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ORIGINAL ARTICLE

Quantitative liver tumor blood volume measurements by a C-arm CT post-processing software before and after hepatic arterial embolization therapy: comparison with MDCT perfusion

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PURPOSE
We aimed to determine whether the C-arm computed tomography (CT) blood volume (BV) imaging of hepatic tumors performed with a new prototype software is capable of measuring the BV changes in response to hepatic arterial treatments and to validate these quantitative measurements with commercially available multidetector computed tomography (MDCT) perfusion software.

METHODS
A total of 34 patients with hepatic tumors who underwent either radioembolization (RE, n=21) or transarterial chemoembolization (TACE, n=13) were included in the study. Using a prototype software by Siemens Healthcare, 74 C-arm CT BV measurements were obtained in both pre- and postembolization settings (three patients had additional BV measurements before and after work-up angiography for RE). Ten of 34 patients underwent MDCT perfusion study before embolization, enabling comparison of BV measurements using C-arm CT versus MDCT methods.

RESULTS
The mean BV of 14 tumor lesions in 10 patients on MDCT perfusion was highly correlated with the BV values on C-arm CT (r=0.97, $P < 0.01$). The BV values obtained by C-arm CT decreased from 140.6±28.3 mL/1000 mL to 45.9±23.5 mL/1000 mL after TACE (66.37% reduction) and from 175.6±29.4 mL/1000 mL to 84.1±22.5 mL/1000 mL after RE (53.75% reduction).

DISCUSSION
Quantitative BV measurement with C-arm CT is well-correlated with MDCT BV measurements, and it is a promising tool to monitor perfusion changes during hepatic arterial embolization.

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Liver perfusion with computed tomography (CT) was first described in 1991 by Miles et al. (1). It has been evolved since then parallel to the development of the CT technology and the post-processing software. However, the clinical implications of the liver perfusion studies have not been validated, and they are not considered to be a part of the routine examination yet. Compared to cerebral perfusion, the most important technical challenges of liver perfusion are the dual blood supply of the liver and the need for motion correction due to breathing movements.

It has long been established that normal liver parenchyma derives most (>75%) of its blood from the portal vein whereas liver tumors derive 80%–100% of their blood supply from the hepatic artery (2, 3). Thus, several hepatic arterial embolization therapies were developed to affect mainly the tumors while preserving the normal parenchyma as much as possible. The two different hepatic arterial therapies used in this study are transarterial chemoembolization (TACE) and radioembolization (RE). The principles and mode of action of RE are fundamentally different compared with TACE (4). As a general rule, the liver tumor bed is fully embolized by chemoembolic material in TACE, while in RE optimal perfusion and blood flow is required to allow the generation of free radicals by ionization of water molecules near the tumor cell DNA (5).

In both of these hepatic arterial treatment alternatives the tumor blood supply is the key factor of success: if arterial perfusion of the tumor is high, the amount of arterial therapy that is targeted to the tumor capillary bed would be high, while preserving the nontumoral liver parenchyma as much as possible. Vice versa, if tumor perfusion is closer to the rest of the normal liver parenchyma, then, the toxicity of any given treatment to the normal liver parenchyma becomes an important issue. So far, there is no real-time quantitative documentation of these vital perfusion preferences. In a pathological study, when yttrium-90 microspheres given for RE were released into the hepatic artery, they preferentially accumulated in the periphery of tumors at a ratio of at least 3:1 to 20:1 compared with the normal liver (5). Knowing the perfusion ratio between the tumor and the normal liver parenchyma is of great interest in any liver-directed therapy in order to achieve the most individualized treatment in every patient.

C-arm CT (syngo DynaCT, Siemens Healthcare, Forchheim, Germany) is a recently developed tool that comes with the advanced technology of flat panel angio suites. In this method, the flat panel of the C-arm used for regular angiographies is acting like a rotational CT detector around the patient and the obtained data are reconstructed to provide a CT

view. As it is essential to use the C-arm angiography table, "C-arm CT" term is used in this study. The field of view is limited to the size of the flat panel detector and the rotation speed is more limited in comparison to the multidetector CT (MDCT) technology.

Herein, a novel "blood volume" (BV) measurement software utilizing C-arm CT images is used to quantify BV values in liver tumors and normal liver parenchyma, thus BV ratio of tumor to parenchyma is obtained prior to the hepatic arterial embolization therapy. Furthermore, as these patients were on the angio table for chemo- or radioembolization procedures, postembolization measurements were also obtained in order to quantify the changes in response to hepatic arterial embolization. The measurements obtained with C-arm CT via transcatheter intra-arterial injection were also compared with commercially available MDCT perfusion study with contrast injected via peripheral intravenous line in a subgroup of patients in order to validate the prototype software of C-arm CT measurements.

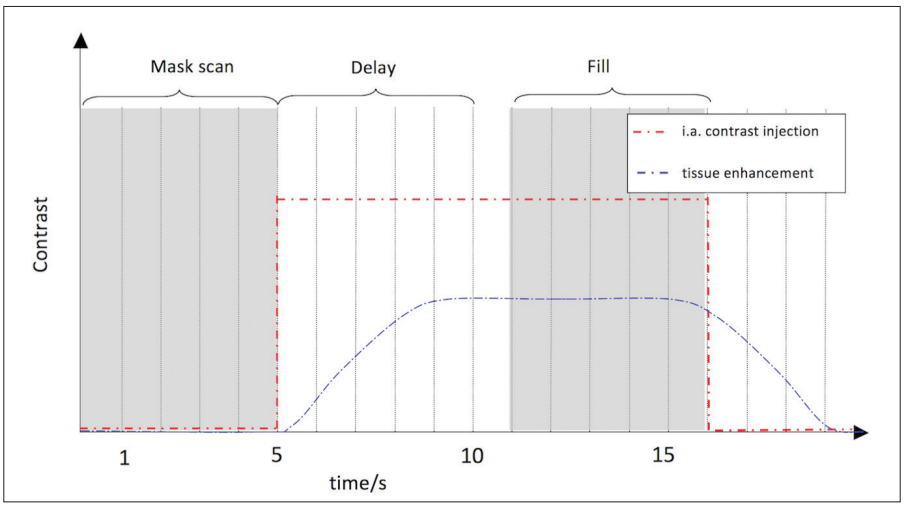

Figure 1. Injection and acquisition protocol for C-arm CT blood volume measurements.

Methods

This study was approved by the university institutional review board. As part of the routine practice in our hospital, the tumor board evaluated all patients before a decision was reached to perform any particular hepatic arterial therapy. All patients gave written informed consent to the study.

A total of 34 consecutive patients (nine female and 25 male patients; median age, 57 years; range, 28–74 years) who had primary or metastatic hepatic malignancy were included in this prospective study. All of them underwent sessions of hepatic arterial therapies including TACE or RE in a 12-month period. Among 34 patients, 12 had hepatocellular carcinoma (HCC) and two had cholangiocarcinoma, while 20 patients had metastatic liver disease (10 colorectal carcinoma, four neuroendocrine tumors, four breast carcinomas, one pancreas carcinoma and one ocular malignant melanoma).

A total of 74 C-arm CT perfusion studies were obtained to analyze alterations in BV in relation to the hepatic arterial therapy in 34 patients. Two C-arm CT perfusion studies were obtained for each patient, prior to and immediately after transarterial therapy (n=68), in both RE (n=42) and TACE (n=26) groups. In three patients who underwent RE, additional C-arm CT perfusion studies (n=6) were obtained before and after a preparation arteriogram for macro-aggregated albumin (MAA) injection prior to actual RE. Of note there was no HCC patient in the study group who had any kind of antiangiogenic therapy prior to the perfusion study (6).

Techniques of hepatic arterial therapies

TACE was performed in 13 patients while 21 patients underwent RE. For TACE; "drug eluting beads" loaded with doxorubicin or irinotecan were used in the study group for HCC and colorectal cancer metastasis (CRCm) respectively. In RE group, resin (SIR-Spheres) and glass microspheres (TheraSpheres) loaded with yttrium-90 were used in 10 and 11 patients, respectively.

A mandatory step prior to RE is called work-up arteriogram. It is performed in order to isolate the hepatic arterial circulation of the target liver lobe with embolization of potential extrahepatic shunts (gastroduodenal artery, right gastric artery, etc.). This step ends with infusion of technetium-tagged MAA, which mimics the behavior of the actual yttrium-90 loaded microspheres given for RE and shows the presence and the ratio of extrahepatic shunts (gastrointestinal system and lungs). C-arm CT with perfusion evaluation was also performed in this first arteriogram in three patients who underwent RE later on.

C-arm CT imaging

As described in detail in Zellerhoff et al. (7), C-arm CT BV imaging is based on the assumption that with an adequate contrast injection, the contrast concentration in the imaged liver tumor is constant for the duration of a single C-arm CT acquisition, thus allowing the calculation of the BV from two measurements: a baseline (mask scan) acquired before contrast administration and the contrast distribution after contrast injection (fill scan).

C-arm CT imaging was performed on a flat-detector angiographic system (Artis Zee, Siemens Healthcare) according to the injection and acquisition protocol shown in Fig. 1. The C-arm CT BV acquisition consists of two runs: an initial rotation (mask scan) followed by a second rotation after contrast medium injection (fill scan). The following parameters were used in data acquisition: acquisition time approximately 5 s, 90 kV, 616×480 matrix, projection on 30×40 cm flat panel, 200° total angle, 0.8°/frame, 248 frames total, detector entrance dose 0.36 μGy/frame. Contrast injection starts immediately after the mask run and is maintained until the end of the fill run. The C-arm rotates back, which takes another 5–6 s, then the fill run starts. By then the contrast has been distributed through the arteries and the parenchyma has reached a homogeneous enhancement. A total volume of 36 mL of contrast

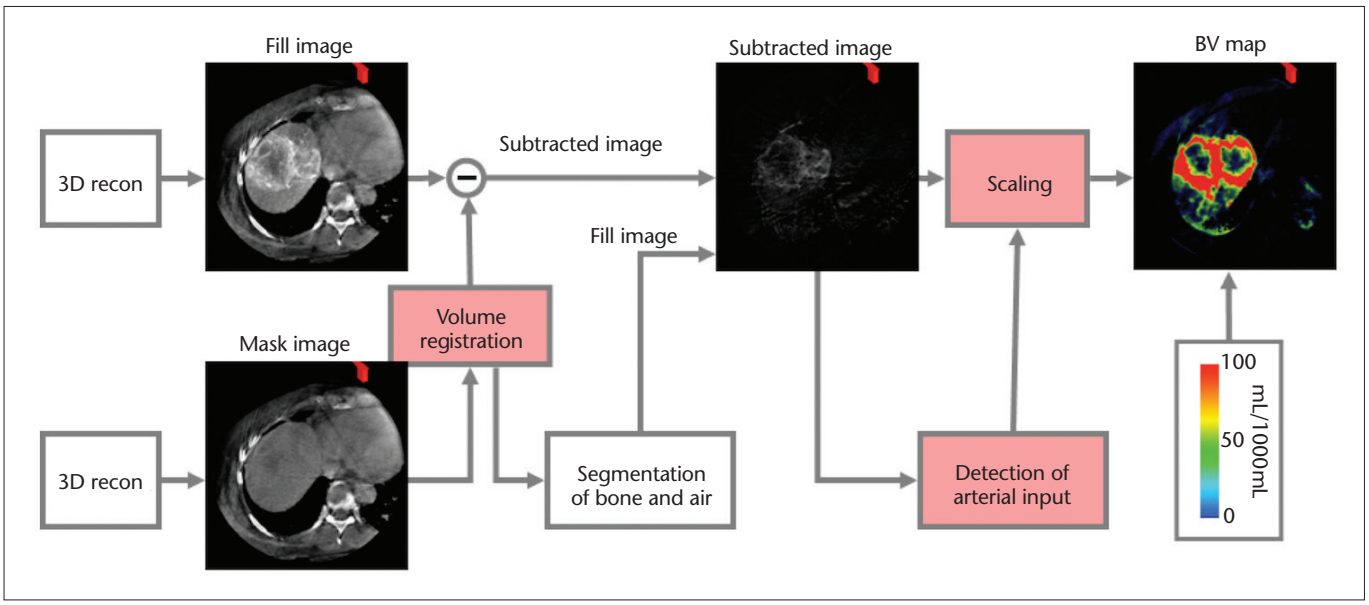

Figure 2. Processing steps for reconstruction of the blood volume (BV) maps.

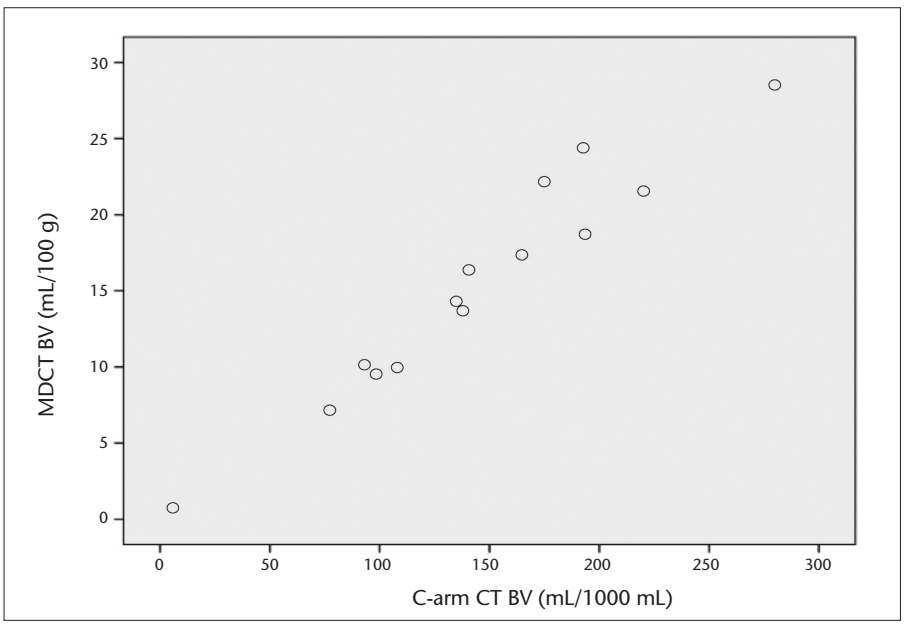

Figure 3. The blood volume (BV) measurements of tumors obtained by both C-arm CT and MDCT perfusion studies show significant correlation ($P < 0.01$, r=0.97).

medium (Ultravist-300, Bayer-Schering Pharma, Berlin, Germany) diluted to 25% was injected into the hepatic artery at a rate of 3 mL/s using a power injector (Medrad, Indianola, PA, USA) at 300 psi, so the total contrast administered is only 9 mL.

The processing steps during calculation of BV maps were shown in Fig. 2. These were performed using prototype software installed on a research workstation (syngo XWP, Siemens Healthcare). Mask and fill run are reconstructed separately. A nonrigid registration algorithm is applied that accounts for organ motion and deformation to register mask and fill volume before the two volumes are subtracted. An algorithm is applied to segment out air and bone. 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 BV map. The quantitative BV values are given in mL/1000 mL and stored as a DICOM (Digital Imaging and Communications in Medicine) gray value volume. The reason why the units differ from MDCT perfusion measurements which are typically given in mL/100 g is that this could facilitate windowing of the BV maps on the XWP which can only handle windowing within integer range. Assuming a liver tissue density of 1.06 g/mL the values can be easily converted. In a final step, a smoothing filter is applied to reduce pixel noise. The BV map is visualized as a color map (8–10).

Multidetector CT perfusion imaging

From the study group 10 patients underwent an additional MDCT perfusion study with Siemens volume perfusion CT software which is commercially available using first generation dual source CT (SOMATOM Definition, Siemens Healthcare). For a healthy comparison, the included MDCT perfusion studies were performed prior to embolization or MAA arteriography within a 30-day period. For MDCT perfusion studies, nonionic contrast medium was given via peripheral intravenous injection at a rate of 5 mL/s (50 mL pure contrast followed by 50 mL saline chase). The images obtained with MDCT were post-processed in another workstation to acquire dynamic CT perfusion color maps. The detailed technique of liver perfusion with volume perfusion CT software was already described elsewhere (11, 12).

Table 1. Comparison of median blood volume of tumors measured by C-arm CT and MDCT perfusion

Lesions	C-arm CT BV* (mL/100 g)	MDCT BV (mL/100 g)
Lesion 1	13.48	14.30
Lesion 2	22.01	21.60
Lesion 3	27.99	28.51
Lesion 4	9.83	9.53
Lesion 5	14.04	16.39
Lesion 6	13.80	13.69
Lesion 7	19.28	24.44
Lesion 8	10.80	9.97
Lesion 9	17.48	22.20
Lesion 10	0.59	0.72
Lesion 11	7.73	7.17
Lesion 12	9.31	10.15
Lesion 13	16.46	17.36
Lesion 14	19.33	18.7
Median	13.92	15.35

The relation of blood volume values between C-arm CT and MDCT perfusion studies are statistically significant ($P < 0.001$, r=0.97).
CT, computed tomography; BV, blood volume; MDCT, multidetector computed tomography.
*C-arm CT BV values measured in mL/1000 mL were converted to mL/100 g assuming a liver density of 1.06 g/mL, for the sake of comparison.

Table 2. Median blood volume measured by C-arm CT perfusion analysis

Group	Pre-embolization BV Median (min–max)	Postembolization BV Median (min–max)	Reduction (%)
TACE (n=13)	154.5 (45.3–207.8)	21.6 (2.4–98.3)	86.0
TheraSphere (n=11)	110.8 (39.1–239.4)	47.1 (5.9–155.7)	57.4
SIR-sphere (n=10)	221.9 (139.2–345.0)	104.2 (2.1–270.8)	53.0
Total (n=34)	160.4 (39.1–345.0)	63.6 (2.1–270.8)	60.3

The blood volume reduction after embolization is statistically significant ($P < 0.001$).
CT, computed tomography; BV, blood volume; TACE, transarterial chemoembolization.

Table 3. Median values of tumor blood volume measured by C-arm CT perfusion study

Group	Pre-embolization BV	Postembolization BV	Reduction (%)
HCC (n=12)	194.2 (45.3–345.0)	71.7 (3.9–270.8)	63.0
CRCm (n=10)	152.2 (39.1–270.8)	81.0 (2.1–155.6)	46.7
BCm (n=4)	122.9 (68.2–160.3)	44.4 (22.2–80.0)	63.8
NETm (n=4)	140.5 (56.9–265.2)	34.3 (2.4–134.8)	75.5
CC (n=2)	104.5 (53.6–154.5)	50.1 (14.7–85.6)	52.0
PCm (n=1)	239.4	155.7	34.9
MMm (n=1)	164.6	24.5	85.1

Blood volume (BV) is presented as median (range), in mL/1000 mL.
The BV reduction after embolization is statistically significant ($P < 0.001$).
BV, blood volume; CT, computed tomography; HCC, hepatocellular carcinoma; CRCm, colorectal cancer metastasis; BCm, breast cancer metastasis; NETm, neuroendocrine tumor metastasis; CC, colangiocellular cancer; PCm, pancreas cancer metastasis; MMm, malignant melanoma metastasis.

Statistical analysis

Mann-Whitney U test was used to determine the differences between two groups. Wilcoxon signed ranks test was used to assess the change in the same group. In patients who underwent MDCT perfusion, Spearman correlation coefficient (r) was used to compare BV values of C-arm CT and MDCT perfusion studies in the whole group and in the HCC subgroup. A P value of less than 0.05 was considered to indicate statistically significant difference. These analyses were performed using SPSS for Windows 16.0 statistical software (SPSS Inc. Chicago, Illinois, USA).

Results

Ten patients (five HCC, two metastatic pancreas carcinoma, one neuroendocrine tumor, one metastatic colon carcinoma, and one malignant melanoma) having a total of 14 lesions underwent MDCT perfusion. The median BV value of these 14 lesions was 15.35 mL/100 g (range, 0.7–28.5 mL/100 g) by MDCT perfusion and 139.20 mL/1000 mL (5.9–279.9 mL/1000 mL) by C-arm CT, showing a high correlation between these two methods ($P < 0.001$; r=0.97) (Table 1 and Fig. 3). An example of axial colored perfusion map obtained by both MDCT and C-arm CT for the same lesion was presented in Fig. 4.

The median tumor perfusion values before the embolization were demonstrated in Table 2. The median tumor BV was 194.25 mL/1000 mL for HCC and 152.25 mL/1000 mL for CRCm. The median BV for normal liver parenchyma measured by C-arm CT perfusion software in all patients was 26.0 mL/1000 mL. Thus, the arterial perfusion ratio of tumor to normal liver parenchyma was 7.5 and 5.8 in patients with HCC (n=12) and CRCm (n=10), respectively ($P = 0.2$).

There were six C-arm CT BV studies performed before and after preparatory arteriograms for RE, in three patients. In two patients with CRCm, no gastroduodenal artery or other side branch artery embolization was performed. As expected, no perfusion alteration was detected by C-arm CT measurement which was repeated twice during the arteriogram before the MAA injection.

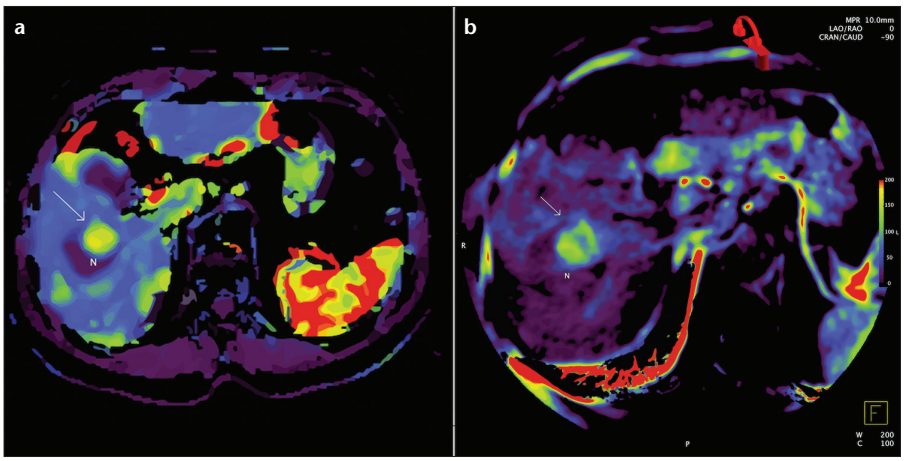

Figure 4. a, b. Axial color map of a MDCT perfusion study **(a)** in a 73-year-old man with HCC shows a partially necrotic (N) lesion with a highly vascular nodule *(arrow)* in the right lobe of the liver. Panel **(b)** shows axial color map of C-arm CT perfusion study of the same lesion *(arrow)* performed five days later. BV values measured by both methods were highly correlated.

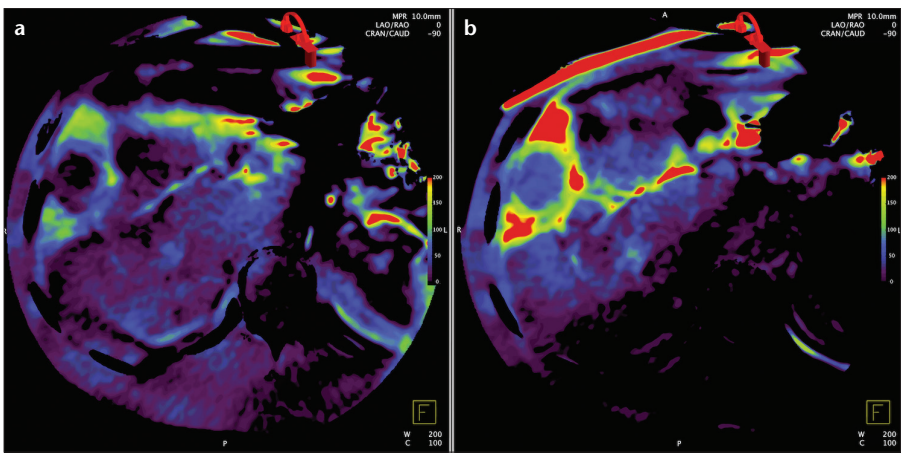

Figure 5. a, b. Axial color map of C-arm CT perfusion study of a 46-year-old patient with metastatic pancreastic adenocarcinoma who underwent a preparatory angiography with macroaggregated albumin infusion test before the radioembolization session. Metastatic lesion **(a)** shows mild-to-moderate rim perfusion of the centrally necrotic metastasis, before the side branch embolization. Axial color map of a subsequent C-arm CT perfusion study **(b)** that is obtained after the embolization of gastroduodenal artery shows significant increase in tumor perfusion caused by redistribution of the hepatic arterial flow.

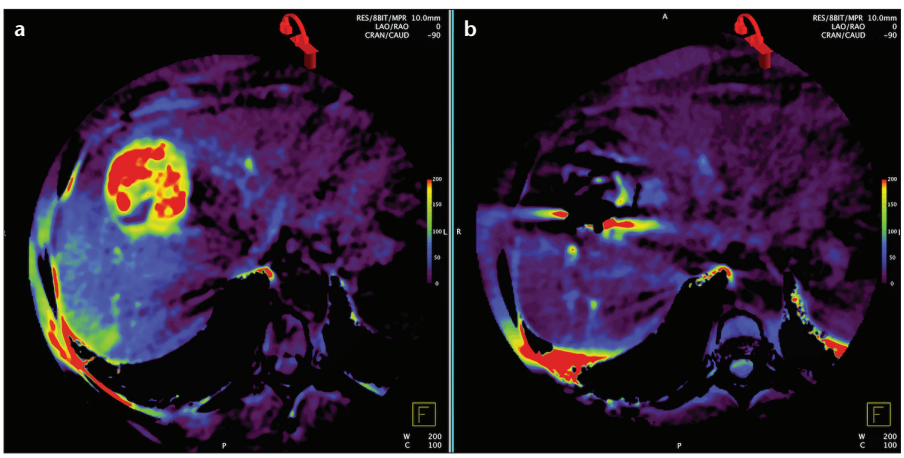

Figure 6. a, b. Axial color map of C-arm CT perfusion study of a 57-year-old woman with hepatocellular carcinoma **(a)** shows a vascular lesion on the right hepatic lobe. Axial color map of C-arm CT perfusion study of the same patient after transarterial chemoembolization **(b)** shows significantly decreased perfusion of the lesion.

This result is encouraging in terms of reproducibility of the quantitative BV measurements obtained by C-arm CT. In the third patient with metastatic pancreastic carcinoma, 158.5 mL/1000 mL (from 121.4 mL/1000 mL to 279.9 mL/1000 mL) perfusion increase was observed immediately after gastroduodenal artery occlusion with coil embolization (Fig. 5). This is an expected finding as a result of redistribution of the blood flow; however, the amount of BV increase should be further studied to better document the quantitative relation between the side branch embolization and the subsequent increase in tumor perfusion.

As shown in Table 3, there was no significant difference between BV reduction of HCC and metastatic liver diseases.

Overall, median value of tumor perfusion was 160.45 mL/1000 mL before embolization and 63.65 mL/1000 mL after embolization, yielding a 60.33% reduction. Considering the different technical aspects of the therapies given, BV decrease was measured separately for TACE and RE groups: in TACE group (n=13), median BV decreased from 154.5 mL/1000 mL to 21.6 mL/1000 mL (86% reduction), while in RE group (n=21) median BV decreased from 163.3 mL/1000 mL to 77.3 mL/1000 mL (52.6% reduction). The percentage of BV decrease after RE (52.6%) is seemingly parallel to the initial tumor perfusion, hence, approximately half of the perfusion diminishes after RE. However, in TACE, more BV loss is noted in relation to the initial tumor perfusion (86%) which may reflect the more embolic potential of the TACE procedure (Figs. 6, 7). The difference between pre- and post-embolization BV was statistically significant in all patients and in all subgroups ($P < 0.001$).

For TACE, BV values measured after embolization were very close to the BV of basal normal liver parenchyma (measurements obtained by C-arm CT perfusion software). On the other hand, significant tumor BV reduction occurred in some cases in both subgroups of SIR-sphere and TheraSphere of RE which is seemingly an unexpected finding at first look. However, the spasm of hepatic arterial bed, which may occasionally cause termination of the procedure well before the planned

Table 4. Comparison of median blood volume in patients with HCC obtained by C-arm CT and MDCT perfusion methods

Lesions	C-arm CT BV* (mL/100 g)	MDCT BV (mL/100 g)
Lesion 1	9.83	9.53
Lesion 2	14.4	16.39
Lesion 3	13.80	13.69
Lesion 4	19.28	24.44
Lesion 5	7.73	7.17
Lesion 6	9.31	10.15
Lesion 7	19.33	18.70
Median	13.80	13.69

The blood volume measurements by C-arm CT and MDCT perfusion studies are highly correlated ($P = 0.003$, r=0.93).
HCC, hepatocellular carcinoma; CT, computed tomography; BV, blood volume; MDCT, multidetector computed tomography.
*C-arm CT BV values measured in mL/1000 mL were converted to mL/100 g assuming a liver density of 1.06 g/mL, for the sake of comparison.

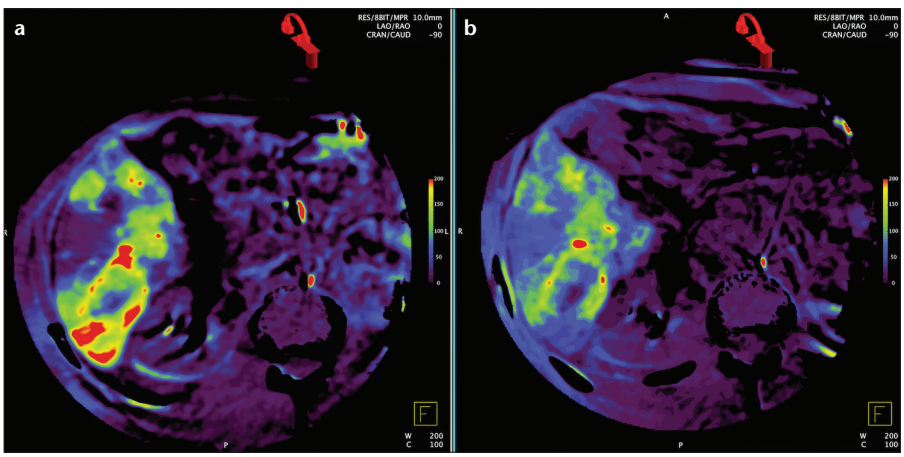

Figure 7. a, b. Axial color map of C-arm CT perfusion study of a 52-year-old man with metastatic neuroendocrine tumor **(a)** shows multiple vascular lesions on the right hepatic lobe. Axial color map of C-arm CT perfusion study of the same patient after radioembolization **(b)** shows decreased perfusion of the lesions.

dose is delivered into the liver, is a known side-effect of RE, particularly when used in metastatic liver diseases.

Among 34 patients included in this study, 12 were diagnosed with HCC. In this HCC subgroup, five patients underwent MDCT perfusion study besides the C-arm CT procedure. The median BV of these seven lesions was 13.69 mL/100 g (range, 7.1–24.4 mL/100 g) on MDCT perfusion and 138.0 mL/1000 mL (range, 77.3–193.3 mL/1000 mL) on C-arm CT, showing a high correlation ($P = 0.003$, r=0.93) between the two methods of BV measurement (Table 4 and Fig. 8).

Regarding the pre- and postembolization settings of HCC subgroup (n=12), median BV values were 194.25 mL/1000 mL and 71.7 mL/1000 mL, respectively. Five HCC patients were treated with RE, yielding 69% reduction in median BV, from 253.1 mL/1000 mL to 78.0 mL/1000 mL. The remaining seven HCC patients were treated with TACE, yielding 87.9% reduction in median BV from 160.6 mL/1000 mL to 19.3 mL/1000 mL. The difference between pre- and postembolization BV values of HCC patients treated with either RE or TACE were both statistically significant ($P < 0.001$).

Discussion

The measurement of BV alterations using the C-arm CT and a prototype software is seemingly a promising method, with the results validated by a commercially available MDCT perfusion software, as seen in Table 1. With this method, any therapy that is planned to be given on the angio table with a capability of C-arm CT, may be individualized according to the extent of tumor perfusion (13). However, further studies are warranted to understand the detailed role of tumor to normal liver BV ratios and the possible target perfusion decreases to be achieved by any hepatic arterial embolization method. Since the patient population in our study was small, it is suggested to investigate perfusion ratio of tumor to normal liver parenchyma in larger patient populations.

Our preliminary data on BV decrease of the given tumors during RE may also be useful in determining the end-point of the procedure and further adjusting the dosimetry to protect normal liver tissue while adequately targeting the tumor. The ratio of tumor to normal liver parenchyma perfusion can be easily obtained during work-up arteriogram; thus, additional dose adjustments may be calculated to prevent radiation-induced liver disease as a late complication.

On the negative side, having two consecutive C-arm CT acquisitions during hepatic arterial embolization is likely to bring additional risk of radiation exposure. Although detailed radiation dose studies are not yet widely available, the amount of radiation given during C-arm CT study is considered to be much less than a MDCT study. Also, in a prospective study of patients undergoing TACE, routine use of C-arm CT was reported to increase stochastic risk but decrease deterministic risk from digital subtraction angiography (14). Besides, C-arm CT is already accepted as a useful tool that is increasingly used during many vascular procedures.

Utilizing the already available arterial access during transarterial embolization procedures, quantitative measurements with C-arm CT were comparable with MDCT perfusion with significantly lower contrast load to the patients. The mandatory side branch embolization in preparatory angiography for RE, in fact, seems to be increasing the tumor perfusion immediately, which may have

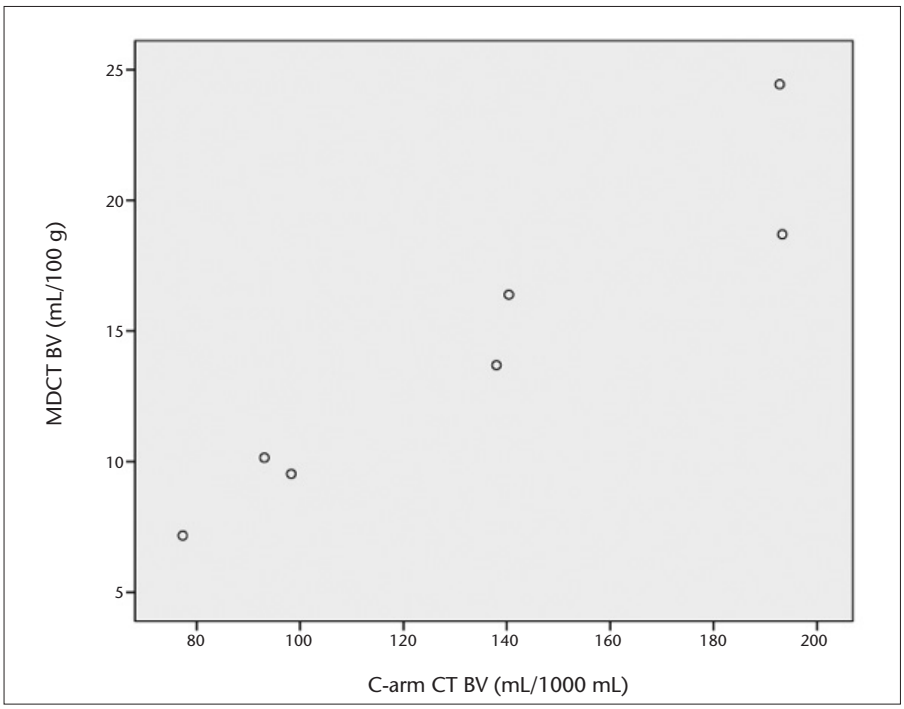

Figure 8. The blood volume measurements obtained by C-arm CT and MDCT perfusion studies for patients with hepatocellular carcinoma show significant correlation ($P = 0.003$, r=0.93).

a hazardous effect on tumor growth, particularly if there is a long waiting period before the actual RE treatment. Therefore, interventional radiologists may have to reconsider this fact during treatment planning for RE.

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

In conclusion, based on our limited data, quantitative BV measurement with C-arm CT is a feasible technique to assess the tumor response to various hepatic arterial embolization therapies. Significant decrease in tumor BV was measured at postembolization settings in comparison to pre-embolization. Irrespective of histopathological type, both primary and metastatic malignancies are suitable for BV measurement using the C-arm CT technique. The BV measurement of these tumors before the embolization treatment is indicative of their vascularity according to their origins.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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