Received:
22 March 2017

Revised:
24 June 2017

Accepted:
25 July 2017

<https://doi.org/10.1259/bjr.20170214>

Cite this article as:

Bretas EAS, Torres US, Torres LR, Bekhor D, Saito Filho CF, Racy DJ, et al. Is liver perfusion CT reproducible? A study on intra- and interobserver agreement of normal hepatic haemodynamic parameters obtained with two different software packages. *Br J Radiol* 2017; **90**: 20170214.

FULL PAPER

Is liver perfusion CT reproducible? A study on intra- and interobserver agreement of normal hepatic haemodynamic parameters obtained with two different software packages

^{1,2}ELISA ALMEIDA SATHLER BRETAS, MD, PhD, ²ULYSSES S. TORRES, MD, PhD, ^{2,3}LUCAS RIOS TORRES, MD, ¹DANIEL BEKHOR, MD, ¹CELSO FERNANDO SAITO FILHO, MD, ³DOUGLAS JORGE RACY, MD, ⁴LORENZO FAGGIONI, MD, PhD and ^{1,2}GIUSEPPE D'IPPOLITO, MD, PhD

¹Department of Imaging, Universidade Federal de São Paulo, São Paulo, Brazil

²Department of Radiology, Grupo Fleury, São Paulo, Brazil

³Department of Imaging, Hospital Beneficência Portuguesa, São Paulo, Brazil

⁴Department of Diagnostic and Interventional Radiology, University Hospital of Pisa, Pisa, Italy

Address correspondence to: Dr Elisa Almeida Sathler Bretas
E-mail: elisabretas@gmail.com

Objective: To evaluate the agreement between the measurements of perfusion CT parameters in normal livers by using two different software packages.

Methods: This retrospective study was based on 78 liver perfusion CT examinations acquired for detecting suspected liver metastasis. Patients with any morphological or functional hepatic abnormalities were excluded. The final analysis included 37 patients (59.7 ± 14.9 y). Two readers (1 and 2) independently measured perfusion parameters using different software packages from two major manufacturers (A and B). Arterial perfusion (AP) and portal perfusion (PP) were determined using the dual-input vascular one-compartmental model. Inter-reader agreement for each package and intrareader agreement between both packages were assessed with intraclass correlation coefficients (ICC) and Bland-Altman statistics.

Results: Inter-reader agreement was substantial for AP using software A (ICC = 0.82) and B (ICC = 0.85–0.86), fair for PP using software A (ICC = 0.44) and fair to moderate for PP using software B (ICC = 0.56–0.77). Intrareader agreement between software A and B ranged from slight to moderate (ICC = 0.32–0.62) for readers 1 and 2 considering the AP parameters, and from fair to moderate (ICC = 0.40–0.69) for readers 1 and 2 considering the PP parameters.

Conclusion: At best there was only moderate agreement between both software packages, resulting in some uncertainty and suboptimal reproducibility.

Advances in knowledge: Software-dependent factors may contribute to variance in perfusion measurements, demanding further technical improvements. AP measurements seem to be the most reproducible parameter to be adopted when evaluating liver perfusion CT.

INTRODUCTION

Dynamic contrast-enhanced imaging techniques, including perfusion CT, are promising modalities to provide functional information at the microcirculation level of some organs. Perfusion CT has the advantages of CT being widely available and the perfusion study can be easily integrated into routine CT imaging protocols.¹ Although largely used in the fields of neuroimaging and cardiac imaging, perfusion CT has gained increasing importance for evaluation of abdominal organs in the past decade, particularly in the study of liver. Liver perfusion CT is most widely used to assess focal lesions, although it has also been used to evaluate chronic liver disease. Current potential applications

include characterization of hepatocellular carcinoma (HCC), distinction of arterialised pseudolesions from HCC, prediction of tumour response to therapies and follow-up of patients submitted to liver transplantation, evaluation of liver damage or severity of chronic liver disease.^{2–7}

Liver perfusion CT is able to provide a quantification of arterial and portal venous perfusion on a global and regional basis to evaluate both focal and diffuse abnormalities. This method is performed by a dynamic series of images of the liver acquired before, during and after contrast material bolus injection and is based on the measurement of temporal changes in tissue density. After acquisition, the

images are postprocessed with a software package that applies a mathematic model for generation of perfusion parameters (quantitative evaluation) and colour maps (qualitative evaluation). Therefore, the development and availability of commercial software perfusion allowed to increase the use of liver perfusion CT in the clinical setting.^{8,9}

Liver perfusion can also be performed through MRI and, consequently, without the use of ionizing radiation. Dynamic contrast-enhanced MRI is the major perfusion MRI technique and also relies on a bolus injection of the contrast agent; such technique is based on rapid and repeated T_1 weighted images used to measure the signal changes induced by the paramagnetic contrast agent in the tissue as a function of time. However, one of the main differences between the CT and MR-based approaches is that changes in MR signal are not linearly related to changes in contrast agent concentration, to the fact that others factors such as relaxation time (T_1) and excitation flip angles also affects the perfusion parameters estimation. Conversely, the linear relationship between contrast agent concentration and X-ray attenuation in CT makes the process simpler in terms of acquisition and postprocessing. Perfusion CT also benefits of its wide availability, low cost and can be readily incorporated into routine CT protocols.¹⁰

Perfusion parameters can be defined as quantitative imaging biomarkers (QIB) inasmuch as they translate characteristics quantitatively measured in the setting of normal biological processes, pathogenic processes, or response to a therapeutic intervention. Like another QIB, it is important to demonstrate that they can be used within a more general set of conditions and analyses.¹¹

Liver perfusion CT has some limitations that need to be overcome in order for it to be used in clinical settings, such as the limited coverage, motion artefacts, and high radiation dose.^{8,12} The use of CT scanners with wide area detectors, development of motion correction algorithms, and low dose and dual-source protocols are strategies that have proven useful to solve these issues.^{1,13–16} Nevertheless, to allow a broader use of perfusion CT, further challenges remain, including the lack of standardization in data analysis and the paucity of studies on the agreement regarding quantification of liver perfusion parameters.^{8,11}

Thus, the aim of our study was to evaluate the agreement between the measurements of perfusion CT parameters in normal livers by using two software packages available from two major CT manufacturers.

METHODS AND MATERIALS

Patients

This retrospective study was approved by the Research Ethics Committee of our institution, and informed consent was waived. From January 2011 to December 2012, 78 consecutive patients with cancer have undergone a liver perfusion CT for screening of *metastases*. All patients older than 18 years and without liver abnormalities detected by abdominal CT scan (i.e. normal studies) were included in the study. Twenty-four patients who

were not included in the study presented the following hepatic abnormalities: liver *benign focal lesions* ($n = 8$), *metastases* ($n = 9$), chronic liver disease ($n = 8$), steatosis ($n = 4$) and HCC ($n = 3$). Some patients had more than one abnormality.

In addition, all clinical data of the included patients were reviewed and patients with abnormal liver function tests ($n = 6$), who developed liver metastases within 1-year period after the CT scan ($n = 1$) or without follow-up CT exams ($n = 6$) after a minimum of 12 months were excluded. This last group was excluded due to the possibility of having micrometastases or other emerging liver abnormality not detected by CT when the examination was performed and which might produce haemodynamic dysregulations with an impact on the measurement perfusion parameters.¹⁷ We also excluded the exams with severe respiratory motion artefacts in perfusion sequences ($n = 4$). Thus, the final analysis included 37 patients without morphological or functional hepatic abnormalities.

Perfusion CT protocol

CT scans were performed in a 64-slice CT system (Brilliance iCT, Philips Medical Systems, Best, the Netherlands). An unenhanced CT scan of the abdomen (120 kV, 120–391 mAs with radiation dose modulation system) was performed initially to identify the portal vein and to plan the scan coverage for the dynamic studies. The dynamic study was performed similarly as described in previous studies^{18,19} as following: a pump injector was used to inject 50 ml of iobitridol (Henetix® 350, 350 mgI ml⁻¹; Guerbet, Rio de Janeiro, Brazil) intravenously at a rate of 5 ml s⁻¹. After a 5-s delay, axial cine contrast-enhanced CT was performed with the following parameters: a single acquisition lasting 60 s, consisting of 20 scans with 40 mm of z-coverage (8 slices x 5-mm thickness, 0.33-s rotation time, at 120 kV, and 150 mA). Image data were reconstructed to 160 cine images (512 × 512 pixel, 8 slices, 350 x 350 mm, 5-mm slice spacing, and 3-s temporal resolution, a value optimized for both software packages). Patients were reminded to take a slow shallow breath during dynamic scan acquisition and a band compressing the abdomen that limited breath-related liver excursions was used to minimize movement.¹⁸ The dynamic study was followed immediately by a diagnostic portal venous phase abdominopelvic study.

Image analysis and postprocessing

Initially, the data were transferred to an image processing workstation (Extended Brilliance Workspace EBW:V4.5.5.51035, Philips Medical Systems, Best, the Netherlands). Regarding postprocessing, there are two mathematic models most frequently used: the compartmental analysis (one or two compartment model) and the distributed parameter model.^{8,20} The one-compartment model allows for estimates of blood flow or perfusion that is defined as the blood flow through the tissue of interest per unit of time (expressed as ml/min/100 ml). The two compartment and distributed parameter models allow to obtain the following additional perfusion parameters: blood volume, mean time transit and permeability. While there is currently no consensus regarding the best method for hepatic perfusion CT analysis, the one-compartmental method has dominated the field of hepatic

Figure 1. Selection of arterial and portal vascular inputs. ROIs placed in aorta, arterial input function (red circle), portal vein (blue circle) and spleen (green line) (a). Time-attenuation curves for aorta (red line), portal vein (blue line) and spleen (green line) (b); arterial perfusion end is estimated as the time to peak of spleen (dashed white line).

perfusion studies probably because it was the first introduced and its underlying principle is relatively simple.^{8,9,21}

Dual-input one compartmental mathematical model was used to obtain the arterial perfusion (AP) and the portal venous perfusion (PP) in milliliters per minute per 100 ml. Time to peak (TTP), which is the time to reach the maximum value in contrast material concentration in the aorta, portal vein and spleen, was also noted as a prerequisite to estimate perfusion parameters.^{8,18}

Firstly, all images were independently analysed by two radiologists (EASB and LRT, with 4 and 6 years of experience in abdominal radiology, respectively). The readers reviewed the correct operation of each software application before performing analyses and practiced performing pilot analyses on each workstation to ensure optimal software usage, which is a recommended procedure in order to minimize inconsistency.²² All perfusion data were transferred to a workstation (EasyVision, Philips Medical Systems, Best, the Netherlands) and processed with a commercially available dedicated software package (software A - ViewForum R5.1, Philips Medical Systems, Best, the Netherlands). Using the dedicated liver perfusion preset, regions of interest (ROIs) were placed in the aorta and in the portal vein on the source images to provide these vascular inputs (TTP). Another ROI was drawn in the spleen parenchyma for separating the arterial from the portal venous phase (Figure 1).

Once again, in order to minimize inconsistency, two circular ROIs with 2.0 cm diameter were placed in a standard manner in the center of segments 6 and 4, the readers using colour maps to help in ROI placement and to avoid heterogeneous areas, vessels and artefacts, as described elsewhere¹ (Figure 2).

In a second session, after 6 months, the same readers analysed random and similarly all images using another commercial software (software B), also based on dual-input one compartmental method (syngo®.via Body Perfusion VA30, Siemens Healthcare, Forchheim, Germany).

Radiation dose estimates

The CT dose index and dose-length product were recorded for each patient.

Statistical analysis

Continuous variables were expressed as means $\pm$ standard deviation (SD), and categorical variables as frequencies or percentages. Variables were assessed for normal distribution by using the Shapiro-Wilks test. In an attempt of generating potential reference values for perfusion parameters and for comparison to previous studies, we calculated mean results across the two readers regarding AP and PP values of the two liver lobes for both software packages and used Wilcoxon test to check

Figure 2. Examples of ROIs placements, time-attenuation curves and colour maps. ROIs in right liver lobe (yellow circle) and left liver lobe (green circle) (a) and time-attenuation curves for right liver lobe (yellow line) and left liver lobe (green line) (b). Arterial and portal perfusion colour maps (c). ROIs, regions of interest.

Table 1. Mean results ($\pm$ SD) across the two readers for arterial and portal perfusion values of the right and left liver lobes obtained using software A and B

Perfusion parameters	Software A	Software B	<i>p</i> -value
AP ml/min/100 ml (right lobe)	14.90 (11.97)	11.47 (9.59)	0.102
AP ml/min/100 ml (left lobe)	20.04 (21.44)	14.34 (12.88)	0.109
PP ml/min/100 ml (right lobe)	82.72 (40.56)	87.58 (28.20)	0.105
PP ml/min/100 ml (left lobe)	78.60 (34.81)	79.02 (26.74)	0.561

AP, arterial perfusion; PP, portal perfusion.

for significant difference between them. In addition, to evaluate if these parameters were related to age and sex, we used a multivariate general linear model. A two-tailed *p* value of less than 0.05 was considered to indicate a statistically significant difference.

To determine the inter-reader and intrareader agreement for the measurements of AP, PP and TTP (aorta, portal vein and spleen), intraclass correlation coefficients (ICCs) were calculated for each pair of variables for each software.²³ Second, the mean differences, SD, and 95% confidence interval (CI) of agreement for each of the perfusion parameters for each observer and for both observers were calculated using the Bland-Altman test.²⁴ The following ICC categories were used for interpretation: 0.00–0.10 = virtually none; 0.11–0.40 = slight; 0.41–0.60 = fair; 0.61–0.80 = moderate and 0.81–1.00 = substantial agreement.^{23,25}

All statistical analyses were conducted using a commercially available software (IBM SPSS 20.0, IBM, New York, NY).

RESULTS

Descriptive analysis

37 subjects (59.9% male) were evaluated (mean age = 59.76 ± 14.95 , ranging from 20 to 88 years). No significant differences were observed between genders in terms of mean age (62.0 ± 12.2 for females, 56.47 ± 8.20 for males, $p = 0.275$). Mean results across the two readers regarding AP and PP values of the two liver lobes, including standard deviations ($\pm$ SD), are presented in Table 1.

Inter-reader agreement for each software package
The ICCs for the inter-reader measurements of each perfusion parameter for each software package are summarized in Table 2. Inter-reader agreement of AP values was substantial in both software packages with ICCs ranging from 0.82 to 0.86. Inter-reader agreement of PP values was fair in software A (ICC = 0.44) and fair to moderate in software B (ICC = 0.56–0.77). Inter-reader agreement of TTP values was substantial for all parameters in both software packages (ICC = 0.82–1.0), except for a moderate one of the portal vein in software A (ICC = 0.76).

Table 2. Inter-reader ICCs and CI 95% for AP and PP values from two liver lobes and times to peak from aorta, spleen and portal vein within each software packet

Perfusion parameters	Software A (Inter-reader)		Software B (Inter-reader)	
	ICC	CI 95%	ICC	CI 95%
AP ml/min/100 ml (right lobe)	0.82	0.71–0.89	0.86	0.72–0.92
AP ml/min/100 ml (left lobe)	0.82	0.71–0.90	0.85	0.71–0.92
PP ml/min/100 ml (right lobe)	0.44	0.23–0.63	0.77	0.55–0.88
PP ml/min/100 ml (left lobe)	0.44	0.23–0.63	0.56	0.15–0.78
TTP seconds - aorta	0.99	0.99–0.99	1	*
TTP seconds - spleen	0.89	0.82–0.94	0.92	0.84–0.96
TTP seconds - portal vein	0.76	0.62–0.86	0.82	0.64–0.90

AP, arterial perfusion; CI, confidence interval; ICCs, intra class correlation coefficients; PP, portal perfusion; TTP, time to peak.

Intra-reader agreement between the two software packages

The ICCs for the intrareader measurements of each perfusion parameter between two software packages are summarized in Table 3. Overall, the intrareader agreement between software A and B ranged from slight to moderate (ICC = 0.32–0.62) for readers 1 and 2 regarding the AP parameters, and from fair to moderate (ICC = 0.40–0.69) for readers 1 and 2 when considering the PP parameters. Intrareader agreement of TTP values was substantial for all parameters and for both readers (ICC = 0.93–0.99), except for a moderate one of the portal vein for reader 1 (ICC = 0.73).

Multivariate analysis

The multivariate general linear model showed that neither age (Pillai's Trace = 0.096, $F(4, 31) = 0.789$, $p = 0.536$) nor sex (Pillai's Trace = 0.180, $F(4, 31) = 1.648$, $p = 0.188$) had significant influence on the variable values of perfusion parameters aforementioned.

Radiation dose estimates

The median CDTI values were 111.56 (± 18.48) and the median DLP values were 446.44 (± 74.00). Using the appropriate conversion factor for abdominal CT examinations ($K = 0.015$ mSv/[mGy cm]), the calculated average effective dose of the perfusion sequence was 6.7 mSv.²⁶

DISCUSSION

In this study we demonstrated that liver perfusion parameters generated by using two different commercially available software packages had only a moderate agreement. In this sense, we also found that AP seems to be the most consistent parameter to be

Table 3. Intrareader ICCs and CI for AP and PP values from two liver lobes and times to peak from aorta, spleen and portal vein obtained between two software programs for each reader

Perfusion parameters	Reader 1		Reader 2	
	(Software A x B)		(Software A x B)	
	ICC	CI 95%	ICC	CI 95%
AP ml/min/100 ml (right lobe)	0.46	0.01–0.71	0.47	0.04–0.72
AP ml/min/100 ml (left lobe)	0.32	0.28–0.64	0.62	0.23–0.79
PP ml/min/100 ml (right lobe)	0.47	0.05–0.72	0.40	0.12–0.68
PP ml/min/100 ml (left lobe)	0.69	0.38–0.84	0.60	0.23–0.79
TTP seconds - aorta	0.99	0.99–1.00	0.99	0.99–1.00
TTP seconds - spleen	0.98	0.95–0.99	0.95	0.90–0.97
TTP seconds - portal vein	0.73	0.48–0.86	0.93	0.87–0.96

AP, arterial perfusion; CI, confidence interval; ICCs, intra class correlation coefficients; PP, portal perfusion; TTP, time to peak.

adopted when analysing a liver CT study, whatever the software employed.

Perfusion CT as a quantitative parameter in liver imaging

In the era of QIB, observations should be as objective and independent as possible.^{27,28} Because liver diseases usually induce alterations at the microcirculation level, an objective measurement of hepatic perfusion can be clinically relevant.¹ Among the many QIB currently being investigated for liver imaging, CT perfusion is among the most promising, and it is rapidly becoming a viable biomarker.^{8,12} Nonetheless, the most relevant issue to be addressed before CT perfusion of the liver can become a broadly adopted tool relies on the lack of standardization and confirmation of reproducibility of perfusion parameters,¹² which we address here.

Technical considerations on CT perfusion of the liver

In this study, liver perfusion parameters were generated by using commercially available software packages provided by two CT manufacturers that use dual-input one-compartmental method for the mathematical model, under similar analysis conditions. The one-compartment model assumes both the intravascular and extravascular spaces as a single compartment, and perfusion is calculated from the maximal slope of the tissue concentration-time curve normalized to the curve of arterial concentration of contrast agent (artery input function).^{9,20,29} Although a simple model, this analysis is quite robust and useful in the evaluation of the liver, as it can be extended to the hepatic dual blood supply through the hepatic artery and the portal vein using dual-vascular

inputs, aorta and portal vein (dual-input one-compartmental method). In this model, arterial and portal venous components of the parenchymal enhancement are resolved distinctly using peak splenic enhancement as a marker of the beginning of portal venous perfusion.³⁰

An important consideration for adequate assessment of perfusion is the contrast medium bolus used for the intravenous injection: compartmental analysis methods need a bolus administered with higher injection rates of between 5 and 10 ml s⁻¹.⁹ In our study, all exams were performed with injection of the contrast medium at a flow rate of 5 ml s⁻¹.

We chose to assess the agreement of AP and PP measurements because these parameters are reportedly useful to provide a good representation of hepatic haemodynamic changes in liver cirrhosis and can be conceived to reflect physiologic markers related to angiogenesis.^{2–4,19} We also noted and compared the TTP from aorta, portal vein and spleen in order to ascertain that intra- and interreader variability of AP and PP parameters were not due to discrepancies occurred in this first basic step, as demonstrated by the elevated ICC found for TTP values. Finally, we decided to study normal liver also to contribute with the definition of reference values for liver perfusion parameters. Although some studies assess the perfusion parameters in normal livers, most of them consider “normal liver” the adjacent parenchyma to focal lesions, such as tumour, whose presence probably affect the perfusion around it.^{31–34}

Reference values for liver CT perfusion parameters and comparison to the literature

The results reported for AP and PP among different previous studies have shown meaningful variances as follows: AP means were reported to vary from 12 to 31 ml/min/100 ml and PP means from 32 to 132 ml/min/100 ml, as recently synthesized by Wang et al.¹ The mean values obtained in our analyses are closely within these previous references, varying from 11.47 to 20.4 ml/min/100 ml for AP and from 78.60 to 87.58 ml/min/100 ml for PP. Although we did not observe the effects of gender or age in the perfusion parameters investigated in any of the software packages, a previous study showed higher AP values for male or younger patients.²¹ Notwithstanding, we noticed that although not statistically significant, the lowest values of AP were found among elderly individuals with atheromatosis of the celiac trunk. A possible degree of stenosis caused by atheromatosis may have underestimated the AP values in these patients. Miles et al stated that when the aorta is used as an “input function” in abdominal perfusion studies, an assumption should be made that there is no significant broadening of the time attenuation curve between aorta and the afferent artery (hepatic artery in liver studies). If there is a stenosis between aorta and the relevant afferent artery, the AP values would be falsely underestimated.⁹ An observation is the wide range of pp values found in the literature, as well as, we found large standard deviations for these values. As PP is calculated from the liver and portal vein concentration–time curves, variations in speed and pressure in the portal vein probably affect the quantitative parameters. This is clear in chronic liver disease occurs an increased resistance to incoming sinusoidal blood

flow, which is known to be responsible for the increased portal vein pressure and decreased PP, and that is counteracted by an increase in AP.⁸

No significant differences were found in our study between two liver lobes regarding all the parameters. This result is in agreement with another study that compared eight hepatic segments in an initial experience of liver perfusion measurement with 320-detector row CT; they found differences only for AP in segments 3 and 5, which were attributed to artifacts.³²

Inter-reader agreement for each software package
We found a substantial inter-reader agreement for all AP values but only a fair to moderate agreement for PP values, for both software packages. As we strictly defined the anatomical locations for placement of ROIs in the liver, inter-reader analysis might have been affected by the following factors: placing an ROI in the aorta or in the portal vein. However, because both the AP and PP values are derived from the same ROI in each anatomical location, the worse inter-reader agreement for PP might be explained most probably by differences in operator-defined portal venous inputs. Indeed, the lower agreement observed in TTP portal vein (ICC = 0.73–0.81) in comparison to TTP aorta (ICC = 0.99–1.00), reflects a greater difficulty in obtaining adequate portal venous inputs than aortic arterial inputs. An explanation for this issue may be that the largest portion of portal vein is usually located in an axial plane, which is more susceptible to partial volume averaging effects and movements. In addition, the duration of PP is longer than AP, yields a greater number of images, resulting in a greater susceptibility to artefacts of respiratory movements.

Intra-reader agreement between the two software packages

Wilcoxon test has not demonstrated significant differences in terms of the mean ICC values for AP and PP between the two software packages when comparing readers 1 and 2. Only a slight to moderate intrareader agreement regarding AP and PP quantitative values was found. Similar results were found in a previous study for HCC that compared the perfusion parameters calculated by using two versions of the same commercial software package (deconvolution method).³⁵ However, as we investigated normal livers, we expected a greater agreement, hypothesizing that the homogeneous liver parenchyma would yield measurements more reproducible, less affected by any variations in operator-defined ROIs within the liver.

It is also important to highlight that we obtained high intra-reader agreement for most of TTPs values between two software programs (ICCs values above 0.9), which suggests that software differences in postprocessing might have been a major cause of variability in the values of CT perfusion parameters in our study. For example, Goh *et al* in a colorectal cancer perfusion study, concluded that in an upgraded software version, the vendors changed how the arrival of contrast is detected, changing the time difference in arrival of contrast within the input vessel and the tumour. They demonstrated a poor agreement for parameters values between software versions.³⁶

We found a larger SD for the mean values of PA and, especially PP obtained by software A in relation to B. In addition, we obtained a lower interobserver agreement for these parameters, especially for the values of PP, in software A compared to B. Such a difference may be related to technical factors intrinsic to each software. Indeed, it should be pointed out that evidences derived from neuroimaging studies suggest that software differences rather than human operator differences constitute the primary cause of variability in CT perfusion results.²²

Radiation dose estimates

In our study the mean effective dose used in liver perfusion was 6.7 mSv, below the radiation doses that have been reported for CT perfusion imaging of the liver, ranging between 7.3 and 30.6 mSv.⁸ The radiation dose used in our study was comparable to the routine abdominal CT examination (~1–14 mSv per phase). The patients in our analysis have undergone a liver perfusion CT for screening of metastases. In patients with cancer, the use of perfusion CT can allow early detection of hepatic metastases, which determines therapeutic decisions that can reduce mortality, justifying therefore the additional radiation dose used in perfusion study.³⁷

Strengths and limitations

Our study addresses the paucity of data on agreement of liver CT parameters in the literature. In addition, focusing on the clinical applicability, we studied commercially available software programs that use the same postprocessing method. Finally, we also encompassed a good sample size, as just a small fraction of studies in this field hitherto have assessed more than 30 patients.⁸

We recognize that our study is not without limitations. Only two readers analysed the images. Probably adding two or more readers could potentially make the findings of our study sounder. However, at the same time, this strategy was out of the initial scope and original design of this preliminary study. Furthermore, two-readers studies are widely accepted and used. Shiraishi *et al*³⁸ found, that nearly 50% of diagnostic accuracy ROC studies published in radiology, for example, included just three, two or one observers. There is a simple suggestion, although, that studies with a small number of observers should be restricted to preliminary investigations.^{38,39} Our preliminary study fits in this category. Moreover, there is a recommendation that, in such cases, adequate statistical tests be reported, like kappa statistics results, intraclass correlation index and confidence interval values, etc.³⁹ We are following this rule, which is an acceptable statistic way of addressing this theoretical limitation.

Although the intraobserver agreement (consistency) of ROI placement was not quantified in this study, previous evidences suggest that pilot analyses and standard protocols as adopted by us reduce the effect of operator differences on CT perfusion reproducibility^{22,40} and that ROI delineation in normal livers for perfusion analyses has lesser impacts on measurements as when compared to tumours, for example.³⁴ We employed strict morphological (CT), laboratorial and temporal (1-year follow-up) criteria to define normal livers. Characterization of other clinical, non-liver-related pathologies would be beyond

the scope of this study. Nevertheless, this would not ultimately affect the main question posed here, which is the inter-reader and inter-software reproducibility of measurements (patients were themselves constant). We used a 64-row CT scanner and did not use the motion correction algorithm, which was not available in one of the software programs. Although some studies have assessed the effects of motion correction on quantitative liver CT perfusion parameters, most of them suggest that the use of motion correction algorithms can improve the spatial alignment, yielding more reliable results, but none of them have assessed the possible impact on reproducibility when commercial motion correction algorithms are used.^{13,14,33,41} Finally, other perfusion parameters such as blood volume and permeability were not evaluated in this study because they were not available in the liver protocol of the software programs that

we used, and we decided to focus on only one mathematical method.

CONCLUSION

Our findings suggest that software-dependent factors may contribute to variance in perfusion measurements, resulting in suboptimal reproducibility, which demands further technical improvements. Therefore, caution should be exercised when interpreting quantitative liver perfusion CT exams. Further studies could focus on providing standardization of analysis methods. AP measurements seem to be the most reproducible parameter to be adopted when evaluating CT liver perfusion employing the one-compartmental model, since we found only a fair to moderate agreement for PP values when using the same software package.

REFERENCES

- Wang X, Xue HD, Jin ZY, Su BY, Li Z, Sun H, et al. Quantitative hepatic CT perfusion measurement: comparison of Couinaud's hepatic segments with dual-source 128-slice CT. *Eur J Radiol* 2013; **82**: 220–6. doi: <https://doi.org/10.1016/j.ejrad.2012.09.015>
- Van Beers BE, Leconte I, Materne R, Smith AM, Jamart J, Horsmans Y. Hepatic perfusion parameters in chronic liver disease: dynamic CT measurements correlated with disease severity. *AJR Am J Roentgenol* 2001; **176**: 667–73. doi: <https://doi.org/10.2214/ajr.176.3.1760667>
- Yang HF, Du Y, Ni JX, Zhou XP, Li JD, Zhang Q, et al. Perfusion computed tomography evaluation of angiogenesis in liver Cancer. *Eur Radiol* 2010; **20**: 1424–30. doi: <https://doi.org/10.1007/s00330-009-1693-y>
- Th S, He W, Jin L, Chen G, Xiao GW. Early response of hepatocellular carcinoma to chemoembolization: volume computed tomography liver perfusion imaging as a short-term response predictor. *J Comput Assist Tomogr* 2017; **41**: 315–20.
- Bader TR, Herneth AM, Blaicher W, Steininger R, Mühlbacher F, Lechner G, et al. Hepatic perfusion after liver transplantation: noninvasive measurement with dynamic single-section CT. *Radiology* 1998; **209**: 129–34. doi: <https://doi.org/10.1148/radiology.209.1.9769823>
- Kaufmann S, Horger T, Oelker A, Kloth C, Nikolaou K, Schulze M, et al. Characterization of hepatocellular carcinoma (HCC) lesions using a novel CT-based volume perfusion (VPCT) technique. *Eur J Radiol* 2015; **84**: 1029–35. doi: <https://doi.org/10.1016/j.ejrad.2015.02.020>
- Fischer MA, Marquez HP, Gordic S, Leidner B, Klotz E, Aspelin P, et al. Arterio-portal shunts in the cirrhotic liver: perfusion computed tomography for distinction of arterialized pseudolesions from hepatocellular carcinoma. *Eur Radiol* 2017; **27**: 1074–80. doi: <https://doi.org/10.1007/s00330-016-4432-1>
- Kim SH, Kamaya A, Willmann JK. CT perfusion of the liver: principles and applications in oncology. *Radiology* 2014; **272**: 322–44. doi: <https://doi.org/10.1148/radiol.14130091>
- Blomley M, Dawson P. Theoretical aspects and physiological models. In: Blomley M, Miles K, Dawson P, eds. *Functional computed tomography*. Oxford, UK: ISIS Medical Media; 1997. pp. 47–61.
- O'Connor JP, Tofts PS, Miles KA, Parkes LM, Thompson G, Jackson A. Dynamic contrast-enhanced imaging techniques: CT and MRI. *Br J Radiol* 2011; **84**(Spec No 2): S112–20. doi: <https://doi.org/10.1259/bjr/55166688>
- Sullivan DC, Obuchowski NA, Kessler LG, Raunig DL, Gatsonis C, Huang EP, et al. Metrology standards for quantitative imaging biomarkers. *Radiology* 2015; **277**: 813–25. doi: <https://doi.org/10.1148/radiol.2015142202>
- Liapi E, Mahesh M, Sahani DV. Is CT perfusion ready for liver cancer treatment evaluation? *J Am Coll Radiol* 2015; **12**: 111–3. doi: <https://doi.org/10.1016/j.jacr.2014.10.007>
- Skornitzke S, Fritz F, Klauss M, Pahn G, Hansen J, Hirsch J, et al. Qualitative and quantitative evaluation of rigid and deformable motion correction algorithms using dual-energy CT images in view of application to CT perfusion measurements in abdominal organs affected by breathing motion. *Br J Radiol* 2015; **88**: 20140683. doi: <https://doi.org/10.1259/bjr.20140683>
- Jensen NK, Lock M, Fisher B, Kozak R, Chen X, Chen J, et al. Prediction and reduction of motion artifacts in free-breathing dynamic contrast enhanced CT perfusion imaging of primary and metastatic intrahepatic tumors. *Acad Radiol* 2013; **20**: 414–22. doi: <https://doi.org/10.1016/j.acra.2012.09.027>
- Topcuoğlu OM, Karcaaltıncaba M, Akata D, Özmen MN. Reproducibility and variability of very low dose hepatic perfusion CT in metastatic liver disease. *Diagn Interv Radiol* 2016; **22**: 495–500. doi: <https://doi.org/10.5152/dir.2016.16612>
- Gordic S, Puippe GD, Krauss B, Klotz E, Desbiolles L, Lesurtel M, et al. Correlation between dual-energy and perfusion CT in patients with hepatocellular carcinoma. *Radiology* 2016; **280**: 78–87. doi: <https://doi.org/10.1148/radiol.2015151560>
- Hatwell C, Zappa M, Wagner M, Michoux N, Paradis V, Vilgrain V, et al. Detection of liver micrometastases from colorectal origin by perfusion CT in a rat model. *Hepatobiliary Pancreat Dis Int* 2014; **13**: 301–8. doi: [https://doi.org/10.1016/S1499-3872\(14\)60043-6](https://doi.org/10.1016/S1499-3872(14)60043-6)
- Ippolito D, Capraro C, Casiraghi A, Cestari C, Sironi S. Quantitative assessment of tumour associated neovascularisation in patients with liver cirrhosis and hepatocellular carcinoma: role of dynamic-CT perfusion imaging. *Eur Radiol* 2012; **22**: 803–11. doi: <https://doi.org/10.1007/s00330-011-2307-z>
- Leggett DA, Kelley BB, Bunce IH, Miles KA. Colorectal cancer: diagnostic potential of CT measurements of hepatic

- perfusion and implications for contrast enhancement protocols. *Radiology* 1997; **205**: 716–20. doi: <https://doi.org/10.1148/radiology.205.3.9393526>
20. García-Figueiras R, Goh VJ, Padhani AR, Baleato-González S, Garrido M, León L, et al. CT perfusion in oncologic imaging: a useful tool? *AJR Am J Roentgenol* 2013; **200**: 8–19. doi: <https://doi.org/10.2214/AJR.11.8476>
 21. Kanda T, Yoshikawa T, Ohno Y, Kanata N, Koyama H, Takenaka D, et al. CT hepatic perfusion measurement: comparison of three analytic methods. *Eur J Radiol* 2012; **81**: 2075–9. doi: <https://doi.org/10.1016/j.ejrad.2011.07.003>
 22. Zussman BM, Boghosian G, Gorniak RJ, Olszewski ME, Read KM, Siddiqui KM, et al. The relative effect of vendor variability in CT perfusion results: a method comparison study. *AJR Am J Roentgenol* 2011; **197**: 468–73. doi: <https://doi.org/10.2214/AJR.10.6058>
 23. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979; **86**: 420–8. doi: <https://doi.org/10.1037/0033-2909.86.2.420>
 24. Myles PS, Cui J. Using the Bland-Altman method to measure agreement with repeated measures. *Br J Anaesth* 2007; **99**: 309–11. doi: <https://doi.org/10.1093/bja/aem214>
 25. Guggenberger R, Nanz D, Puipe G, Ruffbach K, White LM, Sussman MS, et al. Diffusion tensor imaging of the median nerve: intra-, inter-reader agreement, and agreement between two software packages. *Skeletal Radiol* 2012; **41**: 971–80. doi: <https://doi.org/10.1007/s00256-011-1310-4>
 26. Deak PD, Smal Y, Kalender WA. Multisection CT protocols: sex- and age-specific conversion factors used to determine effective dose from dose-length product. *Radiology* 2010; **257**: 158–66. doi: <https://doi.org/10.1148/radiol.10100047>
 27. Di Leo G. Measurements in radiology: the need for high reproducibility. *Pediatr Radiol* 2015; **45**: 32–4. doi: <https://doi.org/10.1007/s00247-014-3081-2>
 28. Obuchowski NA, Reeves AP, Huang EP, Wang XF, Buckler AJ, Kim HJ, et al. Quantitative imaging biomarkers: a review of statistical methods for computer algorithm comparisons. *Stat Methods Med Res* 2015; **24**: 68–106. doi: <https://doi.org/10.1177/0962280214537390>
 29. Sousa J, Bekhor D, Saito Filho CF, Bretas EAS, D'Ippolito G. Abdominal perfusion computed tomography: clinical applications, principles and technique. *Radiol Bras* 2012; **45**: 39–45.
 30. Materne R, Van Beers BE, Smith AM, Leconte I, Jamart J, Dehoux JP, et al. Non-invasive quantification of liver perfusion with dynamic computed tomography and a dual-input one-compartmental model. *Clin Sci (Lond)* 2000; **99**: 517–25. doi: <https://doi.org/10.1042/cs0990517>
 31. Ng CS, Hobbs BP, Chandler AG, Anderson EF, Herron DH, Charnsangavej C, et al. Metastases to the liver from neuroendocrine tumors: effect of duration of scan acquisition on CT perfusion values. *Radiology* 2013; **269**: 758–67. doi: <https://doi.org/10.1148/radiol.13122708>
 32. Kanda T, Yoshikawa T, Ohno Y, Fujisawa Y, Kanata N, Yamaguchi M, et al. Perfusion measurement of the whole upper abdomen of patients with and without liver diseases: initial experience with 320-detector row CT. *Eur J Radiol* 2012; **81**: 2470–5. doi: <https://doi.org/10.1016/j.ejrad.2011.10.009>
 33. Ng CS, Chandler AG, Wei W, Anderson EF, Herron DH, Kurzrock R, et al. Effect of dual vascular input functions on CT perfusion parameter values and reproducibility in liver tumors and normal liver. *J Comput Assist Tomogr* 2012; **36**: 388–93. doi: <https://doi.org/10.1097/RCT.0b013e318256b1e2>
 34. Ng CS, Chandler AG, Wei W, Anderson EF, Herron DH, Charnsangavej C, et al. Reproducibility of perfusion parameters obtained from perfusion CT in lung tumors. *AJR Am J Roentgenol* 2011; **197**: 113–21. doi: <https://doi.org/10.2214/AJR.10.5404>
 35. Petralia G, Summers P, Viotti S, Montefrancesco R, Raimondi S, Bellomi M. Quantification of variability in breath-hold perfusion CT of hepatocellular carcinoma: a step toward clinical use. *Radiology* 2012; **265**: 448–56. doi: <https://doi.org/10.1148/radiol.12111232>
 36. Goh V, Halligan S, Bartram CI. Quantitative tumor perfusion assessment with multidetector CT: are measurements from two commercial software packages interchangeable? *Radiology* 2007; **242**: 777–82. doi: <https://doi.org/10.1148/radiol.2423060279>
 37. McCollough CH, Guimarães L, Fletcher JG. In defense of body CT. *AJR Am J Roentgenol* 2009; **193**: 28–39. doi: <https://doi.org/10.2214/AJR.09.2754>
 38. Shiraishi J, Pesce LL, Metz CE, Doi K. Experimental design and data analysis in receiver operating characteristic studies: lessons learned from reports in radiology from 1997 to 2006. *Radiology* 2009; **253**: 822–30. doi: <https://doi.org/10.1148/radiol.2533081632>
 39. Bankier AA, Levine D, Halpern EF, Kressel HY. Consensus interpretation in imaging research: is there a better way? *Radiology* 2010; **257**: 14–17. doi: <https://doi.org/10.1148/radiol.10100252>
 40. Dighe S, Blake H, Jeyadevan N, Castellano I, Koh DM, Orton M, et al. Perfusion CT vascular parameters do not correlate with immunohistochemically derived microvessel density count in colorectal tumors. *Radiology* 2013; **268**: 400–10. doi: <https://doi.org/10.1148/radiol.13112460>
 41. Bevilacqua A, Barone D, Malavasi S, Gavelli G. Quantitative assessment of effects of motion compensation for liver and lung tumors in CT perfusion. *Acad Radiol* 2014; **21**: 1416–26. doi: <https://doi.org/10.1016/j.acra.2014.06.005>