Prediction and Reduction of Motion Artifacts in Free-Breathing Dynamic Contrast Enhanced CT Perfusion Imaging of Primary and Metastatic Intrahepatic Tumors

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Rationale and Objective: To develop and evaluate a method for predicting and reducing motion artifacts in free-breathing liver perfusion computed tomography (CT) scanning with couch shuttling and to compare tumor and liver parenchyma perfusion values.

Materials and Methods: Thirty patients (23 males, 7 females, median age of 74 years) with primary or metastatic intrahepatic tumors underwent dynamic contrast enhanced CT scans with axial shuttling. A semiautomatic respiratory motion correction algorithm was applied to align the acquired images along the z-axis. Perfusion maps were generated using the dual-input Johnson-Wilson model. Root mean squared deviation (RMSD) maps of the model fit to the pixel time-density curves were calculated.

Results: Precorrection RMSD correlated positively with magnitude of change in functional values resulting from motion. Blood flow, arterial blood flow, and permeability surface product were significantly increased in tumor compared to normal tissue ($P < .05$), blood volume was significantly reduced in tumor compared to normal tissue ($P < .05$). In a subgroup of patients with high-amplitude motion significant difference was observed between uncorrected and motion correction blood flow maps.

Conclusions: Patients can breathe freely during hepatic perfusion imaging if retrospective motion correction is applied to reduce motion artifacts. RMSD provides a regional assessment of motion induced artifacts in liver perfusion maps.

Key Words: Perfusion imaging; hepatocellular carcinoma; liver; liver circulation; image processing; computer-assisted.

Key points:
1. Allowing patients to breathe freely during liver DCE-CT acquisition is possible if images are corrected for motion before functional maps are generated.
2. Free breathing during DCE-CT scans reduces patient discomfort and reduces preparation time.
3. Respiratory motion artifacts can be predicted by elevated RMSD.
4. Axial registration reduces motion artifacts, bringing functional values into line with previously published values.

Intrahepatic tumors, both primary and metastatic, have poor prognoses (1) and increasing incidence rates in both developing and developed countries. For many patients, resection is not an option; for these patients, treatment options include external beam radiotherapy, selective internal radiotherapy, arterial chemo-embolization, or chemotherapy, all of which rely on medical imaging for monitoring treatment response and possible recurrence. Standard anatomical imaging alone may not provide optimal radiographic information for optimal localization, treatment, and outcome assessment. Innovative imaging tools such as tumor perfusion have been shown to add value for prognostication in cerebral tumors (2) and patient selection and radiation treatment planning (3). Two separate blood vessels, the hepatic artery and the portal vein, supply blood to the liver—the hepatic artery delivers...
oxygenated blood from the left ventricle whereas the portal vein delivers partially deoxygenated blood from the gastrointestinal tract and the spleen (4). Normal liver tissue receives about two thirds of its total blood supply from the portal vein and only one third from the hepatic artery (5). It has been suggested that liver tumors receive a majority of their blood supply from the hepatic artery rather than the portal vein because of significant angiogenesis associated with tumor growth, which selectively recruits arterial vessels (6).

Dynamic contrast enhanced computed tomography (DCE-CT) (7) measurement of tissue perfusion has been validated against microspheres in both normal tissue and tumors in the brain (8,9), and in the liver (10,11) in rabbit experiments. Respiratory motion during a DCE–CT scan can lead to fluctuations in the time-density curves of abdominal organs resulting in inaccurate estimates of perfusion parameters. This is especially true of the liver, which has been shown to move as much as 2 cm in the craniocaudal direction resulting from normal respiratory motion (12,13). To minimize artifacts caused by respiratory motion, trials have investigated the use of various techniques.

1. Single breath hold (14,15). This technique reduces the total scan time to approximately 30 seconds, which is not long enough to determine the shape of the portal vein input curve or the contrast washout rate needed to calculate permeability surface product accurately (16).

2. Single breath hold followed by repeated burst cine (10,11,16). Cine scanning over 4 seconds allows acquisition over an entire respiratory cycle and retrospective gating to eliminate breathing motion. Besides concerns of radiation dose, the technique limits the axial field of view of the scan to the axial field of view of the scanner because temporal sampling would be too low if this technique was combined with axial shuttling or low–pitch helical acquisition.

3. Multiple breath holds (17,18). Using multiple breath holds allows for a longer scan, but difficulty reproducing lung volume during repeated breath holds can cause image misalignment and lead to artefacts if image registration is not applied.

4. Abdominal compression band and oxygen mask (19). This approach aims to reduce breathing motion at the cost of increased patient discomfort and increased setup time.

5. Three-dimensional nonrigid registration (20). This implementation of deformable registration uses conservation of organ volume because differential tissue contrast enhancements at each time point have the tendency to lead algorithm to misregister areas with the same contrast but different anatomical location. Volume conservation can only be used in whole organ imaging, which is not feasible with axial imaging on current 64–slice scanners and relies on accurate segmentation of the liver.

We propose an axial shuttling protocol that allows the patient to breathe freely with minimal coaching; followed by a posteriori automatic image registration to minimize motion induced oscillations in the liver time–density curves before calculating functional maps. The benefit of free breathing is less discomfort for the patient during scanning and shorter preparation time; the caveat is that it is necessary to register the images before calculating perfusion parameters. By shuttling the couch between two adjacent positions, the field of view in the axial direction is doubled from 4 cm to 8 cm for a 64-slice CT scanner, allowing better tumor coverage.

The purpose of this article is to determine where and to what extent organ motion may introduce artifacts in the functional maps and to report tumor and liver perfusion values determined from the free-breathing shuttle DCE-CT imaging protocol and the associated image registration algorithm for respiratory motion correction (RMC). In particular, we quantify the effects of respiratory motion on liver perfusion values measured with free-breathing DCE-CT scans by comparing functional information from scans without and with RMC.

**MATERIALS AND METHODS**

We prospectively recruited 30 (23 males, 7 females) patients who have either metastatic or primary intrahepatic cancer (11 metastatic, 17 hepatocellular carcinoma, and 2 cholangiocarcinoma) who were scheduled for external beam radiation therapy for the imaging study. The median age of patients in the study was 74 years (range 43–89). The study protocol was approved by institutional research ethics board and informed consent was obtained in each case. Exclusion criteria were poor liver and renal function determined by enzyme and serum creatinine levels respectively. Patients who received prior treatment with other treatment modalities were not excluded.

The patient was positioned feet first in the supine position on the patient table of a 64-slice scanner (Discovery VCT or CT750HD, GE Healthcare, Waukesha, WI). One of the antecubital veins was catheterized with a 20–23 gauge catheter and the catheter was connected to an automatic injector. Before the DCE scan, a fast helical scan was performed to locate the lesion and an 8 cm long volume was selected to include the tumor and portal vein. The perfusion scan was performed using the dynamic axial shuttle technique to translate the couch between two adjacent positions to cover the selected 8 cm volume. At each couch location a 4 cm long volume of the liver, divided into eight 5-mm-thick slices, was imaged with the following parameters: 120 kVp, 120 mA, and 0.4 second rotation time. The time interval between two successive scans of the same location (passes) was 2.8 seconds and each 4 cm volume was imaged 40 times (2-minute scan time). Contrast (Omnipaque 300, GE Healthcare, Waukesha, WI) at the dose of 0.7 mL/kg bodyweight to a maximum of 70 mL was injected at a rate of 4 mL/second starting after two scans of each 4 cm volume was acquired as baseline. Patient was instructed to breathe normally during the entire scan sequence.

A simple correction algorithm was developed to reduce user interaction and computation time. Image registration for RMC was performed as outlined in Figure 1 and detailed
in Appendix 1 using an in-house algorithm developed in Matlab (MathWorks, Natick, MA). The reference image was chosen during the arterial contrast phase (typically the tenth pass of scanning) to provide maximum tumor enhancement. Images of the two couch positions were registered independently of each other to account for time-lag between acquisitions of adjacent sections. Registration regions of interest (ROIs) were chosen to include high contrast features including liver edge, blood vessels, tumor edge, and hepatic hilum and exclude other organs or bone to achieve maximum sensitivity to liver registration. Images were shifted only in the superoinferior direction because the majority of respiratory motion is along that axis.

To compare and validate the quality of the registration algorithm, a similar approach was performed manually. The same reference image as used by the registration algorithm was selected and the liver in the reference image was contoured. Similar to the semiautomatic registration algorithm, image spacing was reduced to 1.25 mm via weighted interpolation. The reference liver contour was superimposed on all images (both original and interpolated) in the scan and a best match was selected manually for each volume. Images were then shifted to align the best matching slices.

Functional maps of blood flow (BF), blood volume (BV), permeability surface product (PS), hepatic arterial blood flow (HABF), portal vein blood flow (PVBF), and hepatic arterial fraction were generated by fitting the time density curves from the uncorrected and motion corrected images with the dual-input Johnson-Wilson model as outlined in a previous publication (21) which is implemented in CT Perfusion (GE Healthcare, Waukesha, WI). In addition, root mean squared deviation (RMSD) maps of the model fitted curves to the measured liver time density curves (Fig 2) were generated to quantify and localize the effect of liver motion from breathing. The arterial and portal venous input functions were generated by placing ROIs on the abdominal aorta and either the main trunk or the left or right branch of the portal vein respectively.

Data were imported into Analyze 10 (Mayo Clinic, Rochester, MI) for analysis. Tumor ROIs were segmented by applying a threshold-based region growing algorithm to the motion corrected time-averaged CT images (averaged CT), generated by averaging the entire sequence of the motion corrected dynamic images. For each segmented tumor ROI, another ROI of normal liver parenchyma was drawn manually in the averaged CT at least 5 mm from the tumor and liver edge. Both tumor and normal tissue ROIs were then superimposed on the uncorrected and motion corrected BF, BV, PS, HABF, PVBF, and hepatic arterial fraction functional maps and functional values of the tumor and normal tissue were determined as the average inside the appropriate ROI. Mean RMSD was determined using the same tumor and normal tissue ROIs to verify that motion correction reduced the residuals of the fitting algorithm.

Some scans may not have motion-induced artifacts, the scans from these patients would not benefit from motion correction. To reduce workload different metrics were evaluated for stratifying scans that benefit the most from motion correction. Because different effects can cause artifacts in functional maps, the main sources include reconstruction artifacts, motion of the portal vein reducing quality of the vein input curve and organ motion, a simple metric may not be the best choice. To identify which patients benefited the most from motion correction, $t$-statistic maps were calculated from the absolute difference between pre- and postcorrection BF, BV, PS, HABF, and PVBF maps for each patient, the standard deviation used to calculate $t$-stat was found by adding the normal liver variance across all patients and taking the
RESULTS

Tumor blood flow, arterial blood flow, and permeability surface product were all significantly elevated and tumor blood volume was significantly reduced compared to normal tissue (Table 1, Fig 3), no difference was found in portal vein blood flow between tumor and normal tissue—these results were independent of motion correction.

In a subgroup of 10 patients with high amplitude motion, tumor blood flow was not significantly higher than normal tissue blood flow in correction maps, in postcorrection maps tumor blood flow was significantly elevated for these same patients. PS was also found to not be significantly elevated in high-amplitude motion patients in pre-correction scans, whereas the difference between tumor and normal tissue PS did trend higher after correction, it was not enough to reach significance (Table 2).

The registration algorithm and manual correction had good agreement with a mean distance to agreement of 0.3 ± 2.0 mm. Manual registration took between 1 and 3 hours depending on the amount of motion present and availability of features with high variability in the superoinferior direc-

| TABLE 1. Perfusion Parameters in Tumor Versus Normal Tissue |
|---------------------------------|-----------------|----------------|---------|
| Functional Parameter           | Normal Tissue   | Tumor          | P Value* |
| BF (ml/min-100g)               | 140 ± 45        | 182 ± 71       | .006    |
| BV (ml/min-100g)               | 37 ± 7          | 28 ± 9         | <.001   |
| HAF (%)                        | 33 ± 9          | 46 ± 11        | <.001   |
| PS (ml/min-100g)               | 13 ± 5          | 19 ± 9         | .002    |
| HABF (ml/min-100g)             | 47 ± 25         | 85 ± 44        | <.001   |
| PVBF (ml/min-100g)             | 93 ± 31         | 97 ± 40        | .6      |

BF, hepatic blood flow; BV, hepatic blood volume; HABF, hepatic arterial blood flow; HAF, hepatic arterial fraction (fraction of total blood flow that is arterial); PS, permeability surface product; PVBF, portal venous blood flow.

Mean perfusion values for entire patient group after motion correction. Values are mean ± standard deviation.

*Normal tissue vs. tumor.

tion, compared to 10–15 minutes for the registration algorithm, including reading and writing the image DICOM files.

Twelve of 30 patients had a relative change in mean whole-liver blood flow before and after motion correction greater than 24%, whereas 9 of 30 patients had mean relative change in mean whole-liver blood volume after motion correction of greater than 13% (Fig 4). Artifacts from respiratory motion do not preferentially elevate or reduce BF, BV, or any other tested parameter, which explains why mean functional parameters over the entire patient cohort did not change significantly before and after correction for respiratory motion.

Precorrection RMSD correlated positively with the absolute change in BF, BV, HABF, and PVBF after correction (Fig 5) across all patients. RMSD can be used to determine the proneness of perfusion data to suffer from motion artifacts, locally elevated RMSD indicates unreliable perfusion values, whereas low local RMSD indicate reliable perfusion data even in patients with elevated mean RMSD. An example of elevated local RMSD indicating unreliable and reliable can be seen in Figures 6b–d.

Three metrics were tested to determine the most accurate predictive method of stratifying high and low patients:

1. Mean whole liver pre-correction RMSD above 38 HU has 90% sensitivity and 65% specificity.
2. Maximum axial liver displacement during scan greater than or equal to 1.5 cm (range 0.5–3.38 cm) has 90% sensitivity and 55% specificity.
3. Total liver displacement during scan greater than or equal to 20 cm (range 5–56.75 cm) has 90% sensitivity and 60% specificity.

Mean whole-liver RMSD was reduced by an average of 15% (35.2–29.7 HU) following motion correction (P < .001), 29 of 30 patients had reduction in whole-liver RMSD.
DISCUSSION

After motion correction, perfusion results agree with previously published studies (14,23) and indicate that arterial angiogenesis is an important factor in tumor growth. We hypothesize that arterial blood flow maps may be helpful in delineating cancerous tissue as the increase in arterial blood

![Figure 3. Comparison of mean normal tissue and tumor blood volume (a), blood flow (b), arterial blood flow (c), and portal vein blood flow (d) of all patients compared with and without motion correction. **Significant difference at P < .01.](image)

**TABLE 2. Normal Tissue Versus Tumor in Patients with High- and Low-Amplitude Motion**

| Functional Parameter | Motion | Normal Tissue | Tumor    | P Value^
|----------------------|--------|---------------|----------|----------
| BF (ml/min-100g)     | High   | Uncorrected 150 ± 82 | 191 ± 73 | .10*     
|                      | Corrected 160 ± 56 | 222 ± 70 | .03*     |
|                      | Low    | Uncorrected 113 ± 26 | 166 ± 72 | .002     |
|                      | Corrected 130 ± 36 | 163 ± 64 | .03      |
| BV (ml/100g)         | High   | Uncorrected 37 ± 6  | 29 ± 9   | .006     |
|                      | Corrected 39 ± 5  | 31 ± 8   | .003     |
|                      | Low    | Uncorrected 35 ± 6  | 27 ± 10  | <.001    |
|                      | Corrected 37 ± 8  | 27 ± 10  | <.001    |
| HAF (%)              | High   | Uncorrected 35 ± 11 | 50 ± 20  | .007     |
|                      | Corrected 29 ± 12 | 46 ± 12  | <.001    |
|                      | Low    | Uncorrected 34 ± 10 | 44 ± 9   | <.001    |
|                      | Corrected 35 ± 7  | 47 ± 11  | <.001    |
| PS (ml/min-100g)     | High   | Uncorrected 19 ± 10 | 22 ± 14  | .21      |
|                      | Corrected 16 ± 6  | 22 ± 12  | .08      |
|                      | Low    | Uncorrected 12 ± 6  | 16 ± 8   | .01      |
|                      | Corrected 12 ± 3  | 18 ± 8   | .002     |

BF, hepatic blood flow; BV, hepatic blood volume; HAF, hepatic arterial fraction; PS, permeability surface product.

Values are mean ± standard deviation. Paired t-test was used to determine significance. (fraction of total blood flow that is arterial).

^Uncorrected maps failed to reach significance criterion and corrected maps did show significant difference.

^Normal tissue versus tumor.
flow in tumors from angiogenesis is very clearly visualized and aim to test this hypothesis in a future study. In patients with severe cirrhosis or fibrosis of the liver, PS maps may help differentiate cancer from noncancerous disease as PS would be decreased in noncancerous cirrhotic tissue (24) but elevated in tumor tissue. Locally elevated RMSD is a predictor of motion-induced artifacts and may aid in clinical decision-making based on perfusion maps by indicating which perfusion values are reliable and which may be artifactual local perfusion features and not true local perfusion features such as neoplasms, and local hypo- or hyperperfused regions.

Traditional CT perfusion protocols are typically limited to the axial field of view of the CT scanner, but with axial (couch) shuttling/table toggling (25) the axial field of view can be effectively doubled. Increased pitch allows the use of helical imaging techniques (20), which can increase the field of view to cover the entire liver and is an alternative to couch shuttling. Automated three-dimensional registration algorithms often fail when registering image volumes that have significant unshared image space, which is the case for most published liver DCE-CT protocols, including the one presented here. The axial shuttle or helical techniques would not be required for

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**Figure 4.** Histogram of relative change comparing pre- and post-correction mean whole liver blood flow (a) and blood volume (b) in each patient. The black line is the fitted normal distribution with mean of 9% and 3% and standard deviation of 24% and 13% for blood flow and blood volume respectively. For blood flow, 12 patients have relative change greater than one standard deviation, for blood volume 9 patients have relative change greater than one standard deviation.

**Figure 5.** Absolute difference in blood flow (a), blood volume (b), hepatic arterial blood flow (c), portal venous blood flow (d), hepatic arterial fraction (e) and permeability surface product (f) before and after motion correction versus pre-correction root mean square deviation (RMSD) averaged over 30 patients for the whole liver including tumor. The area of each circle is proportional to the number of voxels sampled. Differences from motion increase with RMSD for all four functional values demonstrating the ability of RMSD to predict local motion induced artifacts.
DCE-CT imaging of liver in a 320-slice cardiac CT scanner. However, respiratory motion correction would still be needed for all these alternative image acquisition techniques and our image registration algorithm can be applied without modification to all protocols except for helical acquisitions.

Active breathing control, abdominal compression, or breath hold coaching may reduce patient and/or staff compliance and throughput preventing their widespread use in clinical practice. A free-breathing method requiring no patient coaching or breathing control apparatus and no staff intervention would increase patient comfort and staff compliance. We proposed a simple semiautomatic image registration algorithm to correct respiratory motion of the liver during DCE-CT scans, increasing the accuracy of the perfusion model fit.
Performing a similar correction manually can take as much as 2 hours; the current version of the algorithm completes in less than 15 minutes and requires user interaction for between 20–60 seconds.

Though not all patients imaged in this study benefited noticeably from motion correction, it is our recommendation that all scans of patients allowed to free breathe during DCE-CT imaging should be corrected. Patients with high-amplitude motion was found to benefit more from motion correction than patients with low amplitude motion would be expected. The predictive ability of three different motion metrics to stratify low- and high-artifact patients was analyzed using specificity and sensitivity analysis, none of the three methods was able to separate patients accurately enough.

The image registration algorithm presented here shifts images rigidly in the axial direction only and does not correct organ rotation or translation in the axial plane or organ deformation; this can lead to residual apparent organ motion especially at the dome of the liver where the motion of the diaphragm can cause organ deformation. RMSD calculation may be sensitive to amount of contrast injected and precontrast tissue density in voxels at tissue boundaries, which may compromise the ability to compare RMSD between patients—using locally elevated RMSD to localize artifacts in a single patient would be unaffected by this because these effects are expected to be uniform in any single patient.

Our free-breathing shuffling protocol for liver perfusion measurements delivers 30% higher effective dose (21) (20 mSv estimated from dose-length product) to the patient than a triphasic liver scan (26) (15 mSv). CT imaging dose may be reduced with more advanced reconstruction techniques (27) without sacrificing signal-to-noise ratio, this would allow significant reduction of dose delivered during DCE-CT acquisition. CT perfusion data are absolute, allowing measurements in different patients as well as repeated measurements in the same patient to be compared. CT perfusion allows noninvasive measurement of perfusion parameters in liver cancer, which may aid in radiotherapy treatment planning by improving target delineation accuracy and monitoring of treatment response.

In conclusion, it is possible to perform one-dimensional superoinferior motion correction for DCE-CT hepatic scans of free-breathing patients to reduce motion artifacts in the subsequently generated perfusion maps. RMSD maps provide a regional assessment of motion induced artifacts in the liver perfusion maps.

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REFERENCES


APPENDIX 1

The motion correction algorithm used to register the dynamic contrast enhanced-computed tomography images corrects respiratory motion along the craniocaudal direction. Two-dimensional correlation is used to determine which slice in a volume acquired at each time point best matches a chosen reference image. Amplitude of motion at each time step is the difference in slice position between the reference image and the best matching slice.

Window/level (width 100 HU, length 76 HU) thresholding was applied to all images and all images were filtered with a 3 x 3 median filter followed by a 5 x 5 median filter to reduce noise without shifting or blurring tissue edges. An offset of 1000 HU was added to each voxel of all images to make their values strictly positive.

The algorithm requires the user to select a number of high-contrast features of the liver, such as edges of the liver or tumor, hepatic hilum, major liver blood vessels, or calcifications to use as landmarks. This was done by placing a 40 x 40 voxel box centered on the desired feature. As many landmarks as desired could be selected and typically 6–10 were selected at different high-contrast features to achieve the best sensitivity to motion while reducing sensitivity to image artifacts, deformation, or motion in other dimensions. Voxels outside the chosen regions were not included in the correlation.

Calculation of two-dimensional discrete cross-correlation coefficient, \( r = \frac{\sum_{m=1}^{n_{\text{max}}} \sum_{n=1}^{m_{\text{max}}} (\text{Ref}_{m,n} - \text{Ref}) (\text{Test}_{m,n} - \text{Test})}{\sqrt{\sum_{m=1}^{n_{\text{max}}} \sum_{n=1}^{m_{\text{max}}} (\text{Ref}_{m,n} - \text{Ref})^2 \sum_{m=1}^{n_{\text{max}}} \sum_{n=1}^{m_{\text{max}}} (\text{Test}_{m,n} - \text{Test})^2}} \)

Step 1

Two-dimensional cross correlation coefficient of the reference image with each slice in an image volume was calculated using Equation 1, which only includes voxels inside the selected landmark regions. The matching slice in the registered volume was the one with the highest \( r \).

Step 2

Spatial interpolation between the best matching slice and two of its adjacent slices 5 mm away was applied to generate two new images at 2.5 mm from the best matching slice. Interpolation was performed by averaging nearest neighbor images (if the matching slice from step 1 was the extreme end of the volume, in that case only one image was interpolated). The interpolated images were then cross correlated with the reference image. If the correlation coefficient \( r \) of one of the interpolated images was higher than that of the chosen \( r \) in step 1 that interpolated image became the matching slice; otherwise, the matching slice remained the same as step 1.

Step 3

Images were then interpolated at 1.25 mm spacing around the matching slice from step 2 and cross correlated with reference image. Interpolation was performed using weighted averaging of nearest neighbor images, with weights defined by the ratio of distances between original to derived slices. Their correlation coefficients were compared to the chosen correlation coefficient from step 2 and the matching slice again chosen with highest correlations. We only interpolated images adjacent to the best matching image to limit memory usage and computation time.

Step 4

The matching slice from step 3 in the volume to be registered was then shifted to the same slice position as the reference slice and slices inferior and superior to the matching slice were generated at 5 mm spacing either by shifting original slices if the matching slice was not interpolated or by interpolation between original slices.

Step 5

Slices will be missing at either inferior or superior extreme of a volume if it is shifted from its original position in the registration with the reference volume. These missing slices were generated by interpolating temporally between slices at same slice location from prior and subsequent time points using weighted averaging; no more than four consecutive slices would be interpolated, in the case of more than four slices missing consecutively all slices at that position would be set to 0 to avoid generation of artificial data; this was done in 1 slice location in 7 of the 30 patients.