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Characterisation of urinary stones in the presence of iodinated contrast medium using dual-energy CT: a phantom study

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Abstract

Objective—To develop a dual-energy CT (DECT) method for differentiating uric acid (UA) from non-UA stones in the presence of iodinated contrast medium.

Methods—Thirty UA and 45 non-UA stones were selected after infra-red spectroscopic analysis and independently placed in a 1.5-ml vial, which was filled first with saline and then with increasing concentrations of iodine. For each condition, tubes were put in a 35-cm water phantom and examined using a dual-source CT system at 100 and 140 kV. Virtual unenhanced images created from CT data sets of the stones in iodine-containing solutions provided position and volume information. This map was used to calculate a CT number ratio to differentiate stone type. A region-growing method was developed to improve the ability to differentiate between UA and non-UA stones with iodinated contrast medium.

Results—The sensitivity for detecting UA stones was 100 % for unenhanced images but fell to 18 % with 20 mgI/ml iodine solution and 0 % for higher concentrations. With region growing, the sensitivity for detecting UA stones was increased to 100 %, 82 %, 57 %, 50 % and 21 % for iodine solutions of 20, 40, 60, 80 and 100 mgI/ml.

Conclusion—The region-growing method improves differentiation of UA from non-UA stones on contrast-enhanced DECT urograms.

Keywords

CT Urogram; Dual-energy CT; Urinary stone compositions; Virtual unenhanced CT; Region growing method

Introduction

Computed tomography (CT) has been used as a standard technique for the diagnosis of urinary calculi [1, 2]. It can provide accurate information about the size and location of urinary stones [3-5]. Also, CT attenuation values provide information about stone composition [6, 7]. This is of special interest because treatment strategies differ between patients with stones of different compositions. For example, patients with uric acid (UA) stones can be treated medically with urinary alkalinisation, whereas interventional stone removal is often required for patients with non-UA stones, such as those composed of cystine or calcium oxalate [8]. However, the accuracy of stone differentiation solely based on CT numbers is limited, primarily because of the overlap of densities among different stone types having different effective atomic numbers. This allows a dense stone of a low

atomic number to have the same CT attenuation as a porous stone of high atomic number. Recent developments in dual-energy computed tomography (DECT) have led to substantial progress in the non-invasive differentiation of urinary stone composition [9-16]. DECT utilises the attenuation information from two X-ray energies to de-couple the chemical composition and density of a given material, which cannot be accomplished with single-energy CT [17, 18].

DECT has also been used to create virtual unenhanced images for stone detection from contrast-enhanced acquisitions by subtracting iodinated material, where urinary stones are frequently not distinguishable from iodinated contrast material because they both appear bright on excretory-phase enhanced CT images [19-22]. The virtual unenhanced images created from DECT acquisitions can provide information about the size and location of urinary stones [19, 21, 22].

The purpose of this study was to extend the use of DECT to include stone composition analysis on contrast-enhanced acquisitions. The influence of the presence and concentration of iodine on UA and non-UA stone detection was investigated, and a region-growing correction method was developed to improve the ability to accurately differentiate UA from non-UA stones in the presence of iodine. In addition, the dependence of stone volume estimation on stone composition and contrast concentration was studied.

Materials and methods

Urinary stone samples

A total of 75 urinary stones, each collected from a different patient, were used in this phantom study, including 30 uric acid (UA), 15 cystine (CYS), 15 calcium oxalate (COX) and 15 calcium hydroxyapatite (APA) stones. The stone compositions were determined with Fourier transform infrared spectroscopy in our institutional mineral analysis laboratory. For each stone, the primary component was required to be greater than 90 % by volume so that it could be considered to be an essentially pure stone of a single material. The sizes of the stones ranged from 3 to 9 mm based on volume measurement from CT images.

Five concentrations of iodine solutions were prepared by diluting iodinated contrast medium (iohexol, Omnipaque 350, GE Healthcare) with saline: 20, 40, 60, 80 and 100 mgI/ml, which corresponded to CT numbers of approximately 393, 683, 973, 1,263 and 1,552 HU at 120 kV. Each stone was placed in a 1.5-ml plastic tube (Fig. 1a), and all tubes were then placed in a 35-cm water phantom to simulate realistic attenuation of a standard-sized patient (Fig. 1b). All stones were hydrated in distilled water for 24 h before imaging.

Dual-energy CT acquisitions

The phantom underwent imaging with a dual-source CT system (Definition Flash, Siemens Healthcare, Forchheim, Germany). Based on our clinical DECT stone composition protocol, dual-energy imaging was performed at tube voltages of 100 and 140 kV, with tin filtration applied to the 140-kV tube. The combination of 100 and 140 kV is more frequently used than 80 and 140 kV combinations in our clinical practice because many patients have a large body habitus. Automatic exposure control (CareDose 4D, Siemens Healthcare, Forchheim, Germany) was used with quality reference mAs values of 240 for 100 kV and 185 for 140 kV. Other imaging parameters included: beam collimation, 32×0.6 mm; pitch, 0.6; rotation time, 0.5 s.

Unenhanced imaging was first performed with the stones immersed in saline. The acquisition was then repeated five times, each time replacing the solution with one containing a higher concentration of iodine (20, 40, 60, 80 and 100 mgI/ml). The same

imaging parameters were used for all six acquisitions. Images were reconstructed at 1-mm thickness and a 0.8-mm increment, with a 150-mm field of view and a medium smooth kernel (D30). Linearly mixed images were also generated with equal weighting (0.5) of the two energies.

Post-CT image processing

Iodine-subtracted virtual unenhanced images were generated using commercial software (Syngo, Dual Energy Viewer, Siemens Healthcare, Forchheim, Germany) from the 100- and 140-kV images of the stones in iodine.

Stones were segmented using mixed images from the unenhanced acquisitions and virtual unenhanced images from the acquisitions with iodine. The CT number threshold was 200 HU for all images, which is the default value in our clinical urinary stone protocol. Commercial image processing software (Analyze 10.0, Mayo Clinic, Rochester, MN, USA) was used for stone segmentation and volume calculation. The segmentation results were used to identify the locations of the stones, and CT number ratios (CTRs) were calculated for each stone-containing pixel [15]. The CTR at every pixel of each stone was calculated as the ratio of the CT attenuation values in Hounsfield units at 100 and 140 kV. The CTR values for all pixels of a stone were averaged to represent the CTR of the whole stone.

When a stone was immersed in iodine, the CT number around its boundary was affected by the surrounding iodine solution because of partial volume averaging. This led to inaccurate CTR values and hence inaccurate stone differentiation. To correct for the influence of iodine on CTR values, a region-growing method was developed to identify the pixels in the stone CTR image that were not “contaminated” by iodine. The details of this algorithm are shown in Appendix A. By assuming that the CTR of a urinary stone is homogeneous and that only pixels around the stone boundary were changed by immersion in the iodine solution, the region-growing method was able to find uncontaminated pixels in the central part of the stone (Fig. 2). This method was implemented with a Matlab-based program (Matlab 7.11.0, MathWorks, Inc., Natick, MA, USA) and was fully automatic, requiring no user interaction beyond loading the images.

Statistical analysis

A two-tailed, unequal variance *t* test (Statistics Toolbox, Matlab) was used to analyse three groups of data for each stone composition:

1. Measured volume of each stone from true unenhanced mixed images versus volume from virtual unenhanced images;
2. Calculated CTR of each stone from true unenhanced images versus CTR from contrast-enhanced acquisitions;
3. Calculated CTR of each stone from true unenhanced images versus CTR of contrast-enhanced acquisitions using the region-growing correction method.

The sensitivity for the detection of UA stones has been previously reported for the same DECT devices and imaging protocols (100 and 140 kV) and the optimised threshold was determined through ROC analysis [23]. In this work, the same threshold (CTR=1.17) was used to calculate the sensitivity and specificity of detecting UA stones for the unenhanced acquisitions and the five acquisitions at varying iodine concentrations.

Results

All 75 stones were identifiable on virtual unenhanced images from acquisitions at all five iodine concentrations. Compared with the unenhanced acquisition, the UA stone volumes measured from virtual unenhanced images were similar in iodine solutions of 20 and 40 mgI/ml ($P>0.05$), but overestimated in solutions of 60, 80 and 100 mgI/ml ($P<0.05$; Table 1). For non-UA stones (CYS, COX and APA), virtual unenhanced images underestimated the volumes of stones in 20-, 40- and 60-mgI/ml iodine solutions ($P<0.05$) and overestimated volumes as iodine concentrations increased to 80 ($P<0.05$ only for APA) and 100 mgI/ml ($P<0.05$; Table 1).

With unenhanced acquisitions, the CTRs of the four stone types (UA, CYS, COX and APA) were 0.99 ± 0.03 , 1.31 ± 0.04 , 1.46 ± 0.05 and 1.52 ± 0.04 , respectively (mean $\pm$ standard deviation; Table 2). Except for the COX and APA stones in the 20-mgI/ml solution, the CTR values of all stones increased ($P<0.05$) when stones were immersed in iodine ($\text{CTR}_{\text{iodine}}=1.98\pm0.04$), and the error increased with the iodine concentration. Even for the lowest iodine concentration (20 mgI/ml), the mean CTR of UA stones increased from 0.99 ± 0.03 to 1.21 ± 0.04 , which is close to the CTR values of CYS stones from the true unenhanced acquisition (1.31 ± 0.04). The influence of iodine on the stone led to a substantial overlap between the CTR values of UA and non-UA stones (Fig. 3). Using a previously identified CTR threshold of 1.17 [18] to differentiate UA stones from non-UA stones, stones with CTR values less than or equal to 1.17 were categorised as UA stones, and all others were considered non-UA stones. At this threshold, the sensitivity for correctly identifying UA stones was 100 % for unenhanced acquisitions, and fell to 18 % with 20-mg/ml iodine solution and 0 for all higher concentrations (Table 4).

Using the region-growing correction method described in Appendix A, the error caused by partial volume averaging of the stone with surrounding iodine was reduced (Table 3). The overlap of CTR values between UA and non-UA stones was also substantially reduced (Fig. 4). Using the same CTR threshold value of 1.17, the sensitivity for detecting UA stones was increased to 100 %, 82 %, 57 %, 50 % and 21 % for iodine solutions at concentrations of 20, 40, 60, 80 and 100 mgI/ml, respectively (Table 4).

Discussion

Detection of urinary stones in iodine solutions by using DECT has been previously reported [19-21]. In this work, we further explored the potential for characterising urinary stones in the presence of iodine. Our results showed that, despite partial volume averaging with iodine, UA stones could be identified with the use of a region-growing correction method. This information about composition is of clinical interest. When a DECT urography study is performed without acquiring unenhanced CT, our approach will enable the stone's location, volume and composition to be estimated with reasonable accuracy. This is especially true when the concentration of iodine is low, which may result from the use of vigorous hydration, diuretics (e.g. furosemide), administration of a low dose of iodinated contrast media or diminished renal function. Furthermore, if a conventional CT urogram is performed at a single energy and a stone is detected, then repeat imaging with DECT can be performed immediately while contrast medium is still in the collecting system.

The size of urinary stones evaluated on virtual unenhanced images has been reported in several studies [19, 21]. Our stone segmentation results showed that the virtual unenhanced processing affects the stone volumes differently for UA and non-UA stones. In iodine solutions of concentrations up to 60 mgI/ml, volumes of UA stones remained approximately the same or just slightly increased, whereas volumes of all non-UA stones were substantially

reduced. This is because the three base materials assumed in the process of iodine removal are tissue, fat and iodine, an assumption that holds reasonably well for UA stones because they do not contain any high Z elements. However, for non-UA stones, the calcium components have effective atomic number values that are relatively higher than those of tissue and are therefore partially removed by the commercial algorithm. In iodine solutions of 100 mgI/ml, the measured volume of all stones was larger than the volume in unenhanced acquisitions; this was likely due to inadequate iodine removal at high concentrations [20].

Differentiation of urinary stone composition using DECT is based on the ratio of stone CT numbers at low and high energies. Non-UA stones with high atomic number elements such as calcium result in higher CTRs than UA stones [9, 12, 14]. However, this differentiation mechanism is challenged when iodine is present, because iodine has a higher CTR than both UA and non-UA stones. Because of the partial volume effect, the outer parts of the stones display substantially increased CTR when surrounded by iodine (Fig. 2). The region-growing method was used in this work to account for this error by finding the pixels in the stone that are not influenced by iodine.

Our results showed 100 % specificity for identifying UA stones, which implies that a UA stone could mistakenly be identified as a non-UA stone in iodine solution, but a non-UA stone is not likely to be misclassified as a UA stone. This observation indicates a reliable strategy for identifying UA stones. Even at the highest iodine concentration (100 mgI/ml), the corrected CTR of UA stones was about 1.25, which is close to the true CTR of CYS stones (around 1.3), but still well below the true CTR of calcified stones (from 1.4 to 1.5). CYS stones are much rarer than UA stones, and these two types can be reliably differentiated through a urine test. Thus, in practice, if the CTR of a UA stone falls within the range between UA and CYS using our region-growing method, it is still possible to identify its true composition by ruling out the possibility of CYS with a urine test. This can be beneficial in renal stone management because UA stones can be dissolved through urinary alkalinisation, thus avoiding the invasive treatment options, such as shockwave lithotripsy, needed for other stone types.

There are several limitations in this study. First, our region-growing method is based on two assumptions: first, that the inner part of the stone can be used to represent its composition, an assumption that is valid for stones mostly composed of a single material, but not for mixed stones containing a substantial amount of a second or third material; and second, that only the outer part of the stone is influenced by the surrounding iodine solution. However, if a stone is too small, it is possible that the CTRs of all pixels will be enhanced by iodine, and the correction method used here cannot identify the true CTR in this scenario. Second, studies have shown that small urinary stones can be missed after virtual unenhanced processing [20-22], especially in iodine solutions of high concentration. This limitation implies that enhanced DECT cannot yet replace an unenhanced CT acquisition for the purpose of stone detection. One potential solution is to reduce the iodine dosage to achieve the lowest effective concentration. This may also be facilitated, for example, by vigorous hydration of the patient and diuretics such as furosemide. The performance of these approaches for accurate stone detection in contrast-enhanced CT requires further investigation in a clinical scenario.

To conclude, in this study, we investigated the potential for using DECT to characterise urinary stones in the presence of iodine. The effect on volume and CTR measurements was studied in iodine solutions at five concentrations. Because of the partial volume effect, the CTR of stones was artificially increased by the surrounding iodine. We developed a region-growing correction method to identify the inner core of the stone, where CT numbers were

not influenced by the iodine. This allowed better differentiation of UA from non-UA stone types.

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Appendix

After the stone was segmented from the background soft tissue structures using the commercial virtual unenhanced technique, a binary map of stone position was applied to the CTR image ($CTR = CT_{low\text{ kV}}/CT_{high\text{ kV}}$). For each stone, the centre slice along the z direction was used to determine the starting point of the region-growing iterative process (Fig. A1a). First, an internal region was acquired by performing a four-pixel by four-pixel area of erosion on the CTR map of the centre slice. Then, the pixel with the closest CTR value to the average CTR of the internal region was chosen as the starting point (the seed). Starting from the seed, the nearest 26 neighbouring pixels were searched (Fig. A1b) in an iterative process (Fig. A2) to find all pixels that had CTR values within a certain range relative to the mean CTR of the stone. The width of the range is the only parameter to be defined before the iteration. Here $0.2 (\pm 0.1)$ was used for all stones at all five iodine concentrations. As shown in Fig. A2, the mean CTR was updated at each iteration and, as more pixels were included, it was expected to approach the true CTR of the stone, with those pixels affected by iodinated contrast medium (far away from the centre) excluded.

Abbreviations and acronyms

CT	computed tomography
DECT	dual-energy computed tomography
UA	uric acid
CYS	cystine
COX	calcium oxalate
APA	calcium hydroxyapatite
CTR	CT number ratio

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Key Points

- Computed tomography is widely used to assess renal tract calculi
- Dual-energy CT can assess stone composition and provide virtual unenhanced images
- However, iodinated contrast medium affects the volume estimation for urinary stones.
- CTR of stones is altered by the surrounding iodine in CT urograms.
- The region-growing method improves the identification of uric acid stones.

Fig. 1.
a A urinary stone was placed in a vial filled with either saline or iodine solution. **b** Stone samples were immersed in a 35-cm water phantom for the dual-energy CT acquisition

Fig. 2.
(Top row) The CT number ratio (CTR) map of a uric acid stone in saline (0), and 20, 40, 60, 80 and 100 mg/ml iodine solution. (Bottom row) The CTR map after application of the region-growing method

Fig. 3.

CTRs of uric acid (UA), cystine (CYS), calcium oxalate (COX) and calcium hydroxyapatite (APA) stones in saline and iodine solutions at five different concentrations, calculated by averaging over the whole stone volume. The low and high edge of the box represents the lower and upper quartiles, respectively. The low and high limit of the spread represents the lowest datum within 1.5 IQR of the lower quartile and the highest datum within 1.5 IQR of the upper quartile (IQR is the interquartile range which is the difference between the upper and lower quartiles). The data falling out of this range are considered as outliers as illustrated by a red cross

Fig. 4. Using the region-growing correction method, the CTRs of uric acid (UA), cystine (CYS), calcium oxalate (COX) and calcium hydroxyapatite (APA) stones in saline and iodine solutions showed substantially reduced overlap

Fig. A1.

a A CTR map of a uric acid stone immersed in iodine solution. The red dot in the centre represents the starting point of the region-growing iterative process. **b** The 26 neighbouring pixels of the starting point

Fig. A2.
The iterated steps of the region-growing method

Table 1

Volume measurements of each stone type from unenhanced mixed images and virtual unenhanced images

	Unenhanced	20 mgI/ml	40 mgI/ml	60 mgI/ml	80 mgI/ml	100 mgI/ml
UA	72.01±36.52 ^a	70.56±39.62 ^b	73.35±42.3 ^b	77.02±41.52	79.94±45.39	92.55±53.06
CYS	154.02±79.65	125.19±72.93	134.16±81.6	138±84.44	149±82.57 ^b	179.71±105.63
COX	166.21±101.64	130.98±94.69	131.91±98.4	142.57±104.3	168.38±20.59 ^b	195.73±135.91
APA	127.35±66.31	91.94±58.34	91.74±57.9	97.37±61.15	111.94±78.44	144.46±99.5

UA = uric acid, CYS = cystine, COX = calcium oxalate, APA = calcium hydroxyapatite

^aData are shown as mean± standard deviation, in mm³^bResults are not statistically different from the corresponding unenhanced acquisition

Table 2

CT number ratio for each stone type determined by averaging over the whole stone volume from virtual non-enhanced images

	Unenhanced	20 mgI/ml	40 mgI/ml	60 mgI/ml	80 mgI/ml	100 mgI/ml
UA	0.99±0.03 ^a	1.21±0.04	1.33±0.04	1.41±0.05	1.46±0.05	1.54±0.05
CYS	1.31±0.04	1.36±0.04	1.43±0.04	1.47±0.05	1.52±0.04	1.57±0.06
COX	1.46±0.05	1.46±0.02 ^b	1.48±0.02	1.51±0.03	1.58±0.03	1.61±0.04
APA	1.52±0.04	1.51±0.03 ^b	1.55±0.03	1.58±0.02	1.63±0.02	1.65±0.03

UA = uric acid, CYS = cystine, COX = calcium oxalate, APA = calcium hydroxyapatite

^aData are shown as mean±standard deviation

^bResults are not statistically different from the corresponding unenhanced acquisition

Table 3

CT number ratio for each stone type determined by using the region-growing method

CTR	Unenhanced	20 mgI/ml	40 mgI/ml	60 mgI/ml	80 mgI/ml	100 mgI/ml
UA	0.93±0.04 ^a	1.05±0.05	1.12±0.07	1.15±0.08	1.18±0.11	1.25±0.11
CYS	1.26±0.05	1.28±0.05	1.29±0.05	1.33±0.07	1.32±0.08	1.34±0.08
COX	1.41±0.03	1.42±0.03 ^b	1.41±0.04 ^b	1.4±0.03 ^b	1.42±0.03 ^b	1.41±0.06 ^b
APA	1.47±0.04	1.47±0.04 ^b	1.48±0.05 ^b	1.49±0.05 ^b	1.52±0.05	1.52±0.07

UA = uric acid, CYS = cystine, COX = calcium oxalate, APA = calcium hydroxyapatite

^aData are shown as mean±standard deviation^bResults are not statistically different from the corresponding unenhanced acquisition

Table 4

The sensitivity and specificity of differentiating UA stones ($n=30$) from non-UA stones ($n=45$)

		Unenhanced	20 mgI/ml	40 mgI/ml	60 mgI/ml	80 mgI/ml	100 mgI/ml
Averaging over the whole stone volume	Sensitivity	100 %	36%	0	0	0	0
	Specificity	100 %	100 %	100 %	100 %	100 %	100 %
Region-growing	Sensitivity	100 %	100 %	82%	57%	50%	21 %
	Specificity	100 %	100 %	100 %	100 %	100 %	100 %