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Original article

MR mammography: influence of menstrual cycle on the dynamic contrast enhancement of fibrocystic disease

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Abstract. Magnetic resonance mammography (MRM) provides data regarding the nature of tumours based on contrast medium dynamics; fibrocystic changes in the breast, however, may lead to false-positive results. This study investigated whether the contrast medium dynamics of fibrocystic changes are dependent on the menstrual cycle. Twenty-four patients with palpable lumps but normal mammographies and ultrasound studies were examined. The MRM technique was performed during the first and second part of the menstrual cycle using a FLASH 3D sequence, both native and at 1, 2, 3 and 8 min after intravenous application of 0.15 mmol/kg body weight of gadodiamide. The calculated time–intensity curves were evaluated based on the following criteria: early percentage of contrast medium uptake in relation to the native value; formation of a plateau phenomenon after the second minute; the point of maximal contrast medium uptake; and calculation of the contrast enhancing index. During the second half of the menstrual cycle, a generally greater contrast medium uptake was observed. Nevertheless, when further diagnostic criteria, such as continuous contrast medium increase as a function of time, were considered, there was no increased rate of false-positive findings. The phase of the menstrual cycle may affect the specificity of the examination, if only the quantitative contrast medium uptake and the percentage of contrast medium uptake in the first 2 min are considered. A control MRM during the other half of the cycle may then be indicated and additional diagnostic criteria may improve specificity.

Key words: Breast – Parenchymal pattern – MR imaging – Contrast enhancement – MR mammography – Menstruation

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Introduction

Using MR mammography (MRM), the nature of a tumour is usually determined by observation of its contrast medium dynamics. It is known, however, that increased uptake of gadolinium complexes is characteristic not only of malignant but also of fibrocystic changes in the breast. In most cases this behaviour does not present problems in the differential diagnosis, because in fibrocystic changes and normal breast tissue generally little or no enhancement is noted with a delayed signal increase in time; nevertheless, it may lead to false-positive results, should a benign process exhibit uptake behaviour normally believed to be characteristic of carcinomas [1–4]. A tendency toward stronger and faster contrast enhancement was observed with an increasing degree of proliferation, but the differences between the enhancing dysplasias have not been proven to be sufficiently reliable in individual cases [4, 5]. In addition to the psychic stress, these patients may be subjected to unnecessary biopsies for what are actually benign changes. Similarly, in cases in which carcinoma is present, uptake in benign fibrocystic changes may suggest multifocality or multicentricity: such false-positive results, in turn, can lead to dire consequences for a patient in whom a breast-preserving surgical procedure had been planned.

As is known from conventional mammography, the most favourable time for an examination is during the first half of the menstrual cycle. Hormonal influence on imaging at MRM is thus expected and has been described in the literature [6–8].

The purpose of the present study was to investigate these influences with the objective of minimizing false-positive findings and of identifying the optimal time for performing MRM in premenopausal patients.

Materials and methods

Twenty-four patients (age range 26–47 years, mean age 39.0 years) who presented with a nodular irregular tex-

ture and a localized lump at palpation underwent MRM during both the first and second half of the menstrual cycle. All patients were premenopausal and were not taking any hormone preparations. In all cases current mammograms and sonographic findings showed no abnormalities.

Magnetic resonance mammography was performed in standard fashion. Contrast medium behaviour of the palpable lesions was studied and both series of examinations were compared. All patients underwent follow-up mammography after 12 months and ultrasound after 6 and 12 months.

All MRM examinations were performed using the Magnetom SP 63 (Siemens, Erlangen, Germany) at a field strength of 1.5 T.

Following informed consent and exclusion of contraindications, the patient was placed in the unit in prone position in order to reduce artefacts. Prior to MR mammography, the lump was marked using a capsule of glycerol nitrate (Nitrolingual, Pohl, Germany; bright signal on T2- and T1-weighted images) after palpation of the lump in knee–elbow position of the patient, thus simulating the position of the patient in the breast coil. Examination of the breasts was performed using commercially available bilateral breast surface coils. Firstly, T2-weighted axial images were acquired [spin-echo sequence: TE 103 ms, TR 6900 ms, 2 acquisitions, field of view (FOV) 350 mm, matrix 256 × 256, slice thickness 4 mm]. For the T1-weighted sequence and for the dynamic measurements, a GE sequence [fast low-angle shot (FLASH) 3D, TE 5 ms, TR 12 ms, flip angle 25°] was acquired native, as well as at 1, 2, 3 and 8 min after intravenous application of 0.15 mmol/kg body weight gadodiamide injection (Omniscan, Nycomed, Oslo, Norway). This 3D sequence was performed in 32 partitions, resulting in an effective slice thickness of 4 mm. An FOV of 350 mm was selected. Acquisition time for this sequence was 1 min, 3 s.

Injection of contrast medium was performed via a cubital vein (Braunüle 20 G) using an MR-Injector XD 7000 (H. C. Ulrich Medizintechnik, Ulm, Germany) at a flow rate of 3 ml/s. This injector consists of non-magnetic components and is driven by pressurized air. Furthermore, there is an automatic flushing function using physiological saline. Data acquisition in dynamic contrast-enhanced series was started simultaneously at the beginning of the injection.

All resulting 192 cross-sectional images (32 T2-weighted images, 160 T1-weighted images) were documented. For qualitative determination of contrast medium uptake, subtraction images were obtained by subtracting images acquired during the native series from those acquired 3 min after beginning contrast medium application at the same position. Increase in signal intensity as a function of time (mean curve) was calculated for structures with focal appearance after contrast medium application corresponding to the clinically suspected regions. Evaluation of findings was based on dynamic measurements yielding reproducible results at repeated examinations. The computer programs required for generation of subtraction images and signal intensity curves are part of the Magnetom SP (Siemens, Erlangen, Germany) 63's standard software.

Based on reports in the literature [2, 7, 9–13], the dynamic contrast medium uptake behaviour of the lesions was evaluated based of the following criteria:

Firstly, percentage of increase in signal intensity (SI) was calculated compared with precontrast SI in the first and second minutes after contrast medium application and at the time of maximal contrast enhancement. Secondly, percentage of signal intensity increase after the second minute was measured in comparison with the maximal contrast medium enhancement (same, greater, or less than 10 %; detection and height of the plateau formation. Thirdly, the position in time of maximal contrast medium enhancement (in the first, second, third or eighth minute) was evaluated.

These three criteria were integrated into the following point system:

1. Percentage of increase (first and second minute): 0–50 % increase in SI = 0 points; 50–100 % = 1 point; > 100 % = 2 points
2. Plateau phenomenon: > 10 % = 0 points; < 10 % = 2 points
3. Position of maximum: 8 min after application = 0 points; third minute = 1 point; first or second minute = 2 points; Evaluation: benign = 0–2 points; suspicious = 3 points; malignant = 4–6 points

Signal intensity as a contrast-enhancing index was calculated additionally for each lesion in order to permit interindividual comparison using the following formula:

$$E_{TU} = \frac{(SI_{TU,\,post\text{-}CM} - SI_{TU,\,pre\text{-}CM}) \times 100}{SI_{TU,pre\text{-}CM}}$$

where E is enhancement, TU is tumour, SI is signal intensity and CM is contrast media.

Results

Lesions were located in the left breast in 14 patients and in the right in 10 patients. The lesions ranged in size between 1.0 and 3.5 cm (median 1.6 cm). T2-weighted images revealed abnormal findings in the region of the marked lumps in none of the patients. Some small cysts (< 5 mm) within the normal breast parenchyma in 11 patients were classified as fibrocystic changes.

Based on the phase of the menstrual cycle, the marked lesions showed different contrast medium behaviour.

In 10 patients the marked lesions exhibited contrast medium uptake in both the first and second cycle halves. The degree of contrast enhancement differed quantitatively between cycle phases. In 5 patients each, nodules showed contrast enhancement during either the first or the second cycle halves, respectively, but not in both. In the remaining 4 patients, contrast medium enhancement

Table 1. Percent increase in signal intensity in relation to the phase of the menstrual cycle

	First minute	Second minute	Maximum
First half of cycle	0–97.8 (2.9 %) SD 45.5	0–271.7 (38.8 %) SD 99.3	0–345.7 (68.0 %) SD 104.7
Second half of cycle	0–298 (32.1 %) SD 96.3	0–405.3 (54.1 %) SD 168.4	0–523.3 (93.1 %) SD 198.3

Table 2. Point of maximal contrast medium uptake in relation to the phase of the menstrual cycle ($n = 24$)

	First half of cycle	Second half of cycle
No uptake	9	9
First minute	0	0
Second minute	1	0
Third minute	1	1
Eighth minute	13	14

in the breast was not observed in either the first or the second half of the menstrual cycle.

During the first half of the menstrual cycle, an average percentage of increase in signal intensity of 2.9 % in the first minute and 38.8 % in the second minute was observed. The average maximal increase in signal intensity was 68.0 %. In the second half of the cycle, average values of 32.1, 54.1 and 93.1 % for the first minute, second minute and for the maximum, respectively, were higher (Table 1).

Two of the fibrocystic diseases displayed increases in signal intensity in excess of 100 % during the first 2 min during the first cycle half; six fibrocystic diseases did so during the second cycle half.

The formation of a plateau phenomenon was observed three times during the first and twice during the second cycle half. In all other cases, the increase in signal intensity after the second minute exceeded 10 %.

Early maximum contrast enhancement during the first 3 min was observed in only 2 of 24 cases during the first cycle half and in only 1 of 24 patients during the second cycle half (Table 2).

Contrast-enhancing index

Comparison values were calculated in 12 lesions which showed contrast medium enhancement during both the first and second halves of the menstrual cycle. Values ranged from 1.0 to 3.46 (average 1.82) during the first half and from 0.83 to 5.23 (average 2.62) during the second half of the cycle.

Evaluation

Although 20 of the 24 fibrocystic changes showed more or less variable contrast medium dynamics in relation to the phase of the menstrual cycle, these differences led to a change in the patient's evaluation in only 2 cases. Four lesions exhibited contrast medium enhancement during neither the first nor the second cycle half; thus, fibrocystic changes in 22 patients were classified as benign based on results obtained during both cycle phases. Although in 11 patients there was an increase in signal intensity in excess of 100 % during either the first or second half of the menstrual cycle, the absence of the plateau phenomenon or the position of the maximal signal intensity increase in the eighth minute was decisive: both findings led to the evaluation of the lesion as benign. In only 2 cases were fibrocystic diseases classified as suspicious for malignancy during either the first or second cycle phase; these lesions, however, were classified as benign during the other respective cycle phase (Figs. 1, 2).

Discussion

As early as 1990, Fowler et al. published the first description of cycle-dependent changes in the breast observed at MRT [6]. This publication reported examinations on eight subjects who were studied through four to eight cycles. Fowler found that total breast and glandular volume, T1 relaxation time and water content were lowest between the sixth and fifteenth cycle days [6]. This study included MR tomographic examinations without contrast medium only, so data concerning dynamic measurements were not possible.

In light of the fact that the same time period is considered the best for conventional mammography, these results are not surprising. In 1995 the German Society for Roentgenology recommended that "if MRI of the breast is performed, it should, as with conventional mammography, be performed between the fifth and fifteenth cycle day" [14].

Based on experience with conventional mammography, this recommendation appears justified; however, we must point out that to date only few relevant reports have been published in the literature [7, 8]. Heywang reported that, in their collective using double examinations, two thirds of patients showed lower contrast medium uptake during the first cycle phase than during the second. The remaining third showed no significant difference between cycle halves (S. H. Heywang, unpublished data). Similarly, Müller-Schimpfle et al. found a significantly lower contrast medium uptake between days 7 and 20 of the menstrual cycle [8]; thus, at first glance it seems reasonable to adhere to the recommendation of the German Society for Roentgenology.

It must be taken into consideration that there are various possibilities besides technical and clinical parameters to evaluate the contrast medium uptake of suspicious lesions. The very question "What is malignant?" is given different answers by different authors [1–3, 12, 15–20]. In addition to the qualitative contrast medium uptake, various methods permit judgement of the percentage of quantity and influx velocity. For example, Gilles et al. consider every early contrast medium uptake corresponding to the arterial (aortic) uptake to be malignant [3]. Gribbestadt et al. consider a more than 70 %

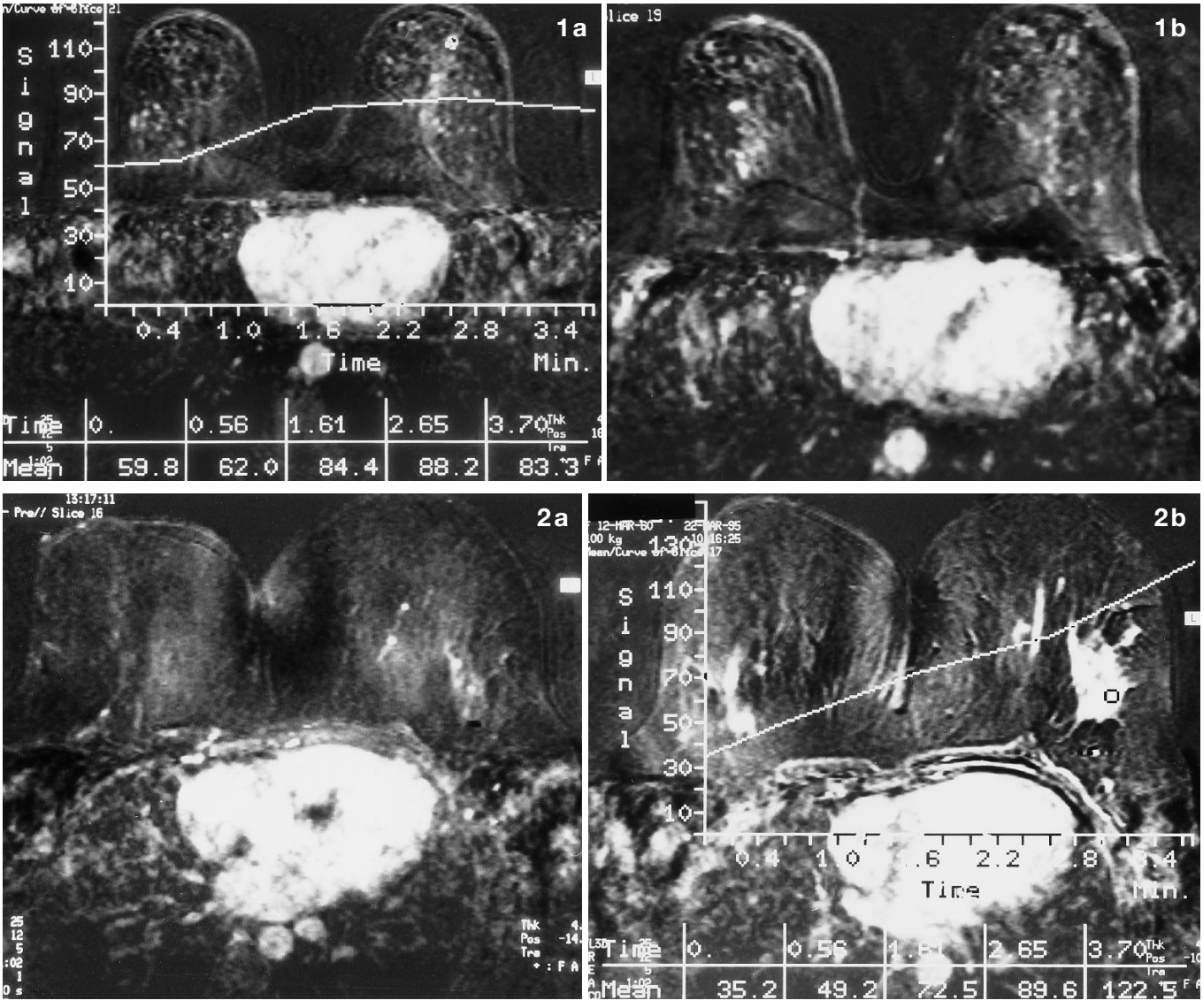

Fig. 1. a A 43-year-old patient with palpable lump in right axilla. During the first half of the cycle, the lesion's appearance is typical of malignancy. **b** Same patient as in **a**. During the second half of the cycle, there is no visible contrast medium uptake in the lesion

Fig. 2. a A 35-year-old patient with palpable lump in the left axilla. During the first half of the cycle, no significant contrast medium uptake. **b** Same patient as in **a**. During the second phase of the cycle, there is significant contrast enhancement. Increase in signal intensity is continuous and maximum enhancement is reached during the eighth minute without plateau formation. The maximal increase in signal intensity exceeded 100 %. Findings were suspicious for malignancy during neither the first nor the second half of the menstrual cycle

contrast medium uptake during the first minute to be suspicious [17]. Hickman et al. hold every early enhancement in excess of 100 % during the first 3 min and over 151 % in the third to seventh minutes to be suggestive of malignancy [21]. According to Kaiser, malignancy must be suspected in cases of contrast enhancement in excess of 90 % and a maximum during the first 2 min [12]. Fischer et al. evaluated, according to a point system with which percentage of enhancement of the lesion was measured, the formation of a plateau and the homogeneous or inhomogeneous contrast medium enhancement of a tumour [2]. Allgayer et al. defined every circumscribed area of contrast medium uptake with signal intensity greater than that of adipose tissue as requiring further investigation [1]. Heywang et al. first based their differentiation of malignant and benign tumours predominantly on morphological criteria and on the lower absolute contrast medium uptake of benign lesions in comparison with malignancies [10]. In later publications, Heywang-Köbrunner and Beck took into account the dynamic contrast medium behaviour of the tumours [4]. We present a score system has been proven to be reliable in the diagnosis of fibrocystic changes and invasive breast carcinomas (specificity 85.7 %, sensitivity 86.8 %) [20].

All authors agree that malignant lesions, in a large proportion of cases, show a high, early contrast medium influx (during the first 3 min), the formation of a plateau and a contrast medium "wash-out" phenomenon; the modifiers "high" and "early", however, are subject to differences in definition [2, 3, 11, 12, 15–21].

Although the higher percentage and absolute contrast medium enhancement in the second cycle phase suggest that pathological changes in fibrocystically enhanced glandular tissue might be obscured, and that this phenomenon could thus exert influence on the sensitivity of the method, it remains unknown to what degree this may compromise the technique's specificity.

By considering only the contrast medium pattern during the first 2 min, numerous false-positive results would be unavoidable; thus, it seems important not to take this as the only criterion for distinguishing benign from malignant changes. If we also take into consideration whether a continuous increase in contrast medium enhancement is present and thus review the configuration of the time–intensity curve, it would seem, as was the case in our collective, that we would be dealing with evaluations of fibrocystic changes of irrelevant divergence, even if these should happen to take up more contrast medium during the second cycle half than during the first. To explain this phenomenon, we must first consider the fact that, at our present stage of understanding, the formation of the typical "malignancy curve" is due to the tumour angiogenesis and to the disturbed permeability of the vascular walls [13, 22–24; E. F. Haran, unpublished data). An explanation for the lack of influence of the hormonal cycle on the formation of the plateau phenomenon and the point of maximum contrast medium enhancement must also be sought in the altered vascular permeability, although the vascularity apparently is subject to certain cycle-related variations.

The limitation of our study and the studies reported in the literature is the absence of histological classification of fibrocystic disease in these healthy patients [7, 8]. Mandatory histological proof was not justified in the reported patient population because of ethical reasons. According to Heywang-Köbrunner and Beck the degree of contrast enhancement of breast parenchyma seems to correlate with the degree of proliferative changes [4]. Gilles et al. confirmed previous published data in which contrast enhancement was reported in various benign lesions and especially those associated with proliferative fibrocystic disease [9].

One other aspect has not yet been addressed in the literature appears to be of great importance in arriving at a final conclusion. The differing contrast medium uptake in the glandular parenchyma in relation to the cycle day leads to formation of "transient" focal lesions; in other words, these lesions usually completely disappear during the other cycle half. Surprisingly, in our fibrocystic-changes group, we had 5 patients with contrast medium enhancement during the first, but not the second, cycle phase, as well as 5 patients in whom enhancement was observed during the second, but not the first, cycle half. This observation confirms findings reported by Kuhl et al. [7]. Based on this phenomenon, the suggestion that suspicious MRM findings in premenopausal patients should be confirmed by repeated examination during the other cycle half, regardless of whether this be the first or second cycle half, would be more consequential. This seems particularly justified in that it would spare patients unnecessary follow-up examinations at half-year intervals, which is associated with high psychic stress in these patients.

In summary, glandular tissue generally takes up contrast medium significantly more strongly during the second half of the menstrual cycle than during the first. This may obscure pathological changes; hence, the recommendation to examine premenopausal women during the first cycle half appears justified, so as not to compromise the sensitivity of the method. A large proportion of fibrocystic lesions showing contrast enhancement are "transient": in doubt, a repeat examination during the other cycle half may lead to clarification. Absence of contrast medium uptake may be observed in both the first and the second half of the menstrual cycle.

Despite the pronounced contrast medium uptake in fibrocystic lesions during the second cycle half, a higher proportion of false-positive findings may be avoided by considering further diagnostic criteria such as continuous contrast medium uptake as a function of time. The phase of the menstrual cycle may affect the specificity of the method, if the quantitative contrast medium uptake and the percentage of increase in contrast enhancement during the first 2 min are the only factors considered.

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