Potential of Gadolinium as contrast material in second generation dual energy computed tomography (DECT): an ex-vivo phantom study

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Aims and objectives

Up to now, all clinically used intravenous contrast materials (CM) for computed tomography (CT) invariably contain iodine. On the one hand iodine guarantees high attenuation levels due to the high anatomic number of Z = 53. The energy dependent attenuation of iodine shows a specific maximum at 33.2 keV (k-edge) and therefore fits to the commonly used energy spectra from about 25 - 150 keV of medical CT. On the other hand, several relative and absolute contraindications towards intravenous iodine administration like hyperthyreodism, impaired renal function and known allergic reaction exist. These patients would profit from non-iodinated CM.

A known alternative to ICM is the use of gadolinium-containing MRI contrast media (GdCM) in CT. In theory, gadolinium (Gd) with higher atomic number (Z = 64) and k-edge (50.2 keV) should cause higher attenuation values than iodine. The main limitation in using GdCM issues from adverse reaction especially from so called nephrogenic systemic fibrosis (NSF). NSF exclusively develops in patients with acute or chronic renal disease and the development of cyclical structured GdCM lowered the incidence of NSF in the risk population to a minimum of 0.06 to 3.5% [1-3]. In the past 20 years several studies investigated the potential of GdCM in CT. In conclusion the commonly used "off label" doses up to 0.5 mmol/kg body weight of GdCM effect contrast values comparable with half-dose ICM [4-6]. Manufacturers of commercially available GdCM recommend standard doses for MRI at about 0.1 mmol/kg body weight. Nevertheless administration of so called double or triple doses up to 0.3 mmol/ kg Gd seem to be safe [7;8].

New software algorithms for post processing of Dual energy computed tomography (DECT) data allow the augmentation of attenuation levels resulting from iodine by computing so called monoenergetic images with virtual energies between 40 and 190 keV. Initial studies show beneficial effects in liver imaging and in detecting thrombosis [9;10]. Additionally, DECT affords the opportunity of calculating virtual non-enhanced images, iodine images and of quantifying the amount of iodine without increasing the radiation dose [11;12]. Benefits in differentiating benign from malign tumors as well as evaluation therapy responses in several malignancies have been reported [13-15].

The objective of this study was to evaluate the potential of GdCM as contrast material in second generation DECT: Figuring out whether it is feasible to achieve suitable attenuation levels using advanced monoenergetic extrapolation, whether it is possible to calculate virtual non enhanced images (Gd-VNC) and Gd-maps as well as to accurately quantify Gd.
Methods and materials

Phantom study

Six different dilutions of GdCM (Gadovist® (Bayer Schering Pharma, Leverkusen, Germany): 400µl, 200µl, 100µl, 50µl, 25µl and 12.5µl in 10 ml of distilled water, respectively) were created and filled into six standard polyethylene 5 ml aspiration syringes (syringe #1 to #6). A 7th syringe contained distilled water exclusively. All seven syringes were placed in the center of an attenuation phantom with a diameter of 26 cm in a circular order to provide homogenous x-ray attenuation (image as supplemental material). In a second setup, ICM (Ultravist® 370, Bayer Schering Pharma, Leverkusen, Germany) was diluted in the same manner an examined.

CT scanning protocol

All CT scans were acquired using a second generation dual source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Germany). To estimate a suitable CTDIvol, the phantom was initially scanned with automatic dose calculation (CareDose4D, Siemens Healthcare, Germany), leading to a CTDIvol of 4.25 mGy. Afterwards automatic dose calculation was switched off and tube currents were set manually to achieve the same CTDIvol in all protocols. The phantom was scanned with a SE protocol at 120 kV and with a DE protocol at 80/Sn140 kV and 100/Sn140 kV (SE120: 63 eff. mAs, DE80/Sn140: 126/49 eff. mAs, DE80/Sn140: 61/47 eff. mAs (DE tube current ratios as supplied by the manufacturer)). In all protocols, pitch was set to 0.6 and collimation to 64 x 0.6 mm. All images were reconstructed using a dedicated non-edge-enhancing medium-soft reconstruction kernel (D30f) with a slice thickness of 1.0 mm and an increment of 1.0 mm.

DE image postprocessing

Monoenergetic images were calculated using a novel algorithm. Previous noise limitations could be overcome by using a frequency split technique, combining high contrast from low energy images with low noise levels from intermediate energy images [16]. Pseudomononoenergetic images were created in equidistant steps of 10 keV from 40 to 110 keV and intervals of 20 keV from 110 to 190 keV using a software prototype including the new algorithm mentioned above (Monoenergetic+, Siemens Healthcare, Erlangen, Germany).

Based on a three-material decomposition model attenuation of CM was separately shown and quantified in CM maps and removed for virtual unenhanced images (VNC) using commercially available postprocessing software (SyngoVia, Liver VNC, Siemens Healthcare, Germany).
**Image analysis**

Image analysis was performed using a custom built Matlab software tool (Version R2011b, MathWorks, Natick, MA). This tool enables the simultaneous assessment of identical ROIs in multiple datasets. Polygonal regions of interest (ROI) of 5.0 cm² were placed into each aspiration syringe in five consecutive slices. The ROIs were copied to all image series of the same CM at identical positions. The noise level was calculated as the standard deviation in a ROI of 20 cm² in the center of the phantom. For each aspiration syringe, HU and signal to noise ratios were calculated.

HU and SNR values of CM MEI 40 keV, CM VNC images as well as CM maps were compared to SE images at 120 kV from ICM and GdCM. CM specific DE ratios were calculated to evaluate the accuracy of CM VNC and CM quantification. A linear regression model was calculated to estimate the maximal attenuation resulting from triple dose GdCM.

**Statistical analysis**

Statistical and graphical analysis was performed using Excel 2010 (Microsoft). To evaluate the precision of iodine and Gd quantification, measured values were compared with the known true concentrations and the measurement error was calculated as follows:

\[
\text{Measurement error (\%)} = \frac{(\text{measured CM concentration} - \text{true CM concentration})}{\text{true CM concentration}}
\]

**Fig. 5:** Formula to calculate measurement errors

**References:** Dept. of Diagnostic and Interventional Radiology, University Hospital of Tübingen - Tübingen/DE

Differences between unenhanced and CM VNC images are shown in Hounsfield Units (HU). Differences between ICM and GdCM are shown in percentage terms.
Results

Monoenergetic extrapolation

Monoenergetic extrapolation works properly between 40 and 190 keV at 80/Sn140 kV and 100/Sn140 kV. Exemplary images are shown in figure 1. Comparison of GdCM MEI 40 keV calculated from 80/Sn140 kV with GdCM MEI 40 keV from 100/Sn140 kV revealed superiority of MEI 40 keV from 100/Sn140 kV. Averaged contrast was at about 20% and averaged SNR values at about 9% higher than from MEI 40 keV at 100/Sn140 kV. Therefore further investigations of this study are based on MEI 40 keV from 100/Sn140 kV.

Equimolar Analysis

Linear regression analysis confirmed higher attenuation from Gd than from ICM at equimolar concentrations as expected due to the higher Z and k-edge of Gd. Comparing Gd 120 kV and ICM 120 kV, contrast of Gd 120 kV (2252 HU) was 150.8% and SNR (75.51) 147.6% of ICM 120 kV (Contrast: 1494 HU; SNR: 51.15). Gd MEI 40 keV showed 442.2% of the contrast (6605 HU) and 233.8% of the SNR (119.57) from ICM SE 120 kV (Contrast: 1494 HU; SNR: 51.15).

Equivolume Analysis

Results of the equivolumen analysis are shown in table 1 and 2. In comparison to ICM 120 kV (Contrast: 16-296 HU; SNR: 0.6-10.1), Gd 120 kV reached averaged 64% (10-187 HU) of the attenuation (HU) and showed at about 54% (0.3-6.2) of the SNR. With Gd MEI 40 keV HU were increased to a maximum of 218% (syringe #2), averaged to 185% (20-619 HU) and SNR up to 103% (syringe #2) averaged to 88% (0.3-10) of ICM 120 kV.

Attenuation of clinical Gd doses

Linear regression models, based on an averaged body weight (BW) of 75 kg and a standard dose of ICM of 1ml/kg BW respectively the manufactures maximal MRI dose of 0.3 mmol/kg BW of GdCM were calculated (Figure 2). The maximum of achievable HU and SNR with Gd 120 kV and Gd MEI 40 keV were compared with ICM at 120 kV. Gd 120 kV (106333 HU) showed 19.19% of the attenuation (HU) from ICM 120 kV (554163 HU). SNR of Gd 120 kV (3572.22) was 18.82% of the SNR from ICM at 120 kV (18978.08). Gd MEI 40 keV (312676 HU) reaches 56.42% of the attenuation (HU) from ICM 120 kV and showed 29.83% (5660.23) of the SNR from ICM at 120 kV.

Gd VNC
Results of ROI analysis of ICM and GdCM dilutions are used to calculate energy specific DE ratios of Gd and iodine. The slopes of the linear equations showed the material specific DE ratios at 80/Sn140 and 100/Sn140 kV (Figure 3). Calculation of Gd VNC images and Gd quantification work superiorly using 80/Sn140 kV than 100/Sn140 kV images, therefore further investigations of this study are based on 80/Sn140 kV. 

Measured HU from calculated VNC images of iodine and Gd dilutions are shown in table 3 and 4. Using the calculated DE ratio of 2.18 the resulting Gd VNC images (deviation 4-11 ± 12-13 HU) have comparable accuracy as iodine VNC images (deviation 1-4 ± 10-12 HU). An exemplary Gd VNC image is shown in figure 4.

**Calculation of Gd maps and Gd quantification**

Using the adapted Gd ratio the calculation of Gd maps works properly. Exemplary images are shown in figure 4.

Based on the calculated iodine ratio of 2.84 and Gd ratio of 2.18 precision of CM quantification was analyzed (Table 5 and 6). Having regard to differing molarity of GdCM (1 molar) and ICM (2.9 molar), the measurement error of CM quantification has the same dimension for iodine and Gd in a wide range of diagnostic relevant CM dilutions (ICM: 9-24%; GdCM: 12-22%).
Fig. 1: Monoenergetic extrapolations of Gd dilution at 100/Sn140 kV from 40 to 190 keV show maximum contrast at 40 keV.
**Fig. 2:** Calculated regression lines of (A) HU and (B) SNR from ICM 120 kV, Gd 120 kV and Gd MEI 40 keV. Values for standard doses of ICM (1ml/kg BW) and Gd (0.3 ml/kg BW) at 75 kg BW are marked (dots).

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![Graph](image1)

**Fig. 3:** Shown are Hounsfield Units (HU) of different iodine and gadolinium concentrations as a function of the low- and high energy image at (A) 80/Sn140 kV and (B) 100/Sn140 kV. The slopes of the linear equation represent the material specific Dual Energy ratios.

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![Graph](image2)

**Fig. 4:** A: Gadolinium (Gd) map, B: Gd virtual non contrast (VNC) image, C: fusion of Gd map and Gd VNC image for anatomic orientation.
Table 1: Comparison of attenuation (HU) from ICM 120 kV, Gd 120 kV and Gd MEI 40 keV.

<table>
<thead>
<tr>
<th>Aspiration syringe</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ICM SECT 120 kV [HU]</td>
<td>296</td>
<td>133</td>
<td>72</td>
<td>34</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Gd 120 kV [HU]</td>
<td>187</td>
<td>92</td>
<td>47</td>
<td>21</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Gd MEI 40 keV [HU]</td>
<td>619</td>
<td>290</td>
<td>139</td>
<td>62</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>ICM 120 kV vs. Gd 120 kV [%]</td>
<td>63</td>
<td>69</td>
<td>65</td>
<td>61</td>
<td>63</td>
<td>53</td>
</tr>
<tr>
<td>ICM 120 kV vs. Gd MEI 40 keV [%]</td>
<td>209</td>
<td>218</td>
<td>193</td>
<td>183</td>
<td>123</td>
<td>40</td>
</tr>
</tbody>
</table>

ICM = iodinated contrast media iopromide 370, Gd = gadolinium containing contrast media Gadobutrol, SECT = Single Energy Computed Tomography, HU = Hounsfield Units, MEI = advanced monoenergetic reconstructions, italic values are not included in the analysis.

Fig. 6
Table 2: Comparison of SNR from ICM 120 kV, Gd 120 kV and Gd MEI 40 keV.

<table>
<thead>
<tr>
<th>Aspiration syringe</th>
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<tbody>
<tr>
<td>ICM SECT 120 kV [HU]</td>
<td>10.1</td>
<td>4.6</td>
<td>2.5</td>
<td>1.1</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Gd 120 kV [HU]</td>
<td>6.2</td>
<td>2.8</td>
<td>1.3</td>
<td>0.6</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Gd MEI 40 keV [HU]</td>
<td>10.0</td>
<td>4.7</td>
<td>2.2</td>
<td>1.0</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>ICM 120 kV vs. Gd 120 kV [%]</td>
<td>61.1</td>
<td>62.5</td>
<td>54.0</td>
<td>48.6</td>
<td>45.3</td>
<td>12.3</td>
</tr>
<tr>
<td>ICM 120 kV vs. Gd MEI 40 keV [%]</td>
<td>98.9</td>
<td>103.0</td>
<td>91.0</td>
<td>86.7</td>
<td>58.0</td>
<td>19.2</td>
</tr>
</tbody>
</table>

ICM = iodinated contrast media iopromide 370, Gd = gadolinium containing contrast media Gadobutrol, SECT = Single Energy Computed Tomography, HU = Hounsfield Units, MEI = advanced monoenergetic reconstructions, italic values are not included in the analysis.

Fig. 7

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Table 3: Comparison of VNC images from different iodine concentrations with reference to SECT 120 kV.

<table>
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<tr>
<th>Aspiration syringe</th>
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<tbody>
<tr>
<td>SECT 120 kV [HU]</td>
<td>296</td>
<td>133</td>
<td>72</td>
<td>34</td>
<td>16</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>VNC (Ratio 2.84) [HU]</td>
<td>4 ± 11</td>
<td>-2 ± 10</td>
<td>-1 ± 11</td>
<td>4 ± 11</td>
<td>3 ± 11</td>
<td>3 ± 12</td>
<td>2 ± 11</td>
</tr>
</tbody>
</table>

SECT = Single Energy Computed Tomography, HU = Hounsfield Units, VNC = virtual non contrast images

Fig. 8

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Table 4: Comparison of VNC images from different Gd concentrations with reference to SECT 120 kV.

<table>
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<tr>
<th>Aspiration syringe</th>
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<th>#7</th>
</tr>
</thead>
<tbody>
<tr>
<td>SECT 120 kV [HU]</td>
<td>187</td>
<td>92</td>
<td>47</td>
<td>21</td>
<td>10</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Gd-VNC (Ratio 2.18) [HU]</td>
<td>6 ± 12</td>
<td>4 ± 13</td>
<td>7 ± 12</td>
<td>5 ± 12</td>
<td>6 ± 12</td>
<td>11 ± 12</td>
<td>5 ± 13</td>
</tr>
</tbody>
</table>

SECT = Single Energy Computed Tomography, HU = Hounsfield Units, Gd-VNC = gadolinium based virtual non contrast images

Fig. 9

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Table 5: Comparison of measured and known iodine amount and resulting measurement error in different iodine concentrations.

<table>
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<tr>
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<tbody>
<tr>
<td>SECT 120 kV [HU]</td>
<td>296</td>
<td>133</td>
<td>72</td>
<td>34</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>True iodine amount [mg/ml]</td>
<td>14.8</td>
<td>7.4</td>
<td>3.7</td>
<td>1.85</td>
<td>0.93</td>
<td>0.5</td>
</tr>
<tr>
<td>Measured iodine (Ratio 2.84) [mg/ml]</td>
<td>14.10</td>
<td>6.60</td>
<td>3.38</td>
<td>1.43</td>
<td>0.70</td>
<td>0.18</td>
</tr>
<tr>
<td>Measurement error [%]</td>
<td>4.73</td>
<td>10.81</td>
<td>8.56</td>
<td>22.52</td>
<td>24.32</td>
<td>60.36</td>
</tr>
</tbody>
</table>

SECT = Single Energy Computed Tomography, HU = Hounsfield Units, italic values are not included in the analysis.

Fig. 10

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Table 6: Comparison of measured and known Gd amount and resulting measurement error in different Gd concentrations.

<table>
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<tr>
<th>Aspiration syringe</th>
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<th>#5</th>
<th>#6</th>
</tr>
</thead>
<tbody>
<tr>
<td>SECT 120 kV [HU]</td>
<td>187</td>
<td>92</td>
<td>47</td>
<td>21</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>True Gd amount [mg/ml]</td>
<td>6.29</td>
<td>3.15</td>
<td>1.57</td>
<td>0.79</td>
<td>0.39</td>
<td>0.19</td>
</tr>
<tr>
<td>Measured Gd (Ratio 2.18) [mg/ml]</td>
<td>5.57</td>
<td>2.77</td>
<td>1.23</td>
<td>0.62</td>
<td>-0.02</td>
<td>-0.12</td>
</tr>
<tr>
<td>Measurement error [%]</td>
<td>11.50</td>
<td>12.03</td>
<td>21.57</td>
<td>21.57</td>
<td>104.24</td>
<td>159.35</td>
</tr>
</tbody>
</table>

SECT = Single Energy Computed Tomography, HU = Hounsfield Units, Gd = Gadolinium, italic values are not included in the analysis.

Fig. 11

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Conclusion

Several patients with contraindications towards intravenous administration of ICM like manifest hyperthyroidism and known allergic reaction on iodine would profit from non-iodinated CM. In general population the prevalence of hyperthyroidism has been estimated at 2 percent for women and 0.2 percent for men [17]. Due to repeated ICM applications in hospitalized patients, the incidence of hyperthyroidism and subclinical thyreotoxicosis as well as adverse reactions seems to be augmented [18-20]. Dermatologic studies revealed in about 50% of hypersensitivity reactions on iodine immunological mechanisms [21].

In preclinical studies especially the potential of gold as alternative contrast material has been investigated [22]. Due to higher atomic number and k-edge (Z = 79, k-edge 80.7 keV) attenuation of gold should be clearly higher than from iodine. Initial animal studies show the benefit of gold in different nanoparticles [23;24]. Additionally, gold seems to offer the potential being used as contrast material in CT and MRI [25]. Furthermore, first ex vivo studies investigated the potential use of heavy metals such as ytterbium, tungsten, gold, and bismuth as potential CM in CT [26]. Nevertheless, none of these new contrast materials are approved for use in human subjects.

Gd containing CM from MRI seems to be a suitable alternative to ICM with broad experience in human use. Studies about safety of high doses of linear non-ionic GdCM in MRI showed incidences of adverse reactions significantly lower to ICM in CT [27]. New macrocyclic non-ionic Gd formulations lowered the minor side effects additionally [28].

The aim of this study was to investigate the potential of Gd as CM in second generation DECT: Evaluating the effect of monoenergetic extrapolations, the possibility of calculating Gd VNC images and Gd maps as well as quantifying the amount of Gd.

The calculation of virtual monoenergetic extrapolations of Gd enhanced images works properly between 40 and 190 keV. With monoenergetic extrapolations at 40 keV contrast values of equimolar CM amounts can be significantly augmented. This beneficial effect makes it possible to reduce the amount of required GdCM. At equivolume doses of GdCM and ICM, MEI 40 keV effects nearly doubled contrast and identical SNR of GdCM compared to ICM 120 kV. With regard to dose limitations (manufacturers maximum at 0.3 mmol/ kg BW), GdCM in DECT seems to be suitable especially for CT angiography. For portal-venous or venous contrast especially concerning the evaluation of the upper abdominal organs higher doses of ICM at about 1 ml/ kg KG are necessary. In case of non impaired renal function it might be thinkable to use Gd doses up to 0.6 ml/ kg BW and profit from contrast augmentation by low keV monoenergetic extrapolation. Therefore, further studies are desirable to evaluate the potential of GdCM in parenchymal CT phase.
Knowing the energy dependent, specific Gd DE ratio it is possible to calculate Gd VNC images. The accuracy of Gd VNC images is high and comparable to iodine VNC images.

The calculated material specific DE ratio for Gd permits a reliable computation of Gd maps and precise quantification of Gd similar to those of iodine using DECT post processing algorithms. The commercially available post processing algorithms used in this study are designed for iodine, therefore it should be possible to optimize the results by an adapted Gd algorithm.

Nevertheless, there are limitations in this ex vivo study design. In vivo the contrast enhancement especially of the upper abdominal organs is a highly dynamic process, depending on parameters like flow rate, ejection fraction and heart rate. These parameters are not considered in our static design.

In conclusion, at doses of 1 ml/kg BW monoenergetic extrapolations at 40 keV of 1 molar GdCM (Gadobutrol) make it possible to achieve attenuation values close to those of standard dose of 2.9 molar ICM (Ultravist 370). Additional features of iodine based DECT like computing VNC images, iodine maps or quantifying the amount of iodine are also reliable possible with the use of GdCM.
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