Dose-Toxicity Relationship of Gadoxetate Disodium and Transient Severe Respiratory Motion Artifact

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OBJECTIVE. The purpose of this article is to determine whether there is a dose-toxicity relationship between gadoxetate disodium and transient severe respiratory motion artifact.

MATERIALS AND METHODS. Gadoxetate disodium–enhanced MRI studies (559 studies of 559 patients) using a fixed 20-mL (2 mL/s; $n = 112$) or 10-mL (1–2 mL/s; $n = 447$) volume at two health systems were included (dose range, 0.05–0.42 mL/kg; mean, 0.15 mL/kg; above-label dosing, 479 [86%]). Each dynamic phase was assigned a respiratory motion score from 1 (none) to 5 (nondiagnostic). Examinations with an unenhanced score of 1–2, arterial score of 4–5, and venous or late-dynamic scores of 1–3 were labeled as transient severe respiratory motion artifact. Stepwise multivariate logistic regression was performed.

RESULTS. The overall incidence of transient severe respiratory motion artifact was 12% (67/559; site 1, 15% [35/232]; site 2, 9.8% [32/327]). The administered volume of contrast material had a statistically significant effect (20 mL, 20% [22/112] vs 10 mL, 10%, [45/447]; multivariate $p = 0.01$; odds ratio, 2.1 [20 vs 10 mL]; 95% CI, 1.2–3.7). There was no dose-toxicity relationship for dose-by-weight ($p = 0.61$ [multivariate]) or above-label dosing ($p = 0.88$ [univariate]; 13% [10/80] rate for at- or below-label dosing vs 12% [57/479] rate for above-label dosing). Chronic obstructive pulmonary disease was the only non-dose-related predictor in the multivariate model ($p < 0.0001$; OR, 5.1 [95% CI, 2.5–11.5]; 39% [12/31] vs 10% [55/528]).

CONCLUSION. Gadoxetate disodium–associated transient severe respiratory motion artifact is significantly more common after 20-mL administration (2 mL/s) and occurs significantly more often in patients with chronic obstructive pulmonary disease. The volume-related effect suggests a nonallergiclike mechanism.

Keywords: artifact, complication, gadoxetate disodium, respiratory motion

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Gadoxetate disodium (Eovist, Bayer HealthCare) is a gadolinium-based contrast agent that was approved for use in the United States in 2008. It offers the ability to perform dynamic contrast-enhanced imaging in a fashion similar to that of extracellular gadolinium-based contrast agents, with the added advantage of hepatocyte-specific uptake that permits acquisition of a hepatobiliary phase imaging series 20 minutes after contrast material administration [1–3]. However, this agent recently has been associated with acute transient dyspnea, resulting in arterial phase image degradation, in a single-center prospective observational trial of 99 administrations of gadoxetate disodium and 99 administrations of gadobenate dimeglumine (MultiHance, Bracco Diagnostics) [4]. Because arterial phase imaging is often critical for liver lesion characterization [5–8], understanding the mechanism and prevalence of this phenomenon is important.

Gadoxetate disodium is approved at a dose that is one fourth that of most other gadolinium-based contrast agents on the market (0.025 mmol/kg [0.1 mL/kg] vs 0.1 mmol/kg), but it is often used off-label at higher doses to improve vascular and parenchymal enhancement and tumor-to-liver contrast [9–12]. Off-label dosing (i.e., higher than the dose recommended by the U.S. Food and Drug Administration [FDA]) is also used for pragmatic purposes because gadoxetate disodium is packaged in 10-mL vials. Off-label dosing was used in the aforementioned study describing the relationship between gadoxetate disodium and transient dyspnea [4]. It would be useful to know whether the adverse events and artifacts described in that report were related to the higher dose of contrast material and, if so, to determine wheth-

er the dose of contrast material contributed to the occurrence of this phenomenon. Such knowledge might allow mitigation of the event. It would also be useful to know whether certain cofactors affect the likelihood of its occurring. The null hypothesis of our study was that gadoxetate disodium–associated transient severe respiratory motion artifact is not mediated by dose. The purpose of our study was to determine whether there is a dose-toxicity relationship between gadoxetate disodium and transient severe respiratory motion artifact.

Materials and Methods

Before this investigation, institutional review board approval was obtained at both participating health systems. The study was performed in compliance with the HIPAA. Patient informed written consent was waived because of the retrospective nature of this study. No industry support was used. No patients included in this study have been previously reported.

Subjects

The study population was recruited retrospectively from two large academic health systems. The study population from site 1 (University of Michigan Health System) included all consecutive unique adult patients who underwent gadoxetate disodium–enhanced abdominal MRI for various indications using a fixed dose of either 10 or 20 mL from December 6, 2009, through March 31, 2011. Two hundred forty-one MRI examinations meeting inclusion criteria were identified through query of the electronic medical record system. Nine patients were excluded because of missing weight data ($n = 3$) and simultaneous administration of another gadolinium-based contrast agent ($n = 6$). This resulted in 232 patients ($n = 142$ men [mean age, 59 years; age range, 29–80 years]; $n = 90$ women [mean age, 56 years; age range, 23–85 years]) who underwent 232 gadoxetate disodium–enhanced abdominal MRI examinations ($n = 120$ received a fixed 10-mL dose; $n = 112$ received a fixed 20-mL dose).

The study population from site 2 (Duke University Medical Center) included all consecutive unique adult patients who underwent gadoxetate disodium–enhanced abdominal MRI for various indications using a fixed dose of 10 mL from September 4, 2012, through February 20, 2013. Three hundred twenty-seven MRI examinations meeting inclusion criteria were identified through query of the electronic medical record system. No patients were excluded because of missing weight data or simultaneous administration of another gadolinium-based contrast agent. The study population included 156 men (mean age, 57 years; age range, 19–82 years) and 171 women (mean age, 53 years; age range, 20–87 years).

The final combined study population from both sites included 559 patients ($n = 298$ men [mean age, 58 years; age range, 19–82 years]; $n = 261$ women [mean age, 54 years; age range, 20–87 years]) who underwent 559 gadoxetate disodium–enhanced abdominal MRI examinations ($n = 447$ received a fixed 10-mL dose; $n = 112$ received a fixed 20-mL dose). Both sites used fixed-volume dosing.

Patient Risk Factors

Covariates in addition to gadoxetate disodium dose that might predispose to developing transient severe respiratory motion artifact were recorded for each patient, including sex, age, body surface area, body mass index, weight, hepatitis, cirrhosis, chronic obstructive pulmonary disease (COPD), anxiety, obstructive sleep apnea, restrictive lung disease, allergy to gadolinium-based contrast material, volume of ascites, volume of pleural effusion, and MRI technologist performing the study. The model for end-stage liver disease (MELD) score was computed for patients with cirrhosis. The MRI technologist performing the study was analyzed as a covariate for site 1 to determine whether one or more technologists were inadvertently biasing patients toward or against the development of transient dyspnea. These data were not retrospectively available at site 2.

Non-imaging-based risk factors were recorded by blinded review (blinded to administered dose [by weight, not by volume, at site 2 because there was a fixed dose of 10 mL at site 2], dynamic contrast-enhanced imaging findings, and imaging-based patient risk factors) of the electronic medical record by one abdominal fellowship–trained radiologist at each site. Ascites and pleural effusions were identified and quantified through blinded image review (blinded to administered dose [by weight, not by volume, at site 2 because there was a fixed dose of 10 mL at site 2], dynamic contrast-enhanced imaging findings, and non-imaging-based patient risk factors) by one abdominal fellowship–trained radiologist at each site. Ascites and pleural effusions were scored on a qualitative scale of 0–3 (0 = absent, 1 = small, 2 = moderate, 3 = large).

Contrast Media

Gadoxetate disodium was administered IV at a fixed dose of either 20 mL ($n = 112$; site 1 only, December 6, 2009, through September 9, 2010, with no exceptions) or 10 mL ($n = 447$; site 1, September 10, 2010, through March 31, 2011, with three exceptions occurring in the 20-mL time period; site 2, entire study period). Off-label dosing (fixed doses of 10 or 20 mL) was used in an attempt to increase vascular and parenchymal enhancement and to improve tumor-to-liver contrast. The fixed dose of 20 mL used exclusively at site 1 was lowered to a fixed dose of 10 mL after statements by the FDA cautioned against using higher doses of gadolinium-based contrast media for concerns regarding nephrogenic systemic fibrosis. Four hundred seventy-nine of the 559 (86%) doses assessed in this study were above label (> 0.1 mL/kg; > 0.025 mmol/kg). Eighty doses (14%) were at or below label (≤ 0.1 mL/kg; ≤ 0.025 mmol/kg).

At site 1, each 10-mL dose of gadoxetate disodium was diluted with 10 mL of saline and was power-injected at a rate of 2 mL/s or was administered undiluted and power-injected at a rate of 1 mL/s. Each 20-mL dose of gadoxetate disodium was administered undiluted and power-injected at a rate of 2 mL/s. Each dose at site 1 was followed by an IV saline chaser of equivalent volume.

At site 2, each 10-mL dose of gadoxetate disodium was administered undiluted and power-injected at a rate of 2 mL/s. Each dose was followed by an IV saline chaser of 20 mL volume.

Image Acquisition

The acquisition parameters for the unenhanced and dynamic contrast-enhanced T1-weighted fat-saturated 3D gradient-echo imaging used at each site in this study are described in Table 1.

Imaging at site 1 was performed on a combination of 1.5- and 3-T magnets (LX Signa Excite 2 and LX Signa HD, both from GE Healthcare; Achieva XR and Ingenia, both from Philips Healthcare) using multichannel phased-array coils with eight, 16, and 32 channels. Each phase was acquired during breath-hold (end-inspiration without hyperventilation). A single arterial phase was used. Arterial phase timing was based on manual fluoroscopic (Philips Healthcare magnets) or automated (SmartPrep, GE Healthcare) contrast material bolus tracking. On the Philips Healthcare magnets, when contrast material arrival was detected within the proximal abdominal aorta according to visual inspection, the patient was instructed to hold his or her breath (without hyperventilation), and the arterial phase scan was initiated at approximately 7 seconds after contrast material detection. On the GE Healthcare magnets, an ROI was placed in the abdominal aorta at the level of the diaphragmatic crus. When contrast agent arrival was first detected within the ROI by the scanner, an 8-second delay was initiated, during which the patient was instructed to hold his or her breath (without hyperventilation) and after which the arterial phase scan was initiated.

Imaging at site 2 was performed on a combination of 1.5- and 3-T magnets (Avanto and Skyra,

TABLE 1: Protocol Details for the Unenhanced and Dynamic Contrast-Enhanced 3D T1-Weighted Spoiled Gradient-Echo Imaging Used for the Gadoxetate Disodium–Enhanced Liver MRI Examinations at Each Participating Site

Parameter	Unenhanced	Arterial[a]	Venous	Late Dynamic or Extracellular
Site 1				
TR/TE	3.6/1.3	3.6/1.3	3.6/1.3	3.6/1.3
FOV	Entire liver	Entire liver	Entire liver	Entire liver
Flip angle (°)	12	12	12	12
Matrix (frequency)	256–320	256–320	256–320	256–320
Matrix (phase)	128–192	128–192	128–192	128–192
Frequency direction	Right-to-left	Right-to-left	Right-to-left	Right-to-left
Section thickness (mm)	4	4	4	4
Receiver bandwidth (Hertz)	31.25–41.67	31.25–41.67	31.25–41.67	31.25–41.67
Parallel acceleration factor	2	2	2	2
Acquisition time (s)	18–22	18–22	18–22	18–22
Delay (s)	NA	20[b]	60–90	120–150
Site 2				
TR/TE	3.7–4.4/1.3–2.1	3.7–4.4/1.3–2.1	3.7–4.4/1.3–2.1	3.7–4.4/1.3–2.1
FOV	Entire liver	Entire liver	Entire liver	Entire liver
Flip angle (°)	9–12	9–12	9–12	9–12
Matrix (frequency)	256	256	256	256
Matrix (phase)	156–192	156–192	156–192	156–192
Frequency direction	Right-to-left	Right-to-left	Right-to-left	Right-to-left
Section thickness (mm)	4	4	4	4
Receiver bandwidth (Hertz/pixel)	400–500	400–500	400–500	400–500
Parallel acceleration factor	2 × 2	2 × 2	2 × 2	2 × 2
Acquisition time (s)	14	23	14	14
Delay (s)	NA	15–20	60–90	120–240

Note—NA = not applicable.

[a]Site 1 used a single arterial phase. Site 2 used three arterial phases. Protocol details for the three arterial phases used at site 2 are identical and listed here.

[b]This is an approximation. Arterial phase timing was based on fluoroscopic or automated contrast material bolus tracking.

both from Siemens Healthcare) using multichannel phased-array coils with 12 or 32 channels. Each of the unenhanced, venous, and late dynamic phases was acquired during breath-hold (end-inspiration without hyperventilation). A triple arterial phase was used, where three complete arterial phases were acquired in succession during a single breath-hold. The first arterial phase was acquired at a standard time of 15 seconds after the initiation of contrast media injection for patients younger than 65 years or 20 seconds after the initiation of contrast media injection for patients 65 years old or older. Breath-holding was begun immediately before image acquisition without hyperventilation. Because the acquisition time for each arterial phase was 7.5 seconds, the second arterial phase was obtained at 22.5 or 27.5 seconds after injection, and the third arterial phase was obtained at 30 or 35 seconds after injection, depending on patient age. To achieve a total acquisition time of 23 seconds for the three arterial phases while maintaining sequence parameters identical to those of the other dynamic phases, use partial Fourier undersampling.

Image Analysis

Each phase of dynamic T1-weighted imaging (unenhanced, arterial, venous, and late dynamic) was reviewed by a blinded (blinded to administered dose [by weight and volume at site 1 and by weight at site 2, which used a single fixed volume] and non-imaging-based risk factors) abdominal fellowship–trained radiologist at each site and was assigned a respiratory motion artifact score on a scale of 1 (no respiratory motion) to 5 (nondiagnostic because of respiratory motion). This task was shown to have high interrater repeatability in a prior study [4]. For examinations obtained at site 2, each arterial phase was evaluated individually, and the highest motion score recorded for any of the three arterial phases was considered to be the overall arterial score. The following scale was derived from that study [4]: 1, no respiratory motion artifact; 2, minimal respiratory motion artifact with no effect on diagnostic quality; 3, moderate respiratory motion artifact with some but no severe effect on diagnostic quality; 4, severe respiratory motion artifact but images still interpretable; and 5, extensive respiratory motion artifact and images nondiagnostic. Gadoxetate disodium administrations associated with an unenhanced score of 1–2, an arterial score of 4–5, and venous or late-dynamic scores of 1–3 were considered to be exhibiting transient severe respiratory motion artifact. A score of 1–2 (instead of 1–3) was mandated for the unenhanced phase to ensure that there was minimal or no respiratory motion artifact before contrast material administration. Transient severe respiratory motion artifact was not based on a direct evaluation of patient symptoms (as was done prospectively in a prior study [4]) but was indirectly assigned on the basis of imaging findings consistent with respiratory motion artifact.

Statistical Analysis

Continuous variables (e.g., age, weight, body mass index, body surface area, MELD score, and dose in milliliters per kilogram) are summarized using means and ranges. Categoric data (e.g., patient sex, other diseases, ascites or pleural effusions, MRI technologist, fixed dosing [milliliters], and above-label dosing) are presented as counts and percentages. The incidence of transient severe respiratory motion artifact was compared between subgroups in this study, as well as overall to a previously reported incidence [4], using chi-square tests.

To account for the possibility that a site bias may have existed with respect to grading motion artifact (only site 1 had 20-mL dosing), one study author from site 2 traveled to site 1 (after institutional review board approval) and read all site 1 data in a blinded fashion (blinded to dose and clinical history) without assistance using the same methods. Motion scores were compared by phase between this reader and the primary site 1 reader using three methods: McNemar test (to compare assigned rates of transient severe respiratory motion artifact), descriptive statistics (to compare

mean motion scores assigned by phase), and intraclass correlation coefficients (ICCs; to compare assigned motion scores in each phase by patient). Site was also incorporated into the multivariate model (with image reviews blinded to dose), and the rate of transient severe respiratory motion artifact for 10-mL dosing at each site by their respective readers (site 1 vs site 2) was compared with a chi-square test.

Univariate logistic regression analysis was performed to assess the effects of each covariate on the occurrence of transient severe respiratory motion artifact. Stepwise multivariate logistic regression analyses were used to test the effect of significant predictors in the presence of other factors. Although the primary analysis was performed with site 1 and site 2 data combined, a secondary analysis was also performed on site 1 data alone (only site 1 had 20-mL dosing). Univariate results with $p < 0.15$ were included in the final multivariate models. A p value of 0.05 or smaller was considered significant for all hypothesis tests. Odds ratios (ORs) and 95% CIs were calculated to compare the odds of transient severe respiratory motion artifact between groups. Statistical tests were performed using statistical software (SPSS version 21, IBM).

Results

The overall rate of transient severe respiratory motion artifact was 12% (67/559; site 1, 15% [35/232]; site 2, 9.8% [32/327]). The aggregate rate was less than what has been previously reported (17% [17/99]) [4], but this difference was not statistically significant ($p = 0.21$). There was substantial agreement between readers for motion score assignment during data validation with site 1 data (n = 232 patients; mean motion scores by phase: unenhanced, 2.1 ± 0.7 vs 1.7 ± 0.6 [ICC, 0.67]; arterial, 2.7 ± 1.1 vs 2.6 ± 1.1 [ICC, 0.90]; venous, 2.2 ± 0.7 vs 1.9 ± 0.7 [ICC, 0.78]; late dynamic, 2.2 ± 0.8 vs 1.9 ± 0.8 [ICC, 0.80]). The incidences of perceived severe transient respiratory motion artifact in the site 1 data were 15% (35/232) and 17% (40/232) for the two blinded readers, respectively ($p = 0.41$).

The details of the overall study population (n = 559) and the subpopulation that developed transient severe respiratory motion artifact (n = 67) are outlined in Table 2. Patient age ($p = 0.60$), patient weight ($p = 0.14$), viral hepatitis ($p = 0.82$), cirrhosis ($p = 0.65$), anxiety ($p = 0.56$), asthma ($p = 0.47$), obstructive sleep apnea ($p = 0.20$), restrictive lung disease ($p = 0.16$), allergy to gadolinium-based contrast media ($p = 0.99$), volume of ascites (p = 0.20–0.86), volume of pleural effusion (p = 0.40–0.95), MRI technologist performing each study ($p = 0.99$), study site (p = 0.06), dose-by-weight ($p = 0.12$), and above-label dosing ($p = 0.88$) were not statistically significant univariate predictors of transient severe respiratory motion artifact. Patient sex ($p = 0.03$), body surface area ($p = 0.03$), body mass index ($p = 0.05$), COPD ($p < 0.0001$), and dose-by-volume ($p = 0.006$) were statistically significant univariate predictors of transient severe respiratory motion artifact.

The majority of administrations were above label (86% [479/559] overall; 85% [57/67] in the transient severe respiratory motion artifact subpopulation), but the transient severe respiratory motion artifact rate was similar for at- or below-label and above-label administrations (13% [10/80] vs 12% [57/479]; $p = 0.88$). The mean dose of gadoxetate disodium was 0.15 mL/kg in the overall population and 0.16 mL/kg in the transient severe respiratory motion artifact subpopulation. This is 50% and 60% greater, respectively, than the FDA-approved dose of 0.10 mL/kg. The mean dose in the 10-mL population (n = 447) was 0.13 mL/kg (range, 0.05–0.24 mL/kg), and the mean dose in the 20-mL population (n = 112) was 0.23 mL/kg (range, 0.13–0.42 mL/kg).

Stepwise multivariate logistic regression found that transient severe respiratory motion artifact was statistically significantly affected by the administered volume of gadoxetate disodium ($p = 0.01$; OR, 2.1 [20 mL vs 10 mL]; 95% CI, 1.2–3.7) and the presence of COPD ($p < 0.0001$; OR, 5.1; 95% CI, 2.5–11.5) (Table 3) . The odds of transient severe respiratory motion artifact occurring was approximately twice as likely in the 20 mL group versus the 10 mL group (OR, 2.1), which nearly matched the observed rate (20-mL incidence of 20% [22/112] vs 10-mL incidence of 10% [45/447]). No significant relationship was found for dose-by-weight ($p = 0.61$), study site ($p = 0.96$), patient sex ($p = 0.86$), body surface area ($p = 0.42$), body mass index ($p = 0.12$), or patient weight ($p = 0.41$).

The rate of transient severe respiratory motion artifact for 10-mL dosing was not significantly different between sites (11% [13/120] for site 1 vs 10% [32/327] for site 2; $p = 0.73$). When site 1 data were considered alone, there was a univariate trend toward significance for administered volume in milliliters ($p = 0.06$), but this remained nonsignificant on multivariate assessment (p = 0.09), likely because of insufficient power.

Of the 31 patients with COPD, 12 (39%) developed transient severe respiratory motion artifact. This is in contrast to a 10% (55/528) transient severe respiratory motion artifact rate in patients without COPD. The transient severe respiratory motion artifact rate was 39% (7/18) among patients with COPD at site 1 (vs 13% [28/214] without COPD at site 1) and 38% (5/13) among patients with COPD at site 2 (vs 8.6% [27/314] without COPD at site 2). The transient severe respiratory motion artifact rates for patients with COPD between sites was not statistically different ($p = 0.73$). Asthma (also an obstructive lung disease) was not found to be a significant predictor ($p = 0.47$). There were 24 patients in the study with a diagnosis of asthma (four of whom developed transient severe respiratory motion artifact [17%]).

Discussion

The principal finding of this study is that gadoxetate disodium–associated transient severe respiratory motion artifact is significantly affected by the administered volume, with a higher off-label administered volume (20-mL fixed dose at 2 mL/s) being associated with a significant increase in the observed rate ($p = 0.01$; OR, 2.1 [20 mL vs 10 mL]; 95% CI, 1.2–3.7). Patients administered a 20-mL dose were approximately twice as likely to develop transient severe respiratory motion artifact compared with patients administered a 10-mL dose (20% [22/112] vs 10% [45/447], respectively). However, transient severe respiratory motion artifact was not related to dose-by-weight ($p = 0.61$) or above-label dosing ($p = 0.88$) in our multivariate analysis. This indicates that the patient's weight is not relevant to the occurrence of the artifact; only the injected volume has an independent role. This conclusion is supported by the wide range of doses assessed in our study (50–420% of the FDA-approved dose) and our large (n = 559 patients) multicenter study design. However, 20-mL doses are not currently used at most centers, even those centers that use higher-than-FDA dosing [4, 9, 10], and volume reduction alone is not likely to eliminate the artifact within the range of clinically administered doses. For example, the transient severe respiratory motion artifact rate was still 13% [10/80] for at- or below-label administrations (vs 12% [57/479] for above-label administrations; $p = 0.88$).

The incidence of transient severe respiratory motion artifact in our study (12% [67/559]) was lower than what has been previously reported (17% [17/99]; $p = 0.21$) [4]. This is, in part, the result of differenc-

TABLE 2: Combined Study Population Details From Site 1 and Site 2

Variable	Overall Population (*n* = 559)	Population With New Severe Arterial Phase Motion Artifact (*n* = 67 [12%])	Population Without New Severe Arterial Phase Motion Artifact (*n* = 492 [88%])	*p*
Demographics				
Age (y), mean ± SEM (range)	56 ± 0.55 (19–87)	57 ± 1.72 (19–84)	56 ± 0.01 (20–87)	0.60
Sex				0.03[a]
Male	298 (53)	41 (61)	257 (52)	
Female	261 (47)	26 (39)	235 (48)	
Body surface area (m^2), mean ± SEM (range)	2.53 ± 0.02 (1.41–3.83)	2.41 ± 0.06 (1.49–3.63)	2.57 ± 0.03 (1.41–3.83)	0.03[a]
Body mass index, mean ± SEM (range)	29 ± 0.28 (16–70)	30 ± 1.03 (19–70)	28 ± 0.28 (16–55)	0.05[a]
Weight (kg), mean ± SEM (range)	85 ± 0.90 (42–197)	88 ± 3.10 (48–197)	84 ± 0.92 (42–163)	0.14[a]
Patient clinical characteristics				
Viral hepatitis	185 (33)	23 (34)	162 (33)	0.82
Cirrhosis	294 (53)	37 (55)	257 (52)	0.65
MELD score, median (range)	10 (6–23)	9 (6–15)	10 (6–23)	NA
Anxiety	34 (6)	3 (4)	31 (6)	0.56
Asthma	24 (4)	4 (6)	20 (4)	0.47
COPD	31 (6)	12 (18)	19 (3.9)	< 0.0001[a]
Obstructive sleep apnea	31 (6)	6 (9)	25 (5)	0.20
Restrictive lung disease	2 (0.4)	1 (1)	1 (0.2)	0.16
Allergy to gadolinium-based contrast agent	4 (0.7)	0 (0)	4 (0.8)	0.99
Imaging findings				
Mild ascites	96 (17)	12 (18)	84 (17)	0.86
Moderate ascites	27 (5)	1 (1)	26 (5)	0.20
Severe ascites	12 (2)	2 (3)	10 (2)	0.62
Any small pleural effusion	47 (8)	9 (13)	38 (8)	0.40
Any moderate or large pleural effusion	8 (1.4)	1 (1.5)	7 (1.4)	0.95
Dose and scan information				
Site				0.06[a]
Site 1	232 (42)	35 (52)	197 (40)	
Site 2	327 (58)	32 (48)	295 (60)	
No. of MRI technologists (site 1 only)	35	7	34	0.99
Dose				0.006[a]
10 mL	447 (80)	45 (67)	402 (82)	
20 mL	112 (20)	22 (33)	90 (18)	
Dose (mL/kg), mean ± SEM (range)	0.15 ± 0.00 (0.05–0.42)	0.16 ± 0.00 (0.05–0.39)	0.15 ± 0.00 (0.06–0.42)	0.12[a]
Dose (mmol/kg), mean ± SEM (range)	0.04 ± 0.00 (0.01–0.11)	0.04 ± 0.00 (0.01–0.10)	0.04 ± 0.00 (0.02–0.10)	
At or below FDA-labeled dose	80 (14)	10 (15)	70 (14)	0.88
Above-label dose (> 0.025 mmol/kg)	479 (86)	57 (85)	422 (86)	

Note—Except where noted otherwise, data are number (%). *p* values refer to univariate logistic analyses for each of the independent factors treating transient severe respiratory motion artifact as the primary outcome measure. SEM = standard error of the mean (shown for data with normal distributions), MELD = model for end-stage liver disease (range, 6–40; exception points for hepatocellular carcinoma are not included in this calculation), COPD = chronic obstructive pulmonary disease, NA = not applicable, FDA = U.S. Food and Drug Administration.

[a]Variable was included in multivariate analysis.

es in incidence between the two sites of our study. Although not statistically significant ($p = 0.09$), there was a lower rate of transient severe respiratory motion artifact at site 2 (9.8% [32/327]) than at site 1 (15% [35/232]). This likely relates to a combination of administered volume ($n = 112$ doses at site 1 were 20 mL), as well as the different arterial phase acquisition parameters used at each site. Site 2 used three arterial phases, and site 1 used a single arterial phase. More rapid arterial phase sequence acquisition at

TABLE 3: Multivariate Logistic Analysis Treating Transient Severe Respiratory Motion Artifact as the Primary Outcome Measure

Variable	Multivariate *p*	Odds Ratio	95% CI	
			Low	High
Demographics				
Sex (male vs female)	0.86	—	—	—
Body surface area (m^2)	0.42	—	—	—
Body mass index	0.12	—	—	—
Weight (kg)	0.41	—	—	—
Chronic obstructive pulmonary disease	< 0.0001[a]	5.1	2.5	11.5
Dose and scan information				
Site 1 vs site 2	0.96	—	—	—
Dose (20 mL vs 10 mL)	0.01[a]	2.1	1.2	3.7
Dose (mL/kg)	0.61	—	—	—

Notes—Covariates with a univariate $p < 0.15$ were included in the stepwise multivariate analysis. Dashes indicate not applicable.

[a]Statistically significant in the final model ($p < 0.05$).

site 2 might have reduced the time each sequence was exposed to respiratory motion and thereby reduced the incidence of transient severe respiratory motion artifact. If true, this could be a generalizable strategy to mitigate this problem.

However, the rate of severe transient respiratory motion artifact with 10-mL dosing was not significantly different between site 1 and site 2 ($p = 0.73$). This is notable because it argues against the presence of a site bias (e.g., technical differences in image acquisition when all arterial phases are considered together) and against the influence of injection rate (site 2 used a higher effective injection rate for 10-mL doses). If the 2 mL/s injection rate for 20-mL dosing was the primary explanation for our findings, we would have expected a significantly higher rate of severe transient respiratory motion artifact for 10-mL dosing at site 2 (2 mL/s) compared with site 1 (1 mL/s [undiluted] or 2 mL/s [diluted]).

COPD was the only patient-related covariate shown to significantly increase the likelihood of transient severe respiratory motion artifact occurring after gadoxetate disodium administration ($p < 0.0001$; OR, 5.1). The artifact was observed in 39% (12/31) of those with a clinical diagnosis of COPD and in 10% (55/528) of those without it. This strong relationship was observed in nearly identical fashion at both sites and provides interesting indirect evidence regarding the mechanism of this phenomenon. Because of the altered lung mechanics characteristic of COPD, it is particularly difficult for patients with COPD, when tachypneic, to fully exhale their inspired volume [13–18]. Tachypnea in this setting leads to increased air trapping and progressive pulmonary impairment (i.e., dynamic hyperinflation) [13–18]. A cyclic physiologic response to tachypnea in patients with COPD may be an explanation for the marked transient respiratory motion that is so prevalent in this subpopulation. If transient severe respiratory motion artifact related to gadoxetate disodium is fundamentally transient tachypnea, patients with COPD would be expected to be more adversely affected than the general population (even if the incidence of contrast agent–mediated transient tachypnea in both populations were the same). It is unlikely that COPD itself (irrespective of the contrast material) is an explanation for this finding. If COPD were the sole explanation, we would have expected the severe respiratory motion to have propagated through all phases and not be isolated to the arterial phase alone.

The cause of gadoxetate disodium–mediated transient severe respiratory motion artifact is unknown. Bronchospasm, which is one possible cause, seems less likely given that patients with asthma in our study group were not at particular risk ($p = 0.47$). Alternatives include CNS-mediated tachypnea and cardiac-mediated tachypnea. Our data are not equipped to investigate these possibilities. However, the administered volume effect we observed for this adverse event lends support for a physiologic (i.e., nonallergiclike) mechanism. Physiologic reactions to contrast media are typically dose or concentration dependent, whereas allergiclike reactions are not [19].

Most covariates we studied were not related to the incidence of transient severe respiratory motion artifact, including cirrhosis, degree of cirrhosis, MELD score, volume of ascites, volume of pleural effusions, and many others. Gadoxetate disodium–associated transient severe respiratory motion artifact does not appear to be related to the presence or severity of underlying liver disease.

Because the original study associating gadoxetate disodium with acute transient dyspnea was a single-center observational trial [4], it raised the possibility that one or more technologists at that location were sensitized to the concern regarding dyspnea and may have "primed" or "coached" patients to exhibit this finding. Neither study site ($p = 0.96$) nor MRI technologist ($p = 0.99$) was a significant predictor of transient severe respiratory motion artifact in our multivariate model. Therefore, it is unlikely that any individual (or group of) MRI technologists was driving the occurrence of this phenomenon in our study.

There were several limitations of our study. It was retrospective, and some of the covariates we assessed are subject to the challenges of a retrospective chart review. Only site 1 used 20-mL dosing, raising the possibility of a site bias. We accounted for this using several methods, including data validation by a reader from site 2 reviewing site 1 data (with substantial agreement between assigned scores), blinding readers to the administered dose, using nearly identical rates of severe transient respiratory motion artifact at the 10-mL dose for site 1 and site 2 ($p = 0.73$), evaluating site 1 data independently (showing similar trends in the data), and incorporating study site into our multivariate model ($p = 0.96$). We did not include a control group of patients who did not receive gadoxetate disodium, but the rate of transient severe respiratory motion artifact was similar to that ($p = 0.21$) of another study that did include a control group [4]. In addition, we did not assess the diagnostic impact of transient severe respiratory motion artifact on image interpretation. The purpose of this study was to establish whether the event rate was affected by the administered dose. We did not directly assess patient symptoms (as was done previously [4]). The primary outcome was determined on the basis of respiratory motion artifact. Adequate pulmonary function testing was not available for the majority of patients with lung diseases and therefore could not be incorporated into our analysis.

In conclusion, gadoxetate disodium–associated transient severe respiratory motion artifact is significantly more common after 20-mL administrations (2 mL/s), is independent of patient weight, and occurs substantially more often in patients with COPD. The postulated mechanism (i.e., nonallergiclike transient tachypnea) warrants further investigation.

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