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FULL PAPER

A semi-automatic method for the extraction of the portal venous input function in quantitative dynamic contrast-enhanced CT of the liver

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Objective: To aid the extraction of the portal venous input function (PVIF) from axial dynamic contrast-enhanced CT images of the liver, eliminating the need for full manual outlining of the vessel across time points.

Methods: A cohort of 20 patients undergoing perfusion CT imaging of the liver was examined. Dynamic images of the liver were reformatted into contiguous thin slices. A region of interest was defined within a transverse section of the portal vein on a single contrast-enhanced image. This region of interest was then computationally projected across all thin slices for all time points to yield a semi-automated PVIF curve. This was compared against the “gold-standard” PVIF curve obtained by conventional manual outlining.

Results: Bland-Altman plots of curve characteristics indicated no substantial difference between automated

and manual PVIF curves [concordance correlation coefficient in the range (0.66, 0.98)]. No substantial differences were shown by Bland-Altman plots of derived pharmacokinetic parameters when a suitable kinetic model was applied in each case [concordance correlation coefficient in range (0.92, 0.95)].

Conclusion: This semi-automated method of extracting the PVIF performed equivalently to a “gold-standard” manual method for assessing liver function.

Advances in knowledge: This technique provides a quick, simple and effective solution to the problems incurred by respiration motion and partial volume factors in the determination of the PVIF in liver dynamic contrast-enhanced CT.

INTRODUCTION

Quantitative dynamic contrast-enhanced (DCE) CT is a technique which seeks to extract measures of blood perfusion to organs and tissue and operates in a manner similar to its counterpart in MRI, DCE-MRI. In both cases, DCE imaging involves the acquisition of a set of baseline images without contrast enhancement followed by a set of images acquired at regular time intervals during and after the administration of a bolus of contrast medium. In the case of CT, attenuation curves can be drawn for the tissue and in the feeding vessel, and these can then be converted into contrast-medium concentration curves. Finally, a pharmacokinetic (PK) model can be applied to the concentration–time curves to yield quantitative estimates of tissue perfusion.^{1–3}

The main disadvantage of DCE-CT is that the dose of ionizing radiation can be considerable, given the need for repeated CT images. It follows that some compromises

between temporal coverage and temporal resolution have to be made to accommodate the restriction on the total number of images and total radiation dose. In practice, this is usually achieved by imaging the first-pass of the signal enhancement curves with a high temporal resolution and obtaining subsequent images at a lower temporal resolution.

In order to perform PK analysis, it is necessary to derive the concentration–time curve within the feeding vessel. This curve is known as the vascular input function and acts as an input to the model. There is a special case when studying hepatic perfusion because the liver is supplied by two blood vessels, the hepatic artery and the portal vein. The PK model used here requires both the arterial input function (AIF) and the portal venous input function (PVIF).⁴ The PVIF is difficult to measure for a variety of reasons, including motion of the portal vein within the abdomen with breathing and the relatively small size of the

vessel in cross-section. This is compounded by the fact that CT images are acquired in the transverse plane and the portal vein moves with respiration through one thin reconstructed axial slice to another.

The aim of this study was to validate a simple semi-automated method for the extraction of the PVIF in DCE-CT which avoids the need for manual outlining of the vessel on all imaged slices and time points.

METHODS AND MATERIALS

Image acquisition

The study was approved by the local ethics committee. 20 patients with liver disease were scanned within 2 weeks of receiving a liver transplant. Each patient gave informed written consent to the study. Imaging was performed using a SOMATOM® Definition Flash CT scanner (Siemens AG, Erlangen, Germany).

A set of abdominal images were taken for localization of the portal vein in order to aid the positioning of later scans. A pre-bolus of 20 ml of iopamidol (Niopam 300, Bracco SpA, Milan, Italy) or iohexol (Omnipaque™, GE Healthcare, Waukesha, WI) followed by a 20 ml saline flush was then injected (at 8 ml s^{-1}) in order to determine the optimal timing for the later dynamic scan.

The dynamic scan was acquired whilst the patient performed gentle free breathing. Scanning parameters for the dynamic scan were as follows: slice collimation, $32 \times 1.2 \text{ mm}$; tube potential, 100 kV; tube current–time product, 150 mAs; matrix 512×512 ; and gantry rotation time, 0.50 s.

The following formula was used to determine the scan delay for the dynamic scan:

$$[\text{Dynamic scan delay}](s) = [\text{Time}(s) \text{ from injection of test bolus peak signal intensity in aorta}] - 2(s)$$

This ensured that at least two points in the upslope of the AIF were recorded before its peak, thus giving sufficient data upon which to fit a gamma-variate curve. The AIF was partially estimated in this way in order to allow more CT time points later in the dynamic acquisition, covering the AIF washout, the PVIF peak and the liver tissue curve.

A baseline anatomical image was taken after the pre-bolus scan and just before administration of the main bolus. The main bolus consisted of 60 ml of iopamidol/iohexol followed by a 20 ml saline flush (both injected at 8 ml s^{-1}) and was imaged using a dynamic scan with time points: [0, 1, 2, 3, 4, 5], [7, 9, 11, ..., 45] and [60, 120, 180, 240, 300] seconds. This comprised 31 measurement points in all. The dynamic data set was reconstructed in 20-, 5- and 1.5-mm (or 2-mm for some patients) slices for image processing.

The estimated effective radiation dose was 18 mSv for the dynamic acquisition and 24 mSv for the examination as a whole. This estimate uses the total dose–length product value of

984 mGy cm and assumes a conversion coefficient of $0.024 \text{ mSv (mGy cm)}^{-1}$ for the abdomen.⁵

Image analysis

Image analysis was performed using custom software written in MATLAB® v. 2014a: 8.3.0 (MathWorks®, Natick, MA).

For the portal vein, one region of interest (ROI) only was drawn by an experienced observer (AG) and subsequently checked, and if necessary corrected, by a radiologist (NH). This ROI was approximately 2–3 cm long and was placed just within the lumen of the portal vein on the thin-slice dynamic series (1.5- or 2.0-mm reconstructed slices) on a slice and time point that showed obvious vessel enhancement. An early time point was therefore selected near or at peak enhancement, but no particular attention was paid to the phase of respiration.

Portal venous input function extraction algorithm

CT number attenuation–time curves were then extracted from the dynamic image data set with an optimizing algorithm in the case of the portal vein. This algorithm was designed to compensate for through-image-plane motion of the portal vein whilst avoiding the need for a radiologist to inspect all slices and time points (typically $19 \text{ slices} \times 31 \text{ time points} = 589 \text{ images}$ in total). The optimizing algorithm is described in the next paragraph and outlined as a skeletal MATLAB function in the [Supplementary material](#).

At any given time point, a part of the central longitudinal cross-section of the portal vein could be assumed to be lying within one of the thin axial CT image slices. The problem of recording the portal venous attenuation without incurring partial volume losses then reduces to identifying this “best slice” and applying the drawn ROI to it. To do this we note that a few seconds ($>5 \text{ s}$) after the start of imaging, the imaged portal vein pixels had a consistently higher CT number [Hounsfield unit (HU)] than those in the surrounding liver. We then assume that the axial images on either side of this “best slice” show the portal vein with a partial volume of the surrounding liver tissue, which has a lower CT number than the blood in the portal vein. Using the one drawn ROI projected in a caudocranial direction onto each slice, the “best slice” is then the image for which the mean CT number in the ROI is at a maximum. The CT number was extracted using this procedure for the “best slice” at each of the dynamic time points in turn in order to assemble the PVIF curve ([Figure 1](#)). Note that an assumption is employed here that the respiratory motion of the portal vein is to a good approximation in a superior–inferior direction only, within the imaged slab.

For the first five data points, this algorithm would not yield correct results as the vessel CT number was in these cases not consistently higher than that of the surrounding liver tissue signal. Instead, for these initial baseline points, the mean ROI CT number was extracted from the image slice used most often (*i.e.* the mode) at later time points.

Gold-standard manually outlined portal venous input function and curve comparisons

In order to validate the portal venous signal extraction algorithm, a second radiologist (SH) outlined a “best” (*i.e.* subjectively most

Figure 1. Schematic diagram of semi-automatic signal extraction from the portal vein (PV); the thin-slice (1.5- or 2-mm) reconstruction was used. It is assumed that the shape of the PV intersection with the slice plane, near the point where PV branches, is constant despite breathing motion, *i.e.* that the PV moves in a superoinferior (S-I) direction only. In (a), the axial view corresponding to the actual CT images is shown together with a sample PV region of interest (ROI). In (b), a supposed coronal view is shown in which the outlined region of the PV occupies three or more slices in the S-I direction. (This coronal view is shown with a scale expanded artificially in the S-I direction.) Owing to the magnitude of the diameter of the PV, partial volume problems would occur in signal extraction unless the central slice was chosen at each time point. In (c), the central slice occupied by the PV is used to give the CT number for that time point in the portal venous input function curve. The extraction algorithm projects the same ROI drawn in (a) across all slices and the mean ROI CT number is recorded for the slice which yields the greatest value [Hounsfield units (HU)].

enhanced) portal venous ROI for all time points assessed across all thin slices. Thus, one ROI was recorded for each time point on the “best slice” in each case. Extraction of the mean attenuation value from these ROIs yielded what is here termed the “gold-standard manual” PVIF for each patient.

PVIF curve comparisons (semi-automated *vs* manual) were carried out on the raw attenuation–time curves in each case, since a linear conversion of CT number (HU) to contrast agent concentration could be assumed. For subsequent kinetic modelling purposes, the concentration–time curve was assumed to be equal to $[CT_{no}(t) - CT_{no}(\text{baseline})]$ since any constant of proportionality ultimately cancels in the applied model equations.

Kinetic modelling

To investigate the effect of the semi-automatically generated PVIF in contrast to that of the manually extracted PVIF on PK modelling, each input function was applied in turn within the Matérn kinetic model on all pixels within a homogeneous (*i.e.* excluding main vessels) liver ROI for each patient data set.

The mathematics of the Matérn kinetic model (or equivalently a “dual-input single-compartment Tofts kinetic model”) and its application to liver perfusion are described in detail elsewhere.^{6,7} The model has been shown to be applicable to normal (as opposed to tumour) tissue in the liver.^{3,8} It accepts as input the two measured vascular input functions and the tissue uptake curve

and yields as estimated parameters the total blood perfusion to the tissue (F), the arterial fraction of that perfusion (A), the distribution volume (DV) and the mean transit time (MTT). This kinetic model was applied using a non-linear fitting process implemented using the MATLAB “lsqcurvefit()” function employing a Levenberg–Marquardt algorithm.

For the two differing PVIF inputs, the ROI median values were then compared for these parameters. A haematocrit value of 0.45 was assumed in converting plasma perfusion to blood perfusion.

For the purposes of kinetic modelling, the AIF was extracted from a ROI drawn just inside the lumen of the aorta (acting as a surrogate for the smaller hepatic artery) at a time point showing obvious contrast enhancement. The baseline image intensity for the aorta was determined from a similar ROI placed on the baseline image. However, since the image acquisitions were started at (“peak-aorta”—2 s) the upslope of the AIF was missing. This was reconstructed by using the baseline value and fitting a gamma-variate function to the rest of the curve (Figure 2). The time interval from the baseline point to the first recorded point was then set according to the zero crossing of the fitted gamma-variate function.

Note that the portal venous attenuation curve was assumed to start at baseline since the image CT number enhancement due to arrival of contrast agent in the portal vein occurs much later than in the aorta.

Statistical treatment

Bland–Altman plots of curve characteristics and derived kinetic parameters were used to compare the two methods for PVIF extraction (manual outlining *vs* semi-automatic). In addition, the concordance correlation coefficient (CCC) was calculated to give a measure of the “departure from the identity line” of the plotted paired observations using each technique.⁹ Statistical analysis was performed in “R” using the “epiR” package.^{10,11}

RESULTS

The manual outlining for each patient involved inspection of 31 CT volumes acquired at successive time points (19 or 25 slices in each) and the drawing of a “best” ROI at each of the 31 time points. This took an experienced radiologist approximately 10 min for each patient. By contrast, the single ROI for semi-automated processing could be drawn in approximately 30 s by an experienced observer: the computational steps took negligible time (<1 s for each patient).

Typical sample PVIFs extracted by both “semi-automatic” and “manual” means are shown plotted in Figure 3 and can be seen to agree largely with the confidence interval (CI) calculated on the “semi-automatic” PVIF points.

Bland–Altman plots¹² relating the curve characteristics of the “semi-automatic” PVIF *vs* those of the gold-standard “manual”

PVIF are shown in Figure 4. Four characteristics are compared: the baseline value (HU) (*i.e.* the mean attenuation in pre-contrast images); the peak value (HU); the mean value in the “washout” (HU) phase (*i.e.* the mean of the last five points on the curve at $t > 50$ s); and the tail point value (HU) (*i.e.* the attenuation recorded at the final time point $t = 300$ s). The biases and CIs are shown in Figure 4 and are small in each case [peak: bias = 3.46 (−11.06, 17.98) HU; mean washout: bias = 2.32 (−6.42, 11.06) HU; tail: bias = 0.92 (−7.52, 9.35) HU; baseline: bias = −0.37 (−12.64, 11.9)] indicating good agreement between the methods. The CCC values are also shown [peak: CCC = 0.98 (0.95, 0.99); mean washout: CCC = 0.91 (0.80, 0.96); tail: CCC = 0.89 (0.75, 0.95); baseline: CCC = 0.66 (0.33, 0.85)]. Although the CCC value for the baseline point is low (CCC = 0.66), it is substantially influenced by an outlier originating from a patient with very noisy images [omitting this outlying point, CCC = 0.86 (0.68, 0.94)].

Bland–Altman plots of perfusion parameters derived from fitting the Matérn model to the data using the “semi-automatic” *vs* “manual” PVIFs are shown in Figure 5. Once again, the biases and overall CIs are small [F: bias = −3.11 (−30.68, 24.47) ml min^{−1} 100 ml^{−1}; A: bias = −1.05 (−11.21, 9.1)]%; MTT: bias = 0.31 [−3.27, 3.89] s; DV: bias = −0.59 (−2.59, 1.41)%] indicating good agreement between the methods. The CCC values [F: CCC = 0.92 (0.81, 0.97); A: CCC = 0.95 (0.91, 0.98); MTT: CCC = 0.95 (0.90, 0.98); DV: CCC = 0.92 (0.82, 0.97)] range between 0.92 and 0.95.

Sample perfusion parameter maps are shown in Figure 6 and display very few apparent differences between those generated using the “semi-automatic” PVIF and those derived using the “manual” gold-standard PVIF.

Figure 2. Schematic diagram of attenuation–curve completion for the arterial input function (AIF) extracted from the aorta. A gamma-variate function is fitted to the measured AIF points marked here on the top axes. The time delay from baseline, Δt , is set to the point where this curve has its zero crossing. The measured curves from the portal vein and the tissue are assumed to include a baseline point since image CT number enhancement in these regions occurs after an initial delay.

Figure 3. Typical sample portal venous input function (PVIF) curves. “Gold standard” PVIF from manual outlines (crosses); fitted, for clarity only, to a gamma-variate function and an exponential decay on the two time axes, respectively (full line). Semi-automatically extracted PVIF shown with error bars (95% confidence interval) (circles).

Figure 4. Bland-Altman plots of portal venous input function (PVIF) characteristics from $n = 20$ subjects; semi-automated method ("auto") vs manually outlined method ("manual"). Four plots are shown: (a) curve maximum value [Hounsfield units (HU)]; (b) curve baseline value (HU); (c) curve tail-point value (HU); and (d) mean value of curve in flat "washout" phase. The biases and confidence intervals are shown in each case, as is the concordance correlation coefficient (CCC).

DISCUSSION

Extraction of the PVIF from typical DCE-CT images is difficult due to respiratory motion and partial volume effects.

To allow for respiratory motion, an attempt could be made to extract the portal vein attenuation from a thick slice, *e.g.* 20 mm; in this case, however, there would be severe partial volume problems since the vein is usually smaller in diameter than this thick slice width. To avoid these problems, a thin (1.5- or 2-mm) slice reconstruction may be used instead though this incurs the converse problem of through-plane vein motion. Some groups have tried to minimize these effects by insisting on a breath-hold throughout the acquisition period, usually employing nasal oxygen to sustain this to a useful duration of 40 s.^{13,14} However, this restricts the form of subsequent analysis to first-pass deconvolution or the maximum-slope method, with their inherent drawbacks.^{3,15}

In free-breathing approaches, an alternative method would be to automatically segment the portal vein from the imaged volume at successive time points. As far as the authors can determine, this is the approach taken by several suppliers of commercial software, although the details of the algorithms used are not published. Automatic segmentation of a tree-like structure from an imaged volume is not a trivial task and the software to accomplish it is, in all likelihood, complex. Our proposed

algorithm is a simple alternative and could be implemented by any physicist or engineer. We would not claim that our algorithm will produce more accurate PVIFs than proprietary systems, but we argue that we have shown that the PVIFs extracted are "good enough" not to introduce any significant additional error into kinetic model parameter values.

Alternatively, it would be possible to manually outline the portal vein on all images recorded in the dynamic series, but this would be very time-consuming since there are many thin slices and many time points (typically ~500 images in all). Some researchers have tried to approximate this by manual displacement of a drawn ROI across slices.¹⁶ This approach suffers from manual registration inaccuracies and is labour intensive. Our method essentially performs this process automatically.

It is possible that automated motion correction by post-acquisition registration of the imaged volume across all time points could produce equivalent or better results. However, in many cases, the imaged tissue volume will be a single relatively thin slab (*e.g.* the 20 mm in our case), which being of the same order as the maximum respiration displacement, makes automatic inter-time-point registration very difficult. In addition, registration software can be complex to develop and time-consuming to run. Other researchers have employed such methods¹⁷ but have not validated them against a manually outlined gold standard.

Figure 5. Bland-Altman plots of perfusion parameters after fitting the Matérn kinetic model to the data from a uniform liver region of interest. The Bland-Altman plots show values from using the semi-automated method vs the manually outlined method (gold-standard) of portal venous signal extraction. Four plots are shown: (a) total perfusion (F) in $\text{ml min}^{-1} 100 \text{ ml}^{-1}$; (b) arterial fraction of total perfusion (A) in %; (c) mean transit time (MTT) in seconds; (d) distribution volume (DV) in %. The biases and confidence intervals (CIs) are shown in each case as is the concordance correlation coefficient (CCC) with its own CI.

With the notable addition of careful design of the acquisition strategy, synchronising this with the respiration cycle, Chandler et al¹⁸ have shown in a validated study that it is possible to register thin-slab liver CT sections with both rigid and non-rigid algorithms. The conclusion reached is that non-rigid registration outperforms both rigid and labour-intensive manual registration techniques. However, this author goes on to state that the differences in results between the techniques were small and manual registration based on selecting the “best slice” visually would suffice in most settings. We claim that our semi-automatic technique achieves the same result with less operator input.

It may be possible to extend the argument further if a relatively thin slab is acquired in the liver tissue, and for the above reasons, automatic registration is not possible. The liver tissue attenuation curve may then be acquired with approximate motion correction by always using the thin (*i.e.* in our case 2 mm) reconstructed slice identified as carrying the portal vein. This slice can be determined automatically at each time point as a beneficial side effect of the PVIF extraction algorithm we have described above.

There are some limitations to the method described in this article. Firstly, as mentioned above, the baseline of the PVIF is extracted from the most utilized “best slice” later in the acquisition. This is a “best-guess” solution employed for simplicity; it

is not theoretically valid in the sense that we do not expect pre-contrast respiratory phase to be necessarily correlated to that later in the acquisition. However, since the pre-contrast grey level of all liver tissue and portal venous vessels appears indistinguishable to the observer, the error introduced by incorrect slice selection is in all likelihood small.

We have also employed some additional assumptions, most importantly that the PV moves with respiration to a good approximation in a superior/inferior direction only, within the imaged slab. We might qualify this by hypothesizing that any in-plane motion is not large enough to take the portal vein outside the extent of the small drawn ROI projected onto the appropriate image slice. The validity of this hypothesis is supported by our results since a partial or full departure of the portal vein outside the ROI would result in a drop in attenuation values recorded for the PVIF (after baseline) relative to the gold standard. We do not observe any such systematic error in the measured data and so conclude that the hypothesis is reasonable.

Increasingly, CT scanners have been able to scan larger volumes in a dynamic mode.¹⁹ We were unable to employ volume registration as a solution since we could acquire data only from a thin slab. Whilst our technique for PVIF extraction would be equally applicable to a full liver DCE-CT analysis, a full

Figure 6. Perfusion and arterial fraction maps from a representative patient derived using the Materne kinetic model and applying the “semi-automatic” and “manual” portal venous input functions (PVIFs), respectively.

registration solution might in that case become attractive as an alternative.¹⁸ Such an approach would need to be validated.

In this study, the Materne dual-input, single-compartment model^{6,7} was applied to the data for validation purposes. However, it should be noted that other models have been suggested for such liver data analyses.^{4,20} The choice of model is probably unimportant here as the issue under investigation is the variation of parameter values with different PVIF extraction techniques; the degree of variation is likely to be similar for any reasonable model applied.

CONCLUSION

We have described a simple and effective semi-automatic method for extracting the PVIF from typical DCE-CT images.

The method has been validated using the Materne PK model and has been shown to perform well in comparison with conventional curve extraction through time-consuming manual outlining.

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