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Imaging with contrast media – an introduction



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The state of the art of imaging techniques is presented, bringing out the advantages and risks of these procedures. Modern imaging is so well regarded that the risks of allergy to iodinated and gadolinium-based contrast agents may be overlooked. Use of these techniques is growing rapidly.

Introduction

Medical imaging is one of the fastest growing disciplines in the hospital. The average radiology department has seen the number of procedures growing at 5–10% annually over the last decade, and the end of this growth is certainly not in sight. The growth in use of imaging has been paralleled by a rapid increase in the use of medical contrast agents. It is important to realise that contrast agents – while very safe in general – are sometimes associated with severe side effects, depending on the class of agents used. In this article a short introduction to the most commonly used imaging techniques is given, with emphasis on the role of contrast agents.

General principles of imaging techniques

X-ray imaging

X-ray-based imaging refers to procedures performed under fluoroscopic guidance such as small or large bowel imaging or coronary and peripheral vascular angiography as well as any form of computed tomography (CT). Contrast agents used in X-ray-based imaging techniques are barium or iodine-based. Barium agents are only used to visualise the gastrointestinal tract, so the vast majority of contrast-enhanced X-ray procedures are performed using iodinated contrast agents. It is estimated that for CT scans over half of all examinations are enhanced using iodinated contrast agents. The purpose of these agents is to increase soft tissue contrast, as the densities of un-enhanced soft tissues are very similar. Dynamic enhancement patterns can also give valuable clues with regard to the differential diagnosis, and

this finding is often used in daily practice for instance to differentiate between different kinds of liver lesions.

It is well known that iodinated contrast agents have the potential to adversely affect renal function, i.e. to cause contrast-induced nephropathy (CIN), especially in patients whose renal function is already compromised. However, careful selection of patients and taking preventive measures such as pre-hydration and, if needed, premedication, make these agents well tolerated in everyday clinical practice. For an up-to-date overview of this topic the reader is referred to the recent meta-analysis on this subject by Kelly et al. who found that N-acetylcysteine is more renoprotective than pre-hydration alone [1]. Allergic-like reactions also comprise a substantial part of the adverse effects associated with the administration of iodinated contrast agents, although with the widespread switch to non-ionic agents the frequency has dropped substantially. Singh et al. provide an excellent overview of iodinated contrast media and their adverse reactions [2].

Ultrasonography

Ultrasonography is a safe and cheap imaging modality that is very widely used as the first choice of imaging method throughout the world. In ultrasonography, grey scale values as seen in the image are related to the acoustic impedance of different tissues. Because of the inherently high contrast between different tissues as visualised with ultrasonography contrast agents are not often used in clinical practice. Contrast agents used for ultrasonography are gas-filled

bubbles giving rise to a (transient) high signal in the vasculature of the organ of interest due to increased back-scatter. The main indication for their use is to characterise the vascular supply of focal lesions in soft tissues such as the liver. Emerging indications are the characterisation and follow-up of tumour microvasculature in the context of focal liver disease and breast and prostate tumours [3].

The adverse effects of ultrasound contrast agents are primarily back pain, headache, urticaria, and rarely anaphylactic reactions (estimated rate of 1 per 10,000) [4]. However, the safety of echocardiographic contrast agents has been the subject of discussion since the FDA issued a ‘black box’ warning for the agents Definity and Optison in October 2007, contraindicating their use in patients with worsening or unstable heart failure, acute myocardial infarction or serious ventricular arrhythmias and in conditions that cause pulmonary hypertension, based on the occurrence of 11 deaths, four of which were caused by cardiac arrest occurring during or within 30 minutes of their use. However, these events occurred over a period of six years and causality was not clear. The FDA reviewed these guidelines in May 2008 and replaced the extended contraindications with warnings after recognising the favourable risk/benefit ratio for these contrast agents and the potential risks of alternative procedures. Current contraindications to the use of echocardiographic contrast agents are right to left or bidirectional cardiac shunts, hypersensitivity to perflutren, intra-arterial injection and, for Optison

only, hypersensitivity to blood or albumin. Thirty minutes of monitoring is required only for patients with pulmonary hypertension and unstable cardiopulmonary diseases [5].

Magnetic resonance imaging

The most versatile modern method of imaging is no doubt magnetic resonance imaging (MRI). MRI is unequalled in the variety and kinds of imaging contrasts that can be generated. In its conventional, most well-known form, MRI soft tissue contrast is based on the phenomenon of relaxation parallel T1 and perpendicular T2 to a strong external magnetic field after radiofrequency stimulation. By manipulating sequence parameters different sequences (also known as weightings) can be generated [6]. Furthermore, in contrast to CT and ultrasonography, MRI is not only capable of imaging 'anatomy' but also physiological processes such as flow, perfusion and diffusion.

There are many MR contrast agents and the reader is referred to the review paper by Bellin [7] for an overview of the class of extracellular gadolinium-based contrast agents which comprise virtually all of the agents used today.

In general, MR contrast agents increase the relative difference between tissues by altering the relaxation times. *Positive* contrast agents cause a reduction in the T1 relaxation time (increased signal intensity on T1 weighted images). They are typically small molecular weight compounds containing as their active element gadolinium, manganese or iron and appear bright on MRI. All of these elements have unpaired electron spins in their outer shells and long relaxivities. Some typical contrast agents such as gadopentetate dimeglumine, gadodiamide, gadoteridol, gadobutrol, gadoxetic acid and gadoterate meglumine are used for the central nervous system and the complete body; mangafodipir trisodium and gadoxetic acid are specially used for lesions of the liver. *Negative* contrast agents (appearing predominantly dark on MRI) are small particulate aggregates

often termed superparamagnetic iron oxide (SPIO). These agents produce predominantly spin-spin relaxation effects (local field inhomogeneities), which result in shorter T1 and T2 relaxation times. SPIOs and ultra-small superparamagnetic iron oxides (USPIO) usually consist of a crystalline iron oxide core containing thousands of iron atoms and a shell of polymer, dextran, polyethylene glycol, and produce very high T2 relaxivities. USPIOs smaller than 300 nm cause a substantial T1 relaxation and T2 weighted effects are predominant. A special group of negative contrast agents (appearing dark on MRI) are perfluorocarbons. The hydrogen atoms responsible for the signal in MRI are replaced by fluorine atoms. These agents are the subject of research and not available clinically at present.

Since the late 1980s many toxicological and pharmacokinetics studies have been conducted by the major contrast vendors with various gadolinium-based contrast agents (GBCA). An extremely favourable safety profile was found in all of these studies. Therefore, the recent discovery of the association between administration of GBCA and nephrogenic systemic fibrosis (NSF) came as a surprise to almost everyone involved, although in retrospect it may not be so surprising. To date, over 200 million patients have been dosed and adverse effects of any kind were very rare, until the discovery of NSF.

NSF is a rare, idiopathic systemic fibrosing disorder and is characterised clinically by pain, dermatopathy and joint contractures. NSF affects the skin, skeletal muscle, oesophagus, lungs, heart and kidneys. The first suggestion of the link between GBCA and NSF, published by Grobner et al. three years ago [8], has sparked intense interest in this subject, illustrating just how important MR contrast media are today. It is now clear that NSF is a condition that almost exclusively affects patients with severely limited renal function. However, surprisingly little is known about the exact pathogenesis of the disease, and who exactly are at risk for developing the disease.

The discovery of NSF has been unfortunate for patients, and particularly for patients with acute or chronic kidney disease (CKD) with severely impaired renal function. Worldwide, regulatory agencies have issued warnings on the use of GBCA in patients with severe kidney dysfunction (CKD stages 4 and 5) [9], which has led to the virtual cessation of use of contrast-enhanced MRI in this vulnerable patient group [10].

Relative merits and shortcomings of imaging techniques

For CT the drawbacks include the relatively higher rate of adverse events associated with contrast media administration and the use of ionizing radiation. Although recent technical developments with regard to multi-detector row technology have addressed many of the concerns regarding radiation, the rapid rise in the number of CT procedures has partially offset these gains again.

Ultrasonography's advantages are many. The technique is widely available, cheap and images are obtained in real time at very high spatial resolution. Disadvantages are the relatively high rate of uninterpretable studies, which is primarily a function of the expertise of the person performing the examination, as well body type, and improper preparation for the exam, i.e. not fasting prior to abdominal imaging.

For MRI the main limitations are cost and availability. A typical MRI examination takes about 30–60 minutes depending on the indication. Also, because of higher equipment and maintenance costs, MRI is much more expensive compared to other imaging modalities. It is also important to realise that not all patients are good candidates for MRI. Patients who suffer from claustrophobia or who cannot lie still in the magnet, or patients with ferromagnetic implants such as pacemakers and aneurysm clips are poor candidates, and are better served with CT or ultrasonography.

MRI – the preferred technique?

From the above discussion it becomes

clear that despite their strengths all imaging modalities have drawbacks. It is important to realise that in clinical practice all techniques are routine employed and no single imaging modality can be fully replaced by another. Despite this caveat, it is safe to say that MRI is probably the most versatile imaging modality due to sheer amount of anatomical and physiological information that can be obtained.

Furthermore, the great advantage of MRI is the entirely non-destructive nature of the imaging process, making the technique of special interest when radiation exposure is of concern, such as in paediatric patients or when imaging especially radiosensitive organs such as the gonads or breast.

Despite the risks associated with administration of gadolinium-based contrast agents it very important to realise that risk is relative, not absolute. Not only is the risk of NSF with GBCA-MRI small compared to the risk of CIN with iodinated CT, but also in comparison with risk of severe allergic reactions with iodine and allergic reactions with GBCA. The concern about NSF has masked our concerns for GBCA's other potential adverse effects. A survey of major American centres published in 1999 by Murphy et al. indicated an inci-

dence of severe allergic reactions to GBCA of approximately 20 cases per million doses administered [11]. This is about 10-fold greater than the incidence of NSF, not to mention the risk of making an incorrect diagnosis because the most appropriate imaging study was not done.

In conclusion, nowadays there are many alternatives available to the referring clinician when it comes to imaging. Basic knowledge of imaging modalities and the contrast media that are used enable patient care to be optimised.

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