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FOURNIER L.S., VANEL D., ATHANASIOU A., GATZEMEIER W., MASUYKOV I.V., PADHANI A.R., DROMAIN C., GALETTI K., SIGAL R., COSTA A., BALLEYGUIER C.

Dynamic optical breast imaging: A novel technique to detect and characterize tumor vessels.

Eur. J. Radiol., 69 (1), 43-49, 2009

(Services cités : LRI)

PURPOSE: To prospectively determine the diagnostic accuracy of optical absorption imaging in patients with Breast Imaging Reporting and Data System (BI-RADS) 3-5 breast lesions.

MATERIALS AND METHODS: Forty-six patients with BI-RADS classification 3 (11%), 4 (44%) or 5 (44%) lesions, underwent a novel optical imaging examination using red light to illuminate the breast. Pressure was applied on the breast, and time-dependent curves of light absorption were recorded. Curves that consistently increased or decreased over time were classified as suspicious for malignancy. All patients underwent a core or surgical biopsy.

RESULTS: Optical mammography showed a statistical difference in numbers of suspect pixels between benign (N=12) and malignant (N=35) lesions (respectively 1325 vs. 3170, P=0.002). In this population, optical imaging had a sensitivity of 74%, specificity of 92%, and diagnostic accuracy of 79%. The optical signal did not vary according to any other parameter including breast size or density, age, hormonal status or histological type of lesions.

CONCLUSION: Optical imaging is a low-cost, non-invasive technique, yielding physiological information dependent on breast blood volume and oxygenation. It appears to have a good potential for discriminating benign from malignant lesions. Further studies are warranted to define its potential role in breast cancer imaging.

2008

SMIRNOV P., POIRIER-QUINOT M., WILHELM C., LAVERGNE E., GINEFRI J.C., COMBADIÈRE B., CLEMENT O., DARRASSE L., GAZEAU F.

In vivo single cell detection of tumor-infiltrating lymphocytes with a clinical 1.5 Tesla MRI system.

Magn. Reson. Med., 60 (6), 1292-1297, 2008

(Services cités : LRI)

We demonstrate the feasibility of detecting individual tumor-infiltrating cells in vivo, by means of cellular magnetic labeling and a 1.5 Tesla clinical MRI device equipped with a high-resolution surface coil. Using a recently developed high-temperature superconducting (HTS) surface coil, single cells were detected in vitro in voxels of (60 microm)³ at magnetic loads as low as 0.2 pg of iron per cell. The same imaging protocol was used in vivo to monitor infiltration of ovalbumin-expressing tumors by transferred OVA antigen-specific cytotoxic lymphocytes with low iron load.

2007

MARTINA M.S., FORTIN J.P., FOURNIER L., MENAGER C., GAZEAU F., CLEMENT O., LESIEUR S.

Magnetic targeting of rhodamine-labeled superparamagnetic liposomes to solid tumors: in vivo tracking by fibered confocal fluorescence microscopy.

Mol. Imaging, 6 (2), 140-146, 2007 ; (Facteur d'Impact 2006 : X)

(Services cités : [LRI](#))

Polyethylene glycol (PEG)ylated and rhodamine-labeled liposomes loaded with maghemite nanocrystals provide a novel nanoscaled hybrid system for magnetic targeting to solid tumors in possible combination with double in vivo imaging by fluorescence microscopy and magnetic resonance imaging (MRI). Human prostate adenocarcinoma tumors implanted in mice were used as a system model. A magnetic field gradient was produced at the tumor level by external apposition of a magnet. Noninvasive fibered confocal fluorescence microscopy was successfully used to track the liposomes in vivo within organs and tumor blood vessels. Active targeting to the magnet-exposed tumors was clearly shown, in agreement with previous MRI studies. The liposomes were driven and accumulated within the microvasculature through a process that preserved vesicle structure and content.

MUHLER M.R., HARTMANN C., WERNER W., MEYER O., BOLLMANN R., KLINGEBIEL R.

Fetal MRI demonstrates gliependymal cyst in a case of sonographic unilateral ventriculomegaly.

Pediat. Radiol., 37 (4), 391-395, 2007 ; (Facteur d'Impact 2006 : **1,076**)

(Services cités : [LRI](#))

We report a fetus of 28 weeks' gestation in which ultrasonography demonstrated unilateral ventriculomegaly and microcephaly. Fetal MRI demonstrated a simple, left paramedian occipital cyst with rarefaction of the corpus callosum and thinning of the adjacent cortical mantle. Ischaemia was suggested as the underlying pathogenesis, but autopsy after termination of pregnancy revealed a gliependymal cyst. This case highlights consideration of the rare diagnosis of gliependymal cyst when a cystic lesion associated with cerebral malformations, particularly dysgenesis of the corpus callosum, is demonstrated and fetal MRI suggests an ischaemic origin.

MUHLER M.R., RAKE A., SCHWABE M., SCHMIDT S., KIVELITZ D., CHAOUI R., HAMM B.

Value of fetal cerebral MRI in sonographically proven cardiac rhabdomyoma.

Pediat. Radiol., 37 (5), 467-474, 2007 ; (Facteur d'Impact 2006 : **1,076**)

(Services cités : [LRI](#))

BACKGROUND: Tuberous sclerosis complex (TSC) is an autosomal dominant phakomatosis associated with intracardiac rhabdomyomas. **OBJECTIVE:** The aim of our study was to examine the value of cerebral MRI in diagnosing TSC in fetuses with intracardiac rhabdomyomas, applying the TSC Consensus Conference (TSCCC) criteria. **MATERIALS AND METHODS:** In a prospective manner six consecutive fetuses with cardiac rhabdomyomas (21-34 weeks'

gestation) underwent cerebral MRI. The MRI results were correlated with clinical follow-up at 10-34 months after birth, histology, and genetic data. **RESULTS:** In five of the six fetuses the diagnosis of TSC was established. In two of five fetuses MRI demonstrated cerebral manifestations of TSC that correlated well with severe epilepsy manifesting during the follow-up period. In another two of five fetuses MRI as well as clinical follow-up were normal. One of five pregnancies was terminated and histology demonstrated microscopically small subependymal nodules not demonstrated by MRI. **CONCLUSION:** The results of our study agree with the available literature that fetal MRI is sufficient for the detection of cerebral lesions in TSC and should be better promoted. The TSCCC criteria can also be applied to fetal MRI.

WILHELM C., BAL L., SMIRNOV P., GALY FAUROUX I., CLEMENT O., GAZEAU F., EMMERICH J.

Magnetic control of vascular network formation with magnetically labeled endothelial progenitor cells.

Biomaterials, 28 (26), 3797-3806, 2007 ; (Facteur d'Impact 2006 : **5,196**)

(Services cités : LRI)

We describe the applications of new cellular magnetic labeling method to endothelial progenitor cells (EPC), which have therapeutic potential for revascularization. Via their negative surface charges, anionic magnetic nanoparticles adsorb non-specifically to the EPC plasma membrane, thereby triggering efficient spontaneous endocytosis. The label is non-toxic and does not affect the cells' proliferative capacity. The expression of major membrane proteins involved in neovascularisation is preserved. Labeled cells continue to differentiate in vitro and to form tubular structures in Matrigel (an in vitro model of neovascularization). This process was followed in situ by using high-resolution MRI. Finally, we show that magnetic forces can be used to move magnetically labeled EPC in vitro and to modify their organization in Matrigel both in vitro and in vivo. Magnetic cell targeting opens up new possibilities for vascular tissue engineering and for delivering localized cell-based therapies.

2006

BROCHOT C., BESSOUD B., BALVAY D., CUENOD C.A., SIAUVE N., BOIS F.Y.

Evaluation of antiangiogenic treatment effects on tumors' microcirculation by Bayesian physiological pharmacokinetic modeling and magnetic resonance imaging.

Magn. Reson. Imag., 24 (8), 1059-1067, 2006

(Services cités : [LRI](#))

A physiological pharmacokinetic (PBPK) model was used to estimate tumor microcirculation in nude mice with a grafted tumor. The kinetics of a rapid clearance blood pool agent, Vistarem, were investigated by dynamic MRI after bolus administration. Signal enhancements were recorded in arterial blood and in tumor tissue. To analyze these data, we developed a whole-body mathematical model of the agent's biodistribution using physiological parameters. The model included six compartments: arterial and venous plasma, tumor (split into capillaries and interstitium), and the rest of the body (also split into capillaries and interstitium). As an application, changes in tumor microcirculation parameters were evaluated in mice receiving either an antiangiogenic treatment (ZD4190) or a placebo. The analysis was performed in a Bayesian framework, and the model was fitted to experimental data using Markov Chain Monte Carlo techniques. Results showed a significant difference in tumor microcirculation between the two groups of mice when the microcirculation parameters are considered together. This whole-body physiological model enables to analyze jointly data in tumor tissue and in arterial blood. This leads to accurate estimates of microcirculation parameters and the evaluation of their uncertainty.

CUENOD C.A., FOURNIER L., BALVAY D., GUINEBRETIERE J.M.

Tumor angiogenesis: pathophysiology and implications for contrast-enhanced MRI and CT assessment.

Abdom. Imaging, 31 (2), 188-193, 2006

(Services cités : [LRI](#))

The process of tumor neoangiogenesis plays a central role in the growth and spread of tumors. It is currently a leading theme in oncology, and many new drugs targeting the tumor neoangiogenic process are under development. Expanding tumors become hypoxic and tumor cells express transcription factors, such as the hypoxia-inducible factor (HIF), which induce the release of proangiogenic growth factors such as vascular endothelial growth factors (VEGF) and transforming growth factors that promote the formation of new capillaries by recruiting, activating, and stimulating endothelial cells. Activated endothelial cells secrete matrix metalloproteases, which degrade the basement membrane and the extracellular matrix, and adhesion receptors such as integrins $\alpha v \beta 3$, which allow their migration into the extracellular matrix toward the tumor cells. The newly grown vessels are immature and differ from normal capillaries. They are tortuous and irregular, resulting in poorly efficient perfusion, they are leaky (especially to macromolecules), and they are independent of the normal mechanisms of regulation of the capillary blood flow. Moreover, tumor microcirculation is heterogeneous. Evaluation of angiogenesis can be used as a prognostic marker to evaluate the aggressiveness of tumor and as a potential predictive marker of antiangiogenic treatment

response. Histopathologic techniques of microvascular density indexes require invasive tissue sampling and need to be standardized. Hemodynamic characteristics of immature neovessels can be noninvasively assessed by dynamic contrast-enhanced magnetic resonance imaging or computed tomography. Tissue enhancement depends on arterial input function, kinetic of distribution of blood into the capillary bed, leakage across the capillary walls, and volume of the interstitial space. Pharmacodynamic models allow the evaluation of microvascular parameters of tissue blood flow, tissue blood volume, tissue interstitial volume, mean transit time, and permeability by surface of capillary wall. Methods based on dynamic contrast enhancement have been shown to correlate with conventional outcome methods such as histopathologic studies and survival. Radiologists must be convinced that, by using this emerging and promising approach, it is becoming possible to gain functional information during routine tumor imaging.

CUENOD C.A., TAILLIEU F., SALOMON L.J., SIAUVE N., CLEMENT O., BALVAY D., VAYSSETTES C., VILLE Y.

CMR 2005: 7.07: Simultaneous placental perfusion and permeability assessment by dual echo contrast-enhanced MRI in mice.

Contrast Media Mol. Imaging, 1 (2), 72-73, 2006

(Services cités : [LRI](#))

FORTIN-RIPOCHE J.P., MARTINA M.S., GAZEAU F., MENAGER C., WILHELM C., BACRI J.C., LESIEUR S., CLEMENT O.

Magnetic Targeting of Magnetoliposomes to Solid Tumors with MR Imaging Monitoring in Mice: Feasibility.

Radiology, 239 (2), 415-424, 2006

(Services cités : [LRI](#))

Purpose: To establish the feasibility of magnetoliposome tumor targeting with an extracorporeal magnet. Materials and Methods: Animal experiments were performed in compliance with Institut National de la Sante Et de la Recherche Medicale animal protection guidelines and were approved by local government authorities. Magnetophoresis was used to measure the velocity of magnetoliposomes constituted of polyethylene glycol-lipids and anionic maghemite nanocrystals in a calibrated magnetic field in vitro. For in vivo studies, 38 male Swiss nude mice bearing a PC3 human prostate carcinoma tumor in each flank received an intravenous injection of magnetoliposomes (n = 27), saline (n = 9), or nonencapsulated superparamagnetic particles (n = 2) after a small magnet with a magnetic field of 0.3 T and a field gradient of 11 T/m was fixed to the skin above one tumor. The animals were examined at magnetic resonance (MR) imaging with eight different sequences, iron doses (13 mice), and magnet-application durations (12 mice). Their excised tumors were then stained with Perls Prussian blue and hematoxylin-eosin and were examined histologically. With use of the paired Student t test, signal intensity, tumor surface enhancement, and number of stained cells were compared between the control and magnet-exposed tumors to determine significant differences ($P \leq .01$). Results: The mean magnetoliposome velocity ranged from 10 to 40 $\mu\text{m}/\text{sec}$ when the magnetic field equaled 0.13 T and the field gradient equaled 25 T/m. At T1-weighted three-dimensional spoiled gradient-echo MR imaging in vivo, the tumor exposed to the magnet showed strong negative enhancement, -52%, compared with the -7% enhancement of the other tumor. Maximal enhancement occurred after 3 hours of magnet application. After 24 hours of magnet application, intracapillary iron particle accumulation was observed in the targeted tumors only. Conclusion: Magnetic targeting of sterically stabilized magnetoliposomes after they are intravenously injected is feasible in vivo.

FOURNIER L.S., FAYE N., CLEMENT O., MARTINA M.S., SIAUVE N., CUENOD C.A.
CMR 2005: 7.02: Exploring microvessels using intravital fluorescence microscopy: role of molecular weight of agents.

Contrast Media Mol. Imaging, 1 (2), 70, 2006

(Services cités : [LRI](#))

NAVEAU A., SMIRNOV P., MENAGER C., GAZEAU F., CLEMENT O., LAFONT A., GOGLY B.

Phenotypic study of human gingival fibroblasts labeled with superparamagnetic anionic nanoparticles.

J. Periodontol., 77 (2), 238-247, 2006

(Services cités : [E 0016](#), [LRI](#))

BACKGROUND: A specific labeler of the human gingival fibroblast (HGF) does not exist. Anionic maghemite nanoparticles allow labeling of a wide cell variety and their recognition in cellular, organotypical, and animal models. **METHODS:** We studied internalization effects of nanoparticles on an HGF phenotype in vitro, evaluating transcription and secretion of connective tissue remodeling molecules, i.e., matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and cytokines controlling their activation/inhibition, i.e., transforming growth factor-beta (TGF-beta1), tumor necrosis factor-alpha (TNF-alpha), and interleukins 1beta and 4 (IL-1beta and IL-4). After proliferation kinetics, cellular uptake was studied by Perls coloration and magnetophoresis on labeled culture. Dot blotting, Western blotting, and zymography were used to detect MMP-1, -2, and -3 and TIMP-1 and -2 secretions in culture supernatants, and reverse transcription-polymerase chain reaction (RT-PCR) was performed to detect the mRNA expression of these molecules. Enzyme-linked immunosorbent assay (ELISA) tests were used to determine TGF-beta1, TNF-alpha, IL-1beta, and IL-4 levels. **RESULTS:** Our data indicated high (15.3+/-5.8 pg/cell) but heterogeneous distribution of nanoparticles in HGF. Twenty-four hours after labeling, MMP-1, -2, and -3 and TIMP-2 secretion increased (P<0.001) with RT-PCR confirmation at 12 hours, whereas TIMP-1 did not. IL-1beta increased at day 1 (D1) (P<0.001) and IL-4 at D3 (P<0.01), but not TGF-beta1 or TNF-alpha. **CONCLUSIONS:** After labeling with these maghemite nanoparticles, HGF increased secretion of IL-1beta at D1, probably inducing the increase of MMP-1, -2, and -3 and TIMP-2. The increase of IL-4 secretion began with the decreased synthesis of MMPs and TIMPs at D3. Despite this transitory inflammatory reaction at 3 days following internalization, maghemite nanoparticles did not affect HGF phenotype, thereby authorizing their use as labelers.

SALOMON L.J., SIAUVE N., TAILLIEU F., BALVAY D., VAYSSETTES C., FRIJA G., VILLE Y., CUENOD C.A., CLEMENT O.

In Vivo Dynamic MRI Measurement of the Noradrenaline-induced Reduction in Placental Blood Flow in Mice.

Placenta, 27 (9-10), 1007-1013, 2006

(Services cités : [LRI](#))

PURPOSE: We developed a new model for in vivo placental perfusion measurements based on dynamic MRI in mice. As noradrenaline has been implicated in the pathogenesis of preeclampsia, we examined whether it reduced placental perfusion in mice, and whether such a reduction could be detected with our MRI model. **MATERIALS AND METHODS:** Mice at 16 days of gestation were injected intramuscularly with saline or noradrenaline solution. A conventional gadolinium

chelate was then injected IV, and a single-slice T1-weighted 2D Fast SPGR sequence was acquired for 200s. Signal intensity was measured on all the images and converted into contrast agent tissue concentrations in the maternal left ventricle (input function) and placentas. A one-compartment model was developed using compartmental and numerical modeling software. Mean blood flow (F) was calculated from a transfer constant. RESULTS: Twenty-six mice were studied, yielding a total of 55 MRI measurements of placental perfusion (29 in the control group and 26 in the noradrenaline group). Mean placental blood flow (F) was significantly lower in the noradrenaline group (0.72±0.84ml/min/g of placenta) than in the control group (1.26±0.54ml/min/g of placenta). CONCLUSION: Noradrenaline reduces placental perfusion in mice. Our MRI dynamic model might be useful for detecting and investigating abnormal placental blood flow, thereby avoiding the need for invasive procedures and animal sacrifice.

SMIRNOV P., POIRIER-QUINOT M., LAVERGNE E., GAZEAU F., GINEFRI J.C., COMBADIÈRE B., CLEMENT O., DARRASSE L.

CMR 2005: 9.04: In vivo single-cell MRI of lymphocytes in tumors at 1.5 T using a superconducting surface coil.

Contrast Media Mol. Imaging, 1 (2), 77-78, 2006

(Services cités : [LRI](#))

SMIRNOV P., LAVERGNE E., GAZEAU F., LEWIN M., BOISSONNAS A., DOAN B.T., GILLET B., COMBADIÈRE C., COMBADIÈRE B., CLEMENT O.

In vivo cellular imaging of lymphocyte trafficking by MRI: A tumor model approach to cell-based anticancer therapy.

Magn. Reson. Med., 56 (3), 498-508, 2006

(Services cités : [LRI](#))

The aim of this study was to demonstrate the feasibility of in vivo cell tracking to monitor anticancer cell therapy by means of a high-resolution noninvasive MRI method. Ovalbumin-specific splenocytes (OT-1) labeled with anionic gamma-Fe(2)O(3) superparamagnetic iron oxide (SPIO) nanoparticles were adoptively transferred into C57BL/6 mice with growing ovalbumin-expressing tumors. OT-1 cells were tracked in vivo by 7 T MRI 24, 48, and 72 hr after they were injected. The results showed significant negative enhancement of the spleen at 24 hr, and of the tumor at 48 and 72 hr, after labeled cell injection. This suggests that the lymphocytes initially homed toward the spleen and were then recruited by the tumor. The presence of labeled cells was confirmed in ex vivo by 9.4 T microimaging of tumors and magnetic sorting of spleen cells. These results confirm that MR tracking of lymphocytes is feasible in vivo. This high-resolution imaging method could be used to improve the monitoring of immune cell therapy. *Magn Reson Med*, 2006. (c) 2006 Wiley-Liss, Inc.

TAILLIEU F., SALOMON L.J., SIAUVE N., CLEMENT O., FAYE N., BALVAY D., VAYSSETTES C., FRIJA G., VILLE Y., CUENOD C.A.

Placental Perfusion and Permeability: Simultaneous Assessment with Dual-Echo Contrast-enhanced MR Imaging in Mice.

Radiology, 241 (3), 737-745, 2006

(Services cités : [LRI](#))

Purpose: To assess placental perfusion and permeability in mice with magnetic resonance (MR) imaging. Materials and Methods: This study was conducted according to French law and National Institutes of Health recommendations for animal care. Twenty-two pregnant BALB/c

mice were examined at 1.5 T with a single-section dual-echo fast spoiled gradient-echo sequence. Two injection protocols were used: monophasic injection (double the clinical dose of contrast agent) and biphasic injection (quadruple the clinical dose). Signal intensities (SIs) were measured in the maternal left ventricle, placenta, and fetus (n = 16). At these high gadolinium doses, a T2* effect correction was used. SIs were converted to gadolinium concentrations and were analyzed by using a three-compartment model. Quantitative microcirculation parameters were calculated. Results with the monophasic and biphasic protocols were compared, and final arterial concentrations determined with MR imaging were compared with those determined with atomic emission spectrophotometry by using the unpaired Student t test. Results: Perfusion and permeability parameters for monophasic and biphasic injections were similar: Mean placental blood flow was 180 mL/min/100 g, mean permeability surface coefficient from maternal placental to fetal placental compartment was $10.3 \times 10^{-4} \text{ sec}^{-1} \pm 6.81$ (standard deviation), mean permeability surface coefficient from fetal placental to maternal placental compartment was $4.65 \times 10^{-4} \text{ sec}^{-1} \pm 4.37$, and mean fractional volume of the maternal vascular placental compartment was 36.5% ± 0.9 . Placental (146 vs 105 $\mu\text{mol/L}$, $P < .004$) and fetal (33.3 vs 19.1 $\mu\text{mol/L}$, $P < .001$) gadolinium concentrations were higher with the biphasic than with the monophasic protocol. Arterial gadolinium concentrations at MR imaging did not differ significantly from those at spectrophotometry for the monophasic ($P = .254$) or biphasic ($P = .776$) injection protocol. Conclusion: Placental perfusion and permeability can be measured in vivo by using high gadolinium doses and a dual-echo MR imaging sequence. Supplemental material: <http://radiology.rsna.org/cgi/content/full/2413051168/DC1> (c) RSNA, 2006.

2005

BALVAY D., FROUIN F., CALMON G., BESSOUD B., KAHN E., SIAUVE N., CLEMENT O., CUENOD C.A.

New criteria for assessing fit quality in dynamic contrast-enhanced T1-weighted MRI for perfusion and permeability imaging.

Magn. Reson. Med., 54 (4), 868-877, 2005

(Services cités : [LRI](#))

Contrast-enhanced (CE) MRI provides in vivo physiological information that cannot be obtained by conventional imaging methods. This information is generally extracted by using models to represent the circulation of contrast agent in the body. However, the results depend on the quality of the fit obtained with the chosen model. Therefore, one must check the fit quality to avoid working on physiologically irrelevant parameters. In this study two dimensionless criteria—the fraction of modeling information (FMI) and the fraction of residual information (FRI)—are proposed to identify errors caused by poor fit. These are compared with more conventional criteria, namely the quadratic error and the correlation coefficient, both theoretically and with the use of simulated and real CE-MRI data. The results indicate the superiority of the new criteria. It is also shown that these new criteria can be used to detect oversimplified models.

CLEMENT O.

Iatrogenic complications from contrast materials.

J. Radiol., 86 (5 Pt 2), 567-572, 2005

(Services cités : [LRI](#))

Iodinated or gadolinium-based contrast agents are usually well tolerated, but some adverse events can happen due to a direct toxicity of the injected molecule (contrast-induced nephropathy, abnormal thyroid function), or to an indirect effect like in true allergic reactions. Radiologists

must be familiar with the possibility of adverse events from contrast agents or injection procedures, and should be able to treat the patient. Also, they should take all necessary actions to minimize the occurrence of possible reactions in the presence of risk factors.

MARTINA M.S., FORTIN J.P., MENAGER C., CLEMENT O., BARRATT G., GRABIELLE-MADELMONT C., GAZEAU F., CABUIL V., LESIEUR S.

Generation of Superparamagnetic Liposomes Revealed as Highly Efficient MRI Contrast Agents for in Vivo Imaging.

J. Amer. Chem. Soc., 127 (30), 10676-10685, 2005

(Services cités : [LRI](#))

Maghemite ($\gamma\text{-Fe}_2\text{O}_3$) nanocrystals stable at neutral pH and in isotonic aqueous media were synthesized and encapsulated within large unilamellar vesicles of egg phosphatidylcholine (EPC) and distearoyl-SN-glycero-3-phosphoethanolamine-N-[methoxy(poly(ethylene glycol))-2000] (DSPE-PEG(2000), 5 mol %), formed by film hydration coupled with sequential extrusion. The nontrapped particles were removed by flash gel exclusion chromatography. The magnetic-fluid-loaded liposomes (MFLs) were homogeneous in size (195 ± 33 hydrodynamic diameters from quasi-elastic light scattering). Iron loading was varied from 35 up to 167 Fe(III)/lipid mol %. Physical and superparamagnetic characteristics of the iron oxide particles were preserved after liposome encapsulation as shown by cryogenic transmission electron microscopy and magnetization curve recording. In biological media, MFLs were highly stable and avoided ferrofluid flocculation while being nontoxic toward the J774 macrophage cell line. Moreover, steric stabilization ensured by PEG-surface-grafting significantly reduced liposome association with the macrophages. The ratios of the transversal ($r(2)$) and longitudinal ($r(1)$) magnetic resonance (MR) relaxivities of water protons in MFL dispersions ($6 < r(2)/r(1) < 18$) ranked them among the best T₂ contrast agents, the higher iron loading the better the T₂ contrast enhancement. Magnetophoresis demonstrated the possible guidance of MFLs by applying a magnetic field gradient. Mouse MR imaging assessed MFLs efficiency as contrast agents in vivo: MR angiography performed 24 h after intravenous injection of the contrast agent provided the first direct evidence of the stealthiness of PEG-ylated magnetic-fluid-loaded liposomes.

ROBERT K., MAURIN N., VAYSSETTES C., SIAUVE N., JANEL N.

Cystathionine beta synthase deficiency affects mouse endochondral ossification.

Anat. Rec.(A), 282A (1), 1-7, 2005

(Services cités : [LRI](#))

Cystathionine beta synthase (CBS) is a crucial regulator of plasma concentrations of homocysteine. Severe hyperhomocysteinemia due to CBS deficiency confers diverse clinical manifestations, notably characteristic skeletal abnormalities. To investigate this aspect of hyperhomocysteinemia, we analyzed the skeleton of CBS-deficient mice, a murine model of severe hyperhomocysteinemia. Radiography, Alcian Blue/Alizarin Red S-stained whole skeletal preparations, and histological comparisons were used to determine the extent, pattern, and distribution of skeletal abnormalities in CBS-deficient mice. Disruption of the murine CBS gene leads to skeletal abnormalities, notably kyphoscoliosis, with temporal shortening of long bones due to impaired cartilage differentiation, albeit to differing degrees. (c) 2004 Wiley-Liss, Inc.

SALOMON L.J., SIAUVE N., TAILLIEU F., BALVAY D., CLEMENT O., VAYSSETTES C., FRIJA G., VILLE Y., CUENOD C.A.

Placental functional assessment using MRI: mice today, humans tomorrow?

J. Gynécol. Obst. Biol. Reprod., 34 (7), 666-673, 2005

(Services cités : LRI)

Placental insufficiency, a process due to either poor placental perfusion or permeability, may lead to progressive deterioration in placental function and materno-fetal morbidity. Advances in MR contrast media pharmacokinetic studies of transit through tissues and dynamic MRI allow to characterize organs microcirculation in vivo. Placental function assessment might be achieved using analysis of dynamic contrast enhanced MRI of tracers. A murine model of placental assessment has been constructed. Herein, principles, results and limitations of such techniques are discussed as well as their potential interest and weaknesses in humans.

SALOMON L.J., SIAUVE N., BALVAY D., CUENOD C.A., VAYSSETTES C., LUCIANI A., FRIJA G., VILLE Y., CLEMENT O.

Placental Perfusion MR Imaging with Contrast Agents in a Mouse Model.

Radiology, 235 (1), 73-80, 2005

(Services cités : LRI)

PURPOSE: To quantitatively analyze placental perfusion by using magnetic resonance (MR) imaging with contrast agents in a mouse model. **MATERIALS AND METHODS:** Study was conducted according to French law and in full compliance with National Institutes of Health recommendations for animal care. Thirty-six pregnant Balb/c mice at 16 days of gestation were injected intravenously with either a conventional or macromolecular gadolinium chelate, and 1.5-T single-section T1-weighted two-dimensional fast spoiled gradient-echo sequential MR imaging was then performed for 14 minutes. Images were analyzed qualitatively, and parametric map analysis was performed in the resultant 25 mice included in the study. Signal intensity was measured in maternal left ventricle (input function), placenta, and fetus on all images. After converting signal intensity into contrast agent tissue concentrations, a three-compartment model was developed with compartmental and numeric modeling software. Placental perfusion was calculated for conventional (n = 12) and macromolecular (n = 13) gadolinium chelates. Finally, placental and fetal gadolinium concentrations were assayed by means of atomic emission spectrophotometry (n = 15). Perfusion values and placental and fetal gadolinium concentrations for conventional and macromolecular chelates were compared by using an unpaired t test. **RESULTS:** Based on a constant transfer parameter, estimated placental perfusion did not differ between procedures with conventional and macromolecular gadolinium chelates (0.99 mL/min/g +/- 0.5 [standard deviation] and 1.28 mL/min/g +/- 0.6, respectively, P =.22). Likewise, mean placental gadolinium concentrations did not differ after injection of conventional and macromolecular chelates. In contrast, mean fetal gadolinium concentration was 9.83 μ mol/L after conventional chelate injection and below detection limit after macromolecular chelate injection. **CONCLUSION:** Placental perfusion can be calculated by using dynamic contrast-enhanced MR imaging, as shown in this mouse model. (c) RSNA, 2005.

2004

FOURNIER L.S., CUENOD C.A., de BAZELAIRE C., SIAUVE N., ROSTY C., TRAN P.L., FRIJA G., CLEMENT O.

Early modifications of hepatic perfusion measured by functional CT in a rat model of hepatocellular carcinoma using a blood pool contrast agent.

Eur. Radiol., 14 (11), 2125-2133, 2004

(Services cités : LRI, U370)

Macromolecular contrast-enhanced functional CT was performed to characterize early perfusion

changes in hepatocellular carcinoma (HCC). Fourteen rats with chemically induced primary liver tumors ranging pathologically from hyperplasia to HCC and 15 control rats were investigated. Two dynamic CT scans using an experimental macromolecular contrast agent were performed on a single slice 11 and 18 weeks after tumor induction followed by pathological examination. A deconvolution mathematical model was applied, yielding the hepatic perfusion index (HPI), mean transit time (MTT), liver distribution volume (LDV) and arterial, portal and total blood flows (FA, FP, FT). Analysis was performed on one slice per rat, containing overall two hyperplasia, six dysplasia and 15 HCC. On the first scans, HCC at an early pathological stage had a low FP (-30%, $P=0.002$) but a normal arterial-portal balance. On the scan contemporary to pathology, HCC perfusion parameters showed an inversion of the arterial-portal balance (HPI +212%, $P<0.0001$), with a high FA (+56%, $P=0.002$) and a low FP (-69%, $P<0.0001$). Sensitivity and specificity of detection of HCC by perfusion CT were high (87 and 80%) on late scans; but also on the earlier scans (86 and 65%), even though only one (7%) was visible to the eye. Perfusion-CT allowed early detection of HCC. This technique could contribute in the detection and characterization of liver lesions in clinical studies.

LUCIANI A., OLIVIER J.C., CLEMENT O., SIAUVE N., BRILLET P.Y., BESSOUD B., GAZEAU F., UCHEGBU I.F., KAHN E., FRIJA G., CUENOD C.A.

Glucose-Receptor MR Imaging of Tumors: Study in Mice with PEGylated Paramagnetic Niosomes1.

Radiology, 231 135-142, 2004

(Services cités : LRI)

PURPOSE: To evaluate a magnetic resonance (MR) imaging contrast agent for tumor detection based on paramagnetic nonionic vesicles (niosomes) bearing polyethylene glycol (PEG) and glucose conjugates for the targeting of overexpressed glucose receptors. **MATERIALS AND METHODS:** Four gadobenate dimeglumine-loaded niosome preparations including nonconjugated niosomes, niosomes bearing glucose conjugates (N-palmitoyl glucosamine [NPG]), niosomes bearing PEG 4400, and niosomes bearing both PEG and NPG were tested. In vitro cellular uptake was measured at electron paramagnetic resonance (EPR) after incubation with human prostate carcinoma, PC3, cells. In vivo distribution was studied at MR imaging 6, 12, and 24 hours after injection, with assessment of tumor, brain, liver, and muscle signal intensity (SI) in 49 mice bearing PC3 cells. Efficiency of targeted contrast agents was assessed with tumor-to-muscle contrast-to-noise ratio (CNR). Testing for differences was performed with analysis of variance followed by a posteriori Fisher test. **RESULTS:** In vitro, gadolinium could be detected at EPR only in cell pellets incubated with niosomes bearing glucose conjugates or niosomes bearing both glucose conjugates and PEG ($4.9 \cdot 10^{-15}$ and $4.5 \cdot 10^{-15}$ mol gadolinium per PC3 cell). In vivo, marked predominant tumor enhancement was demonstrated 24 hours after injection of glycosylated PEG niosomes ($P < .01$); no significant differences were observed following injection of nonconjugated niosomes, glycosylated niosomes, or PEG 4400 niosomes. Twenty-four hours after injection, sole presence of NPG or PEG 4400 on the surface of the niosome led to higher tumor-to-muscle CNR than that observed after injection of nonconjugated niosomes (CNR of 3.3 ± 0.7 [SD], 3.4 ± 2.2 , and 0 ± 1.9). Combination of NPG and PEG led to even higher tumor-to-muscle CNR (6.3 ± 2.2). **CONCLUSION:** Combination of PEG and glucose conjugates on the surface of niosomes significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging in a human carcinoma xenograft model.

SMIRNOV P., GAZEAU F., LEWIN M., BACRI J.C., SIAUVE N., VAYSETTES C., CUENOD C.A., CLEMENT O.

In vivo cellular imaging of magnetically labeled hybridomas in the spleen with a 1.5-T clinical MRI system.

Magn. Reson. Med., 52 (1), 73-79, 2004

(Services cités : [LRI](#))

The feasibility of in vivo cellular imaging using a 1.5 T clinical magnet was studied in the mouse. Hybridoma cells were labeled with anionic gamma-Fe₂O₃ superparamagnetic iron oxide nanoparticles. These were internalized by the endocytose pathway. Both electron spin resonance and magnetophoresis as a measure of the labeled cells migration velocity under a magnetic field were used to quantify particle uptake. A fast (< 2 hr) and substantial (up to 5 pg of iron per cell) internalization of nanoparticles by hybridomas was found, with good agreement between the two methods used. Hybridomas labeled with 2.5 pg iron per cell were injected intraperitoneally to male Swiss nude mice. A decrease in the spleen signal, suggesting a "homing" of labeled hybridomas to this organ, was found 24 hr later by MRI performed at 1.5 T. Furthermore, in labeled cells recovered from the spleen by ex vivo magnetic sorting, a mean of 0.5 pg iron per cell was found, i.e., a value five times lower than that of the injected hybridomas. This finding is consistent with in vivo proliferation of these cells. In addition, the amount of labeled hybridomas present in the spleen was found to correlate with MRI signal intensity.

2003

PRADEL C., SIAUVE N., BRUNETEAU G., CLEMENT O., de BAZELAIRE C., FROUIN F., WEDGE S.R., TESSIER J.L., ROBERT P.H., FRIJA G., CUENOD C.A.

Reduced capillary perfusion and permeability in human tumour xenografts treated with the VEGF signalling inhibitor ZD4190: an in vivo assessment using dynamic MR imaging and macromolecular contrast media.

Magn. Reson. Imaging, 21 (8), 845-851, 2003

(Services cités : [LRI](#))

We describe the use of perfusion-permeability magnetic resonance imaging (ppMRI) to study hemodynamic parameters in human prostate tumor xenografts, following treatment with the vascular endothelial growth factor-A (VEGF) receptor tyrosine kinase inhibitor, ZD4190. Using a macromolecular contrast agent (P792), a fast MR imaging protocol and a compartmental data analysis, we were able to demonstrate a significant simultaneous reduction in tumor vascular permeability, tumor vascular volume and tumor blood flow (43%, 30% and 42%, respectively) following ZD4190 treatment (100 mg/kg orally, 24 h and 2 h prior to imaging). This study indicates that MR imaging can be used to measure multiple hemodynamic parameters in tumors, and that tumor vascular permeability, volume and flow, can change in response to acute treatment with a VEGF signaling inhibitor.

2002

CLEMENT O., ROBERT P., CUENOD C.A., SIAUVE N., SOBOTKA A., KAHN E., FRIJA G.

Functional imaging of tumors using CT and iodinated contrast media of different molecular weights.

Acad. Radiol., 9 Suppl 1 S212-S214, 2002

(Services cités : [LRI](#))

CLEMENT O., PRADEL C., SIAUVE N., FROUIN F., BRUNETEAU G., KAHN E., FRIJA G., CUENOD C.A.

Assessing perfusion and capillary permeability changes induced by a VEGF inhibitor in human tumor xenografts using macromolecular MR imaging contrast media.

Acad. Radiol., 9 Suppl 2 S328-S329, 2002

(Services cités : [LRI](#))

CUENOD C.A., LECONTE I., SIAUVE N., FROUIN F., DROMAIN C., CLEMENT O., FRIJA G.

Deconvolution technique for measuring tissue perfusion by dynamic CT: application to normal and metastatic liver.

Acad. Radiol., 9 Suppl 1 S205-S211, 2002

(Services cités : [LRI](#))

2001

LEWIN M., CLEMENT O., BELGUISE-VALLADIER P., TRAN L., CUENOD C.A., SIAUVE N., FRIJA G.

Hepatocyte targeting with gd-eob-dtpa - potential application for gene therapy.

Invest. Radiol., 36 (1), 9-14, 2001

(Services cités : [U370](#), [LRI](#))

RATIONALE AND OBJECTIVES. TO evaluate the suitability of the liver-specific MRI contrast agent Gd-EOB-DTPA as a nonviral vector for gene therapy of hepatocellular carcinoma.

METHODS. Specific uptake of Gd-EOB-DTPA was quantified by relaxometry in rat cultured hepatocytes and the hepatoma cells HepG2 and Huh7. Nonviral vectors for gene transfer were synthesized by coupling Gd-EOB-DTPA to polyethyleneimine or polylysine as DNA condensing agents, and their efficiency was studied using P-galactosidase (lacZ) as the reporter gene.

RESULTS. Gd-EOB-DTPA was specifically taken up by rat cultured hepatocytes (4.32 vs. 1.08 mmol/L in nonhepatocyte control cells) but not by the hepatoma cells; this uptake was concentration-dependently inhibited by Bromsulphthalein, Polycation linkages were achieved with yields of 0.9 Gd-EOB-DTPA molecule per polyethyleneimine molecule and 10 Gd-EOB-DTPA molecules per polylysine molecule. Incubating the cells with plasmids containing lacZ reporter gene and polyethyleneimine-Gd-EOB-DTPA resulted in a few blue (transfected) cells, whereas no blue cells were observed on incubation with polylysine-Gd-EOB-DTPA. **CONCLUSIONS.** Gd-EOB-DTPA is taken up by normal hepatocytes but not by HepG2 and Huh7 cells, probably because of the lack of the organic anion transporter in these hepatoma cells. The Gd-EOB-DTPA polycation conjugates, such as polyethyleneimine-Gd-EOB-DTPA, could serve as transfer vectors of interest for gene targeting imagery at the early stage of hepatocarcinogenesis.

However, the transfer efficiency of such conjugates is low and requires improvement.

[References: 25]

2000

BORDAT C., SICH M., RETY F., BOUET O., COURNOT G., CUENOD C.A., CLEMENT O.

Distribution of iron oxide nanoparticles in rat lymph nodes studied using electron energy loss spectroscopy (eels) and electron spectroscopic imaging (esi).

J. Magn. Reson. Imag., 12 (3), 505-509, 2000

(Services cités : [LRI](#))

Superparamagnetic iron nanoparticles have been developed as contrast agents for magnetic resonance lymphography. The kinetics of uptake of these particles has not yet been accurately determined. We have therefore monitored the distribution of Individual iron particles (ferumoxtran, AMI-227, Sinerem) in rat lymph nodes 1.5, 3, 6, 12, and 24 hours after i.v. injection (two rats per time point). The ultrastructural distribution of the iron was determined by energy-filtered transmission electron microscopy (EFTEM). This method allows the identification of elements using element-specific energy-loss electrons. Iron was Identified by the Fe-L-2,L-3 edge (EELS), and Iron maps were obtained using Iron-specific electrons for imaging (ESI). The background was calculated by simplex optimization (EELS) and by the two-window method (ESI). Ferumoxtran particles were regularly observed at the periphery of the lymph nodes but not In their centers. Isolated iron particles were seen extracellularly within lymph vessels and, 3 hours after injection, as small dots in phagocytic cells. Numerous dense clusters appeared within the cells at later times (6 and 12 hours after injection). These results suggest that the contrast agent moves rapidly across the capillary wall to the lymph and is then taken up by phagocytic cells. (C) 2000 Wiley-Liss, Inc. [References: 23]

RETY F., CLEMENT O., SIAUVE N., CUENOD C.A., CARNOT F., SICH M., BUISINE A., FRIJA G.

Mr lymphography using iron oxide nanoparticles in rats: pharmacokinetics in the lymphatic system after intravenous injection.

J. Magn. Reson. Imag., 12 (5), 734-739, 2000

(Services cités : LRI)

The objective of the study was to quantify the kinetics of the superparamagnetic nanoparticle ferumoxtran (AMI 227, Sinerem((R)), Combidex((R))) in the efferent lymph of the subdiaphragmatic lymph nodes and in various node groups of the rat to elucidate the uptake mechanism. The thoracic lymph duct was catheterized in 24 rats after an IV injection of 40 μ mol Fe/kg ferumoxtran. Three rats were studied at several time points between 1.5 and 24 hours. At each time point, 0.3 ml of lymph were collected over 45 minutes. Lymph nodes were differentiated into five groups. The iron concentration in the samples and in plasma was measured by relaxometry at 0.47 T and atomic absorption spectrometry. Cytology was performed on the lymph. High concentrations of nanoparticles were found in the thoracic lymph soon after injection (90 minutes). No particle was found in the lymph cells, indicating that ferumoxtran was extracellular in the lymph fluid. The maximum concentration was reached later in all node groups, at 12 hours, and then plateaued. The transcapillary pathway and subsequent lymph drainage of the particles seem to play a major role in the delivery to the lymph nodes. (C) 2000 Wiley-Liss, Inc. [References: 23]

1999

SIAUVE N., CUENOD C.A., CLEMENT O., RASIO E., BENDAYAN M., FRIJA G.

The rete mirabile of the eel: a useful model for the study of transcapillary passage of MR contrast agents.

J. Magn. Reson. Imag., 9 (2), 353-361, 1999

(Services cités : LRI)

Our purpose was to study the capillary leakage of MR contrast media using a pure capillary model. the rete mirabile of the eel. The rete is a countercurrent-exchange organ composed of an arterial and a venous capillary system that can be catheterized and perfused. Substances are introduced at the arterial input by a constant Infusion, and their steady-state concentrations are

measured at the arterial and venous outputs, The capillary leakage of four MR contrast agents- Gd-DOTA (MW = 561 D), carboxymethyl-dextran-Gd-DTPA (MW = 38,900 D), albumin-Gd-DTPA (MW = 92,000 D), AMI-227 (400,000 D < MW < 900,000 D)-was characterized by reference to radioactive tracers ((³H)-H₂O, ²²Na, ¹⁴C-sucrose, ¹²⁵I-albumin) by two parameters. These parameters were the concentration ratio of the venous output over the arterial input [C-VOUT(%)] and the permeability coefficient (P), The transcapillary pathway mechanisms for carboxymethyl-dextran-Gd-DTPA and albumin-Gd-DTPA were studied by electron microscopy, P values for Gd-DOTA (9.4 +/- 3.6 10⁻⁷) cm/s and albumin-Gd-DTPA (11.8 +/- 5.5 10⁻⁷) cm/s were close to P values for C-14-sucrose, while P values for carboxymethyl-dextran-Gd-DTPA (6.4 +/- 4.9 10⁻⁷) cm/sec were similar to P values for ¹²⁵I-albumin. The lowest permeability was observed with AMI-227 (2.7 +/- 2 10⁻⁷) cm/sec, Vesicular transport was demonstrated for carboxymethyl-dextran-Gd-DTPA and albumin-Gd-DTPA. The transcapillary passage of several MR contrast agents can be characterized with the rete mirabile model. Molecular weight is the major factor influencing transport, J. Magn. Reson. Imaging 1999;9:353-361, (C) 1999 Wiley-Liss, Inc. [References: 31]