Dual Energy CT for the detection of venous thrombosis

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Aims and objectives

Introduction

Venous thrombembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a frequent pathology in daily clinical routine with an annual age adjusted incidence of about 95-130/100000 individuals in general population [1-3], further increasing due to aging population [1, 4]. Besides myocardial infarction and stroke, venous thrombembolism is the third common cardiovascular condition [5]. Mortality within one month after incident is about 6% in DVT and 12% in PE, overall ten year survival rate is about 80% [6].

In daily clinical routine, ultrasonography, CT and MRI are used in the diagnosis of thrombembolism. In patients with clinical suspicion of PE, contrast enhanced chest CT is indicated to exclude PE. The sensitivity in detecting thrombosis in femoral veins by ultrasound is high [7]. However, ultrasonography is limited in the pelvic and abdominal veins. In these cases, CT venography is the method of choice, although even CT is limited by inflow artifacts and inhomogenous venous contrastation. The x-ray density and thus the attenuation of thrombotic material changes with age [8, 9] and can be close to the attenuation of blood.

Dual energy CT (DECT) allows an improved visualization of iodine using two different approaches: On the one hand, virtual monoenergetic images (MEI) with photon energies lower than in the source images can be created, leading to higher Hounsfield values of materials with a high atomic number. This technique might facilitate the differentiation of thrombus and iodine by selectively enhancing the iodine contrast. On the other hand, the iodine content in each image pixel can be quantified using three material decomposition, leading to iodine-selective images (IM). Both techniques might lead to improved visualization of blood clots in the presence of low contrast.

The aim of this study was to evaluate the diagnostic benefit of MEI and IM for the detection of venous thrombosis compared to standard Single-Energy-CT (SECT), using an ex vivo phantom to allow repeated examinations in standardized conditions.
Methods and materials

Phantom study

Seven blood clots of about 3 cm$^3$ were produced by placing pure human blood in 5 cc aspiration syringes for 3 days (Inject Solo, BBraun, Melsungen, Germany). In order to simulate blood with different levels of venous contrast, fresh blood was anticoagulated using citrate buffer (ACDA Citrat buffer, Fresenius Medical Care AG & Co. KGaA, Bad Homburg vor der Höhe, Germany), and six samples of blood were produced by adding small amounts of contrast media to achieve attenuation levels between 90 and 50 HU (increment 5-10 HU). Each sample was placed within a 10 cc aspiration syringe with one clot. Aspiration syringe #7 only contained anticoagulated blood and clot without contrast media and was used as negative control. All seven syringes were placed in a circular order in the center of a 10 l anthropomorphic water phantom to provide sufficient x-ray attenuation (Figure 1).

CT protocol

All CT scans were acquired using a second generation dual source CT-scanner (SOMATOM Definition Flash, Siemens Healthcare, Erlangen, Germany). The phantom was scanned with a SE protocol at 120 kV and with a DE protocol at 80/140 kV. Pitch was always set to 0.6, tube currents were set to achieve a CTDI vol of 18 mGy in both scans. Collimation was 64 x 0.6 mm. Using commercially available software (SyngoVia Dual Energy Liver, Siemens Healthcare, Erlangen, Germany), iodine and virtual non contrast (VNC) images were calculated based on a three-material decomposition model [10].

Furthermore, pseudo monoenergetic 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 (Monoenergetic+, Siemens Healthcare, Erlangen, Germany). This software prototype applies a frequency based mixing of the low keV images (which contain the high contrast signal) and a noise-wise optimal image (typ. round 70 keV) to combine the benefits of both images stacks - the low noise and the improved contrast. Thus, the increased image noise levels which were previously reported for standard monoenergetic interpolation at lower simulated energy levels are reduced.

Image analysis

Image analysis was performed using a custom built Matlab software tool (Version R2011b, MathWorks, Natick, MA). Five polygonal regions of interest (ROI) of 1.0 cm$^2$ were placed into each thrombus in consecutive slices. Five further ROIs were placed in the surrounding contrast media enhanced blood of each aspiration syringe. The ROIs
were propagated to all scans. For each pair of measurements, differences of absolute HU between thrombus and blood (contrast) as well as CNR (formula see Figure 2) were calculated.

After acquiring the measurements, in a first step the MEI (from 40 to 190 keV) were compared regarding differences in HU and CNR to pick out MEI with best effects (results shown below).

Afterwards, differences in HU and CNR were compared between the MEI, IM, VNC images and SE images.

**Statistical analysis**
To determine differences in contrast and in CNR between MEI, IM, VNC images and SE images, comparison of means were calculated using paired t-tests. Measurements are shown as mean ± standard deviation. A p-value less than 0.05 was considered to be statistically significant.
Fig. 1: 3D model of in house built ex vivo phantom including 7 aspiration syringes each containing a human thrombus of 3 cm³ at about 73 HU and contrast media enhanced, citrat buffered blood with attenuation levels between 90 and 50 HU.

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\[
\text{CNR} = \frac{|\text{HU}_{\text{thrombus}} - \text{HU}_{\text{blood}}|}{\left(\frac{\text{SD}_{\text{thrombus}} + \text{SD}_{\text{blood}}}{2}\right)}
\]

Fig. 2: Formula to calculate CNR.

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Results

MEI 40 keV provide best contrast and CNR at high and intermediate and MEI 190 keV at low iodine concentrations (Figure 3 and 4). Additional advantages of MEI between 50 and 170 keV could not be found. Therefore MEI 40 and 190 keV were chosen for further analysis.

Comparing all performed DECT reconstructions (MEI 40/190 keV, IM and VNC images) with SE at 120 kV differences in contrast and CNR of each aspiration syringe were studied (Figure 5 and 6). MEI 40 keV and IM showed significantly higher contrast and CNR values at high and intermediate iodine concentrations in aspiration syringes #1 to #4 (Figure 7 and 8). Comparing MEI 40 keV with IM, MEI 40 keV showed significantly higher contrast values at high and intermediate iodine concentrations in aspiration syringe #1 to #4 ($p_{#1-#4} < .0005$) and significantly higher CNR values at high iodine concentrations in aspiration syringe #1 and #2 ($p_{#1} = 0.016$, $p_{#2} = 0.023$).

Contrast of MEI 190 keV was significantly higher in aspiration syringe #2 and CNR values of MEI 190 keV were higher in aspiration syringes #2 to #6, except #5 in comparison with SE 120 kV (Figure 7 and 8).

Comparing VNC images with SE 120 kV images, VNC images showed significantly higher contrast and CNR values in aspiration syringe #2 and #3 (Figure 7 and 8). VNC images showed at high (aspiration syringe #1) and low (aspiration syringe #5 to #7) iodine concentrations significantly higher contrast values ($p_{#1} = 0.0008$, $p_{#5} = 0.01$, $p_{#6} = 0.0005$, $p_{#7} < .0001$) as MEI 190 keV. There were no significant differences in CNR values between VNC images and MEI 190 keV.
Fig. 3: Contrast values in HU between thrombus and blood of aspiration syringes #1 to #7 from MEI 40 to 190 keV ± standard deviation. Positive effect of MEI 40 keV (dark blue) is dominating at high and intermediate iodine concentration in aspiration syringes #1 to #4. Inverse contrast towards higher HU in thrombus increases with MEI 190 keV (orange) at low and very low iodine concentrations in aspiration syringes #5 to #7.

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Fig. 4: CNR values of aspiration syringes #1 to #7 from MEI 40 to 190 keV ± standard deviation. Positive effect of MEI 40 keV (dark blue) is dominating at high and intermediate iodine concentration in aspiration syringes #1 to #4. At low and very low iodine concentrations (aspiration syringes #5 - #7) MEI at 190 keV (orange) show best results.

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Fig. 5: Contrast values of MEI 40 keV, IM, SE 120 kV images, MEI 190 keV and VNC images between thrombus and blood ± standard deviation. MEI 40 keV and IM are dominating in high and intermediate iodine concentrations (aspiration syringe #1-#4). In low and very low iodine concentrations (aspiration syringe #5-#7) beneficial effects of MEI 190 keV and VNC images with inverted contrast towards higher HU in thrombus rise. MEI = monoenergetic interpolations, IM = iodine-selective images, SE = single energy, VNC = virtual non contrast.

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Fig. 6: CNR of MEI 40 keV, IM, SE 120 kV images, MEI 190 keV and VNC images ± standard deviation. MEI 40 keV and IM is dominating in high and intermediate iodine concentrations (aspiration syringe #1 - #4). In low and very low iodine concentrations (aspiration syringe #5-#7) beneficial effects of MEI 190 keV and VNC images show up. MEI = monoenergetic interpolations, IM = iodine-selective images, SE = single energy, VNC = virtual non contrast.

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Table 1. Comparison of the means of contrast values in HU between thrombus and blood from MEI at 40 and 190 keV, IM and VNC images with SECT 120 kV separated for each aspiration syringe. Values are shown as means ± standard deviations and corresponding significance levels.

<table>
<thead>
<tr>
<th>Aspiration syringe</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE 120 kV</td>
<td>14.59 ± 2.80</td>
<td>3.45 ± 2.99</td>
<td>6.89 ± 3.81</td>
<td>6.30 ± 5.23</td>
<td>16.89 ± 3.26</td>
<td>17.22 ± 3.13</td>
<td>21.21 ± 2.49</td>
</tr>
<tr>
<td>MEI 40 keV</td>
<td>115.79 ± 13.50</td>
<td>76.30 ± 12.52</td>
<td>39.31 ± 6.29</td>
<td>36.48 ± 4.86</td>
<td>5.46 ± 4.24</td>
<td>7.09 ± 3.35</td>
<td>21.59 ± 3.06</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.0001</td>
<td>p = 0.0004</td>
<td>p = 0.0001</td>
<td>p &lt; 0.0001</td>
<td>p = 0.0026</td>
<td>p = 0.0015</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>IM</td>
<td>41.90 ± 3.79</td>
<td>28.37 ± 6.93</td>
<td>16.59 ± 1.32</td>
<td>16.18 ± 4.71</td>
<td>8.73 ± 3.77</td>
<td>5.68 ± 1.93</td>
<td>4.50 ± 1.55</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.0001</td>
<td>p = 0.0041</td>
<td>p = 0.0022</td>
<td>p = 0.0060</td>
<td>p = 0.0060</td>
<td>p = 0.0020</td>
<td>p = 0.0005</td>
</tr>
<tr>
<td>VNC images</td>
<td>19.51 ± 3.73</td>
<td>19.15 ± 6.36</td>
<td>15.88 ± 3.29</td>
<td>15.57 ± 9.45</td>
<td>22.01 ± 5.52</td>
<td>21.10 ± 3.37</td>
<td>26.44 ± 3.02</td>
</tr>
<tr>
<td></td>
<td>n.s.</td>
<td>p = 0.0172</td>
<td>p = 0.0438</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p = 0.0477</td>
<td></td>
</tr>
</tbody>
</table>

Comparisons of the means are based on paired t-test. SE = single energy, MEI = monoenergetic interpolations, IM = iodine-selective images, VNC = virtual non contrast. N.s. = not significant. Italic p values show significant superiority of SE 120 kV.

Fig. 7

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Table 2. Comparison of the means of CNR values from MEI at 40 and 190 keV, IM and VNC images with SECT 120 kV separated for each aspiration syringe. Values are shown as means ± standard deviations and corresponding significance levels.

<table>
<thead>
<tr>
<th>Aspiration syringe</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE 120 kV</td>
<td>0.98 ± 0.23</td>
<td>0.22 ± 0.18</td>
<td>0.45 ± 0.24</td>
<td>0.40 ± 0.36</td>
<td>1.15 ± 0.22</td>
<td>1.14 ± 0.21</td>
<td>1.44 ± 0.23</td>
</tr>
<tr>
<td>MEI 40 keV</td>
<td>3.73 ± 0.54</td>
<td>2.66 ± 0.49</td>
<td>1.49 ± 0.31</td>
<td>1.52 ± 0.37</td>
<td>0.22 ± 0.17</td>
<td>0.28 ± 0.14</td>
<td>0.76 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>p &lt; .0001</td>
<td>p = 0.0023</td>
<td>p = 0.0009</td>
<td>p = 0.0215</td>
<td>p = 0.0002</td>
<td>p = 0.0002</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>MEI 190 keV</td>
<td>1.13 ± 0.23</td>
<td>1.32 ± 0.33</td>
<td>1.17 ± 0.36</td>
<td>1.17 ± 0.75</td>
<td>1.64 ± 0.44</td>
<td>1.54 ± 0.27</td>
<td>1.73 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>n.s.</td>
<td>p = 0.0425</td>
<td>p = 0.0077</td>
<td>p = 0.0012</td>
<td>n.s.</td>
<td>p = 0.0099</td>
<td>n.s.</td>
</tr>
<tr>
<td>IM</td>
<td>3.09 ± 0.28</td>
<td>2.28 ± 0.69</td>
<td>1.34 ± 0.14</td>
<td>1.43 ± 0.47</td>
<td>0.78 ± 0.34</td>
<td>0.49 ± 0.16</td>
<td>0.39 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>p &lt; .0001</td>
<td>p = 0.0027</td>
<td>p = 0.0047</td>
<td>p = 0.0163</td>
<td>p = 0.0005</td>
<td>p = 0.0003</td>
<td>p = 0.0013</td>
</tr>
<tr>
<td>VNC images</td>
<td>1.19 ± 0.29</td>
<td>1.19 ± 0.41</td>
<td>1.00 ± 0.31</td>
<td>1.02 ± 0.67</td>
<td>1.42 ± 0.40</td>
<td>1.36 ± 0.22</td>
<td>1.64 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>n.s.</td>
<td>p = 0.0182</td>
<td>p = 0.0824</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Comparisons of the means are based on paired t-test. SE = single energy; MEI = monoenergetic interpolations; IM = iodine-selective images; VNC = virtual non contrast. N.s. = not significant. Italic p values show significant superiority of SE 120 kV.

Fig. 8

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Conclusion

The phantom study with 7 aspiration syringes including 7 thrombi surrounded by blood with different amounts of contrast media was initiated to evaluate possible benefits resulting from DECT in detecting venous thrombosis. DECT allows optimization of iodine contrast using MEI and IM. MEI at 40 and 190 keV, IM and VNC images were calculated and contrast respectively CNR values were compared with standard SECT at 120 kV.

Our ex vivo phantom study, simulating venous thrombosis showed the beneficial effects of MEI 40 keV and IM at high and intermediate iodine concentrations in surrounding blood. The effect of MEI 40 keV in augmenting contrast and CNR values was higher than from IM. The new software algorithm for calculating MEI, based on mixing of low keV images and a noise-wise optimal image is capable to enhance contrast and CNR without severe increase of image noise. Therefore, MEI especially at low keV offers a new diagnostic potential in detecting thrombosis.

In general, attenuation levels of thrombotic material is changing with age (7, 8) and iodine concentration of surrounding blood is depending on the timing of contrast media administration, mainly influenced by patients circulation time. These dynamic factors of influence can provoke low contrast between thrombotic material and blood.

In case of comparable attenuation levels between thrombus and blood with high and intermediate iodine concentration in surrounding blood IM and especially MEI 40 keV offer highest diagnostic benefit.

In case of comparable attenuation levels between thrombus and blood and only low iodine concentrations in surrounding blood MEI 190 keV is capable to enhance detectability of thrombotic material. MEI 190 keV cause inverted contrast towards higher HU in thrombus at low and very low iodine concentrations by suppressing iodine attenuation. But iodine suppression from VNC images seems to be more efficient than from MEI 190 keV, justifying application of VNC images in diagnosing thrombosis in case of low and very low iodine concentrations.

Furthermore, the above mentioned possibilities to improve contrast and CNR values by using MEI and IM have the potential to lower required amounts of contrast media in patients with kidney failure.

In conclusion, limiting factors in diagnosing venous thrombosis are resulting from varying attenuation of thrombotic material by age, poor iodine concentration e.g. due to restricted circulation time and inflow as well as blending artifacts. IM and MEI provide significantly
higher contrast and CNR values in detecting venous thrombosis in comparison with SECT, which might facilitate the detection of DVT especially in difficult cases.
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