

# Reproducibility of Parenchymal Blood Volume Measurements Using an Angiographic C-arm CT System

Kerstin Mueller, PhD, Rebecca Fahrig, PhD<sup>1</sup>, Michael Manhart, PhD, Yu Deuerling-Zheng, MS, Jarrett Rosenberg, PhD, Teri Moore, BS, RT, Arundhuti Ganguly, PhD, Nishita Kothary, MD

**Rationale and Objectives:** Intra-procedural measurement of hepatic perfusion following liver embolization continues to be a challenge. Blood volume imaging before and after interventional procedures would allow identifying the treatment end point or even allow predicting treatment outcome. Recent liver oncology studies showed the feasibility of parenchymal blood volume (PBV) imaging using an angiographic C-arm system. This study was done to evaluate the reproducibility of PBV measurements using cone beam computed tomography (CBCT) before and after embolization of the liver in a swine model.

**Materials and Methods:** CBCT imaging was performed before and after partial bland embolization of the left lobe of the liver in five adult pigs. Intra-arterial injection of iodinated contrast with a 6-second x-ray delay was used with a two-sweep 8-second rotation imaging protocol. Three acquisitions, each separated by 10 minutes to allow for contrast clearance, were obtained before and after embolization in each animal. Post-processing was carried out using dedicated software to generate three-dimensional (3D) PBV maps. Two region-of-interest measurements were placed on two views within the right and left lobe on each CBCT 3D PBV map. Variation in PBV for scans acquired within each animal was determined by the coefficient of variation and intraclass correlation. A Wilcoxon signed-rank test was used to test post-procedure reduction in PBV.

**Results:** The CBCT PBV maps showed mean coefficients of variation of 7% (range: 2%–16%) and 25% (range: 13%–34%) for baseline and embolized PBV maps, respectively. The intraclass correlation for PBV measurements was 0.89, demonstrating high reproducibility, with measurable reduction in PBV displayed after embolization ( $P = 0.007$ ).

**Conclusions:** Intra-procedural acquisition of 3D PBV maps before and after liver embolization using CBCT is highly reproducible and shows promising application for obtaining intra-procedural PBV maps during locoregional therapy.

**Key Words:** Parenchymal blood volume (PBV); CBCT; porcine study; chemoembolization.

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## INTRODUCTION

Objective measurement of hepatic perfusion during locoregional treatment could aid in the treatment of hepatocellular carcinoma (HCC). Although hepatic blood circulation is approximately 25% arterial and 75% portal venous in the healthy liver (1), the onset of neoangiogenesis

in HCC leads to the domination of arterial supply to the tumor (1–3). For patients with underlying cirrhosis, the degree of arterialization reflects the stage (4), with dysplastic nodules and early HCC demonstrating some portal flow, but as HCC progresses the supply to the tumor rapidly morphs into exclusively arterial supply (2,3). In vivo assessment of organ perfusion, including measurement of blood volume contribution from the hepatic arterial and portal flow, is an established and reproducible technique using dynamic contrast-enhanced computed tomography (CT) (1,4–7). Specifically, pathologic changes during neoangiogenesis, the evolution from dysplasia to poorly differentiated HCC, and changes following transarterial chemoembolization have been studied by dynamic contrast-enhanced CT (5–8). Assessment of tumor characteristics during locoregional treatments, vis-à-vis quantitative hemodynamic characteristics, may offer a valuable diagnostic or treatment end point biomarker (8). Intra-procedural dynamic contrast-enhanced CT at the present time is infeasible. In contrast, the use of cone beam CT (CBCT) or C-arm CT as a complementary modality to digital subtraction angiography (DSA) during therapy is widely accepted and continues to become a routine part of the procedure (9,10).

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From the Department of Radiology, Stanford University, 1201 Welch Road, Stanford, CA 94305 (K.M., R.F., J.R., A.G., N.K.); Siemens Healthcare GmbH, Forchheim, Germany (M.M., Y.D.-Z.); Siemens Medical Solutions Inc., Malvern, Pennsylvania (T.M.); Department of Radiology, Stanford University Medical Center, Stanford, California (N.K.). Received March 24, 2016; revised August 5, 2016; accepted August 7, 2016. Funding/Grant Support: Siemens Business Area Advanced Therapies. Contributions of this paper: Recently, quantitative measurements of parenchymal blood volume (PBV) in the interventional suite became of more and more interest. The current clinical studies investigate the PBV values derived with a C-arm CT system to a conventional CT system. First results are quite promising. We carefully investigated the reproducibility of the imaging protocol for PBV in five animal models. Our study proves the reproducibility of PBV measurements using C-arm CT. <sup>1</sup>Rebecca Fahrig is now with Siemens Healthcare GmbH, Forchheim, Germany. **Address correspondence to:** K.M. e-mail: [kmuell@stanford.edu](mailto:kmuell@stanford.edu)

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Moreover, within the past few years, a modified injection and reconstruction protocol designed for CBCT imaging has demonstrated the feasibility of calculating cerebral perfusion in canines and humans (11–14). Using a similar approach, it was shown that a modified injection and reconstruction protocol enables the calculation of parenchymal blood volume (PBV) within the liver using CBCT (15–18). These first clinical studies show the feasibility of PBV measurements before and after hepatic arterial treatment with its correlation to CT perfusion studies. However, up to now, no study has carefully evaluated the reproducibility of PBV measurements in the liver for one subject. Therefore, the objective of this study was to investigate the reproducibility of obtaining PBV measurements in a swine model using CBCT, before and after partial transarterial (bland) embolization of the liver.

## MATERIALS AND METHODS

Under approval by the Administrative Panel on Laboratory Animal Care, five female adult Yorkshire breed pigs ( $53 \pm 0.9$  kg) underwent CBCT imaging of the liver before and after partial embolization of the left lobe. During the duration of the experiments, animals were under the attendance of two licensed veterinary technicians. Prior to imaging, the animals were given intramuscular injection of Telazol (Fort Dodge Animal Health, KS) (5–7 mg/kg) combined with atropine (0.5 mg/kg). Following intubation, isoflurane was maintained at 1%–2% by mechanical ventilation. Assessment of vital signs, including heart rate,  $O_2$  saturation, and end tidal  $CO_2$ , was performed every 15 minutes. Primary dosage of 300 IU/kg of heparin was given intra-arterially and supplemented as needed. Directly prior to imaging procedures, a 7Fr sheath (Vanguard; Medrad, Indianola, PA) was placed within the right common femoral artery. Following an aortogram, a standard 5Fr end-hole catheter (AngioDynamics, Latham, NY) was placed in the common hepatic artery under fluoroscopic guidance. All pre-embolization and post-embolization imaging was performed following injection of iodinated contrast into the common hepatic artery using a dual-syringe power injector (MEDTRON Accutron HP-D, Saarbrücken, Germany). CBCT acquisition details are described later. A 2.3Fr microcatheter (Renegade HI-FLO; Boston Scientific, Natick, MA) was advanced through the 5Fr catheter, with the tip positioned in the left hepatic artery, under fluoroscopic guidance. The embolization to near stasis was performed by injecting 150–300 micron diameter microspheres (Embospheres; Merit Medical Systems, Inc, South Jordan, UT) to parts of the left lobe of the liver and was confirmed using DSA.

### CBCT Image Acquisition Protocol

A monoplane flat panel detector angiographic CBCT system (Axiom Artis dTA; Siemens Healthcare GmbH, Forchheim, Germany) was used to perform an 8-second rotational protocol, resulting in approximately 400 projections over  $200^\circ$  during each rotation, while allowing 150-mm craniocaudal scan length coverage. The dose to the detector was set at

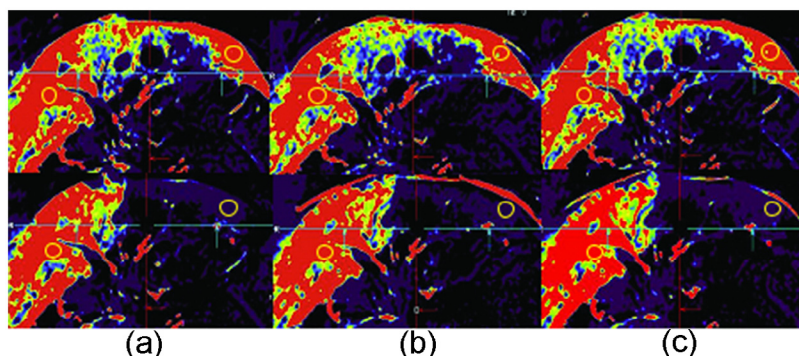
1.2  $\mu$ Gy per projection, 81 kVp, with automatic exposure control enabled such that x-ray dose modification occurred on a per-projection basis. The imaging protocol consisted of an initial 8-second rotation (mask run), followed by a second 8-second rotation (fill run) using a 6-second x-ray delay. To achieve steady-state opacification within the liver, 21-mL contrast (Omnipaque 350; GE Healthcare, Pewaukee, WI) in 21-mL saline was administered over 14 seconds at a rate of 3 mL/s during a 6-second turnaround and during the fill run. To allow clearance of contrast from the liver, a 10-minute washout period was incorporated between each mask-fill acquisition. No contrast uptake from the baseline images have been observed measured in HU values. A total of six acquisitions (three baseline and three post-embolization) were performed across all animals during suspended respiration.

### Post-processing

Following each 8-second acquisition, all images were reconstructed, and PBV maps were successfully calculated using a dedicated workstation (Siemens Healthcare GmbH). The post-processing method used to calculate parenchymal PBV was based on a compartmental model used in the calculation of cerebral blood volume in canines and humans (19,20).

### Statistical Analysis

The reproducibility of CBCT three-dimensional (3D) PBV maps was evaluated using all data from the five cases. Assessment of variation within CBCT 3D PBV maps obtained before (three baseline maps/case) and after partial embolization (three embolized maps/case) was done on each animal (six total maps/case). To compare the same anatomic regions within each animal across each set of three scans, CBCT 3D PBV maps were coregistered to the same slices using a dedicated workstation (Siemens Healthcare GmbH). After image registration, two  $2\text{ cm}^2$  regions-of-interest (ROIs) were placed on two views (one axial and one coronal) within the right and left lobe on each CBCT 3D PBV map, resulting in 12 ROIs/animal (2 ROIs/lobe  $\times$  2 lobes  $\times$  3 maps/animal). Similarly, CBCT 3D PBV maps corresponding to post-procedure scans were coregistered to the same three slices, and two  $2\text{ cm}^2$  ROIs were placed on two views (one axial and one coronal) within the right and left lobe, resulting in a 12 ROIs/animal set. To obtain relative measurements for each animal, the left/right lobe ratio was calculated using PBV measurements within  $2\text{ cm}^2$  ROIs in each set of baseline and embolized CBCT 3D PBV maps. Variability in PBV within each animal was assessed by calculating the coefficient of variation for the relative measurements obtained from each of the five cases. Measurement reproducibility was assessed by intraclass correlation among scans, estimated by a mixed-effects regression of PBV on the mixed effect of time (pre-embolization vs post-embolization), as well as the random effect of animal and animal-by-time interaction. To evaluate the significance of reduction in blood volume following the embolization



**Figure 1.** Coronal view of parenchymal blood volume (PBV) maps generated from three consecutive scans (a, b, and c) in a single study animal. Baseline PBV (top row) and post-partial embolization of the left lobe of the liver PBV (bottom row) are shown. (Color version of figure is available online.)

**TABLE 1.** Parenchymal Blood Volume Measurements Obtained Within a 2 cm<sup>2</sup> ROI Placed on Identical Regions of the Left and the Right Lobes, Across a Total of Six 3D Maps Corresponding to Three Scans Performed Before and Three Scans Performed After Partial Embolization for Each Study Animal

ID	Baseline PBV (mL/1000 mL): Left Lobe				Post-left Lobe Embolization PBV (mL/1000 mL): Left Lobe			
	Scan 1	Scan 2	Scan 3	Mean Across 3 Scans	Scan 1	Scan 2	Scan 3	Mean Across 3 Scans
1	64.40	71.35	52.05	62.60	16.70	15.25	18.30	16.75
2	87.25	107.55	90.80	95.20	38.15	24.90	22.25	28.43
3	100.15	83.25	89.15	90.85	11.20	6.20	5.95	7.78
4	55.20	51.75	52.95	53.30	14.10	7.15	12.00	11.08
5	159.90	150.05	150.05	153.33	35.15	16.95	34.35	28.82
ID	Baseline PBV (mL/1000 mL): Right Lobe				Post-left Lobe Embolization PBV (mL/1000 mL): Right Lobe			
	Scan 1	Scan 2	Scan 3	Mean Across 3 Scans	Scan 1	Scan 2	Scan 3	Mean Across 3 Scans
1	99.65	117.15	87.25	101.35	189.25	149.75	158.35	165.78
2	101.85	101.95	118.35	107.38	105.15	92.15	76.65	91.32
3	126.65	105.25	103.70	111.87	119.20	110.05	90.30	106.52
4	85.40	81.50	81.00	82.63	99.10	100.95	98.90	99.65
5	127.55	139.90	128.45	131.97	137.05	128.60	134.05	133.23

3D, three-dimensional; PBV, parenchymal blood volume; ROI, region-of-interest.

procedure, a Wilcoxon signed-rank test based on relative measurements for baseline and embolized CBCT 3D PBV maps was used. All statistical analyses were done with Stata Release 11.1 software (StataCorp LP, College Station, TX).

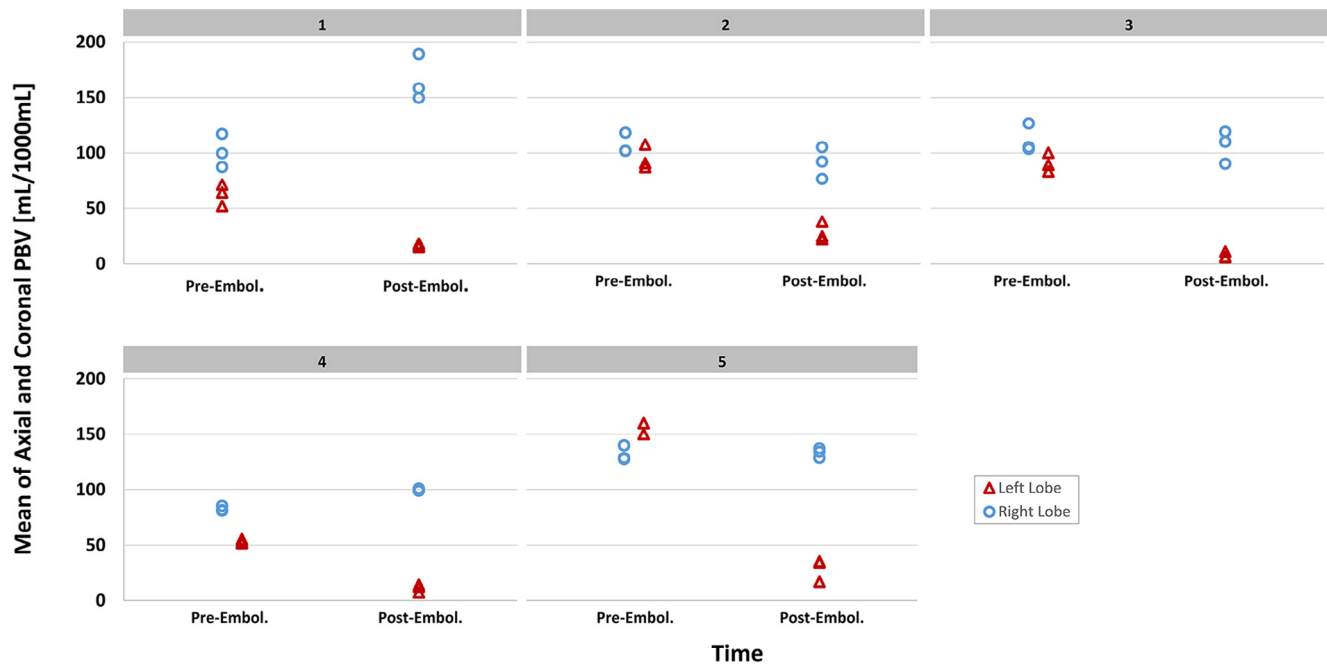
## RESULTS

Qualitatively reproducible color maps before and after partial embolization of the liver were obtained in all animals (Fig 1). Pre-embolization blood volume depicted by the red area predictably decreased following partial embolization of the left lobe, as demonstrated by the yellow, green, blue, and black colors, representing decreasing blood volume (Fig 1). Overall, there was good agreement between PBV measurements obtained from the axial and coronal ROIs (concordance correlation = 0.94), and hence the mean of the two views' measurements was used in the subsequent analyses. Table 1 lists the PBV value of each animal across three pre-embolization and three post-embolization scans. Before embolization, the average PBV of the left and right lobe was 91.06 and 107.04 mL/1000 mL, respectively (range:

53.30–153.33 mL/1000 mL, standard deviation [SD]: 39.15; and 82.63–131.97 mL/1000 mL, SD: 17.84, respectively). Following partial embolization, the mean calculated PBV of the left lobe decreased to 18.57 mL/1000 mL (range: 7.78–28.82 mL/1000 mL, SD: 9.72), an average of 80% reduction ( $P = 0.0007$ ), without any significant immediate change in the PBV of the right lobe ( $P = 0.2115$ ) (Fig 2). As expected, correspondingly, there was also a significant reduction in the left to right PBV ratio ( $P = 0.0007$ ). Assessment of variability in CBCT 3D PBV maps obtained from the five pigs (Fig 2) resulted in mean intragroup coefficients of variation of 7% (range: 2%–16%) and 25% (range: 13%–34%) for baseline and embolized PBV maps, respectively. The intraclass correlation among relative PBV measurements (left lobe PBV/right lobe PBV) was 0.89.

## DISCUSSION

Over the last two decades, researchers have attempted to determine a surrogate biomarker that accurately and consistently predicts the end point for transarterial chemoembolization.



Graphs by Case

**Figure 2.** Repeated parenchymal blood volume measurements (mL/1000 mL) obtained before and after embolization of the left lobe of the liver of each of the five study animals.

Unfortunately, the methods described in this sometimes contradicting literature are either subjective, with operator and institution variability, and are often cumbersome. The most widely used end point is angiographic stasis in the treated vessel or uptake of iodized oil (lipiodol) in the tumor itself (21,22). The extent of embolization required for adequate treatment continues to be scrutinized (21,23) and relies heavily on operator perception, which results in variance (24). The recent use of conformal drug-eluting embolics muddies the issue further. In the past, volumetric intense uptake of lipiodol has been correlated with favorable tumor response (22,25), or for drug-eluting beads circumferential contrast retention (26), including a quasi-objective method using semi-automated volumetric segmentation (27). However, the degree of response varies greatly for tumors that demonstrate non-uniform uptake, and thus, is not a reliable surrogate across all tumors (25). Further, with the development of drug-eluting microspheres, lipiodol uptake is rapidly becoming a moot point. Immediate post-procedure perfusion imaging using magnetic resonance imaging has been published for small series of patients (23,24,28) but lacks widespread application. Although valuable, these data still do not provide the operator with feedback during the procedure and are often cumbersome. The complementary use of CBCT with DSA as a problem-solving tool and to provide angiographic guidance for liver-directed therapies is now well established and backed by a growing body of literature (9,10). The next natural step, then, would be to exploit its volumetric capability to study tissue perfusion, similar to perfusion CT. The use of CBCT to study the changes in perfusion in cerebral ischemia has been a recent topic of research, with investigators obtaining

consistent and reproducible metrics such as PBV (12–14,20,29–31). Although the liver differs from the brain in its hemodynamics, and the images are subject to respiratory degradation, technological advances in the imaging hardware and software may put this goal within reach. Recent clinical studies showed the feasibility of PBV measurements using CBCT (15–17,32). The statistical evaluation of the presented study demonstrated repeatability for measurements obtained on 3D PBV maps generated within each animal. A limitation of this study is that variation in blood volume was not assessed across animals. However, differences in physiology unique to each animal would skew the overall measurements; therefore, only intragroup variation was measured. Although the assessment of three scans demonstrated low variation within each animal, increasing the number of scans for each animal may also help measure variability in blood volume within scans in further detail. Previous studies evaluating hemodynamics within the liver using perfusion CT imaging have compared results obtained using different software and demonstrated variability in measurements (33). Therefore, comparison against measurements obtained using different modalities, imaging protocols, and post-processing algorithms may reflect differences in measured values. Further investigation of measurements obtained within this study against measurements obtained using different methods may provide valuable insight. Finally, our experiment was undertaken as a proof of principle and is a mere first step toward more robust experiments that compare PBV values between perfusion CT and CBCT in diseased humans, as well as expand to other quantitative perfusion parameters such as hepatic parenchymal flow and mean transit time.

## SUMMARY AND CONCLUSIONS

The findings of this study demonstrate the consistent reproducibility of obtaining intra-procedural measurement of hepatic blood volume using CBCT. The consistency of PBV measurements within the animal, before and after embolization, leads credibility to its use in humans during locoregional therapies, particularly in determining the degree of embolization required to treat the tumor completely. One can extrapolate that for tumors that may be incompletely treated due to competing supply from another artery, identifying residual PBV could help interrogate and discover the additional supply. Future refinement in the technique that allows additional hemodynamic measurements, eg, blood flow measurements, could allow the translation of this novel imaging technology to liver-directed therapies in human. By enabling complementary qualitative and quantitative information, this technique may serve as a useful biomarker with which to acquire detailed assessment of hemodynamics within the interventional suite.

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