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BAMRR news

THE NEWSLETTER OF
THE BRITISH ASSOCIATION OF MR RADIOGRAPHERS

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IN THIS ISSUE:

welcome

from your BAMRR PRESIDENT

Hello and welcome to the Winter 2016 BAMRR Newsletter. The volunteer team on the Policy board at BAMRR pride themselves in communicating, educating and informing the MRI Radiographers community in the UK, and the Newsletter serves as a great media to convey MRI safety updates, tips and tricks in scanning and of course providing CPD and educational material for you to enjoy and reflect on.

2016 has been a busy year for MRI as the EUPAD has come into effect. Prof Stephen Keevil Consultant Physicist and Professor of Medical Physics from King's College London, gave an engaging lecture on **"The Physical Agents (EMF) Directive is now law"** at the Cardiff Conference this October. He has kindly agreed to write a piece for the Newsletter.

As a result of the EMF Directive, MRI units need to complete the risk grading and risk reduction. It is recommended that the MR Responsible Person undertakes this task, supported by the MR Safety Expert. The links to the EMF **Risk Assessments** can be found on the BAMRR Website.

BAMRR have also been involved in the **e-learning module** for MRI safety as part of a working party in collaboration with Health Education England's e-Learning for Healthcare (HEE e-LfH) programme and with the support of other professional bodies and organisations across the UK (SCoR, MRAG, IPEM, MHRA, BIR MR SIG, RCR, HFS, AAGBI and ISMRM). A live link was emailed to the members to evaluate a test module and your feedback was gratefully received. This should help shape the future module structure and content. An important step on setting an good standard for a reproducible and robust MRI safety training program going forward.

SCoR and BAMRR has published an update **"Safety Guidelines to MRI 2016"** which can be found on both institutes websites and is useful to increase awareness and reiterate safety issues which are uniquely associated with MRI and offers practical advice for the development of an MR Safety Framework. It is designed to be a practical reference guide and pointer.

It is with great pleasure that I welcome new members to the BAMRR team from all around the UK, we have Zoe Lingham joining from Cardiff, Jonathan Coupland from Nottingham and Lisa McBain from Hull.

Finally, an overview for 2017 and the New Year to come. The Introduction to MRI Courses dates and venue will be announced in January on the website, UKRC is in Manchester in 2017 and BAMMR session will be Weds 14th June. The Annual BAMRR Conference will be held in Scotland on Oct 7th and we are hoping to announce a Conference Evening Event for the delegates to enjoy a warm Scottish welcome. Come join us in Glasgow 2017 and be part of something special.

We look forward to meeting you there.

Paola Griffiths
BAMRR President

from your EDITOR

Hello all.

Once again I have been busy compiling this edition BAMRR News, which I hope you will enjoy reading. BAMRR News is a great option for writing your first article and I have a couple of first time authors in this edition. Therefore if you believe that you also have something you think you could contribute, please get in contact with me - there may even be a small reward in it for you. I will happily receive any suitable content including case studies, reports on your study days, interesting work that you are doing locally or safety issues that you have come across that others might find interesting.

We really want the BAMRR News content to be inclusive and compiled by as many members as possible. I have not received any letters to print this time so please also remember that if you have anything to get off your chest, why not send it to me so we can share it with other readers. After another successful BAMRR conference in October, this time in Cardiff, we look forward very much to next year moving to Glasgow and I hope to see you all there.

Matthew Benbow
BAMRR Editor

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WELCOME from our sponsor GUERBET

Have a great 2017!

Welcome to the first edition of BAMRR News in 2017. We do hope you had an enjoyable break and are ready to start 2017 on a high.

With some exciting education event planned throughout the year we continue with our commitment to supporting CPD for MR radiographers. As always these will be organised together with radiologists and radiographers who are passionate about sharing their knowledge.

Please visit our website **www.guerbet.co.uk** to find out more about the events we hold or sponsor. Do not hesitate to get in touch on **0121 733 8542** or **uk.info@guerbet-group.com**

if there is something you would like to tell us. As always, we welcome your comments and suggestions as we are here because of you.

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34th Annual BAMRR CONFERENCE

Saturday 7th October 2017

Golden Jubilee Conference Hotel, Beardmore, Glasgow

Details on the website to follow soon http://www.bamrr.org

BAMRR Policy Board Members, Winter 2017

The co-ordination of the Associations activities is overseen and undertaken by an elected Policy Board. BAMRR consists of up to 11 individuals who are full members of BAMRR and are working in different regions of the UK

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BAMRR Conference October 2016

Marriott Hotel in Cardiff

Busy Sponsors Area

Happy faces at registration

Poster display

Yet another successful BAMRR conference was held on Saturday 1st October 2016 in the Marriott Hotel in Cardiff.

This was an excellent venue for the 33rd annual conference and AGM

A full day of informative lectures kept the 80 delegates well engrossed and the sponsors' stands offered a wide variety of opportunities to gain more information.

This was made possible by our most generous sponsors, whose support added to the success of this event.

Platinum	Gold	Silver	Bronze
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After welcoming delegates, speakers and sponsors, Jill McKenna (BAMRR President) introduced the three speakers who were talking before the morning coffee break;

Dr Geoff Charles Edwards (Principal Clinical Scientist, Guys & St Thomas' Hospital, London), Professor Steve Keevil (Head of MRI Physics, Guys & St Thomas' Hospital, London) and Dr John Morlese (Consultant Radiologist, Leicester Royal Infirmary)

Dr Charles-Edwards explained the importance of understanding MRI Conditional safety statements and talked the audience through a risk benefit analysis algorithm and a strategy for scanning patients with conditional implants.

Professor Keevil brought all present up to speed with the EU-PAD regulations, which included the requirements for documenting staff induction / training and having specific risk assessments in place.

Dr Morlese's return as a speaker was welcomed by all and his lecture on the retention of gadolinium in the brain was exceedingly thought provoking, resulting in lots of questions from the audience.

During the coffee break, the delegates enjoyed a chance to network, speak to the stand holders from a wide range of companies associated with MRI and view the posters.

This year there were three excelled posters submitted:

1) Carlos Romero (MRI Radiographer NHS Grampian, Aberdeen) whose poster illustrated the 'Use of DWI in Prostate imaging',

2) Aishling Ryan (Student Radiographer, UWE Bristol) & Janice St. John-Matthews (Associate Head of Department, UWE Bristol), whose poster was titled 'Diagnostic Imaging in Crohn's Disease: The Role of Cross-Sectional Imaging'

3) Jack Lannie (Student Radiographer, UWE Bristol) & Janice St. John-Matthews (Associate Head of Department, UWE Bristol), submitted the winning poster- 'The role of Magnetic Resonance Imaging in the diagnosis and management of patients with clinically suspected scaphoid fractures', gaining him the £ 150 prize money.

Feeling refreshed after coffee the audience settled down to listen to two further lectures and a proffered paper before the BAMRR AGM.

Will McGuire (Deputy Superintendent Radiographer from Paul Strickland Mount Vernon Hospital) shared his tips for optimising whole body MRI examinations and presented some interesting case studies.

Matthew Benbow (CT/MRI Superintendent Radiographer, Royal Bournemouth Hospital) and BAMRR Policy Board member did not fail to entertain the delegates with his effervescent explanation of how he established a service to improve the care of stroke patients using his Fast Brain Protocol.

Janice St-John Matthews (Associate Head of Department, UWE Bristol) closed the morning session with her proffered paper entitled #SoMe: Fun, Free and Fabulous MRI CPD, which highlighted the uses of social media for recording CPD activities. This paper resulted in her winning the Proffered paper prize of $300, which she kindly donated to a personal charity.

This was followed by the BAMRR AGM, where the membership secretary and treasurer gave an update on the membership and financial status of the organisation, before everyone enjoyed a beautiful lunch in the Zest restaurant.

The afternoon session commenced with the new BAMRR President Paola Griffiths introducing the first speaker, Patricia Feuchter (Operational Lead Cross-Sectional Radiographer, St Bartholomew's Hospital London) whose presentation was entitled 'Cardiac MRI Top Tips" .

Patricia explained why we do CMR and gave some common indications, which were reinforced by sharing relevant case studies.

This was followed by Chris Alvey (Senior Lecturer in Diagnostic Imaging, University of Derby) whose interactive session involved audience participation in an opinion poll by means of an app on their mobile phones.

Prof Rhodri Evans (Head and Neck Radiologist, Swansea University) gave an excellent synopsis on head and neck MRI, with an overview of anatomy and highlighted the importance of the selection of appropriate sequences in relation to patient management.

The afternoon's proceedings were brought to a close by Dr Miaad Al Attar (Consultant Radiologist, Leicester Royal Infirmary) whose presentation titled ""Breast Family History MRI"" covered the requirements of running such a service.

Work is already underway for our 2017 projects, the BAMRR session at UKRC (June 9th Liverpool) and the 34th annual BAMRR conference in Glasgow (Sat 7th October)

Hope to see you there....

Ready to begin....

Incoming and Outgoing Presidents, Paola Griffiths and Jill McKenna

Janice St. John-Matthews from the University of the West of England accepts the poster prize on behalf of Student Radiographer Jack Lannie. 'You can read this poster on page 15 of this journal'

The Physical Agents (EMF) Directive is now law: is it time to panic?

Stephen Keevil

Having been involved with the EMF Directive for the past 13 years, it was a pleasure to be invited to speak on this topic at the BAMRR Annual Conference following implementation of the directive in the UK on 1st July (or 1st August in Northern Ireland).

The short answer to the question posed in my title is 'no'. Following successful negotiations in Brussels, and sensible and proportionate implementation in the UK by the Health and Safety Executive, the directive should have very little impact on clinical and research MRI facilities: some initial work perhaps to check that risk assessments are in place and that training covers the required ground, but there should be essentially no impact on day to day activities.

Readers will probably be aware that the original Physical Agents (EMF) Directive 2004 posed considerable challenges because it contained mandatory occupational EMF exposure limits that would have been exceeded in a range of situations in MRI. Following a long process of lobbying and negotiation, this was replaced with a new directive in 2013 which has less stringent exposure limits and also an exemption for many MRI activities, subject to meeting certain conditions.

The directive has been implemented in Great Britain as the Control of EMF at Work (CEMFAW) Regulations 2016 (there are essentially identical regulations in Northern Ireland). The really keen can read the regulations at http://www.legislation.gov.uk/uksi/2016/588/pdfs/uksi_20160588_en.pdf, but unsurprisingly they are couched in legal language and need interpretation. Guidance is available from the HSE at http://www.hse.gov.uk/pubns/priced/hsg281.pdf, but is very generic: reading this on its own could give an exaggerated view of what needs to be done in the context of MRI. There is also Europe-wide guidance at http://ec.europa.eu/social/main.jsp?catId=738&langId=en&pubId=7845&type=2&furtherPubs=yes, which does deal with MRI specifically but does not take account of the particularly helpful way in which the HSE has worded the CEMFAW regulations. Sector-specific guidance is needed for the MRI community in the UK. A brief paper on this topic has been submitted to the British Journal of Radiology and is currently under review. HSE has seen this paper and has agreed that the approach described (which was the same as the approach taken in my talk in Cardiff and in this brief summary) is consistent with the approach they have taken in the CEMFAW regulations. More detailed guidance from all of the relevant professional bodies is expected in due course.

I want to make one important point here, which is that having been implemented in UK law, the CEMFAW regulations are unaffected by Brexit! They will remain in force once the UK leaves the EU, until such time as Parliament repeals or amends them. They do contain some references to the EU which presumably will need to change, but this is unlikely to be the government's first priority post-Brexit!

In implementing the directive, the HSE has stripped out requirements that are already contained in existing legislation and greatly simplified the complex structure and language of the directive. The result is a set of regulation that are much easier to understand and less onerous to manage, although as I have said they do need careful interpretation in the context at MRI and we are seeking to provide this at national level so as to avoid duplication of effort.

By taking advantage of additional powers that the directive gives to member states, the HSE has exempted all uses of MRI from the exposure limits in the directive. This is good news, as the text of the directive itself left some grey areas, particularly in research, and some areas that were definitely not included in the exemption such as veterinary uses of MRI. The exemption is subject to two conditions: (i) that exposures are kept as low as is reasonably practicable, and (ii) that workers are protected from health and safety risks. Condition (ii) is something we are hopefully all doing anyway, by means of things like appropriate safety training, good design of MRI facilities, access control and screening, and appointment of suitable people as MR Responsible Persons and MR Safety Experts. Condition (i) is capable of over-interpretation, given the use of similar terminology in relation to ionising radiation, but in the context of MRI I think simply means training staff to avoid the physiological effects that can occur (e.g. some people report nausea when moving the head rapidly close to a 3 T magnet). So as long as we already have good working practices in place, there should be no problem demonstrating compliance with these conditions.

The regulations are not just about exposure limits though. There is also a requirement to assess EMF exposure and the resulting risk. The emphasis is on assessment: because of the exemptions that exist for MRI there is no need to measure or model exposure. It should be sufficient to refer to published material (such as the forthcoming BJR paper and references therein). Risk assessments are a requirement of existing legislation, and should have been in place for the past 15 years (not because we are working in MRI, but because risk assessments are legally required for all risks in the workplace). Realising that some centres may have overlooked this, and that existing risk assessments may need to be reviewed to ensure that they cover the requirements of the CEMFAW regulations, the British Institute of Radiology (BIR) has published a set of generic risk assessments, covering a range of MRI-related risks, not just occupational EMF exposure. They also cover the ground needed for exposure assessment and demonstrating compliance with the conditions attached to exemption from the exposure limits. They can be found online at http://www.bir.org.uk/professional-resources/special-interest-groups/bir-magnetic-resonance/emf-risk-assessments/. They will of course need to be adapted to suit local circumstances and documentation. The HSE has agreed that these risk assessments are consistent with the approach taken in the regulations. There is also a requirement to provide staff with appropriate information and training, which again we are hopefully all doing already but may wish to review to ensure that the appropriate ground is covered. Finally, workers who experience health effects due to EMF exposure in MRI are entitled to medical examination, which could easily be delivered through occupational health services in the unlikely event of this happening.

In summary, we have little to fear from the CEMFAW regulations, which given where we were a few years ago represents a triumph for common sense, hard work and collaborative working. Tools are becoming available to make the process even more straightforward.

I recently gave a somewhat longer version of my presentation as a BIR Webinar, which was recorded and can be viewed online at https://bir.adobeconnect.com/p8rj8mq0opj/.

Should the presence of an

MRI unsafe pacemaker ?

always be an absolute contra-indication for MR examinations?

Robert Wilson, MRI Applications Specialist, Siemens Healthineers

Most clinical sites consider the presence of a conventional (MR-Unsafe) pacemaker to be an absolute contra-indication for MR. The reasons for this are the risks related to the static magnetic field, malfunction due to RF pulsed exposure and time varying magnetic gradients heating due to induced current causing damage to myocardium. (Zikra, 2011, p390). The magnetohydrodynamic effect in MRI are the interactions between flowing charged ions in blood and the externally applied magnetic field. (Syed, 2015, p139). These interactions are a potential risk factor as they can cause changes to the patient's ECG (such as elevated T-wave and alterations to ST segments) and can simulate arrhymias causing the pacemaker to function abnormally. There have also been concerns raised over the potential deleterious effects to pacemaker battery life and function. (Ferreria, 2014).

It has been estimated that between 50 and 75% of patients with cardiac pacemakers will require an MRI in their lifetimes. (Muehling, 2014, p39). Some modern pacemakers are now MR conditional and as such are regularly taken safely into MR environments provided they are first put into a 'safe mode' and manufacturers guidance on field and gradient strengths adhered to. There are still however large numbers of patients who have conventional pacemakers which are usually precluded from any MR investigations regardless of clinical need.

A range of reported adverse events including deaths have occurred following the introduction of patients with pacemakers into the MR environment. All the events in reported literature which led to deaths occurred when the clinical site did not have knowledge of the pacemaker prior to the examination due to failures in procedure or difficulty in obtaining full clinical history (Martin, 2005, p325). No deaths have been reported in which the pacemaker was known to be present prior to the examination and a clinician was present during the procedure. (Martin, 2005, p325).

Despite these risks a growing body of evidence over the last 10 years indicates that in certain circumstances patients with conventional pacemakers can be safety examined using MRI. This article will review some of this evidence, explore the safety measures are being used to reduce risk and examine the ethical questions arising from these examinations.

Discussion

The European Society of Cardiology guidelines (Brignole, 2013) on cardiac pacing and cardiac resynchronisation therapy state that MR can be safely performed even on pacemakers which are not conditional if a strict range of safety parameters are met. Numerous specialist centres now offer an MRI service to patients with conventional pacemakers in selected circumstances (when MRI is the only suitable modality and the risks of not proceeding with the MR are potentially life threatening) and have not reported any fatalities. (Zikra, 2011, p390). A range of current peer reviewed literature will now be examined to illustrate some of the research on the safety of scanning patients with conventional pacemakers using MR.

The first piece of literature to be highlighted by this article is a prospective study of 32 patients by Naehle, et al., 2011 during which patients with conventional pacemakers received a cardiac MR scan. The study used a protocol in which the SAR heating was limited to 1.5W/kg and pacemakers were examined before and after the procedure with a 3 month follow up. Patients were excluded if alternative imaging was available, if they were pacemaker dependent or if the battery life of the pacemaker was limited. As this study found no adverse incidents it concluded that cardiac MR in the presence of conventional pacemakers can be performed safety if carefully planned and monitored. The limitations of this study included its small number of participants and the broad conclusions it reaches (that MR unsafe pacemakers can be scanned safety under certain circumstances) based on these small numbers.

A more comprehensive analysis conducted by Zikria, Machnicki, Rhim, Bhatti, and Graham, 2011 examined a range of literature regarding patients with conventional pacemakers who received MR scans. The total number of examinations in this analysis was 1,412 examinations and found no deaths or significant adverse events reported in any of the in vitro studies examined. The in vivo animal studies however found pacemakers exposed to MR sometimes paced incorrectly rapidly and lead to a dramatic decrease in arterial blood pressure along with some significant temperature increases. These in vivo studies however still found no fatalities and did not match the experience found in the human studies. The review concluded that MR unsafe pacemakers can be scanned successfully if safety conditions were adhered to and the patients being scanned were not pacemaker dependent.

A 2012 prospective study by Baher, et al (2012) was conducted on 74 consecutive patients all of which had conventional pacemakers using a 1.5T Siemens Avanto magnet to complete cardiovascular examinations. A range of tests were performed before and after the procedure including pacemaker battery and troponin T blood tests. Troponin T is a protein released following damage to heart muscle and as the levels following the MR examination were not increased the study concluded no damage to heart muscle had occurred. As with the previous studies examined in this review a range of safety procedures were utilised such as written informed consent, pre-programming of the pacemaker, monitoring before, during and after the procedure which takes conducted in the presence of a cardiologist. This prospective study concluded that MR unsafe pacemakers can be scanned when adhering to strict safety guidelines and having the appropriately trained staff ready to assist. The weaknesses of this study include that only a limited follow up of patients was undertaken and that only limited details of the checks performed on the pacemakers was included when compared to the other studies in this review.

A recent review (Van der Graaf and Gotte, 2014) focused on the safety conditions required for safe MR scanning of conventional MR pacemakers. The main findings of this review were that most centres require a 6-week interval before pacemaker implantation and MR scan, that clinicians should conduct a risk / benefit analysis prior to the scan, that due to the risk of heating and damage to the pacemaker no first level should be selected and that staff trained in resuscitation and pacemaker programming should be present. They also examined the various reported deaths attributed to the presence of pacemakers and found that the changing magnetic gradients may have produced asynchronous pacing which then induced ventricular fibrillation in these patients.

A large prospective study (Muehling and Wakili, 2014) consisting of 356 consecutive patients all of which had conventional pacemakers received MR examinations of the head. The centre performing the study used a careful selection process including that no acceptable alternative imaging was available,

cont/d..... page 10

that the pacemaker battery was not low and excluded patients with significant comorbidities who were pacemaker dependent. There was a protocol set up to check the pacemaker prior to the scan, with the pacemaker programmed to disable atrial fibrillation and tachycardia functions and to enter a full time asynchronous pacing mode which will avoid it being inhibited by the MRI. The patients were all carefully monitored during the scan in the presence of a cardiologist and following the scan pacemaker function was checked and set back to original settings. This study reported no immediate adverse events with no procedures being prematurely terminated due to clinical symptoms. Immediately following the MR the pacemakers were checked and found to have suffered no complications and significantly the study followed up with assessments of the pacemaker at 2 weeks and then at 2, 6 and 12 months assessing loss of capture, generator malfunction, resetting or battery depletion. The study concluded that no significant changes occurred to the pacemakers during this study and that with careful monitoring safe MR examinations were possible. The limitations of the study are that only cranial MR scans were performed and that only a limited 12 month follow up was completed. Despite these limitations the significant numbers of patients examined prospectively without incident and the follow-up addressing some of the concerns regarding battery issues this study is good evidence that conventional pacemakers can scanned without incident if safety guidelines are obeyed.

Nordbeck et al (2015) completed a prospective analysis of over 806 patients using 1.5T strength MR scanners and reported no major difficulties or adverse events during the study. They did find however that 3% of patients pacemakers experienced a pacing threshold increase and that in one case an electrical reset occurred which required pacemaker reprogramming. These incidents underlined the need to have personnel present capable of reprogramming the pacemaker present during the examination. The conclusion of this analysis was again that patients with MR unsafe pacemakers can be examined safety using MR provided strict safety guidelines were followed.

A review by Ferreria et al (2014) reviewed a range of topics on MR pacemaker safety including the scanning of both conventional MR unsafe pacemakers and MR safe pacemakers. This review examined many of the deaths which have been attributed to exposing conventional pacemakers to the MR environment and concluded that the numbers may have been underestimated as several legal cases had been brought on which had not been reported in the medical literature. (Ferreria et al, 2014, p120). This review noted the specific risks to conventional pacemakers of heating leading to tissue destruction, damage to the pulse generator circuitry and depletion of the pacemaker battery. This review however did not quantify any of these risks and citations for some of these only stated theoretical or animal study based risks. This review also noted that causal links to adverse events reported in medical literature were often not firmly established and generally occurred in patients with old models or without appropriate programming and monitoring of the pacemaker. (Ferriria et al, 2014, p122).

A study by Boilson et al (2012) supported the conclusion that adverse events following MR examination of conventional pacemakers usually occur in older model types. This prospective study found a small number of older devices had unpredictable programming changes following the scan but still concluded that conventional pacemakers could be scanned safely. This study stressed that careful device interrogation was post scan was essential particularly with any older modal pacemakers. The weaknesses of this study included the small numbers of participants (32) and limited follow-up following the scan.

All the articles located for this review concluded the MR unsafe pacemakers can be scanned without significant incident if careful planning is used. The following list shows some of the safety features described by different sources included in this article.

1) A consultant Cardiologist and Radiologist led risk / benefit analysis prior to the examination.
2) Agreement between consultants that MR is the only suitable modality to answer the clinical question and that the result has the potential to change patient management.
3) The exclusion of patients with significant arrthymias who are pacemaker dependent.
4) The informed written consent of the patient.
5) Limiting the static magnetic field strength to 1.5T.
6) Ensuring that a cardiac technologist is present to adjust pacemaker settings as recommended by the cardiologist to reduce risk while in the MR environment. Most studies recommended the pacemaker being programmed to disable atrial fibrillation and tachycardia functions and to enter a full time asynchronous pacing mode to avoid abnormal pacing during to distortions of the ECG caused by the MR environment.
7) Monitoring of the patient throughout the examination using both electrocardiography and pulse oximetry.
8) The presence of the cardiologist during the examination to monitor the patient.
9) No first level controlled mode to be selected.

Clinicians and healthcare professionals have a duty of care of patients as a requirement of registration to the General Medical Council and the Health and Care Professions Council. This duty of care is also required under English tort law and covers both negligence and the prevention of harm. (Herring, 2010). Most trusts would currently consider the presence of MR unsafe pacemakers an absolute contraindication based on the perceived risk of the examination and the duty of care they have to the patient. If conventional pacemakers can be relatively safely examined (given the correct safety procedures being in place) it raises questions around the ethics of automatically withholding these examinations. There are not always acceptable alternative imaging modalities available and for some patients there could be considerable risks to health from automatically excluding MR which could aid diagnosis and guide treatment. The best interest of the patients should always be paramount and the potential risks of not performing the MR should be weighed against the apparently small risk of complications arising from the scan.

Conclusion

Based on the studies found for this article it can be concluded that scanning of conventional pacemakers can be safely achieved but only in the correct clinical setting with full consideration given to the risks and benefits of the scan, informed consent, monitoring of the patient and with appropriate clinicians on hand to ensure that any complications are safely dealt with. These safety measures require careful planning and are clearly associated with a higher cost than standard MRI however we owe it to our patients to complete a risk-benefit analysis to ensure that we are always acting in their best interests.

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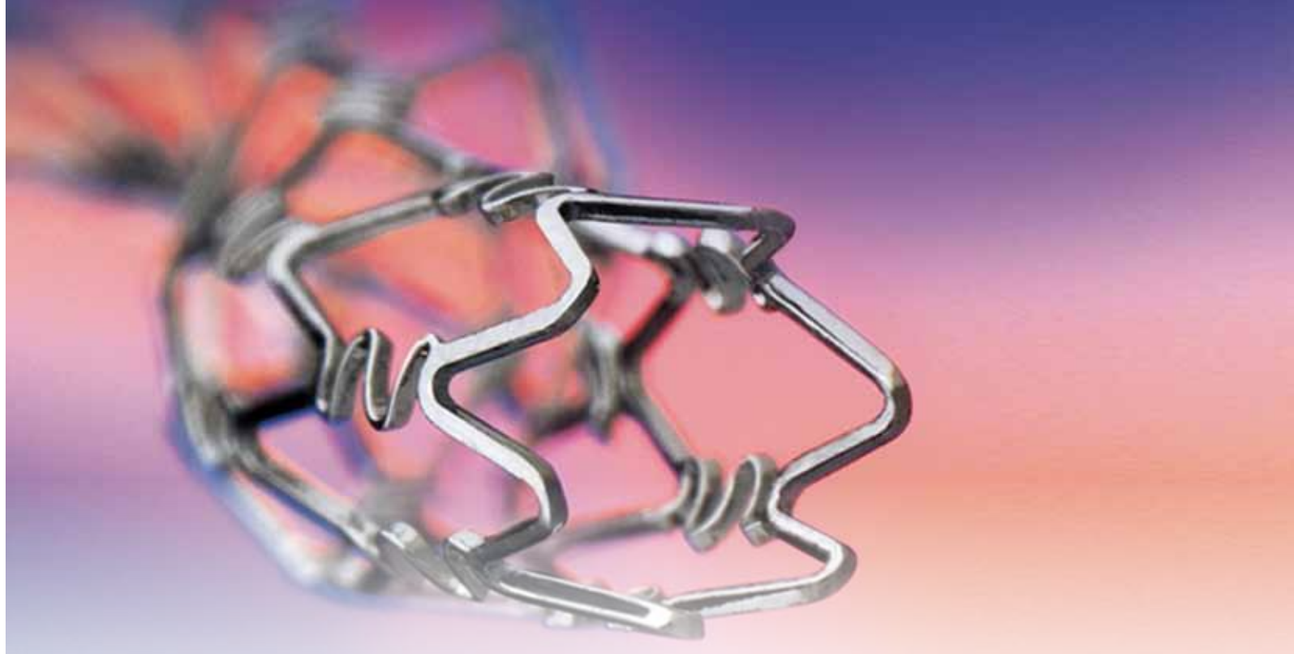


MRI Manager Nottingham University Hospitals NHS Trust and BAMRR Policy Board member

There is often a great deal of confusion and a great deal of disparity between MRI centres regarding the safety of cardiac stents.

Should I wait 6 weeks post implantation?

Should I scan it?

What if they have one or more overlapping stents?

A recent update by Shellock on MRIsafety.com may have provided an easier process for the checking of cardiac stents, especially for those patients whom are unsure of the make or model.

In the update Shellock reports that 'the previous belief that it may be necessary to wait six weeks or longer after implantation has been refuted because there are no known coronary artery stents made from ferromagnetic materials'.

The labelling of many cardiac stents exists and makes it easy for the operator to scan safely and in an informed way. Importantly there have been no reported adverse events associated with coronary stents and clinical MRI scanning at 1.5T or 3T.

There are unfortunately many incidences where the type of coronary stent is unknown or no MRI safety considerations have been taken by the manufacturer which thereforerestricts these patients from undergoing an important diagnostic test.

Shellock however reports that 'in consideration of the relevant peer-reviewed literature and other related documents, it is acceptable and safe to perform MRI examinations in all patients with coronary artery stents by following specific guidelines developed by taking into consideration possible safety concerns (i.e., magnetic field interactions and MRI-related heating) for these implants.'

By adhering to these admittedly conservative MRI conditions, all patients with coronary artery stents can benefit from the diagnostic imaging information provided by one of the most important noninvasive imaging modalities.

Guidelines:

The following guidelines apply to using MRI in all patients with coronary artery stents (including two or more overlapped stents) that have unknown labeling information:

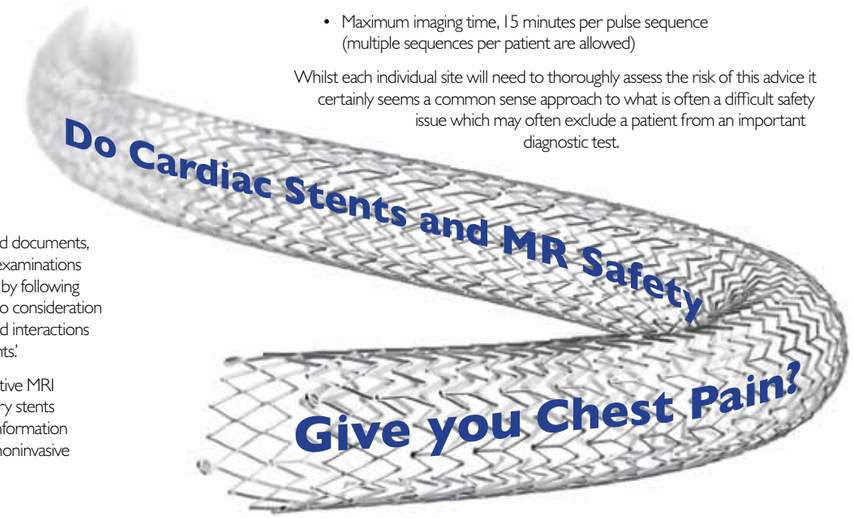
(1) Patients with all commercially available coronary artery stents (including drug-eluting and non-drug eluting or bare metal versions) can be scanned at 1.5-Tesla/64-MHz or 3-T/128-MHz, regardless of the value of the spatial gradient magnetic field.

(2) Patients with all commercially available coronary artery stents can undergo MRI immediately after placement of these implants.

(3) The MRI examination must be performed using the following parameters:

- 1.5-Tesla or 3-Tesla, only
- Whole body averaged specific absorption rate (SAR) of 2-W/kg, operating in the Normal Operating Mode for the MR system
- Maximum imaging time, 15 minutes per pulse sequence (multiple sequences per patient are allowed)

Whilst each individual site will need to thoroughly assess the risk of this advice it certainly seems a common sense approach to what is often a difficult safety issue which may often exclude a patient from an important diagnostic test.



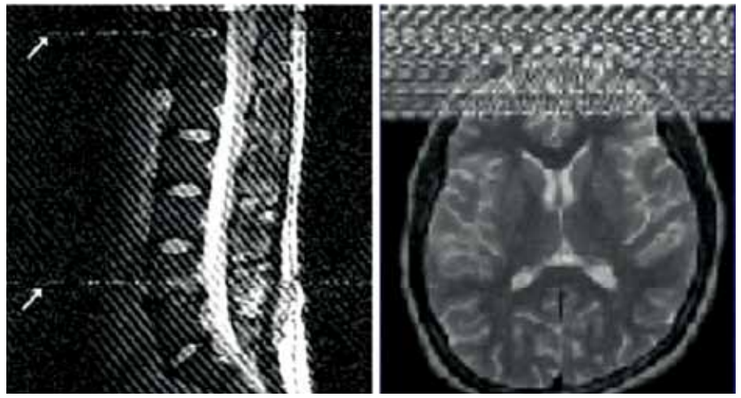
http://mrisafety.com/SafetyInfov.asp?s_keyword=coronary+stent&s_Anywords=&SafetyInfoID=352

BITESIZE PHYSICS

Wave Guides

Matthew Benbow *Superintendent Radiographer, CT & MRI, Royal Bournemouth Hospital, BAMRR Policy Board Member*

Almost certainly near to your scanning console you will have one or more waveguides leading into the scan room. These give an open channel through which you can pass ventilation tubing, infusion lines or oxygen to your patient whilst they are having an MRI scan. But how is this possible? We spend a great deal of effort, not to mention money, in ensuring we have a leak proof RF cage around our scanners with the aim being to prevent stray radio frequencies entering the scan room. Leaked RF is likely to be detected by the receive coils and ultimately form unwanted artefacts in our images as it overpowers the relatively weak signal being received from the patient. The answer is that a waveguide is not simply any hole. There are some important mathematical design features that are necessary to ensure it does its job.



◆ **RF Interference**

◆ **Industrial waveguide**

Unlike in MRI rooms, industrial waveguides are in fact usually employed for the exact opposite – that being to confine and assist the passage of signals in the similar way that sound passes well along a hollow tube, or, through a taught wire such as guitar string or kids bean-can intercom. So as the name suggests, they guide waves. This works at its most efficient at high frequencies where the wavelength of the signal approaches the cross sectional dimension of the waveguide. They should be thought of as being channels to direct electromagnetic energy rather than conductors of it. In open space, electromagnetic waves propagate in all directions and as such their power intensity decreases greatly with distance (the familiar inverse square law). Waveguides operate by preventing the waves from spreading out and losses resulting from this effect are therefore almost eliminated.

There is therefore a cut-off point where higher frequencies will get through but those below will be blocked, and this can be exploited for the purpose needed in MRI, i.e. to maintain the integrity of the RF cage. This cut-off frequency depends on the shape and size of the cross section of the waveguide. The larger the waveguide is, the lower the cut-off frequency for that waveguide. Waveguides can have either a circular or rectangular cross section, but those commonly used in MRI RF cages are commonly circular and the cut-off frequency for a waveguide with a circular cross section of radius ☐ is given by:

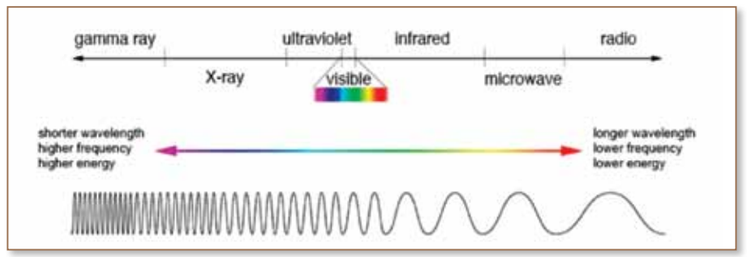
$$\text{Cut-Off Frequency } f_c = \frac{1.8412}{2\pi a\sqrt{\mu\varepsilon}} = \frac{1.8412c}{2\pi a}$$

Where c is the speed of light within the waveguide, μ is the permeability of the material that fills the waveguide and ☐ is the permittivity of the material that fills the waveguide.

An MRI waveguide must therefore be built to have a certain diameter relative to the wavelength of the signal. It needs to be sufficiently narrow to ensure that the relevant electromagnetic fields cannot propagate, and this diameter is consequently dependent on the frequency of the RF that needs blocking.

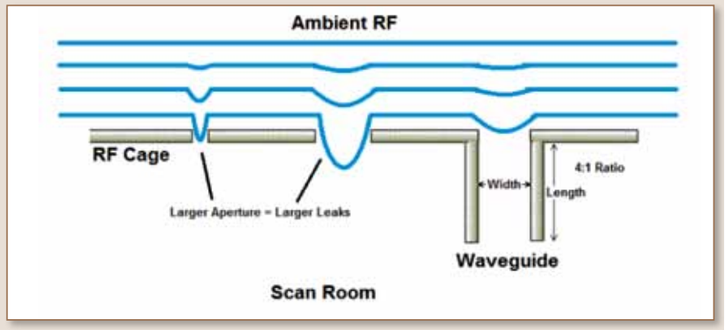
Electromagnetic Spectrum

The range of frequencies used in MRI (10-300 MHz) are relatively low - from the radio wave end of the electromagnetic spectrum and so a cylinder with a length : width ratio of 4:1 or greater will be effective at blocking radiofrequencies in the desired range.



RF Cage

So, by designing a waveguide to be purposely too small for the wave to propagate however, it can be made to become a blocker of waves, rather than a channel to assist their passage. As such we can be provided with a channel that allows activities such as general anaesthetic MRI examinations without the expense of highly specialist MRI conditional equipment within the scan room.



LATEST SIG NEWS

EMF - Control of Electromagnetic Fields at Work *Regulations (CEMFAW) 2016*

The BIR's MR Safety Working Party has developed generic risk assessments to help employers assess exposure to electromagnetic fields and then assess the resulting risks to their staff. These will need to be adapted to suit local circumstances, and some contain options which individual MRI facilities will need to choose between. The MR Safety Working Party includes representatives from BIR, IPEM, RCR, SCoR, BAMRR, ISMRM, as well as representatives from HSE, MHRA and PHE. Search 'BIR EMF Risk Assessments' for more information.

BAMRR

Supporting MR Radiographers in their professional development and continuing education.

Join us for access to MR safety resources, educational information, reduced course/conference fees and much more!

@

http://www.bamrr.org/home

Free membership for student Radiographers

Members receive:

- Twice yearly Newsletter
- Guidance on MRI issues including safety available via email contact with policy board members
- Access to reduced fees for validated courses and conferences
- Members only website information
- The annual conference includes a carefully thought out agenda to share the latest MR techniques and best practice.

BAMRR

Treasurer Report
Helen Estall
01.10.16

Financial statements for year ended 30 April 2016 approved by the policy board.

Published on BAMRR web site at beginning of September, more than 21 days prior to the AGM.

Trustee's/Policy Board remuneration is nil.

Balance in the accounts at end of September 2016 is £46,458.97.

Expenses

Courses & Conference	£16,990	(£18,325)
Accountant	£4,170	(£3,840)
Policy Board	£2,619	(£2,579)

For 2016

Basic course x 2	£11,285
Conference 16 sponsors	£6,260
Conference 16 delegates	£7515
Membership	£7,815

Thank you

Highlights from the Management Group meeting September 2016

In this meeting, we outlined the on-going work of the SIG with input from several liaison personnel. We continue to review MRI safety issues, with the EU PAD generic risk assessment awaiting feedback after it has been presented to BAMRR Conference on 1 October 2016.

The Radiation Protection User Group has published a booklet and video for PPE for diagnostic X-ray use, and we made plans for working towards publishing an MRI equivalent booklet and video, perhaps to include a Clinicians guide to MRI referrals. An MRI safety booklet for July 2017 will be planned to coincide with the MRI Safety Week.

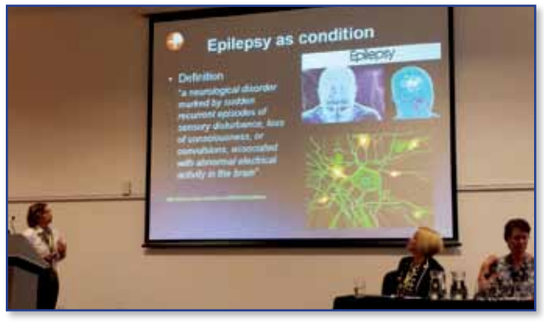
BAMRR UKRC Report 2016

It was another successful BAMRR session at UKRC in Liverpool on Wednesday 8th June 2016

◆ Jill McKenna (President, BAMRR) and Paola Griffiths (President Elect, BAMRR) chaired the session titled 'Contemporary Practice in MRI'

◆ Three erudite speakers shared their expertise with an captivated audience of MRI Radiographers.

In her talk entitled 'Paws for thoughts: MRI epilepsy in small animals', Ms Eli Jovanovik, Head of Imaging Fitzpatrick Referrals shared her experiences in implementing a standardised protocol for scanning canine brains.



She explained the importance of slice orientation, use of dedicated protocols and correct RF coil selection when imaging a dog's skull to diagnose epilepsy and highlighted the challenges that arise as a result of the shape of the dog's skull.

There were some interesting questions from the audience on RF chipping, reporting of canine MRI scans and RF coil options..

Dr Tony Blakeborough, Consultant GI Radiologist, Royal Hallamshire Hospital enlightened everyone with his practice in dealing with the increasing demand for In-patient MRCP examinations - a subject close to the hearts of all present.

Added to this, he discussed his findings from the sequences used in non-contrast and contrast enhanced 'Hepatobiliary MRI' examinations.

He also answered questions on the use of different contrast agents for diagnosing certain pathologies and the use of DWI.

Our final speaker, Mr. David Grainger, Senior Device Specialist, from the Medicines & Healthcare Products Regulatory Agency brought all present up to speed with the updates in the 'MHRA MRI Safety Guidance' document

Work is already underway to secure speakers for next year's BAMMR session at UKRC 2017 to be held at Manchester Convention Centre on 12-14 June 2017, so save the date...

Your attendance of the BAMRR session at UKRC conference is both appreciated and valued.

Thank You.

Rachel Watt

BAMRR UKRC co-ordinator

The role of Magnetic Resonance Imaging (MRI) in the diagnosis and management of patients with suspected scaphoid fractures

Jack Lannie and Janice St. John-Matthews
Department of Allied health Professions; Faculty of Health and Applied Sciences,
University of the West of England

INTRODUCTION The scaphoid is the most commonly fractured carpal bone (1). Radiography has a low diagnostic accuracy resulting in missed diagnoses and conditions such as osteoarthritis and avascular necrosis (1). In UK practice, equal weighting is given to alternative techniques for second line imaging (2) and there is a lack of clarity in regards to the best imaging techniques for diagnosing scaphoid fractures in clinical guidelines. MRI is more sensitive and specific than radiography (3,4) and could be more ethical and economical due to reduced immobilization and outpatient visits (5).

AIMS

- To understand the role of MRI in the diagnosis and management of patients with scaphoid fractures
- To compare MRI to other imaging modalities and
- To establish the best imaging method
- To assess economic viability of MRI over traditional protocol
- To define a new protocol allowing fast scanning and accurate diagnosis

METHODOLOGY
A literature review took place using a systematic method. Five databases were searched using key terms and all research published from 2006 onwards was subject to inclusion criteria to ensure relevant literature. Selected literature was then critiqued using critical appraisal tools (6) to reduce bias. The critical appraisal primarily used neglected analysis of statistics identified within research. Hence a statistical model flow chart was used to ensure that each study utilized the correct statistical analysis (7).

USING MRI

A meta-analysis (8), excluded from the review, calculated MRI has sensitivity and specificity of 97.7% and 99.8%, respectively. Research comparing radiography to MRI often found an increased prevalence of scaphoid fractures of 7-11% when patients had MRI (9,10,11). Just one study used 3.0T scanning but reasons and justifications for this were not discussed (10). Likewise, one study used a 0.2T extremity scanner but neglected its impact on patient pathway and experience (9), and so the benefits and impact upon patient experience are not discussed.

MODALITY COMPARISON

MRI demonstrated better diagnostic capabilities than CT (4,12) although both had higher specificities indicating their ability to exclude than diagnose. Nuclear medicine had a better sensitivity, making it a better tool for diagnosing, however, it poses problems in that it is an invasive procedure with a high radiation dos where as MRI has the advantage of no ionizing radiation However, much of the literature is flawed by small sample sizes, absent reference standards and inappropriate statistical analysis.

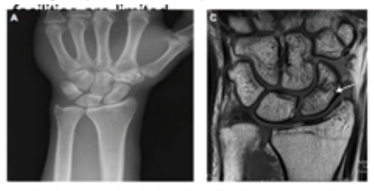
ECONOMICS

Raw data suggested a saving when using MRI through reduced immobilization and outpatient visits, however, this was not deemed statistically significant (13, 14,15). This is an under researched area that would benefit from larger samples and longitudinal methodology. Blue-Collar workers were most affected by immobilization with more time spent off work resulting in a higher loss of earnings. Because of this, it was suggested in this project to prioritize workers in more laborious trades for MRI in order to reduce the time spent in cast, thus reducing the cost to the patient and society, which is both ethical and economical.

		MRI		CT		BS	
Study	n	Sens	Spec	Sens	Spec	Sens	Spec
3	40	67	96	67	96	-	-
4	29	100	100	73	100	-	-
16	33	n/a	100	n/a	100	n/a	97
17	100	80	100	-	-	100	90

PROPOSED PROTOCOL

A fast scan protocol of coronal T1-SE and STIR sequences was recommended, allowing demonstration of fractures and lesions (T1-SE) and oedema (STIR). High risk groups should be prioritized when MRI



Undetected minimally displaced scaphoid fracture on radiograph demonstrated on T1 weighted image (16)

CONCLUSION

MRI is a useful tool for diagnosing and managing scaphoid fractures, with reduced immobilization and no ionizing radiation although it does have contraindications and is more time consuming. It is less invasive than nuclear medicine whilst having a better diagnostic accuracy than CT, although it is better at excluding than diagnosing. The limited research in regards to economic viability indicates a financial saving when using MRI although further research is required to support this. A general flaw throughout the research of this project was the absence of reference standards and adequate sample sizes. MRI should be used as first choice second line imaging where facilities allow it.

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An Update on the Stability of Gadolinium Based Contrast Agents (GBCAs)

Dr Imran Shahid *Department of Medical Affairs Guerbet Laboratories UK.*

Extracellular gadolinium-based contrast agents (GBCAs) are the most widely used contrast agents for MR imaging. Currently, it is estimated that 40–50% of all MR studies performed worldwide are contrast-enhanced [Bellin & Molen, 2008] . The contrast agent typically makes diseased tissue appear brighter (or in some cases darker) than the surrounding tissue. Each GBCA is composed of two main components [Brucher and Sherry, 2001; Morcos, 2007 & 2008; Port et al., 2008]:

1) **Gadolinium metal (Gd3+)** which leads to the MR-image by relaxing the nearby protons in the tissue of interest. Gadolinium is acidic in nature and bears three positive charges (i.e. Gd+++).

2) **A protective chelate** surrounding the Gadolinium. This is crucial for safety as gadolinium is toxic in its free form. This protective chelate (or 'chemical cage') is basic (or alkaline) in nature and contains amine and carboxyl groups and has following key structural features:

   a. If the surrounding chelate is completely surrounding the gadolinium metal, it's referred to as macrocyclic molecule; this by far is the most stable configuration.

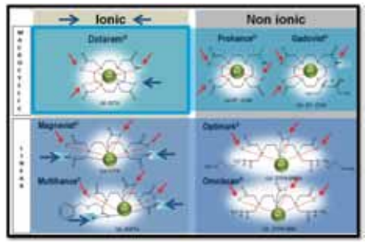
   b. If the surrounding chelate is partially surrounding the gadolinium metal, it's referred to as a linear molecule; this configuration is less stable than the macrocyclic configuration.

   c. All the gadolinium chelates must have a minimum of three carboxyl groups. This is pivotal for the stability of the molecule. Each of these carboxyl groups contributes one negative charge, therefore in order to balance the three positive charges of gadolinium ion (Gd+++), three carboxyl groups are needed to stabalise the molecule.

   d. GBCAs containing only three carboxyl groups in the outer chelate are called non-ionic (or neutral) molecules, as the three negative charges of carboxyl groups will neutralise the three positive charges of gadolinium.

   e. GBCAs containing more than three carboxyl groups in the outer chelate are called ionic molecules. This is because there is a surplus of negative charge. **Ionic configuration is more stable than the non-ionic configuration**.

This led to the four main classes of GBCAs, i.e. Linear ionic & non-ionic and Macrocyclic ionic & non-ionic. (Figure 1). It's clear that all the molecules must have a minimum of three carboxyl groups (red arrows), while in the case of ionic molecules there is an excess of negative charge (blue arrows). These negative charges form reversible electrostatic interactions with the central gadolinium, shown by the dotted lines in Figure 1. In the case of macrocyclic molecules the chelate is completely encapsulating the central gadolinium (like a cage), hence giving the maximum protection to the molecule.



◆ **Figure 1**. *Showing the four main classes of GBCAs; Primovist, a linear ionic molecule, is not shown. The red and blue dotted lines, as indicated by arrows, represent the electrostatic interactions between gadolinium metal ion (Gd3+) and carboxyl groups (COO-).*

Since their use in MRI, these GBCAs have enjoyed a very good reputation in terms of safety for a very long time. However, the involvement of these GBCAs in the development of nephrogenic systemic fibrosis (NSF) as reported by two European teams [Grobner et al., 2006; Marckmann et al., 2006] have raised serious questions on the safety and the stability of these molecules [Ramalho et al., 2016]. More recently, Kanda et al. (2014) & Macdonald et al. (2015) reported hypersignals in unenhanced T1 images which were attributed to gadolinium retention in the brain.

In vivo animal measurements have previously shown retention of gadolinium in the body, with approximately three times more gadolinium deposition in the tissues of mice and rats, with normal renal function, 2 weeks after the non-ionic linear agent Omniscan than after the ionic linear agent Magnevist. Only very small quantities of gadolinium were present in the tissues after the macrocyclic agents Gadovist, Dotarem and Prohance [Wedeking et al., 1992; Tweedle et al., 1995]. Free gadolinium is highly toxic to the tissues [Idée et al., 2009; Palasz & Czekaj, 2000]. The ionic radius of gadolinium ion (Gd3+) is close to that of calcium ion (Ca2+), hence, gadolinium can act as a blocker of voltage-gated calcium channels [Adding et al., 2001]. In addition, calcium-sensing receptors on hepatocytes, fibroblasts, renal cells etc. could be activated by gadolinium [Korolenko et al., 2006]. The most pronounced acute toxicity shown by gadolinium in its free form is in the liver, where it may cause hepatocellular necrosis [Spencer et al., 1997].

NSF Cases with GBCAs:

NSF, previously known as nephrogenic fibrosing dermopathy (NFD), was first reported in 1997 and the initial cases were published in 2000 [Cowper et al., 2000]. The link with GBCAs was first described via a study published in Austria by Grobner et al. (2006), whereby five patients with end-stage renal failure developed signs of NSF within four weeks of the administration of GBCA. This was followed by 25 cases of NSF (5 in Austria and 20 in Denmark) in patients with severe kidney impairment, to whom Omniscan had been administered [Grobner, 2006]. Since June 2006, other GBCAs have also been reported to be associated with NSF, as such, this matter has been subject to strict regulatory reviews leading to key risk minimisation measures both at the national and the international level. European Medicines Agency (EMA/EMEA) & Medicines and Healthcare products Regulatory Agency (MHRA) have classified GBCAs according to the risk of NSF based on their thermodynamic and kinetic stabilities, as follows:

1) High risk:

a) Linear non-ionic chelates including gadodiamide (Omniscan) and gadoversetamide (Optimark).

b) Linear ionic chelate gadopentetate dimeglumine (Magnevist).

2) Medium risk:

Linear ionic chelates including gadobenate dimeglumine (Multihance), gadoxetic acid disodium (Primovist) and gadofosveset trisodium (Vasovist).

3) Low risk:

Macrocyclic chelates including gadoteric acid (Dotarem), gadobutrol (Gadovist) and gadoteridol (ProHance).

Data reported to EMA and Food and Drug Administration (FDA) show that Omniscan and Magnevist, both belonging to the high risk class, have been associated with the highest number of unconfounded (single agent) cases of NSF to date (Table 1). An Un-confounded & Un-doubtful case of NSF is based on the criteria that; a) only one GBCA administered to the patient & b) a known dose of specific GBCA is administered to the patient. Macrocyclic agents are considered to be the most stable compounds among the current GBCAs and therefore categorised as the low risk agents with regards to NSF. Unfortunately, they have also been associated with a small number of NSF cases. Data received by the FDA and EMA show that Prohance has been associate with two unconfounded cases of NSF (Table 1). One case was reported in Switzerland in 2006 and involved a 51 year old male patient, with end stage renal failure (ESRF) undergoing dialysis, whom, after tissue biopsy and histological findings, was diagnosed with a non-severe form of NFD, a term used for NSF previously. The second unconfounded case of NSF was reported in USA in 2008, however, no biopsy was done for this patient. Gadovist has also been associated with two unconfounded cases of NSF (Table 1), however, there has been some uncertainty about the histopathological findings in the biopsy results [Thomsen et al. 2013]. The first case was reported in 2009; a 69 year old male patient with ESRF undergoing dialysis, whereby histopathological findings showed an increased number of CD34+ fibrocytes, one of the key parameters in diagnosing NSF [Wollanka et al. 2009]. The second case of NSF was reported in 2010 in Denmark; a 59 year old man, who had chronic kidney disease (CKD) stage 3 and had no history of dialysis. He was diagnosed with NSF after the histopathological and biopsy results [Elmholdt et al. 2010, 2011 & 2013]. There was one case of NSF reported with Dotarem, however, an unknown GBCA was administered prior to Dotarem [Elmholdt et al. 2011]. In addition, no mucin was found in the histopathological results and the biopsy did not show an increase in the CD34+ fibrocytes [Elmholdt et al. 2013], therefore, this NSF case is considered to be a doubtful and confounded case (i.e. involving more than one agent). Among the macrocyclic GBCAs, currently, Dotarem is the only agent which has no confirmed unconfounded case of NSF. Combining the data submitted to FDA, EMA and various published studies, the updated number of NSF cases are shown in **Table 1**.

Class of GBCA	GBCA	Number of Single Agent NSF reports*	References
Macrocyclic Ionic	Dotarem	**0**	EMA assessment report 1st July 2010 (EMA/740640/2010); Thomsen et al. 2007 & 2013, Stinson B., Regulatory update on NSF cases, FDA, 21/01/2011; Wollanka et al., 2009; Elmholdt et al., 2010, 2011 & 2013; Drug Safety & Risk Management Advisory Committee on Gadolinium Based Contrast Agents, NDAs 20-131/21-489, October 30, 2009 (data submitted for Prohance by it's manufacturers); Idée et al., 2008
Macrocyclic Non-Ionic	Gadovist	2	
	ProHance	2	
Linear Ionic	Magnevist	179	
	MultiHance	**0**	
Linear Non-Ionic	Omniscan	505	
	Optimark	35	

◆ **Table 1**. *Showing number of single agent cases of NSF reported to EMA & FDA database; *Not all cases of a GBCA might be confirmed by the manufacturer.*

Brain Hypersignals with GBCAs:

Over the past few years, due to awareness and better clinical practices, the number of NSF cases have significantly reduced. While the anxiety of NSF was extinguishing, the MRI world was taken by the breaking news of the reports of unexpected brain hypersignals in unenhanced T1 weighted images of patients in certain areas of the brain, namely dentate nucleus and globus pallidus.

Kanda et al. (2014) showed that signal intensity ratios of globus pallidus to thalamus and dentate nucleus to pons in patients with previous history of contrast-enhanced examinations were significantly greater than those of patients who had undergone unenhanced examinations. This

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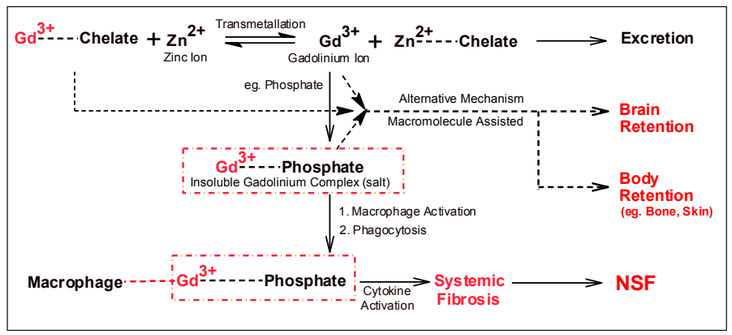
	Structural Stability	*In Vitro* Stability			*In Vivo* Stability	
	Configuration	Thermo-dynamic Stability pH: ~11.0	Conditional Stability pH: ~7.4	Kinetic Stability pH: ~1.0	NSF Cases	Brain Hyper-Signals Observed
Dotarem	Macrocyclic Ionic	25.6	19.3	338 hours	0	No
Gadovist	Macrocyclic Non-Ionic	21.8	14.7	43 hours	**2**	No
Prohance		23.8	17.1	3.9 hours	**2**	No
Multihance	Linear Ionic	22.6	18.4	<5 seconds	0	**Yes**
Magnevist		22.1	17.7		**179**	**Yes**
Omniscan	Linear Non-Ionic	16.9	14.9		**505**	**Yes**
Optimark		16.6	15.0		**35**	**NA**

◆ **Table 2**. ***Showing the stability constants of various GBCAs, NA=Not Available***; *[Morcos 2008; Idée et al., 2008; Port et al., 2008].*



◆ **Figure 2**. ***Showing the different pathways Gadolinium and its Chelate in vivo.***

study raised new concerns about gadolinium's safety, in particular, the clinical outcome of these hypersignals. As this study did not include histopathologies of the brains, it could not conclusively demonstrate whether or not the hypersignals resulted due to gadolinium retention. McDonald et al. (2015), in a pivotal study, conclusively showed that the hypersignals were indeed due to the presence of gadolinium in the brain. The researchers used inductively coupled plasma mass spectroscopy (ICP-MS) to evaluate the retention of gadolinium in respective brain tissues, including the globus pallidus and dentate nucleus. Their results showed that gadolinium traces were present in the brain several years after administration of MRI contrast and recorded between 0.1 µg and 58.8 µg of gadolinium per gram of tissue in the four regions of the brain of the patients, who had a relatively **normal renal function**.

A new study by Weberling et al. (2015) found an increased signal intensity in the dentate nucleus on unenhanced T1-weighted images after the administration of Multihance, a medium risk linear ionic agent. The study included a cohort of 50 patients that had at least five consecutive brain MRI scans with Multihance. The study found an increased signal intensity in the dentate nucleus to cerebrospinal fluid and dentate nucleus to pons ratios on unenhanced T1-weighted images.

In another study, Radbruch et al. (2015) retrospectively compared signal intensity ratios in a study including two groups of 50 patients who underwent at least six consecutive MRI scans with either Magnevist or Dotarem. They found greater signal intensity in the dentate nucleus and globus pallidus on T1-weighted images among patients who received Magnevist, while there was no such hypersignals observed in patients who received Dotarem, despite the fact that a substantially larger dose of the contrast was used in the Dotarem group.

A new study, later, by Radbruch et al. (2015) also did not find hypersignals in the dentate nucleus or in the globus pallidus after serial administrations of the macrocyclic agent Gadovist. The study included 30 patients who had received at least 5 MRI examinations with only Gadovist. In another study, Robert et al. (2015) administered healthy rats with 20 intravenous injections of Dotarem or Omniscan at a dose of 0.6 mmol per kilogram (i.e. 4 injections per week for 5 weeks). They found that rats receiving the linear GBCA Omniscan were associated with progressive and persistent T1 signal hyperintensity in the deep cerebellar nuclei (DCN), while such an effect was not observed with the macrocyclic GBCA Dotarem. To date, the hypersignals have been observed primarily with the linear agents; Omniscan, Magnevist and Multihance, while no such hypersignals have been observed with the macrocyclic agents; Dotarem, Prohance and Gadovist. These hypersignals are also been observed in patients with relatively normal renal function and intact blood brain barrier. The clinical outcome of these hypersignals, however, is still not clear.

The published data conclusively demonstrate that gadolinium has the ability to be deposited in various parts of the body [Tweedle et al., 1995; McDonald et al., 2015]. It's still not clear, whether gadolinium is deposited in an un-chelated (free) form or chelated (original chelated) form [Ramalho et al., 2016]. The process of gadolinium leaving its protective chelate is referred to as de-chelation, however, the exact mechanism by which it undergoes this behaviour is still under debate. Transmetallation is considered to be the most acceptable hypothesis via which GBCAs undergo de-chelation [Morcos, 2008]. Transmetallation is the gradual release of free gadolinium ion (Gd^{3+}) from the outer chelate of GBCAs and a subsequent replacement of this gadolinium ion (Gd^{3+}) by an endogenous metal ion [e.g. zinc (Zn^{2+}), iron (Fe^{2+}), calcium (Ca^{2+}) ions etc.) [Laurent et al., 2001]. Transmetalation between gadolinium ion (Gd^{3+}) and for example zinc ion (Zn^{2+}) will result in the formation of zinc chelate which is later excreted in urine [Morcos, 2007 & 2008]. The released Gd^{3+} becomes attached to endogenous anions such as phosphates, citrates, hydroxides or carbonates and get deposited in tissues as insoluble compounds (salts, Figure 2). This leads to an immune response and the gadolinium salts would be phagocytosed by nearby macrophages leading to the release of cytokines, namely transforming growth factor beta (TGF-ß) which is a potent fibrogenic cytokine. TGF-ß would attract circulating fibrocytes which will leave the circulation and deposit in the dermis and other organs containing gadolinium salts. They mature into fibroblasts leading to fibrotic changes and deposition of collagen and mucin in the affected tissues [Douthwaite et al., 1999; Perazella, 2007]. There is an alternative hypothesis which proposes that the dissociated gadolinium could also bind to proteins or other macromolecules and then transported to various tissues [Ramalho et al., 2016].

Figure 2. Shows the different pathways gadolinium chelate can take which can result into transmetallation and gadolinium deposition in the body. In vivo [Corot et al., 1998], in vitro [Laurent et al., 2001& 2006] and human studies [Puttagunta et al., 1996; Kimura et al., 2005] have shown that linear chelates particularly the non-ionic ones such as Omniscan cause a large increase in zinc excretion in urine. The non-ionic linear chelate Omniscan induced a decrease of 32% of plasma zinc after a single injection in healthy volunteers [Puttagunta et al., 1996].

The molecular structure affects the stability of the molecules, i.e. how tightly the gadolinium is held within the surrounding protective chelate. In vitro measurements of the chemical stability of gadolinium contrast media show that the macrocyclic chelates are the most stable and that the non-ionic linear chelates are the least stable [Morcos, 2009]. Although the exact prediction of in vivo stability of GBCAs on the basis of physical and chemical properties remains debatable [Caravan et al., 1999], a number of important studies have been published in the last decade showing a progressive evolution in the robustness of experimental models to more closely reproduce and mimic physiologic conditions [Idée et al., 2009; Port et al., 2008].

The stability of a GBCAs can be determined by means of stability constants via in vitro studies measuring the release of Gd^{3+} from the body of the protective chelate; these include:

i) **Thermodynamic stability constant**: measures the amount of Gd^{3+} released at alkaline pH of ~11.

ii) **Conditional stability constant:** measures the amount of Gd^{3+} released at physiological pH of ~7.4.

iii) **Kinetic stability constant**: measures the speed of dissociation of Gd^{3+} from its chelate at an acidic pH of ~1.

Thermodynamic & conditional stability constants are logarithmic values, therefore a higher number indicates higher stability. These in vitro measurements are shown in **Table 2**.

Table 2 gives us a good indication of a possible trend in the stability profiles of the GBCAs. Agents with poor structural stability also tend to have poor in vitro stability as well as poor in vivo stability and vice versa. GBCAs which are neither ionic nor macrocyclic have the lowest kinetic and thermodynamic stabilities and are also associated with numerous NSF cases and hypersignals in the brain. Agents with good structural stability (macrocyclic Ionic & non-ionic) show a very good in vitro and in vivo stabilities (in most cases). Currently, Macrocyclic agents are the only agents which are not associated with recent reports of hypersignals in the brain. While among the macrocyclic agents, Dotarem is the only agent which is neither associated with hypersignals nor have any unconfounded case of NSF.

Conclusion

According to in vivo data, macrocyclic agents possess high stability and should be used in order to prevent NSF and gadolinium deposition in the body especially in the case of patients with poor renal function. The chemical structure of GBCAs determines the stability of these agents. With regards to the stability of the GBCAs, macrocyclic chelates are more stable than linear chelates while ionic GBCAs are more stable than non-ionic GBCAs. As such, the non-ionic linear molecules (i.e. Omniscan & Optimark) have the least stable configuration while ionic-macrocyclic chelate (i.e. Dotarem) has the most stable configuration [Morcos, 2007, 2008 & 2009; Idée et al., 2008 & 2009; Port et al., 2008].

References:

Over 40 references; available on request.

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