Predictors of Physiologic Variation in Normal Breast Parenchymal Contrast Enhancement: A Dynamic Contrast-enhanced MR Mammography Study in a Large Population-based Sample

**Poster No.:** C-0642  
**Congress:** ECR 2012  
**Type:** Scientific Exhibit  
**Authors:** K. Hegenscheid\(^1\), C. O. Schmidt\(^1\), R. Seipel\(^1\), R. Ohlinger\(^1\), R. Laqua\(^1\), J.-P. Kühn\(^1\), N. Hosten\(^1\), R. Puls\(^2\);  
\(^1\)Greifswald/DE,  
\(^2\)Insel Riems/DE  
**Keywords:** Haemodynamics / Flow dynamics, Normal variants, Contrast agent-intravenous, MR, Breast  
**DOI:** 10.1594/ecr2012/C-0642

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method ist strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.
Purpose

Background:

Dynamic magnetic resonance mammography (MRM) is the most sensitive method for detecting early invasive breast cancer, combining morphological information with functional characterization based on analysis of contrast enhancement kinetics of the breast (1). Especially with increasing use of MRM for screening of asymptomatic women at high risk for breast cancer, it is desirable to have comprehensive qualitative and quantitative data on morphological and kinetic features of the healthy breast from a large, unselected population of women. However, such studies are sparse (2) and limited to small study populations (3-5) or selection of symptomatic patients with examination of the contralateral "normal" breast (6-10). To our knowledge, no study evaluated contrast enhancement kinetics of normal breast parenchyma in women from a general population.

Therefore, the objectives of this study were:

1. To study baseline T1 signal intensity (BSI) and contrast enhancement (CE) kinetics of normal breast parenchyma in a large population-based cohort study using MRM, and
2. To identify predictors of their variability such as anthropometric measures, menopausal status, and hormone intake.
Methods and Materials

Study Population:

All women were consecutively enrolled in the Study of Health in Pomerania (SHIP), a prospective population-based cohort study in Northeast Germany (11). SHIP aims to estimate the prevalence and incidence of risk factors and diseases and to investigate the complex associations among risk factors, subclinical disorders, and diseases. Since 2008, whole-body MRI has been part of SHIP, including an optional MRM (12). Women with known allergies to any kind of contrast agent or drugs were excluded from MRI, as were pregnant or breastfeeding women.

Of 1475 female study participants, aged 20 to 83, who were enrolled in the MRI examination between June 2008 and September 2011, a total of 651 (44.1%) underwent MRM.

All women underwent a structured interview to obtain information on history of breast diseases, history of breast surgery including breast implants, menopausal status, day of the menstrual cycle, and medication history including postmenopausal hormone therapy (HT) and oral contraceptives (OC). Menopause was defined as cessation of menstrual bleeding for at least 12 months. Body height and weight were measured, and the body mass index (BMI) was calculated.

SHIP was approved by the institutional review board, and written informed consent was obtained from each participant prior to enrollment.

Inclusion and Exclusion Criteria:

Inclusion criteria for analysis of normal breast parenchyma were: females > 20 years.

Exclusion criteria were:

- history of recent or previous breast disease or history of breast surgery including breast implants (n=12),
- breasts with complete involution precluding measurement of representative parenchyma (n=68),
- breasts with mass lesions according to the BI-RADS MRI lexicon (n=97),
- perimenopausal women with cessation of menstrual bleeding for less than 12 months (n=15),
Because previous studies found a relationship between contrast enhancement and use of HT (7) and OC (4), these women (n=33, n=81) were also excluded.

Therefore, a total of 306 (47.0%) subjects were excluded from the analysis of anthropometric measures and menopausal status, resulting in a final study population of 345 women. For the analysis of the influence of hormone use groups of HT and OC users were compared with groups of non-HT and non-OC users.

Dynamic Contrast-enhanced MR Mammography Examination:

MR imaging was performed at 1.5 Tesla on a whole-body MR imager (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). An intravenous access was established, and the woman was placed prone with the uncompressed breasts suspended in a commercial circularly polarized bilateral breast phased-array receiver coil (Siemens AG Healthcare Sector, Erlangen, Germany). The protocol was identical for all participants and included axial dynamic, T1-weighted, time-resolved angiography with stochastic trajectories (TWIST) and three-dimensional imaging (8.86 / 4.51 [repetition time msec / echo time msec]; 25° flip angle; 340 mm field of view; 0.9 mm x 0.7 mm x 1.5 mm voxels). Following acquisition of the first unenhanced sequence, an intravenous gadobutrol bolus (Gadovist, Bayer Healthcare, Leverkusen, Germany) was administered with a power injector at a dose of 0.1 mmol/kg body weight at a rate of 1.0 mL/sec, followed by a saline flush (20 mL) injected at the same rate. The sequence was repeated five times without time gaps. Each sequence took 58.27 sec.

Quantitative Analysis of Baseline T1 Signal Intensity and Contrast Enhancement in Normal Breast Parenchyma:

First, images were postprocessed for quantitative analysis using the Syngo 2008A MultiModality Workplace (Siemens Medical Solutions, Erlangen, Germany). Image subtraction was done to identify any non-mass-like enhancement. To limit possible bias in the reproducibility of measurement resulting from variable repartitioning of fibroglandular tissue throughout the breast, measurements were performed in two slices above and two slices below the nipple, where breast tissue is usually constant and more homogeneous (6,7). Second, a region of interest (ROI) was drawn manually to include all fibroglandular tissue of the breast in the four slices selected, while excluding visible fat, cysts, or non-mass-like enhancement. Third, a time-signal intensity curve was created automatically for each ROI on a pixel-by-pixel basis representing mean values of T1 signal intensity (SI) and standard deviations for all dynamic frames. Percent contrast enhancement was calculated as 

\[ \frac{\text{SI}_{(t1-5)} - \text{SI}_{(t0)}}{\text{SI}_{(t0)}} \times 100, \]

where SI_{(t0)} is the signal intensity before and SI_{(t1-5)} after gadobutrol administration (6,7,10). To exclude interreader variability only one radiologist performed all readings.
**Statistical Analysis:**

Two-level random effects models (13) were applied to analyze BSI and CE, using the STATA xtmixed routine with six time points at level 1 and individuals at level 2. Regression model building was based on deviance tests. Restricted maximum likelihood estimates were applied to determine variance components of the model. A random intercept model strongly outperformed a model without random effects ($\chi^2=3701.63$, df=1: $p<0.001$), as did a linear time random slope model versus the random intercept model ($\chi^2=984.11$, df=1: $p<0.001$). An unstructured covariance matrix performed better than an independent matrix in the random slope model ($\chi^2=5.42$, df=1: $p=0.02$) and was therefore chosen.

All continuous variables were checked for nonlinear associations based on fractional polynomials (FPs) (14). Second-degree FPs were used with the following selection of power terms {-2,-1,-0.5,0,0.5,1,2,3}. Selection of powers was based on a cut-off at $\alpha=0.10$. Regarding our four continuous indicators, age, body weight, body mass index (BMI), and body height, linear models performed best and were used in the analyses.

Full maximum likelihood estimation was used to decide on the inclusion of fixed-effects terms into the models. In addition to time, which was included in all models, we used two sets of predictors: (1) age and the anthropometric measures height and weight, and (2) menopausal status.

To assess the robustness of our results regarding potential selection bias all analyses were repeated using statistical inverse probability weights.

A p-value <0.05 was considered statistically significant. Analysis was performed using STATA 12 (StataCorp LP, College Station, Texas, USA) and SPSS 15.0.1 (SPSS GmbH Software, Munich, Germany).
Results

Baseline T1 Signal Intensity:

BSI varied considerably across individuals with a mean of 167.73 ± 49.16 (standard deviation) and 175.86 ± 48.85 in the right and left breast, respectively. The initial mean difference in BSI of 8.14 was statistically significant, based on a paired t-test (p<0.001).

BSI increased linearly with age, body weight, and BMI (Figure 1, 2 and 3). BSI decreased linearly with body height, but this association was weaker and showed no significance (p=0.38). Age, body weight, and BMI effects were higher in postmenopausal women compared to premenopausal women as well (p<0.01). Postmenopausal status was associated with a significantly higher BSI in the single model but this effect ceased to be of relevance when including age in the full model (p=0.26).

Modeling Contrast Enhancement after Injection of Gadobutrol:

CE time courses, displayed separately for the right and left breast in Figure 4, showed a monotonous increase in SI over time that gradually leveled off. Because the time courses were similar in both breasts, we modeled the mean CE across both breasts in all further analyses.

Mean RCE was 8.07%, 13.78%, 18.23%, 22.14%, and 24.56% at 1, 2, 3, 4, and 5 min, respectively. However, RCE varied strongly across individuals (Figure 5).

Influence of Anthropometric Measures and Menopausal Status:

CE increased significantly with body weight (p<0.01, Figure 6). Additionally, women with higher BSI tended to have a higher CE slope. Age had minor effects on the time course when including menopausal status (p=0.68) and also within the strata of pre- and postmenopausal women (p=0.54).

CE of normal breast parenchyma was approximately 30% higher in premenopausal than in postmenopausal women (p< 0.001, Figure 7). Mean CE was 6.07%, 10.72%, 14.88%, 18.27%, and 20.27% in postmenopausal women and 11.51, 19.83, 25.54, 30.13, and 33.74 in premenopausal women at 1, 2, 3, 4, and 5 min after contrast, respectively.

Influence of Postmenopausal Hormone Therapy and Oral Contraceptives:
Before menopause, CE decreased significantly in OC users compared to non-OC users (p< 0.01, Figure 8). The largest change was observed between baseline and the first minute after contrast medium injection. After menopause, enhancement was similar in HT users and non-HT users (p= 0.94, Figure 8).
Fig. 1: Graph illustrates the strong association ($z=7.36$, $p=1.9\times10^{-13}$) between baseline T1 signal intensity (BSI) of unenhanced breast parenchyma and age calculated with a linear random effects model. The smallest BSI variance was observed at the age when women entered menopause. BSI was 68.2% higher for the eldest (81 years) compared to the youngest participant (22 years). Dark green line = mean values of T1 signal intensity, light green shaded area = 95% confidence interval.

© Diagnostic Radiology and Neuroradiology, Ernst-Moritz-Arndt University Greifswald, Ernst-Moritz-Arndt University Medical Center Greifswald - Greifswald/DE
Fig. 2: Graph illustrates the strong association (z=5.1, p=3.5exp-07) between baseline T1 signal intensity (BSI) of unenhanced breast parenchyma and body weight calculated with a linear random effects model. The smallest BSI variance was observed around the mean body weight of the sample. Only seven subjects weighted more than 100kg, explaining the large confidence interval in this range. BSI was 46.3% higher for the heaviest (121.5 kg) versus the lightest participant (47.7 kg). Dark green line = mean values of T1 signal intensity, light green shaded area = 95% confidence interval.
Fig. 3: Graph illustrates the strong association ($z=5.05$, $p=4.5\times10^{-7}$) between baseline T1 signal intensity (BSI) of unenhanced breast parenchyma and body mass index (BMI) calculated with a linear random effects model. The smallest BSI variance was observed for a BMI between 24 and 28 kg/m². Only 13 subjects had a BMI higher than 35, explaining the large confidence interval in this range. BSI was 36.7% higher for subjects with the highest BMI (40.6 m/kg²) versus subjects with the lowest BMI (18.3 m/kg²). Dark green line = mean values of T1 signal intensity, light green shaded area = 95% confidence interval.

© Diagnostic Radiology and Neuroradiology, Ernst-Moritz-Arndt University Greifswald, Ernst-Moritz-Arndt University Medical Center Greifswald - Greifswald/DE
Fig. 4: Graphs illustrate contrast enhancement (CE) (mean T1 signal intensity ± 95% confidence interval) of breast parenchyma 1-5min after injection of gadobutrol separately for the right and left breast calculated with a linear random effects model. CE was significantly lower in the right breast than in the left breast for all time points (p
Fig. 5: Graphs illustrate the variation of relative contrast enhancement (RCE) 1-5min after injection of gadobutrol in our sample. A single line displays the mean RCE within each quintile of the contrast enhancement distribution in our sample, as calculated from the random slope parameter. The graphs illustrate a substantial and statistically significant variation (Likelihood ratio $\chi^2=984.11$, df=2, $p=2.0\times 10^{-214}$). The mean increase for the lowest quintile after 5 min was 9.25% versus 47.43% in the highest quintile with 14.52%, 20.53%, and 28.29% for the 2nd to 4th quintiles.
Fig. 6: Graphs illustrate the strong association between contrast enhancement (CE) kinetics and body weight calculated with a linear random effects model. This interaction effect was statistically significant (Likelihood ratio $\chi^2=43.4$, df=5, $p=3.1\times10^{-8}$). CE (mean T1 signal intensity ± 95% confidence interval) increased significantly with body weight: the heavier the woman the steeper the increase. The relative increase was 16.6%, 20.9%, 24.7%, 28.1%, 31.1%, and 33.9%, after five minutes in women weighting 50, 60, 70, 80, 90, and 100 kg respectively. Women with higher BSI tended to have higher CE slopes.

© Diagnostic Radiology and Neuroradiology, Ernst-Moritz-Arndt University Greifswald, Ernst-Moritz-Arndt University Medical Center Greifswald - Greifswald/DE
Fig. 7: Graphs illustrate the strong association between contrast enhancement (CE) kinetics and menopausal status calculated with a linear random effects model. Premenopausal women showed a lower baseline T1 signal intensity ($z=7.00$, $p=2.5\times10^{-10}$), but a steeper CE (mean T1 signal intensity ± 95% confidence interval) (Likelihood ratio $\chi^2=48.6$, df=5, $p=2.7\times10^{-09}$) compared to postmenopausal women. The difference in slopes leveled off towards the end of the observation period.

© Diagnostic Radiology and Neuroradiology, Ernst-Moritz-Arndt University Greifswald, Ernst-Moritz-Arndt University Medical Center Greifswald - Greifswald/DE
Fig. 8: Graphs illustrate the variation in contrast enhancement 1 to 5 min after injection of gadobutrol in our sample as a function of use of oral contraceptives (OC) or postmenopausal hormone therapy (HT). In non-OC users mean RCE was 11.85%, 19.74%, 24.67%, 29.52%, and 32.79% at 1, 2, 3, 4, and 5 min, respectively. RCE decreased significantly (p< 0.01) with the use of OC to 8.11%, 16.09%, 22.50%, 25.92%, and 29.88%. In non-HT users mean RCE was 5.68%, 9.95%, 13.99%, 17.29%, and 19.16% and was only slightly higher (p= 0.94) with the use of HT: 6.74%, 11.65%, 16.80%, 20.96%, and 22.16%.

© Diagnostic Radiology and Neuroradiology, Ernst-Moritz-Arndt University Greifswald, Ernst-Moritz-Arndt University Medical Center Greifswald - Greifswald/DE
Conclusion

This prospective population-based study assessed contrast enhancement (CE) kinetics of normal breast parenchyma based on the analysis of 345 MRM datasets of healthy women from a general population cohort. Our results indicate that:

1. T1 baseline signal intensity (BSI) and CE of healthy breast parenchyma varied considerably across individuals from a population-based cohort.
2. Body weight and age were significant predictors of BSI, while body weight and menopausal status were significant predictors of CE kinetics.
3. Calculation of contrast medium dose on the basis of total body weight resulted in an increased CE with rising body weight.
4. CE of normal breast parenchyma is approximately 30% higher in premenopausal than in postmenopausal women.
5. Oral contraceptives (OC) in premenopausal women are associated with a significantly lower CE, while hormone therapy (HT) in postmenopausal women has negligible effects.

Therefore we conclude that:

1. When analyzing dynamic contrast kinetics curves of breast mass and non-mass lesions the impact of patient-related factors, especially menopausal status and body weight, on contrast enhancement should be considered precisely.
2. Determining contrast medium dose for breast MR imaging on the basis of total body weight should be reconsidered.
3. Discontinuation of postmenopausal hormone therapy or oral contraceptives prior to MRM does not seem to be necessary.
References


