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Abbreviations:
A_z = area under the ROC curve
ROC = receiver operating characteristic

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Appendicitis in Children: Low-Dose CT with a Phantom-based Simulation Technique—Initial Observations[1]

PURPOSE: To retrospectively determine the accuracy of low-dose (20-mAs) computed tomography (CT) in the diagnosis of acute appendicitis in children by using a technique that enables the simulation of human CT scans acquired at a lower tube current given the image acquired at a standard dose.

MATERIALS AND METHODS: Institutional review board approval was obtained, informed consent was not required, and the study was HIPAA compliant. The authors reviewed 100 standard-dose pediatric abdominal-pelvic CT scans (50 positive and 50 negative scans) obtained in 100 patients and corresponding simulated low-dose (20-mAs) scans. The standard-dose scans were obtained for evaluation in patients suspected of having appendicitis. Scans were reviewed in randomized order by four experienced pediatric radiologists. The patients with positive findings included 21 girls (mean age, 9.2 years) and 29 boys (mean age, 8.4 years). The patients with negative findings included 28 girls (mean age, 9.2 years) and 22 boys (mean age, 8.4 years). Simulation was achieved by adding noise patterns from repeated 20-mAs scans of a pediatric pelvis phantom to the original scans obtained with a standard tube current. Observers recorded their confidence in the diagnosis of appendicitis by using a six-point scale. Dose-related changes were analyzed with generalized estimating equations and the nonparametric sign test.

RESULTS: There was a statistically significant ($P < .001$, sign test) decrease in both sensitivity and accuracy with a lower tube current, from 91.5% with the original tube current to 77% with the lower tube current. A low dose was the only statistically significant ($P < .001$) risk factor for a false-negative result. The specificity was unchanged at 94% for both the images obtained with the original tube current and the simulated low-dose images. The overall accuracy decreased from 92% with the original dose to 86% with the low dose.

CONCLUSION: Preliminary findings indicate that it is feasible to optimize the CT dose used to evaluate appendicitis in children by using phantom-based computer simulations.

The recent technologic advances in computed tomography (CT), which have allowed a more rapid scanning time, have improved the diagnostic utility of CT in children (1). As a result, the number of annual pediatric CT examinations has increased considerably (2). The increased use of CT as an imaging modality in children has raised concerns with respect to the radiation dose (3–7). Brenner et al (3) estimated a lifetime increased risk of cancer for children younger than 15 years that results from CT scans. Compared with the cancer risk for adults, the risk for children is equivalent to an additional 550 cases of cancer per 600 000 abdominal CT scans obtained. Although this represents a relative risk of 0.35% above the natural background incidence of cancer, the absolute numbers become more meaningful when we consider the total number of pediatric CT scans being obtained (3,4).

The complex relationship between radiation exposure risk and the benefits of added diagnostic information, however, is difficult to measure and remains largely unexplored.

For helical CT at a fixed x-ray energy, scanning time, and pitch, the radiation dose to the patient is directly related to the x-ray tube current. In contrast to conventional radiography, in which excessive tube current results in overpenetration and subsequent image degradation, at CT an increased tube current improves image quality by reducing noise. Because the minimum x-ray exposure needed for an accurate diagnosis is not known, many pediatric CT examinations are performed with unnecessarily elevated tube currents (5,6). Although radiologists strive to use "as low as reasonably achievable" exposure (known as the ALARA concept) (8), there is limited practical guidance that prescribes "reasonable" CT radiation levels that are compatible with diagnostic image quality. Thus, there is a strong need for clinical investigations to explore protocols and measure the trade-offs between radiation dose and diagnostic accuracy in pediatric CT.

In general, results of several studies have shown that diagnostic CT of the pediatric chest, abdomen, and pelvis can be performed by using tube currents lower than those previously accepted as the standard (9–12). From their experience, Donnelly et al (6) proposed a pediatric CT protocol for tube current based on a subject's weight. To the best of our knowledge, a systematic evaluation of the benefit and cost of a reduced radiation dose has not been performed. Moreover, such evaluation is not available even for specific disease entities, such as appendicitis. CT dose analysis is of particular interest in view of the recent trend toward the use of CT for evaluating children suspected of having appendicitis, with a multitude of suggested protocols. It has been suggested that focused CT of the lower abdomen can reduce the patient dose without compromising the sensitivity and specificity in the evaluation of appendicitis (13,14). It is unknown, however, whether the tube current could be reduced without the loss of diagnostic information in the evaluation of suspected appendicitis.

Comparison of images obtained through the appendix in the same patient and with varying tube currents would be the most direct method of optimizing a CT protocol. Ethical considerations, however, preclude such a study design owing to the radiation risks of repeated radiation exposure.

Thus, the purpose of our study was to retrospectively determine the accuracy of low-dose (20-mAs) CT in the diagnosis of acute appendicitis in children by using a technique that enables the simulation of human CT images obtained at a lower tube current given the image acquired at a standard dose.

MATERIALS AND METHODS

Study Subjects and Reference Standard

Institutional review board approval was obtained for this study, which was compliant with the Health Insurance Portability and Accountability Act. Patient informed consent was not required by the institutional review board.

Consecutive CT scans from pediatric patients admitted to a large metropolitan hospital were retrospectively reviewed in consensus by one pediatric radiologist with 9 years of experience in the interpretation of pediatric abdominal CT scans (N.R.F.) and a 4th-year medical student (A.M.Y.). Among patients aged 1–14 years (mean age, 8.7 years) who were clinically suspected of having acute appendicitis, we accumulated chronologically 50 positive and 50 negative scans. The age range was selected to include those patients presumed to be at greatest risk of the carcinogenic effects of radiation, attributed to the increased radiosensitivity of this young age group and the long lifetime in which these patients have to manifest the effects (3,7).

Patients were determined to have positive findings on the basis of a positive imaging interpretation for appendicitis with confirmation at postoperative histopathologic examination. Patients were determined to have negative findings on the basis of a negative imaging interpretation and no subsequent surgical intervention. Confirmation in the patients with negative findings was based on chart review and discharge diagnosis. Patients who were discharged without surgical intervention were assumed not to have appendicitis. None of these patients were readmitted to our hospital. Of the 50 patients with negative findings, discharge diagnoses included gastroenteritis (n = 32), lymphadenitis (n = 4), colitis (n = 2), terminal ileitis (n = 2), ovarian cyst (n = 2), pyelonephritis (n = 2), constipation (n = 2), pneumonia (n = 1), streptococcal pharyngitis (n = 1), Henoch-Schönlein purpura (n = 1), and epiploic appendagitis (n = 1). Fifty-two patients were male and 48 were female.

The true-positive group was well matched with the true-negative group in terms of age and sex, with no statistically significant difference in age (t test for mean age, t = 0.235, P = .815) or sex (Pearson χ^2 test, χ^2 = 1.91, P = .230). The patients with positive findings included 21 girls (mean age ± standard deviation, 9.2 years ± 2.6; age range, 5–14 years) and 29 boys (mean age, 8.4 years ± 2.7; age range, 3–13 years). The patients with negative findings included 28 girls (mean age, 9.2 years ± 3.1; age range, 2–14 years) and 22 boys (mean age, 8.4 years ± 3.4; age range, 2–13 years).

Scanning Protocol

All scans were obtained with the same helical CT scanner (Hi Speed RP; GE Medical Systems, Milwaukee, Wis). Scans were obtained approximately 2 hours after the oral administration of a contrast material consisting of 2% diatrizoate meglumine (Gastrografin; Bristol Meyers Squibb, Evansville, Ind) and immediately after the intravenous administration of a nonionic contrast material (2 mL per kilogram of body weight) (either iopamidol [Isovue; Bracco Diagnostics, Princeton, NJ] or ioversol [Optiray; Mallinckrodt Medical, St Louis, Mo]). Images selected for the study included the region from the lower pole of the right kidney through the symphysis. Images were obtained with 5-mm-thick sections at 4-mm intervals, 120 kVp, 1-second rotation time, pitch of 1.5, and 512 × 512 pixel matrix by using a standard reconstruction algorithm. The tube current ranged from 60 to 280 mAs, with a median tube current of 112 mAs, an average tube current of 126 mAs, and a standard deviation of 49 mAs, which reflects those parameters used in clinical practice at the time (scans were obtained during a 3-year period beginning in January 2000).

The 100 original CT scans were used to simulate a 20-mAs CT scan for each original scan. This process yielded a combined data set consisting of 200 CT scans of the right lower quadrant: 100 scans obtained at the original tube current and 100 simulated scans at a tube current of 20 mAs.

Low-Dose Image Simulation

Low-dose image simulation was achieved by adding measured noise samples to clinical CT scans. Noise samples were obtained by repeatedly scanning a

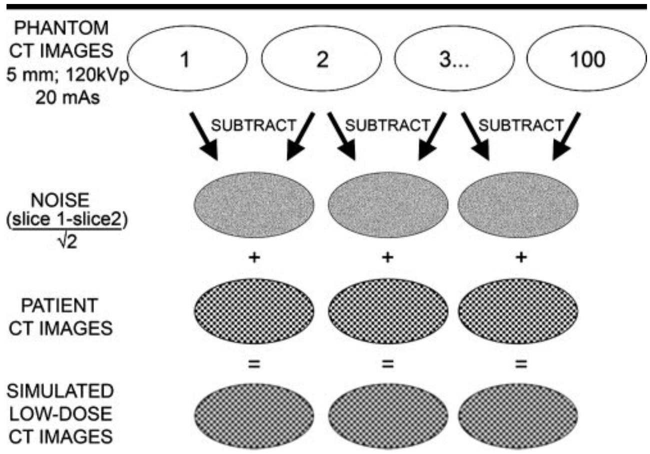


Figure 1. Schematic illustration shows the phantom-based simulation method.

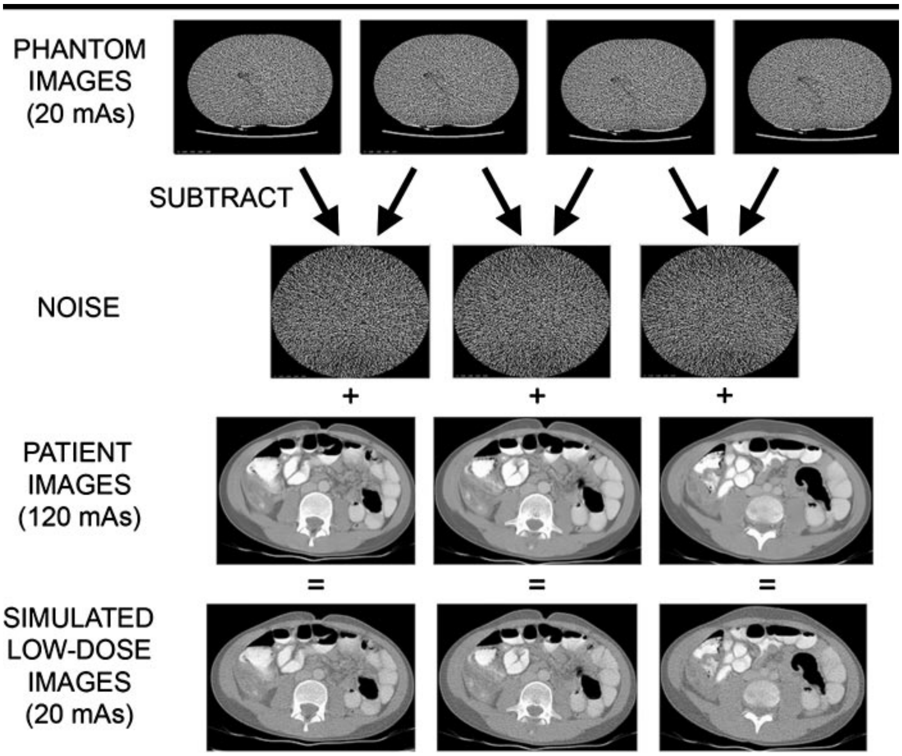


Figure 2. Diagram illustrates the application of the phantom-based simulation technique.

specially manufactured phantom composed of epoxy matrix that was developed to have an attenuation equal to that of soft tissue (Computerized Imaging Reference Systems, Norfolk, Va). The phantom was made to approximate the shape of a pediatric pelvis measuring 24 cm in transverse dimension, which is the approximate size of the pelvis in an average 7-year-old child. One hundred repeated scans of the phantom were obtained at several z-axis levels by using the same clinical scanner at a setting of 20 mAs. The other acquisition parameters were constant and equal to those used for the clinical CT protocol. On the basis of the principle of additivity of variance, the difference in attenuation between any two independent scans of the phantom divided by the square root of two provides an unbiased sample of the noise. The calculated random noise samples were added to clinical patient scans obtained at a higher tube current to generate simulated 20-mAs images (Figs 1, 2).

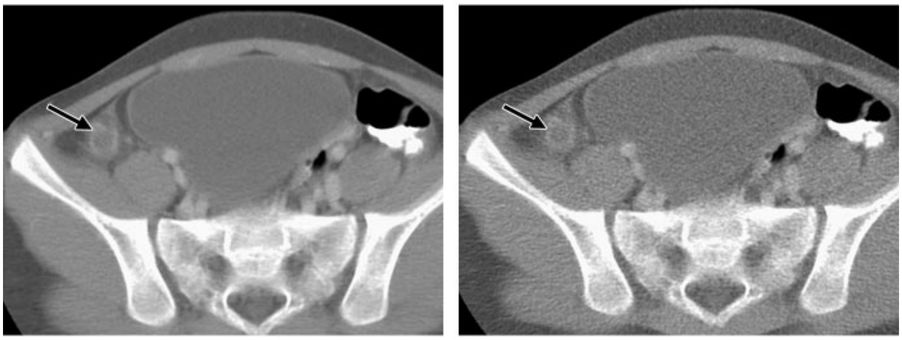
Image Analysis

The 200 data sets (100 original scans and 100 corresponding 20-mAs scans) were reviewed independently by four pediatric radiologists (J.B.A., L.P.P., R.R., N.A.S.) with 2–19 years of experience. To minimize memory bias, the radiologist who selected the patients did not serve as a reader. The observers were blinded to all technical parameters and clinical data; they were unaware of the ratio of positive to negative studies, the dose levels, and the order in which the cases were presented. Scans were presented in four reading sessions consisting of 50 randomly selected image sets comprised of approximately 20–25 images through the right lower quadrant. Each session consisted exclusively of simulated low-dose image sets or original standard-dose image sets. The reading sessions were separated by a minimum of 2 weeks. For each patient, the review of the simulated low-dose image set always preceded the review of the corresponding original standard-dose image set. This was done to eliminate memory bias, with the explicit assumption that standard-dose scans are more informative. The images were viewed on a diagnostic-quality picture archiving and communications system black-and-white monitor (M21LMAS; Image Systems, Minnetonka, Minn). The monitor satisfied the American College of Radiology's standards for teleradiology and digital image data management and had a luminance of 65 foot-lamberts, 0.25-mm aperture grill pitch, 1200 × 1600 resolution, and 75-Hz refresh rate. The window width was fixed at 450 HU and the window level at 10 HU, which are routine settings for evaluating appendicitis.

The CT scans were graded on a six-point Likert scale, as follows: score of 5, definitely positive for appendicitis; score of 4, probably appendicitis; score of 3+, uncertain but tending to favor appendicitis; score of 3−, uncertain but tending toward no appendicitis; score of 2, probably no appendicitis; and score of 1, definitely negative for appendicitis. The diagnosis of appendicitis was made by using the standard CT criteria, including a peripherally enhancing fluid-filled tubular structure with a diameter of more than 8 mm, identification of an appendicolith in association with inflammatory changes, and inflammatory changes in the right lower quadrant without visualization of a normal appendix (15).

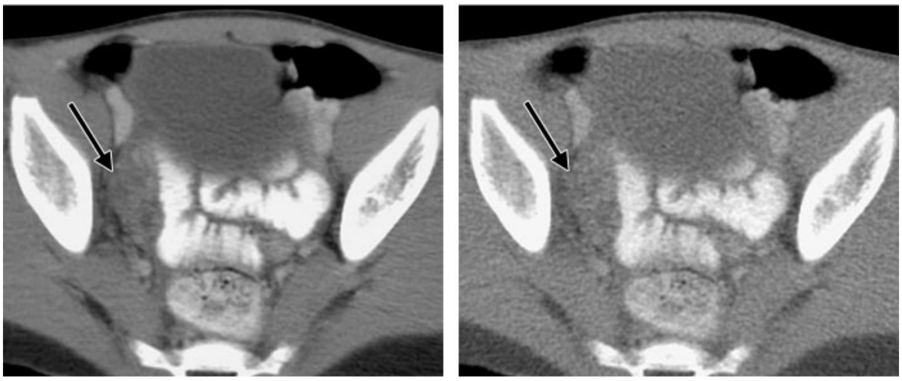
Data and Statistical Analyses

Generalized estimating equation analysis with unstructured correlation structure and logit link function was used to identify factors predictive of a false-negative reading, accounting for the correlations among readers and dose within subjects. The nonparametric sign test was used to compare the original scans with the low-dose scans. For the sign test, the data were reduced to a single binary (yes or no) observation per subject: Specifically, was the number of correct diagnoses the same between the original and low-dose images? Sensitivity, specificity, and accuracy were calculated for the diagnosis of appendicitis by considering scores of at least 3+ as a positive diagnosis and scores of 3− or less as a negative diagnosis. Reader performance was expressed as the area under the receiver operating characteristic (ROC) curve (A_z). Maximum likelihood estimation was used to generate binormal ROC curves and their associated parameters from a set of categorical rating-scale data. Computations were performed by using software developed by Metz (16) (ROCFIT program, June 1989, FORTRAN version for personal computer) and a statistical software package (version 10.0; SAS Institute, Cary, NC). Interobserver agreement about the diagnosis of appendicitis was measured by using the intraclass correlation coefficient. $P < .05$ indicated a statistically significant difference.



a. b.

Figure 3. Original and simulated CT scans in an 8-year-old boy with abdominal pain. **(a)** Transverse contrast material–enhanced helical CT scan obtained with a tube current of 180 mAs demonstrates an inflamed appendix (arrow) in the right lower quadrant. **(b)** Simulated low-dose (20-mAs) scan at the same z-axis level as in **a** also demonstrates the inflamed appendix (arrow).



a. b.

Figure 4. Original and simulated CT scans in a 7-year-old girl with abdominal pain. **(a)** Transverse contrast-enhanced helical CT scan obtained with a tube current of 80 mAs demonstrates an inflamed appendix (arrow) in the lower right side of the pelvis. **(b)** Simulated low-dose (20-mAs) scan at the same z-axis level as in **a**. The inflamed appendix (arrow) is substantially less conspicuous, owing to the increased noise.

Comparison of Standard and Low-Dose CT Scans in the Diagnosis of Appendicitis in Children

Imaging Technique	Sensitivity (%)	Specificity (%)	Accuracy (%)
Standard dose	91.5	93.5	92.5
Simulated low dose (20 mAs)	77.0	94.5	86.0

RESULTS

For the original scans (ie, those obtained with the standard tube current), the pooled sensitivity of the four readers in the diagnosis of appendicitis was 91.5% (183 of 200 positive scans [ie, 50 positive scans each read by four readers]). Sensitivity of the individual reader ranged from 86% to 94%. The pooled sensitivity for the low-dose (20-mAs) scans decreased significantly to 77% (154 of 200 positive scans; $P < .001$, sign test). Sensitivity of the individual reader ranged from 70% to 84%, depending on the reader. The correct diagnosis of appendicitis was consistently missed by all readers for seven of the 50 simulated low-dose scans. In five of these seven cases, the patients were girls. In addition, five of seven scans showed that the appendicitis was located low in the pelvis adjacent to the bladder, and five scans showed that there was minimal surrounding mesenteric fat (Fig 3). The readers consistently correctly diagnosed appendicitis in 36 of the 50 patients at both the standard tube current and the simulated 20-mAs tube current (Fig 4).

There was a decrease in accuracy, to a lesser degree, from 92.5% (370 of 400 scans [ie, 100 scans each read by four readers]) for the standard scans to 86% (343 of 400 scans) for the simulated low-dose scans ($P < .001$, sign test). Lowering the dose did not significantly change the specificity, which was 93.5% (187 of 200 scans) at standard-dose CT and 94.5% (189 of 200 scans) at low-dose CT ($P = .834$) (Table). The Likert scale scores of the four observers were in relatively good agreement, as demonstrated with an intraclass correlation coefficient of 0.89 (95% confidence interval: 0.86, 0.91).

Analysis of the positive scans by using generalized estimating equations identified low dose as the only statistically significant ($P < .001$) risk factor for a false-negative result. The model included dose type (standard vs simulated 20 mAs), age,

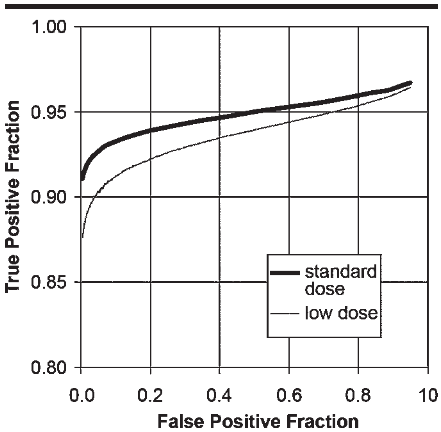


Figure 5. Graph shows the ROC curves (pooled for four readers) in the diagnosis of appendicitis at standard-dose and simulated low-dose (20-mAs) CT. There is a decrease in sensitivity with the low-dose images.

sex, and the radiologist who interpreted the CT scan. The odds ratio for missing the diagnosis of appendicitis at low-dose CT was 3.3 (95% confidence interval: 1.8, 5.8). These results were confirmed with ROC analysis of reader's responses (Fig 5). The A_z was 0.95 for the standard dose, which is higher than that for the simulated 20-mAs dose (0.88; $P < .05$, z-score test for the difference between the areas under two ROC curves; A_z difference, 0.07; 95% confidence interval: 0.00, 0.14).

For the standard-dose examinations, sensitivity was independent of actual dose, with a pooled sensitivity of 93.8% (60 of 64 scans) for those scans obtained with a tube current less than the median of 112 mAs and 90.4% (123 of 136 scans) for those scans obtained with a tube current of more than 112 mAs ($P = .42$, sign test). In addition, the sensitivity in the diagnosis of appendicitis for the simulated low-dose group was independent of the dose used to obtain the original images ($P = .26$, generalized estimating equation test). The pooled sensitivity was 72% (46 of 64 scans) for the simulated low-dose images originally obtained with a tube current less than the median of 112 mAs and 79% (108 of 136 scans) for the simulated low-dose images originally obtained with a tube current of more than 112 mAs.

Among the negative scans, the normal appendix was identified by the readers on 43% of the standard-dose images (range, 18%–52%) and 52.5% of the low-dose images (range, 34%–64%). This difference was statistically significant ($P = .01$, sign test).

DISCUSSION

Concerns have been raised with respect to CT radiation dose in view of the increasing use of CT for imaging children. The "as low as reasonably achievable" principle asserts that the radiation dose necessary to generate diagnostic CT scans be kept to a minimum. However, it is challenging to design experiments that help investigate the relationship between diagnostic accuracy and radiation dose because ethical considerations preclude repeated CT of the same patient at differing tube currents for comparison of images. An alternative strategy is to simulate images obtained with a lower tube current. Mayo et al (17) described one such technique based on randomized perturbations of projection data. Frush et al (18) recently applied the technique used by Mayo et al to abdominal multi–detector row CT in children to evaluate tube current reduction. With such a method, however, it is necessary to access the projection data that are kept in proprietary format and are typically not archived.

The noninvasive simulation technique developed in this investigation is based on repeated scans of a stationary phantom. If the dimensions and distribution of photon linear attenuation coefficients between the phantom and the patient are equal, the random noise in the projection values will also be equivalent. The subtraction of pairs of phantom scans yields samples of noise that are representative of a given x-ray tube current. We have developed software that enables us to transfer random noise sampled on phantoms to patient scans, thus generating simulated CT scans obtained at a reduced dose level. A markedly reduced tube current of 20 mAs was selected in this study to exaggerate the differences in image quality between the standard-dose and simulated low-dose images.

A variant of the phantom-based simulation technique that we have used in this investigation was recently presented by Britten et al (19) for CT of the brain. Phantom-based techniques have the advantages of broad applicability, allowing one to simulate low-dose CT scans independent of the vendor and without access to proprietary or raw data. In addition, the phantom-based simulation technique addresses both the random noise and the structural noise, both of which contribute to image degradation at lower tube currents.

The observed significant decrease ($P < .001$) in reader sensitivity from 91.5% to 77% appears unacceptable as a general protocol for the CT evaluation of appendicitis in children. It is interesting to note, however, that of the 50 patients with positive findings, there were only seven in whom the correct diagnosis of appendicitis was consistently compromised by the decrease in tube current for all readers, which largely accounts for the 14% decrease in sensitivity from the standard-dose group to the simulated low-dose group. Further analysis of these seven patients revealed that five of the seven were girls. In addition, the appendicitis was located low in the pelvis adjacent to the bladder in five patients, and there was minimal surrounding mesenteric fat in five patients. These factors can be associated with a false-negative diagnosis of appendicitis. Conversely, and perhaps more important, the readers were able to correctly diagnose appendicitis in 43 patients at both the standard tube current and the simulated 20-mAs tube current (Fig 5). It is also interesting to note that visualization of the normal appendix was not compromised on the simulated low-dose images compared with the standard images. This is important because identification of the normal appendix is the most confident means of excluding acute appendicitis. In addition, the actual dose did not affect the sensitivity for the standard-dose cases, a finding that suggests that the optimum dose may be somewhere between 112 and 20 mAs.

The 20-mAs tube current that we simulated opens the possibility for the evaluation of appendicitis with tube currents lower than the standard yet higher than the extreme 20 mAs used in this study. Additional studies with incremental low-dose image simulation are under way and may help identify this lower tube current range. Such reader studies, however, are very time intensive, necessitating several months to overcome the element of memory bias. These studies also entail a large case volume (on the order of hundreds of cases) to prove that the sensitivity at two different doses is equivalent.

The preliminary data also support the feasibility of this phantom-based simulation technique in the optimization of pediatric body CT protocols. Tube current reduction and the subsequent increase in noise can result in a loss of diagnostic information. The identification of the threshold at which this becomes statistically significant is one of the keys to dose reduction in pediatric CT. Because the phantom-based simulation technique can be applied to any CT scan, it has the potential to be a powerful tool for establishing lower-dose pediatric CT protocols that do not compromise the diagnostic utility of the examination.

Our study has several limitations. First, although the phantom-based simulation technique is based on well-accepted principles of radiation physics, a full direct in vivo validation of the simulation method remains unlikely because it requires multiple scans of the same child at different tube currents. Such a validation study will not be approved at our institution for ethical reasons. A validation study is currently in progress with an anthropomorphic phantom.

Second, we used only one body phantom measuring approximately 24 cm in transverse diameter (approximating the size of a typical 7-year-old child) to generate the noise associated with specific tube currents. As a result, the simulated images in this study may correspond to doses slightly lower or higher than 20 mAs, depending on the actual size and density of the child's abdomen because for a fixed x-ray tube current (in milliampere seconds) and fixed energy (in kilovolt peaks), image noise increases with the patient's size and weight. Additional body phantoms of varying sizes will be used to generate noise profiles that are customized to the child's size for use in future investigations.

Third, for consistency and standardization, the readers were restricted from changing the window width and level. At times, alteration of the window width and level can help better resolve anatomic detail. It is not clear whether the fixed viewing window protocol affects the diagnostic accuracy differently at different doses, perhaps resulting in an increase in the false-negative rate of the simulated low-dose images.

It is likely that the optimal tube current threshold will vary directly with patient size. The number of CT scans obtained within each size or age group, however, was not large enough to assess the relationship between tube current and patient size. It will, therefore, be necessary to increase the number of CT scans obtained to generate meaningful data specific to a patient's age and/or size.

In conclusion, we have shown that, in the evaluation of appendicitis in children, decreasing the radiation dose associated with CT by reducing the tube current results in a statistically significant loss of diagnostic sensitivity without affecting radiologic specificity. These study results open the possibility of determining the relationship between radiation dose and diagnostic performance of CT with tube currents in the full clinically relevant range of 20–112 mAs in children suspected of having acute appendicitis with a phantom-based method.

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