SPIO enhanced liver MRI with SHU 555 A (RESOVIST): new protocol infusion to improve arterial phase evaluation - a prospective study

Original Research

Superparamagnetic Iron Oxide-Enhanced Liver MRI With SHU 555 A (RESOVIST®): New Protocol Infusion to Improve Arterial Phase Evaluation—A Prospective Study

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Purpose: To compare the arterial enhancement of hypervascular hepatic lesions by T1-weighted 3D-GRE (gradient-recalled echo) fat-sat sequence after slow (0.5 mL/sec) and fast (2 mL/sec) RESOVIST® infusion.

Materials and Methods: We prospectively enrolled 71 patients with hypervascular hepatic lesions to undergo dynamic magnetic resonance imaging (MRI) examination with RESOVIST®. A total of 92 benign and malignant lesions, 44 of which histologically confirmed, were examined. Three blinded and independent readers visually assessed the arterial enhancement using a score from 0 (none) to 3 (maximum), the latter score comparable to that achievable by MultiHance administration.

Results: Out of the 92 hypervascular lesions, 41, 31, and 20 nodules were examined using the slow, fast, and both protocols, respectively. Relevant enhancement (scores 2–3) was found in 42% vs. 14.5% of cases for slow and fast protocols, respectively. Intraindividual comparison evaluation confirmed the better results obtained by slow than fast protocol (25% vs. 10%), with statistically relevant difference in distribution of scores ($P = 0.0004$). The slow protocol showed values between 0 and 3 with an arithmetic mean of 1.1; the fast one, on the other hand, showed values between 0 and 2 with an arithmetic mean of 0.66.

Conclusion: Slow infusion improves arterial enhancement after RESOVIST® administration.

Key Words: contrast media; dynamic MR imaging; ferucarbotran; liver MRI; RESOVIST®; superparamagnetic iron oxide (SPIO)
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FERUCARBOTRAN (RESOVIST®, SHU 555 A, Bayer Schering Pharma, Berlin, Germany) is a contrast agent (CA) composed of superparamagnetic iron oxide (SPIO) particles. RESOVIST® allows a potential improvement in diagnostic capability compared with the first-generation SPIO CAs such as ferumoxide (ENDOREM® Guerbet, Aulnay-sous-Bois, France, and Feridex). Due to a large distributed particle size, ranging from 21–60 nm (1,2), the mean hydrodynamic diameter of ferucarbotran is smaller than that of ferumoxide particles, 60 versus 150 nm, respectively. Particles are coated with carboxydextran (rather than dextran, as in ferumoxide) which ensures aqueous solubility and prevents aggregation.

Ferumoxide is infused slowly to avoid lumbar pain and hypotensive reaction. Conversely, RESOVIST® does not cause side effects after rapid intravenous injection, therefore allowing dynamic examination and, similar to ferumoxide, reticulo-endothelial system (RES) specific imaging in the delayed phase (3). RESOVIST® is taken up by phagocytic Kupffer cells of the liver (80%), spleen (8%–10%) (4), bone marrow, and lymph nodes (10%). Following uptake by Kupffer cells, a decrease in signal intensity (SI) can be seen in tissues that take up RESOVIST® (5). Generally, iron oxide particles are used as negative enhancers because they have a high R_2/R_1 relaxivity ratio, meaning that the effect on T2 shortening is generally much stronger than that on T1 shortening. As the particles are taken up by Kupffer cells in the liver, the T2 effect becomes the dominant mechanism due to accumulation of the CA at higher concentrations. Therefore, RESOVIST® induces a decrease in SI in lesions that contain phagocytic cells (benign lesions) or a significant blood-pool (hemangiomas) on T2-

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weighted accumulation phase images (6). Conversely, malignant lesions without phagocytic cells do not show any SI decrease on T2-weighted accumulation phase images (4,7). Hepatocellular lesion conspicuity in SPIO-enhanced imaging depends on the number and activity of Kupffer cells within the nodule, and therefore moderately and poorly differentiated hepatocellular carcinomas (HCCs) can be distinguished from well-differentiated ones.

However, RESOVIST® also has an effect on T1 shortening and positive signal enhancement can be obtained on T1-weighted images. If the SPIO concentration is low, the T1 effect is more relevant because the few CA particles are surrounded by many water molecules (8,9). RESOVIST® solution contains a percentage of particles with smaller mean hydrodynamic diameter (21, 33, and 46 nm) (1,2) which are responsible for a stronger T1 effect and a longer blood half-life because of slower uptake into the RES (4). The T1 effect is time-dependent; in particular, the improvement in liver signal intensity is observed 30 seconds after bolus injection, due to the intravascular dispersion and low liver uptake of RESOVIST® particles at this time (SPIO blood-pool effect). The signal intensity of the liver decreases with increased liver RES uptake of CA, usually 480 seconds after RESOVIST® injection (7). The T1 effect of RESOVIST® is also correlated to its dose and plasma concentration. In clinical practice the RESOVIST® dose administered is within a range of 7.0–12.9 μmol iron per kilogram (4); then, in comparison with gadolinium chelates CA such as gadopentate dimeglumine, RESOVIST® is usually used at a 10-fold lower dose (≈0.01 mmol iron per kg of body weight).

Despite the theoretical considerations set out above, some authors (10,11) reported that in clinical use the SPIO arterial phase was not always adequate and lesion conspicuity therefore not fully satisfactory, probably due to the rapid injection of CA, which leads to a high concentration and short duration of enhanced bolus (12).

Against this background, we decided to try a new RESOVIST® injection protocol with slow injection designed to improve the enhancement of the arterial phase. Since no clear indications about the administration rate were available in the literature or in the instructions of the vendor, we have arbitrarily decided to define as "fast protocol" a rate of 2 mL/sec and as "slow protocol" a rate of 0.5 mL/sec.

The aim of our prospective study was to evaluate the performance efficacy of the new protocol as compared with the standard one currently in use. In this first part, described below, we subjectively evaluate the results with a visual assessment as done in daily practice; in a forthcoming second part we will try to objectively quantify the enhancement. We evaluated both the reliability of these protocols and the scores they provided in a sample of patients with hypervascular benign and malignant liver lesions assessed by three independent radiologists.

MATERIALS AND METHODS

Study Population

From April 2005 to March 2008 we prospectively enrolled 71 patients (21 males and 50 females, age range 23–66 years) with 92 known hypervascular focal liver lesions to undergo MR examination(s) with RESOVIST®. A total of 92 lesions were examined: 48 focal nodular hyperplasia (FNH), 11 hepatic adenomas (HA), 12 HCCs, 11 hypervascular metastases, and 10 nodular regenerative hyperplasia (NRH). None of the patients with HA suffered from glycogenosis or other metabolic diseases. The final diagnosis was provided by surgical and/or needle biopsy in patients with malignant lesions (n = 23), HA (n = 11), or NRH (n = 10), and by MR examination after liver-specific gadolinium chelates (MULTIHANCE®, gadopentate dimeglumine, Bracco, Milan, Italy), and follow-up in patients with FNH (n = 48).

All patients were included in the study as part of routine clinical practice and the MR examinations were performed for follow-up of known focal lesion(s). The study protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

All data and information derived from and relative to the study were under the exclusive control of the investigating radiologists.

Study Design

Of the total 71 patients (with 92 focal lesions), 31 (with 41), 28 (with 31), and 12 (with 20) underwent only the slow, only the fast, and both protocols, respectively; then 43 patients (31 + 12 patients with 61 focal lesions) were evaluated using the slow protocol, and 40 patients (28 + 12 patients with 51 focal lesions) using the fast one.

When patients underwent both protocols, the two examinations were performed with a median delay of months (from 2–4 months).

Our study consisted of two parts. In the first part we investigated the reliability of the slow and fast protocols by comparing the results provided by the different radiologists using each protocol. In the second part we compared the results obtained using the different protocols in patients examined with both in order to evaluate which protocol produced the higher score.

The inclusion criterion was: of-age patients with previously diagnosed focal liver lesions, referred for MR follow-up examinations.

The main exclusion criteria were: minority age, pregnant or nursing women, or patients that: received any investigational products within 30 days before the study and/or liver-specific CAs within 2 weeks prior to RESOVIST® administration; were treated with other contrast media within 24 hours prior to the administration of RESOVIST®; were scheduled for biopsy or surgery within 24 hours after administration of RESOVIST®; or were considered clinically unstable or with a history of anaphylactic reaction to medications or contrast media.

We performed a patient's randomization for the two protocols. A total of 43 and 40 patients comprised the groups of the slow and fast infusion protocols, respectively; the latter excluded two subjects due to technical reasons and motion artifacts.

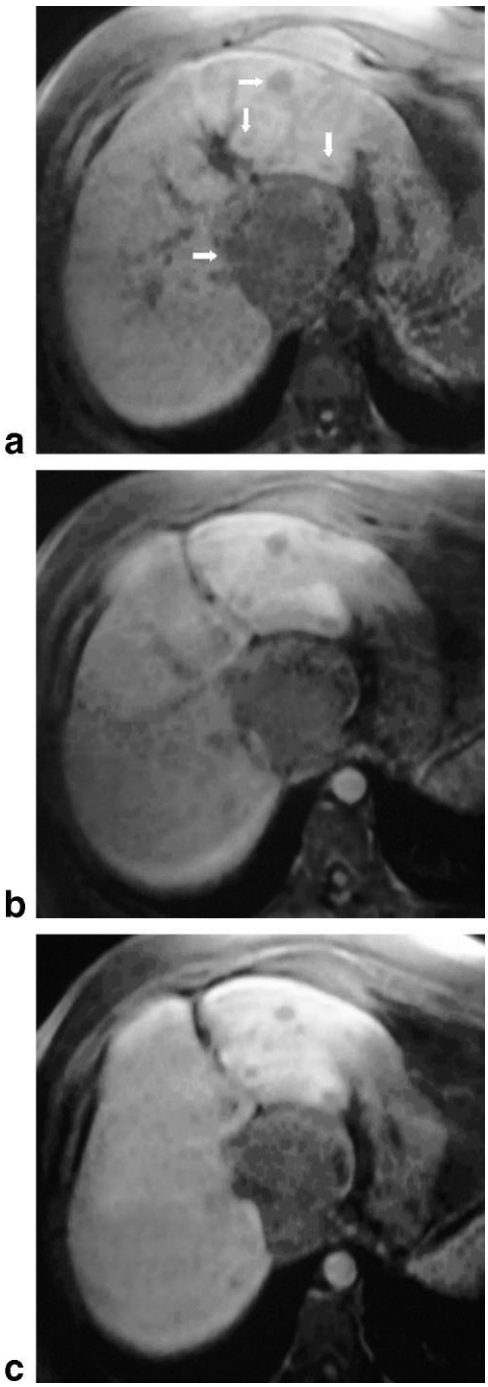

Figure 1. a–c: Liver adenomatosis. On precontrast VIBE sequence four well-defined, hypointense nodules (arrows) can be detected. During the arterial phase after RESOVIST® administration (b) and in the portal venous phase (c) the nodules do not show significant enhancement (score 0).

MRI Protocol

All MR examinations were performed using a 1.5T imaging system (Symphony, TIM Class, Siemens, Erlangen, Germany) equipped with a four-channel phased-array multicoil, adequately positioned to cover the upper abdomen of the patient lying in a supine position. The scanner provides a maximum gradient strength of 30 mT/m, with a peak slew rate of 120mT/m/msec.

The baseline MRI protocol included the following transverse acquisitions: T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence (TR/TE = 8/79 msec, echo-train length = 90, slice thickness = 5 mm, intersection gap = 10%, field of view (FOV) = 350–400 mm, effective matrix size = 256 × 165, signal averages = 1, acquisition time = 2–3

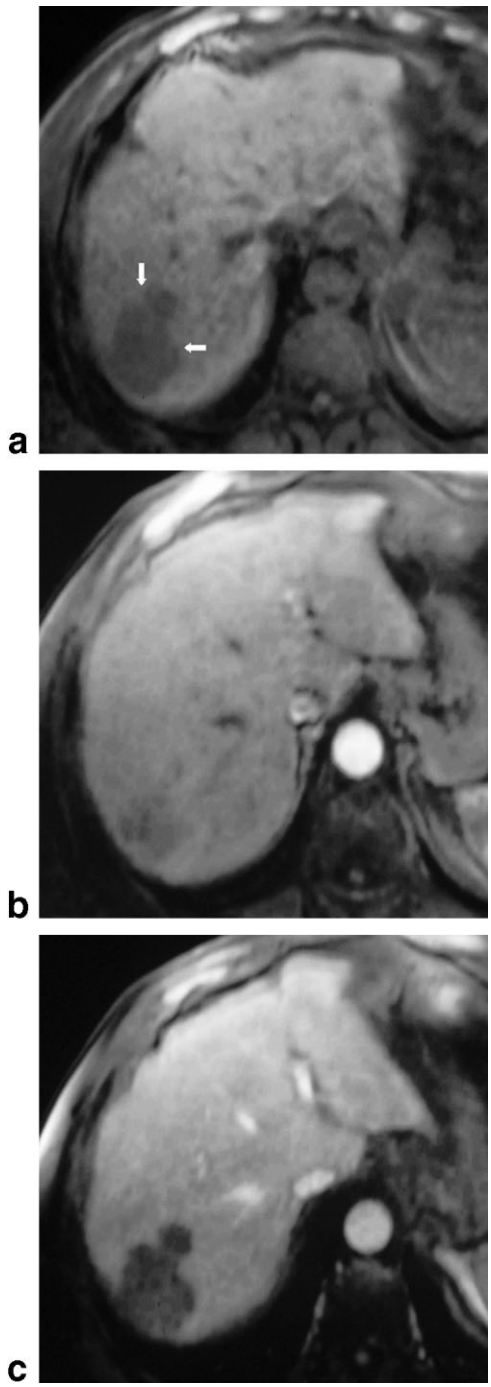

Figure 2. a–c: Hepatocellular carcinoma. Precontrast VIBE sequence (a) shows, in the VII segment of the liver, a lobulated, hypointense lesion (arrows). During the arterial phase after RESOVIST® administration (b) a weak nodular enhancement can be detected (score 1), with a rapid washout in the subsequent portal venous phase (c).

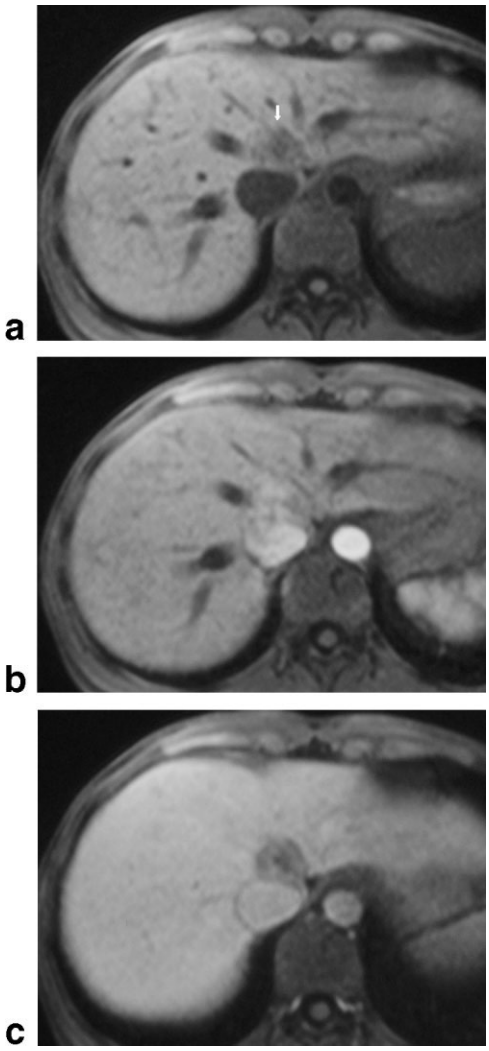

Figure 3. a–c: Focal nodular hyperplasia. On the precontrast VIBE sequence (a) a heterogeneously, slightly hypointense lesion is appreciable in the IV segment of the liver (arrow). During the arterial phase after RESOVIST® administration (b) a discrete lesion enhancement can be observed (score 2), with a rapid washout in the portal venous phase (c).

minutes); T2*-weighted 2D-GRE (gradient-recalled echo) sequence (TR/TE = 175/10 msec, slice thickness = 5 mm, intersection gap = 10%, FOV = 350–400 mm, effective matrix size = 256 × 165, signal averages = 1, acquisition time = 20 seconds); T1-weighted 2D fast low angle shot (FLASH) spoiled gradient echo in and out phase sequence (TR/TE = 131/2.6–5 msec, slice thickness = 5 mm, intersection gap = 10%, FOV = 350–400 mm, effective matrix size = 256 × 165, signal averages = 1, acquisition time = 18 seconds).

The study of the enhancement was obtained by the adoption of a T1-weighted 3D-GRE sequence with volumetric interpolated breath-hold examination (VIBE) fat sat (TR/TE = 3.8/1.5 msec, slice thickness = 4 mm, intersection gap = 10%, FOV = 350–400 mm, effective matrix size = 256 × 169, signal averages = 1, acquisition time = 16 seconds). After the unenhanced acquisition, this sequence was repeated at 25/40 seconds (hepatic artery phase), 70/80 seconds (portal vein phase) [the range is due to the interindividual variations detected by Care Bolus], 180 seconds (equilibrium phase), 5 and 10 minutes (RES specific phases), following the beginning of CA administration.

The Care Bolus technique in the sagittal and parasagittal orientations was used to determine the exact

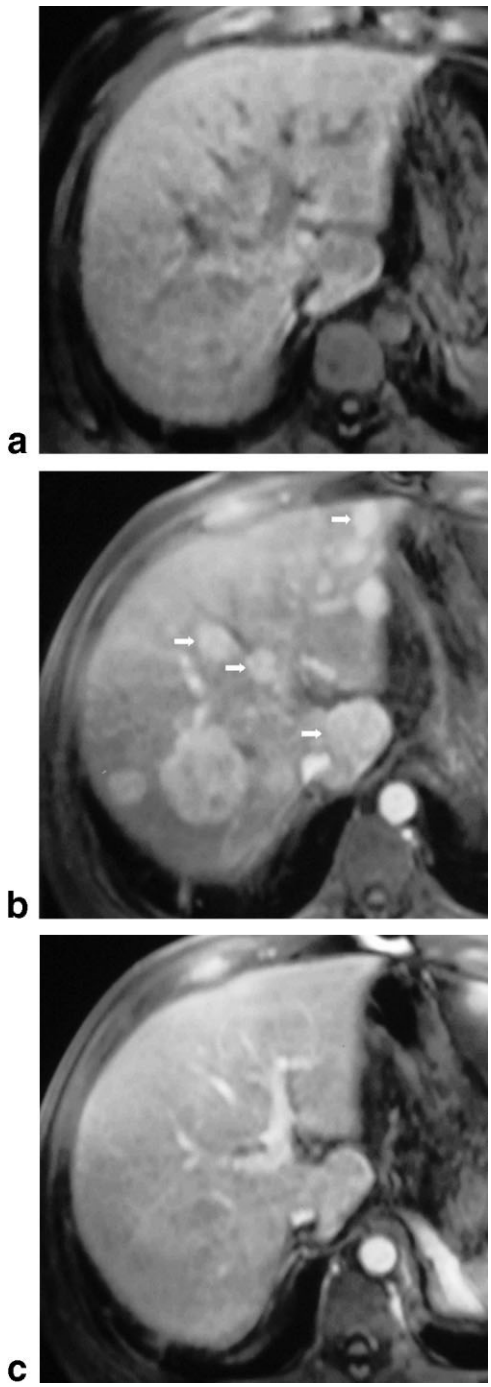

Figure 4. a–c: Nodular regenerative hyperplasia. On the precontrast VIBE sequence (a) some poorly defined, iso- and slightly hypointense nodules are identified. After RESOVIST® administration in the arterial phase (b) numerous markedly homogeneously hyperintense nodules are detected (score 3) in both lobes of the liver. The lesions appear isointense in the portal venous phase (c).

Table 1
Slow and Fast Protocol Arterial Scores Evaluation

		Readers			
Slow protocol arterial phase scores		1	2	3	Total
0	No.	15	12	14	41
	%	24.59	19.67	22.95	22.40
1	No.	19	27	19	65
	%	31.15	44.26	31.15	35.52
2	No.	19	15	21	55
	%	31.15	24.59	34.43	30.05
3	No.	8	7	7	22
	%	13.11	11.48	11.48	12.02
Total	No.	61	61	61	183
	%	100.00	100.00	100.00	100.00
		Readers			
Fast protocol arterial phase scores		1	2	3	Total
0	No.	27	24	26	77
	%	52.94	47.05	50.98	50.32
1	No.	18	18	18	54
	%	35.29	35.29	35.29	35.29
2	No.	4	7	5	16
	%	7.84	13.72	9.80	10.45
3	No.	2	2	2	6
	%	3.92	3.92	3.92	3.92
Total	No.	51	51	51	153
	%	100.00	100.00	100.00	100.00

Chi-square test: $P > 0.1$.

time to begin the arterial acquisition, considering one scan per second (TR/TE = 3.5/1.1 msec, slice thickness = 60 mm, intersection gap = 20%, FOV = 400 mm, effective matrix size = 128 × 128, signal averages = 2). The region of interest (ROI) with appropriate size was located in the abdominal aorta at the level of the celiac trunk. Also, the T2*-weighted sequence was repeated during the RES phase at 10 minutes.

RESOVIST® (at the dose of 1.4 and 0.9 mL in patients with a body weight higher or lesser than 60 kg) was administered in a bolus by prefilled syringe in the distal part of a connecting line into an antecubital vein, followed for both protocols by flushing with 20 mL of saline solution using an automated injector (Spectris Solaris EP, MedRad, Indianola, PA), at the rate of 0.5 and 2 mL/sec for the slow and fast infusion protocols, respectively. The duration time of the entire administration (CA plus 20 mL saline flush) was ≈40–42 seconds and 10–11 seconds for the slow and fast protocols, respectively. The arterial phase acquisition started during the administration and 15 seconds after the end of the administration of saline flush for the slow and the fast protocols, respectively.

The same VIBE sequence with the Care Bolus technique was previously adopted to obtain data with liver-specific gadolinium chelates. The sequence was repeated at 25/40, 70/80, 180 seconds, and 90 minutes (liver specific phase) following the beginning of MULTIHANCE® administration (1.5 mL per 10 kg of patient body weight plus 20 mL of saline flush at the rate of 2 mL/sec with an automated injector).

Image Analysis

All patients' MR images were reviewed by three experienced radiologists in a blinded and independent fashion. The images were analyzed separately by each radiologist in three different reading sessions and arterial enhancement was read and scored by visual qualitative assessment. The signal intensity of the hepatic artery phase was compared with that of the unenhanced and portal vein phase, and scored as follows: when lesion showed none, little, fair, and strong enhancement, a score 0 (Fig. 1), score 1 (Fig. 2), score 2 (Fig. 3), score 3 (Fig. 4) was assigned, respectively.

If a lesion was hypointense when compared to the liver parenchyma at the unenhanced examination, enhancement was also rated as follows: when the lesion remained hypointense, equaled, became brighter or much brighter versus the surrounding parenchyma (in the latter case with enhancement comparable to that of the hepatic vessels) a score 0, 1, 2, or 3 was assigned, correspondingly.

The reference for the enhancement evaluation was the improvement obtained in each patient by previous multiphase MRI examination after extracellular-intravascular gadolinium chelates bolus injection: then a score of 3 was assigned when the enhancement post-RESOVIST® administration was almost similar (or slightly inferior) to that achievable by MULTIHANCE®.

The order of the MRI sets was randomly established for both reading protocols. No statistically significant difference was observed in the distribution of the hepatic lesions according to their histology between patients undergoing the slow and fast protocols, respectively (exact test: $P > 0.1$).

Statistical Analysis

We assessed the reliability of the slow and fast protocols by measuring the agreement between each pair of radiologists, computing both Cohen's kappa statistic (K), considering the enhancement as a categorical variable, and the intraclass correlation coefficient (ICC), considering the enhancement as an ordinal semiquantitative variable (13).

Each analysis was performed for the slow and fast protocols separately. The strength of agreement was evaluated according to Altman's suggestions for interpreting K values: poor <0.20, fair 0.21–0.40, moderate 0.41–0.60, good 0.61–0.80, and very good 0.81–1.00. (14).

Statistical tests were performed for each kappa and ICC value using the 0.05 alpha level for rejecting the null hypothesis in a two-tailed test.

In the second part of the study we evaluated the distribution of the arterial phase score between the slow and fast protocols for the lesions that were analyzed with both protocols. We compared the score distributions obtained for both protocols using the nonparametric Wilcoxon test for paired data.

All the analyses were performed using the Stata program for personal computers (StataCorp 2003, Stata Statistical Software: Release 8.0. College Station, TX).

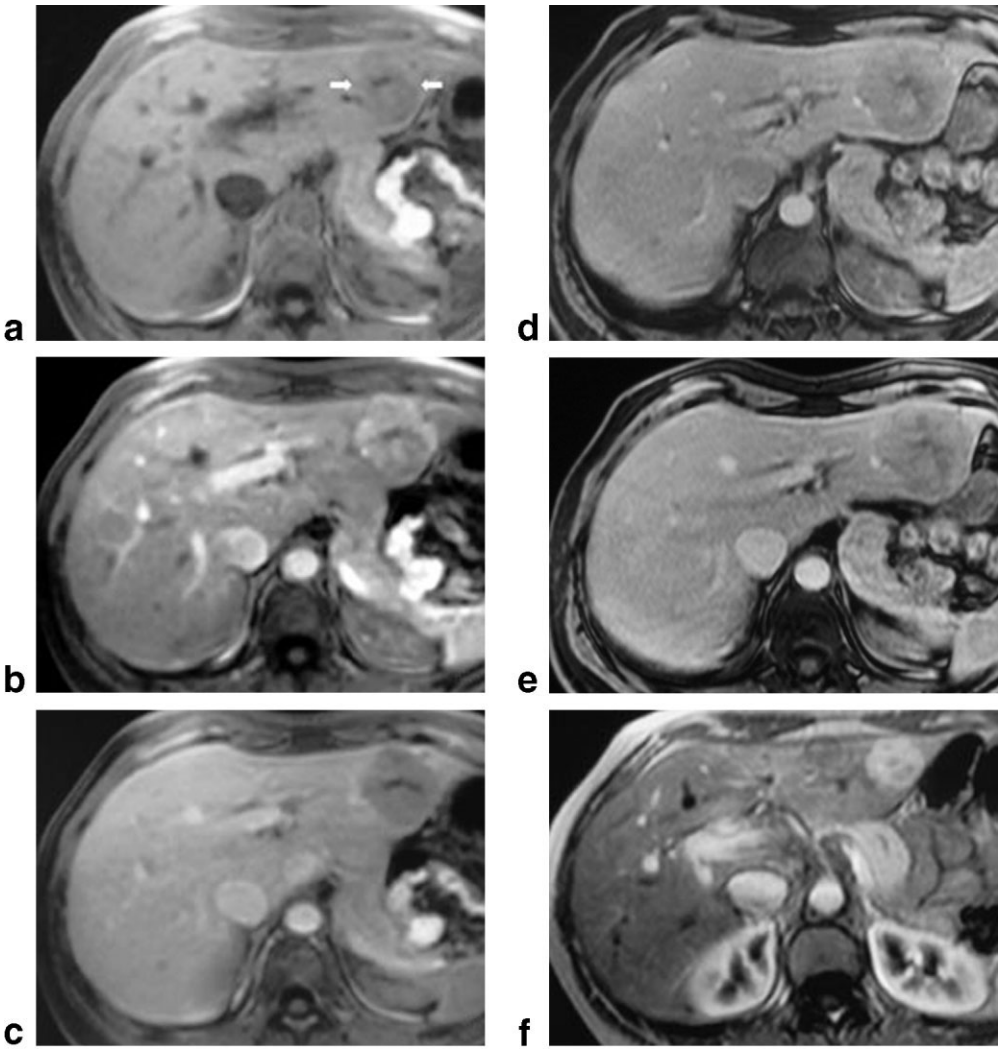

Figure 5. a–f: Focal nodular hyperplasia. On the precontrast VIBE sequence (a) a round well-defined, slightly hypointense nodule with a central hypointense scar is visible in the left lobe of the liver (arrows). During the arterial phase after 0.5 mL/sec of RESOVIST® (slow injection protocol) (b) the lesion shows discrete enhancement (score 2), with a rapid washout in the portal venous phase (c). Using a bolus of 2 mL/sec of RESOVIST® (fast injection protocol during the follow-up) (d) the nodule does not shows significant enhancement in the arterial phase (score 0). The lesion appears homogeneously slightly hypointense in the portal venous phase, except central scar (e). After Gd-BOPTA administration (1 year before) (f) in the arterial phase the lesion appears markedly homogeneously hyperintense.

RESULTS

No adverse effects were observed in any patients after RESOVIST® administration.

Reliability of Each Infusion Protocol

The results provided by each radiologist are shown in Table 1. The slow infusion protocol was tested in 43 patients with 61 hepatic lesions. Taking together scores 2–3 as diagnostic in recognizing nodule hypervascularity, 22–29 (minimum 15 + 7, maximum 21 + 8, and then about 42%) of the 61 liver lesions were identified with the slow protocol.

The fast infusion protocol was used in 40 patients with 51 hypervascular lesions. Considering together scores 2–3 as diagnostic in distinguishing the nodule hypervascularity, 6–9 (minimum 4 + 2, maximum 7 + 2, and then about 14.5%) of the 51 liver lesions were recognized with the fast protocol (Figs. 5a–e, 6a–e, and 7a–c).

The comparison of reliability indexes between the readers for each protocol is shown in Table 2. For the slow protocol the agreement was between 68.85% and 88.52%, the kappa between 0.57 and 0.84, and the ICC between 0.83 and 0.94. The fast protocol showed a lower reliability than the slow protocol, with agreement of between 64.71% and 84.31%, a kappa between 0.43 and 0.74, and an ICC between 0.74 and 0.88. The mean kappas and intraclass correlation coefficients were 0.55 and 0.80, and 0.67 and 0.87, for the fast and slow protocols, respectively.

Intraindividual Comparison

Twelve patients with 20 hypervascular nodules were examined with both slow and fast infusion protocols (Table 3). The distribution of the scores of the two protocols was statistically different ($P = 0.0004$ in the Wilcoxon test for paired data) as also shown in taking together scores 2–3 as diagnostic in recognizing nodule hypervascularity, 5 (25%) and 2 (10%) of the 20 liver lesions were identified with the slow and fast protocols, respectively.

The slow protocol showed values between 0 and 3 with an arithmetic mean of 1.1, whereas the fast protocol showed values between 0 and 2 with a median and arithmetic mean of 0.66.

At visual assessment the differences in the enhancement between the two protocols were equally evident in all histological types of lesions.

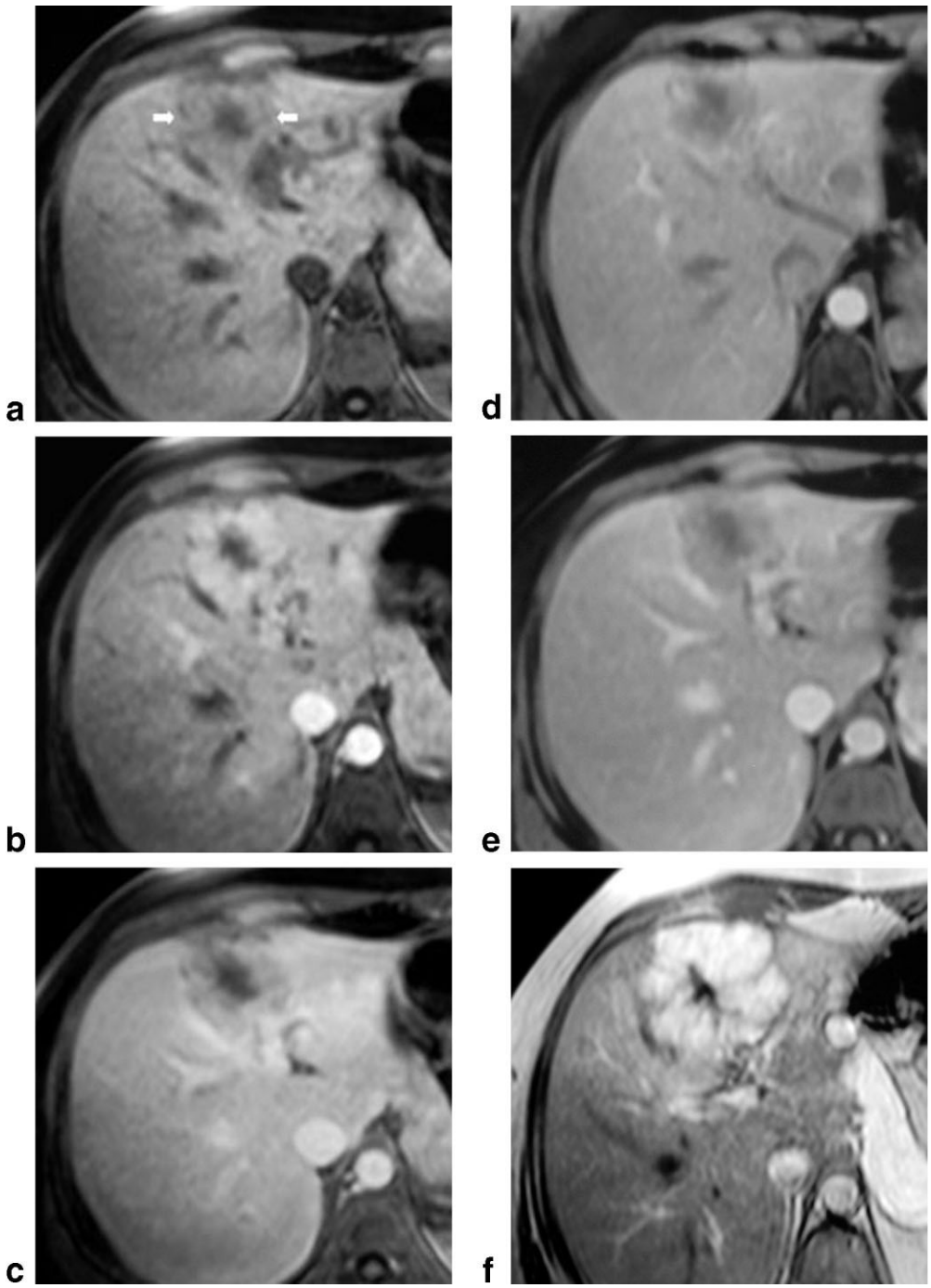

Figure 6. a–f: Focal nodular hyperplasia with large central scar. The precontrast VIBE sequence (a) reveals, in segment IV of the liver, a well-defined, slightly hypointense nodule (arrows) with a large hypointense central scar. During the arterial phase, using the slow injection protocol (0.5 mL/sec of RESOVIST®) (b), the nodule demonstrates discrete enhancement (score 2), and appears hypointense in the portal venous phase (c). Using the fast protocol (2 mL/sec of RESOVIST®, follow-up) in the arterial phase (d) a weak enhancement is visible within the lesion (score 1). The lesion appears hypointense in the portal venous phase (e). During the arterial phase after Gd-BOPTA administration (1 year after) (f) the nodule appears markedly hyperintense with a central hypointense scar.

DISCUSSION

RESOVIST® is a second-generation SPIO CA used for liver MRI studies because of its T2/T1 reliability and good biocompatibility.

According to the indexed literature (5,7,10), this CA demonstrates its effectiveness mainly in the delayed T2-weighted RES phase in which the extent of the signal drop is proportional to the amount and the activity of RES in both liver parenchyma and lesions. The lesion-to-liver parenchyma contrast difference may improve either detection and/or characterization capability (diagnostic performance) (15). Conversely, as reported, in clinical practice the arterial phase studies have not demonstrated a real effectiveness, especially in the evaluation of hypervascular lesions. Moreover the standard procedure of RESOVIST® administration with an empiric arterial time delay demonstrated poor reproducibility (16). This poor efficacy in comparison with the arterial enhancement provided by T1 agents appears to be mainly related to the low dose and rapid injection of RESOVIST®, which leads to a high concentration and short length of enhanced bolus. Since significant modification of the dose is not possible, in order to improve the T1 effect during the arterial phase we modified the bolus/length CA concentration (from 2.0 mL/sec in the classic fast protocol to 0.5 mL/sec in the new slow procedure).

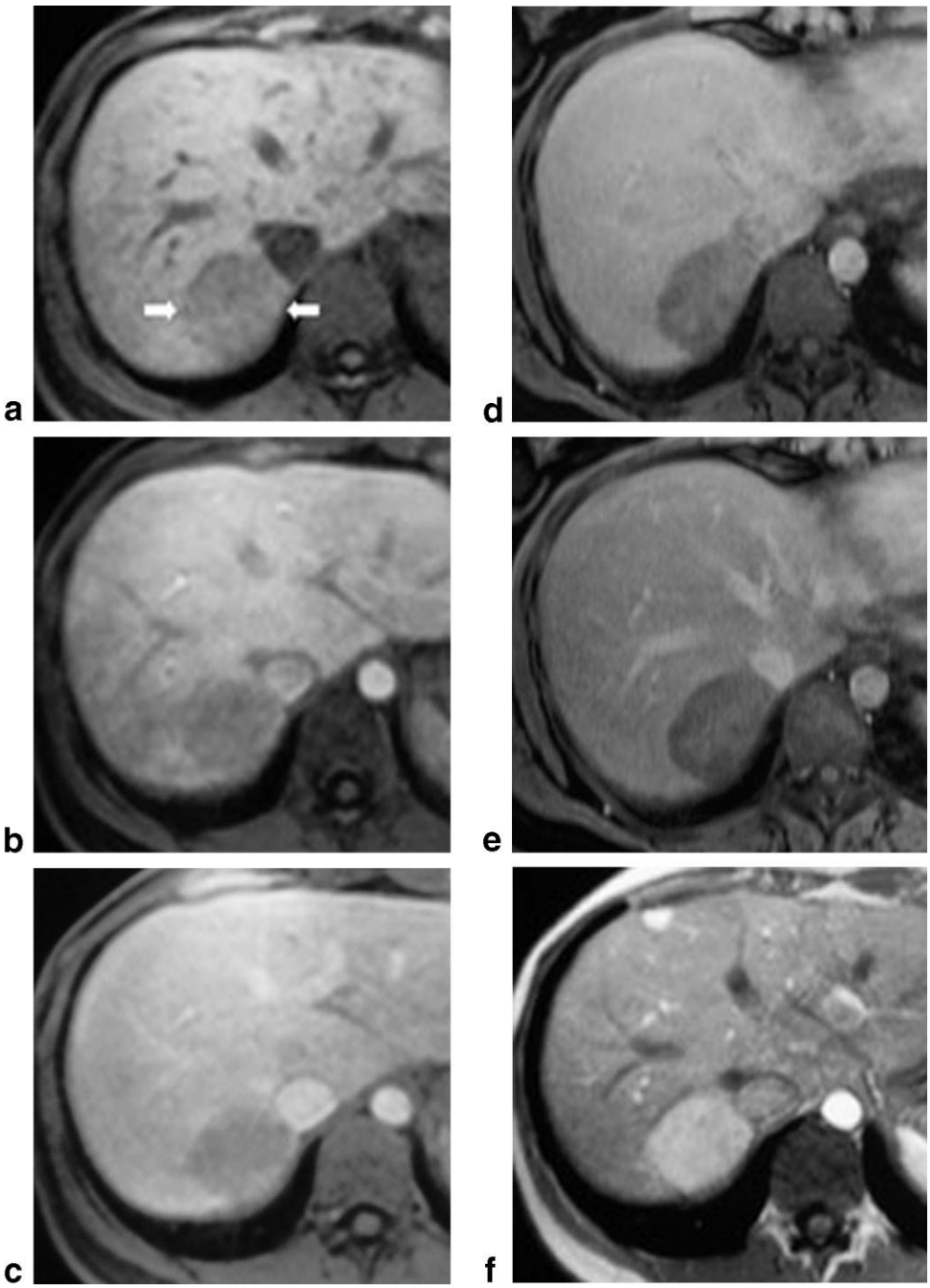

Figure 7. a–f: Hepatic adenoma. On the precontrast VIBE sequence (a) a round, well-defined, hypointense nodule located in the VII segment of the liver is detectable (arrows). After RESOVIST® administration, using the slow injection protocol (0.5 mL/sec of RESOVIST®), the nodule does not shows significant enhancement and appears hypointense in the arterial (b) and portal venous phases (c) (score 0). The same behavior can be observed using a bolus of 2 mL/sec of RESOVIST® (fast injection protocol) (d,e). Conversely, in the arterial phase after Gd-BOPTA administration (f) the lesion appears markedly and homogeneously hyperintense. Note a small markedly hyperintense FNH in the IV segment of the liver at the periphery.

The proposed modifications were based on theoretical considerations, synthetically reminded in the introduction. Although relaxivity is essentially independent of concentration, SPIO particles are not solely negative enhancers and they also influence T1 (7). This effect is improved by low concentration of SPIO particles, a strongly T1-weighted sequence (short TR/TE as in VIBE sequence) adoption, and surrounding the CA by many water molecules (7). Since the strongly T1-weighted sequence is the same for both protocols, lowering the CA SPIO concentration in a well-hydrated medium such as the blood results in a more pronounced T1 effect (17). Such an outcome is due to the so-called "dipole–dipole term" of the correlation time (Solomon–Bloembergen theory) (8,9). This effect is well explainable even without mathematic algorithms, in an intuitive way. When many large SPIO molecules are closely located they show a tendency to cluster, improving susceptibility effects and then T2* effects. On the contrary, the reduction in concentration (and/or the increase of water molecules) provides a greater rate of coordination between SPIO particles and water molecules: a single molecule slowly tumbling in the blood can reduce the T1 relaxation time of several water molecules, with T1 signal intensity improvement.

Table 2
Agreement Between Radiologists According to Protocol: Percent of Agreement

	Slow protocol	Fast protocol
Radiologist 1 vs. 2	% agreement = 68.85% K = 0.57 ICC = 0.83	% agreement = 68.63% K = 0.49 ICC = 0.77
Radiologist 1 vs. 3	% agreement = 88.52% K = 0.84 ICC = 0.94	% agreement = 84.31% K = 0.74 ICC = 0.88
Radiologist 2 vs. 3	% agreement = 70.49% K = 0.59 ICC = 0.83	% agreement = 64.71% K = 0.43 ICC = 0.74
Mean of the 3 comparisons	K = 0.67 ICC = 0.87	K = 0.55 ICC = 0.80

Cohen's kappa (K) and intraclass correlation coefficient (ICC).

Such an improvement is dependent on the ability of the water molecules to approach the CA center. If RESOVIST® is not clustered due to low concentration and high hydration, many water molecules are nearer to the superparamagnetic center and this improves T1 relaxation (8,9).

This effect seems not limited to the early phase. In fact, as the SPIO particles are taken up by the SRE in the liver, susceptibility/T2* effects due to clustering are increased. However, because the intrinsic T1 of a tissue is much longer than the intrinsic T2, the signal enhancement due to decreased T1 is more evident than the signal loss due to decreased T2 (7).

Our results confirmed the above-reported theoretical considerations. The slow infusion protocol significantly improved the artery phase enhancement. Considering as reference the enhancement obtained in all patients by previous MULTIHANCE® enhanced examination, the addition of the mean percentage of the diagnostically relevant scores (2: moderate; plus 3: intense enhancement), was ≈42% and 14.5% for the slow and fast infusion protocols, respectively. This improvement in percentage of diagnostically relevant enhancement determined by the slow protocol (almost 3 times more than the fast one) was confirmed by the intraindividual comparison (25% vs. 10%). Finally, considering the mean percentages of all nodules (61 of the slow and 51 of the fast protocol) with appreciable enhancement (scores 1 plus 2 plus 3), the percentages obtained were 78% and 50% for the slow and fast infusion protocols, respectively.

Table 3
Comparison of the Distribution of Arterial Phase Scores of the Slow and Fast Protocol in 20 Hypervascular Nodules

Arterial Phase scores	Slow protocol		Fast protocol	
	Frequency	%	Frequency	%
0	4	20	11	55
1	11	55	7	35
2	4	20	2	10
3	1	5	/	/
Total	20	100		100

Wilcoxon test for paired data: $P = 0.0004$.

Finally, this improved percentage of better enhancement does not seem related to a particular type of focal lesion; indeed, in our experience the superior results achievable by the slow protocol were appreciable in all histological types with the same evidence.

The agreement between each pair of radiologists was higher for the slow protocol than the fast protocol, with a mean Cohen's kappa statistic of 0.67 (good agreement) and 0.55 (fair agreement), respectively. Moreover, the slow protocol showed higher median and average values than the fast one when considering the 20 lesions evaluated with both techniques by the same reader. The better performance of the slow with respect to the fast protocol is probably due to the more pronounced T1 effect.

Our study has two main limitations. First, we did not perform any quantitative evaluation since our aim was to reproduce the routinely clinical practice, as stated in the introduction; therefore, we adopted only a qualitative visual assessment. The forthcoming second part of this prospective study will be performed quantitatively, on an ROI-based evaluation method. The second limitation is represented by the small number of lesions examined in the intraindividual comparison study. However, since our results clearly showed the better contrastographic efficacy of the slow protocol we considered it unethical to pursue the study merely in order to improve the statistical strength of our series.

Finally, our experience suggests the following key conclusions:

1) The arterial enhancement achievable by RESOVIST® administration even with the slow protocol is only rarely (12% of the presented nodules) comparable with the enhancement obtained with liver-specific gadolinium chelates, which generally ensures better conspicuity.
2) A qualitative analysis of the data obtained using the slow infusion protocol of RESOVIST® administration showed a better percentage of diagnostically relevant enhancement when compared to the classic fast protocol.
3) No additional cost or time is required for the slow infusion protocol.

In conclusion, if RESOVIST® is chosen as the CA for MR examination of the liver, the slow infusion protocol is to be preferred.

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