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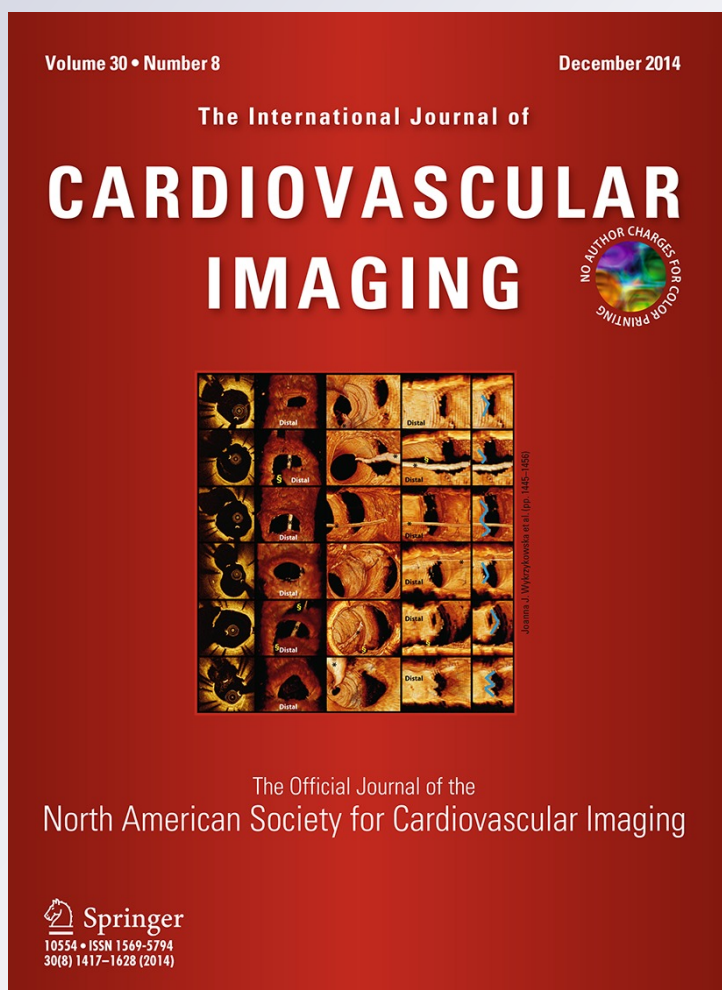
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Substantial iodine volume load reduction in CT angiography with dual-energy imaging: insights from a pilot randomized study

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Abstract We explored whether dual-energy computed tomography (DECT) can allow a significant reduction in iodinated contrast volume during computed tomography angiography (CTA) without hampering image quality or assessability. We prospectively randomized patients clinically referred to CTA to single energy computed tomography (SECT) with full iodine volume load (group A), DECT with 50 % iodine volume load (group B), DECT with 40 % iodine volume load (group C), and DECT with 30 % iodine volume load (group D); and compared image quality and assessability. Eighty patients were enrolled and prospectively randomized. The mean age was 61.7 ± 15.0 years and 56 (71 %) patients were male. The demographical characteristics, body mass index, or mean radiation dose did not differ between groups. Significant reductions in total contrast volume were achieved in groups B, C, and D; with mean administrated contrast volumes of 90.3 ± 10.1 , 39.5 ± 4.6 , 28.3 ± 6.5 , and 23.9 ± 6.0 mL, respectively, in groups A to D ($p < 0.0001$). With regard to image quality, no significant decrease in the Likert scale was observed with reductions of up to 60 % of the contrast volume (groups B and C). DECT at 50–60 keV in association with up to 60 % iodine load reduction, allowed similar signal density, image noise, and signal to noise ratio that SECT imaging with full iodine load. In this pilot, prospective, randomized study, dual energy CTA with up to 60 % iodine volume load reduction provided

similar image quality and assessability than full iodine load with conventional SECT imaging.

Keywords Spectral · Computed tomography · Contrast · Nephropathy

Introduction

The past decade has witnessed a significant increase in the number of computed tomography angiography (CTA) studies. While a powerful test, it is limited in its applicability to those patients with impaired renal function. Contrast-induced acute kidney injury (CIAKI) is a relatively common, though usually clinically silent, complication after intravenous administration of iodinated contrast during CTA studies, and it is highly related to several risk factors such as baseline renal function, diabetes, heart failure, male sex, hypertension, peripheral vascular disease, and anemia, among others [1, 2]. Indeed, CIAKI is the third cause of acute renal failure in hospitalized patients [3]. In addition, the incidence of CIAKI is related to iodinated contrast volume, type, and to the administration route [4]. Within the elective setting in stable patients, it has been shown that more than 20 % of patients with normal creatinine levels have underlying subclinical renal dysfunction [5]. For the aforementioned reasons, there is an increasing call for measures that can achieve a substantial reduction in the iodinated contrast volume load.

Dual-energy CT (DECT) with rapid kV switching allows the reconstruction of low and high energy projections and generation of monochromatic image reconstructions [6]. Accordingly, by means of low energy monochromatic imaging, higher intravascular attenuation levels can be attained, since with the administration of

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iodinated contrast material vessels portray higher attenuation levels at lower energies than at higher energies, being this attributed to the fact that lower energies are closer to 33.2 keV, the K edge of iodine [7]. We therefore attempted to explore whether this attribute of DECT can allow a significant reduction in iodinated contrast volume during CTA without hampering image quality or assessability.

Methods

Study population

In this investigator driven, pilot prospective study, patients clinically referred to thoracic and/or abdominal aortic CTA due to suspected aortic disease (dissection, aneurysm, connective tissue disorders, or complex atherosclerosis) between February and July 2013, were randomly assigned (block randomization in order to balance sample size across groups) to single energy CT (SECT) with full iodine volume load (group A), DECT with 50 % iodine volume load (group B), DECT with 40 % iodine volume load (group C), and DECT with 30 % iodine volume load (group D). All patients included were more than 18 years old, without a history of contrast related allergy, renal failure, hemodynamic instability, or a body mass index $>32 \text{ kg/m}^2$.

CTA acquisition

All CTA studies were acquired using a DECT scanner equipped with gemstone detectors with fast primary speed and low afterglow designed for spectral imaging (Discovery HD 750, GE Medical Systems, Milwaukee, USA), capable of rapid switching (0.3–0.5 ms) between low and high tube potentials (80–140 kV) from a single source, thereby allowing the reconstruction of low and high energy projections and generation of simulated monochromatic image reconstructions with 10 keV increments from 40 to 80 keV.

Scanning parameters for SECT imaging were the following: tube voltage 120 kV; tube current 250–350, slice thickness 2.0/1.0 mm; rotation time 350 ms. Scanning parameters for DECT imaging were the following: tube voltage 80–140 kV; tube current 250–375 mA, slice thickness and rotation time was the same as for SECT.

In order to reduce the contrast medium to a minimum, timing bolus was not used, since it would have implied an administration of additional 20 mL of iodinated contrast. Instead, to synchronize the data acquisition with the arrival of contrast material in the aorta, contrast injection phases were designed to last 12 s, and a bolus tracking technique located was used to monitor the intravascular traffic of

contrast medium. The region of interest for synchronization of data acquisition was located at the mid ventricular level (with acquisition start after contrast arrival to the right ventricle).

Conventional SECT angiograms were obtained after administration of 60–100 mL of iodinated contrast (iobitridol, Xenetix 350TM, Guerbet, France) according to the body mass index (BMI) and body habitus. On a per protocol basis, patients with a BMI $\leq 25 \text{ kg/m}^2$ received 60 mL, patients BMI between 25 and 27 kg/m^2 received 70–80 mL, patients with a BMI between 28 and 30 kg/m^2 received 80–100 mL, and patients with a BMI equal or greater that 30 kg/m^2 received 100 mL. Likewise, the same approach was adopted for DECT angiograms, though with respective contrast volume reductions for groups B, C, and D.

SECT angiograms were performed using a dual phase protocol, with the total undiluted contrast medium injected at a rate of 4–4.5 mL/s, followed by a 30 mL chasing bolus of normal saline at 3–4 mL/s.

DECT angiograms were obtained after administration of 50 % the contrast medium volume (group B), 40 % of the contrast medium volume (group C), and 30 % of the contrast medium volume (group D). All DECT angiograms were obtained using a three-phase protocol, as follows. Phase 1: 50 % of the total iodinated contrast volume being injected undiluted at a rate of 3.5–4.0 mL/s; phase 2: the other 50 % of the contrast medium mixed at a 50 % saline dilution, injected at a rate of 2.5–4.0 mL/s; and phase 3: a 20–30 mL saline chasing bolus at a rate of 2.5–3.0 mL/s.

CTA analysis

All studies were analyzed offline using a dedicated workstation (AW 4.6 Advantage WS; GE Healthcare) by consensus of two experienced observers (PC; 15 years of experience in CTA, and CC; 15 years of experience in CTA). All DECT studies (with 50, 40, and 30 % iodine volume load) were analyzed by observers blinded to the clinical data and randomization allocation. Single energy CT studies were not blinded to the observers since the coding of the dedicated workstation does not allow modifications in the labeling of the data source. SECT studies were reconstructed using a standard iterative reconstruction algorithm, at 40 % ASIR (adaptive statistical iterative reconstruction). DECT studies were reconstructed at independent monochromatic energy levels ranging from 40 to 80 keV, with incremental levels of 10 keV. 60 keV is the lowest monoenergetic level available for the reconstruction of images utilizing an iterative reconstruction algorithm. The raw data was processed using axial views, multiplanar reconstructions, and maximum intensity projections.

Both on SECT images and on each energy level (40–80 keV) at DECT, image quality, vessel attenuation and signal noise was evaluated at central vessels (thoracic aorta for thoracic CTA and abdominal aorta for abdominal CTA). In addition, at DECT imaging, the best energy level was determined subjectively by consensus of the two observers.

In addition, quantitative image quality assessment was performed using a 10-point Likert scale, being the scores 1–3 defined as poor image quality, with excessive noise and/or poor vessel wall definition; scores 4–5 defined as adequate, though reduced image quality either with excessive image noise or poor vessel wall definition; scores 6–7 defined as good image quality with some image noise and minimal limitations of vessel wall definition; scores 8–9 defined as very good image quality with minimal image noise; and 10 define as excellent image quality, with excellent attenuation of the vessel lumen and clear delineation of vessel walls. Scores below 5/10 were deemed non-diagnostic.

The extent of vascular attenuation (in Hounsfield units) was measured using standardized regions of interest (ROI) of 20 mm² at the aorta (at the ventricular level for thoracic studies and at the celiac trunk for abdominal studies). For DECT studies, the location and size of the ROIs were automatically propagated to all energy levels.

Image noise and signal-to-noise ratios (SNR) were further calculated. Image noise was defined as mean standard deviation of the signal density (in Hounsfield units) within the aforementioned ROIs. The signal-to-noise ratio was defined as the ratio between the mean signal density and the image noise.

The institutional review board approved the study protocol, which complied with the Declaration of Helsinki, and written informed consent was obtained from all patients.

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as mean \pm SD. Comparisons among groups were performed using independent samples *t* test, one-way analysis of variance, and Bonferroni tests, as indicated. On the basis of an interim analysis showing that the mean SNR was 20 with SECT and 15 with DECT, we calculated a sample size of 58 experimental subjects and 15 control subjects in order to achieve a power of 80 % to detect a true difference in population means, considering a type I error of 0.05 (two-sided) and a within group standard deviation of 6. Intra- and interobserver variability analyses were performed in 12 randomly selected cases of each dual energy group (50 % iodine volume load reduction, 60 % reduction, and 70 % reduction) at all energy levels (40, 50, 60, 70, and 80 keV). Three variables were evaluated in this regard: signal density, image noise, and signal to noise ratio. Given the large amount of data and the excellent intraobserver and

interobserver correlations (Pearson correlation coefficients), Bland–Altman analyses were deemed unnecessary. Statistical analyses were performed using SPSS software, version 13.0 (Chicago, Illinois, USA). A two-sided *p* value of <0.05 indicated statistical significance.

Results

Eighty patients with clinical indication to undergo CTA were enrolled and prospectively randomized to SECT with full iodine load (group A, *n* = 20), DECT with 50 % iodine load (group B, *n* = 20), DECT with 40 % iodine load (group C, *n* = 20), and DECT with 30 % iodine load (group D, *n* = 20). The mean age was 61.7 \pm 15.0 years. Fifty-six (71 %) patients were male. The demographic characteristics, including the body mass index, did not differ between groups (Table 1). The mean radiation dose was similar (SECT 6.0 \pm 1.3 vs. DECT 5.0 \pm 1.8, *p* = 0.34) between groups.

Contrast volume and image quality

As expected by the protocol design, significant reductions in total contrast volume were achieved in groups B, C, and D; with mean administered contrast volumes of 90.3 \pm 10.1, 39.5 \pm 4.6, 28.3 \pm 6.5, and 23.9 \pm 6.0 mL, respectively, in groups A to D (*p* < 0.0001).

All studies were classified as interpretable, with Likert scale classification \geq 6/10 in all cases. No significant decrease in the Likert scale (Table 1) was observed with reductions of up to 60 % of the contrast volume (groups B and C); whereas CTA with a 70 % reduction of contrast volume (group D) was associated with a significant drop in image quality (8.8 \pm 1.0 vs. 7.9 \pm 1.0, *p* = 0.046).

Within DECT groups, the best energy level was selected by consensus of the two readers. The best energy level was 60 keV for group B (90 % 60 keV, 10 % 70 keV), 50 keV for group C (70 % 50 keV, 30 % 60 keV), and 50 keV for group D (60 % 50 keV, 35 % 40 keV, 5 % 60 keV).

Signal density and signal to noise ratio

SECT studies with full iodine load achieved mean signal density levels of 334.3 \pm 97.9 HU, with a mean noise levels of 28.7 \pm 26.5 HU, and a mean SNR of 15.7 \pm 8.7. An excellent correlation was found regarding intraobserver and interobserver measurements of signal density levels, image noise, and signal-to-noise ratios, all significant with an *r* \geq 0.94 (Table 2). Table 2 and Fig. 1 portray the signal density values, noise, and SNR of DECT studies with different contrast load reductions and reconstructions at independent monochromatic energy levels ranging from 40 to 80 keV, with incremental levels of 10 keV. It is evident

Table 1 Demographical characteristics and image quality according to iodine volume load

	n	Iodine load	Male	Age	BMI	Contrast volume	Image quality
Single energy CT							
Group A	20	100 %	75 %	64.8 ± 15.7	27.2 ± 1.7	90.3 ± 10.1	8.8 ± 1.0
Dual energy CT							
Group B	20	50 %	65 %	59.7 ± 12.5	26.2 ± 1.9	39.5 ± 4.6*	8.8 ± 1.0
Group C	20	40 %	68 %	64.1 ± 17.5	27.1 ± 4.9	28.3 ± 6.5*	8.9 ± 1.0
Group D	20	30 %	75 %	58.1 ± 14.0	26.3 ± 6.0	23.9 ± 6.0*	7.9 ± 1.0**
ANOVA				0.41	0.81	<0.0001	0.008
Chi square			0.87				

ANOVA one-way analysis of variance, BMI body mass index

* $p < 0.0001$; ** $p = 0.046$ versus full contrast load with single energy CT

Table 2 Signal density and image noise levels according to iodine volume load

Iodine load	keV	Signal density (HU)	Noise	SNR	SNR Variability (r)	
					Interobserver <i>r</i> (<i>p</i> value)	Intraobserver <i>r</i> (<i>p</i> value)
Single energy CT (group A)						
100 %		334.3 ± 97.9	28.7 ± 26.5	15.7 ± 8.7		
Dual energy CT (group B)						
50 %	40	658.0 ± 84.6*	44.5 ± 11.9**	15.3 ± 5.9	0.99 (<0.0001)	0.99 (<0.0001)
50 %	50	459.1 ± 54.2*	33.9 ± 9.2	14.5 ± 6.1	0.99 (<0.0001)	0.99 (<0.0001)
50 %	60	329.2 ± 47.6	25.0 ± 8.2	14.0 ± 6.2	0.98 (<0.0001)	0.97 (<0.0001)
50 %	70	227.9 ± 30.8**	19.3 ± 6.2	12.5 ± 4.5	0.98 (<0.0001)	0.96 (<0.0001)
50 %	80	186.8 ± 34.1*	17.1 ± 5.8	12.2 ± 6.7	0.99 (<0.0001)	0.96 (<0.0001)
Group C						
40 %	40	544.3 ± 117.1*	39.4 ± 14.7	16.2 ± 8.3	0.99 (<0.0001)	0.96 (<0.0001)
40 %	50	380.6 ± 89.5	28.0 ± 10.2	16.1 ± 8.5	0.99 (<0.0001)	0.96 (<0.0001)
40 %	60	273.4 ± 67.2	20.4 ± 8.0	16.7 ± 10.4	0.99 (<0.0001)	0.94 (<0.0001)
40 %	70	199.7 ± 47.3*	15.7 ± 6.9**	16.3 ± 10.8	0.99 (<0.0001)	0.94 (<0.0001)
40 %	80	156.9 ± 36.1*	14.2 ± 5.9**	13.7 ± 8.3	0.99 (<0.0001)	0.94 (<0.0001)
Group D						
30 %	40	487.5 ± 128.2*	38.7 ± 13.5	14.1 ± 5.6	0.99 (<0.0001)	0.97 (<0.0001)
30 %	50	326.9 ± 86.5	26.5 ± 10.3	14.3 ± 6.7	0.98 (<0.0001)	0.98 (<0.0001)
30 %	60	229.0 ± 54.5**	18.3 ± 8.0	15.0 ± 7.7	0.99 (<0.0001)	0.98 (<0.0001)
30 %	70	170.4 ± 44.8*	12.4 ± 5.3**	15.8 ± 6.4	0.99 (<0.0001)	0.99 (<0.0001)
30 %	80	127.0 ± 28.0*	12.6 ± 5.9**	12.0 ± 5.2	0.95 (<0.0001)	0.99 (<0.0001)

DECT dual energy computed tomography, SNR signal-to-noise ratio

* $p < 0.0001$; ** $p < 0.05$ versus full contrast load with SECT (single energy computed tomography)

from these data that compared to SECT with full iodine load, low energy reconstructions (40 keV) were related to higher signal density levels, and higher image noise, while high energy reconstructions (80 keV) were associated with lower signal density levels and lower image noise.

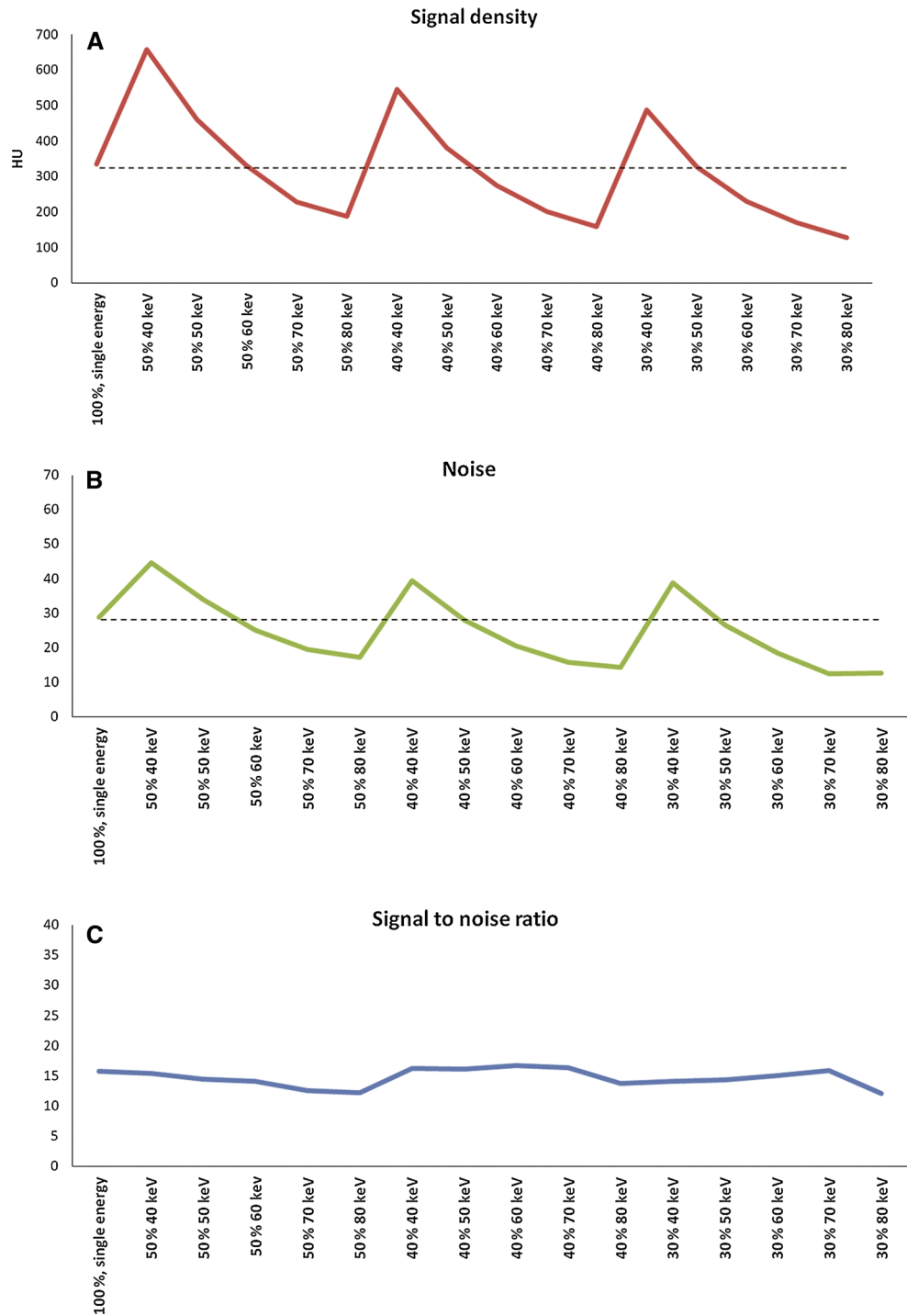
As depicted in Table 2 and Fig. 2, DECT at mid energetic levels (60 keV for 50 % iodine load, and 50 keV for 30–40 % iodine load) in association with up to 60 % iodine volume load reduction, allowed similar signal density, image noise, and SNR that SECT imaging with full iodine

load. Nevertheless, 70 % iodine load reduction was related to a significant decrease in signal density values.

Discussion

The main finding of the present study was that dual energy CTA imaging allowed up to 60 % iodine volume load reduction, with similar image quality and assessability than full iodine load with conventional SECT imaging.

Fig. 1 Line graph illustrating the signal density values (a), image noise (b), and signal-to-noise ratio (c) at SECT angiography and at DECT angiography, according to the percent of iodine volume load (100, 50, 40, and 30 %). For DECT imaging, the different monochromatic keV levels (40 to 80 keV) are depicted



The incidence of CIAKI is low in patients with normal renal function. Nevertheless, despite a considerable heterogeneity between populations included, CIAKI definition, or types of procedures evaluated, there is general agreement that the risk of CIAKI is significantly higher in patients with established risk factors [8]. Indeed, a recent prospective study reported a 11 % incidence of CIAKI after contrast-enhanced CT in the outpatient setting [9].

A great number of preventive strategies have been proposed and attempted in order to reduce the incidence of CIAKI associated to iodinated contrast exposure, most of them having failed to demonstrate a consistent beneficial effect. Indeed, the most effective strategy has been to encourage an adequate volume expansion with intravenous hydration before and after the procedure.

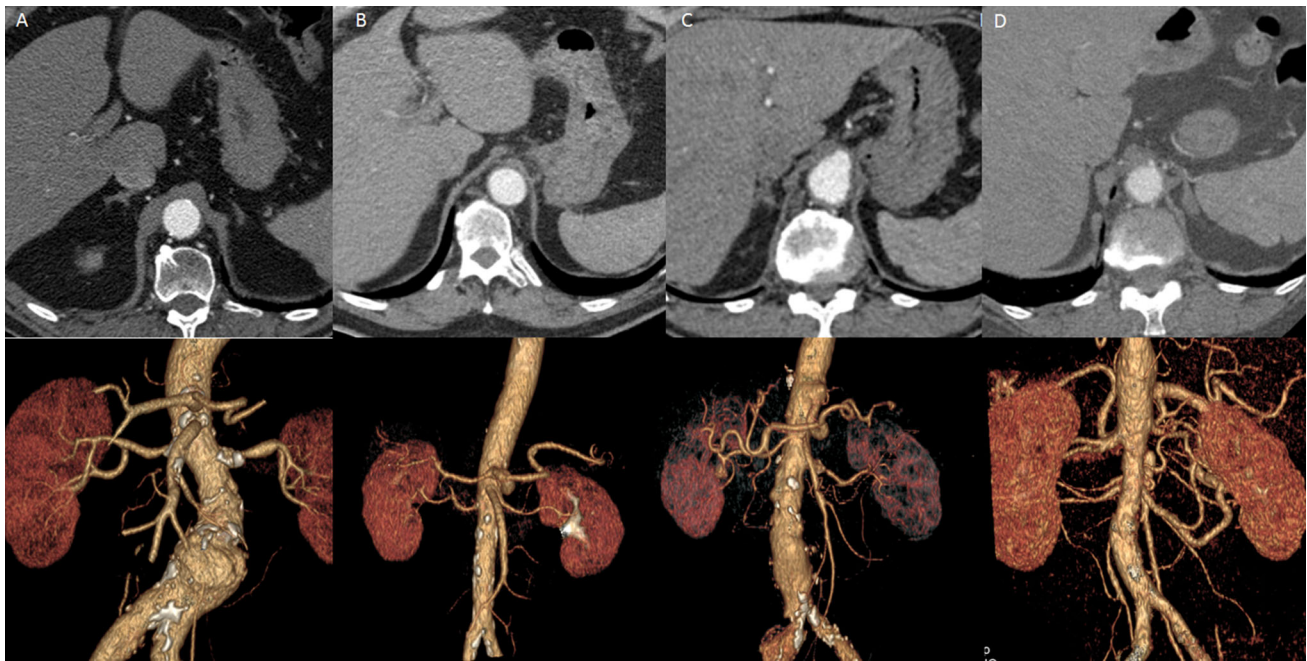


Fig. 2 Axial views (*upper panel*) and volume rendering reconstructions (*lower panel*) of computed tomography aortic angiograms (CTA) with conventional SECT will full iodine volume load and DECT imaging at different levels of iodine volume reduction. **a** Conventional SECT CTA with 100 % iodine volume load. The mean signal density was 301.0 ± 38.9 HU. **b** DECT CTA with 50 %

iodine volume load, at 60 keV reconstruction. The mean signal density was 301.7 ± 28.3 HU. **c** DECT CTA with 40 % iodine volume load, at 50 keV reconstruction. The mean signal density was 389.6 ± 35.4 HU. **d** DECT CTA with 30 % iodine volume load, at 50 keV reconstruction. The mean signal density was 339.3 ± 43.8 HU

The total volume of contrast material administered is related to the risk of CIAKI. In fact, in patients with chronic kidney disease undergoing invasive angiography, the use of ultra low (<50 mL) contrast volume was associated with a reduction in CIAKI, with each additional 20 mL leading to a twofold increase in risk [10].

A previous study has established the feasibility to perform pulmonary CTA with low contrast volume by means of a low tube voltage setting (80 kV) [11]. In addition, a recently published report has demonstrated the ability of dual energy CTA with low concentration contrast medium to achieve suppression of streak artifacts around systemic veins, whilst preserving intravascular enhancement [12]. Our study differs from such investigation in two main aspects. Firstly, the approach of Delesalle et al. was to reduce iodine concentration, using a contrast medium with a concentration of 240 mg of iodine per milliliter, whereas ours was to reduce iodine volume load, using the standard iodine concentration for angiographic studies (350 mg of iodine per milliliter).

Lastly, in their investigation, dual energy CT was based on a CT scanner equipped with two independent X-ray tubes and set of detectors at an angular offset of 90° – 94° , with one tube operating at 80 or 100 kV and the other operating at 140 kV. Such approach has certain established limitations: a

limited field of view, increased scattered radiation, and potential mismatch in the projection views between the high and low tube projections when scanning moving objects such as the ascending aorta. On the other side, the detector oriented approach that we explored comprises a CT scanner with a single X-ray tube capable of rapid switching between 80 and 140 kV, hence shows promise to overcome most of the aforementioned limitations.

Further studies using DECT imaging are warranted to explore the safety profile and image quality outcomes of different strategies (volume vs. concentration) aimed to reduce the iodine load.

To the best of our knowledge, our study is the first prospective investigation aimed to explore and demonstrate the feasibility and assessability of CTA performed with up to 70 % reduction in iodine volume load. Differences between the injection protocols applied (biphasic for SECT and triphasic for DECT angiograms) were based on the fact that since SECT angiograms were performed with full iodine volume, a conventional biphasic protocol was sufficient to allow stable attenuation levels throughout the entire acquisition. On the contrary, the limited contrast volumes associated with DECT angiograms required triphasic protocols that would enable stable attenuation levels throughout the entire acquisition, and minimization of beam hardening artifacts [13].

The demonstration of the viability of CTA with such reductions in iodine load with comparable image quality might have relevant clinical implications, setting the grounds for the potential use of dual energy CTA with low iodine load as an alternative strategy in patients at high risk of CIAKI.

Moreover, dual energy CTA achieved an adequate image quality, though significantly lower than SECT, in acquisitions with iodine load lower than 30 mL (70 % reduction). It is confirmatory yet remarkable that DECT reconstructions at low energy levels afford a significant increase in signal density levels, though at an expense of higher image noise.

Indeed, it should be emphasized that within the subset of patients with 70 % reduction, satisfactory signal density levels could be achieved only at low energy levels (40–50 keV), where signal noise is higher and iterative reconstruction is not feasible. These findings deserve further exploration, since it has been recently shown that in azotemic patients with diabetes undergoing coronary angiography, the incidence of CIAKI can be minimized by using <30 mL of contrast volume [14]. In parallel, although CT angiography studies are not aimed at evaluating low contrast object detection, DECT imaging at low energy levels might provide additional relevant information regarding surrounding tissues [15].

Finally, it is noteworthy that DECT imaging was not related to an increase in effective dose radiation levels.

Several limitations of our study have to be acknowledged. Although statistically powered, the relatively small sample size might potentially lead to selection bias. Furthermore, even though similar image quality and assessability were attained with the different strategies, it should be recognized that the primary outcome were mainly intravascular enhancement and noise levels, whereas assessment of plaque characteristics or determination of specific diagnostic scenarios, hence diagnostic accuracy, remained outside the Scopus of the current investigation. Notwithstanding, it should be stressed that with the advent of CTA invasive aortic angiograms are no longer performed for confirmation of vascular disease, yielding CTA already a reference standard. The clinical impact of performing low iodine CTA with DECT should be assessed in prospective studies with clinically driven endpoints. In addition, low energy DECT imaging is contraindicated in obese patients since it is associated to increased image noise. With the aim to reproduce routine CTA studies to be used as control group, SECT angiograms were obtained using dual phase injection protocols, as routinely used in our institution. Instead, all DECT angiograms required a triple phase injection, since the significantly lower contrast volume demands triple phase injections. Whether this might have influenced intravascular attenuation levels

cannot be fully discarded. Lastly, with regards to any potential clinical implications among patients at risk of CIAKI, our results can only be judged as hypothesis generating, since we neither tested at risk patients, nor we screened serum creatinine levels before and after the scans.

In conclusion, in this pilot, prospective, randomized study, dual energy CTA imaging with up to 60 % iodine volume load reduction provided similar image quality and assessability than full iodine load with conventional single energy CTA imaging. Although preliminary and hypothesis generating, our findings might potentially have relevant clinical implications for patients at risk for CIAKI.

Conflict of interest We declare that Drs. Patricia Carrascosa and Jonathon Leipsic are Consultants of GE. There are no competing interests related to the manuscript for any of the other authors.

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