EUROPEAN SOCIETY OF RADIOLOGY

eBook for Undergraduate Education in Radiology

CHAPTER: Contrast Agents

Preface

Undergraduate teaching of radiology in Europe is provided according to national schemes and may vary considerably from one academic institution to another. Sometimes, the field of radiology is considered as a "cross-cutting discipline" or taught within the context of other clinical disciplines, e.g., internal medicine or surgery.

This e-book has been created in order to serve medical students and academic teachers throughout Europe to understand and teach radiology as a whole coherent discipline, respectively. Its contents are based on the *Undergraduate Level of the ESR European Training Curriculum for Radiology* and summarize the so-called ***core elements*** that may be considered as the basics that every medical student should be familiar with. Although specific radiologic diagnostic skills for image interpretation cannot be acquired by all students and rather belong to the learning objectives of the *Postgraduate Levels of the ESR Training Curricula*, the present e-book also contains some ***further insights*** related to modern imaging in the form of examples of key pathologies, as seen by the different imaging modalities. These are intended to give the interested undergraduate student an understanding of modern radiology, reflecting its multidisciplinary character as an organ-based specialty.

We would like to extend our special thanks to the authors and members of the ESR Education Committee who have contributed to this eBook, to Carlo Catalano, Andrea Laghi and András Palkó, who initiated this project, and to the ESR Office, in particular Bettina Leimberger and Danijel Lepir, for all their support in realising this project.

We hope that this e-book may fulfil its purpose as a useful tool for undergraduate academic radiology teaching.

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How to cite this work:

European Society of Radiology, Johannes Fröhlich, Gabriella Hänggi (2023) eBook for Undergraduate Education in Radiology: Contrast Agents. DOI 10.26044/esr-undergraduate-ebook-10

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eBook for Undergraduate Education in Radiology

Based on the ESR Curriculum for Undergraduate Radiological Education

Chapter: **Contrast Agents**

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Contrast Agents

Contrast agents are used to improve visualization of an organ, tissue, or pathologic condition in diagnostic imaging by altering the attenuation of x-rays or by changing the response to the applied electromagnetic or ultrasound energy. They are substances used for diagnostic purposes only, without any pharmacodynamic activity, and are generally eliminated rapidly without metabolization.

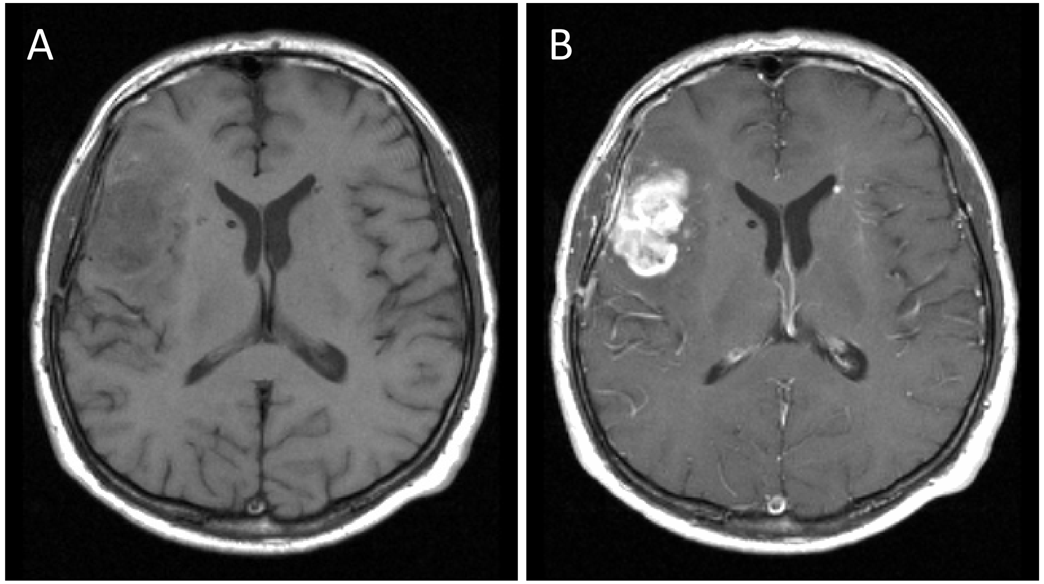

Fig. 1. Brain MR-image pre-contrast (A) and after iv. administration of contrast

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X-Ray Contrast Media (RCM)

Classification

X-ray contrast media, also called **radiographic contrast media (RCM)**, enhance image contrast by locally inducing a change in x-ray absorptivity, which can be stronger (positive RCM) or weaker (negative RCM) than in the adjacent normal tissue.

Positive RCM.

Substances with a high radiodensity, containing atoms with a high atomic number such as Barium ($^{56}Ba^{2+}$), Iodine ($^{53}I^{-}$) or Gadolinium ($^{64}Gd^{3+}$) (off-label), lead to enhanced absorption of X-rays.

Fig. 2. Positive contrast due to the bones.

Negative RCM

Substances with a low density, such as CO_2, Xe and air, lead to reduced absorption of X-rays.

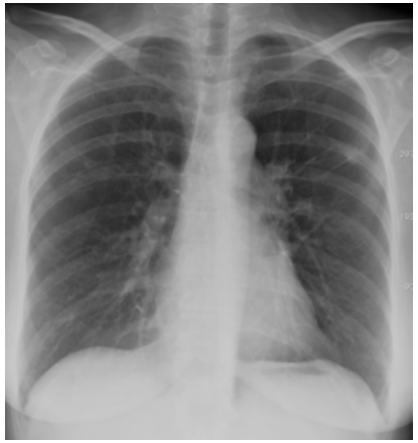

Fig. 3. Air in the lungs appears black because of less absorption of the X-rays: negative contrast.

Iodinated RCM

Iodinated RCM are available as water soluble, hydrophilic RCM or as oily, lipophilic RCM.

Oily, lipophilic iodinated RCM

Lipiodol is an oily lipophilic iodinated RCM, which is made of poppy seed oil whose unsaturated fatty acids were substituted with iodine. It is used for visualization of fine structures in:

- direct lymphography (imaging of the lymphatic system)
- transarterial chemoembolization of hepatocellular carcinoma (Fig. 4)
- or in some countries for hysterosalpingography. (to determine tubal patency)

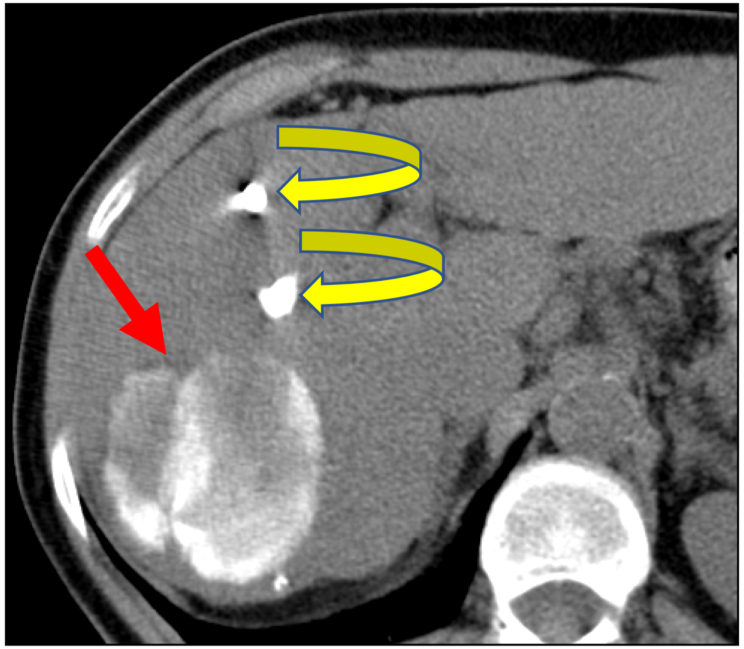

Fig. 4. Control CT image obtained after transarterial chemoembolisation of a hepatocellular carcinoma (HCC) with Doxorubicine/Lipiodol and portal vein embolisation with Lipiodol/bucrylate (to induce left liver lobe hypertrophy). Residual Lipiodol in HCC (red arrow) and in the embolised portal branches (yellow arrows). Image courtesy: Christoph Becker, MD, University of Geneva

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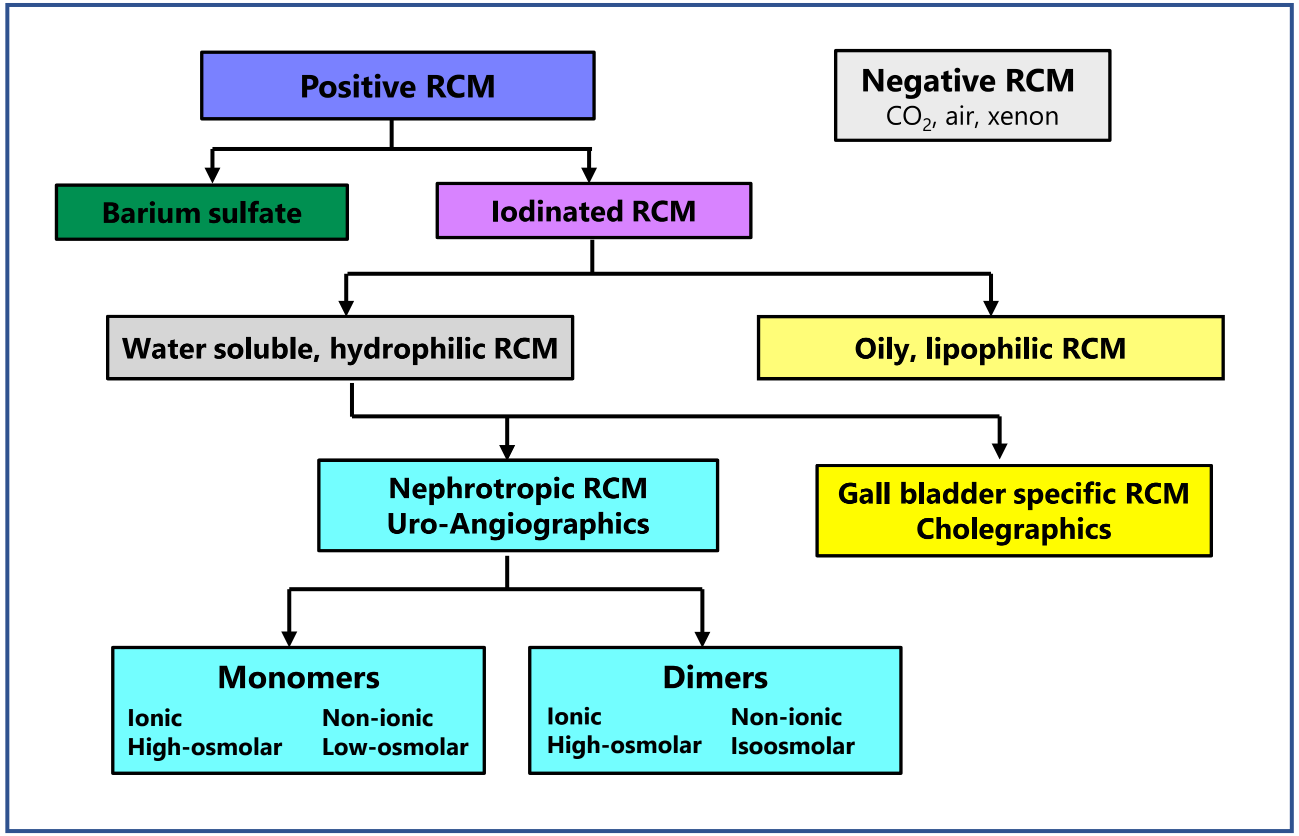

Fig. 5. Classification of X-ray contrast media

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Water soluble, hydrophilic iodinated RCM

The water soluble, hydrophilic RCM comprise nephrotropic RCM, which are employed for uro-angiographics, and gallbladder specific RCM, which were used for intravenous cholangiography.

Structure of water soluble, iodinated RCM

The basic structure of water-soluble iodinated RCM is a benzene ring, which is symmetrically substituted with three covalently bound iodine atoms

- The presence of three iodine atoms in one molecule provides a high X-ray absorptivity with correspondingly high contrast density
- The covalent binding ensures a strong chemical bond of iodine and thus reduces the risk of toxic effects from released free iodide
- The remaining three, non-iodinated carbons of the benzene ring are substituted with respective chemical side-groups R_1, R_2 and R_3

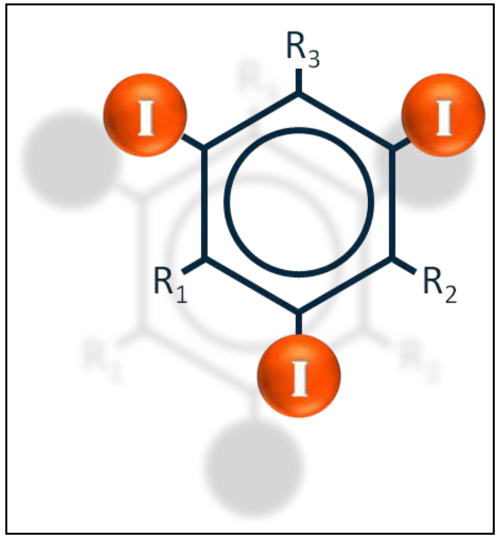

Fig. 6. Basic structure of iodinated RCM.

Classification of the nephrotropic RCM

Two major chemical variations, namely, monomeric versus dimeric, and ionic versus non-ionic, result in four classes of RCM:

Ionic monomeric RCM: one triiodinated benzene ring with a carboxylate functional group ($-COO^-$) in one of the substituent groups

Ionic dimeric RCM: two triiodinated benzene rings linked by an organic bridging group with at least one carboxylate functional group ($-COO^-$) in one of the substituent groups (no marketed anymore).

Non-ionic monomeric RCM: one triiodinated benzene ring without $-COO^-$ functional group, e.g. having an amide (-CO-NH-R) group instead of the $-COO^-$ functional group

Non-ionic dimeric RCM: two triiodinated benzene rings without $-COO^-$ functional group, e.g. having an amide (-CO-NH-R) group instead of the $-COO^-$ functional group, linked by an organic bridging group

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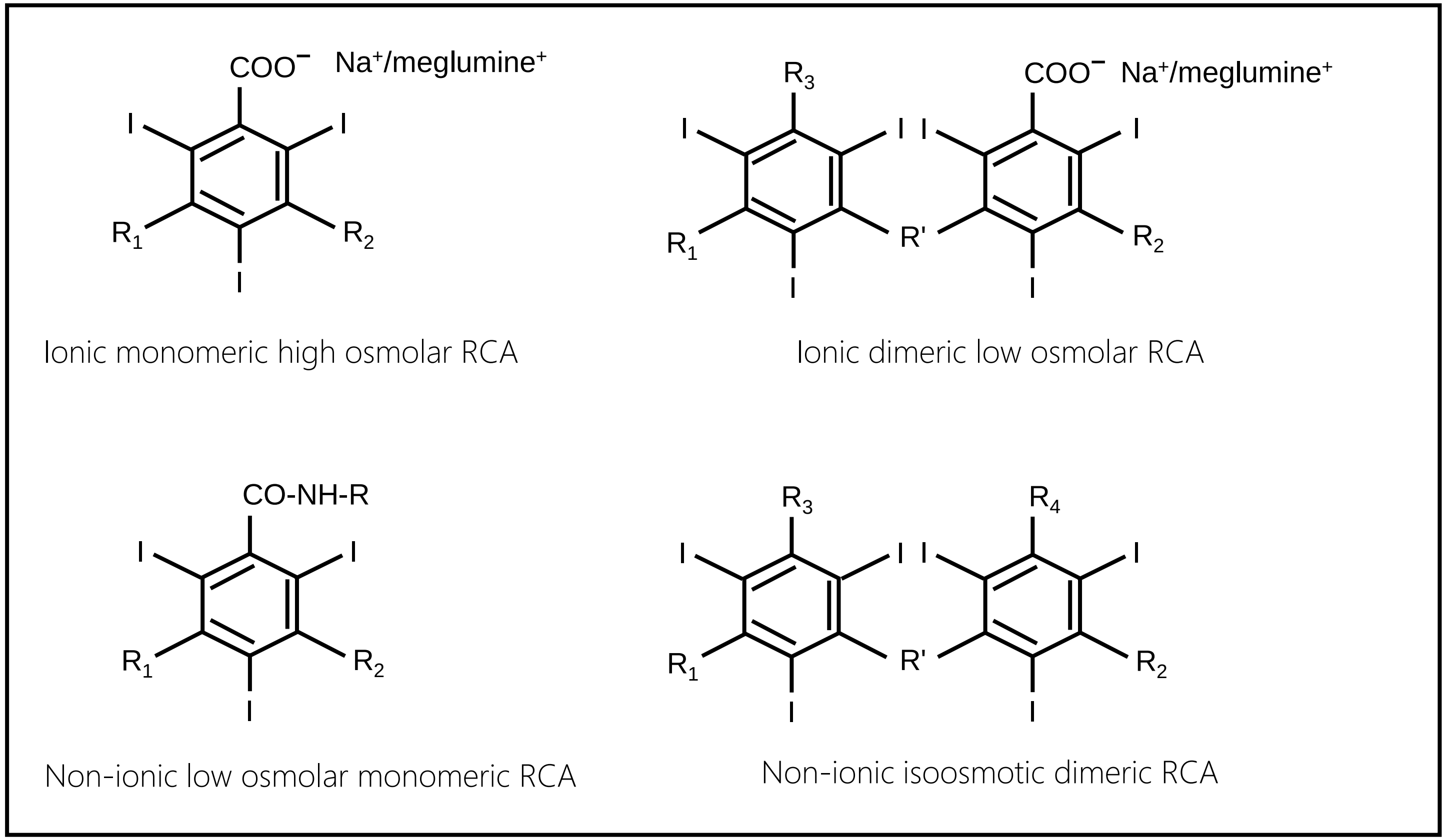

Fig. 7. Structure of the 4 classes of nephrotropic RCM

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Ionic contrast agent – once dissolved there's a dissociation into an anion and cation in the aqueous solution

In the ionic RCM, the presence of a carboxylate group contributes to a net negative charge to the molecule, which is made available in neutral form, usually as a salt of sodium, calcium, or methylglucamine cations.

The dissociation into negative and positive ions in ionic RCM ensures water solubility, while in non-ionic RCM any polar groups of the substituents R_1, R_2 and R_3, particularly hydroxyl groups, are responsible for the water solubility.

The other substituents may further improve water solubility and other pharmacokinetics and safety properties, such as elimination pathway, protein binding and tolerability.

Gallbladder specific RCM

An intravenous gallbladder specific RCM available as a salt of meglumine has a dimeric structure with two triiodinated benzene rings linked by an organic bridging group. This cholegraphic RCM comprises a carboxylate functional group at each benzene ring with no further side chains. The unsubstituted position in each benzene ring promotes plasma protein binding and a delayed glomerular filtration leading to excretion in the bile without chemically modifying the molecule.

However, the cholegraphic RCM have shown a higher incidence of adverse effects than the nephrotropic explaining the non-availability of these RCMs.

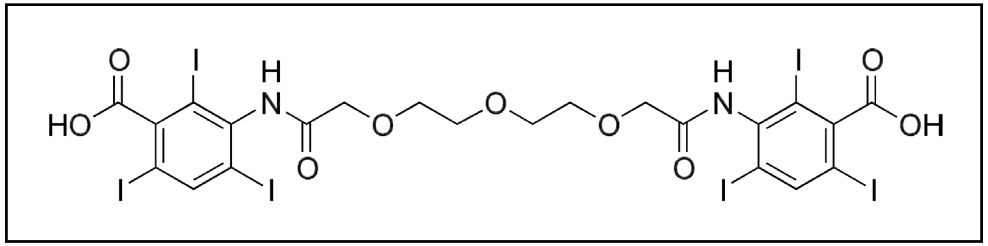

Fig. 8. Structure of the gallbladder specific RCM

Physicochemical properties of iodinated RCM

The most important physicochemical properties of iodinated RCM which affect clinical practice are iodine concentration, osmolality, viscosity, and hydrophilicity.

Iodine concentration

The contrast enhancement is directly related to the local iodine concentration in the tissue.

Intravenous iodinated RCM are available in concentrations from 200 to 400 mg of iodine per milliliter of the contrast solution, with a dosage of 300 mg/ml being clinically used in most cases.

Fig. 9. Example of a iodinated contrast agent: 300 mg/mL = 30% of iodine

The choice of the appropriate iodine concentration depends on the type of investigation, the disease and the diagnostic device used.

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Osmolality

Osmolality is a measure of the number of dissolved active particles per kilogram of solvent, i.e. water, expressed in mOsm/kg H_2O at 20°C.

The osmolality of blood is 300 mOsm/kg H_2O, and the osmolality of the pain threshold is 600 mOsm/kg H_2O.

For a given iodinated RCM, osmolality increases linearly with iodine concentration.

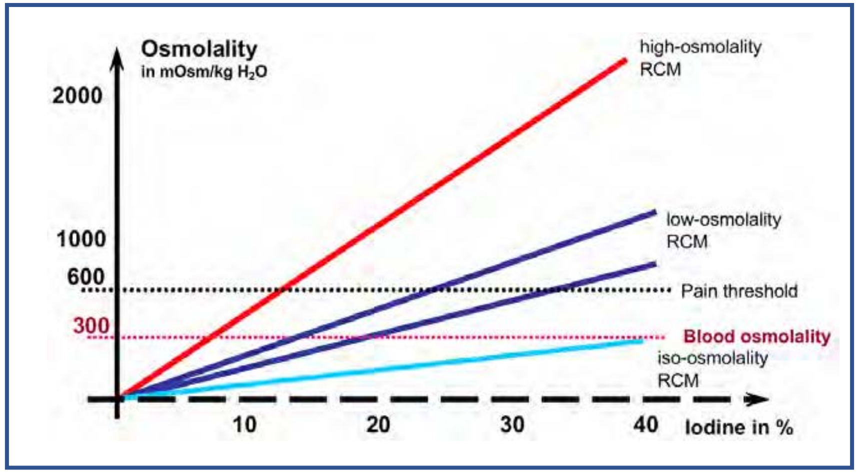

Fig. 10. Osmolality as function of the iodine concentration. Osmolality e.g. influences the pain sensation of the patient

High-osmolality agents include ionic monomers, which for every 3 iodine atoms generate 2 solute particles, with the resultant osmolality being 5-8 times that of blood.

Low-osmolality agents include ionic dimers and non-ionic monomers, which for every 3 iodine atoms generate 1 solute particle; with the resultant osmolality being 1-3 times that of blood.

Iso-osmolal agents include non-ionic dimers, which for every 6 iodine atoms generate 1 solute particle; with the resultant osmolality being approximately equal to that of blood.

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Table 1. Osmolality and viscosity of iodinated contrast media

Structure	Osmolality	Viscosity
High-osmolality ionic momomeres	1500 - 2100 mOsm/kg H_2O	+
Low-osmolality non-ionic monomers	500 - 900 mOsm/kg H_2O	++
Low-osmolality ionic dimers	600 mOsm/kg H_2O	+
Iso-osmolal non-ionic dimers	300 mOsm/kg H_2O	+++

Administration of a RCM with a high osmolality stimulates an inflow of water from the interstitial spaces into the vascular compartment, leading to hypervolaemia, vasodilatation, an increased cardio-vascular charge, bradycardia, a reflectoric drop in blood pressure, pulmonary hypertension and possibly endothelial damage.

Adverse effects attributable to high osmolality include vascular pain, flushing, discomfort, nausea, vomiting and an increase of diuresis and dehydration.

Viscosity

Viscosity describes the flow properties of the contrast agent solution and is expressed in mPa·s.

Viscosity increases disproportionately with iodine concentration and it decreases significantly with increasing temperature.

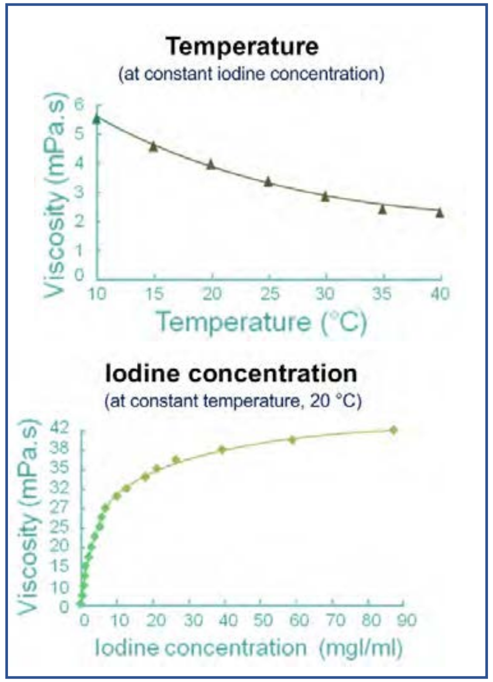

Fig. 11. Viscosity in relation to the temperature and iodine concentration

The viscosity of a contrast medium has an impact on the **maximum possible injection rate** and on the mixing behavior in the blood vessels.

Warming contrast medium to a temperature of 37 to 40°C reduces its viscosity and increases the efficiency of delivering high-viscosity agents in case of fast injection and/or passage through tiny catheters.

Viscosity plays an important role in **renal tolerance** of RCM, with near-serum viscosity reducing the risk of contrast-induced nephrotoxicity associated with iodinated RCM.

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Hydrophilicity

Hydrophilicity refers to an affinity for water, e.g. to the tendency of a substance to dissolve in water, and can be expressed as log P (octanol-water distribution coefficient).

In iodinated RCM, the hydrophilicity depends on the number of hydrophilic groups such as OH and N groups that are present in the substituent chains of the inherently hydrophobic triiodobenzene core.

The increased water solubility of highly hydrophilic RCM reduces the binding to plasma proteins, thereby slowing down intracellular distribution of the RCM, accelerating renal elimination and reducing the passage through the blood-brain barrier. Accordingly, a high hydrophilicity reduces neurotoxicity, immunogenicity and nephrotoxicity and lowers the risk of allergic reactions.

Pharmacokinetics of iodinated RCM

Two-compartment model

The pharmacokinetics of iodinated RCM are best described using a two-compartment model:

Following intravascular administration, the iodinated RCM is rapidly distributed throughout the intravascular space, reaching a peak plasma concentration within 2 minutes, followed by a passage into the interstitial liquid, which is accessible through pores in the capillary walls.

The iodinated RCM thus introduced into the extracellular space cannot pass an intact blood brain barrier and is not distributed in the cellular compartment. However, it can cross the placental barrier in small amounts and is excreted in very small amounts in breast milk.

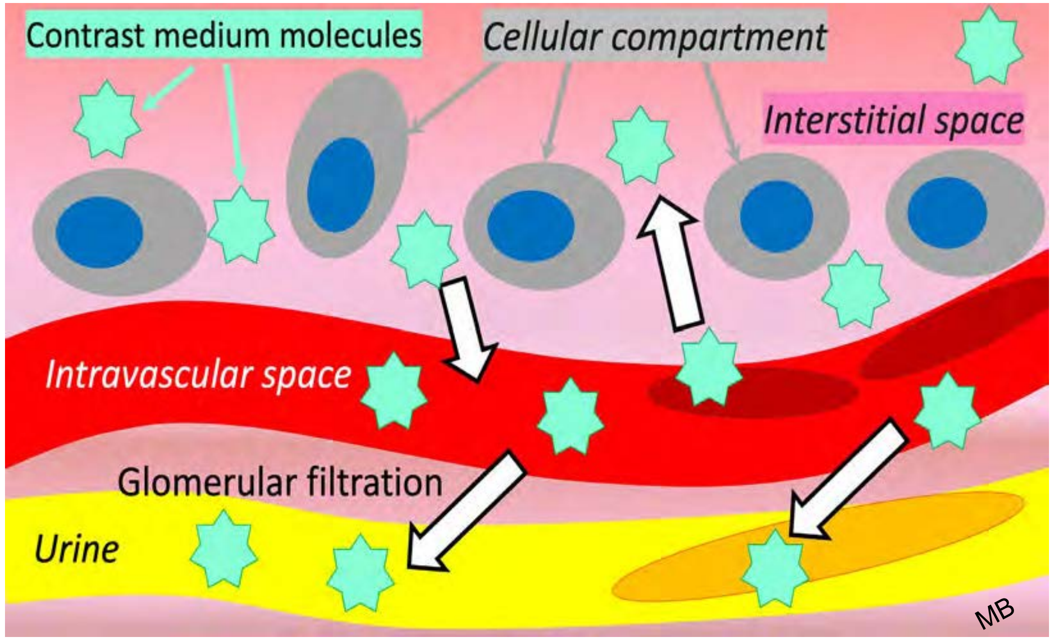

Fig. 12. Two-compartment model with renal elimination.

Elimination of iodinated RCM occurs almost exclusively by passive glomerular filtration. With normal kidney function, the elimination half-life is approximately 90 minutes, and almost the entire applied dose is excreted within 24 hours. In case of renal impairment, the elimination half-life is considerably prolonged.

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Pharmacokinetics and imaging

With regard to imaging with iodinated RCM, there are three post-injection phases:

- Vascular phase, which is of very short duration of less than 1 minute, for imaging of arteries
- Interstitial phase, which is of short duration of 1.5-10 minutes, for imaging of organs
- Elimination phase, which is of long duration of up to 30 minutes, for imaging of the urinary tract

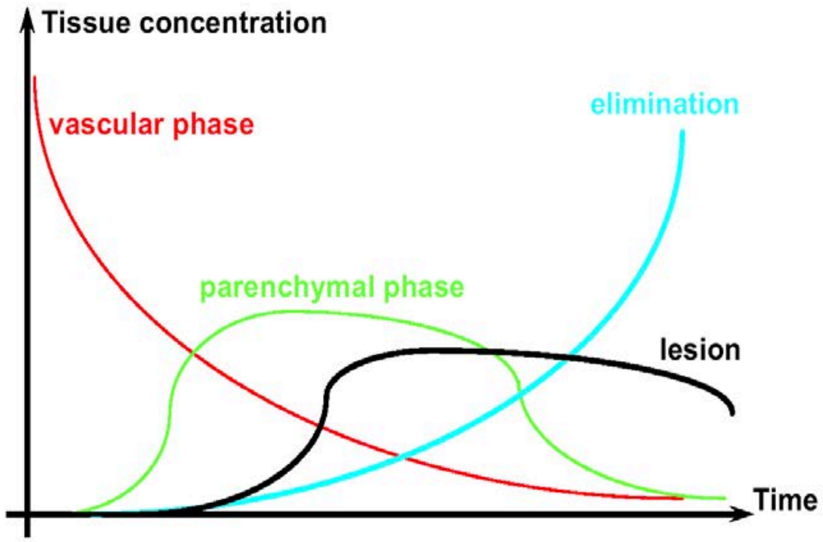

Fig. 13. Post injection phase with iodinated RCM. Note the temporal contrast differences between the various spaces.

In general, the distribution from the intravascular compartment to highly perfused organs, such as brain, liver, and kidney, is rapid, whereas distribution to less perfused organs and tissues, such as bone and fat, is much slower.

Opacification modes of RCM

RCM are extensively used to visualize certain structures in the organism and to obtain information on organ function, which is achieved by applying four different modes of opacification:

Direct luminal filling

The identification of morphological structures is the main objective of direct luminal filling, which can occur through a natural access (Fig. 14) or through an iatrogenically created access. This mode of opacification permits the differentiation of superficial or mural changes, and it can provide functional information, e.g. about changes in tone or peristalsis in hollow passages.

Functional organ imaging

Functional opacification, which is applied in urography (Fig. 15) and cholegraphy, exploits the fact that the contrast density depends significantly on the functionality of the kidneys and urinary tract or the hepatobiliary system. Consequently, the radiographic assessment of these organs reveals both morphological and functional changes.

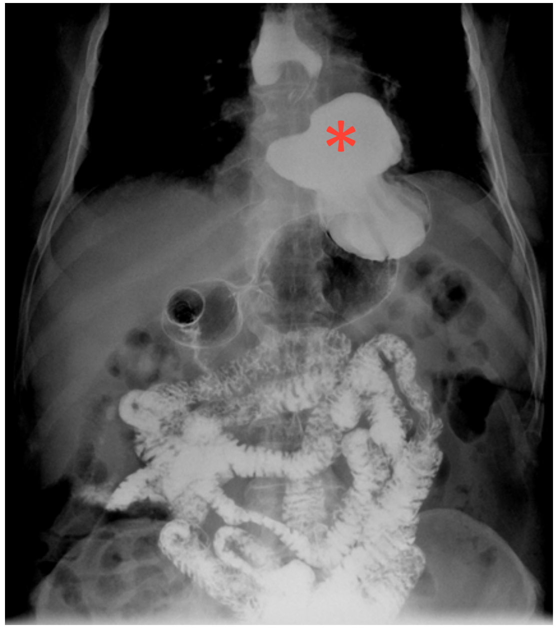

Fig. 14. Barium X-ray (upper gastro-intestinal tract) in a patient with hiatal hernia (asterisk). Note normal opacification of small bowel loops. Courtesy: Georgy Varnay, MD, University Hospitals Geneva

Fig. 15. Normal urography. Case courtesy of Dr. MT. Niknejad, Radiopedia.org, rID: 85286

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Parenchymal enhancement

In parenchymal staining, enhancement of contrasts between tissues results from the passage and selective accumulation of RCM in different organs or tissues, thereby improving the differentiation of morphological structures, especially between normal and pathological tissues. This allows, or at least facilitates, the demonstration of pathological processes and of their etiology as well (Fig. 16).

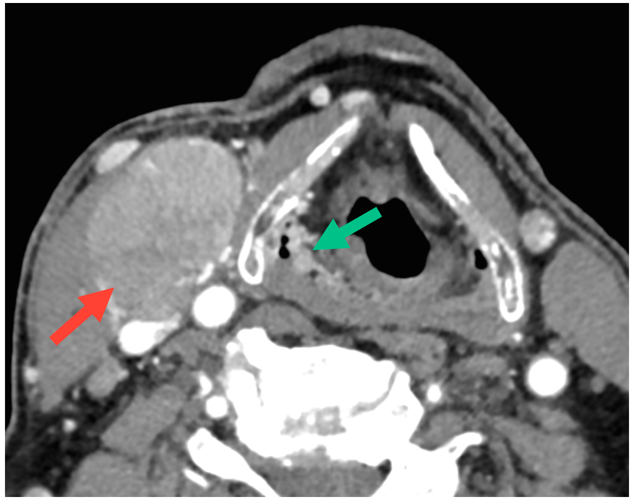

Fig. 16. Contrast enhanced CT (parenchymal staining) showing a small tumour arising from the hypopharynx (green arrow) and a right lymph node metastasis (red arrow). Case courtesy: Minerva Becker, MD, University Hospitals Geneva

Angiography

In angiography (Fig. 17), selective opacification can be achieved by direct RCM injection into the vessel of interest, followed by evaluation of RCM distribution and filling patterns including gaps in opacification of the target anatomy. This evaluation yields detailed diagnostic information regarding normal and abnormal morphology and function.

Fig. 17. Normal angiography of the carotid arteries. Lateral view.

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Indications of RCM application

Intravenous RCM injection

Intravenous RCM administration for the purpose of CT scanning is the most common use of iodinated RCM and has a wide variety of indications. Intravenous administration first leads to an arterial opacification, which is followed by a parenchymal contrast enhancement.

For arterial opacification, the rate of iodine delivery plays a key role.

For the evaluation of a solid organ, such as the liver or pancreas, parenchymal organ enhancement depends primarily on the total amount of iodine administered, because lesion conspicuity may require a larger volume of contrast medium to be injected.

Applications of intravenous RCM administration

- Computed tomography
- Digital subtraction angiography
- Intravenous urography
- Venography (phlebography)
  - Inferior vena cava and its tributaries
  - Superior vena cava and its tributaries
  - Extremities
- Other venous sites
  - Epidural venography

The timing of image acquisition, relative to the time of injection of the contrast agent, has an impact on which anatomic structures have accumulated the greatest concentration of the administered RCM and thus can be optimally visualized.

Five phases of contrast enhancement for CT imaging:

Non-enhanced phase: imaging prior to RCM injection: determination of the baseline status of the anatomy and detection of calcified structures (e.g. calculi, vascular calcifications, and dystrophic calcification in some tumors)

Early arterial phase: image acquisition a few seconds after bolus administration of intravenous RCM: detection of arterial abnormalities (e.g. arterial dissections)

Late arterial phase: image acquisition 15 to 20 seconds after the early arterial phase: examination of highly vascularized anatomic structures (e.g. liver, spleen, kidneys), especially for the identification of masses

Portal venous phase: later phase of image acquisition, when the RCM is maximally concentrated in the mesenteric venous structures: assessing liver perfusion, examining cirrhotic patients for portal hypertension

Delayed phase or wash out phase or the equilibrium phase: visualization of lesions that retain RCM (e.g. tumors)

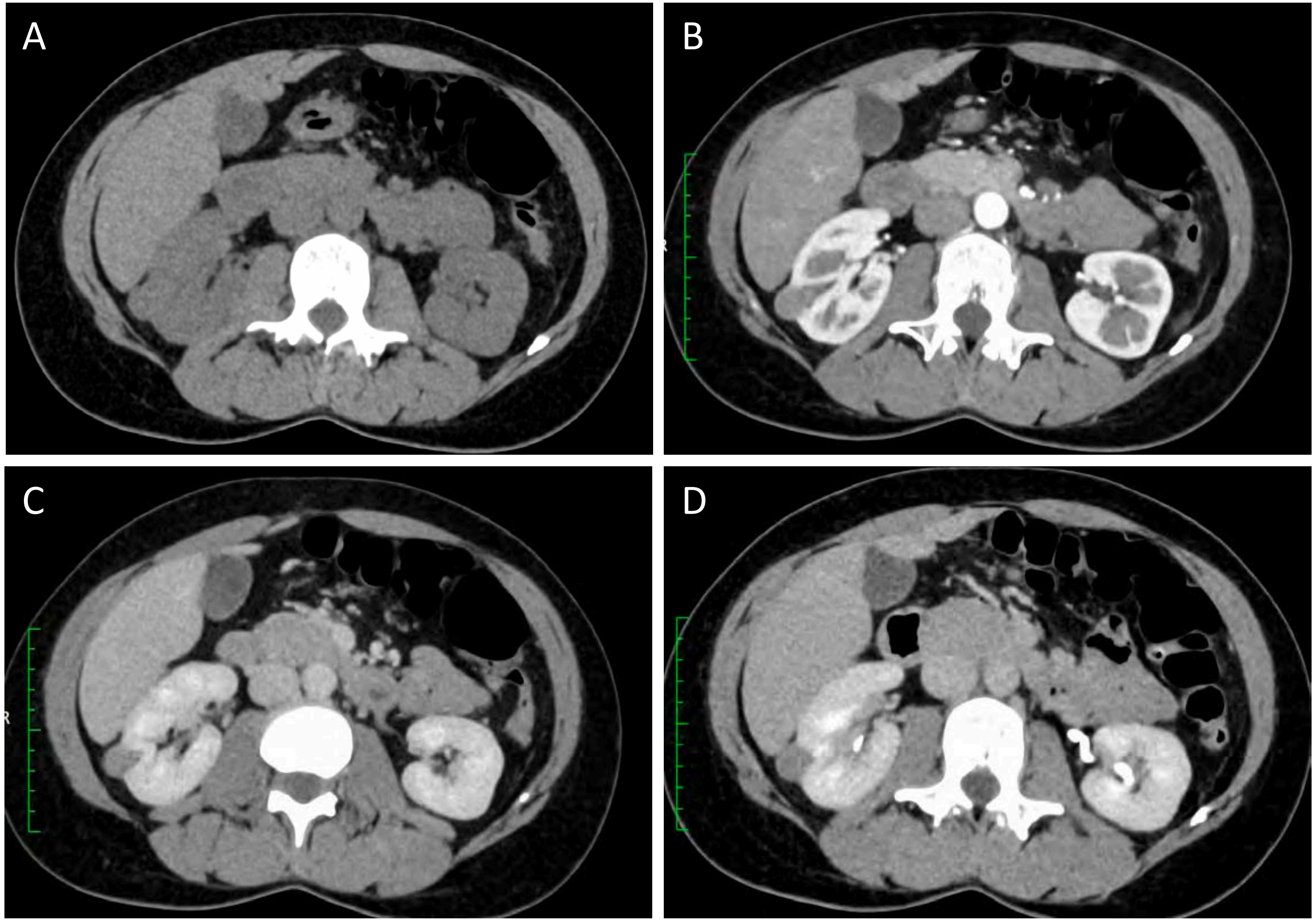

Fig. 18. Example of a CT of the abdomen with different phases of contrast enhancement. A. Non-enhanced phase. B. arterial phase. C. Venous phase. D. Late phase. Case courtesy: Thomas de Perrot, MD, University Hospitals Geneva

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Intraarterial RCM injection

Intraarterial injection is the primary method of iodinated RCM delivery used in diagnostic catheter angiography and catheter-directed arterial intervention, such as percutaneous angioplasty and stent placement.

High rates of RCM administration are required to opacify the target vessels due to the high arterial flow rate.

Applications of intraarterial RCM administration:

Angiocardiography
Computed tomography angiography
Coronary angiography
Pulmonary angiography
Aortography
Visceral and peripheral arteriography
Digital subtraction angiography
Central nervous system
Cerebral, vertebral, and spinal angiography

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Oral and rectal RCM applications

Oral or rectal contrast media are utilized in a variety of ways for imaging of the gastrointestinal tract, which is predominantly done with barium sulfate suspensions and, in selected cases, with iodinated contrast media.

Barium sulfate

For radiographic imaging of the gastrointestinal tract, barium sulfate suspension is administered orally, rectally, or instilled into an enterostomy tube or catheter, and is employed to fill the gastrointestinal tract lumen or to coat the mucosal surface.

Improved delineation of the gastrointestinal tract lumen and mucosa may be achieved by double-contrast examination with filling of the lumen with gas and coating of the wall with barium sulfate (Fig. 19, see next page). For this purpose, barium sulfate is either mixed with a carbon dioxide additive or as gas-forming agent.

Barium sulfate is neither absorbed nor metabolized in subjects with a normal gastrointestinal tract and is excreted unchanged in the feces.

Indications of barium sulfate in radiographic imaging include differentiation of morphological structures, especially between normal and pathological tissue, as well as functional changes through the entire gastrointestinal tract.

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Adverse reactions

The most common adverse reactions of barium sulfate include nausea, vomiting, and abdominal cramping or discomfort during and after the examination and mild allergic reactions. The hypoosmolality of the suspension causes water withdrawal from the GI tract, which can lead to colon obstruction.

The most serious complication from the use of barium sulfate in the GI tract is leakage into the mediastinum or peritoneal cavity, leading to persistent peritonitis or mediastinitis.

Contraindications

Contraindications for barium sulfate include suspected perforation and postoperative insufficiency of suture as well as previous allergic reactions to barium products.

Barium sulfate should not be used in individuals who are suspected or known to suffer from necrotic colitis, ileus and deglutition difficulties due to the risk of aspiration, and particular caution is required for newborns, elderly and critically ill persons.

Fig. 19. Colon with barium sulfate followed by a gel: double contrast image

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Oral iodinated RCM

The current applications of oral iodinated RCM (Fig. 20) are primarily limited to visualization of the GI tract when barium sulfate is contraindicated.

Diluted water-soluble ionic high-osmolality RCM are preferred for oral use, but diluted non-ionic contrast agents can also be employed.

Water-soluble contrast media are absorbed rapidly from the interstitial spaces and peritoneal cavity, which makes them uniquely useful in examining patients with a suspected hollow viscus perforation. No permanent deleterious effects from the presence of water-soluble contrast media in the mediastinum, pleural cavity, or peritoneal cavity have been reported.

Excretion of orally administered iodinated RCM occurs mainly through the fecal route and is dependent on GI transit time, while only a small volume of iodinated RCM is absorbed from the GI tract and subsequently excreted into the urinary tract.

Fig. 20. CT with oral iodinated RCM. Note the heterogenous contrast in the small bowel with higher absorption rate in the distal part (red arrows)

Contraindications

Hyperosmolal RCM may lead to **deglutition difficulties** and are, therefore, contraindicated for oral administration in patients at **risk for aspiration**. In such patients, non-ionic low-osmolality or iso-osmolality iodinated RCM should be used for oral administration because, even if aspirated, they are associated with only minimal bronchogenic toxicity.

Enteric hyperosmolal RCM should also be avoided in patients with **fluid and electrolyte imbalances**, particularly the very young or elderly patients with hypovolemia or dehydration.

Due to a **slight systemic uptake** of orally administered RCM, a careful use is indicated in case of pregnancy, renal insufficiency and underlying thyroid disorder.

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Adverse reactions to RCM

The incidence of adverse reactions related to the intravascular administration of iodinated RCM, which has been drastically reduced with the change in usage from ionic high-osmolality RCM to non-ionic low-osmolality or iso-osmolality RCM, is now generally low.

Acute adverse reactions

Acute adverse reactions to RCM occur within 1 hour after application, and the severity of such reactions can range from mild to severe and life-threatening. Acute reactions are categorized as either hypersensitivity reactions and allergy-like reactions, or chemotoxic reactions.

Hypersensitivity and allergic-like reactions are likely independent of dose and concentration of the RCM and tend to be unpredictable.

Symptoms of hypersensitivity and allergic-like reactions include urticaria, pruritis, cutaneous edema, itching and diffuse erythema. Severe acute reactions typically manifest as facial and laryngeal edema, hypotension, bronchospasm and dyspnea, up to hypotensive shock and respiratory or cardiac arrest.

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Chemotoxic adverse reactions relate to a specific molecular attribute of the RCM such as osmolality, viscosity and ionicity, and they are generally dose and concentration dependent.

Common chemotoxic adverse reactions include nausea and vomiting, flushing, warmth, chills, headache, dizziness, anxiety, taste alterations and hypertension. Vasovagal reactions can occur and appear as bradycardia with hypotension.

Serious chemotoxic adverse reactions can manifest as cardiac arrhythmias, depressed myocardial contractility, cardiogenic pulmonary edema, convulsions and seizures. They are more frequent and significant in patients with underlying cardiac disease.

Patient-related risk factors for an acute reaction to RCM are a history of a previous allergic-like reaction to an iodine-based contrast agent and a history of asthma and atopy, while contrast medium related risk factors are high-osmolality ionic contrast media.

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Delayed adverse reactions

Delayed adverse reactions may develop from 60 minutes to up to one week following RCM exposure and are most commonly cutaneous reactions.

Typical delayed cutaneous reactions can manifest as rashes, pruritus, erythema and swelling, while delayed non-cutaneous symptoms include nausea, vomiting, headache, musculoskeletal pain, diarrhea, and, occasionally, hypotension.

Risk factors for a delayed reaction to RCM are a previous late contrast medium reaction and a treatment with interleukin-2, as well as use of non-ionic dimers.

Pregnancy and lactation

In pregnant women, when radiographic examination is essential, iodine-based contrast media may be given. Following such administration, the thyroid function should be checked in the neonate during the first week.

Breast feeding may be continued normally when iodine-based contrast media is given to the mother.

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Thyrotoxicosis

A contributing factor to adverse reactions is the deiodination process and iodide impurity in the solutions thus leading to traces of free iodide in the body with concentrations above the recommended daily intake.

In subjects with a normal thyroid function, the exposure with excess iodide can be compensated by a transient decrease of thyroid hormone synthesis, the so-called Wolff-Chaikoff-Effect.

This intrinsic regulatory mechanism is impaired in subjects with an underlying thyroid disorder, so that the application of iodinated contrast media may lead to a thyrotoxicosis.

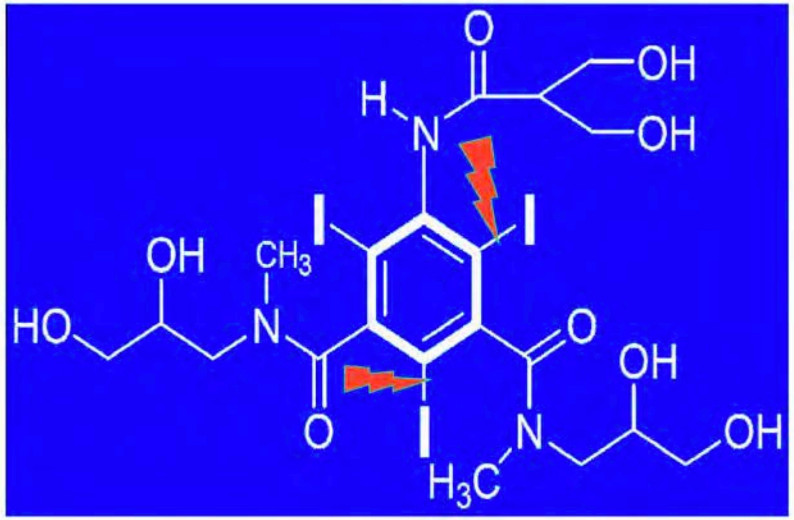


Fig. 21. Light exposure might lead to a deiodination with iodide release.

Risk factors for development of **thyrotoxicosis** are Graves' disease and multinodular goiter with thyroid autonomy, especially in elderly individuals and/or in areas of dietary iodine deficiency.

For individuals suspected of being at risk of thyrotoxicosis, knowledge of thyroid function before administration of iodinated RCM is helpful, and close monitoring after administration is recommended. Selected high-risk patients may benefit from prophylactic thyrostatic therapy.

In patients with established **hyperthyroidism**, administration of iodinated contrast media is contraindicated.

Following administration of iodine-based contrast media to a pregnant woman, thyroid function should be checked in the neonate during the first week.

Premature infants and **neonates** might be particularly susceptible to developing clinically significant **hypothyroidism** because the immature gland may not be able to fully reverse the acute Wolff-Chaikoff effect. Thyroid function should be monitored up to the age of three.

Chapter Outline

Renal adverse reactions

Intravascular administration of a contrast medium may result in a deterioration of the renal function and even in acute kidney failure.

The standard diagnostic criterion for Post-Contrast Acute Kidney Injury (PC-AKI) is defined as an increase in serum creatinine by > 0.3 mg/dl (or > 26.5 µmol/l), or to > 1.5 times baseline within 48-72 hours of intravascular administration of a contrast medium.

A preexisting renal dysfunction is the greatest risk factor for developing PC-AKI, and the risk becomes larger with increasing baseline renal impairment.

The estimated glomerular filtration rate (eGFR), calculated from the serum creatinine, is the recommended parameter to estimate renal function before contrast medium administration. The current guidelines of the **European Society of Urogenital Radiology (ESUR)** define the following threshold values for patient related risk of developing PC-AKI:

eGFR < 45 ml/min/1.73 m^2	before intraarterial contrast medium administration with first pass renal exposure or in intensive care unit patients
eGFR < 30 ml/min/1.73 m^2	before intravenous contrast medium or intra-arterial contrast medium administration with second pass renal exposure

Chapter Outline

In their Manual on Contrast Media 2021, the **ACR Committee on Drugs and Contrast Media of the American College of Radiology**, mention the following threshold value for patient related risk of developing PC-AKI:

$eGFR < 30\ ml/min/1.73\ m^2$

Further risk factors for developing PC-AKI include diabetes mellitus, cardiovascular disease, hypertension, hyperuricemia, proteinuria, diuretic use, dehydration, advanced age, and multiple iodinated contrast medium doses administered in a short time interval.

Preventive strategies comprise 1-12 hours of prehydration with intravenous saline or sodium bicarbonate followed by 4-12 hours of posthydration and the use of low- or iso-osmolal RCM with the minimum dose.

Extravasation

An unintended extravascular injection of iodinated RCM occurs in very rare cases only and typically causes self-limiting symptoms such as pain, erythema and swelling, but in severe cases, skin ulceration and necrosis may occur. The most commonly reported severe injury after extravasation is the development of the compartment syndrome.

A severe extravasation injury is more likely to result in patients with arterial insufficiency or compromised venous or lymphatic drainage in the affected extremity.

Extravasations involving larger volumes of RCM, especially high-osmolality and high-viscosity agents, or the use of a power injector, and those occurring at problematic injection sites such as the dorsum of the hand, foot, or ankle, are more likely to result in severe tissue injury.

Continuous monitoring and accurate conservative management help to avoid sequelae. The treatment consists in elevation of the affected extremity, ice cooling, topical application of silver sulfadiazine and, in extreme cases, surgical intervention.

Magnetic Resonance Contrast Agents

Magnetic resonance imaging (MRI) contrast agents are diagnostic pharmaceutical compounds that affect the **nuclear magnetic resonance signal of the ^{1}H-hydrogen nuclei (protons) of water molecules** contained in the surrounding tissue.

The contrast of an MR image results from a complex interplay of various factors such as proton density, the longitudinal (spin-lattice) relaxation time T_1 and the transverse (spin-spin) relaxation time T_2, and on the applied MRI sequences.

Contrast agents (CAs) used in MRI either consist of **paramagnetic metal ions or of superparamagnetic particles**, and they act to modify T_1 and T_2 of water protons present in the tissue.

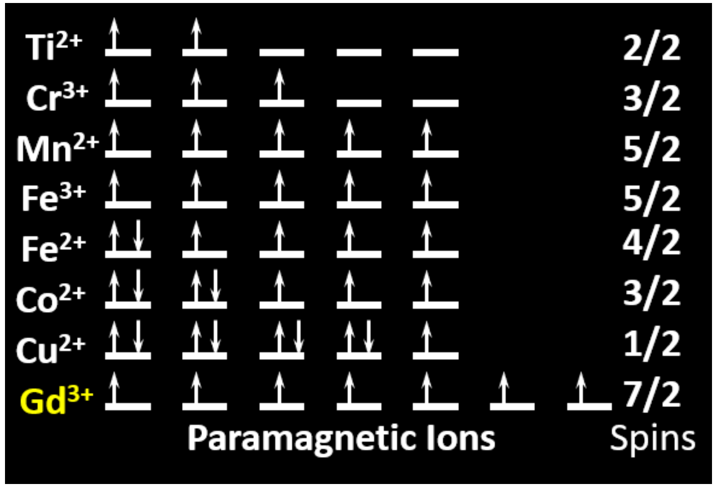


Fig. 22. Single spins (here electrons) are magnetised in the MR and interact with protons thus changing the tissue signal.

Chapter Outline

Paramagnetic contrast agents

Paramagnetic CAs contain metal ions that have unpaired electrons in their outer shell, which implies a resultant electron spin and a permanent magnetic moment.

The magnetic moment of a tumbling paramagnetic CA molecule induces an additional, time-variable magnetic field in the hydrogen nuclei of the surrounding water molecules, which in turn can increase the rate r_1 of longitudinal spin-lattice relaxation and the rate r_2 of transverse spin-spin relaxation.

The increase in relaxation rate caused by a CA leads to a corresponding shortening of T_1 and T_2 in the region of interest, producing hyperintense signals in T_1-weighted images and hypointense signals in T_2-weighted images.

The effect on T_1 is already evident at low concentrations of the contrast agent, whereas the effect on T_2 becomes increasingly significant at higher concentrations.

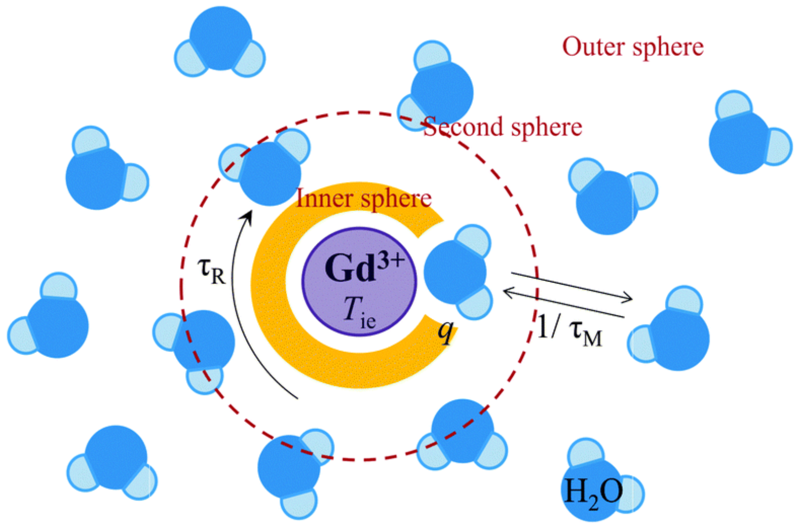


Fig. 23. Gadolinium interacting with the surrounding water protons at different levels. Usually 1-2 water protons get closer to the central atom surrounded by a ligand.

Chapter Outline

Relaxivity

The efficacy of a MR contrast agent is expressed in terms of relaxivity R, which refers to the ability of the CA to enhance the proton relaxation rate. It is generally measured experimentally in water and is defined as the increase in relaxation time of the solvent (water) induced by 1 mmol L^{-1} of the active ion of the contrast agent:

$$R_1 = 1 / T_1 \text{ (1 Mol, 20°C)}$$

The contrast efficiency is expressed as the r_2/r_1 ratio: the higher the ratio, the greater the relative effect on T_2 and vice versa on T_1.

Chapter Outline

Manganese-based contrast agents

Manganese-based CAs contain bivalent manganese, a transition metal with five unpaired electrons, which is also naturally present in the body.

Paramagnetic manganese is available either in the form of small molecules or as the more recently developed nanometer sized materials.

Mangafodipir trisodium (Mn-DPDP) is a liver specific CA in which a manganese ion Mn^{2+} is chelated with a dipyridoxyldiphosphate ligand.

Chapter Outline

Gadolinium-based contrast agents

Gadolinium-based CAs, which contain trivalent gadolinium – a metal from the lanthanide series with seven unpaired electrons – **are the most clinically used CAs in MRI** because of their high magnetic moment and long electronic spin relaxation time.

However, the cytotoxicity of gadolinium in its free ionic form Gd^{3+} makes it necessary to mask the gadolinium by providing **chelating ligands** which form chemically stable complexes.

Administering gadolinium as an inert and stable coordination complex prevents the cellular uptake of free Gd^{3+} and maintains the biodistribution within the extracellular space, thereby enhancing renal filtration and urinary excretion.

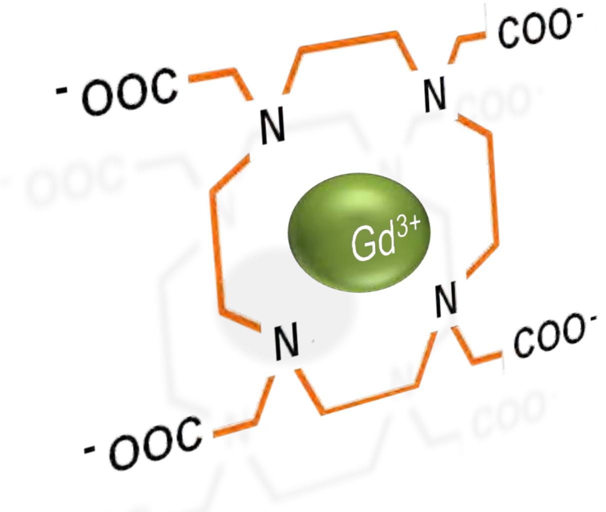


Fig. 24. Macrocyclic gadolinium complex with Gd^{3+} as the central atom bound tightly to a lignd presenting a ring-like structure

Chapter Outline

Structure of the Gd complexes

The currently available Gd-based contrast agents can be classified into four main categories according to their structure, particularly the nature of the chelating moiety, and to their ionicity.

In linear complexes, the gadolinium ion is only partially surrounded by a chain-like structure of the ligand, whereas in macrocyclic complexes, the gadolinium ion is enclosed within a cage-like structure formed by the ligand.

Both, the linear and the macrocyclic gadolinium complexes can either be non-ionic or ionic. In the ionic gadolinium complexes, the remaining anionic groups are salified with meglumine or sodium cations.

The molecular characteristics of the four classes of gadolinium complexes have a significant impact on some key properties such as osmolality and viscosity, but also on their relaxivity and biodistribution.

The molecular characteristics are also responsible for the differences between the various gadolinium complexes regarding their thermodynamic stability constants and kinetic rate constants.

Chapter Outline

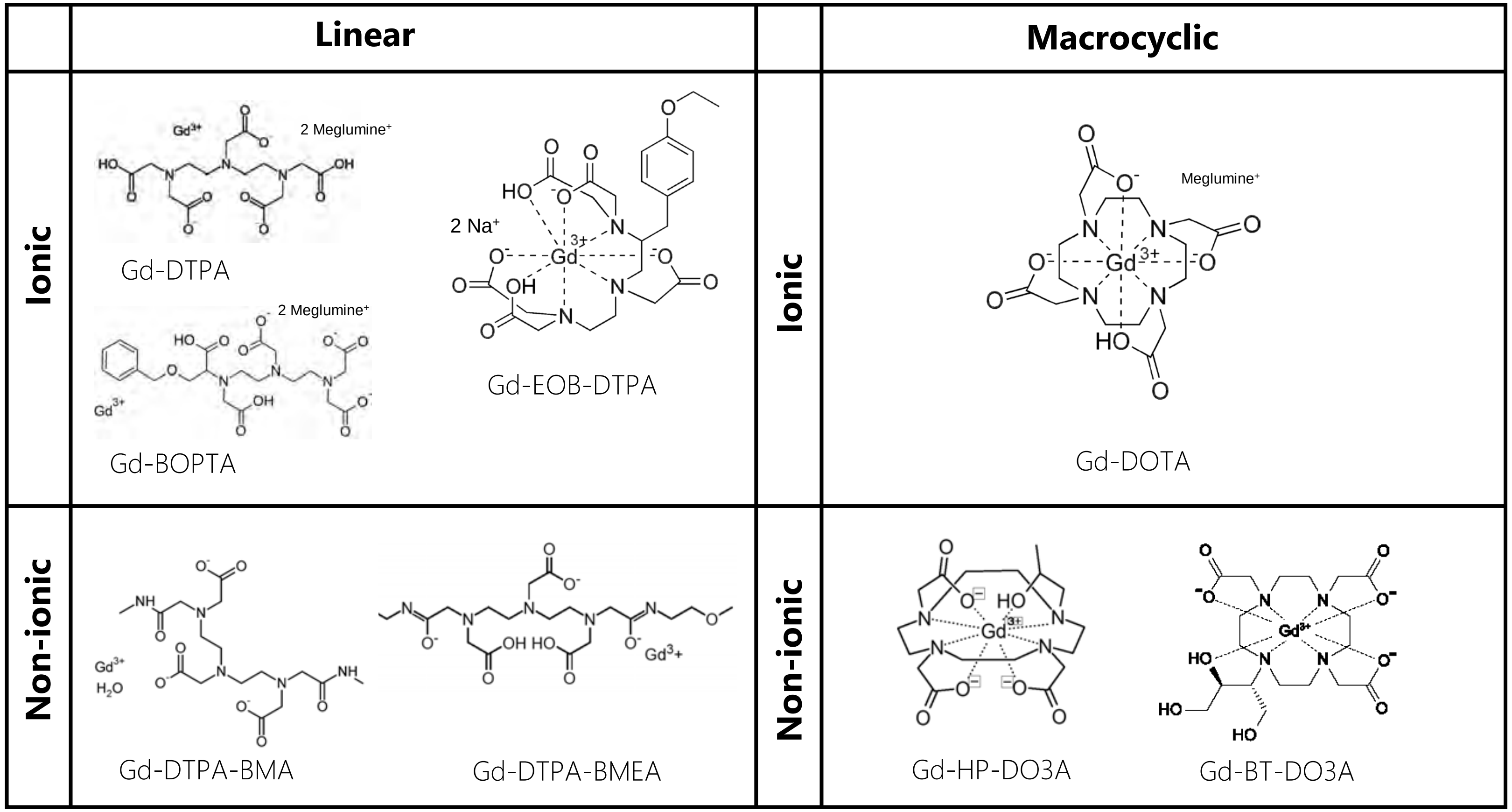


Fig. 25. Classification and structure of Gd-based CAs

Chapter Outline

Stability of Gd complexes

In solutions of Gd-containing CAs, there is always an equilibrium between complexed gadolinium (Gd-Ligand) and free gadolinium ions (Gd^{3+}):

$$Gd^{3+} + \text{Ligand} \leftrightarrow \text{Gd-Ligand}$$

The equilibrium state can be characterized by the thermodynamic stability constant

$$K_{TD} = \frac{[\text{Gd-Ligand}]}{[Gd^{3+}] \cdot [\text{Ligand}]}$$

which is often expressed in logarithmic form log K_{TD}. For the Gd complexes used as contrast agents, this equilibrium strongly favors the side of the complexed gadolinium, with log K_{TD} ranging from 16.6 to 25.6.

Table 2. Stability of gadolinium complexes

Complexes	Structure	Thermodynamic stability -log K	Kinetic stability at pH 7.4	Dissociation half-life at 25°C, pH 1.0
Gd-DOTA	macrocyclic-ionic	25.6	high	338 hours
Gd-HP-DO3A	macrocyclic-non-ionic	23.8	high	3.9 hours
Gd-BT-DO3A	macrocyclic-non-ionic	21.8	high	43 hours
Gd-BOPTA	inear-ionic	22.6	medium	< 5 sec
Gd-DTPA	linear-ionic	22.1	low	< 5 sec
Gd-DTPA-BMA	linear-non-ionic	16.9	low	< 5 sec
Gd-DTPA-BMEA	linear-non-.ionic	16.6	low	< 5 sec

The thermodynamic stability of Gd complexes decreases with **decreasing pH**, so that in acidic environment the complexes are more prone to decomplexation.

Macrocyclic complexes generally have a **higher** thermodynamic and kinetic stability than linear complexes.

Ionic compounds tend to have a slightly **higher** thermodynamic and kinetic stability than non-ionic compounds.

Chapter Outline

Transmetallation

Decomplexation of the Gd complexes may result from **reactions with other metal ions that are present in human body fluids.**

In particular, the Gd^{3+} ion in a chelate complex may be replaced by Zn^{2+}, which leads to release of toxic Gd^{3+} ions and to formation of zinc complexes resulting in an undesirable zinc washout via renal elimination.

An important reason for the toxicity of free Gd^{3+} ions is the size similarity and resulting competition with Ca^{2+} ions in cellular and biochemical processes, leading to an inhibition of calcium channels and a blockage of Ca^{2+} dependent enzymes.

A further factor contributing to the toxicity of Gd^{3+} ions is their tendency to bind to endogenous anions, particularly phosphates and carbonates, creating insoluble salts which are taken up by the reticuloendothelial system (RES) through phagocytosis and accumulate in human tissues. This process is accompanied by a stimulation of local macrophages to initiate an inflammatory response with the release of cytokines and cytokine triggered transcription factors.

Chapter Outline

Biodistribution

After intravenous administration, gadolinium complexes are rapidly distributed into the intravascular space and then passed, through the capillaries, into the interstitial space, with the intravascular half-life time being dependent on the molecular weight and on the extent of plasma protein binding.

Depending on its structure, a gadolinium complex may also be partially distributed in the liver through passive diffusion or through a selective uptake by hepatocytes via carrier-mediated transport across the cell membranes.

Gadolinium contrast agents do not penetrate the intact blood-brain barrier.

Low molecular weight gadolinium complexes are generally not metabolized.

Fig. 26. Early vascular distribution of the iv injected Gd contrast agent

The gadolinium complexes are **excreted either almost exclusively via the kidneys**, or they have a **dual elimination** pathway via the kidneys and via the hepatobiliary system.

Patients with **normal renal function** eliminate more than 90% of low molecular weight gadolinium CAs within the first 12 hours after injection and more than 90% of high molecular weight CAs within 72 hours after injection.

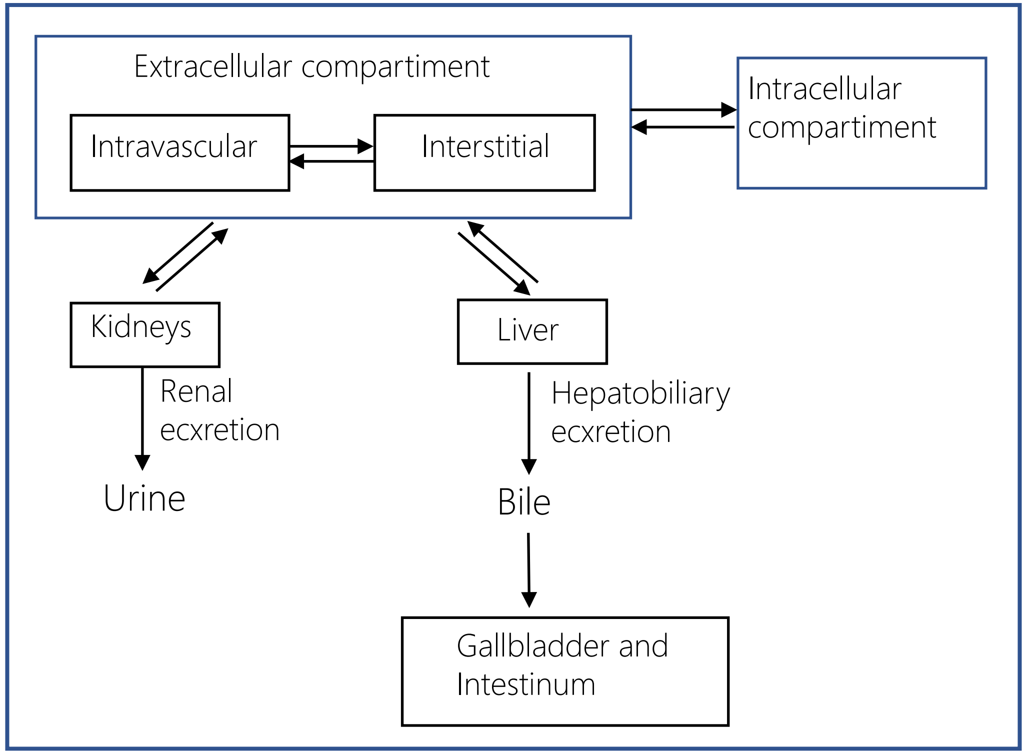


Fig. 27. Distribution sites and elimination pathways for intravenously administered gadolinium complexes

Superparamagnetic contrast agents

Superparamagnetic contrast agents consist of iron oxide nanoparticle cores coated with a protective layer of a biocompatible material like polyethylene glycol, dextran, heparin or albumin.

The magnetic moment of the superparamagnetic cores tends to align with the external magnetic field, inducing local magnetic field gradients that dephase the transverse magnetization of water protons, which predominantly leads to a shortened T_2 and concomitant negative contrast enhancement in pathologically relevant T_2-weighted images. With decreasing size of the superparamagnetic particles, shortening of T_1 becomes more pronounced, so that small superparamagnetic particles with core diameters of less than 10 nm can produce positive contrast in anatomically relevant T_1-weighted images.

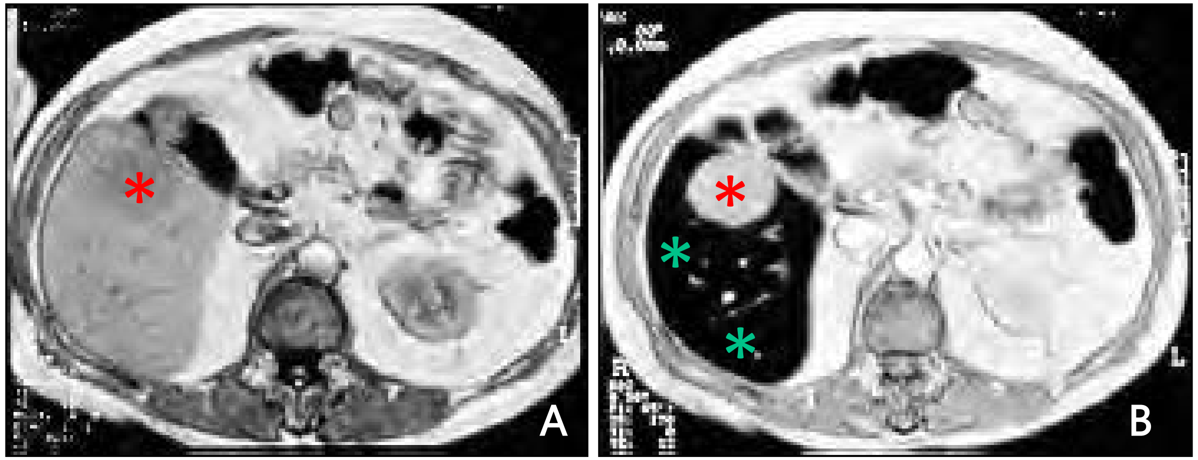


Fig. 28. Liver MRI pre (A) and post (B) iv administration of iron oxide nanoparticles with no uptake in the hepatocellular carcinoma (red asterisk) and uptake in normal liver tissue (green asterisks).

Indications

MR contrast agents can be classified according to their biodistribution pattern and the consequent applications in the morphological and functional diagnostic practice.

Non-specific extracellular contrast agents

Extracellular MR contrast agents are low molecular weight gadolinium complexes which, after injection, rapidly diffuse from the intravascular space into the extracellular space, from where they are then gradually eliminated by the kidneys.

These contrast agents circulate freely in the extracellular space but do not penetrate into tissues with specialized vascular barriers. Accordingly, they tend to accumulate in tissues with abnormal perfusion or capillary permeability and in regions where the blood-brain barrier permeability is altered.

The extracellular MR contrast agents are mainly applied for CNS examinations aimed at the detection of various neoplasms, the assessment of demyelinating diseases, infectious and inflammatory processes, the characterization of vascular anomalies and the diagnosis of cerebral ischemia and infarction. These agents are also extensively used in body imaging to asses certain pathologic processes, such as hepatocellular carcinoma or renal cell carcinoma and also for certain muskuloskeletal applications (see next page).

Chapter Outline

Some extracellular MR contrast agents can also be employed in MR angiography but due to their short residence time in the intravascular space, the imaging acquisition time window is very limited.

For the use as extracellular nonspecific contrast agents, most gadolinium complexes are equally effective because of their similar relaxivities and biodistributions.

Fig. 29. Gd-enhanced MRI of the carotid arteries

Indications for non-specific extracellular CAs

Central nervous system
Detection of primary neoplasms and brain metastases, assessment of demyelinating diseases, detection of infectious and inflammatory processes, characterization of vascular anomalies and diagnosis of cerebral ischemia and infarction

Abdomen and pelvis
Detection and characterization of lesions, and determination of the extent of malignant tumor dissemination

MR angiography
Assessment of vascular anatomy and disease

Breast
Differentiation of malign and benign lesions, detection of multicentric malignancies, recurrent local breast cancer or benign post therapeutic fibrosis

Musculoskeletal system
Detection and characterization of mass lesions and inflammatory processes and evaluation of the extent of disease

Chapter Outline

Blood pool agents

Blood pool agents are high molecular weight gadolinium compounds which have a slow diffusion rate from the intravascular into the extracellular space because of their albumin binding and which require metabolization of their macromolecular moiety before renal excretion, so that their concentration in plasma remains stable for over one hour.

Blood pool agents cause a significant reduction in the T_1 relaxation time of circulating blood; thus, these agents are used for MR angiography, including coronary artery imaging, and for assessing tumor angiogenesis.

Chapter Outline

Organ-specific Gd-based contrast agents

The two linear ionic complexes **Gd-BOPTA and Gd-EOB-DTPA** exhibit **liver specificity because of their selective uptake by hepatocytes and their partial hepatobiliary excretion.**

After intravenous administration, these CAs have an initial extracellular phase, which allows imaging of **hepatic vasculature,** followed by a **delayed hepatocytic uptake and biliary elimination phase**, which permits the evaluation of **hepatic tissue with altered functionality**.

The uptake by hepatocytes selectively increases the signal intensity of normal liver parenchyma, while focal lesions containing mutated cells or altered structure do not uptake the CA and will appear hypointense, enhancing the visualization of the lesion and helping to characterize its nature.

They can also be useful to improve detection of metastases and hepatocellular carcinoma.

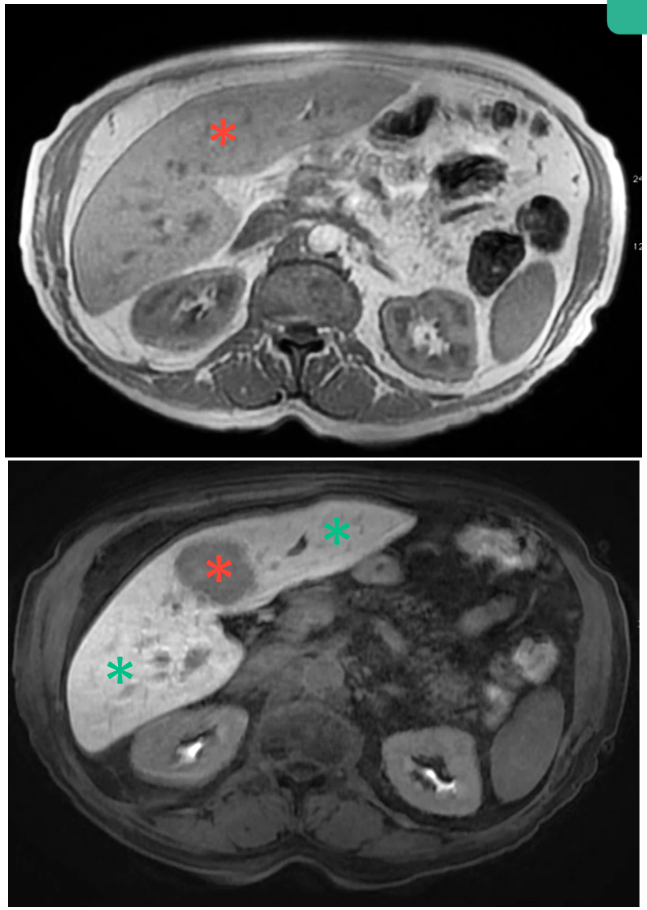


Fig. 30. Liver MRI pre and 20 min post iv administration of Gd-EOB-DTPA with no uptake in an adenoma (red asterisk) and contrast agent uptake in normal liver tissue (green asterisk).

Chapter Outline

Tissue specific reticuloendothelial and lymph node agents

Superparamagnetic iron oxide particles (SPIO) are selectively taken up by the reticuloendothelial system (RES) through phagocytosis, with the size of the particles determining the tissue specificity.

Large SPIO are rapidly metabolized by phagocytic cells like Kupffer cells in the liver and spleen, producing negative contrast in T_2 weighted images. Since most liver lesions, including metastases and the vast majority of hepatocellular carcinomas, do not have an intact RES, their signal intensity is unchanged by administration of SPIO, so that the contrast between normal and abnormal liver tissue is increased as the lesion appears hyperintense relative to the normal tissue.

Large SPIO particles can be used in liver and spleen imaging.

Small SPIO with a core size under 10 nm enter the lymphatic system and are metabolized by phagocytes in normal lymph nodes, whereas metastatic lymph nodes retain a certain quantity of the CA, allowing to differentiate between normal tissue, which has a negative contrast enhancement in T_2 weighted images, and metastatic tissue, which maintaining high signal intensity.

Small SPIO particles are utilized in the study of lymph nodes and bone marrow (limited availability).

Chapter Outline

Direct MR arthrography

Direct MR arthrography involves the injection of a contrast agent into a joint region under fluoroscopic or ultrasound guidance, followed by magnetic resonance imaging. MR arthrography provides clearer images of the tendons, ligaments and cartilage in the affected region.

The low concentrated solutions correspond to 1:200-250 fold dilutions (2-2.5 mM) of the iv approved products (500-1000 mM).

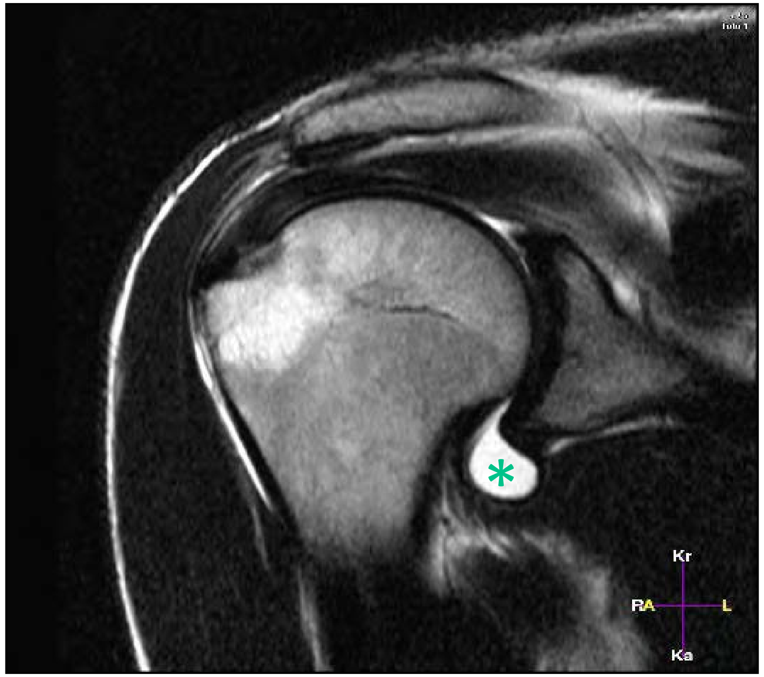


Fig. 31. Direct MR arthrography of the shoulder using a 2.5 mM GBCA (Artirem®). GBCA in the joint space is indicated by an asterisk.

Dosage of gadolinium contrast agents

For clinical use, the recommended dose of extracellular MR contrast agents is 0.1 mmol/kg of body weight for most of body imaging examinations. When used in MR angiography and CNS imaging, the extracellular MR contrast agents may be utilized with a higher dose up to 0.3 mmol/kg body-weight.

Liver-specific contrast agents are effective in lower doses of 0.05 to 0.1 mmol/kg for Gadobenate (Gd-BOPTA) and 0.025 mmol/kg for Gadoxetate (Gd-EOB-DTPA).

Chapter Outline

Adverse reactions

The most frequently reported adverse events of gadolinium contrast agents are rated as mild and include coldness, warmth or pain at the injection site, nausea, vomiting and headache, paresthesias and dizziness.

Allergic-like reactions with gadolinium complexes, which occur only very rarely, consist of sweating, rash, urticaria, itching and facial swelling.

Risk factors for developing an allergic-like reaction are a previous moderate or severe acute reaction to a gadolinium-based or iodinated contrast agent, asthma, and various other allergies.

Hypersensitivity is the major risk

Pregnancy and lactation

In pregnant women, when there is a very strong indication for an enhanced MRI, a macrocyclic gadolinium contrast agent may be administered using the smallest possible dose.

Breast feeding may be continued normally when macrocyclic gadolinium-based contrast agents are given to the mother.

Chapter Outline

Nephrogenic systemic fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is a rare but highly disabling disorder, which can occur in patients with impaired renal function exposed to less stable gadolinium-based CAs.

Clinical manifestations of NSF are extensive thickening and hardening of the skin and subcutaneous tissues associated with erythematous papules, as well as muscle weakness, bone pain and joint contractures.

Progressed NSF may also involve other organs, such as the liver, lungs, esophagus, heart, and skeletal muscle.

Symptoms develop and progress rapidly, are irreversible and can lead to extreme disability and death because of scarring alterations of the organs with consequent loss of function.

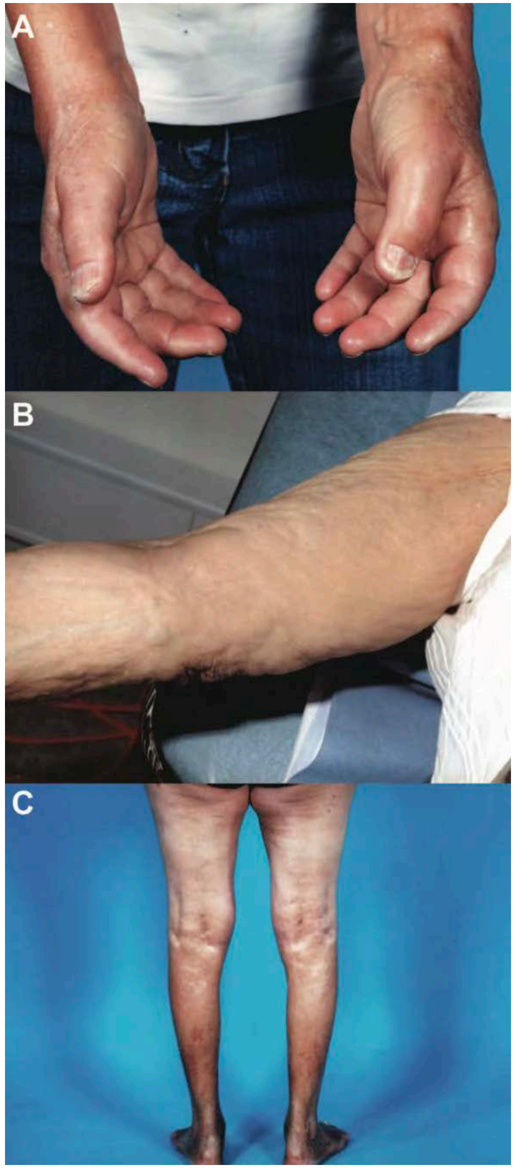


Fig. 32. Manifestations of nephrogenic systemic fibrosis. A: Tightness and hardness of the hands combined with joint contractures. B: Firm nodules establishing a cobblestone configuration. C: Tight and firm skin on lower legs.

Reproduced from: Elmholdt TR et al., Nephrogenic Systemic Fibrosis in Denmark– A Nationwide Investigation. PLOS ONE 2013; 8(12): e82037. doi:10.1371/iournal.pone.0082037.0001

Chapter Outline

As a pathophysiological mechanism, it is assumed that a reduced renal function, which is associated with a considerably prolonged tissue exposure to the gadolinium complex, increases the probability for precipitation of insoluble, toxic gadolinium salts. This process is supposed to stimulate a subsequent proinflammatory cascade of events leading to the fibrosing process.

Risk factors for the development of NSF

The greatest risk factors for the development of NSF are a reduced renal function, particularly with a glomerular filtration rate of eGFR < 15 ml/min/1.73 m^2, and patients on dialysis.

The risk for developing NSF is substantially more pronounced after the administration of non-ionic and ionic linear gadolinium complexes, and it increases with contrast agent dose and multiple exposure.

Further risk factors include metabolic acidosis, elevated blood levels of iron, calcium or phosphate, a high-dose erythropoietin therapy, immunosuppression, vasculopathy, and infection or other acute proinflammatory events.

Chapter Outline

Gadolinium retention in the brain

Repeated administration of gadolinium-based contrast agents is associated with gadolinium accumulation in the brain regions of the dentate nucleus and globus pallidus even in subjects with normal renal function.

While such deposits have been reported for all gadolinium-based agents, the highest levels found after the administration of linear agents were substantially higher than after the use of macrocyclic agents.

A significant positive correlation exists between the amount of gadolinium accumulated and the cumulative dose of previous administrations of gadolinium-based contrast agents.

To date, no neurological symptoms associated with gadolinium retention in the brain have been reported.

Gadolinium deposits may also occur in the bone, liver and skin, independently of renal function.

Bone and liver retention do not produce any clinical symptoms, whereas skin deposits manifest as red skin plaques.

Chapter Outline

Safety recommendation

The **European Medicines Agency (EMA)** has classified the linear complexes Gd-DTPA-BMA, Gd-DTPA and Gd-DTPA-BMEA as high risk agents and suspended their intravenous usage, with the exception that Gd-DTPA may still be employed for direct MR arthrography.

The linear complexes Gd-BOPTA and Gd-EOB-DTPA, which are rated as intermediate risk agents, remain approved by EMA for hepato-biliary imaging only.

The macrocyclic agents are considered as low-risk and are maintained by EMA as non-specific Gd contrast agents. However, they should be used with caution in patients with GFR < 30 ml/min, observing a period of at least 7 days between two injections.

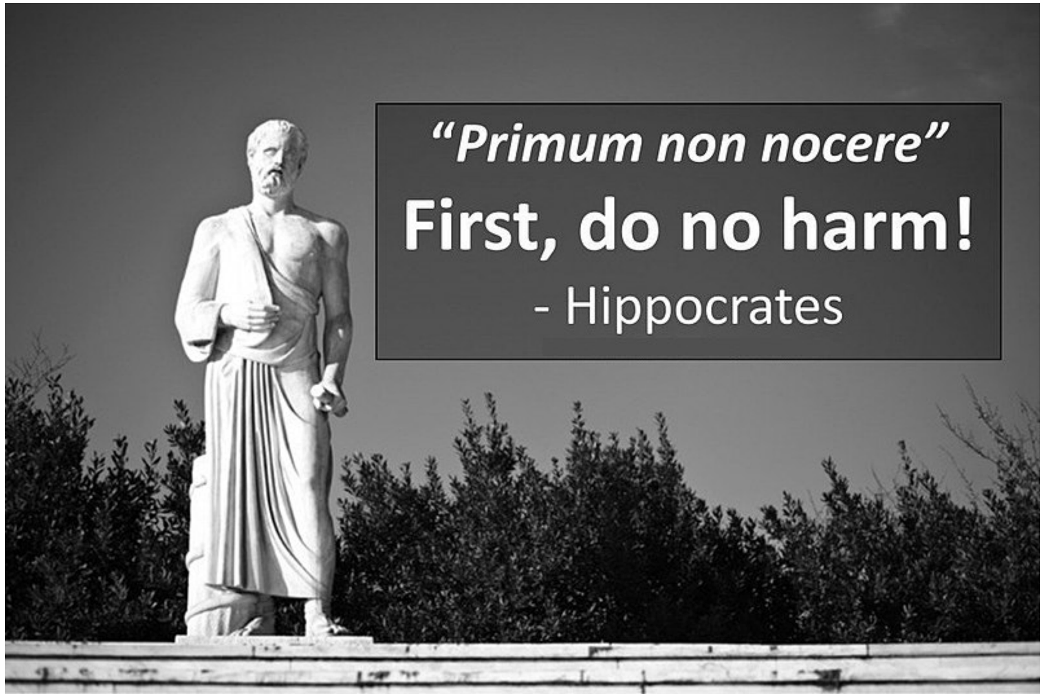


Fig. 33. Image from Wikimedia Commons https://commons.wikimedia.org/wiki/File:Primum_Non_Nocere.jpg#filelinks

Chapter Outline

Table 3. Recommendation of the use of gadolinium-based CAs according to the European Medicines Agency (EMA)

Type	Ionicity	Product	Complex	EMA recommendation
Linear	ionic	Gd-DTPA	gadopentetate dimeglumine	restricted use for direct MR arthrography
		Gd-BOPTA	gadobenate dimeglumine	restricted use as for hepato-biliary imaging
		Gd-EOB-DTPA	gadoxetate	restricted use as for hepato-biliary imaging
	non-ionic	Gd-DTPA-BMA	gadodiamide	suspended
		Gd-DTPA-BMEA	gadoversetamide	suspended
Macrocyclic	ionic	Gd-DOTA	gadoterate meglimine	maintained as non-specific GdCA
	non-ionic	Gd-HP-DO3A	gadoteridol	maintained as non-specific GdCA
		Gd-BT-DO3A	gadobutrol	maintained as non-specific Gd-CA

Chapter Outline

Ultrasound Contrast Agents

Ultrasound contrast agents are used in order to increase the reflection of ultrasound waves from blood, thus resulting in an enhancement of the contrast between blood and surrounding tissue.

Microbubbles

Ultrasound contrast agents consist of suspensions containing microscopically small gas bubbles encapsulated in thin stabilizing shells.

The gas core of the microbubbles is generally composed of an inert high molecular weight and low solubility gas such as a perfluorocarbon or sulfur hexafluoride which does not diffuse across the shell and maintains an elevated vapor concentration within the microbubble.

The stabilizing shell is made of a biodegradable material, such as phospholipids or albumin, which reduces the likelihood of coalescence and allows the microbubbles to persist in the vasculature and permit diagnostic evaluation for several minutes.

Chapter Outline

Commercially available ultrasound contrast agents contain a **mixture of microbubbles of various sizes in the range of 1-10 µm, which is approximately the same size range as erythrocytes**. After intravenous injection, the microbubbles **move passively with the blood** flow and act as tracers providing an enhanced ultrasound signal.

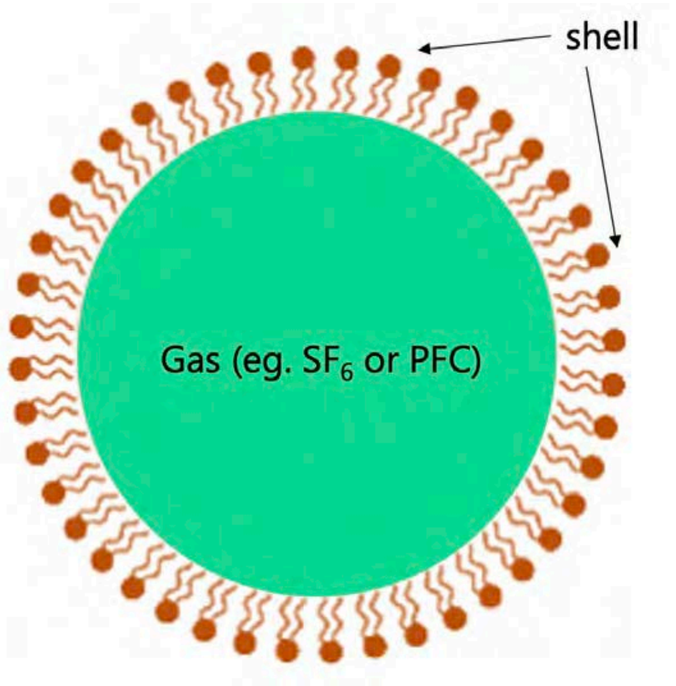


Fig. 34. Structure of microbubble composed of a core of sulfur hexafluoride gas and a monolayer phospholipid shell.

Composition of currently used ultrasound contrast agents

- Air microbubbles encapsulated in a shell of galactose stabilized with palmitic acid
- Sulfur hexafluoride (SF_6) microbubbles encapsulated in a shell of phospholipids and palmitic acid
- Perfluoropropane (perflutren, C_3F_8) microbubbles encapsulated in an albumin shell
- Perfluoropropane (perflutren, C_3F_8) microbubbles encapsulated in a shell of phospholipids

Chapter Outline

Ultrasound echo enhancement by microbubbles

The contrast enhancement achieved with microbubbles is due to a substantial difference in acoustic impedance at the interface between the microbubble structure and the surrounding blood plasma, which leads to backscattering of the sound wave at the microbubble surface.

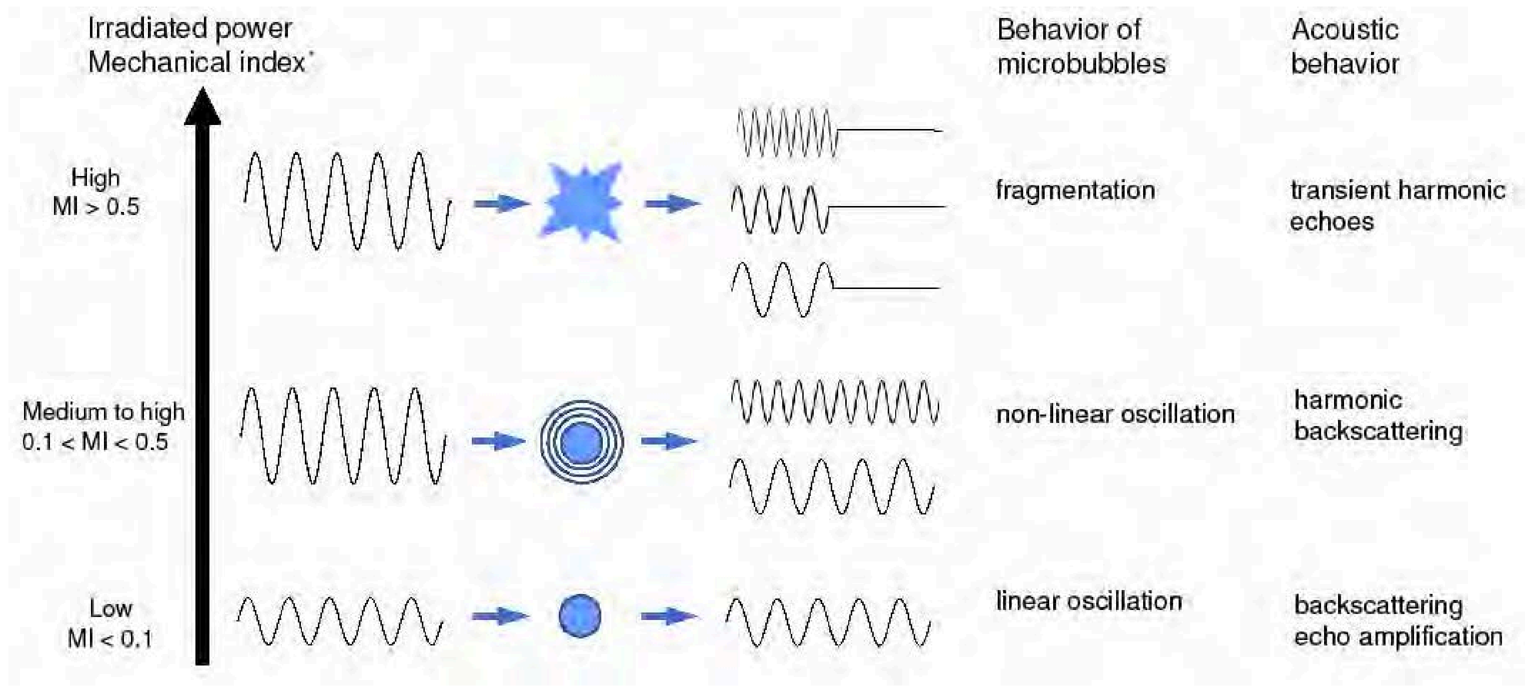
This acoustic response of an ultrasound contrast agent is specific for the microbubbles used and also depends on the acoustic power of the irradiated ultrasound wave.

At low acoustic powers, the microbubbles act as simple reflectors, so that only a backscattered linear signal can be received.

At intermediate acoustic powers, the microbubbles are induced to oscillate and thereby to emit an intensive non-linear resonance signal, which contains, in addition to the fundamental vibration frequency, also harmonic upper frequencies.

At even higher acoustic powers, the microbubble vibration is so violent that the microbubbles are destroyed by tearing of the membranes. This process is accompanied by emission of a detectable ultrasound pulse.

Chapter Outline



* The mechanical index (MI) is a unitless metric for the bioeffects of an ultrasound beam. It is proportional to the peak rarefaction pressure and inversely proportional to the frequency of the ultrasound wave.

Fig. 35. Influence of irradiated ultrasound power on the acoustic behavior of microbubbles.

Chapter Outline

Implementation of contrast-specific ultrasound techniques such as harmonic and coded imaging and, particularly, phase and amplitude modulation, allows discrimination of the specific signal generated by the contrast agent microbubbles from other acoustic signals such as from specular reflection and tissue scattering.

The improved contrast effect permits real time scanning with the possibility of prolonged organ insonation, thus enabling dynamic imaging of blood flow and measuring organ perfusion with high sensitivity.

Biodistribution and elimination

The intravascularly administered microbubbles are small enough to pass through the pulmonary capillaries and reach the systemic capillary network, but they generally remain confined to the blood pool and do not extravasate into the interstitial space.

However, some ultrasound contrast agents exhibit a postvascular hepato- and/or spleno-specific phase from 2 to 5 minutes after intravenous injection. This phenomenon is probably due to an adherence of the microbubbles to the hepatic sinusoids or to a selective uptake by the phagocytic Kupffer cells of the reticuloendothelial system.

After spontaneous dissolution of the microbubbles, the inert gas content is released and is mostly eliminated within 10 to 20 minutes by lung ventilation, whereas the shell material is metabolized and eliminated by the liver.

Ultrasound contrast agents are not excreted through the kidneys, and thus have no known nephrotoxicity.

No evidence of biological effects resulting from inertial cavitation – the rapid formation, growth, and collapse of a gas cavity in a fluid as a result of intense ultrasound exposure – has been reported in humans.

Administration of ultrasound contrast agents

Ultrasound contrast agents are administered intravenously as a bolus injection or as a continuous infusion, or they are instilled into hollow structures, such as the urinary bladder.

Bolus injection produces a rapid rise in enhancement followed by a slower washout, and it is the most commonly used administration form for imaging with low and intermediate acoustic power.

Continuous infusion leads to a plateau-like enhancement and thus to a prolongation of the diagnostic time window that is important for quantifying tissue perfusion.

Chapter Outline

Indications

Ultrasound contrast agents are primarily used for cardiovascular imaging, including echocardiography, and for ultrasound diagnostics of the liver and, less frequently, of other parenchymatous organs.

Cardiovascular imaging

In echocardiography, contrast agents are used for direct visualization of the left ventricular chamber and endocardial surfaces, which permits clinical assessment of the left ventricular systolic function, structure and filling status. Ultrasound contrast agents are also applied for the examination of left ventricular structural abnormalities such as intracavitary thrombi, left ventricular aneurysms and pseudo aneurysms, the study of Takotsubo cardiomyopathy and myocardial perfusion.

Vascular imaging

The clinical vascular applications using ultrasound contrast agents include contrast enhancement of the aorta, carotid arteries and the peripheral venous system. Specifically, ultrasound contrast agents are applied for examination of the carotid artery lumen and of atherosclerotic plaque neovascularization, but also for the assessment of the intima-media-thickness as surrogate marker of systemic atherosclerosis.

Chapter Outline

Liver lesions

The main application area of contrast-enhanced ultrasound imaging is the detection and characterization of focal liver lesions, particularly the distinction between benign and malignant nodules.

The differential diagnosis of hepatic tumors is facilitated by the highly sensitive visualization of the capillary network achieved with ultrasound contrast media and the reliable information about tissue perfusion, which can be deduced from the influx and washout of the contrast agent.

After intravenous administration of the ultrasound contrast agent, three phases of enhancement in the liver can be distinguished:

- **the arterial phase**, in which the contrast agent reaches the liver first via the hepatic artery (up to 25s after injection)
- **the portal phase**, where the contrast agent has passed circulation and spreads through the liver in the portal branches (between 25 and 45s after injection); and
- **the late or parenchymal phase,** in which the agent slowly distributes within the entire liver parenchyma (>2minutes after injection)

The characteristic features in these three phases allow detection of a hepatocellular carcinoma with high sensitivity and specificity, and they enable a differentiation of metastases in the liver.

Further indications

Other applications of ultrasound contrast agents include the detection and characterization of breast, pancreatic, renal and endocrine tumors. Moreover, these agents are also used for the assessment of fallopian tube patency and of the vesico-ureteric reflux, but also for the identification of solid organ traumatic injury (Fig. 38).

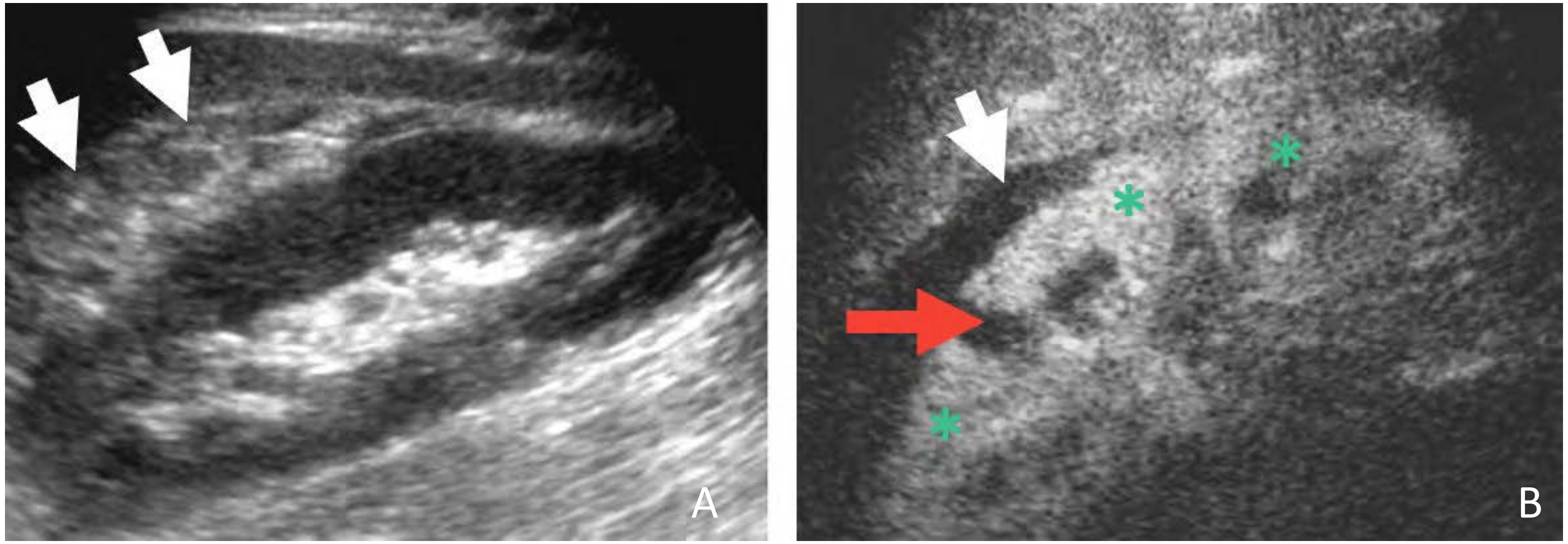


Fig. 36. US images of the right kidney in a trauma patient before (A) and after (B) intravenous injection of a sonographic CA. On the image before CA administration (A), a heterogeneous peri-renal hematoma (white arrows) is seen, however, no kidney injury. The image after CA administration (B) shows in addition to the perirenal hematoma (white arrows) also a parenchymal laceration (red arrow). Note that following CA administration, the normal kidney parenchyma is strongly hyperechoic (asterisks). Images courtesy: Alexandra Platon, MD, University Hospitals Geneva.

Adverse reactions

Adverse reactions associated with ultrasound contrast administration are rare and usually of transient nature and mild intensity.

The most common adverse events include tissue irritation at the site of injection, headache, nausea and vomiting, taste alterations, dyspnea, chest pain, hypo- or hypertension, vertigo, a sensation of warmth or flushing, cutaneous eruptions and asymptomatic premature ventricular contractions.

Hypersensitivity events are due to anaphylactoid reactions to the gas or shell and include hypotension, bronchospasm, urticaria and pruritus.

Chapter Outline

Contraindications

Contraindications to intravenously administered microbubble contrast agents are a history of hypersensitivity reaction to the constituent gas or shell of the agents.

Due to the possible risk for a serious cardiopulmonary reaction, intravenous microbubble contrast agents should not be used in individuals with an unstable cardiopulmonary condition such as severe pulmonary hypertension, acute coronary syndrome, unstable angina, recent myocardial infarction, clinically unstable congestive heart failure and cardiac rhythm disorder.

Microbubble contrast agents should be avoided in the 24 hours before extracorporeal shock wave treatment.

Microbubble contrast agents should be used in pregnancy only if the benefit outweighs the risk. Breast feeding women may consider pumping and discarding of milk.

Take-Home Messages (1)

- Contrast agents developed for radiographic examinations, magnetic resonance imaging and sonography have revolutionized the application field of diagnostic imaging in clinical practice.
- Today's contrast agents are remarkably well tolerated and safe, but it remains the physician's responsibility to understand the potential adverse effects, and the specific situations, in which a particular patient might be at increased risk.
- Radiographic contrast media (RCM) mainly comprise iodinated compounds that enhance image contrast by locally inducing a change in x-ray absorptivity.
- Radiographic examinations using contrast media, which provide reliable diagnostic information regarding normal and abnormal morphology and function, are applied routinely in clinical practice for a plurality of indications.
- The incidence of adverse reactions related to the intravascular administration of iodinated RCM, which has been drastically reduced with the change in usage from ionic high-osmolality RCM to nonionic low-osmolality or iso-osmolality RCM, is now generally low.

Take-Home Messages (2)

- In patients with established hyperthyroidism, administration of iodinated RCM is contraindicated due to the risk for development of thyrotoxicosis.
- Preexisting renal dysfunction is a significant risk factor for developing a contrast media-induced nephropathy.
- MR contrast agents primarily comprise paramagnetic gadolinium complexes, which affect the relaxation times of water protons present in the surrounding tissue and thereby cause an increase or decrease in signal intensity.
- Non-specific extracellular MR contrast agents are used for CNS and body imaging to asses pathologic processes and functional abnormalities, whereas organ and tissue specific contrast agents are used for detection and characterization of tumors in liver, spleen, lymph nodes and bone marrow.
- Gadolinium-based MR contrast agents are well tolerated by the vast majority of patients, but the rate of adverse events tends to be higher with liver specific contrast agents than with extracellular gadolinium agents.

Chapter Outline

Take-Home Messages (3)

- Patients with impaired renal function may develop a nephrogenic systemic fibrosis after the administration of linear gadolinium complexes, which is why the European Medicines Agency (EMA) has suspended or restricted intravenous use of all high risk linear Gd-based contrast agents.
- Repeated administration of linear Gd-based contrast agents is associated with a dose-dependent accumulation of gadolinium in brain regions even in subjects with normal renal function.
- Ultrasound contrast agents consist of microbubbles composed of a high molecular weight and low solubility gas encapsulated in a stabilizing shell, which backscatter the impinging ultrasound waves at their membrane due to a local change in acoustic impedance.
- Indications for ultrasound contrast agents primarily comprise cardiovascular imaging, including echocardiography, and the detection and characterization of focal liver lesions, particularly the distinction between benign and malignant lesions.
- Ultrasound contrast agents benefit from an excellent safety profile, with the only, very rarely occurring adverse event being a hypersensitivity reaction.

Chapter Outline

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Test Your Knowledge

1 - Which elements are incorporated in routinely used RCM?

- Manganese in form of superparamagnetic particles
- Iodine in form of organic molecules
- Barium as barium sulfate suspension
- Gadolinium in form of chelating complexes
- Xenon as gas

Chapter Outline

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Test Your Knowledge

2 - Which of the following statements regarding iodinated RCM are correct?

- RCM with a carboxylate substituent dissociate in solution forming ionic compounds
- Highly hydrophilic RCM have an enhanced plasma protein binding
- Iodinated RCM in solution undergo a deiodination process releasing free iodide
- A cholegraphic RCM has an accelerated glomerular filtration rate
- Osmolality is higher in ionic RCM than in non-ionic RCM, each with the monomeric agents having a higher osmolality

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Chapter Outline

Test Your Knowledge

3 - Which factors are associated with an increased risk for adverse effects using RCM?

- Radiographic imaging of the gastrointestinal tract using barium sulfate suspension
- Intravenous administration of high osmolality RCM
- Intravenous cholangiographic contrast media to patients with an undelaying thyroid disorder
- Intravenous administration of high viscosity RCM
- Visualization of the gastrointestinal tract with oral iodinated RCM

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Test Your Knowledge

4 – Which patients are at risk for developing post-contrast acute kidney injury after administration of iodinated RCM?

- Patients with impaired renal function with eGFR < 45 ml/min/1.73 m^2
- Patients suffering from multiple myeloma
- Patients suffering from diabetes mellitus
- Patients suffering from cardiovascular disease

Chapter Outline

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Test Your Knowledge

5 – Which compounds are routinely used as MR contrast agents?

- Gd^{3+} in form of complexes with chelating ligands
- Perfluorocarbon nanoparticles for ^{19}F imaging
- Fe_2O_3 nanoparticles
- Mn^{2+} in form of complexes with chelating ligands

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Chapter Outline

Test Your Knowledge

6 - Which statements about non-specific extracellular contrast agents are correct?

- They circulate freely in the extracellular space but do not penetrate the intact blood-brain barrier
- They require metabolization of their macromolecular moiety before renal excretion
- They are applied for CNS examinations
- The various extracellular gadolinium contrast agents show widely varying efficiencies with respect to their relaxivity

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Chapter Outline

Test Your Knowledge

7 - Which MR contrast agents are recommended for detection and characterization of liver tumors?

- Linear ionic Gd^{3+} complexes
- Linear non-ionic Gd^{3+} complexes
- Macrocyclic Gd^{3+} complexes
- Large superparamagnetic iron oxide particles
- Small superparamagnetic iron oxide particles

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Test Your Knowledge

8 - Which of the following are risk factors for developing a nephrogenic systemic fibrosis after administration of a Gd-based contrast agent?

- Impaired renal function with a glomerular filtration rate of eGFR < 15 ml/min/1.73 m^2
- Patients suffering from a hepatic disease
- Administration of a linear gadolinium contrast agent
- Patients with elevated blood levels of iron
- Application of superparamagnetic iron oxide particles

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Chapter Outline

Test Your Knowledge

9 - What are the recommendations of the European Medicines Agency (EMA) about the use of gadolinium-based CAs regarding the risk of developing nephrogenic systemic fibrosis?

- The use of all linear gadolinium-based complexes is suspended
- The use of macrocyclic ionic gadolinium-based complexes is restricted to hepato-biliary imaging
- The use of linear non-ionic gadolinium-based complexes is suspended
- The use of linear ionic gadolinium-based complexes is restricted to hepato-biliary imaging and arthrography, respectively

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Test Your Knowledge

10 - Which statements regarding the use of microbubbles as ultrasound contrast agents are correct?

- They are excreted through the kidneys
- They are mostly eliminated through the lung
- They cannot be used for measuring the tissue perfusion of the liver
- They can rapidly pass an intact blood-brain barrier
- They generally remain confined to the blood pool

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Chapter Outline

Test Your Knowledge

11 - What are the advantages of ultrasound imaging using microbubble contrast agents?

- They allow real time imaging of blood flow and organ perfusion with high sensitivity
- The microbubbles can also be therapeutically used for targeted drug delivery
- They have an excellent safety profile
- The new generation microbubbles with improved stability can persist under insonation with high acoustic power

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Test Your Knowledge

12 - Which imaging method is indicated for the detection of a hepatocellular carcinoma in a patient with renal insufficiency?

- Radiographic imaging using iodinated RCM
- Ultrasound imaging using microbubbles contrast agents
- MR imaging using the liver-specific linear gadolinium complexes

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Test Your Knowledge

13 - Which functional principles determine liver specificity in the different imaging methods?

- Partial distribution of contrast agent in the liver through passive diffusion, used in radiographic examinations
- Selective uptake of contrast agent by phagocytic cells in the liver, used in MR imaging
- Partial hepatobiliary excretion and uptake of contrast agent by hepatocytes, used in MR imaging
- Accumulation of contrast media depending on the functionality of the hepatobiliary system, used in ultrasound imaging

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Chapter Outline

Test Your Knowledge

14 - Which statements concerning adverse reactions in respect of the various imaging methods are correct?

- The incidence of adverse reactions related to iodinated RCM has been reduced in routine clinical practice due to the restricted use of ionic high-osmolality RCM
- Orally administered iodinated contrast media for radiographic imaging of the gastrointestinal tract are contraindicated in patients with suspected perforation
- Repeated administration of linear Gd-based contrast agents is associated with a dose-dependent accumulation of gadolinium in brain regions even in subjects with normal renal function.
- Microbubble ultrasound contrast agents increase the risk for pulmonary embolism
- In patients with established hyperthyroidism, administration of iodinated contrast media is contraindicated

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