DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN - 9 2001

TRANSMITTED VIA FACSIMILE

Madhu Anant
Associate Director, Regulatory Affairs
Bracco Diagnostics, Inc.
107 College Road
Princeton, NJ 08543-5225

RE: **IND[ ]**
MultiHance (gadobenate dimeglumine, Gd-BOPTA)
MACMIS # 9603

Dear Mr. Anant:

This letter notifies Bracco Diagnostics, Inc. (Bracco) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional materials[1] for MultiHance, an investigational new drug, that are in violation of the Federal Food, Drug, and Cosmetic Act (act) and its implementing regulations. These materials were distributed at Bracco's promotional exhibit at the Radiological Society of North America's annual meeting in Chicago, November 2000. Our specific objections follow:

Promotion of an Unapproved New Drug

Sponsors may not represent in a promotional context that an investigational new drug is safe or effective for the uses that are under investigation (see 21 CFR 312.7(a)). Your brochures, however, include several claims and representations concerning the safety and efficacy of MultiHance, an investigational new drug. For example, in the brochure titled "Advances in Magnetic Resonance Angiography," you state that MultiHance is "a novel gadolinium-based magnetic resonance imaging contrast agent" that, compared to other available gadolinium agents, "has the highest relaxivity in aqueous solution and in protein-containing aqueous solutions." You imply that this makes MultiHance an effective contrast agent in MR imaging. You also claim that MultiHance "has been shown to improve intravascular contrast due to a higher relaxivity mediated through weak and transient interaction with serum proteins such as albumin."

As another example, in the brochure titled "New Perspectives in Contrast Enhanced Vascular Imaging," you claim that MultiHance has a stronger vascular enhancement and higher signal intensity compared to Magnevist. Additionally, you highlight the claim that

1. Three brochures titled "Advances in Magnetic Resonance Angiography" ESMRMB Meeting-Seville 1999, "New Perspectives in Contrast Enhanced Vascular Imaging" Highlights from the Satellite Symposium CIRSE Meeting-Prague, 1999, and "MultiHance High Efficiency in CNS Imaging, Dual Imaging Capability in Liver MRI."

Madhu Anant
Bracco Diagnostics, Inc.
IND [redacted]

"gadobenate dimeglumine is a newer contrast agent which appears promising for MRA given its higher intravascular relaxivity due to a capacity for weak and reversible protein interaction."

In the brochure titled "MultiHance High Efficiency in CNS Imaging, Dual Imaging Capability in Liver MRI" you claim that MultiHance has high relaxivity that "constitutes the basis for the unique and advantageous imaging characteristics of MultiHance in most applications requiring ECF (extracellular fluid) agents." You further claim that "in imaging of CNS lesions, MultiHance significantly improves the diagnostic usefulness of MRI scans, providing additional information in more than 50% of cases." Despite the fact that MultiHance is an investigational new drug, your brochures promote MultiHance as safe and effective, and in some cases, more effective, than current treatment.

Requested Action

You should immediately discontinue the use of the above brochures, and any other promotional materials that promote the unapproved drug MultiHance as safe or effective. You should respond to me regarding this violation by letter no later than January 24, 2001. In your response, you should state how Bracco has addressed this violation.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-40; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Bracco that only written communications are considered official.

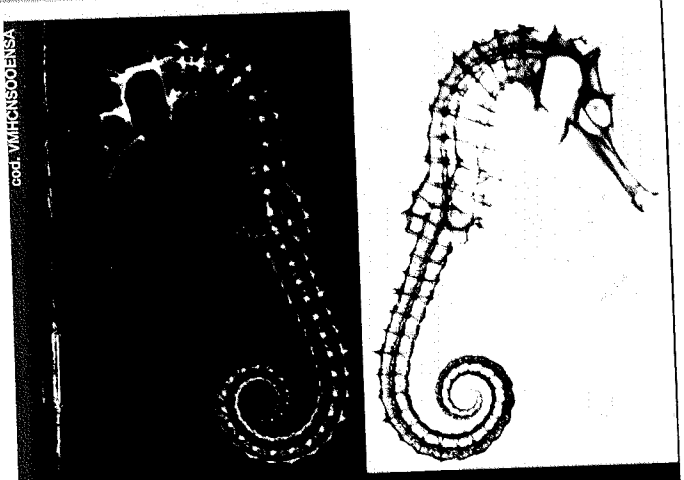
In all future correspondence regarding this matter, please refer to MACMIS # 9603 and IND [redacted]

Sincerely,

/S/

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

cod. VMIHCNISODENSA

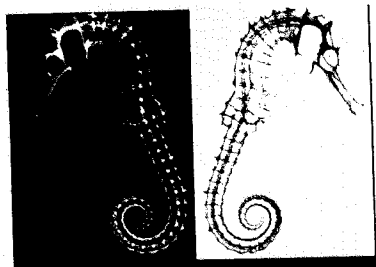


multihance®
Gadobenate dimeglumine

High Efficiency in CNS Imaging

Dual Imaging Capability in Liver MRI

THE INFORMATION IN THIS BROCHURE IS NOT INTENDED FOR THE NORTH AMERICAN MARKET

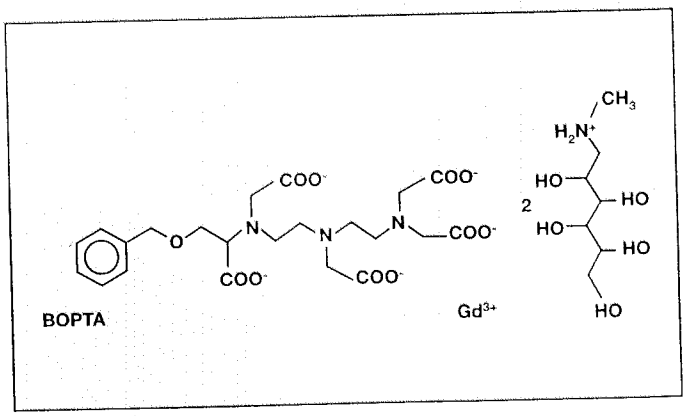


New Generation Molecule

MultiHance® (gadobenate dimeglumine) is a paramagnetic, positive contrast agent for MRI.

Thanks to its physicochemical properties MultiHance® retains all the features of currently available extracellular fluid (ECF) agents, but presents several unique characteristics that distinguish it from other compounds of its class:

- a unique pharmacokinetic profile among gadolinium extracellular agents due to a lipophilic side chain in the gadobenate dimeglumine complex[1]:
- weak and highly reversible protein interaction which benefits relaxivity[2]
- dual route of elimination, through the kidney and, to a lesser extent, through the liver[3]



Molecular structure of gadobenate dimeglumine (MultiHance)®

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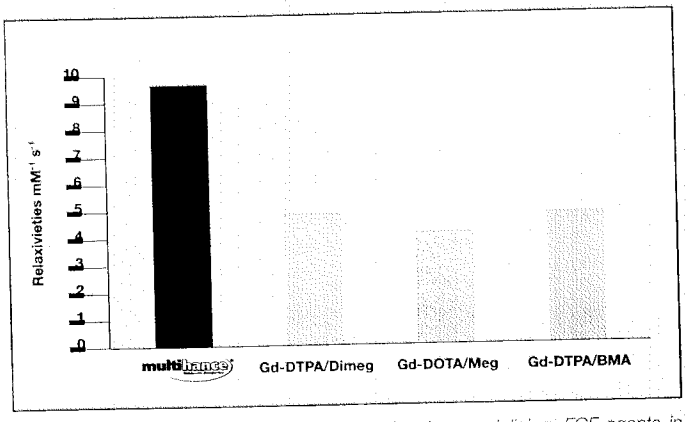
Gadobenate dimeglumine

The Highest Relaxivity Among ECF Gadolinium Contrast Agents

Relaxivity is a measure of the contrastographic capacity of a contrast agent for MRI.

MultiHance® is characterized by a weak, highly reversible interaction with serum proteins [4], that results in a proton magnetic relaxivity nearly twice that of other paramagnetic agents currently on the market [5].

The high relaxivity constitutes the basis for the unique and advantageous imaging characteristics of MultiHance® in most applications requiring ECF agents[5].



Relaxivity ($mM^{-1}s^{-1}$) of MultiHance® and that of various gadolinium ECF agents in human serum.

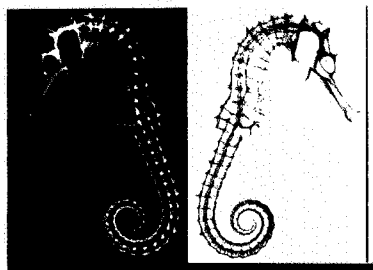
1 Uggeri F, et al. Novel Contrast Agents for Magnetic Resonance Imaging. Synthesis and Characterisation of the Ligand BOPTA and its Ln(III) Complexes (Ln = Gd, La, Lu). X-ray Structure of Disodium(TPS-9-145337286-C-S)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)] gadolinate (2-) in a Mixture with its Enantiomer. Inorg. Chem. 34, 1995, 633-642.

2 Cavagna FM., et al. Binding of gadobenate dimeglumine to proteins extravasated into interstitial space enhances conspicuity of reperfused infarcts. Invest. Radiol., 1994, 29 (suppl.2), S50-S53.

3 Spinazzi A, et al. MultiHance clinical pharmacology: biodistribution and MR enhancement of the liver. Acad. Radiol. 1998; 5: S86-S89.

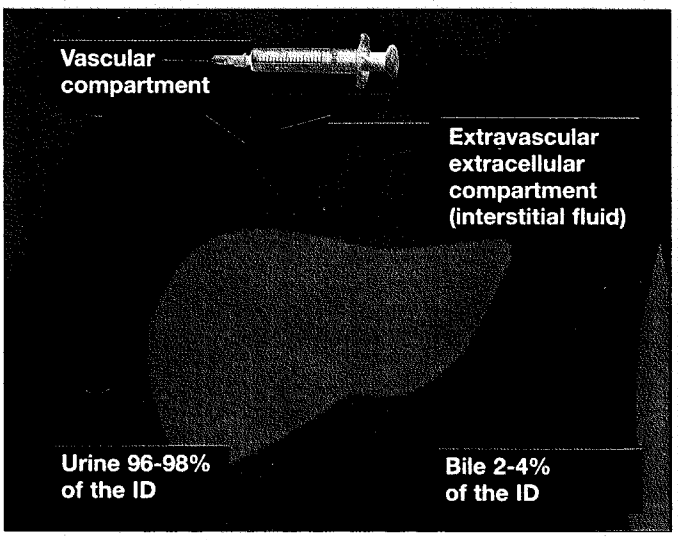
4 Cavagna FM., et al. Gadolinium Chelates with Weak Binding to Serum Proteins. Invest Radiol, 1997, 32:780-796.

5 De Haen C. et al. Gadobenate Dimeglumine 0.5 M Solution for Injection (MultiHance®): Pharmaceutical Formulation and Physicochemical Properties of a New Magnetic Resonance Imaging Contrast Medium. JCAT, 23 (supplement 1), 1999:S161-S168.



Unique Pharmacokinetic Profile

Uptake of a small portion (2-4%) of the injected dose (ID) into hepatocytes, and biliary excretion in addition to renal excretion, give MultiHance® the characteristics of an extracellular fluid agent but also of a liver specific product[1].



Blood half-life and plasma clearance of MultiHance® are superimposable to those of ECF agents. Most of the injected dose is eliminated unchanged within 72 hours[2].

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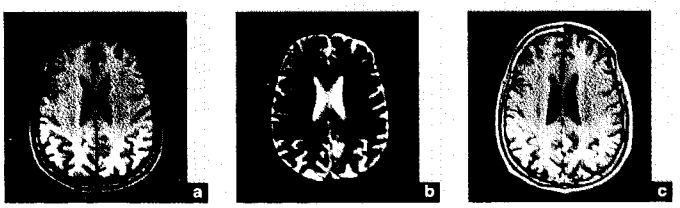
Efficiency in CNS Imaging

The outstanding relaxivity of MultiHance® provides high efficiency in CNS imaging at the dose of 0.1 mmol/kg. No significant improvement of imaging was observed with administration of higher doses[3].

In imaging of CNS lesions, MultiHance® significantly improves the diagnostic usefulness of MRI scans, providing additional information in more than 50% of cases[3].

Radiological usefulness of MultiHance® enhanced images is considered excellent in 60.4% of cases after a dose of 0.1 mmol/kg[3].

MultiHance® enhanced scans provide better lesion detection and delineation compared to plain MRI in 95% of cases[1].

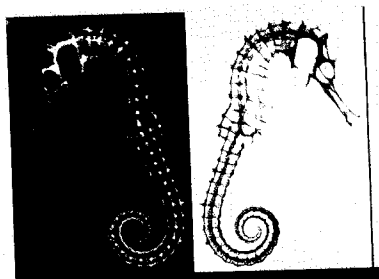


Precontrast T1 (a) and T2-weighted (b) and MultiHance®-enhanced T1-weighted (c) images of meningioma. The post-MultiHance® T1-weighted image reveals a small extraaxial lesion, not seen in pre-contrast scans, consistent with a meningioma of the posterior third of the falx cerebri. Courtesy of Dr. Ruscalleda, Spain.

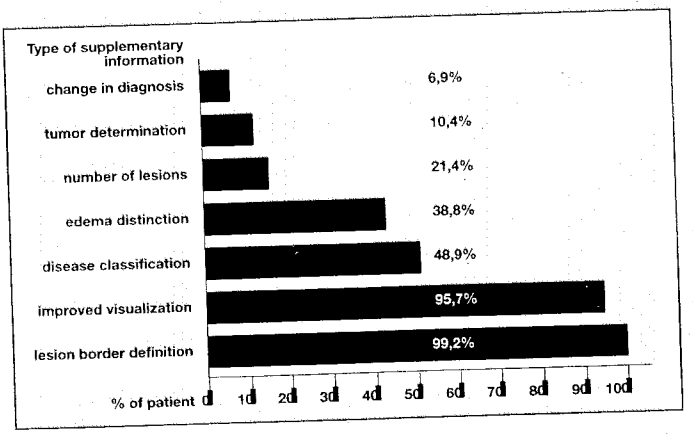
1 Kirchin M. Gadobenate Dimeglumine (Gd-BOPTA): An Overview. Invest Radiol, November, 33(11), 1998:798-809.

2 Spinazzi A., et al. Safety, Tolerance, Biodistribution, and MR Imaging Enhancement of the Liver with Gadobenate Dimeglumine: Results of Clinical Pharmacologic and Pilot Imaging Studies in Nonpatient and Patient Volunteers. Acad Radiol, 6, 1999:282-291.

3 Ruscalleda J., et al. MultiHance® in the Assessment of Intracranial Tumors: results of Phase II Clinical Studies. JCAT, 23 (supplement 1), 1999:S19-S23.



Additional Diagnostic Information in CNS Imaging

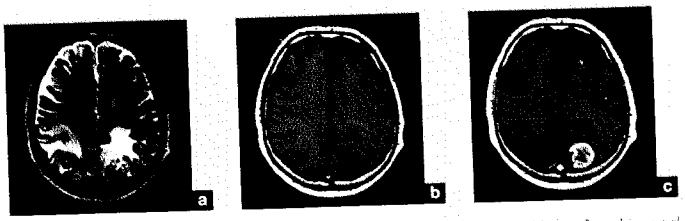


Additional diagnostic information provided by 0.1 mmol/kg dose of MultiHance® in comparison to pre-contrast in patients with either intra-cranial or extra-cranial lesions[1].

In patients with CNS metastases, MultiHance® provides significant improvement in lesion detection and conspicuity[2].

The dose of 0.1 mmol/kg of MultiHance® provides extra diagnostic information in more than 50% of patients[2,3].

Additional lesions can be evidenced in 30% of patients administered with the dose of 0.1 mmol/kg of MultiHance®.[3]



Pre-contrast T2- and T1-weighted images (a,b) and MultiHance®-enhanced image (c) of brain metastases. Pre-contrast images shows abnormalities in the cerebral cortex. MultiHance® -enhanced image clearly delineates an additional

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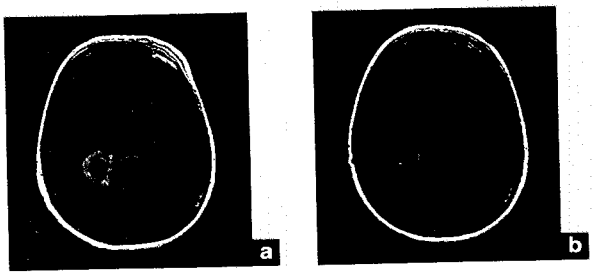
Advantage over Conventional ECF Agents

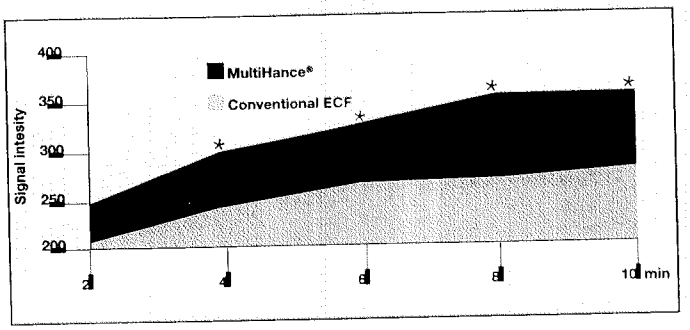
Thanks to its outstanding relaxivity, contrast enhancement of CNS lesions with MultiHance®, in a pilot study, was significantly better than that observed with conventional ECF agents[4].



Comparison of MultiHance® -enhanced image (a) and conventional ECF agent -enhanced image (b) of brain metastases in an intraindividual cross-over pilot study (N=24). Lesion contrast is clearly superior after MultiHance® administration.

Images courtesy of Prof. Knopp, Heidelberg, Germany.

The advantages of MultiHance® over conventional ECF agents could also be expressed in terms of degree of CNS-to-lesion contrast, lesion delineation, of information on internal lesion morphology and of visualization of tumor vascularization[4].



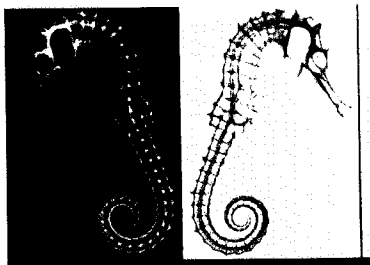
Signal intensity time curve (normalized by pre-contrast values) after administration of equal doses of MultiHance® or a conventional ECF agent in a cross-over intraindividual comparison of patients with CNS lesions.

1 Ruscalleda J., et al. MultiHance® in the Assessment of Intracranial Tumors: results of Phase II Clinical Studies. JCAT, 23 (supplement 1), 1999:S19-S23.

2 La Noce A., et al. Evaluation of the Safety and Efficacy of Gadobenate Dimeglumine (Gd-BOPTA) in MRI of CNS Metastatic Disease. Presented at the ISMRM Meeting, Philadelphia, USA, May 1999.

3 Kirchin M. Gadobenate Dimeglumine (Gd-BOPTA): An Overview. Invest Radiol, November, 33(11), 1998:798-809.

4 Essig M., et al. Comparison of the Contrastographic Behaviour of Gd-BOPTA and Gd-DTPA for MR Imaging of CNS Tumors. Presented at the ISMRM Meeting, Denver, USA, April 2000



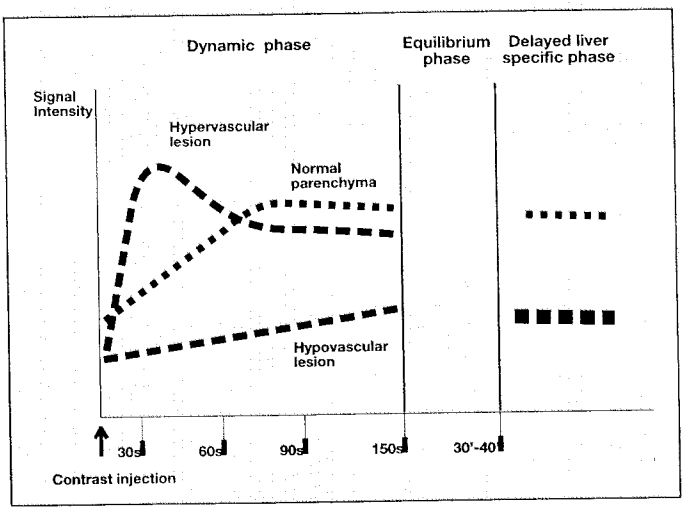
Dual Imaging Capability in Liver MRI

MultiHance® is distributed not only to the extracellular space but is also selectively uptaken by the hepatocytes[1].

MultiHance® has dynamic imaging capability for liver lesions detection and characterization during arterial and venous phases few seconds after contrast administration.

MultiHance® also offers the second opportunity of delayed liver specific phase for increased contrast enhancement of individual lesions up to two hours after contrast administration.

The high relaxivity allows a high signal intensity in T1 weighted images even at the dose of 0.05 mmol/kg.



The unique pharmacokinetics of MultiHance® allows an extended imaging window in liver imaging. In addition to dynamic and equilibrium imaging, MultiHance® allows a delayed liver-specific phase of enhancement useful for detection and characterization of focal liver lesions (as shown in this theoretical model).

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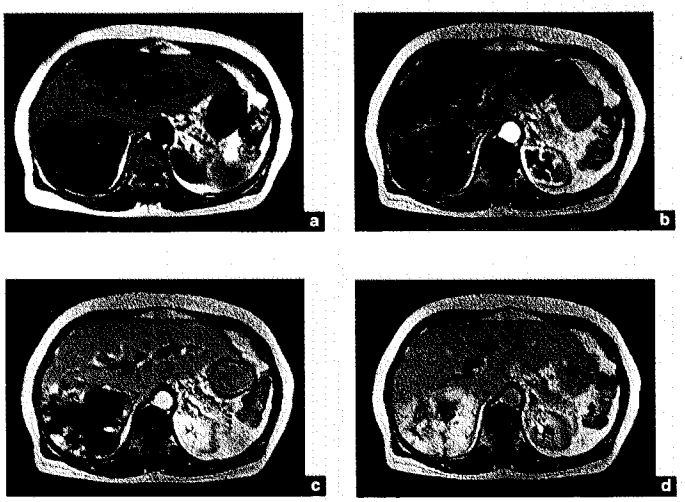
Dynamic Liver Imaging

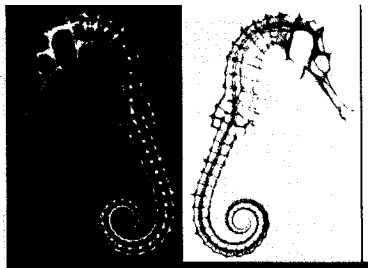
Bolus administration of MultiHance® coupled with dynamic imaging improve the physician confidence in the distinction between solid and nonsolid lesions, with additional information for better lesion characterization in up to 30% of patients[2].

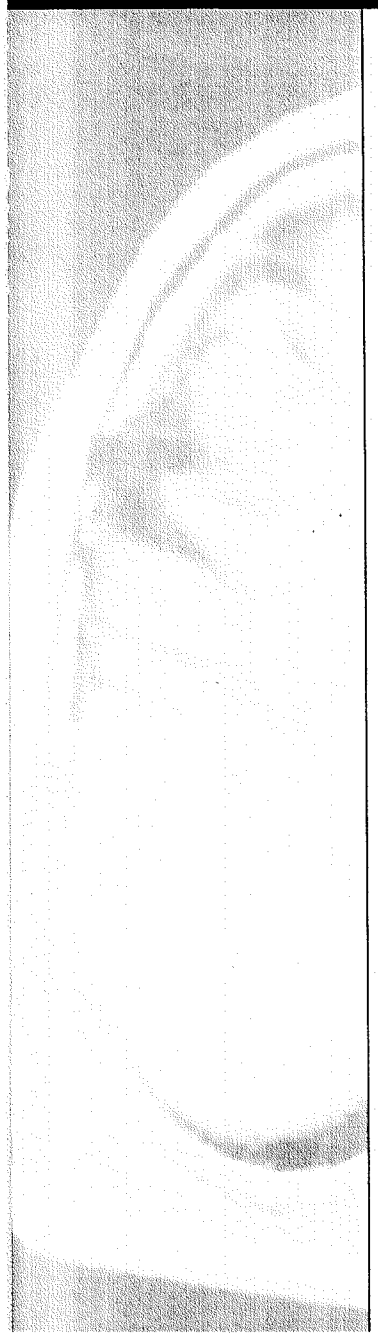


MultiHance®-enhanced images of a giant haemangioma. Pre-contrast (a) and arterial (b), venous (c) and equilibrium (d) phases after MultiHance® administration. Hypointense lesion in precontrast phase demonstrates multiple, typical focal areas of globular enhancement in arterial phase, centripetal filling in during portal venous phase and incomplete filling, due to stromal components, during equilibrium phase. Courtesy of Dr. Grazioli, Brescia, Italy.

1 Spinazzi A., et al. Safety, Tolerance, Biodistribution, and MR Imaging Enhancement of the Liver with Gadobenate Dimeglumine: Results of Clinical Pharmacologic and Pilot Imaging Studies in Nonpatient and Patient Volunteers. Acad Radiol, 6, 1999:282-291.

2 Hamm B., et al. Clinical Utility and Safety of MultiHance® in Magnetic Resonance Imaging of Liver Cancer: Results of Multicenter Studies in Europe and the USA. JCAT, 23 (supplement 1), 1999:S53-S60.





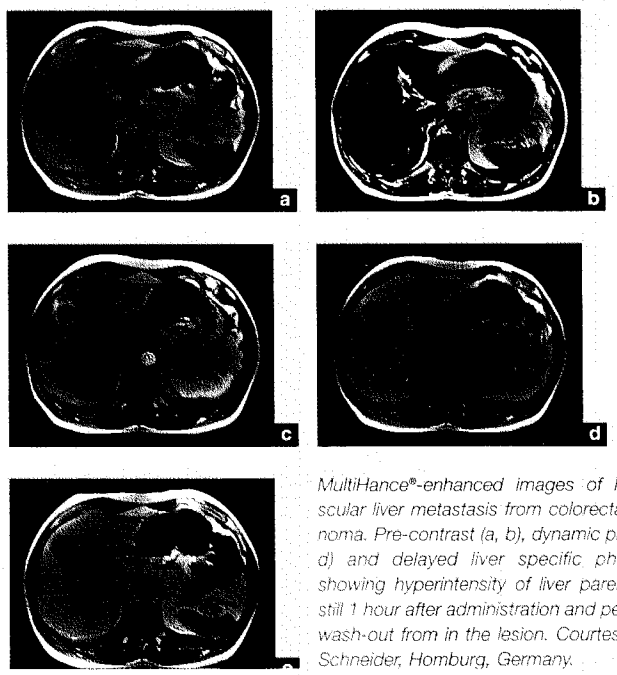
Delayed Liver Specific Imaging

High and long lasting liver signal intensity allows an extended imaging window between 40-120 minutes after MultiHance® administration[1].

MultiHance® enhanced scans provide additional diagnostic information in up to 30% of patients compared to both plain MRI and contrast-enhanced CT[1].

Change in planning and delivery of subsequent treatment is found in up to 23% of patients[2].

Sensitivity of MultiHance®-enhanced imaging is similar to that of invasive procedures like CTAP but with higher specificity[3].



MultiHance®-enhanced images of hypovascular liver metastasis from colorectal carcinoma. Pre-contrast (a, b), dynamic phase (c, d) and delayed liver specific phase (e) showing hyperintensity of liver parenchyma still 1 hour after administration and peripheral wash-out from in the lesion. Courtesy of Dr. Schneider, Homburg, Germany.

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Outstanding Safety Profile in CNS and Liver Imaging

MultiHance® proves to be a safe contrast agent for imaging of the CNS and the liver with a tolerability profile superimposable to that of other gadolinium agents. It is well tolerated and safe up to a cumulative dose of 0.3 mmol/kg. [1]

- The majority of the observed events/reactions was transient, self-limiting, and mild in intensity.
- There were no sex-, age-, or dose-related differences in the incidence of either adverse events or adverse reactions.
- No consistent trends could be observed in vital signs, laboratory parameters or electro cardiographic profile.
- There were no clinically significant alterations in vital signs or laboratory parameters.

1 Hamm B., et al. Clinical Utility and Safety of MultiHance® in Magnetic Resonance Imaging of Liver Cancer: Results of Multicenter Studies in Europe and the USA. JCAT, 23 (supplement 1), 1999:S53-S60.

2 Petersein J., et al. Evaluation of the Efficacy of Gadobenate Dimeglumine in Magnetic Resonance Imaging of Focal Liver Lesions: A Multicenter Phase III Clinical Study. Radiology 2000, in press.

3 Baron RL., et al. Liver Tumor Detection: Comaprison of Gd-BOPTA-enhanced MR, contrast-enhanced CT, and CT Arterial Portography. Radiology 1995, 197(P) supplement to Radiology. Presented at the RSNA, 1995, abstract #1754.

4 Kirchin M. Gadobenate Dimeglumine (Gd-BOPTA): An Overview. Invest Radiol, November, 33(11), 1998:798-809.

[redacted]

PLEASE CONSULT FULL LOCALLY APPROVED INFORMATION BEFORE USING

1. TRADE NAME OF THE MEDICINAL PRODUCT MultiHance 334 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains: gadobenic acid 334 mg (0.5M) as the dimeglumine salt. [Gadobenate dimeglumine 529 mg = gadobenic acid 334 mg + meglumine 195 mg]. Osmolality at 37°C: 1.970 osmol/kg. Viscosity at 37°C: 5.3 mPa.s. For excipients, see 6.1.

3. PHARMACEUTICAL FORM Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) of the liver and Central Nervous System (CNS). MultiHance is indicated, for the detection of focal liver lesions in patients with known or suspected primary liver cancer (eg. hepatocellular carcinoma) or metastatic disease. MultiHance is also indicated for the MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.

4.2 Posology and method of administration Liver: the recommended dose of MultiHance injection in adult patients is 0.05 mmol/kg body weight. This corresponds to 0.1 mL/kg of the 0.5 M solution. CNS: the recommended dose of MultiHance injection in adult patients is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution. The product should be administered intravenously either as a bolus or slow injection (10 mL/min.) without dilution. Post-contrast imaging can be performed immediately following bolus injection (dynamic MRI). In the CNS the imaging window has been shown to be up to 60 minutes after the administration. In the liver delayed imaging can be performed between 40 and 120 minutes following the injection, depending on the individual imaging needs. MultiHance should be drawn up into the syringe immediately before use and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations. To minimise the potential risks of soft tissue extravasation of MultiHance, it is important to ensure that the i.v. needle or cannula is correctly inserted into a vein. The injection should be followed by a saline flush. The safety and efficacy of MultiHance have not been established in patients under 18 years old. Therefore, use of MultiHance in this patient group cannot be recommended.

4.3 Contra-indications MultiHance is contra-indicated in patients with hypersensitivity to any of the ingredients. MultiHance should not be used in patients with a history of allergic or adverse reactions to other gadolinium chelates. There are no studies with MultiHance in patients with impaired renal function (creatinine clearance < 30 mL/min.). Therefore, MultiHance cannot be recommended for use in this group of patients. The safety and efficacy of MultiHance have not been established in pregnant women and, therefore, MultiHance cannot be recommended for use during pregnancy (see section 4.6).

4.4 Special warnings and special precaution for use The safety and efficacy of MultiHance have not been established in patients under 18 years old. Therefore, use of MultiHance in this patient group cannot be recommended. Patients with a history of allergy or hypersensivity should be kept under observation. The accepted general safety procedures for Magnetic Resonance Imaging, in particular the exclusion of ferromagnetic objects, for example cardiac pace-makers or aneurysm clips, are also applicable when MultiHance is used. Caution is advised in patients with cardiovascular disease. The use of diagnostic contrast media, such as MultiHance, should be restricted to hospitals or clinics staffed for intensive care emergencies and where cardiopulmonary resuscitation equipment is readily available. Small quantities of benzyl alcohol (<0.2%) may be released by gadobenate dimeglumine during storage. Thus MultiHance should not be used in patients with a history of sensitivity to benzyl alcohol.

4.5 Interaction with other medicaments and other forms of interaction Interaction studies with other medicinal products were not carried out during the clinical development of MultiHance. However no drug interactions were reported during the clinical development programme.

4.6 Pregnancy and lactation The use of MultiHance cannot be recommended in pregnant women because there are no clinical data to support its use in this group of patients (information regarding findings in reproductive toxicity studies can be found in section 5.3). Although it is not known to what extent gadobenate dimeglumine is excreted in human milk, it is known from animal experiments that minimal amounts, less than 0.5% of the administered dose were transferred via milk from mother to neonates. Although the clinical relevance of this observation is unknown, breast-feeding should be discontinued prior to the administration of MultiHance and should not be recommenced until at least 24 hours after the administration of MultiHance.

4.7 Effects on ability to drive and use machines None known.

4.8 Undesirable effects The following adverse events were seen during the clinical development of MultiHance: more than 1%: hypertension; 0.5 – 1%: altered sensation or pain at injection site, tachycardia, headache, nausea, vomiting; less than 0.5%: pruritus, diarrhoea, dry mouth, vasodilation, skin rash, dizziness, tremor, abdominal pain, hypotension, arrythmia, taste perversion, localized edema. The majority of these events were non-serious, transient and spontaneously resolved without residual effects. There was no evidence of any correlation with age, gender or dose administered. During the clinical development of MultiHance, one possible moderate anaphylactic reaction (dyspnoe and laryngeal spasm) has been reported. Also reported were single incidents of myalgia, convulsion, urinary incontinence and faecal incontinence. Laboratory abnormalities, such as albuminuria, leukokytosis, glucosuria, decrease in ferrol iron and increases in serum transaminases, alkaline phosphatase, serum creatinine and serum [illegible] less than 1% of patients following the administration of MultiHance. However these findings were mostly seen in patients with evidence of pre-existing impairment of hepatic function.

4.9 Overdose There have been no cases of overdose reported. Therefore, the signs and symptoms of overdosage have not been characterised. In the event of overdosage, the patient should be carefully monitored and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

multihance®
Gadobenate dimeglumine

may detect lesions not visualised in pre-contrast enhanced MRI examination of patients with known or suspected hepatocellular cancer or metastatic disease. The nature of the lesions visualised after contrast enhancement with MultiHance has not been verified by pathological anatomical investigation. Furthermore, where the effect on patient management was assessed, the visualisation of post-contrast-enhanced lesions was not always associated with a change in the patient management. The gadolinium chelate, gadobenate dimeglumine, shortens longitudinal (T1), and, to a lesser extent, transversal (T2) relaxation times of tissue water protons. The relaxivities of gadobenate dimeglumine in aqueous solution are r1 = 4.39 and r2 = 5.56 mM-1s-1 at 20 MHz. Gadobenate dimeglumine experiences a strong increase in relaxivity on going from aqueous solution to solutions containing serum proteins, r1 and r2 values were 9.7 and 12.5 respectively in human plasma. In the liver MultiHance provides strong and persistent signal intensity enhancement of normal parenchyma on T1-weighted imaging. The signal intensity enhancement persists at high level for at least two hours after the administration of doses of either 0.05 or 0.10 mmol/kg. Contrast between focal liver lesions and normal parenchyma is observed almost immediately after bolus injection (up to 2-3 minutes) on T1-weighted dynamic imaging. Contrast tends to decrease at later time points because of non-specific lesion enhancement. However, progressive washout of MultiHance from the lesions and persistent signal intensity enhancement of normal parenchyma are considered to result in enhanced lesion detection and a lower detection threshold for lesion site between 40 and 120 minutes after MultiHance administration. Data from pivotal Phase II and Phase III studies in patients with liver cancer indicate that, compared with other reference imaging modalities (e.g. intraoperative ultrasonography, computed tomographic angio-portography, CTAP, or computed tomography following intra-arterial injection of iodized oil), with MultiHance enhanced MRI scans there was a mean sensitivity of 95% and a mean specificity of 80% for detection of liver cancer or metastasis in patients with a high suspicion of these conditions. In CNS imaging, MultiHance enhances normal tissues lacking a blood-brain barrier, extra axial tumours and regions in which the blood-brain-barrier has broken down. In the pivotal phase III clinical trials in this indication, off-site readers reported an improvement in level of diagnostic information in 32-69% of images with MultiHance, and 35-69% of images with the active comparator.

5.2 Pharmacokinetic properties Modelling of the human pharmacokinetics was well described using a biexponential decay model. The apparent distribution and elimination half-times range from 0.085 to 0.117 h and from 1.17 to 1.68 respectively. The apparent total volume of distribution, ranging from 0.170 to 0.248 L/kg body weight, indicates that the compound is distributed in plasma and in the extracellular space. Gadobenate ion is rapidly cleared from plasma and is eliminated mainly in urine and to a lesser extent in bile. Total plasma clearance, ranging from 0.098 to 0.133 L/h kg body weight, and renal clearance, ranging from 0.082 to 0.104 L/h kg body weight, indicate that the compound is predominantly eliminated by glomerular filtration. Plasma concentration and area under the curve (AUC) values show statistically significant linear dependence on the administered dose. Gadobenate ion is excreted unchanged in urine in amounts corresponding to 78%-94% of the injected dose within 24 hours. Between 2% and 4% of the dose is recovered in the faeces. Gadobenate ion does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that have a normal blood-brain barrier. However, disruption of the blood-brain barrier or abnormal vascularity allows gadobenate ion penetration into the lesion.

5.3 Preclinical safety data

Toxicity After repeated administration of high doses to rats and dogs haematological and blood chemistry changes (mainly in dogs) were observed which were shown to be reversible after cessation of treatment.
In the kidneys of both species there was evidence of tubular epithel cell vacuolisation which was still present after a recovery period of 4 weeks in some rats of the highest dose group. Nearly all dog showed lymphatic infiltration of the liver and 2 out of 6 male dogs of the highest dose group developed liver necrosis.
Animal experiments revealed a poor local tolerance of MultiHance, especially in case of accidental paravenous application where severe local reaction, such as necrosis and eschars, could be observed.
Local tolerance in case of accidental intra-arterial application has not been investigated, so that it is particularly important to ensure that the i.v. needle or cannula is correctly inserted into a vein
(see section 4.2).

Mutagenicity Gadobenate dimeglumine showed no effects in a range of in vitro and in vivo tests.

Carcinogenicity Carcinogenicity studies were not conducted because MultiHance is for single dose administration and has no mutagenic potential.

Impairment of fertility No changes in reproductive performance and outcome of pregnancy were caused in rats by daily intravenous administration of gadobenate to parent animals before and during gestation.

Pregnancy and lactation In animal studies no untoward effects on the embryonic or foetal development were exerted by daily intravenous administration of gadobenate dimeglumine in rats. Also, no adverse effects on physical and behavioural development were observed in the offspring of rats. However, after repeated daily dosing in rabbit, isolated cases of skeletal variations and two cases of visceral malformations were reported.

6.1 List of excipients Water for injections.

6.2 Incompatibilities MultiHance should not be admixed with any other drug.

6.3 Shelf life 36 months

6.4 Special precautions for storage Do not freeze.

6.5 Nature and contents of container 5 mL, 10 mL, 15 mL and 20 mL of a clear aqueous solution filled into colourless type I glass vials with elastomeric closures, aluminium sealing crimps and polypropylene caps.

6.6 Instruction for use/handling MultiHance should be drawn up into the syringe immediately before use and should not be diluted. Before use, examine the product to assure that the container and closure have not been damaged. Any unused product should be discarded.

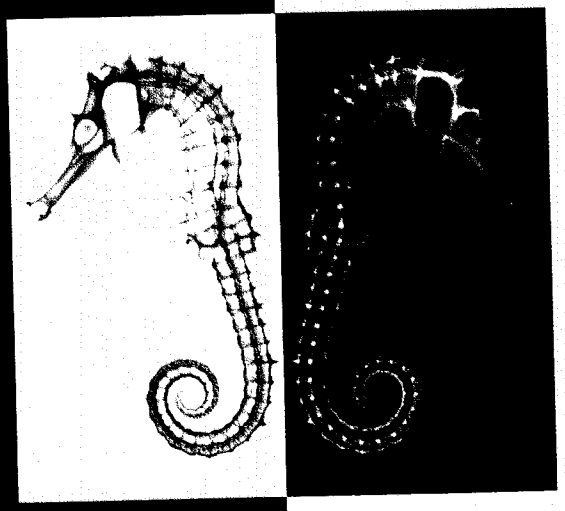
September 15, 2000

Advances in Magnetic Resonance Angiography

HIGHLIGHTS FROM THE SATELLITE SYMPOSIUM

ESMRMB MEETING

SEVILLE, 1999



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Index

Introduction

In the 15 years since the first magnetic resonance (MR) imaging contrast agent was approved, innovation in techniques, technology and imaging pharmaceuticals has led to the development of an extensive array of new MR products. A recent product in the pharmaceutical imaging sector is MultiHance®.

MultiHance® a novel gadolinium-based magnetic resonance imaging contrast agent

MultiHance® (gadobenate dimeglumine, Gd-BOPTA) is a novel gadolinium-based magnetic resonance (MR) imaging contrast agent. MultiHance® belongs to the Gd+3-chelate group of paramagnetic MR contrast agents which includes Dotarem®, Magnevist®, Omniscan®, ProHance®. The GD+3-chelates are general purpose imaging products which, following intravenous administration, distribute throughout the extracellular fluid space before undergoing renal excretion. Compared to the other gadolinium chelates on the market, MultiHance® has the highest relaxivity in aqueous solution and in protein-containing aqueous solutions. This is an important feature since relaxivity reflects the ability of a contrast agent to influence the relaxation time of water protons in tissue and hence indicates the contrasting efficacy of a contrast agent in MR imaging.

Initially 3D contrast enhanced MR Angiography was used in patients suspected of having pulmonary embolism and in the visualization of aorta coarctation and aneurysmal dilatations. Currently, MR Angiography in combination with the use of gadolinium chelates is being seen as a serious alternative to other techniques for the assessment of renal vascular disease.

Clinical implications in diagnosis of renal vascular disease

Renal artery stenosis (RAS) is the leading cause of renovascular hypertension. Although RAS accounts for only 1-5% of all cases of hypertension, its diagnosis is imperative because of the possibility of a cure by means of percutaneous transluminal angioplasty, stenting, or surgical revascularization. Currently, conventional X-ray angiography provides definitive anatomic confirmation of stenosis. However, this technique is invasive, costly and inappropriate for the delineation of narrowings that actually cause hypertension. Ultrasound allows assessment of the renal arteries but is operator-dependent and of limited usefulness for a definitive presurgical evaluation of the renal vascular anatomy. CT angiography is a readily available robust procedure but requires a dose of radiation and suffers from the possibility of nephrotoxicity due to the iodinated contrast agents required for this procedure. These drawbacks have increased the need for a reliable, noninvasive, and nonionizing imaging method.

New technological advances in MR imaging combined with the introduction of contrast-enhanced gadolinium chelate angiography have addressed shortcomings such as motion artifacts and saturation effects. Furthermore, advances in gradient performance and MRI sequence design have enabled high speed imaging with resolution up to 1 mm and visualization of the entire renovascular tree. Excellent sensitivity and

specificity in the renal arteries to the level of the renal hilium as well as in the superior mesenteric artery and the celiac trunk have been reported.

In MRA an optimized image of the renal arteries depends on synchronization of peak vascular enhancement and central K-space acquisition. Optimized synchronization has traditionally been determined by means of prior test bolus tracking using 1 to 2 ml of gadolinium chelate injected at the same flow rate as the full dose. Vascular enhancement is then assessed at the chosen location by single slice acquisition. The operator then determines the start time for the angiographic sequence. The disadvantages of this technique include firstly, operator-dependent error, resulting for example, in a delay in the administration of the contrast agent and hence acquisition, and secondly, pelvic enhancement overlay in which enhancement of vascular structures by test bolus and full dose are superimposed.

Multiphase MRA is a new technique which does not require a prior test bolus of contrast agent; it allows the distinct vascular phases to be viewed separately and is preferred for assessment of the distal renal arteries.

Optimized vascular contrast is the most important criteria for successful 3D contrast enhanced MR imaging. Gadobenate dimeglumine (MultiHance®) has been shown to improve intravascular contrast due to a higher relaxivity mediated through weak and transient interaction with serum proteins such as albumin. A recent study has shown that gadobenate dimeglumine provides higher and longer-lasting vascular enhancement than the non-protein binding gadolinium chelate Gd-DTPA.

In the clinical management of renal vascular disease consideration is given to the hemodynamic extent of stenosis as well as to the morphologic pathology. MRA together with a non nephrotoxic contrast agent permits a comprehensive and reproducible assessment of renal artery stenosis in a single exam. MRA combines within a single exam an assessment of the morphology of the renal artery with a quantification of flow dynamics and a semi-quantitative visualization of renal perfusion and excretion. This gives MRA an advantage over other techniques in terms of cost effectiveness and patient quality of life.

Essential reading

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Vascular imaging of renal arteries: from morphology to function

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Vascular imaging has in recent years undergone a transformation from an invasive to a non-invasive procedure. Although morphology remains an important aspect of diagnosis, MR Angiography (MRA) is providing diagnostic examinations with functional information. It is now possible to image the vasculature in terms of perfusion and excretion properties. Indeed, MRA can be considered a state of the art technique for non-invasive imaging.

MRA INTEGRATES FUNCTIONAL INFORMATION AND MORPHOLOGY INTO DIAGNOSTIC EXAMINATIONS

The possibility to integrate imaging of parenchymal tissue permits not only vascular information to be obtained, but also information on cortical tissue. This additional information has led to the development of techniques to image during the arterial phase, the venous medullary phase and the excretory phase. Adding this information to morphology can dramatically improve diagnostic capabilities.

Advances in renal MRA

The important advances that have been made in renal MRA in recent years are summarized in **Table 1**.

Table 1. Advances in renal MRA

• Introduction of 3D-Gd-MRA
• Increasing speed (gradients systems)
• Use of coils (phased array)
• Improved timing techniques
• Breath-hold flow measurements
• Time resolved techniques
• New contrast agents
• T2* perfusion imaging

Scan times

SCAN TIMES HAVE BEEN REDUCED TO ALLOW MULTIPLE ACQUISITIONS WITHIN A SINGLE BREATH-HOLD

Until 1995, scan times for contrast-enhanced MRA were around 3.3 minutes and image quality was generally poor. However, scan times were subsequently reduced to within a single breath-hold and there is increasing awareness of how to optimize central K-space and timing in order to improve image quality.

Bolus tracking

The importance of bolus tracking and the very short window of time available to optimize imaging as the contrast agent passes through the vascular system cannot be over-emphasized. An optimized image depends on the synchronization of peak vascular enhancement and central K-space acquisition. The timing of the contrast injection and the start of the sequence can be determined for the individual patient by means of bolus tracking.

Triggering technique

One of the biggest advances in timing has been the introduction of triggering techniques[1]. The ability to overcome mistiming, for example, may lead to a further improvement in consistent image quality, which, combined with a reproducible technique, is very important in everyday practice. However, while these techniques appear robust in theory, in practice they pose a number of challenges.

Enhancement kinetics

An understanding of enhancement kinetics is vital and studies are underway to assess this in the renal artery **(Figure 1)**. Tailoring the multiphasic time-resolved acquisition to the enhancement kinetics of the region of interest will enable imaging of the distinct phases[2]. Although morphology can be analyzed, repeating the process will provide information on the early and late arterial phases.

This additional information will provide more information not only on the vasculature,

Figure 1. Renovascular system: enhancement kinetics

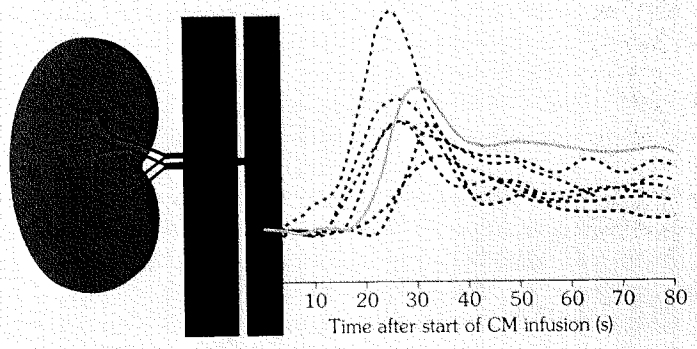
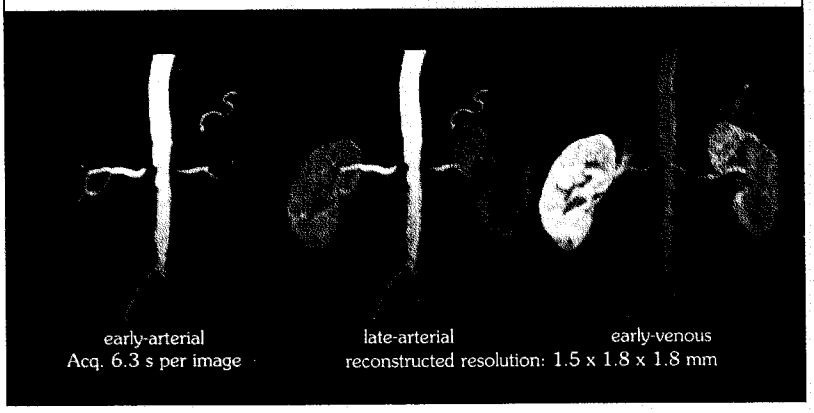


Figure 2. Multiphasic 3D-Gd-MRA



but also on renal performance **(Figure 2)**. The next step will be to integrate this information for use on a reliable basis in order to image large vascular territories – an important aspect of patient management [3].

Multiphasic MRA – the benefits

The initial aim of multiphasic MRA was to have a fast and reliable imaging technique that did not require bolus timing. However, time-resolved visualization of anatomic structures should also be able to show the different enhancement kinetics. These differences can then be used to characterize functional and pathological changes and to take flow measurements.

K-space

One of the approaches currently being investigated is that of increasing the speed by means of innovative techniques to read the K-space. With this approach, K-space acquisition can be tailored to provide high contrast and good contrast resolution. Although a reduction in the K-space to 60%, or even 25%, has very little impact on image quality, a reduction to 13% is associated with a deterioration in image quality.

A SUBSTANTIAL REDUCTION OF K-SPACE READOUT HAS LIMITED IMPACT ON IMAGE QUALITY

Multiphasic MRA has been especially helpful for the assessment of renal artery stenosis, as it is possible to evaluate not only the morphology, but also the time of parenchymal enhancement. There is also the advantage of improved visualization of distal vessels. There is no requirement for bolus tracking and hence contrast agent is not found in the renal pelvis – this is a reliable and consistent advantage for this method. Application of this technique is continually leading to improvements in the diagnostic capabilities for the intra-renal branches. However, it is important not only to rely on Maximum Intensity Projection (MIP) images, but also to evaluate the source images and multiplanar reconstructions. A blinded reader analysis, published earlier this year compared multiphase acquisition to the standard single-phase acquisition. There were significant advantages for the multiphasic MRA, thus showing the clear diagnostic advantages of this method.

CLEAR DIAGNOSTIC ADVANTAGES WITH MULTIPHASIC MRA

Exciting developments in contrast agents

One of the most exciting aspects in the development of MRA has been the introduction of new contrast agents [4]. There are basically two main categories of contrast agent: the paramagnetic and the superparamagnetic. Most of the work to date has been conducted with the standard gadolinium chelates which can be mainly characterized as non protein binding. The variations now emerging include the introduction of weakly protein interacting contrast agents, such as gadobenate dimeglumine (MultiHance®), and the future introduction of agents which undergo strong protein interaction, such as MS-325 (AngioMARK®).

ONE OF THE MOST EXCITING ASPECTS IN THE RECENT DEVELOPMENT OF **MRA** HAS BEEN THE INTRODUCTION OF NEW CONTRAST AGENTS

The advances in contrast agent development are summarized in **Table 2** [5,6].

Table 2. Advances in contrast media

• Different types of contrast agent available
• Higher concentrations
• Protein-interacting gadolinium chelates – weak (e.g. MultiHance®) – strong (e.g. AngioMARK®)
• Supraparamagnetic intravascular contrast agents

Only small modifications required for clear differences

Only small modifications to the structure of gadolinium chelates were necessary to achieve quite striking differences in properties; for example, using the same dose, contrast agents undergoing weak protein interaction give a higher signal intensity and a wider peak, as well as a higher contrast intensity in the later venous phase [7]. Daily clinical experience suggests that improved homogeneity and increased overall enhancement of the vasculature is possible with agents that undergo weak protein interaction as compared with standard agents. This has been demonstrated by a recent phase I study comparing gadobenate dimeglumine and gadopentetate dimeglumine [8]. In this study it was shown that gadobenate dimeglumine provides higher and longer-lasting vascular enhancement than the non protein binding gadolinium chelate **(Figure 3)** [9]. However, it is important to continue to develop improved techniques for differentiation and segmentation in order to be able to clearly delineate the different venous and arterial vasculatures.

ONLY VERY SMALL MODIFICATIONS TO THE STRUCTURE OF GADOLINIUM CHELATES ARE NECESSARY TO ACHIEVE QUITE STRIKING DIFFERENCES IN PROPERTIES

How good is MRA in assessment of stenosis?

Recent animal studies have been conducted to evaluate the use of MRA in the assessment of stenosis [10]. In one study the animals were implanted with ultrasound measurement probes and various clamping techniques were employed to create different degrees of stenosis in the renal artery [11]. There was excellent agreement (up to 80%) between the degree of stenosis measured with MRA and the actual degree

THERE WAS EXCELLENT AGREEMENT BETWEEN THE DEGREE OF STENOSIS MEASURED WITH **MRA** AND THE ACTUAL DEGREE OF STENOSIS

Figure 3. Gd-DTPA (Magnevist®) *vs.* Gd-BOPTA (MultiHance®) image quality

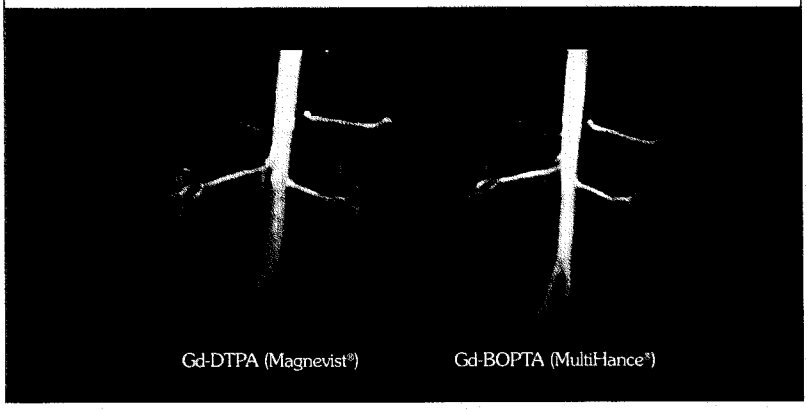
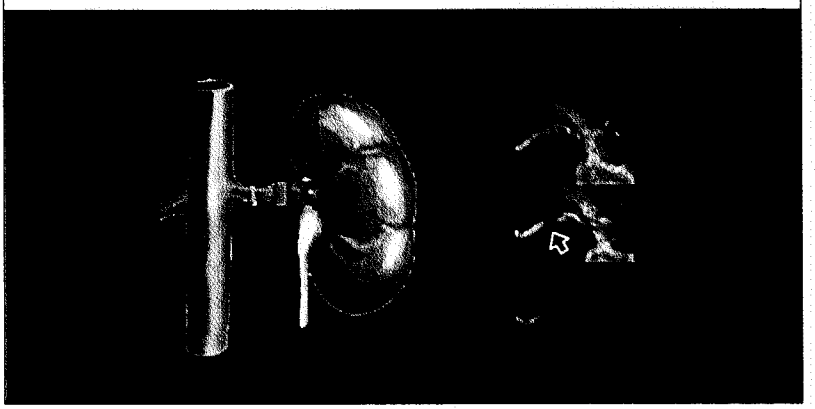


Figure 4. Invasive validation in animal model



of stenosis measured with the ultrasound probe **(Figure 4)**. However, it is possible that over-estimation might occur in cases where there is a high degree of stenosis.

What can we achieve with MRA?

MRA PROVIDES AN EXCELLENT TOOL TO QUANTIFY THE FLOW PROFILE AND ASSESS HEMODYNAMICS

The ultimate goal of current research is to integrate morphology with hemodynamics and eventually also to incorporate perfusion parameters; in other words, to assess the hemodynamic relevance of morphological changes. For a long time MR phase contrast flow measurement has been used. This permits the rapid acquisition of a flow profile and an evaluation of the true hemodynamics of flow, as well as an assessment of mean flow. The flow curve can be useful for qualitative analysis and for the evaluation of characteristic patterns, which are of great diagnostic value. The good agreement between MRA and the invasive ultrasound probes for the measurement of flow indicates that MRA is an excellent tool for the quantification of the flow profile and the assessment of hemodynamics.

INTER-OBSERVER AND INTER-MODALITY VARIABILITY ARE CONSIDERABLY BETTER FOR **MRA** COMBINED WITH FLOW MEASUREMENT THAN FOR **DSA**

A grading system has been developed to grade the different levels of stenosis. A multi-reader analysis showed that inter-observer and inter-modality variability are considerably better for MRA combined with flow measurement than for DSA. Thus, while DSA is considered to be the gold standard, it is important to remember the great variability in quality with this technique. Combining MR with flow measurement appears to give the best diagnostic capability [12].

COMBINING MRA WITH FLOW MEASUREMENT GIVES THE BEST DIAGNOSTIC CAPABILITY

MRA for assessment of perfusion

Changes in renal arteries may not only be due to stenosis, but also to parenchymal damage. 'Fine tuning' of renal evaluations is now possible which permit evaluation of perfusion characteristics. One of the techniques that has been developed is to measure parenchymal perfusion using a T2*-weighted technique and to compare this with renal scintigraphy. Excellent assessment of perfusion can be achieved using this technique. Thus, it is now possible to use MRA for assessment of morphology, for flow measurement assessment of hemodynamics and now for assessment of the true perfusion of the kidneys.

EXCELLENT ASSESSMENT OF PERFUSION CAN BE ACHIEVED USING A T2*-WEIGHTED TECHNIQUE

Differentiation between contrast agents

It is now becoming clear that reproducible differences between contrast agents exist and a future challenge will be to use these distinct properties to improve diagnostic capability. A multiphasic MRA study is currently underway to assess contrast agent-dependent vascular enhancement following administration of gadobenate dimeglumine (MultiHance®) and gadopentetate dimeglumine (Magnevist®) [1]. In this study it has so far been observed that signal intensity in the suprarenal aorta during each phase is stronger for MultiHance® than for Magnevist® at 0.15 mmol/kg BW and 3 ml/s. The capacity of MultiHance® for weak protein interaction leads to a higher vascular enhancement during the early arterial and late venous phases.

REPRODUCIBLE DIFFERENCES BETWEEN CONTRAST AGENTS EXIST

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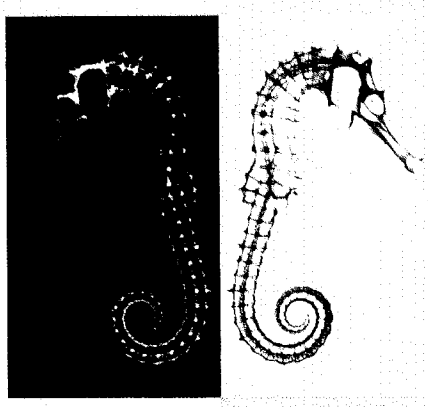
New Perspectives in Contrast Enhanced Vascular Imaging

HIGHLIGHTS FROM THE SATELLITE SYMPOSIUM

CIRSE MEETING

PRAGUE, 1999



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Contents

New Perspectives in Magnetic Resonance Angiography

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MRA IS AN ACCURATE, RAPID, REPRODUCIBLE, INEXPENSIVE AND CLINICALLY VALID TECHNIQUE WHICH PERMITS A COMPREHENSIVE, TRULY THREE-DIMENSIONAL ASSESSMENT OF BOTH MORPHOLOGY AND FUNCTIONALITY

Contrast enhanced 3D-MR Angiography (MRA) has recently received a lot of attention as it has undergone development from a research procedure to state of the art in diagnostic imaging [1]. Outside of the central nervous system, imaging of the renal arteries is currently of great interest in every day diagnostic patient work-up. In the elderly, patient imaging of vascular disease is particularly important because of its comparatively high incidence and severity in this population.

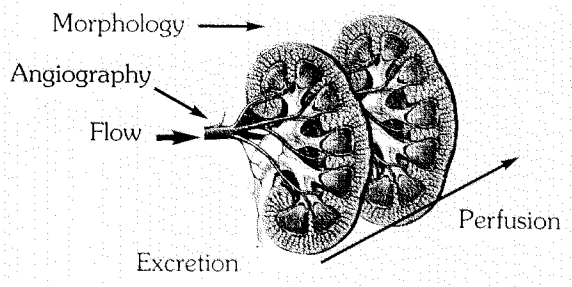
Compared with other non-invasive imaging techniques such as ultrasonography which is highly operator-dependent and subject to bowel gas or fat overlay, and CT Angiography which requires exposure to radiation and to potentially nephrotoxic complications due to the iodinated contrast agents, MRA is an accurate, rapid, reproducible, inexpensive and clinically valid technique which permits a comprehensive, truly three-dimensional assessment of both morphology and functionality.

Advances in MR Angiography

MRA IS BEING RECOGNIZED FOR VASCULAR IMAGING DUE TO THE INTRODUCTION OF THREE-DIMENSIONAL ASSESSMENT AND NEW TIMING TECHNIQUES, TO THE INCREASING SPEED, TO THE USE OF NEW COILS AND THE AVAILABILITY OF NEW CONTRAST AGENTS

Until recently, the potential of MR contrast agents such as the conventional Gd-chelates has not readily been recognized for vascular imaging [2]. Their potential has become obvious recently due to the advances in MR Angiography [3]. These advances include the introduction of 3D-Gd-MRA, increased speed, the use of coils, new timing techniques such as bolus tracking [4] or time resolved (multiphasic) imaging [5], the possible acquisition of functional information through breath-hold flow measurements, the availability of newer MR contrast agents with improved properties over conventional Gd-agents, and the development of T2*-weighted techniques, which allow excellent assessment of perfusion **(Figure 1)** [3-7].

Figure 1. MRA techniques allow imaging of the vasculature, perfusion and excretion of the renal arteries

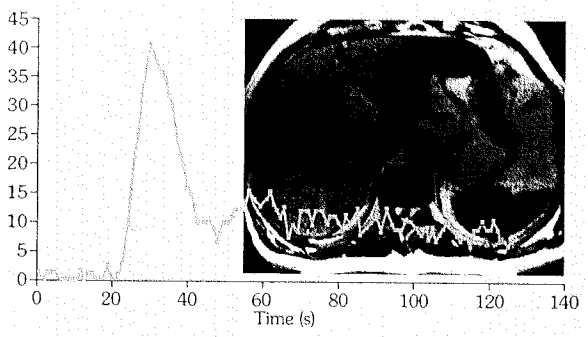


What is needed to improve image quality?

To improve image quality the angiographer needs to have an understanding of MR physics, to supervise image acquisition and to develop a "feel" for the injection. Furthermore, exams need to be performed on an emergency basis with fast set-up, fast image processing and ready interpretation of results.

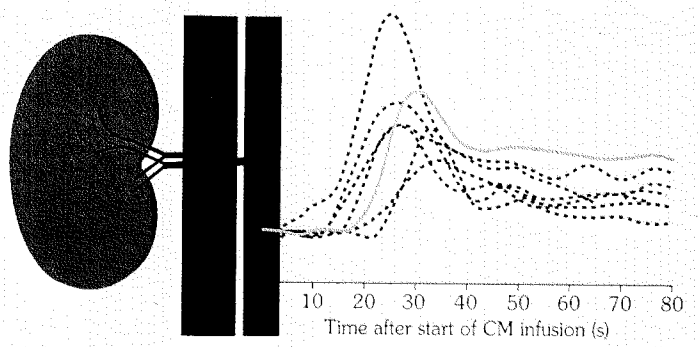
In MR Angiography timing is everything, in fact there is a very short time frame available to optimize imaging as the contrast agent flows through the vascular system **(Figure 2)**.

Figure 2. Example of the short time frame of the availability of a contrast test bolus



Understanding and using temporal resolved contrast enhancement techniques in the region of interest (e.g. the renovascular system) will enable imaging of the distinct phases. In fact, by looking at the time intensity curves obtained while the contrast bolus passes through the aorta, the renal arteries and the distant vessels, we can use timing of the enhancement techniques in order to get time-resolved images **(Figure 3)**.

Figure 3. Renovascular system: enhancement kinetics



THERE ARE FOUR APPROACHES TO TIMING IN MR ANGIOGRAPHY: EMPIRIC APPROACH, TEST BOLUS APPROACH, USE OF AUTOMATIC DETECTION TECHNIQUES AND MULTIPHASIC FAST (TIME-RESOLVED) IMAGING

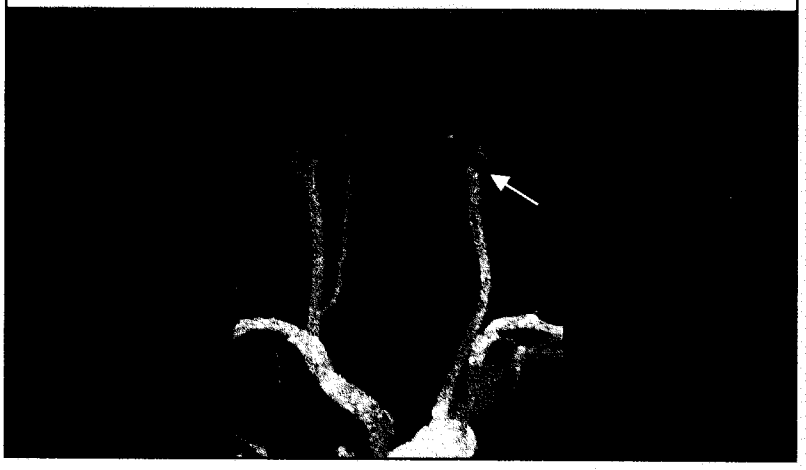
There are four approaches to timing in MR Angiography. The easiest one, if the angiographer is very experienced, is the empiric approach, which is a valid method but not very reproducible in a general setting. Currently, the standard approach is to use a test bolus, which is comparable to other techniques used in Angiography and CT. Recently, automatic detection techniques, like MR Smartprep® and Bolus Trak MR Fluoroscopy have been introduced [6,7]. Another technique actively being developed is multiphasic fast (time-resolved) imaging.

Before 1995, scan times for contrast-enhanced MRA were around 3.3 minutes and image quality was considered poor. Today, scan times have been reduced to within a single breath-hold. Furthermore, there is increasing awareness on how to optimize K-space readout and sequence design in order to improve image quality.

Bolus tracking technique

Optimized MR Angiography depends on the synchronization of peak vascular enhancement and central K-space acquisition. The highest image contrast is achieved only during the peak vascular gadolinium concentration. A bolus tracking technique is one way to synchronize the timing of the acquisition **(Figure 4)**.

Figure 4. Bolus timed MRA with Gd-BOPTA of the carotid arteries

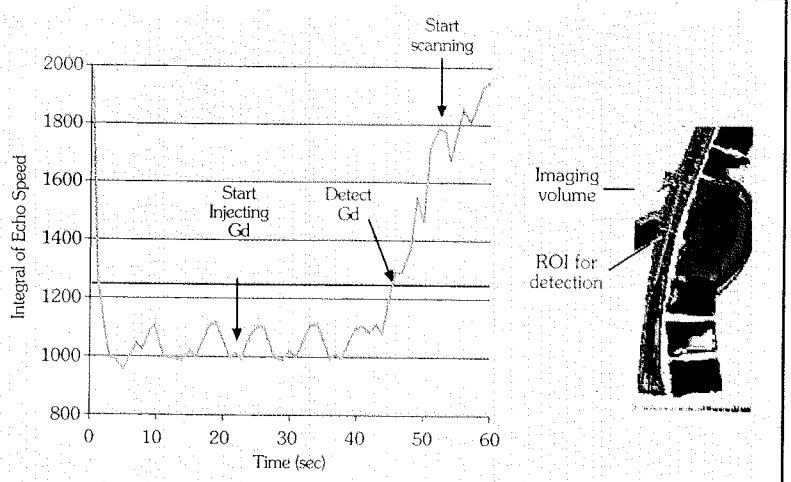


With this technique, a small volume of gadolinium chelate is injected with the same flow rate as the full dose with vascular enhancement assessed by means of dynamic single slice acquisition at the desired location. A subsequent analysis of the time enhancement curve allows calculation of the optimized start time for the full angiographic sequence. A major disadvantage of this approach however is that it is often subject to operator-related variations.

Triggering technique

Smartprep® is an automated on-line trigger technique, introduced in 1996, for detecting vascular contrast enhancement [8]. The approach used in Smartprep® is to set the

Figure 5. Automatic Gd Detection with MR Smartprep®



Courtesy of M. Prince

trigger the image acquisition phase **(Figure 5)**. This technique has led to significant improvements in reproducible image quality of the vasculature.

Multiphasic MR Angiography

A multiphasic or time-resolved approach has the advantage of not requiring an individual acquisition window to be predetermined. Moreover, it is reasonably operator- and equipment-independent, and provides information on both morphology and function [8]. The use of multiphasic MRA allows rapid sequential visualization of distinct vascular phases within one breath-hold, and provides more information than standard single-phase MRA. In **Figure 6** five sequential acquisitions, performed every 6.3 seconds, using 0.15 mmol/kg BW of gadobenate dimeglumine are shown. The image shows strong homogeneous vascular enhancement and all the different vascular phases.

MULTIPHASIC MRA MAKES IT POSSIBLE TO LOOK AT THE EARLY ARTERIAL, LATE ARTERIAL AND EARLY VENOUS PHASES AND ALSO TO GET INFORMATION ON THE MORPHOLOGY AND PHYSIOLOGY OF CERTAIN ORGANS, E.G. THE RENAL VESSELS AND RENAL PERFORMANCE

This approach makes it possible to look at the early arterial, late arterial and early venous phases and also to get information on the morphology and physiology of certain organs, e.g. the renal vessels and renal performance **(Figure 7)**.

The initial aims of multiphasic MRA were to have a fast and reliable imaging technique that did not require bolus timing and to visualize anatomic structures in a time-resolved fashion in order to show the different enhancement kinetics. Differences in enhancement kinetics can be used to characterize functional and pathological changes.

One of the approaches currently being investigated is to increase the speed by means of innovative techniques to read the K-space. A reduction in the K-space of 60% has very little impact on image quality.

Multiphasic MRA is also very helpful in assessing the time to parenchymal enhance-

Figure 6. Multiphasic MRA with Gd-BOPTA (MultiHance®)

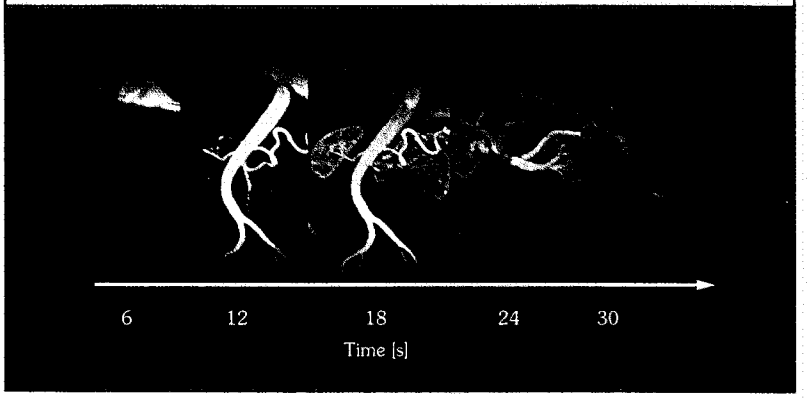


Figure 7. Multiphasic 3D-Gd-MRA

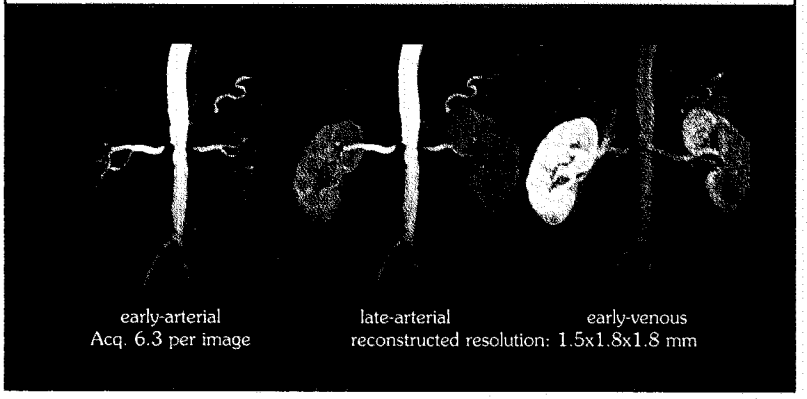
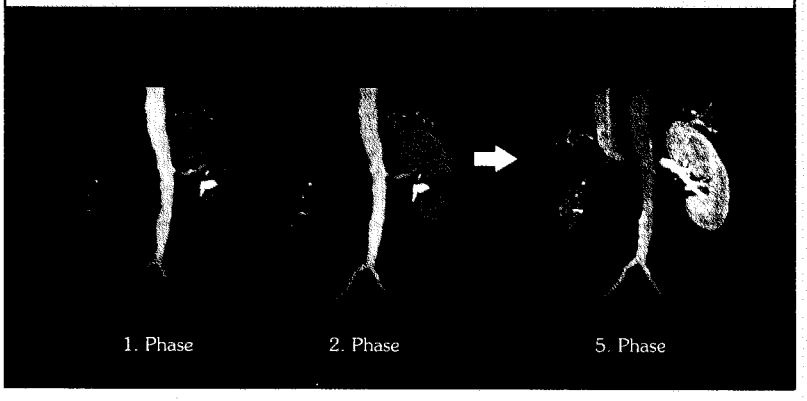


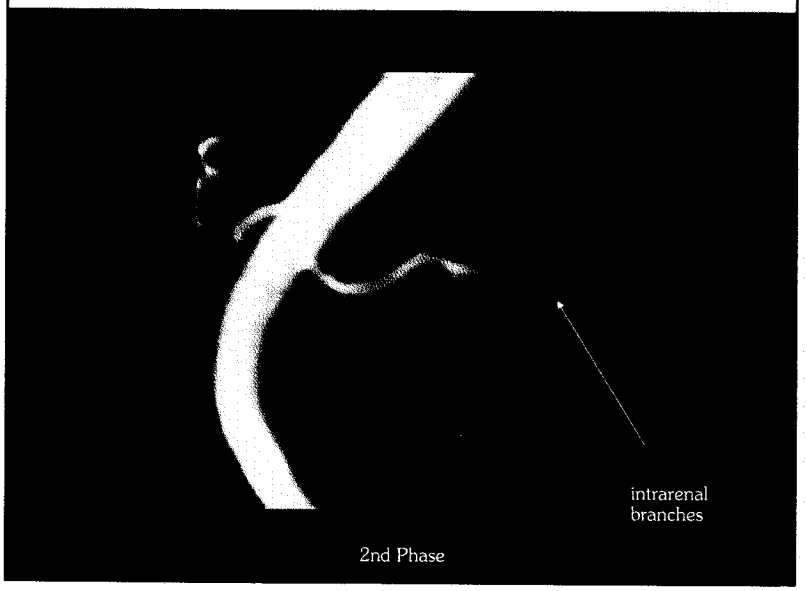
Figure 8. Multiphasic 3D-Gd-MRA: Renal artery stenosis



Applications of MR Angiography to extrarenal vascular territories

Compared to X-ray DSA, MR Angiography needs still to improve image resolution. By means of the above improvements, intrarenal vessels can be detected and evaluated; this is still the biggest challenge in renal MRA **(Figure 9)**. MR Angiography can be applied not only to the renovascular system but also to all vascular territories, e.g. the carotid arteries, the iliac vessels and run-off vessels.

Figure 9. Multiphasic MRA with Gd-BOPTA (MultiHance®)



MR Angiography and the pulmonary vasculature

One of the most recent challenges of MR Angiography is to use this technique to evaluate the pulmonary vasculature [9]. The aim is to separate angiograms of lung arteries and veins without venous or arterial overlay with the use of a 3D multiphase technique and by having a mean bolus transit time between the arterial and the venous pulmonary vasculature of approximately 3 seconds. The subtraction of the base image can be used to obtain reproducible images of high quality in the pulmonary vasculature. Another improved technique is the use of a correlation procedure to determine separation of the arterio-venous system. This permits the acquisition of high resolution pulmonary images **(Figure 10)** [10].

THE TAILORED INJECTION SCHEME DETERMINES THE OPTIMIZATION AND VISUALIZATION OF THE DIFFERENCES BETWEEN THE PULMONARY ARTERIAL AND VENOUS SYSTEM

One approach is to tailor the injections of the contrast agent on the basis of the vascular territory and the acquisition scheme. The Tailored Injection Scheme follows the concept of very small multiple boli injections, and permits optimization of the differences between the arterial and venous systems. Using the correlation technique the differentiation between the arterial and venous pulmonary vessels can be further optimized **(Figure 11)**. This technique can be used not only for the pulmonary system, but also for other vascular territories.

Figure 10. Subtraction and correlation techniques

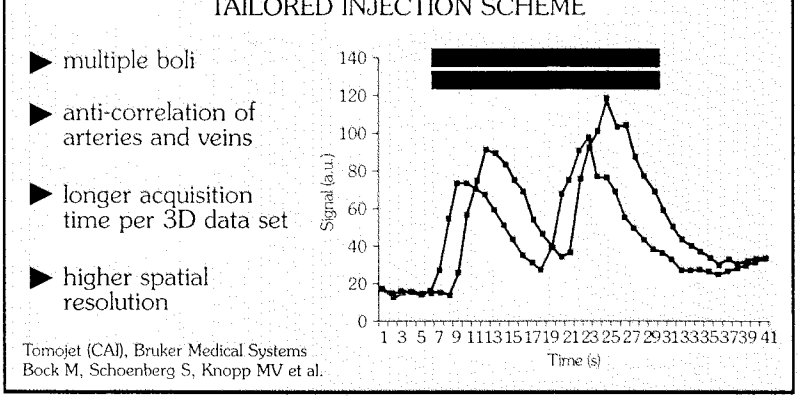


Figure 11. Multiple Bolus Injection

MR Angiography and the porto-venous system

A concept similar to the one described above is used to evaluate the liver. Dual-phasic imaging allows the angiographer to look at the arterial and porto-venous phases, in order to obtain remarkable image quality and a potential correlation between information on the vasculature and the parenchyma **(Figure 12)**.

In a recent study, we performed triphasic 3D acquisitions of liver lesions in order to determine whether the angiographic information available with this technique would be of benefit in the clinical setting[11]. **Figure 13** shows a case of hepatocellular carcinoma and metastases in which the Angiography provided a great deal of additional information to that obtained in the morphological evaluation.

It is very important not only to look at the Maximum Intensity Projection (MIP), but also to go back to the source images and look at multiplanar reconstructions **(Figure 14)**. These images provide a lot of information, due to their truly three-dimensional nature. The high vascular contrast obtained allows the detection of small variations in the vascular system thereby improving the diagnosis of hepatocellular carcinoma

This can lead to improved collaboration with surgery and benefit concepts such as minimal invasive surgery with virtual surgical planning.

By combining angiographic features with morphology, we establish our diagnostic reports on the basis of the early-arterial phase, the late-arterial phase and the porto-venous phase of the liver. Hence we can provide an assessment of the parenchyma, of the vasculature and of the microcirculation of liver lesions.

COMBINING ANGIOGRAPHIC FEATURES WITH MORPHOLOGY, WE CAN PROVIDE AN ASSESSMENT OF THE PARENCHYMA, OF THE VASCULATURE AND OF THE MICROCIRCULATION OF LIVER LESIONS

Figure 12. Porto-venous system: Dual-phasic Imaging

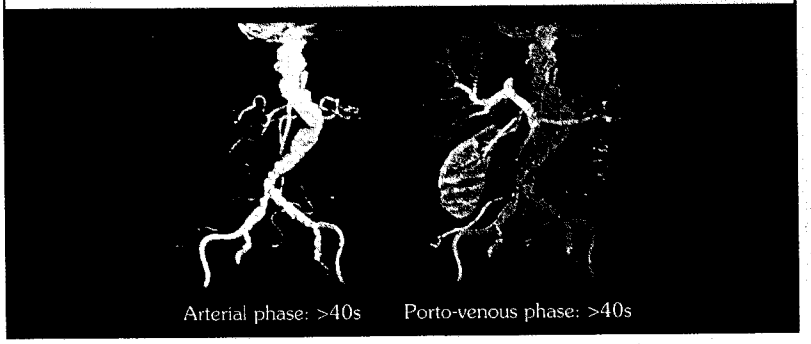


Figure 13. Triphasic 3D imaging for liver lesions

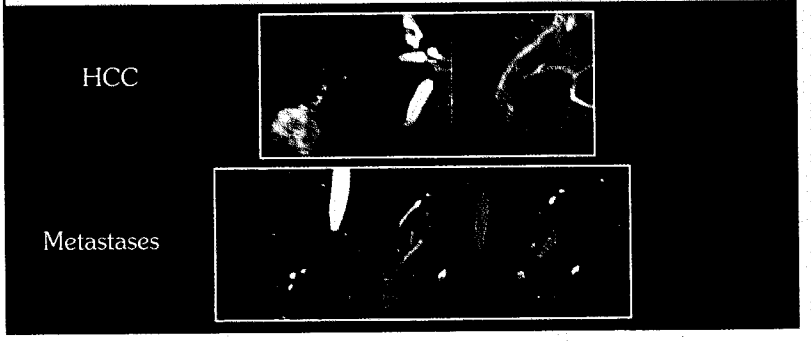
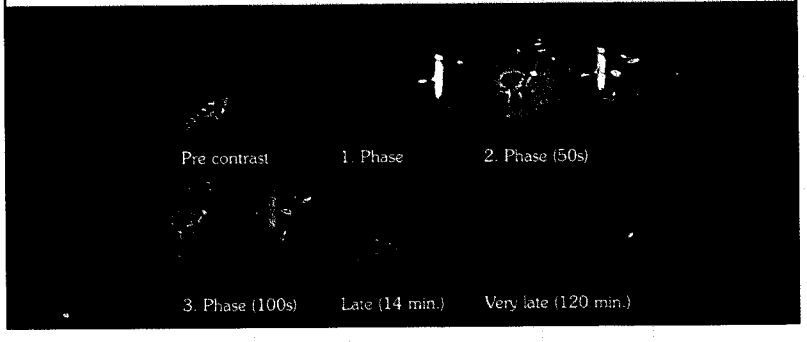


Figure 14. Multiphasic MRA of the liver



Bolus chase peripheral MR Angiography

With the bolus chase technique it is possible to visualize large volumes of the cardiovascular system with superb quality[12,13]. If bolus chase technique is not available, then many images have to be acquired and put together in order to image large areas of the cardiovascular system.

Phase contrast flow measurements

Another aim of MR Angiography is to assess the hemodynamic relevance of morphological changes. For quantitative assessment of hemodynamics in the vessels, we have the possibility to use MR phase-contrast flow measurements[14]. This technique establishes the flow pattern in the vasculature. As an example, **Figure 15** shows the flow pattern separated as early systolic peak, incision, main systolic peak and diastolic flow in the renal vasculature. Any changes in the flow profile can be used to assess the hemodynamic relevance.

This method has been validated in collaboration with physiologists. We have verified that the MRA flow gives extremely reproducible results compared to invasive ultrasound measurements[15]. MRA is therefore an excellent tool to quantify the flow profile and to assess the hemodynamically relevant stenoses **(Figure 16)**. As the degree of stenosis increases, there is a significant change in the flow profile pattern.

This has been integrated into a one-stop exam combining the angiographic images and the flow measurements of the right and left renal arteries. This clearly demonstrates the hemodynamic relevance of the renal artery stenoses (RAS) **(Figure 17)**[16].

Figure 15. MR phase contrast flow measurement

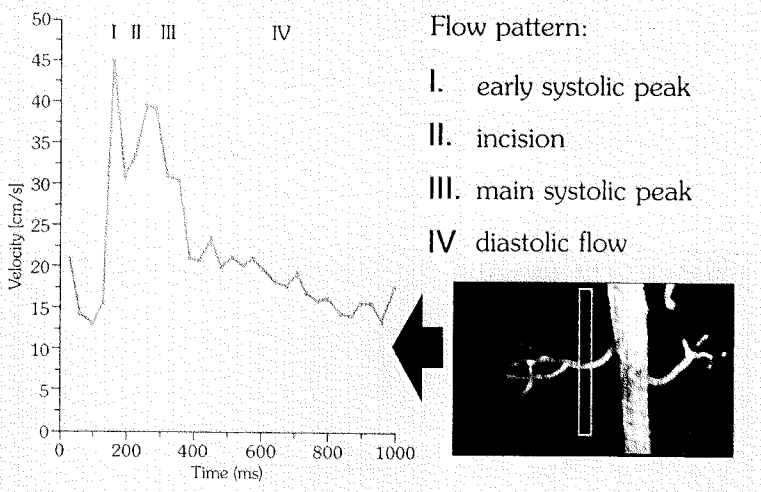


Figure 16. Invasive validation: MRA flow *versus* TT-US

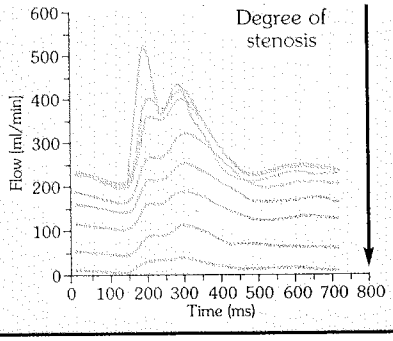
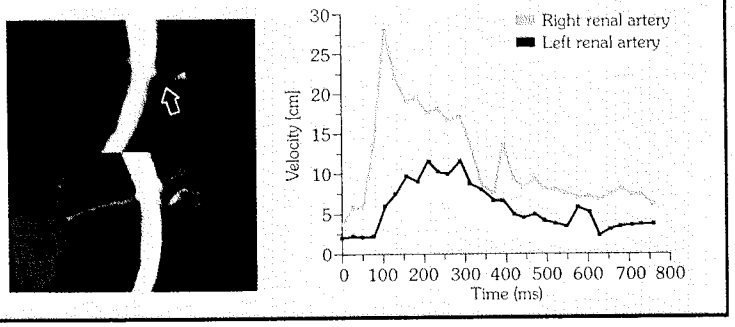


Figure 17. RAS: Morphologic, functional and hemodynamic changes



Contrast agents for MR Angiography

One of the most important aspects in the further development of MRA has been the availability of different contrast agents and the introduction of new ones[17]. There are basically two main categories of contrast agent: the paramagnetic and the superparamagnetic **(Table 1)**.

THE AVAILABILITY OF DIFFERENT CONTRAST AGENTS AND THE INTRODUCTION OF NEW ONES ARE IMPORTANT ASPECTS IN THE DEVELOPMENT OF MRA

Table 1. Contrast agents for MR Angiography

PARAMAGNETIC			SUPERPARAMAGNETIC	
Non protein binding	Weakly protein interaction	Strong protein binding	SPIO	USPIO
Gd-DTPA, Magnevist® Gd-DO3A-butriol, Gadovist® Gd-DOTA, Dotarem® Gd-DTPA-BMA, Omniscan® Gd-HP-DO3A, ProHance®	Gd-BOPTA, MultiHance®	MS-325, AngioMark®	Coated with dextran SHU 555, Resovist®	Coated with Starch NC100150, Clariscan®

Most of the work to date has been conducted with standard "extracellular" gadolinium (Gd) chelates (i.e. Magnevist®, Gadovist®, Dotarem®, Omniscan®, and ProHance®). These agents are largely comparable among themselves and do not possess any capacity for protein interaction.

GADOBENATE DIMEGLUMINE IS A NEWER CONTRAST AGENT WHICH APPEARS PROMISING FOR MRA GIVEN ITS HIGHER INTRAVASCULAR RELAXIVITY DUE TO A CAPACITY FOR WEAK AND REVERSIBLE PROTEIN INTERACTION

Newer contrast agents which appear promising for MRA demonstrate higher intravascular relaxivity due to a capacity for weak and reversible protein interaction, e.g. gadobenate dimeglumine (Gd-BOPTA, MultiHance®)[18,19] or strong protein interaction e.g. MS-325 (AngioMark®)[20].

Other promising contrast agents are the superparamagnetic ones such as Nc100150 (Clariscan®). These agents have an iron or manganese base and are considered to be "intravascular" agents[17,21]. The main difference between the extracellular contrast agents and the intravascular agents is that most intravascular agents are currently not suitable for first pass 3D MRA and hence are used in the equilibrium phase only. While providing excellent vascular contrast, the inherent drawback of these agents is the concurrent enhancement in the arterial and venous systems with subsequent extensive vascular overlay. As a consequence, sophisticated post processing is required in most cases. Further developments are needed to utilize the potential of these agents in a more optimized way. Recent developments in contrast agents include also introducing higher concentrations such as 1.0 M Gadovist®. The development of contrast agents with new features such as the weak or strong protein interaction as seen in MultiHance® and AngioMark® or supraparamagnetic properties such as Clariscan® is a particularly exciting ongoing process.

The molecular structure of gadobenate dimeglumine (MultiHance®, **Figure 18**) is very similar to that of gadopentetate dimeglumine (Magnevist®) indicating that only very small modifications to the structure of gadolinium chelates are necessary to achieve weak protein interaction.

In an intra-individual comparison of gadolinium chelates at the same dose, it was observed repeatedly that contrast agents with weak protein interaction give a higher signal intensity and a wider peak, as well as a higher contrast intensity in the later venous phase **(Figure 19)**[19].

Figure 18. Molecular structures of Gd-BOPTA (MultiHance®)

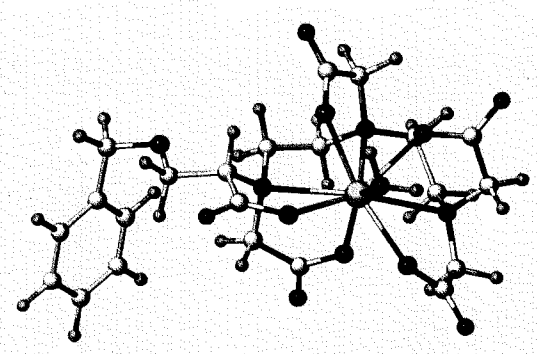
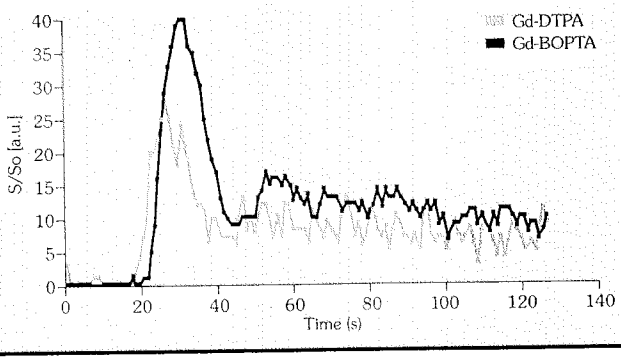


Figure 19. Phase I: Intra-individual comparison of Gd-BOPTA (MultiHance®) *versus* Gd-DTPA (Magnevist®)



In daily practice, we have found improved homogeneity and increased overall enhancement of the vasculature with agents that have weak protein interactions as compared with standard agents **(Figure 20)**.

The stronger vascular enhancement and higher signal intensity obtained with MultiHance® in comparison with Magnevist® [5], can also be seen when using techniques that involve multiphasic acquisitions **(Figure 21)** [22].

CONTRAST AGENTS WITH WEAK PROTEIN INTERACTION, LIKE GADOBENATE DIMEGLUMINE, GIVE A HIGHER SIGNAL INTENSITY AND A WIDER PEAK, AS WELL AS A HIGHER CONTRAST INTENSITY IN THE LATER VENOUS PHASE, ALSO WHEN USING TECHNIQUES THAT INVOLVE MULTIPHASIC ACQUISITIONS

Figure 20. Gd-DTPA (Magnevist®) *versus* Gd-BOPTA (MultiHance®)

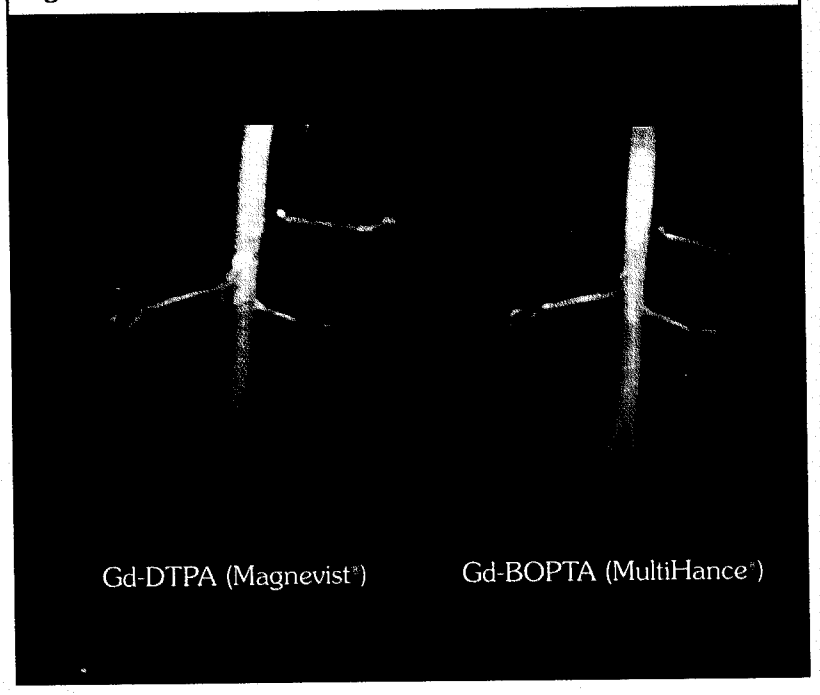
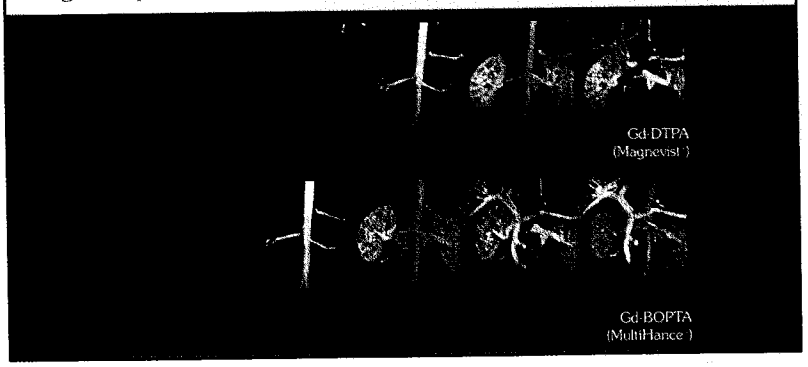


Figure 21. Gd-DTPA (Magnevist®) *versus* Gd-BOPTA (MultiHance®) using Multiphase Acquisition



Conclusions

In summary the following points have been introduced during this talk:

- The recent advances made in MR Angiography.
- The further developments we would like to achieve in this field in order for this technique to be integrated in clinical practice and to be helpful in clinical interpretation and diagnosis.
- The importance of not only the hardware features but also of the contrast agent characteristics.

These advances will make MR Angiography the state of the art technique for diagnostic vascular imaging in the new millennium. MR Angiography will be the predominant non invasive vascular imaging technique in the future due to its non invasiveness, rapidity, large imaging window and potential for hemodynamic assessment. The availability of novel, safe contrast agents will increase the applicability of MRA for routine clinical practice.

THE AVAILABILITY OF NOVEL, SAFE CONTRAST AGENTS WILL INCREASE THE APPLICABILITY OF MRA FOR ROUTINE CLINICAL PRACTICE

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