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Abstract

The introduction of MR-PET systems into medical practice not only may lead to a gain in clinical diagnosis as compared to PET-CT imaging due to the superior soft tissue contrast of the MR technology but can also substantially reduce exposure of patients to ionizing radiation. On the other hand, there are also risks and health effects associated with the use of diagnostic MR devices that have to be considered carefully. In this chapter, the biophysical and biological aspects relevant for the assessment of health effects related to the use of ionizing radiation in PET and (electro)magnetic fields in MR are summarized. On this basis, the current safety standards will be presented – which, however, do not address the possibility of synergistic effects of ionizing radiation and (electro)magnetic fields. In the light of the developing MR-PET technology, it is of utmost importance to investigate this aspect in more detail for exposure levels that will occur at MR-PET systems. Finally, some considerations concerning the justification and optimization of MR-PET examination will be made.

10.1 Introduction

Clinical adoption of combined PET-CT imaging has been surprisingly rapid, and, despite continuing debate, this technology has advanced the use of metabolic and molecular imaging [49],

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particularly for oncology [11, 39, 40, 43]. However, when discussing the immediate benefits of combined PET-CT examinations, the issue of patient exposure must be taken into account as well. As shown in a multicenter study, whole-body PET-CT examinations – comprising a PET scan after the administration of the glucose analogue 2-[¹⁸F] fluoro-2-deoxy-D-glucose (FDG) and a fully diagnostic contrast-enhanced CT scan – result in an effective dose to patients in the order of 25 mSv and thus mandate a thorough medical justification for each individual patient [5, 8]. A detailed analysis of protocols, which are representative for the imaging scenarios reported in the literature, revealed that up to 70 % of the total exposure is contributed by CT [8]. It would thus be very welcome from a radiation protection point of view if PET-CT could be replaced whenever possible by MR-PET as soon as the methodological challenges of this new imaging technology have been overcome.

As no ionizing radiation is used in MR, it is generally deemed safer than CT or PET in terms of associated health risks. Nevertheless, there are possible risks and health effects associated with the use of diagnostic MR devices that have to be considered carefully [4, 45]. In this context, a fundamental difference between ionizing and nonionizing radiation has to be noted: Radiation doses related to CT or PET procedures may result in stochastic effects (occurring many years later), whereas biological effects of (electro)magnetic fields used in MR are of deterministic nature (occurring immediately). A stochastic process is one where the exposure determines the probability of the occurrence of an event but not the severity of the effect. In contrast, the severity of a deterministic effect is related to the level of exposure and a threshold may be defined [21]. As a consequence, the probability of detrimental effects caused by PET or CT examinations performed over many years accumulate, whereas biophysical and biological effects induced by (electro)magnetic fields used for MR examinations (such as cardiovascular reactions or peripheral nerve stimulation) are related to the acute exposure levels of a particular examination and does, to our present knowledge, not accumulate over years.

Following the presentation in Brix et al. [9], this chapter presents (a) an overview on biophysical and biological aspects relevant for the assessment of detrimental health effects related to the exposure of patients to ionizing radiation in PET and to (electro)magnetic fields in MR as well as (b) some preliminary considerations on the justification and optimization of MR-PET procedures. A comprehensive discussion of aspects which are beyond the scope of this chapter – as, for example, layout and shielding of a PET facility or protection of the staff – can be found in a safety report issued by the “International Atomic Energy Agency” [19] and guidelines of the “International Commission on Non-Ionizing Radiation Protection” [20, 24, 26].

10.2 PET: Ionizing Radiation

10.2.1 Detrimental Health Effects Induced by Ionizing Radiation

Low-level exposure of patients undergoing a PET or CT examination may lead to stochastic radiation effects, the most significant being induction of cancer. Cancers caused by ionizing radiation occur several years to decades after the exposure has taken place (latency time). They do not differ in their clinical appearance from cancers that are caused by other factors. A radiation-induced cancer cannot be recognized as such, and it is only by means of epidemiological studies that increases in the spontaneous cancer incidence rates of irradiated groups can be detected. Ionizing radiation is the carcinogen that has been studied most intensely.

Increased cancer rates have been demonstrated in humans through various radio-epidemiological studies at moderate or high doses, i.e., organ or whole-body doses exceeding 50–100 mSv, delivered acutely or over a prolonged period. The so-called Life Span Study (LSS) of the survivors of the atomic bombings in Hiroshima and Nagasaki is the most important of these studies [41]. The follow-up of the atomic bomb survivors has provided detailed knowledge of the relationships between radiation risk and a variety of factors, such as the absorbed dose, the age at exposure, the

age at diagnosis, and other parameters. The LSS provides data with good radio-epidemiological evidence due to the large size of the study population (about 86,600 individuals with individual dose estimates), the broad age and dose distribution, the long follow-up period (about half a century), and an internal control group (individuals exposed only at a minute level or not at all). The LSS is, therefore, the major source for predicting radiation-induced risks for the general population. However, radiation risk estimates are not merely based on the follow-up of the atomic bomb survivors. They are also largely supported by a multitude of smaller studies, mostly on groups of persons exposed for medical reasons, both in diagnostics and in therapy [1].

There is considerable controversy regarding the risk of low levels of radiation, typical for diagnostic radiation exposures, since radiation risks evaluated at low dose levels are not based on experimental and epidemiological evidence. Given this lack of evidence, estimates on risk, derived from high doses, have been extrapolated down to low dose levels by various scientific bodies, including the “International Commission on Radiological Protection” [30], the “United Nations Scientific Committee on the Effects of Atomic Radiation” [50], and the “Biological Effects on Ionizing Radiation” committee [1]. Estimates on risk per unit of dose have been derived using the so-called linear, non-threshold (LNT) hypothesis, which is based on the assumptions that (a) any radiation dose – no matter how small – may cause an increase in risk and (b) the probability of this increase is proportional to the dose absorbed in the tissue. Although the risk evaluated at low dose levels is thus hypothetical, it is prudent to assume that it exists and that the LNT model represents an upper bound for it. It is for this reason that current radiation protection standards as well as risk assessments are based on the LNT hypothesis [30].

10.2.2 Principles of Radiation Protection

In line with the LNT philosophy, the ICRP emphasizes that proper justification and

optimization of medical procedures are indispensable principles of radiation protection in medicine [31]:

There are two different levels of *justification* (§§ 60, 67): At the *generic* level, a specified radiological procedure with a specified objective is defined and justified. The aim is to judge whether the procedure will improve the diagnosis or treatment or will provide necessary information about the exposed individuals. At the next level, the application of the procedure to an *individual patient* should be justified (i.e., the particular application should be judged to do more good than harm to the individual patient). Hence all individual medical exposures should be justified in advance, taking into account all available information including the details of the proposed procedure and of alternative procedures, the characteristics of the individual patient, the expected dose to the patient, and the availability of information on previous or expected examinations or treatment.

Optimization of radiological protection (§ 70) means the same as keeping the doses “as low as reasonably achievable, economic and societal factors being taken into account” (ALARA), and is best described as management of the radiation dose to the patient to be commensurate with the medical purpose (§ 71). Although dose constraints for patients are inappropriate, management of patient dose is important. This often can be facilitated for diagnostic and interventional procedures by use of a diagnostic reference level, which is a method for evaluating whether the patient dose is unusually high or low for a particular medical imaging procedure.

The ethical and procedural aspects related to the *exposure of volunteers in biomedical research* have also been addressed (§ 121). The key aspects include the need to guarantee a free and informed choice by the volunteers, the adoption of dose constraints linked to the societal worth of the studies, and the use of an ethics committee that can influence the design and conduct of the studies. It is important that the ethics committee should have easy access to radiological protection advice.

10.2.3 Dosimetry

10.2.3.1 Fundamental Dose Quantities

It is generally assumed that the probability of detrimental radiation effects is directly proportional to the energy deposited by ionizing radiation in a specified organ or tissue, T . Therefore, the fundamental dosimetric quantity is the *absorbed dose*, which is defined as the radiation energy absorbed in a small volume element of matter divided by its mass. In the SI system the absorbed dose, D , is given in the unit *Gray* (1 Gy = 1 J/kg). For radiological protection purposes, the absorbed dose is averaged over an organ or tissue and weighted by a dimensionless *radiation weighting factor*, w_R , to reflect the higher biological effectiveness of high-LET as compared to low-LET radiations. The resulting weighted dose is designated as the *organ or equivalent dose*, H_T , and given in the unit *Sievert* (1 Sv = 1 J/kg). For γ -radiation used in PET, w_R is equal to 1.

Tissues and organs are not equally sensitive to the effects of ionizing radiation. Due to this reason, *tissue weighting factors*, w_T , are provided by the ICRP for a reference population of equal numbers of both sexes and a wide range of ages [30]. These factors indicate the relative proportion of each organ or tissue to the total health detriment resulting from a uniform irradiation of the whole body. Detriment is a multidimensional concept: Its principal components are the stochastic quantities probability of the attributable fatal cancer, the weighted probability of attributable nonfatal cancer, the weighted probability of severe heritable effects, and the length of life lost if the harm occurs [30]. If the body is exposed in a nonuniform manner, as, for example, in a patient undergoing a PET examination, the sum of the products of the organ doses and the corresponding tissue weighting factors determined for each of the various organ or tissue exposed has to be computed:

$$E = \sum_T w_T \cdot H_T \quad \text{with} \quad \sum_T w_T = 1. \quad (10.1)$$

The resulting quantity is denoted as *effective dose* E (in Sv). Based on this dose quantity, it is possible to assess and to compare the

probability of stochastic radiation effects resulting from different radiation exposures – as, for example, PET examinations using different radiopharmaceuticals yielding a different pattern of dose distribution in the body. It should be noted, however, that the concept of the effective dose facilitates only an overall, not an organ-specific assessment of stochastic radiation risks and is aimed at large, age and gender averaged collectives such as the working population or the whole population in a country. Nevertheless, this generic approach provides a rational framework for the justification and optimization of imaging procedures.

Based on the latest available scientific information, the tissue weighting factors, w_T , given in Table 10.1 have been modified in 2007 by the ICRP [30]. The most significant changes from the previous held values [28] relate to breast (0.05 → 0.12), gonads (0.2 → 0.08), and the remainder tissues (0.05 → 0.12 using a simplified additive system). Moreover, in the new concept sex-averaged tissue doses are used for the calculation of the effective dose.

10.2.3.2 Estimation of Organ and Effective Doses

Doses from the intake of radiolabeled compounds, such as PET radiopharmaceuticals, cannot be measured; they can only be estimated on the basis of biokinetic and dosimetric models.

Table 10.1 Tissue weighting factors, w_T , given in ICRP-103 [30]. They characterize the relative susceptibility of various tissues and organs, T , to ionizing radiation

Tissue or organ	w_T
Bone marrow (red), colon, lung, stomach, breast, remainder tissues ^a	0.12
Gonads	0.08
Bladder, esophagus, liver, thyroid	0.04
Bone surface, brain, salivary glands, skin	0.01

^aThe “remainder tissues” consist of the following group of additional organs and tissues with a lower sensitivity for radiation-induced effects for which the arithmetic average of organ doses must be used: adrenals, extrathoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, and uterus/cervix

Biokinetic models describe the uptake and retention of incorporated radionuclides in source regions of the body where they accumulate as well as their excretion from the body. They are used to calculate the numbers of nuclear transformations in the source regions which are needed to calculate the dose to target tissues by dosimetric models. In general, biokinetic models are formulated as compartment models. If the tracer is intravenously injected, the starting compartment represents the blood pool from where the material is transported to other tissue compartments representing the source regions where it accumulates and to (mainly urinary and fecal) excretion. In general, the retention in a compartment can be described by biological half-life, i.e., by a period of time within which half of the material is removed from the compartment.

Dosimetric models are used to calculate the dose to a target tissue due to a nuclear transformation in the considered source regions. For this, absorbed fractions $AF(r_T \leftarrow r_S)$ are determined, i.e., the fraction of the energy emitted in a source region r_S which is absorbed in a target tissue r_T . In case of non-penetrating radiation (α and β radiation), the simplifying assumption $AF(r_T \leftarrow r_S) = 1$ for $S=T$ and $=0$ for $S \neq T$ is used for most pairs of source regions and target tissues. For penetrating radiation (γ radiation), absorbed fractions are calculated by Monte Carlo methods based on

anthropomorphic phantoms which describe the position and the form of the source regions and target tissues. These phantoms were for a long time mathematical phantoms describing both source regions and target tissues by simple geometric objects. They are now being replaced by much more realistic voxel phantoms derived from MRI or CT images of real persons. For purposes of radiation protection, voxel phantoms are adjusted to the dimensions of the reference persons as defined by the ICRP [29]. Reference voxel phantoms for an adult male and female are published in ICRP Publication 110 [33]. However, AF values computed on the basis of the new models are not yet available.

Combining the results from both biokinetic and dosimetric models, dose coefficients $h(r_T)$ (in mSv/MBq) are computed that give the dose H_T to an organ T per unit activity intake. The effective dose resulting from the activity A of a radiopharmaceutical administered to a patient can thus be estimated by

$$E = \sum_T w_T \cdot H_T = A \cdot \sum_T w_T \cdot h(r_T) = A \cdot d_E \quad (10.2)$$

with d_E being the dose coefficient for the effective dose. For PET tracers more frequently used in clinical routine [6], values for d_E are listed in Table 10.2.

Table 10.2 Dose coefficients to estimate the effective dose related to the administration of PET radiopharmaceuticals frequently administered in clinical routine. The given values were calculated for the adult mathematical reference phantom using the new tissue weighting factors of ICRP-103 (2007). The biodistribution of the PET tracers was described by the biokinetic models given in ICRP-53 (2001) and ICRP-106 (2008) assuming that the bladder is emptied at 3.5 h after tracer administration

Nuclide	Radiolabeled compound	Function	Dose coefficient d_E ($\mu\text{Sv}/\text{MBq}$)
^{11}C	L-Methionine	Amino acid transport and protein synthesis	7.6
	Acetate	Myocardial oxidative metabolism	2.8
^{13}N	Ammonia	Myocardial blood flow	2.2
^{15}O	Water	Regional blood flow	1.1
18F	2-Fluoro-2-deoxy-D-glucose	Glucose transport and phosphorylation	18
	L-Dopa	Presynaptic dopaminergic function	22
	Fluoride	Bone metabolism	21
^{82}Rb	Rubidium chloride	Myocardial blood flow	3.8

The given values were calculated for voxel phantoms using the biokinetic models given in ICRP-53 [27] and ICRP-106 [32] under the assumption that the bladder is emptied at 3.5 h after tracer administration and the new tissue weighting factors given in ICRP-103 [30]. They hold for a standard patient with a body weight of about 70 kg

In case of *pregnant patients* undergoing a PET examination – either based on a stringent clinical indication or due to the unawareness of pregnancy – the effective dose to the offspring as well as the resulting radiation risks have to be carefully assessed. In the early stage of pregnancy, the uterine dose is often used as surrogate for the embryonic dose. For [¹⁸F]FDG, the dose coefficient for the uterine dose is 29 μSv/MBq.

10.2.4 Estimation of Radiation Risks

The effective dose is not recommended for epidemiological evaluations, nor should it be used for detailed specific retrospective investigations of individual exposure and risk ([30], § 157). For the estimation of the potential consequences of a radiation exposure to *individual patients*, it is necessary to use specific data characterizing the exposed individual.

The standard approaches to generate age, gender, and organ-specific risk estimates are based on the so-called excess absolute risk, *ear*. It denotes the *additional* risk of a person of gender *S*, after an exposure to organ dose D_T at the age *e*, to be clinically diseased with a specific radiation-induced cancer at the age *a* or, more specifically, in the interval $[a, a + 1)$. It is commonly calculated from

$$ar_T(e, a, D_T, S) = r_T(a, S) + ear_T(e, a, D_T, S) \quad (10.3)$$

where ar_T denotes the absolute risk and r_T the normal or baseline risk of a person of gender *S* to be diseased with a specific cancer in the interval $[a, a + 1)$. If a *relative* risk model is used, Eq. (3) can be written as

$$ar_T(e, a, D_T, S) = r_T(a, S) \cdot [1 + err_T(e, a, D_T, S)] \quad (10.4)$$

with $err_T(e, a, D_T, S)$ representing the excess relative risk. For example, an $err_T(e, a, D_T, S) = 1$ means that the additional, radiation-induced cancer risk for a person of gender *S* who was exposed at age *e* to an organ dose D_T and attained age *a* is as high as his normal cancer risk. Estimates of the

excess (relative) risk for specific organs are usually derived from cancer incidence data of the *LSS*, where a linear dose dependence is commonly assumed for solid tumors, while a linear-quadratic approach provides better results for leukemia. The most recent models are summarized in the BEIR-VII report [1].

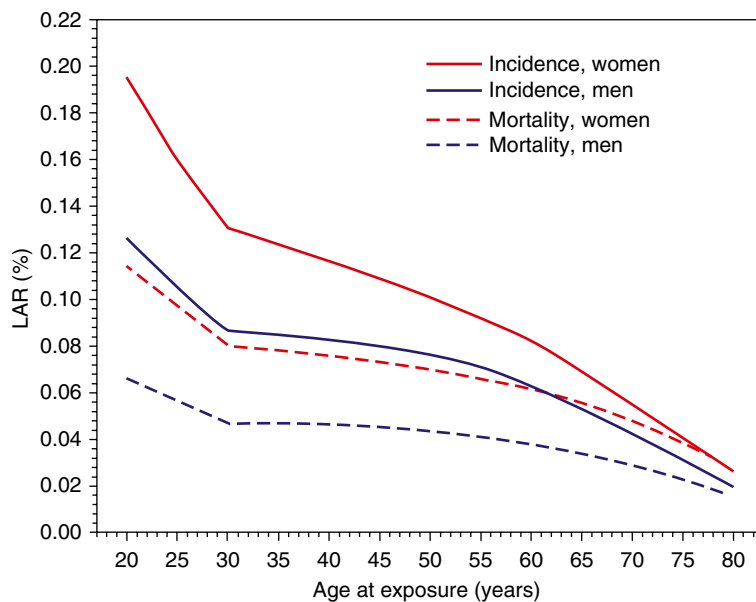
The site-specific *excess absolute lifetime risk* or *lifetime attributable risk*, LAR_T , for a person of gender *S* who was exposed at age *e* to an organ dose D_T is calculated by summing up all $ear_T(e, a, D_T, S)$ values between $e + \Delta t$ (with Δt being the minimum latency period) and the age of, e.g., 85 years, commonly used for lifetime risk estimates. The *ear* should be corrected for competing risks by the conditional probability $P(e, a)$, i.e., the probability that a person of age *e* survives beyond the age *a*:

$$LAR_T(e, D_T, S) = \int_{a=e+\Delta t}^{85} \frac{ear_T(e, a, D_T, S)}{P(e, a)} da \quad (10.5)$$

The minimum latency period Δt is the time during which the radiation-induced cancer typically does not show clinical symptoms. A Δt of about 5 years for carcinoma and of about 2 years for leukemia is widely applied for incidence data. To determine the total *LAR* for a PET examination, all site-specific LAR_T estimates (i.e., for sites with appreciable organ doses) have to be summed up.

Based on this approach as well as German disease and life table data [12, 13, 15], Fig. 10.1 gives *LAR* estimates for both cancer incidence and mortality for female and male individuals attributed to the administration of 370 MBq [¹⁸F]FDG at different ages. The plots reveal that the *LAR* decreases markedly with increasing age at exposure and is always somewhat higher for females as compared to males. But even for young adults, the estimated radiation-induced risks are at least two orders of magnitude lower than the corresponding baseline lifetime risks, i.e., the “normal” risk to incur cancer during the remaining lifetime. In Germany, for example, the lifetime baseline risk for cancer incidence (mortality) is about 47 % (26 %) for men and about 39 % (21 %) for women (all cancers excluding skin cancer).

Fig. 10.1 Lifetime attributable risk for both cancer incidence and mortality for a female and male person resulting from the administration of 370 MBq [^{18}F] FDG at different ages. Risks were estimated from organ doses (computed for the adult reference phantom) using the BEIR-VII models as well as German life tables and cancer incidence rates



10.2.5 Diagnostic Reference Levels

In its publication on “Radiological Protection in Medicine” [31] the ICRP recommends the use of diagnostic reference levels (*DRLs*) for patient examinations as a measure of optimization of protection and gives the following guidance (§§ 78–84): As a form of *investigation level*, *DRLs* apply to easily measurable quantities, in nuclear medicine to the activity of administered radiopharmaceutical, and are intended for use as a simple test for evaluating whether the patient dose (with regard to stochastic effects) is unusually high for a particular imaging procedure. It should be noted that they do not apply to individual patients but rather to the mean activity value determined in practice for a suitable reference group (comprising at least 10 patients). If patient activities related to a specific diagnostic nuclear medicine procedure are consistently exceeding the corresponding *DRL*, there should be a local review (clinical audit) of the procedures and equipment. Actions aimed at the reduction of activity levels should be taken, if necessary.

DRLs are set by professional medical bodies in conjunction with national health or radiological protection authorities and reviewed at intervals that represent a compromise between the necessary stability of the protection system and the changes in the observed dose distributions. The fraction of the amount of a PET radiopharmaceutical to an adult to be administered in *pediatrics* can be calculated from the child’s body weight either according to the dosage card published by the European Association of Nuclear Medicine [36] or the North American consensus guidelines [16].

10.3 MR: Nonionizing Radiation

10.3.1 Interaction Mechanisms and Biological Effects of (Electro) Magnetic Fields

In MR imaging and spatially localized MR spectroscopy, three variants of magnetic fields are employed to form cross-sectional images of the human body: (1) a high static magnetic field, B_0 , generating a macroscopic nuclear magnetization,

(2) rapidly alternating magnetic gradient fields for spatial encoding of the MR signal, and (3) radiofrequency (RF) electromagnetic fields for excitation and preparation of the spin system. The biophysical interaction mechanisms and biological effects of these fields are shortly summarized in the following; a more comprehensive review can be found in [4].

10.3.1.1 Static Magnetic Fields

There are several established biophysical mechanisms through which static magnetic fields can interact with biological tissues and organisms [44]. The two most relevant mechanisms are:

Magneto-mechanical interactions. Even in a uniform magnetic field, molecules, structurally ordered molecule assemblies, or cells with a magnetic moment (e.g., outer segments of retinal rod cells, muscle fibers, filamentous virus particles, and erythrocytes) experience a mechanical torque that tends to align their magnetic moment (anti) parallel to the external magnetic field and thus to minimize the potential energy. *Orientation effects*, however, can only occur when molecular or cellular objects have a nonspherical structure and/or when the magnetic properties are anisotropically distributed. At higher temperatures, as, for example, in the human body, the alignment of structures with small magnetic moments is prevented by their thermal movement (Brownian movement). Additionally, paramagnetic and ferromagnetic objects are attracted in a nonuniform magnetic field, as, for example, in the periphery of an MR system, and thus can quickly become dangerous projectiles (*missile effect*).

Magneto-hydrromechanical interactions. Static magnetic fields also exert (Lorentz) forces on moving electrolytes (ionic charge carriers), giving rise to induced electric fields and currents. Since electrolytes with a positive or negative charge moving, for example, through a cylindrical blood vessel orientated perpendicular to a magnetic field are accelerated into opposite directions, this mechanism gives rise to an electrical voltage across the vessel, which is commonly referred to as a *blood flow potential*. In

humans, the largest potentials occur across the aorta after ventricular contraction and appear superimposed on the T-wave amplitude of the ECG at fields in excess of 100 mT.

A large number of studies have been conducted to detect biological responses to static magnetic fields with flux densities ranging from milliteslas to several teslas (T). These studies have been reviewed comprehensively – among others – by ICNIRP [22] and the World Health Organization [53]. Overall there is little convincing evidence from cellular, animal, human, and epidemiological studies for biologically harmful effects of short-term exposure resulting from static magnetic fields with a strength up to several teslas. Until now, most MR examinations have been performed using static magnetic fields up to 3 T, although whole-body MR systems with static magnetic fields up to 9 T are already used in clinical tests. The literature does not indicate any serious adverse health effects from the exposure of healthy human beings up to 8 T. However, sensations of nausea, vertigo, and metallic taste may occur in magnetic fields above 2 T [23]. The greatest potential health hazard comes from metallic, in particular, ferromagnetic materials (such as scissors, coins, pins, oxygen cylinders) that are accelerated in the inhomogeneous magnetic field in the periphery of an MR system and quickly become dangerous projectiles (*missile effect*). This risk can only be minimized by a strict and careful management of both patients and staff.

10.3.1.2 Alternating Magnetic Gradient Fields

Due to their low magnetic flux density, magnetic gradient fields used in MRI for spatial encoding of the MR signal can be neglected compared to the strong static magnetic field B_0 as far as interactions of *magnetic* fields with biological tissues and organisms are concerned. In contrary, however, biophysical effects related to the *electric* fields and currents induced by their temporal variation have to be considered carefully. Rapidly switched magnetic fields induce electric fields in

the human body, the strength of which is proportional to the time rate of change of the magnetic field, dB/dt . In conductive media, such as biological tissues, the electric fields result in *circulating eddy currents*. In general, rise times of magnetic gradients in MR are longer than 100 μ s, resulting in time-varying electric fields and currents with frequencies below 100 kHz. In this frequency range, the conductivity of cell membranes is several orders of magnitude lower than that of the extra- and intracellular fluid [14]. As a consequence, the current flow is restricted to the extracellular fluid and voltages are induced across the membrane of cells. When these voltages are above a tissue-specific threshold level, they can stimulate nerve and muscle cells [42].

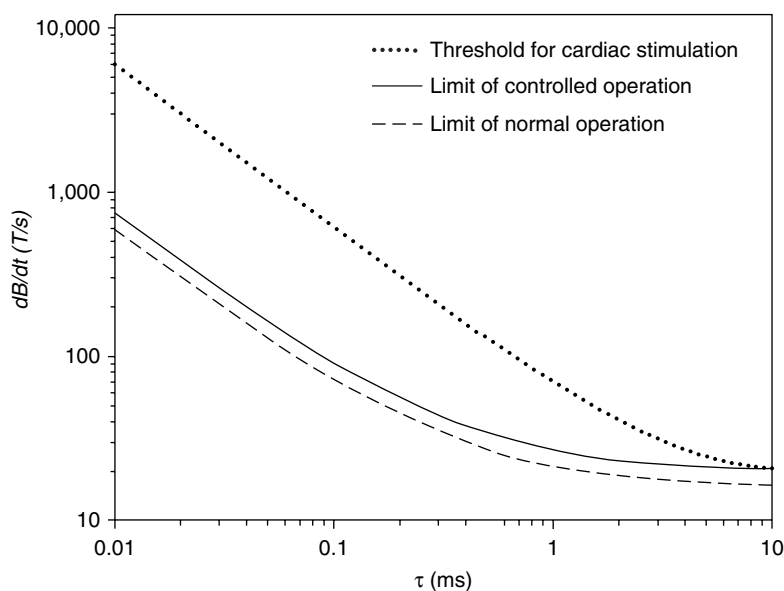
The primary concern with regard to time-varying magnetic gradient fields is *cardiac fibrillation*, because it is a life-threatening condition. In contrast, *peripheral nerve stimulation* (PNS) is of practical concern because uncomfortable or intolerable stimulations would interfere with the examination (e.g., due to patient movements) or would even result in a termination of the examination [51]. Bourland et al. [3] analyzed stimulation data in the form of cumulative frequency distributions that relate a dB/dt level to the number of healthy volunteers that

had already reported on perceptible, uncomfortable, or even intolerable sensations. Their results indicate that the lowest percentile for intolerable stimulation is approximately 20 % above the median threshold for the perception of peripheral nerve stimulation. The threshold for cardiac stimulation is well above the median perception threshold for peripheral nerve stimulation, except at very long pulse durations which are, however, not relevant for clinical MR examinations (see Fig. 10.2, [42]).

10.3.1.3 RF Electromagnetic Fields

Time-varying magnetic fields used for the excitation and preparation of the spin system in MR have typically frequencies above 10 MHz. In this RF range, the conductivity of cell membranes is comparable to that of the extra- and intracellular fluid which means that no substantial voltages are induced across the membranes [14]. Due to this reason, stimulation of nerve and muscle cells is no longer a matter of concern. Instead, *thermal effects* due to tissue heating are of importance. The increase in tissue temperature is dependent not only on localized power absorption and the duration of RF exposure but also on heat transfer and the activation of thermoregulatory mechanisms leading to thermal equalization within the body. It

Fig. 10.2 Limits for the normal and controlled operating mode of an MR gradient system expressed as dB/dt as a function of the effective stimulus duration τ . The limit for the controlled operating mode is given by the median perception threshold for peripheral nerve stimulation. For comparison, the threshold for cardiac stimulation is also plotted [42]



is important to note that energy absorption is proportional to the square of the static magnetic field, B_0 , which means it is markedly higher at high-field as compared to low-field MR systems.

Established biological effects of RF fields used for MR examinations are primarily caused by tissue heating. In contrast, nonthermal (or athermal) effects are not well understood but seem – as far as this can be assessed at the moment – to have no relevance with respect to the assessment of adverse effects associated with MR examinations. According to published studies, no adverse health effects are expected if the RF-induced increase in body-core temperature of healthy persons does not exceed 1 °C [23]. However, some organs of the human body are particularly vulnerable to raised temperatures. The most sensitive organs are the testes and brain as well as portions of the eye. Since temperature changes in the various organs and tissues of the body during an MR procedure are difficult to measure in clinical routine, RF exposure is usually characterized by means of the *specific absorption rate* (SAR in W/kg), which is defined as the average energy dissipated in the body per unit of mass and time.

10.3.2 Operating Modes and Safety Regulations

To minimize health hazards and risks to patients undergoing MR procedures, exposure limits for the three different magnetic fields used in MR are specified in:

- The safety recommendation issued by ICNIRP [23] that has been updated by an amendment concerning the exposure of patients to static magnetic fields [25]
- The product standard IEC 60601-2-33 provided by the International Electrotechnical Commission [34] for manufacturers of MR equipment to follow

In order to reflect the still existing uncertainty about deleterious effects of (electro)magnetic fields and to offer the necessary flexibility for the development and clinical evaluation of new MR technologies, both safety guidelines give exposure limits for three different modes of operation:

- *Normal mode (IEC: normal operating mode)*: Routine MR examinations that do not cause any field-induced physiological stress to patients.
- *Controlled mode (IEC: first level controlled operating mode)*: Specific MR examinations outside the normal operating range where discomfort and/or physiological stress to some patients may occur. Therefore, a clinical decision must be taken to balance such effects against expected benefits and exposure must be carried out under medical supervision.
- *Experimental mode (IEC: second level controlled operating mode)*: Experimental MR procedures with exposure levels beyond the controlled operating range. In view of the potential risks for patients and volunteers, special ethical approval and adequate medical supervision is required.

All manufacturers of MR equipment have adopted the regulations of the IEC product standard for magnetic gradient and RF fields and ensure compliance with the specified exposure limits by integrated *monitor systems*. With respect to the examination of patients in clinical routine, both the IEC standard and the ICNIRP guidelines recommended the following exposure limits:

- *Static magnetic field*: The upper limit for the normal and controlled operating mode recommended by the IEC is 3 and 4 T, respectively. In its recent amendment to static magnetic fields, ICNIRP recommends 4 and 8 T, respectively.
- *Alternating magnetic gradient fields*: The maximum recommended exposure level is set equal to a dB/dt value of 80 % of the PNS perception threshold for normal operation and 100 % of the PNS for controlled operation. To this end, perception threshold levels have to be determined by the manufacturers for a given type of gradient system by means of experimental studies on human volunteers. As an alternative, the generic hyperbolic strength-duration expression shown in Fig. 10.2 can be used.
- *RF electromagnetic fields*: The increase in body-core temperature is limited to 0.5 and 1.0 °C in the normal and controlled operating mode, respectively. The relatively

low-temperature threshold of the normal operating mode takes into account that heat tolerance or thermoregulation may be compromised in some individuals, such as the elderly, infants, and patients with certain medical conditions and/or taking certain medications. Additionally, local temperatures under exposure to the head, trunk, and extremities are limited to 38, 39, and 40 °C, respectively. For MR practice, the SAR limits summarized in Table 10.3 have been derived on the basis of experimental and theoretical studies. They should not be exceeded in order to limit the temperature rise to the stated values. But even then, severe burns can occur under unfavorable conditions at small focal skin-to-skin contact zones (e.g., between the calves). Therefore, patients should always be positioned in such a way that focal skin-to-skin contacts are avoided.

10.3.3 Contraindications

MR examinations of patients with *passive implants* (e.g., vascular clips and clamps, intra-vascular stents and filters, vascular access ports and catheters, heart valve prostheses, orthopedic prostheses, sheets and screws, intrauterine contraceptive devices), *active implants* (e.g., cardiac

pacemakers and defibrillators, cochlear implants, electronic drug infusion pumps), or other objects of ferromagnetic or unknown material (pellets, bullets) are always associated with a serious risk, even if all procedures are performed within the established exposure limits summarized in the previous section. This risk can only be minimized by a careful interview of the patient, evaluation of the patient's file, and contacting the implanting clinician and/or the manufacturer for advice on MR safety and compatibility of the implant. MR examinations of patients with active implants are strictly contraindicated, provided that the patient implant card does not explicitly state their safety in the MR environment. Comprehensive information on the MR-compatibility of implants and other metallic objects is available in a reference manual published by Shellock [46] and online at www.MRIsafety.com. In contrast, side effects associated with the use of iron oxide or other metal-based pigments in tattoos occur extremely seldom and should not prevent patients – after informed consent – from undergoing a clinically indicated MR procedure [48].

Pregnant patients undergoing MR examinations are exposed to the combined (electro)magnetic fields discussed above. The few studies on pregnancy outcome in humans following MR examinations have not revealed any adverse effects but are very limited because of the small

Table 10.3 SAR limits for patients (and volunteers) undergoing MR procedures [22, 33] in clinical routine. They hold at environmental temperatures below 24 °C

Body region → Operating mode ↓	Averaging time: 6 min					
	Whole-body SAR (W/kg)	Partial-body SAR (W/kg)		Local SAR (averaged over 10 g tissue) (W/kg)		
	Whole-body	Any region, except the head	Head ^c	Head	Trunk	Extremities
Normal	2	2–10 ^a	3.2	10 ^b	10	20
Controlled	4	4–10 ^a	3.2	10 ^b	10	20
Experimental	>4	>(4–10) ^a	>3.2	10 ^b	>10	>20
Short-term SAR	The SAR limit over any 10 s period shall not exceed 3 times the corresponding average SAR limit					

^aPartial-body SARs scale dynamically with the ratio r between the patient mass exposed and the total patient mass

Normal operating mode: $SAR = (10 - 8 \cdot r)$ W/kg

Controlled operating mode: $SAR = (10 - 6 \cdot r)$ W/kg

^bIn cases where the eye is in the field of a small local coil used for RF transmission, care should be taken to ensure that the temperature rise is limited to 1 °C

^cPartial volume SARs given by IEC; ICNIRP limits SAR exposure to the head to 3 W/kg

numbers of patients involved and difficulties in the interpretation of the results [23]. It is thus advisable that MR procedures may be performed in pregnant patients, in particular in the first trimester, only after critical risk/benefit assessment and with informed consent of the expectant mother [10].

10.4 MR-PET: Synergistic Effects of Ionizing and Nonionizing Radiation?

The data and considerations presented in this chapter provide an appropriate foundation for the initial assessment of possible health risks for patients undergoing combined MR-PET examinations. It has to be noted, however, that they are based solely on established biophysical and biological effects related to the exposure of either ionizing radiation or (electro)magnetic fields, whereas *synergistic or antagonistic effects* are not taken into account. There are a few studies indicating that static [37] and low-frequency [17, 35, 38, 52] magnetic fields might enhance the genotoxic potential of ionizing radiation. Moreover, it is well recognized that mild hyperthermia, as, for example, caused by RF fields, has a radiosensitizing effect in tumors [18, 47]. In the light of the developing MR-PET technology, further biological studies are thus urgently required to investigate – for exposure levels and examination scenarios that will occur at MR-PET systems – whether there are synergistic effects in normal tissues and, if so, to clarify their relevance for risk assessment of patients that will be examined with this innovative imaging modality.

10.5 Justification and Optimization of MR-PET Examinations

Indications for MR-PET have not yet been established on the basis of clinical studies. Accordingly, there is at present no *generic justification* of MR-PET procedures by professional bodies in conjunction with health and radiological protection authorities as required by ICRP-105 ([31]; cf.

Sect. 10.2.2). In this context, not only the improvement in diagnostic accuracy achieved by this new imaging modality will be of relevance but also its practicability, availability, and cost-effectiveness. From a radiation hygienic point of view, an MR-PET examination should be performed instead of a PET-CT examination wherever practicable as long as it provides the same or even superior diagnostic information. Nevertheless, there will be a whole string of clinical situations in which PET-CT will remain the method of choice, as, for example, when CT data are required for radiation treatment planning, when CT is indicated instead of MR for morphological imaging, or when an MR examination is contraindicated in patients due to implants or metallic objects. It goes without saying that an MR-PET examination can only be justified clinically, when there is an *individual justification* for a PET scan.

In case of combined MR-PET examinations, optimization of the entire procedure with respect to the exposure of patients to ionizing radiation reduces to the question: What *activity* of the radiopharmaceutical has to be administered for the emission scan? [¹⁸F]FDG activities administered for PET-CT examinations vary between about 300 and 450 MBq [19] depending on the detector material and count rate behavior of the PET scanner, the acquisition mode used (2D vs. 3D), and, of course, the body region to be investigated. They will presumably also be adequate for MR-PET examinations.

From a clinical point of view, lower activities will eventually result in longer emission *scan times*, and thus longer overall examination times. However, excessive examination times should be avoided in multimodality imaging as they may result in patient discomfort and, thus, in motion-induced misregistrations of the complementary images. Due to this reason, diagnostic reference levels for [¹⁸F]FDG studies performed at conventional PET scanners – that have meanwhile been established by many states – may not be appropriate for combined MR-PET examinations. To balance the potentially higher activities that are injected into patients in an attempt to reduce emission scan time, *voiding of the bladder* should be forced, e.g., by oral hydration with water or

the administration of a diuretic. This is a very effective measure, because FDG in the bladder is the major source of internal exposure to the bladder itself as well as to neighboring organs.

In contrast to CT, the acquisition of whole-body MR images for *transmission correction* of emission data and morpho-functional image correlation is much more challenging [2]. To realize short examination times, the measurement has to be performed with fast MR sequences relying on the use of high-performance gradient and RF systems. At least at high-field MR systems, it will therefore be necessary to carefully optimize the imaging sequences, as, for example, by utilizing SAR reduction techniques like parallel imaging or hyperechos. In this context it has to be noted that – contrary to a common opinion held among MR users – the SAR limits given in Table 10.3 do not relate to an individual MR sequence but rather to *running SAR averages* computed over each 6 min period, which is assumed to be a typical thermal equilibration time (Brix [7]). This means that sequences can be employed for which SAR levels exceed the defined values, if the acquisition time is short in relation to the averaging period and energy deposition has been low previous to the applied high-power sequence.

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