Clinical evaluation of a computer simulated prediction model of contrast enhancement of the liver in spiral CT

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Abstract

Objective: A software program was developed simulating a compartmental model of blood circulation based on differential equations. The aim of this study was to compare software-simulated levels of hepatic enhancement with the true values in patients and to test how many patients reach the simulated hepatic enhancement level.

Methods: As software program the CT application software carebolus 2® (Siemens, Forchheim, Germany) was used. Hepatic contrast-enhancement curves were simulated prior to CT examinations to evaluate a patient specific time delay after contrast application. At the time delay, when the simulation curve showed an enhancement threshold of 40 Hounsfield Units (HU), the CT spiral scan was started applying 120 ml contrast media with 2 ml/s. The simulated curves were compared with the empiric curves of each patient.

Results: 25 of 28 patients (89%) achieved 40 HU. The mean enhancement of empiric patients curves was 46.32 ± 11.9 HU, the mean simulated enhancement was 46.62 ± 4.3 HU S.D. (P = 0.48). 4.4 values per patient liver could be compared with the simulation curve (122 points for 28 patients): 50% of the patient curves were within a range of 5 HU compared with the simulation curve. Conclusion: Software simulation of contrast enhancement curves of the liver is a feasible and valuable method to predict individual liver enhancement curves. Improvements concerning the integration of cardiovascular parameters and preexisting liver parenchymal diseases into the simulation software have to be arranged.

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Keywords: Spiral CT; Liver; Contrast enhancement; Computer simulation model

1. Introduction

The shortened acquisition time in computed tomography, especially in modern multislice CT scanner needs an optimization of contrast enhancement to get the optimal time window [1–3].

The various different parameters influencing parenchymal enhancement after intravenous application of contrast media like contrast medium type, volume and concentration, flow, tissue and patient characteristics makes it very difficult to achieve the exact time window for performing the spiral CT during the optimal phase of enhancement.

Bolus tracking technique is one method to optimize contrast enhancement of organs and vessels in helical CT [4–6].

Another method is to use computer based software models to predict individual patient related contrast enhancement curves. Bae et al. developed a computer-based physiologic model to simulate contrast medium enhancement [7]. Therefore, they generated a compartment model of the cardiovascular system by using human physiologic parameters and more than 100 differential equations. Blood volume, extracellular fluid volume and regional blood flow were estimated from available data. By a mathematical model local structures were generated to describe dispersion and distribution of an intravascular administered iodinated contrast medium. Afterwards a global model was formed by integrating regional circulation parameters with the models of local structures. This software model is the basis of the CARE-
The objectives of this study were to prospectively test Carebolus 2® (Siemens) software simulation curves against the individually patient enhancement curves after abdominal spiral CT. The first endpoint was to simulate 40 Hounsfield Units (HU) contrast enhancement level to evaluate how the empiric enhancement level distribution is in comparison to the simulated. The second endpoint was to compare the group of simulated enhancement levels of the liver against the group of empiric enhancement levels in patients.

2. Materials and methods

The 28 patients included (13 men, 15 women; age range 21–76 years; medium age 53.8 ± 14.9 years; Table 1) were planned to get a native liver CT and a following i.v. contrast medium enhanced abdominal CT in the portal venous phase. Before examination the contrast enhancement curve of the liver was prospectively simulated for each patient by a computer simulated physiological model (carebolus 2®, Siemens) that was implemented at the CT scanner. The software model is based on the principles described from Bae et al. [7]. They developed a computer-based, compartmental model of the cardiovascular system by using human physiologic parameters and more than 100 differential equations to describe the transport of contrast medium. The following input parameters had to be fed into the simulation computer program: patient related information: age, height, weight, gender, percent of cardiac output. Intravenous contrast medium characteristics: volume, concentration and flow rate. Cardiac output was estimated to be 100% in each patient prior excluding heart disease.

Patient exclusion criteria for the study were heart diseases, renal insufficiency, fever, multi-organ-failure, liver disease and pregnancy. The included patient population is listed in Tables 1 and 2.

After giving their informed consent the patients were asked for the above mentioned patient data. Then the contrast media characteristics and the patient related information were added in the simulation program and a liver enhancement curve was simulated (Fig. 1). These procedures last in average 1 min. The Carebolus 2 program allows to determine a threshold of liver enhancement level that we established at 40 HU in this study for hepatic portal venous phase. For each patient the program calculates an individual delay time. After the simulation curve of the patient and the delay time was calculated, the patients were examined with a spiral CT scanner (Somatom Plus 4, Siemens, Erlangen, Germany). Scan parameters were 8 mm collimation, pitch 1.5, rotation time 0.75 s, 120 kV, 240 mA. Images were reconstructed at 7 mm increment using a standard reconstruction kernel. An unenhanced spiral CT of the liver was performed before i.v. contrast administration in a cubital vein. With a power injector all patients got a uniphasic injection of 120 ml iopromid (Ultravist 300 mg/ml, Schering AG, Berlin, Germany) with a flow of 2 ml/s after the individual time delay figured out with the help of the simulation program (threshold of enhancement level 40 HE). Scan direction was cranial-caudal.

Stating that the average dimension of a normal liver is at maximum 16 cm cephalad-caudal, a given table speed of 12 mm/rotation and a rotation speed of 0.75 s (pitch 1.5) allows a coverage of the whole liver within 10 s.

To evaluate the empiric patient liver enhancement curves for each patient, the pre-contrast hepatic density was measured by calculating the mean of eight regions of interest’s (ROI) measurements (area of each ROI: 5 cm²). On the post-contrast scans the mean attenuation of normal liver parenchyma (avoiding measurements in liver lesions or large vessels) for each slice separately was assessed by the mean of three ROI measurements (area: 5 cm²). Then the mean, the maximum, and the minimum hepatic density of the contrast enhanced liver was calculated. The pre-contrast hepatic density was subtracted from the mean post-contrast enhancement giving the mean hepatic contrast enhancement level. The curves of the empiric patient data were compared with the simulated curves. The simulation program gener-

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>53.8</td>
<td>76.18</td>
<td>160.96</td>
<td></td>
<td></td>
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<tr>
<td>S.E.M.</td>
<td>14.88</td>
<td></td>
<td></td>
<td>12.77</td>
<td>10.30</td>
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<tr>
<td>S</td>
<td>13</td>
<td>15</td>
<td></td>
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</table>

Table 2

<table>
<thead>
<tr>
<th>Diseases of the included patients</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germ cell tumor</td>
<td>2</td>
</tr>
<tr>
<td>Esophageal carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>2</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>7</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>3</td>
</tr>
<tr>
<td>Uterus carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Cancer of unknown primary</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>3</td>
</tr>
<tr>
<td>Oat cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>28</td>
</tr>
</tbody>
</table>
Fig. 1. Example of a simulation curve and an empiric value curve.

ated simulated enhancement levels every 2.5 s. For the above mentioned scan-parameters there was a time window of approximately 10 s to compare the empiric with the simulated values (in average 4.4 values could be compared for each patient).

The following evaluation was performed:

– The number of patients reached the threshold of 40 HU within the liver scanning window of about 10 s after the individual time delay.
– Calculation of the mean, the maximum, and minimum hepatic enhancement of the simulation group and the empiric group.
– The HUs for each patient (in average 4.4 slices) were compared with the corresponding simulated data: 122 paired data points could be compared. Differences were calculated between the simulated and the empiric enhancement levels of 5 HU at maximum was accepted.

Statistical significance between the empiric group and the simulation group was assessed by the two-tailed paired Student’s t-test. \( P < 0.05 \) was defined statistically significant.

3. Result

The mean delay time before starting the contrast enhanced spiral CT was 63.64 ± 8.93 s (minimum 48 s, maximum 85 s; Table 3). The input of parameters into the simulation program and the generation of the prediction enhancement curve did not take longer than 1 min.

25 of 28 (89%) patients had a maximum hepatic enhancement of 40 HU (Figs. 2 and 3 and Table 3). The three patients who did not reach the threshold had enhancement values between 33 and 37 HU.

For the mean value of liver enhancement as an average of the whole liver 22 of 28 (79%) patients reached 40 HU (Figs. 4 and 5 and Table 3). Three of the patients who did not reach 40 HU had a mean enhancement of 35 HU and more. Two out of four patients with fatty liver (native liver densities between 21 and 55 HU) did not reach the threshold of 40 HU. One patient with a lymphoma and a hyperdense liver (83 HU) only reached a mean enhancement level of 37 HU. The distribution of the empiric enhancement levels is shown in Fig. 7.

When regarding the minimum enhancement of the slice with the lowest values only 46% reached 40 HU (13 of 28 patients; Fig. 6).

The maximum liver-enhancement between the empiric and the simulated group was not statistically significant (52.68 ± 12.59 vs. 50.18 ± 4.91 HU; \( P = 0.31 \); Fig. 3). For the mean hepatic enhancement values the empiric patient curves and the simulated curves showed no significant differences (46.32 ± 11.9 vs. 46.62 ± 4.27 HU; \( P = 0.48 \); Figs. 4 and 5). The minimum enhancement level of the liver was 39.6 ± 11.1 HU for the empiric patient group, 42.7 ± 3.8 HU for the simulation group (\( P = 0.15 \); Fig. 6).

122 paired points could be compared. 45 of 122 measurements (37%) were within a deviation of ± 5 HU between the simulated and the empiric enhancement levels. When
Table 3

<table>
<thead>
<tr>
<th>Pre-contrast liver density (HU)</th>
<th>Individualized time delay as simulated by program</th>
<th>Simulated and empiric enhancement levels for each patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delay (s) Mean empiric enhancement (HU)</td>
<td>Mean simulated enhancement (HU)</td>
</tr>
<tr>
<td>Average 65.54</td>
<td>63.64 46.32</td>
<td>46.61 52.68</td>
</tr>
</tbody>
</table>

comparing the differences of the mean liver enhancement level of each patient 14 of 28 patients (50%) showed a difference between the empiric values and the simulated values of not more than 5 HU. Nine patients showed an insufficient low hepatic enhancement comparing with the simulation (32%), five patients showed a significant higher enhancement than the simulation (18%).

4. Discussion

The daily problem in intravenously contrast enhanced computed tomography is to find out the correct time window for optimal parenchymal enhancement of organs. Therefore, optimization of contrast material enhanced CT to maximize lesion detection within the liver is necessary and was subject of numerous investigations [8–11]. Many protocols describe a fixed time delay between 40 and 80 s for hepatic portal venous phase for generating appropriate images, but in some patients the time delay will be inappropriately short or long [12]. Especially in patients with a large body habitus, cardiac dysfunction or a hyperdynamic cardiovascular state are problematic concerning the timing of hepatic enhancement [13,14]. Individualized scan delays seems to be mandatory to achieve a better liver attenuation.

One method to find out the right time window for hepatic enhancement is the bolustracking technique, which considers the interindividual differences in circulation time [4,12,15,16]. When performing a test bolus application pre-scans with an additional amount of radiation, time, and additional contrast material has to be performed. Another very elegant method is to simulate parenchymal enhancement with a computer based software model like Bae et al. did in their prior investigations [7,17,18]. The software model tested in this study was Carebolus 2® (Siemens) that is based on the theoretical principles of their paper.

We used 40 HU as a threshold of liver enhancement for the portal venous phase with regard of the results of Silverman et al. [19]. They reported that in patients examined with 125 ml contrast media with a flow of 3.0 ml/s 100% reached a contrast enhancement of 40 HU and 98% of 50 HU. Concerning the first endpoint of the study—achievement of the threshold of 40 HU—only three out of 28 patients concerning maximum slice enhancement and six out of 28 patients (21%) of the mean average group did not reach the threshold. Two out of four patient with fatty liver and one patient with an increased native liver density did not reach the enhancement level of 40 HU. Therefore, we propose to integrate the parameter of native liver density in the simulation program to achieve a more appropriate attenuation level for patients with liver density abnormalities.

The influence of cardiac output on the contrast medium enhancement on CT is well known. Bae et al. [17] could show in a porcine model, that the time until the arrival of a contrast media bolus in the aorta and to peak aortic and hepatic enhancement is increased in decreased cardiac out-
put. Reduction in cardiac output results in a substantial increase in peak aortic enhancement but not in peak hepatic enhancement. We excluded all patients with heart diseases, heart insufficiency and a hyperdynamic cardiovascular status. Being aware of the tremendous influence of the cardiac system on the contrast agent distribution and dispersion it is necessary to integrate other parameters of the cardiovascular function in the simulation program such as pulse rate and blood pressure. But nevertheless—because heart and circulatory diseases were exclusion criteria for the study, it is unlikely that decreased cardiac output is responsible for the small group of patients who did not reach the threshold.

The model of Bae et al. assumes fixed volumes for blood and extracellular volumes and for volumetric flow. Individual deviations from these standard values may explain that some patients did not reach the threshold enhancement even if only patients with normal cardiac functions were included in the study. Enhancement curves in the liver depend not only on cardiac function, but also on variations of blood volume and flow in the macro-circulation and the micro-circulation.

Fig. 2. Comparison of the maximum enhancement levels in HU of each patient liver with the corresponding simulated values.

Fig. 3. Mean values of maximum enhancement levels of the empiric and the simulation group. n.s., not significant for a two tailed paired Student’s t-test.
Fig. 4. Comparison of the mean enhancement level of each patient liver with the corresponding simulated values.

Modifications of the micro-circulatory parameters in liver disease may explain that the threshold enhancement was not reached in two patients with fatty liver and one patient with lymphoma. Factors affecting the hepatic enhancement are complex and the theoretical model assuming fixed values for blood flow and volume cannot account for all these variables even if heart rate, blood pressure, and native liver density are inserted in the simulation program.

The time window of the empiric enhancement curve was only about 10 s (e.g. for a 16 cm liver for the given scan parameters). In this study for each patient in average 4.4 points of liver enhancement levels over time could be compared with the simulated curve points. Altogether we could compare 122 points. When considering a difference of 5 HUs, 50% of the patient’s empiric liver enhancement levels were within this range. 18% showed a higher enhancement level, 32% a lower level. The diagnostic value is not impaired when reaching higher levels when the simulated, so the main problem are the patients who showed a lower enhancement curve than simulated. Seven of the nine patients who showed an insufficient low liver enhancement compared with the simulation curve would have probably reached the threshold of 40 HU when the delay time would have been between 6 and 12 s. longer because the enhancement curve was still rising. Because most of the empiric attenuation levels were lower than the simulated, we would propose to adapt the simulation program to this fact.

Fig. 5. Mean values of mean enhancement levels of the empiric and the simulation group. n.s., not significant for a two tailed paired Student’s t-test.
In this study we used a monophasic protocol with native scans and acquisition of the portal venous phase. Therefore, there is a possibility to miss hypervascular metastases in some patients. Further studies concerning simulation of different circulatory phases like the hepatic artery phase, the portal venous phase and a late venous phase [20,21] for optimizing liver to lesion conspicuity and detection are relevant. Improvements to simulate the circulatory time of each patient and the native liver density as an additional parameter in the simulation program seems to be mandatory. Even different injection protocols with different flow rates and different contrast medium quantities should be tested to evaluate the software simulation program in further studies.

In this study we could show, that simulation of organ enhancement levels for the liver with CAREBOLUS 2® is a feasible and fast method in daily routine work. In order to simulate a distinctive threshold of enhancement it is an reliable method. As mentioned above more parameters have to be inserted into the software simulation program like heart rate, blood pressure and native liver densities to achieve better correlations between the simulation and the empiric values being aware that liver enhancement is complex and that a few patients with alteration of their micro-circulation in the liver will not follow the predicted time delay figured out with the software simulation.
References