Evaluation of perfusion alterations in response to intraarterial embolization of hepatic malignancies via DynaCT and validation of results via comparing dynamic CT perfusion

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Purpose

Liver perfusion with computed tomography (CT) was first described in 1991 (Miles) (1). It has been evolved since then parallel to the development of the CT technology and post-processing software. However, the clinical implications of the liver perfusion studies have not been validated, and not being a part of the routine examination yet. Cerebral perfusion studies are just becoming ready to be used in the routine part of neuro imaging. Comparing to the cerebral perfusion, the most important technical issues with liver perfusion are the fact of dual blood supply of the liver and the breathing movements which are not the cases in head imaging. However, demands for functional imaging features of every other diseases and better therapeutic effect evaluation after various therapies force people to obtain or seek more data out of every single imaging technique.

In general, the dual blood supply of the liver has several advantages in functional means. Also, the tendency of the liver tumors to get fed by almost exclusively from the hepatic artery allows several hepatic arterial embolization therapies to affect mainly the tumors while preserving the normal parenchyma as much as possible. The rough approximation of the ratio of blood supply from hepatic artery and portal vein in the normal liver parenchyma is somewhere from 25% to 33%.

Liver perfusion studies in the literature may be evaluated in 2 groups; parenchymal and tumor related studies. In 2001, Van Beers et al reported that the total liver perfusion (TLP) is decreased in patients with cirrhosis and non-cirrhotic chronic liver disease, while Hepatic arterial perfusion index (HPI) and mean transit time (MTT) are increased (2). Besides, the severity of liver disease, which was categorized into five classes (normal, non-cirrhotic liver disease, Child A, Child B, Child C), was correlated significantly with TLP, HPI, and MTT. They were also able to define an ideal cutoff point to differentiate patients with cirrhosis from those without cirrhosis; a MTT of 22.6 s (with a sensitivity of 81% and a specificity of 81%, respectively).

CT angiography (CTA) and CT arterial portography (CTAP) is routinely being used to detect the blood flow of hepatic artery and portal vein to study the changes in HCC hemodynamics. Additional color mapping of perfusion is just a matter of post processing software with continuous scanning of the patient during a specific time period. Dynamic contrast material-enhanced perfusion computed tomography (CT) enables the quantification of various tissue perfusion parameters. Kinetic modeling is used to analyze the time-attenuation curve generated from a dynamic contrast-enhanced cine CT examination performed at a fixed tissue location after a bolus injection of contrast material. Thus, the BF, blood volume (BV), mean transit time (MTT), and capillary permeability-surface area product of tissue can be calculated. In addition, automated image analysis on a pixel-by-pixel basis can be used to generate parametric images (ie, functional maps) for displaying the perfusion parameters.
The main advantages of CT imaging in liver cases are obvious; one is the high anatomic resolution allowing recognition of small quantitative measurements, and second is the adequate speed of the image acquisition that would allow perfusion measurements in different time points. Of course, relatively high radiation exposure is needed to obtain such images under CT imaging even with high-end multi detector CT (MDCT) technology.

On the other hand, Dyna CT is an established tool that comes with the advanced technology of the flat panel angio suites. With this, the flat panel of the C-arm used for regular angiographies, is acting like a rotational CT detector around the patient and the data obtained is processed as CT view at the end. Because it is essential to use the C-arm angiography table we use the term of "C-arm CT" in this study. The field of view is limited to the size of the flat panel detector and speed is lower in comparison to MDCT technology. However, it has a vital role in neuro-interventional cases as well as some aortic interventions.

Herein, we attempted to validate a C-arm-CT perfusion method via arterial injection for the measurement of regional parenchymal blood volume (PBV) in liver tumors, and to apply this method by creating perfusion maps before and after chemo and radio-embolization. Furthermore, semi-quantitative perfusion measurements obtained from the C-arm-CT method are also being tried to be validated with comparison to the subgroup of patients whom also underwent multi-detector CT perfusion study with contrast injected via peripheral IV line.

**Methods and Materials**

Total of 26 patients who had primary or metastatic hepatic malignancy were included in this study. All of them underwent sessions of hepatic arterial therapies including chemo and radio embolization therapies between January and September 2011. Total of 8 patients had HCC and 2 had cholangio-cellular carcinoma while 16 patients had metastatic liver disease. Among these metastatic tumors, 8 colorectal carcinoma, 3 neuro-endocrin tumors, 2 pancreas carcinoma, 2 ocular malign melanoma, and one breast carcinoma. In total, 7 female and 19 male patients were included in the study with the mean age of 59.9 (range from 28 to 74 years).

Sixteen patients were treated with radioembolization while 9 patients had chemoembolization, one patient had both radio and chemoembolization therapies. Among the patients whom were treated with radioembolization, only one patient had two sessions during the study period while 2 patients underwent 2 sessions of chemoembolization. Lobar treatment was planned routinely in case of bilobar disease for all hepatic arterial therapies.

In all patients, C-arm CT perfusion studies were obtained twice on the treatment day both pre and post embolization. Additionally in 5 of those patients who underwent
radioembolization, the C-arm CT perfusion studies were obtained twice during macroalbumine aggregate (MAA) infusion test again pre and post embolization.

Ten patients underwent MDCT perfusion study with Siemens Volume Perfusion CT software which is commercially available using first generation dual source CT (Siemens Definition, Erlangen, Germany). All these MDCT perfusion studies were performed at a certain time points in order to be able to compare the semi-quantitative perfusion measurements with the ones measured with C-arm CT. So, MDCT perfusion studies were performed prior to embolization or MAA test angiography not earlier than a 30 day period. Non-ionic contrast media was given via peripheral IV injection rate of 5 by 50 cc pure contrast followed by 50cc saline chase. The detailed technique of liver perfusion with VPCT software was already described in the literature (3,4).

In all patients, mean 6 months routine follow up data is available for any targeted lesion in the liver, range from 3 to 12 months. Treatment response evaluation of all targeted lesions was evaluated according to EASL criteria.

Local ethics committee approval was obtained for the study and all patients gave written informed consent to the study. As a part of the routine process in the hospital, all patients were evaluated by the tumor board and then the decision was made to perform any particular hepatic arterial therapy.

**Imaging Protocol**

**C-arm CT**

C-arm CT imaging was performed on a flat-detector angiographic system (Artis Zee; Siemens Healthcare, Forchheim, Germany). The acquisition consisted of 2 rotations: an initial rotation (mask run) followed by a second rotation after contrast medium injection (fill run). Data acquisition per run was carried out using the following parameters: acquisition time 5 seconds, 90 kV, 616x480 Matrix, projection on 30x40 cm flat panel size, 200° total angle, 0.8°/Frame, 248 frames total, dose 0.36 µGy/Frame. The contrast was injected immediately after the mask run has been finished. Then the C-arm rotates back before the fill run starts, which takes another 5-6 seconds. The contrast was then distributed through the arteries and reaches a homogeneous enhancement in the target structure like tumour. We used total 36 mL of contrast medium (Ultravist-300, Bayer-Schering Pharma) diluted to 25% that was injected into the hepatic artery at a rate of 3 mL/s using a power injector (Medrad, Indianola, PA, USA) at 300PSI, so the total contrast administrated was only 9 mL.

**Post-processing of C-arm PBV imaging**

PBV post-processing was performed using prototype software installed on a research workstation (syngo XWP, Siemens AG Healthcare Sector, Forchheim, Germany). We used a similar post-processing algorithm as previously described (5). In summary, the mask and the fill run were reconstructed and subtracted. An algorithm to segment out
air and bone is applied. The arterial input function value is calculated from an automated histogram analysis of the vessel tree. This arterial input function value is then applied as a scaling factor to obtain the quantitative PBV map. In a final step, a smoothing filter is applied to reduce pixel noise. The PBV map can be visualized with a color map. The only difference is that a non-rigid motion correction algorithm is used to compensate the possible motion artifacts between the mask and fill runs.

Currently, dynamic measurement with C-arm CT for blood flow measurement is not implemented yet. With the current algorithm for perfusion analysis, a faster acquisition speed would be required (~one volume every 3 seconds) than the current C-arm systems could provide. However, preclinical studies have showed that dynamic measurement could be already feasible in neuro applications (6-9).

Results

The semi-quantitative tumor perfusion values for all patients that were acquired both before and after the hepatic artery embolization treatments are displayed in Table 1. It has to be emphasized that even in this relatively small study group, there are several different hepatic arterial anatomical variations including totally replaced right hepatic arteries and segmental anatomical variations. Besides, there were tumors that already had blood supply from parasitic feeders out of hepatic arterial bed. Having said that, mean value of tumor perfusion before the embolization for all patients was 170.2±31.2 ml/1000ml, which dropped down to a mean value of 79.5±23.5 ml/1000ml after the embolizations. Considering the fact of distinguished technical aspects of radioembolization from other hepatic arterial therapies, it was further evaluated. There are 2 steps for radioembolization procedure, one is the preparatory arteriography with coil embolization of potential extrahepatic arterial shunts (most frequently embolization of gastroduodenal artery and right gastric artery) in order to have an isolated hepatic arterial circulation followed by a technetium tagged macroaggregated albumin(MAA) infusion (mimicking the behavior of actual therapy agent-Yttrium90), and the second is the actual radioembolization session with pure emitter agent, Yttrium 90 (Y90). Both pre and post C-arm CT perfusion studies were obtained in all 2 steps.

Table 1.

Mean values of C arm-CT perfusion analysis before and after the embolization

<table>
<thead>
<tr>
<th>Group</th>
<th>Onset of sessions*</th>
<th>Preembolization</th>
<th>Postembolization</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sessions</td>
<td>25</td>
<td>178.7 ± 32.8</td>
<td>78.3 ± 23.8</td>
</tr>
<tr>
<td>RE</td>
<td>13</td>
<td>212.6 ± 34.7</td>
<td>109.1 ± 23.5</td>
</tr>
<tr>
<td>CE</td>
<td>12</td>
<td>138.6 ± 29.6</td>
<td>47.7 ± 24.1</td>
</tr>
</tbody>
</table>
The decrease of the blood volume after the embolization # in the chemoembolization (CE) and radioembolization (RE) treatments # was measured separately. As it is shown in Table 1, results in each treatment were similar. Mean value before the CE was 138.6±29.6 ml/1000ml and 47.7±24.1 ml/1000ml after the CE, in parallel to these results that value was 212.6±34.7 ml/1000ml before the RE and 109.1±23.5 ml/1000ml after the RE.

In four of the CE patients there was a distinctive blood volume supply in the border zone of the lesions. In these patients we measured additional perfusion values that show post embolization values of perfusion with C-arm CT was higher in two and stable in the other two of the four patients (Table 2).

Table 2.

<table>
<thead>
<tr>
<th>Case</th>
<th>Preembolization mean value</th>
<th>Postembolization mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>248.9 ± 16.1</td>
<td>305.4 ± 41.0</td>
</tr>
<tr>
<td>Case 2</td>
<td>151.6 ± 25.4</td>
<td>142.6 ± 50.0</td>
</tr>
<tr>
<td>Case 3</td>
<td>232.9 ± 53.1</td>
<td>237.0 ± 67.5</td>
</tr>
<tr>
<td>Case 4</td>
<td>85.9 ± 13.9</td>
<td>110.2 ± 29.9</td>
</tr>
</tbody>
</table>

As it is seen in Table 3, the decrease of the blood volume in patients among HCC and metastatic hepatic malignancies such as, colon carcinoma, NET, colangiocellular carcinoma did not show significant difference. For HCC, pre and post-embolization mean blood volume values were 196.3±36.4 ml/1000ml and 81.5±32.0 ml/1000ml, respectively. For colon carcinoma metastasis those values were calculated as 160.2±29.7 ml/1000ml before and 84.6±17.3 ml/1000ml after the embolization. Also those values were calculated as 166.2±21.0 ml/1000ml before and 52.9±13.3 after the embolization for NET, 104.0±33.0 ml/1000ml before and 50.1±19.2 ml/1000ml after the embolization for
colangioceullary carcinoma. The blood volume measurement with C-arm CT of these tumors before the embolization is therefore indicative for the angiogenesis of the tumors according to their origins.

Table 3.

Mean perfusion values of pre and postembolization of the primary and metastatic liver tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Preembolization</th>
<th>Postembolization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma (11)</td>
<td>160.2 ± 29.7</td>
<td>84.5 ± 17.2</td>
</tr>
<tr>
<td>Colon carcinoma (8)</td>
<td>212.2 ± 52.8</td>
<td>35.0 ± 22.7</td>
</tr>
<tr>
<td>Colangioceullary carcinoma (2)</td>
<td>166.2 ± 21.0</td>
<td>52.9 ± 13.3</td>
</tr>
<tr>
<td>NET (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note.
# Data are means ± standard deviations

NET: neuroendocrine tumor

* Numbers inside the parentheses indicates the sessions of embolization treatments. Some patients had multiple sessions of embolization treatment

In patients who underwent chemoembolization, tumor perfusion diminished significantly as expected (Fig.1). The mean value of pre-embolization blood volume (BV) was 156.6±32.9 ml/1000ml and post-embolization BV 45.2±24.7 ml/1000ml on C-arm CT. During routine follow up of these 10 patients, 5 stable, 5 partial response were detected after one session treatments. 2 of the patients had partial response to the treatment after a second session.
Radioembolization sessions were planned on a lobar based therapy which means one lob treatment at a time. The mean value of pre-embolization blood volume was 212.6±34.7 and post-embolization BV 109.1±23.5 on C-arm CT measurements (range from 267.7±64.2 to 33.2±14.8 and mean value of 103.5±29.1). The maximum decrease of C-arm CT blood volume of the patients treated via RE was 267.7±64.2 ml/1000ml where the minimum decrease was 33.2±14.8 ml/1000ml and mean value of decrease was 103.5±29.1 ml/1000ml. Interestingly the level of perfusion decrease in pre and post embolization correlates well with the tumor response. During routine follow up of these 12 patients; 6 stable, 5 partial response and 1 progressive disease were detected. Interestingly the level of perfusion decrease in pre and post embolization correlates well with the tumor response. The difference between decrease of the mean blood volume values on C-arm CT after the radioembolization are displayed in Table 4. The decrease level of the mean value of C-arm CT perfusion analysis of only patient with progressive disease (from 173.3±18.4 ml/1000ml to 117.5±14.8 ml/1000ml) is significantly lower than the decrease level of the patients with partial response and regression (from 200.1±28.0 ml/1000ml to 112.2±24.0 ml/1000ml) that is similar to patients with stable disease (from 202.1±39.9 ml/1000ml to 104.2±23.3 ml/1000ml).

Table 4.

The Decrease Level of Mean Blood Volumes of Patients Treated via RE related to tumor response

<table>
<thead>
<tr>
<th></th>
<th>Preembolization mean value</th>
<th>Postembolization mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable (n=6)</td>
<td>202.1 ± 39.9</td>
<td>104.2 ± 23.3</td>
</tr>
<tr>
<td>Partial response (n=5)</td>
<td>200.1 ± 28.0</td>
<td>112.2 ± 24.0</td>
</tr>
<tr>
<td>Progressive disease (n=1)</td>
<td>173.3 ± 18.4</td>
<td>117.5 ± 14.8</td>
</tr>
</tbody>
</table>

Note.# Data are means ± standard deviations

RE: radioembolization

Quantitative measurements of 'liver blood volume' obtained from the tumors with C-arm CT were correlated with the ones obtained with MDCT perfusion. The mean blood volume value of 12 lesions in 8 patients # one lesion was selected from each lobe of the liver except one patient that had a lesion only on the right lobe # on CT perfusion was 14.89 ml/100g, which is correlated with the blood volume values on C-arm CT (138.6±21.9 ml/1000ml). The results are displayed in Table 5.
Table 5.

Comparison of mean blood volume values of the tumors via C arm CT and MDCT perfusion

<table>
<thead>
<tr>
<th>Lesions</th>
<th>C arm CT</th>
<th>BV(P) ±</th>
<th>PMB(P)</th>
<th>BF</th>
<th>MIP(HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion 1</td>
<td>134.8 ± 19.1</td>
<td>14.30</td>
<td>35.73</td>
<td>61.80</td>
<td>127.54</td>
</tr>
<tr>
<td>Lesion 2</td>
<td>220.1 ± 44.2</td>
<td>21.60</td>
<td>52.84</td>
<td>62.01</td>
<td>150.29</td>
</tr>
<tr>
<td>Lesion 3</td>
<td>279.9 ± 17.6</td>
<td>28.51</td>
<td>44.29</td>
<td>73.70</td>
<td>162.76</td>
</tr>
<tr>
<td>Lesion 4</td>
<td>98.3 ± 54.2</td>
<td>9.53</td>
<td>37.07</td>
<td>38.86</td>
<td>113.39</td>
</tr>
<tr>
<td>Lesion 5</td>
<td>140.4 ± 11.8</td>
<td>16.39</td>
<td>1.52</td>
<td>47.20</td>
<td>126.27</td>
</tr>
<tr>
<td>Lesion 6</td>
<td>138.0 ± 20.0</td>
<td>13.69</td>
<td>39.69</td>
<td>67.74</td>
<td>149.96</td>
</tr>
<tr>
<td>Lesion 7</td>
<td>192.8 ± 8.3</td>
<td>24.44</td>
<td>19.20</td>
<td>70.00</td>
<td>170.70</td>
</tr>
<tr>
<td>Lesion 8</td>
<td>108.0 ± 17.0</td>
<td>9.97</td>
<td>38.03</td>
<td>49.79</td>
<td>103.49</td>
</tr>
<tr>
<td>Lesion 9</td>
<td>174.8 ± 7.7</td>
<td>22.20</td>
<td>14.01</td>
<td>35.54</td>
<td>98.42</td>
</tr>
<tr>
<td>Lesion 10</td>
<td>5.9 ± 14.3</td>
<td>0.72</td>
<td>109.45</td>
<td>11.34</td>
<td>30.20</td>
</tr>
<tr>
<td>Lesion 11</td>
<td>77.3 ± 37.0</td>
<td>7.17</td>
<td>138.20</td>
<td>22.97</td>
<td>32.67</td>
</tr>
<tr>
<td>Lesion 12</td>
<td>93.1 ± 11.3</td>
<td>10.15</td>
<td>122.65</td>
<td>35.76</td>
<td>63.80</td>
</tr>
<tr>
<td>Mean</td>
<td>138.6 ± 21.9</td>
<td>14.89</td>
<td>131.42</td>
<td>46.81</td>
<td>33.94</td>
</tr>
</tbody>
</table>

Note. Data are means ± standard deviations.

Images for this section:

Figure 1. The C arm CT perfusion mapping displays a large HCC lesion on the right lobe of the liver (right). The blood volume in the HCC lesion decreased significantly after embolization via the beads eluted with chemotherapeutics (left).

Fig. 1
Figure 2. The patient has multifocal HCC (right). A few minutes after the radioembolization therapy almost all of the lesions diminished (left).

Fig. 2
Conclusion

Transarterial treatment of the liver tumors has been performed for 30 years all over the world. Chemoembolization was first introduced at late 1970s and then spread throughout the world in treatment of unresectable liver tumors. Today, transarterial chemoembolization (TACE) is widely accepted treatment technique for patients with uncontrolled hepatocellular cancer (HCC) or metastatic liver cancer primarily caused by colorectal carcinoma. Drug eluting beads have been widely used for TACE within the last 3 years. Hepaspheres (BioSphere Medical, France) loaded with Doxorubusin or Irinotecan were used in the study group for hepatocellular cancer and colorectal cancer metastasis respectively. The dry form of the Hepaspheres is at a range of 50 to 100 micron while the reconstituted size is approximately between 200 to 400 micron range.

Radioembolization as a new form of transarterial therapy involving infusion of radioactive microparticles has shown promise for the treatment of patients with unresectable liver tumors. The therapeutic advantage in the hepatic arterial approach is based on the unique dual vascular supply of the liver. It is known that hepatic tumors receive 80-100 % of afferent blood exclusively from the hepatic artery. Radioembolization utilizes this main advantage as a liver-directed transarterial therapy. There are two distinct aspects of the procedure: the first being the injection of embolic particles ("embolization") as the vehicle and the second being the delivery and administration, via this embolic vehicle, of radiation ("radio"). Radioembolization, as a kind of brachytherapy, has a different treatment mechanism than embolization. Microspheres laden with the beta-emitting isotope $^{90}$Y are used which are small enough to pass deep into tumor vasculature, but too large to pass through the capillary bed and reach venous circulation denying deposition in the lungs. On the other hand, fluoroscopic guidance, angiographic end points of embolization and stasis, and the need to modify this based on angiographic findings make this treatment a true embolization procedure (10-15).

Quantitative blood volume measurement with C-arm CT is a feasible technique, from our limited data, to assess the tumor response to the any kind of embolization treatment. We observed significant decrease in post-embolization mean perfusion value in comparison to the pre-embolization. According to C-arm CT perfusion values there is no significant difference among the embolization techniques to reduce the tumor perfusion immediately after the embolization procedure (Table 1). Both primary and metastatic malignancies are suitable for the C-arm CT technique to evaluate the perfusion, unrelated to the histopathologic type of metastasis (Table 3). The blood volume measurement on C-arm CT of these tumors before the embolization treatment is indicative for the vascularities of the tumors according to their origins.

In four patients treated via CE, despite the decrease in tumor perfusion detected by C-arm CT, in the border zone of the tumor there was stagnation of blood volume supply or even an increased perfusion in two of them. Hence the embolic particle size is formidable
in CE, due to the excessive embolization of the tumor, a slight or clear increase in the blood volume in the adjacent liver parenchyma could occur, as the re-distribution of the blood supply (Fig. 3).

There are certain limitations of the present study beginning with the small patient population limiting the significance of statistical conclusions. Breathing artifacts in abdomen is of course very important issue and light sedation was preferred in all study patients for that reason. Acceptable images can still be obtained by this method via C-arm CT perfusion software. The reproducibility of the quantitative measurements is to be studied as well. Although the current results are encouraging, small catheter movements can potentially cause significant perfusion alterations at the celiac axis.

In the subgroup of patients who underwent MDCT perfusion examination, perfusion analysis with C-arm CT is capable of demonstrating the lesions that is shown to be enhanced after iv contrast medium injection and is revealed to have blood volume supply via dynamic MDCT perfusion technique.

Utilizing the already available arterial access during trans-arterial embolization procedures, quantitative measurements with C-arm CT were validated with MDCT perfusion method with significantly lower contrast load to the patients. Considering the fact of having limited patient number in the study, larger volume of C-arm CT perfusion data is needed to comment on the adequate cutoff value for immediate perfusion decrease for at least partial response after radioembolization. The mandatory side branch embolizations in preparation angiography for radioembolization, in fact, do increase the tumoral perfusion immediately which may have a hazardous effect on the tumor growth particularly in longer waiting periods for treatments. Therefore, interventional radiologists may have to reconsider this fact during treatment planning for radioembolization.

Further perfusion studies with higher volume of patients are now warranted in order to understand the real role of embolic component of radioembolization therapies in combination with ideal dosimetry.

Images for this section:
Figure 3. There are metastases of colon carcinoma on the right lobe of the liver (right). It is obvious that there is contrast medium stagnation in the border zone of the metastatic lesions just after the chemoembolization (left).

Fig. 3
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Personal Information