:

"We have changed the prescribing instructions and approved a Boxed Warning, FDA's strongest type of warning, regarding these serious risks. Also added is a new Contraindication, a strong recommendation against use of Feraheme in patients who have had an allergic reaction to any intravenous (IV) iron replacement product. Health care professionals should follow the new recommendations in the drug label. Patients should immediately alert their health care professional or seek emergency care if they develop breathing problems, low blood pressure, lightheadedness, dizziness, swelling, a rash, or itching during or after Feraheme administration."

Of course, one can also try to make a living out of the problems: It's rumored one US-American professor of radiology has begun selling chelates like DTPA to "detox" anxious people who have undergone contrast-enhanced MR examinations and who now feel "gadolinium-toxic".

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Mapping the biological world

Peter A. Rinck

Relaxation and relaxation constants is a rather complicated topic, both to explain and to understand. There are two main relaxation constants important for MRI: T1 and T2.

T2* which is also often mentioned in this context is not a time constant, it is a capricious global parameter representing a fluctuant time or time range.

An excursion into scientific history

This is not the place to go into the science of relaxation; a textbook is better suited for this [1]. Here I will just tell a bit about the history and background of relaxation times in biomedicine.

It all began in 1953 with Eric Odeblad. He was the first to describe relaxation times in biological systems. His first paper on the topic was entitled “Some preliminary observations on the proton magnetic resonance in biological samples” and published in Acta Radiologica Stockholm in early 1955 [2].

Odeblad had found that different tissues had distinct relaxation times, most likely due to water content but also to different bindings to lipids. Soon others joined in the new research field: Studies in blood, plasma and red blood cells, followed by T1- and T2-measurements of living frog muscle, the relaxation of water in living animals and in the arms of living humans.

Research groups in Brooklyn and in Baltimore got involved in the early 1970s. They measured relaxation times of excised normal and cancerous rat tissue, and the leader of the Brooklyn group stated that tumorous tissue had longer relaxation times than normal tissue and promoted these findings as the ultimate technology to screen for cancer [3].

However, already some months later the Baltimore group stated that independent verification on the same NMR instrument could not be provided; the results were not reproducible [4].

Later, the New York Times pointed out major discrepancies between what was claimed by the researchers from Brooklyn and what was actually accomplished, "discrepancies sufficient to make the author [Raymond Damadian] appear a fool if not a fraud." [5]

The summary of a paper published in 1975 – 42 years ago – by the group of Donald Hollis stated [6]:

“The direct use of NMR T1 measurements for cancer diagnosis is clearly not feasible because of the lack of specificity … classification of tumors in this manner does not seem realistic.”

Shortly afterwards clinical MR imaging arrived and relaxation time measurements were considered very important during its first years. All machines were programmed to create true T1 and T2 images (T1- and T2-mapping), based on reliable and reproducible spin-echo (SE) and inversion-recovery (IR) sequences.

After absolute T1 and T2 values had been used unsuccessfully by researchers, combinations of T1 and T2, histogram techniques, and sophisticated three dimensional display techniques of factor representations were used. At that time, these approaches were called ‘electronic contrast agents’, today ‘fingerprinting’ or ‘biomarkers’.

However, soon it became clear that relaxation time values were not the claimed invaluable addition to diagnostics, and these applications were skipped in the early 1990s.

“A spin-echo sequence with 24 echoes (Carr-Purcell-Meiboom-Gill sequence) was evaluated to determine the usefulness of magnetic resonance (MR) in detecting and typing brain tumors. ... T2 values calculated from an eight-point fit, however, did not allow discrimination of different tumors, nor did they allow differentiation between tumor, inflammatory tissue, and demyelination.” [7]

It was the time when the *Relaxation Times Blues* arrived [8], and Ian Young, one of the leading and influential scientists in MRI summed up the trials and errors in a short history of MRI as follows:

"Sadly, the many attempts that were made to correlate pathology and relaxation behavior have yielded none of the precise numerical relationships that were hoped for in the early days of MRI, so that this line of investigation ... has now been abandoned." [9]

A grant-creating perpetuum mobile?

It is rare that a method appears, disappears, and then re-appears again as is the case of tissue characterization based on relaxation time constants. Yet some years later these obsolete methods were dug out again, grants were given to answer questions which had been discarded 25 years earlier [10, 11]. New pulse sequences and algorithms were developed – researchers tried their luck again.

Still, there is no easily explainable causality nor any evidence of a straight connection between these numbers and a distinct pathology. There is no unique signature of distinct malignancies or other pathologies in tissue relaxation times, be it in ex vivo or in vivo measurements. Many people believe that numbers (or, more fashionable, data) are the truth but they do not understand how the numbers were acquired and what they stand for. Nature doesn't care about numbers. Believing in such postulations many years after they have been dismissed is a sign of scientific naiveté.

What's wrong in relaxation time mapping and applications: the precondition and presumption that a difficult biological structure such as a tissue or tissue changes in the human body can be quantified and qualified with NMR proton relaxation parameters.

Quantity and quality are being confused; it's so easy counting something – which doesn't mean that one can classify or characterize with numbers what one counts. The components and chemical and electrical processes in a tiny volume element, no matter how small it is, are far too complex and fickle to be expressed in bare figures. More so, on closer inspection, "objective" procedures, "objectively" defined range values as well as "objective" quality indicators for measurements often prove to be biased and interest-driven. There is no precise numerical fingerprinting based on relaxation constants in biomedicine.

It is helpful to once look into a microscope and to see how complex and complicated tissue structures are, both in normal and in pathological tissues – and in not-normal, but not (yet) pathological tissues.

In the end, it is not necessarily the errors or procedural "confounders" connected to the most elaborate and sophisticated data acquisition that make typing of normal and pathological tissues or grading of diseases impossible – but rather the complexity of tissue composition and the overlapping of relaxation time values of heterogeneous volume elements examined and processed into a single number or number range.

Nowadays lessons are rediscovered that became clear 25 years ago … and finally admitted, though diplomatically beating around the bush:

"In conclusion, our question, whether native T1 mapping in cardiac MR imaging can differentiate between healthy and diffuse diseased myocardium, must be answered with 'yes' and 'no', since the native myocardial T1 relaxation time allows discriminating between groups of patients with certain diffuse myocardial pathologies and a group of healthy individuals, but does not allow differencing between healthy and diffuse diseased myocardium in individual subjects." [12]

Researchers also came to realize that novel methods for faster data acquisition deliver crude estimations but not accurate data. The higher the magnetic field, the larger seems to be the spread of T1 and T2 relaxation time estimations.

"A vast extent of methods and sequences has been developed to calculate the T1 and T2 relaxation times of different tissues in diverse centers. Surprisingly, a wide range of values has been reported for similar tissues (e.g. T1 of white matter from 699 to 1735 ms and T2 of fat from 41 to 371 ms), and the true values that represent each specific tissue are still unclear, which have deterred their common use in clinical diagnostic imaging." [13]

Exceptions from the rule

Few isolated cases allow tissue discrimination based on relaxation time alterations, but they are the exception. One needs massive changes of relaxation time constants, as well as large homogeneously altered volumes to be able to use such data for diagnostic purposes.

The data you get is not fake, it is not necessarily false, no, worse: it's half-true.

Does this mean that relaxation time maps cannot be used at all? Here are some insights into my own experiences:

We started creating maps of relaxation constants and proton density as well as derivatives of these maps, called “synthetic images”, in the early 1980s and presented the idea of synthetic MR images and simulating entire MR exams in the early 1980s at a conference in the United States. In 1994 we finally published the image simulation software MR Image Expert for teaching and research purposes. More than 12,000 copies of MR Image Expert were licensed since then.

The simulations were based on the three main contrast parameters in MRI: T1, T2, and proton density acquired with time-consuming, but precise data acquisitions and exact calculations – with “clean” basic pulse sequences: inversion recovery and spin echo. For a reliable T1 determination one needs between 15 and 30 IR measurements, for T2 we usually used 24 echoes of a SE echo train. They allowed the creation of outstandingly good simulations of MR images – but still simulations.

In general, from a scientific point of view, MR imaging is a crude and not very exact technology. Thus, in most cases, relaxation time mapping and derivatives of it – such as synthetic images – cannot be used to quantify exact tissue data (e.g., relaxation constants or proton density in tissues) since the calculated or estimated relaxation constants and proton density values are unreliable – and impracticable in diagnostic routine; they are not accurate and not conclusive.

The only way to exploit relaxation time values would be situations when the values change drastically under specific physiological or pathological circumstances. This can be the case before and after the application of an MR contrast agent. There are uses for such rough estimations.

An area of application of relaxation times measurements might be the follow-up of massive T1 changes after the injection of a targeted contrast agent, such as Mn-DPDP and the comparison of plain and contrast-enhanced tissue, e.g., in heart diseases. Here imprecise measurements might be of diagnostic value. However, such indications are limited because increasingly different and simpler MR techniques exist that may lead to the wanted result.

In one of the next columns I will try to discuss the non-scientific and non-medical reasons why these measurements returned and why they will stay with us for some time.

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