

# The usefulness of agent emission imaging - high mechanical index ultrasound mode in the diagnosis of urolithiasis: a prospective preliminary study

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## PURPOSE

We aimed to determine the feasibility and effectiveness of agent emission imaging - high mechanical index (AEI-High MI) mode ultrasonography (US) compared with gray-scale and color Doppler US, alone or in combination, for the diagnosis of urolithiasis with reference to unenhanced computed tomography (CT).

## METHODS

This prospective study included 72 consecutive patients (40 males, 32 females; mean age, 45.9±14.7 years) referred by the department of urology for acute or elective symptoms of urolithiasis and confirmed to have urinary calculi on unenhanced abdominal CT, between January 2015 and June 2015. Gray-scale, color Doppler, and AEI-High MI US were performed by two radiologists to determine the effectiveness of these methods in the diagnosis of urinary stones and to compare them with the reference modality.

## RESULTS

A total of 189 calculi were detected on CT examination. Gray-scale US had a sensitivity of 66.1% and positive predictive value (PPV) of 88.7% for detecting calculi, while twinkling artifact of color Doppler had a sensitivity of 70.4% and PPV of 94.3%. The scintillation artifact of AEI-High MI mode had a sensitivity of 75.1% and PPV of 95.9%. When all ultrasound-based modalities were combined, the sensitivity and PPV rose to 83.1% and 88.2%, respectively. When calculi were grouped according to their size (<5 mm, 5–10 mm, >10 mm), AEI-High MI mode had a higher sensitivity (60%) compared with gray-scale (32.5%) and color Doppler (41.3%) for calculi <5 mm.

## CONCLUSION

AEI-High MI mode had a higher sensitivity compared with gray-scale and color Doppler for the detection of calculi smaller than 5 mm, but it did not make a significant contribution to detection of larger calculi. The combined use of gray-scale US with AEI-High MI mode could increase the detection rate of calculi smaller than 5 mm and provide a method for verification of suspected calculi on gray-scale US.

Urolithiasis is an important public health problem worldwide owing to its high prevalence and recurrence rates as high as 50%. It is more common in men, and it affects nearly 5%–10% of the European and North American population, although it may be more prevalent in other regions of the world (1). Radiologic imaging techniques have an important role in the diagnosis, treatment, and follow-up of urolithiasis. Abdominal X-ray, intravenous pyelography (IVP), sonography, and computed tomography (CT) have long been used as the primary imaging modalities (2). Thin-section unenhanced abdominal CT is regarded as the gold standard imaging modality for the diagnosis of urinary system calculi due to high specificity and sensitivity values (2). Nevertheless, there is a growing concern about radiation exposure and associated cancer risk with the use of CT examinations (3). Despite many advantages of CT in the diagnosis of calculi, it has some important limitations including repeated radiation exposure, increased sensitivity to radiation's harmful effects in pregnancy and childhood, relatively high cost, and limited availability (4).

Ultrasonography (US), a widely available and reliable imaging modality, has some disadvantages in the diagnosis of urinary calculi due to certain factors such as obesity, intes-

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tinal gas superposition, small calculi without posterior acoustic enhancement, and the echogenic fatty tissue of renal sinus (4, 5). These factors have led researchers and device manufacturers to develop novel modalities and techniques to aid in the diagnostic process. If additional ultrasonographic signs associated with urinary calculi could be identified, the diagnostic sensitivity of this modality could be increased (4, 5).

Agent emission imaging - high mechanical index mode (AEI-High MI) is an imaging option used for the visualization of contrast agents and is part of the Cadence Contrast Agent Imaging (CCAI) package in Siemens ultrasound devices. We observed that some urinary stones detected during routine abdominal US were exhibiting an artifact similar to scintillations in the AEI-High MI mode, which made them more easily detectable (Figs. 1 and 2; see also movie clip for Fig. 2b). A screen of the existing medical literature revealed no reports of such an observation. Thus, we designed a study to determine the potential role of AEI-High MI mode in the diagnosis of urinary calculi.

Herein, we aimed to determine the feasibility and effectiveness of AEI-High MI imaging mode compared with B-mode gray-scale and color Doppler US, alone or in combination, for the diagnosis of urolithiasis with reference to unenhanced CT, the reference imaging method.

## Methods

### Patients

Our hospital ethics committee approved this prospective study (approval number: 2014-1962). A written informed consent was obtained from each participant. Ninety-two consecutive patients (52 male, 40 female) who underwent an abdominal CT that detected urinary calculi between January 2015 and June 2015 were prospectively enrolled. The study subjects were either

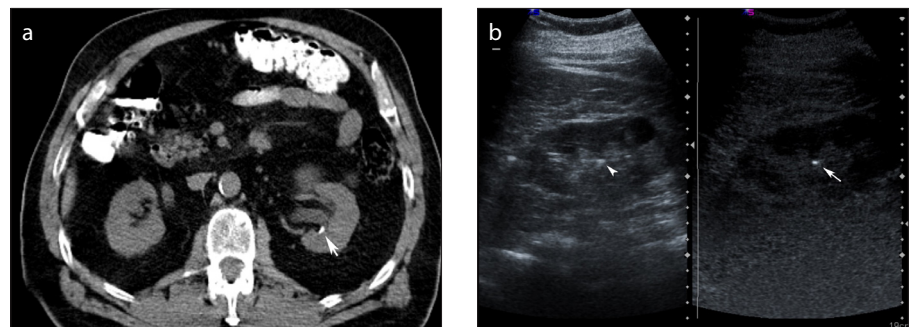
acute or elective patients referred to us by the urology department. CT examinations were unenhanced in 88 patients and contrast-enhanced in 4 patients. Twenty patients were excluded from the study for an interval of more than 14 days between CT and sonographic examination (n=15) and clinical suspicion of passage of calculi after the last CT examination (n=5). The remaining 72 patients formed our study group (40 males, 32 females). All of the patients were above the age of 18 years; mean age was  $45.85 \pm 14.68$  years (range, 21–77 years).

### Imaging techniques

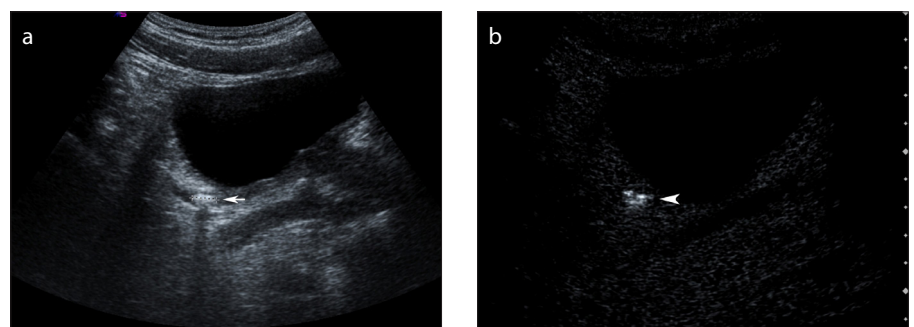
All US examinations were performed at supine or lateral position, using a Siemens Sonoline Antares US device (Siemens Healthcare) with a broadband curved-array transducer (CH4-1, bandwidth: 1.5–4.5 MHz). For gray-scale imaging, the frequency was set at 2.2 MHz and tissue harmonics mode was activated in all patients. Compound imaging mode was turned off for all US modes (gray-scale, color Doppler, and AEI-High MI). A single focus, placed at the level of the kidney was used. It was ensured that urinary bladder was distended

before the examination. The device settings were optimized to obtain the best quality images. All patients were examined by a standardized US scanning procedure. Both kidneys, ureteropelvic and ureterovesical junctions, other visible ureteric segments, and urinary bladder lumen were scanned for the presence of urinary calculi. The kidneys were scanned at both longitudinal and axial planes with anterior and lateral approaches. A standardized form was used for reporting US examination findings. Color Doppler box was placed in a way to involve the entire body of stone and the twinkling artifact. Color gain, pulse repetition frequency, and wall filter settings were optimized for each patient to minimize noise arising from blood flow. AEI-High MI mode imaging was performed using the same transducer operating at 1.82 MHz, with a single focus placed at the level of the kidney or at a slightly deeper location.

Unenhanced CT scans were performed with the standard dose protocol of our department with a 64-detector row CT scanner (Aquilion 64, Toshiba Medical Systems). The helical CT parameters were set as follows: collimation, 64×0.5 mm; tube current, 300



**Figure 1. a, b.** CT image (a) of a 67-year-old male patient with a small urinary stone (arrow) at the mid level of the left pelvicalyceal system). Gray scale ultrasound on the left half of the image (b) demonstrates the stone as an echogenic focus without acoustic shadowing (arrowhead). The stone is more pronounced and easier to pinpoint (arrow) on AEI - High MI mode as seen on the right half of the image (b).



**Figure 2. a, b.** A 42-year-old male patient with renal colic. Ultrasound demonstrates a stone with acoustic shadowing in distal ureter (arrow, a). The stone generates a scintillating artifact in AEI - High MI mode (arrowhead - also see movie clip 2b.mp4) (b).

### Main points

- Agent emission imaging - high mechanical index mode (AEI-High MI mode) can be used for the diagnosis of urinary calculi.
- AEI-High MI mode is more sensitive than gray-scale US and color Doppler US for the diagnosis of calculi smaller than 5 mm.
- The addition of AEI-High MI imaging to gray-scale US and color Doppler US increases the overall sensitivity and positive predictive value for the diagnosis of urinary calculi.

mA; tube potential, 120 kV; gantry rotation time, 0.5 s; pitch factor, 1.1; couch speed, 35.2 mm/rot. The scans included body parts from the dome of diaphragm to symphysis pubis. FC13 reconstruction algorithm using an image matrix of 512×512 pixels, an image thickness of 1 mm, and a reconstruction interval of 1 mm was employed to reconstruct CT images. Conventional filtered back projection was the method of image reconstruction used in this study.

### Image interpretation

All sonographic examinations were performed by one of two experienced radiologists (A.S. with 15 years of experience and M.B. with 10 years of experience) blinded to the CT data. The radiologist performing the study recorded still images to document the study. Movie clips were also recorded if there were pathologic findings. Hyperechoic foci that were distinct from the surrounding tissues, independent of presence of a posterior acoustic shadowing, were regarded as calculi. The presence and appearance of artifacts visualized in color Doppler and AEI-High MI mode were recorded. At the end of the study period, when all patients were imaged, both radiologists reviewed these findings together, decided in consensus on the presence or absence of the stones and artifacts and compared them with CT findings.

CT image analysis was performed on a commercially available workstation (Vitrea 2, version 4.1.14.0, Vital Images). Analysis of CT images was conducted in consensus. CT images were analyzed at axial, coronal, and sagittal planes, and localization, number, and size of detected calculi were recorded. The longest diameter was used for the measurement of all stones. The calculi were categorized by their location that included kidneys (right and left kidney), ureter (right/left) and bladder lumen. The mean interval from CT examination to US was 6.4±4.8 days (range, 0–14 days).

### Statistical analysis

SPSS 21.0 statistical package (IBM Corp.) was used for all statistical analyses. Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed quantitative variables. Considering CT as the reference method, the overall sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated with a confidence interval (CI) of 95% for gray-scale, color Doppler, and AEI-High MI modes, both alone and in combina-

tion. In addition, the diagnostic efficacies of gray-scale and AEI-High MI were compared with each other in reference to stone size (≤5 mm, 6–10 mm, and >10 mm). The sensitivity, PPV, true positivity, false positivity and false positivity values were calculated for each modality. As the evaluation was on a per stone basis, true negativity, specificity and negative predictive value were not calculated. McNemar's test was selected for the statistical comparison of the data across the groups. A *P* value of less than 0.05 was considered statistically significant.

## Results

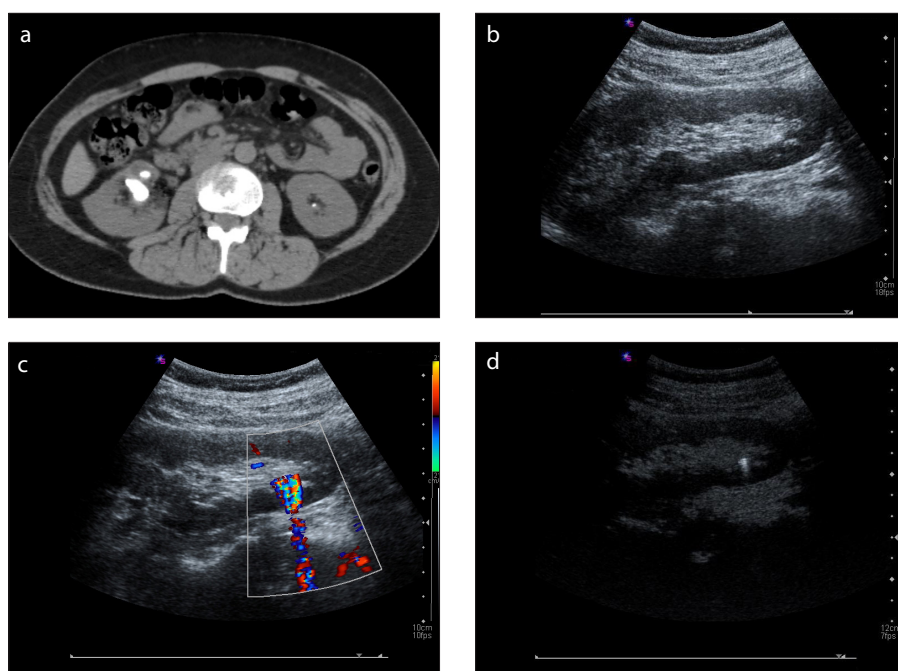
Seventy-two patients had a total of 189 calculi on CT imaging, with a mean size of

8.07±6.4 mm (range, 1–35 mm) measured on the longest axis. CT demonstrated multiple calculi in 46 patients (64%). In total, 46 stones (24.3%) were larger than 10 mm, 63 (33.3%) were 5–10 mm, and 80 (42.3%) were smaller than 5 mm. There were over 167 renal foci (88.4%), 20 ureteric foci (10.6%) and 2 urinary bladder foci (1.1%). Of the ureteric stones, 6 (30%) were located to proximal ureter, 6 (30%) to mid ureter, and 8 (40%) to distal ureter. On gray-scale US examination, 141 echogenic foci were reported as calculi; however, 16 (11.3%) of them could not be verified on CT examination and were accepted as false positive. Of the 189 calculi detected on CT, 64 (33.9%) could not be visualized by gray-scale US. On color Dop-

**Table 1.** Diagnostic accuracy in detecting urolithiasis for different modalities and their combinations

Modality	Sensitivity (95% CI)	PPV (95% CI)
US	66.1 (59.9–72.9)	88.7 (82.2–93.4)
AEI-High MI	75.1 (68.3–81.1)	95.9 (91.4–98.5)
CDUS	70.4 (63.3–76.8)	94.3 (89.1–97.5)
US+AEI-High MI	81.5 (75.2–86.7)	88.5 (82.8–92.8)
US+CDUS	78.3 (71.7–84.0)	89.2 (83.4–93.5)
US+CDUS+AEI-High MI	83.1 (76.9–88.1)	88.2 (82.5–92.5)

PPV, positive predictive value; CI, confidence interval; US, ultrasonography; AEI-High MI, agent emission imaging - high mechanical index; CDUS, color Doppler ultrasonography.



**Figure 3.** a–d. A 44-year-old female patient. CT image (a) demonstrates multiple large urinary stones on the right kidney and a 3 mm stone on the lower pole of left kidney. Gray-scale US (b) was positive for right kidney but inconclusive for the left kidney. Color Doppler US (c) and AEI-High MI mode (d) were able to demonstrate the presence of the calculus (see also movie clip Fig3d.mp4).

pler examination, 141 foci demonstrated twinkling artifact but CT was negative in 8 (5.7%) of these cases and no twinkling artifact was detected in 56 calculi (29.6%). On AEI-High MI mode, the scintillation artifact was detected in 148 cases, 6 of which could not be verified on CT (4%). Of 189 stones, 47 (24.9%) did not create a visible artifact on AEI-High MI mode. Gray-scale US had a sensitivity of 66.1% and PPV of 88.7% for detecting calculi, while color Doppler twinkling artifact had a sensitivity of 70.4% and PPV of 94.3%. AEI-High MI scintillation artifact had a sensitivity of 75.1% and a PPV of 95.9%. When gray-scale US and twinkling artifact were combined, the sensitivity increased to 78.3% with a PPV of 89.2% and when gray-scale US and the scintillation artifact were combined the sensitivity and PPV were 81.5% and 88.5%, respectively. When all ultrasound-based modalities were

combined the sensitivity and PPV rose to 83.1% and 88.2%, respectively (Table 1 and Figs. 3, 4, and 5; see also movie clips for Figs. 3d, 4c, and 5e). Color Doppler twinkling artifact yielded a positive result in 6 of 7 stones located to proximal ureter (85.7%), 3 of 7 stones located to mid ureter (42.9%), and 9 of 11 (81.8%) stones located to distal ureter, while AEI-High MI scintillation artifact yielded a positive result in 4 (57.1%), 2 (28.5%), and 7 (63.6%) stones in similar locations. Two bladder stones measuring 13 and 4 mm were considered positive in all modalities.

Comparison between the color Doppler and AEI-High MI modes with McNemar's test revealed that AEI-High MI mode had a higher, albeit nonsignificant ( $P = 0.311$ ), sensitivity (75% vs. 70%) and PPV (97% vs. 94%) than color Doppler US. It similarly had a higher sensitivity (75% vs. 65%) and PPV

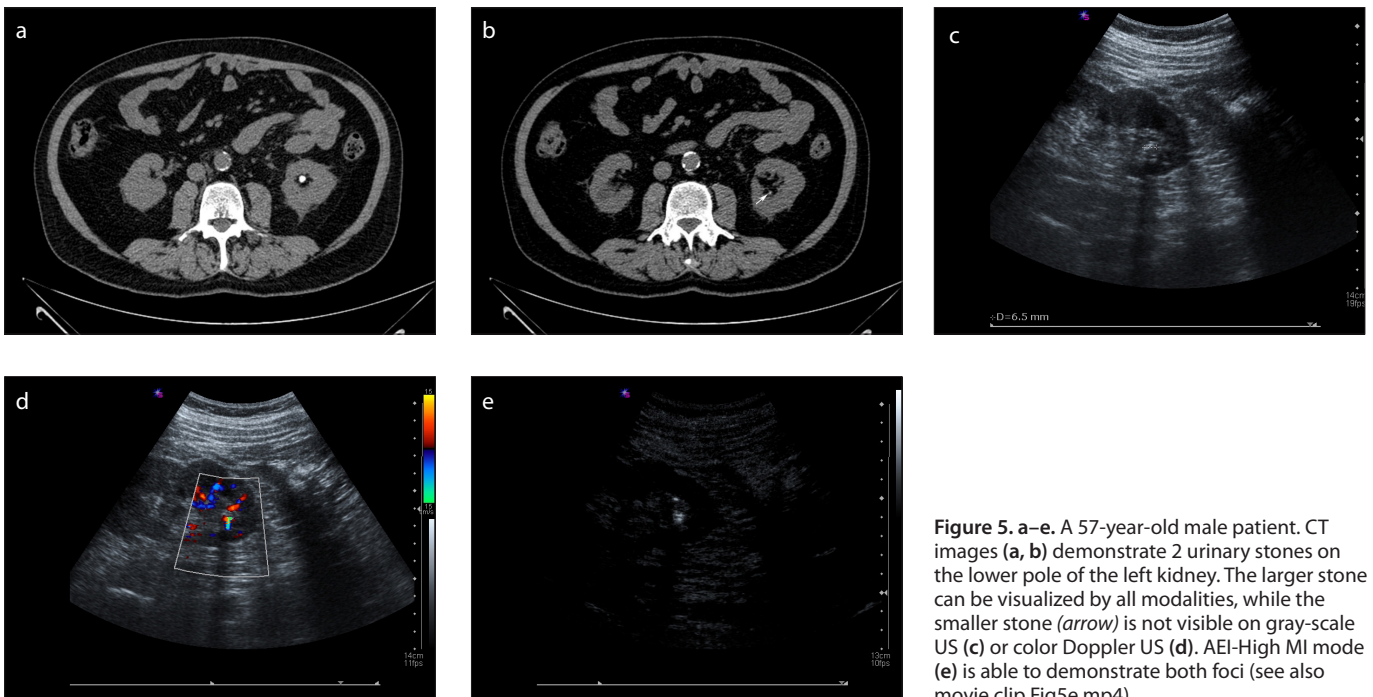
(97% vs. 90%) compared with gray-scale US, although these differences did not reach statistical significance ( $P = 0.109$ ). When calculi were categorized according to their size (<5 mm, 5–10 mm, >10 mm), AEI-High MI mode scintillation artifact had a higher sensitivity (60%) compared with gray-scale US (32.5%) and color Doppler US (41.3%) for calculi <5 mm (Table 2, Fig. 6).

## Discussion

Our study revealed that AEI-High MI mode was superior to gray-scale US in detecting calculi smaller than 5 mm, which are generally harder to observe. The sensitivity of gray-scale US in detecting calculi in this group was 32.5% (95% CI, 22.5–43.9), while the scintillation artifact of AEI-High MI mode had a sensitivity of 60% (95% CI, 48.4–70.8). The combined sensitivity of both modalities was 63.7% (95% CI, 52.2–74.2).



**Figure 4. a–c.** A 41-year-old male patient with a 3 mm stone on the lower pole of the left kidney on CT examination (a). No stone was detected on gray scale US (b) but AEI - High MI scintillation artifact (c) was able to demonstrate its presence (arrow - see also movie clip Fig4c.mp4).



**Figure 5. a–e.** A 57-year-old male patient. CT images (a, b) demonstrate 2 urinary stones on the lower pole of the left kidney. The larger stone can be visualized by all modalities, while the smaller stone (arrow) is not visible on gray-scale US (c) or color Doppler US (d). AEI-High MI mode (e) is able to demonstrate both foci (see also movie clip Fig5e.mp4).

These findings suggest that the addition of AEI-High MI mode to gray-scale US could be beneficial especially for the detection of calculi smaller than 5 mm.

Similar to our study, many authors reported low sensitivity rates for the gray-scale US diagnosis of calculi smaller than 5 mm. Uluhan et al. (6) reported that only 37% of calculi smaller than 5 mm could be detected by US compared with CT. Sorensen et al. (7) reported the sensitivity of gray-scale US for the same size range to be 52%. In clinical practice, the color Doppler twinkling artifact has been accepted as an adjunct to gray-scale US for increasing its diagnostic accuracy. However, a review of the published literature about the artifact's sensitivity in detecting calculi smaller than 5 mm reveals a wide range. In a study by Korkmaz et al. (4) color Doppler US was found to be significantly more successful (93.4% detection rate) compared with gray-scale US (19.7% detection rate) for calculi smaller than 5 mm, and a combination of the two methods resulted in very high (96%) detection rates. Lee et al. (5) detected this artifact in 83% of calculi. A study by Park et al. (2) demonstrated similarly high detection rates (184 of 214 calculi, 86%). In their study, Mitterberger et al. (8) found that twinkling artifact was superior to gray-scale US (with 66% and 97% detection rates, respectively). However, lower detection rates have also been reported in the literature. Dillman et al. (9) reported the sensitivity of twinkling artifact to be 55% (9). Our results for color Doppler US were closer to their study, with 41.3% (95% CI, 30.3–52.8) sensitivity for detection of calculi smaller than 5 mm. In this group, the addition of color Doppler US to gray scale increased the sensitivity to 52.5% (95% CI, 41.0–63.8). This value was lower than the combined sensitivity of gray-scale US and AEI-High MI mode (63.7%; 95% CI, 52.2–74.2). Our findings suggest that, for calculi smaller than 5 mm, the combination of gray-scale US with AEI-High MI mode can be more sensitive than the combination of gray-scale US with color Doppler US. This result needs to be validated in larger series.

Twinkling artifact is considered as a major sonographic diagnostic sign for the detection of urinary calculi (10); however, it can sometimes be obscured by the vascular signals originating from hilar vessels. In contrast, and as an important advantage, AEI-High MI mode does not share this problem, as vascular signals are not visible in this mode. Another advantage of AEI-High

MI imaging compared with Doppler US is the possibility to examine the entire field of view simultaneously. Doppler US requires a color box to be placed on the interrogated area and while this area can be enlarged to include the entire kidney, the frame rate also suffers, which could result in a less optimal examination.

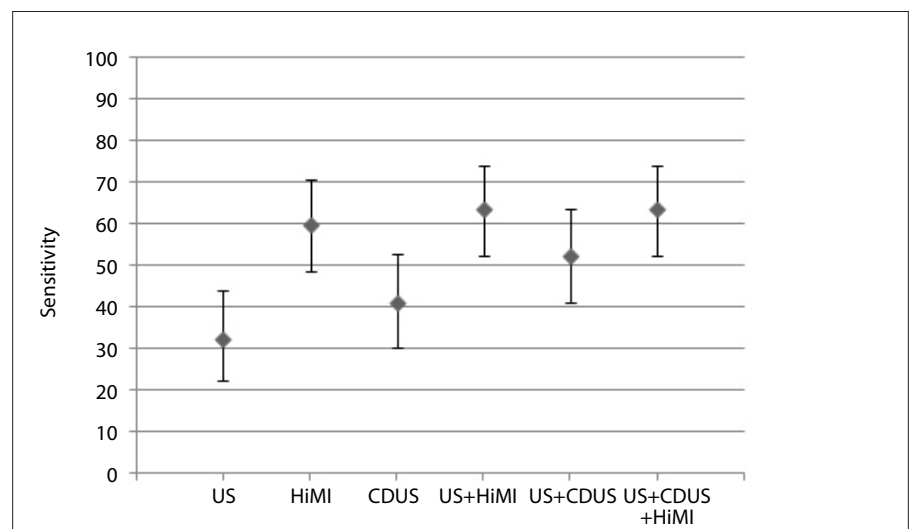
An important limitation of the twinkling artifact is its high rate of false positivity. In a study by Dillman et al. (9), the false positivity of twinkling artifact compared with CT was 51% (75 of 148 twinkling foci). Winkel et al. (11) also compared CT findings with sonographic and Doppler findings and reported that the addition of color Doppler to gray-scale US decreased the PPV for the diagnosis of calculi from 81% to 67% due to increased

false positive foci on Doppler US. In a study by Masch et al. (12) comparing CT results with sonographic examination results, color Doppler US demonstrated low specificity (40%) and high false positivity (60%). Our results demonstrated a lower false positivity rate for color Doppler US. In our series, false positivity rates for B-Mode gray-scale US, color Doppler US and AEI High MI mode were 11.34%, 5.6%, and 4.05% respectively. The false positivity rate for AEI-High MI mode was slightly lower than color Doppler US. A reason for the difference could be the lack of flow related signals in AEI-High MI mode. Larger series are required to demonstrate if, in addition to its higher sensitivity, the AEI High MI mode has a statistically significant lower false positivity.

**Table 2.** Sensitivity of diagnostic modalities according to stone size

Modality	Size		
	<5 mm	5–10 mm	>10 mm
US	Sensitivity (95% CI) 32.5 (22.5–43.9)	Sensitivity (95% CI) 85.7 (74.6–93.3)	Sensitivity (95% CI) 97.8 (88.5–99.9)
AEI-High MI	60 (48.4–70.8)	88.9 (78.4–95.4)	82.6 (68.6–92.2)
CDUS	41.3 (30.3–52.8)	93.7 (84.5–98.2)	89.1 (76.4–96.4)
US+AEI-High MI	63.7 (52.2–74.2)	92.1 (82.4–97.4)	97.8 (88.5–99.9)
US+CDUS	52.5 (41.0–63.8)	96.8 (89.0–99.6)	97.8 (88.5–99.9)
US+CDUS+AEI-High MI	63.7 (52.2–74.2)	96.8 (89.0–99.6)	97.8 (88.5–99.9)

CI, confidence interval; US, ultrasonography; AEI-High MI, agent emission imaging - high mechanical index; CDUS, color Doppler ultrasonography.



**Figure 6.** Individual and combined sensitivities and confidence intervals for gray-scale US, AEI-High MI mode and color Doppler US for the diagnosis of calculi smaller than 5 mm. (US, ultrasonography; HiMI, agent emission imaging - high mechanical index; CDUS, color Doppler US).

For calculi larger than 5 mm, gray-scale US had a high sensitivity (85.7% for 5–10 mm, and 97.8% for calculi larger than 10 mm). The contribution of color Doppler US and AEI High MI mode for calculi measuring 5–10 mm was very limited. For calculi larger than 10 mm, the sensitivity of gray-scale US (97.8%) was better than color Doppler US (89.1%) and AEI High MI mode (82.6%). This could be explained by more pronounced echogenicity and acoustic shadowing of larger calculi, making them more obvious in gray-scale US.

While we did not perform any experimental studies to reveal why some calculi demonstrated the AEI-High MI scintillation artifact, visual similarities suggest that both twinkling artifact and scintillation artifact might have a common origin. A recent study by Lu et al. (13) suggested that twinkling artifact could be generated by the interaction of sound waves with micro air bubbles trapped at the surface of the stone. The AEI-High MI mode uses high intensity ultrasound waves to detect bubbles for loss of correlation (LOC) imaging. LOC imaging, also known as sonoscintigraphy or stimulated acoustic emission and transient scattering uses an ultrasound pulse which is powerful enough to destroy the bubbles and produces a strong backscatter echo (14). The hypothesis of the destruction of trapped air bubbles suggested by Lu et al. (13) could be a possible explanation of the scintillation artifact; however, it might not be the only reason why the artifact is visible only on AEI-High MI mode and not on B-mode gray-scale imaging. In our study, the mechanical index values for gray-scale imaging and AEI-High MI mode imaging were recorded and were between 1.1–1.4 for gray-scale imaging and between 1.13–1.4 for AEI-High MI. This similarity suggests that the mechanical properties of the sound waves might not be the only influential factors, but the ultrasonic pulse creation techniques or post-processing techniques used by the AEI-High MI mode could also be equally or more important for the creation and visualization of the artifact; however, these technical details were not available on the sources provided by the manufacturer. Proper experimental studies would be required to verify these statements.

Our study had some limitations. Since our patient population included both elective

cases and urgent patients who had calculi detected on CT, the radiologists performing the US examinations were aware of the presence of urinary stones, but they were blinded to their count and their location. This could have created some bias during sonographic examinations. Another source of bias could be the fact that the images were interpreted by the same radiologists who also conducted the examinations; however, during the interpretation session, only one of the radiologists was familiar with the sonographic findings of that particular patient and the presence or absence of the artifacts were decided in consensus to be able to minimize the effects of bias. As examination results were reviewed and decided by two radiologists in consensus, it was not possible to test for intra- and interobserver variability, which could be accepted as another limitation. There was an interval of 0 to 14 days (average 6.4 days) between CT and US examinations, which could be sufficient for displacement or passage of the calculi; however, patients were questioned at the time of US examination for the presence of clinical symptoms suggesting such occurrences. Most of the calculi in our study were located at the level of the kidneys, with a small number of ureteric and bladder calculi. A study including more ureteric stones would be helpful in determining the performance of AEI-High MI mode imaging in this problematic group.

Another limitation of our study was that the Siemens Sonoline Antares device used in the study was the only ultrasound device in our department with contrast agent imaging capabilities, which includes the AEI-High MI mode. As a result, we did not have the opportunity to check if a similar artifact is created on other ultrasound devices with access to LOC imaging technique, produced by different manufacturers. Until such studies are conducted, it should be assumed that the artifact could be manufacturer or device specific.

In conclusion, we have observed that the scintillation artifact visualized on AEI-High MI mode could be used as an additional tool for the detection of urinary calculi. AEI-High MI had a higher sensitivity compared with gray-scale US and color Doppler US for the detection of calculi smaller than 5 mm, but it did not have a significant contribution for the detection of larger calculi. The combined use of US with AEI-High MI mode

could increase the detection rate of calculi smaller than 5 mm and also could be used as a method for verification of suspected calculi on gray-scale US.

#### Conflict of interest disclosure

The authors declared no conflicts of interest.



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