Non-invasive quantification of liver perfusion with dynamic computed tomography and a dual-input one-compartmental model

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ABSTRACT

Various liver diseases lead to significant alterations of the hepatic microcirculation. Therefore, quantification of hepatic perfusion has the potential to improve the assessment and management of liver diseases. Most methods used to quantify liver perfusion are invasive or controversial. This paper describes and validates a non-invasive method for the quantification of liver perfusion using computed tomography (CT). Dynamic single-section CT of the liver was performed after intravenous bolus administration of a low-molecular-mass iodinated contrast agent. Hepatic, aortic and portal-venous time–density curves were fitted with a dual-input one-compartmental model to calculate liver perfusion. Validation studies consisted of simultaneous measurements of hepatic perfusion with CT and with radiolabelled microspheres in rabbits at rest and after adenosine infusion. The feasibility and reproducibility of the CT method in humans was assessed by three observers in 10 patients without liver disease. In rabbits, significant correlations were observed between perfusion measurements obtained with CT and with microspheres ($r = 0.92$ for total liver perfusion, $r = 0.81$ for arterial perfusion and $r = 0.85$ for portal perfusion). In patients, total liver plasma perfusion measured with CT was $112 \pm 28$ ml·min$^{-1}$·100 ml$^{-1}$, arterial plasma perfusion was $18 \pm 12$ ml·min$^{-1}$·100 ml$^{-1}$ and portal plasma perfusion was $93 \pm 31$ ml·min$^{-1}$·100 ml$^{-1}$. The measurements obtained by the three observers were not significantly different from each other ($P > 0.1$). Our results indicate that dynamic CT combined with a dual-input one-compartmental model provides a valid and reliable method for the non-invasive quantification of perfusion in the normal liver.

INTRODUCTION

Quantitative measurement of hepatic perfusion has the potential to provide important information in the assessment and management of various liver diseases and in the determination of their outcome [1–10]. Several methods of quantification have been reported, but most of them either are invasive or remain controversial [11–15]. Dynamic computed tomography (CT) and mathematical modelling have been proposed for the quantification of liver perfusion from first-pass dynamic analysis of iodinated contrast agents using a gradient method [16]. The principle of the gradient method was originally described and validated by Peters et al. in the
kidney [17,18]. To the best of our knowledge, this method has not been validated in the liver, which has a dual blood supply.

Low-molecular-mass iodinated contrast agents are diffusible tracers, and redistribute from the capillaries to the interstitial space [19]. In the normal liver, sinusoids are fenestrated, allowing free access of these molecules to the extravascular space of Disse [20]. Therefore it is expected that compartmental analysis can be applied for the quantification of liver perfusion with CT. Compartmental modelling has been used with positron emission tomography and \(^{15}O\)-labelled water by Taniguchi et al. [14] and Ziegler et al. [15]. However, the dual vascular input of the liver via the hepatic artery and the portal vein is difficult to measure separately with positron emission tomography, because of the limited spatial resolution of the method. In contrast, dynamic CT has high spatial and temporal resolution, allowing for separate measurement of the arterial and portal-venous input functions.

The purpose of the present study was to determine whether dynamic CT and a dual-input one-compartmental model can be used for the non-invasive absolute quantification of liver perfusion. Validation studies consisted of simultaneous measurements of hepatic perfusion with CT and with radio-labelled microspheres in rabbits at rest and after adenosine infusion. The feasibility and reproducibility of the CT method in humans was assessed in patients without liver disease.

**MATERIAL AND METHODS**

**Animal studies**

**Animals**

Experiments were performed on 18 male New Zealand White rabbits (Iffa Credo Belgium, Brussels, Belgium) weighing 3.4 \(\pm\) 0.3 kg. Animals were housed in individual cages at 19 °C with light from 08.00 to 22.00 hours, and were fed on rabbit chow and water *ad libitum*. Animals were randomly assigned into two groups of nine rabbits (experimental and control groups). CT and microsphere studies were performed on the experimental group, while the control group received only microspheres after infusion of a volume of saline equal to the volume of contrast material used in the experimental group. In the experimental group, six rabbits were used for baseline studies only, while three rabbits were used for baseline and vasodilation studies. The study protocol was reviewed and approved by the Ethics Committee on animal care at our institution.

**Surgical procedures**

Catheters were placed into the carotid and the femoral arteries of the rabbits 2 days before the perfusion studies. Surgery was performed under sterile conditions. The animals were anaesthetized by intramuscular injection of ketamine hydrochloride (35 mg/kg body weight) and xylazine hydrochloride (8 mg/kg body weight). The right common carotid artery was cannulated with a 3-F polyethylene catheter (William Cook Europe, Bjaerverskov, Denmark), which contained heparinized saline to prevent clotting. The catheter tip was advanced into the left ventricle [21], and its positioning was verified under fluoroscopy. A second 3-F polyethylene catheter was introduced into the right femoral artery and advanced into the abdominal aorta just above the iliac bifurcation. The two catheters were tunnelled into subcutaneous tissue, and taken out on the back of the neck and on the medial thigh respectively. The animals were then allowed to recover for 48 h before the perfusion studies. One rabbit from the control group died during the surgical procedure and could not be included in the analysis.

**CT scanning protocol**

The CT studies were performed using a Twin RTS scanner (Elscint, Haifa, Israel). For these studies, the rabbits were anaesthetized with ketamine hydrochloride and xylazine hydrochloride after an 18-h fast. First, a scout image was acquired in the coronal plane, followed by unenhanced transverse images through the entire liver. Then a fixed slice level, which was selected to include the liver, aorta and portal vein, was scanned continuously during 60 s after contrast injection (Figure 1). The following parameters were used: 2 mm thickness, 180 mm field-of-view, \(512 \times 512\) matrix, 120 kV, 100 mA, 1 s scan time, 360° scan angle, and 0.3 s reconstruction interval. A contrast agent [1 ml/kg body weight of a 350 mg/ml solution of iohexol (Omnipaque; Nycomed, Oslo, Norway)] was injected at the beginning of the CT data acquisition period. The contrast material was injected through a 24-gauge catheter placed in the central ear vein at a rate of 1 ml/s by using an automated power injector (CT 9000 ADV; Liebel-Flarsheim, Cincinnati, OH, U.S.A.). The contrast material was pushed by 10 ml of saline solution [22]. Vasodilation was performed 60 min after the baseline study, and was obtained by infusion of adenosine (0.33 mg/min\(^{-1}\)kg\(^{-1}\)) into the left ventricle. Arterial blood pressure was monitored throughout the adenosine infusion. The dynamic CT protocol was repeated 5 min after the start of the adenosine infusion.

**Microsphere measurements**

Immediately after completion of the dynamic CT study, perfusion was measured with microspheres by using the arterial reference sample method [23]. Microspheres of 15.5 \(\pm\) 0.1 \(\mu\)m diameter, labelled with \(^{48}\)Sc (normal specific radioactivity 531.75 MBq/g) or \(^{151}\)Ce (normal specific radioactivity 493.42 MBq/g) and suspended in
Non-invasive quantification of liver perfusion

Figure 1  CT scan of the rabbit liver
Upper panel: dynamic single-section CT scan after intravenous bolus administration of 1 ml/kg iohexol in the rabbit shows enhancement in the aorta (arrows) and in the portal vein (arrowheads). Lower panel: corresponding time–density curves of relative enhancement (ΔHU) of the liver, the aorta and the portal vein.

Patient studies

Subjects
Ten patients without liver disease (four men and six women; mean age 54 years; age range 28–79 years) who underwent a CT examination of the abdomen were included in the study. The CT protocol was approved by the Ethics Committee of our institution, and the patients gave written informed consent to participate in the study. The absence of liver disease was documented by history, physical examination, laboratory screening and Doppler ultrasonography.

CT scanning protocol
The patients had fasted for 12 h, and were asked to lie down for 1 h before the CT examination to minimize variations in portal flow [25]. CT scanning was performed on a Twin RTS scanner. The CT scanning protocol was modified from that used in rabbits to increase the acquisition time up to 2 min, due to the longer blood circulation time in humans. The dynamic CT protocol acquired 40 images (10 mm slice thickness, 430 mm field-of-view, 512 × 512 matrix, 120 kV, 100 mA, 1 s scan time and 3 s repetition time). An aliquot of 40 ml of iohexol pushed by 30 ml of saline solution was administered via a 16-gauge catheter placed in the antecubital fossa at a rate of 7 ml/s by a Liebel-Flarsheim power injector [1,26]. The injection of contrast material started simultaneously with the beginning of the acquisition. The patients were asked to breathe as quietly as possible during the acquisition.

Image analysis
CT data processing was performed on a Silicon Graphics O2 workstation (Silicon Graphics Inc., Mountain View, CA, U.S.A.). The data analysis programs were implemented using IDL (Research Systems Inc., Boulder, CO, U.S.A.). No smoothing was performed on the images in either space or time. Mean signal intensity measurements...
and S.Ds were obtained in Hounsfield units (HU) by drawing the largest possible user-defined regions of interest (ROIs) on the aorta, the main portal vein and the liver parenchyma using the dynamic CT images. It was particularly important to use the largest possible ROI in the aorta, to take into account the layering effect of contrast material in this vessel [27]. In addition, care was taken to exclude large vessels from the ROIs placed in the liver. Due to respiratory motion, the portal-venous ROI often had to be adjusted from slice to slice. The sampled ROIs were used to generate time–density curves (Figure 1) that were analysed using a liver compartmental perfusion model. The first time points of the concentration–time curves were averaged and subtracted from the subsequent time points to ensure that the initial baseline concentration of the contrast agent was zero. After this normalization, the post-contrast density measurement at CT is directly proportional to the concentration of contrast agent [28,29], i.e. $C(t) = K \cdot \Delta \text{HU}(t)$, where $C$ is the concentration of contrast agent, $\Delta \text{HU}$ is the relative measure of contrast enhancement, and $K$ is a constant of proportionality. Since this proportionality constant is the same for the blood and liver tissue curves [29], this constant $K$ will cancel out in eqn (1) below, and therefore does not need to be calculated or known. In order to determine the reproducibility of the CT perfusion method, three observers independently performed hepatic perfusion measurements in the 10 patients in two sessions that were separated by several days (range 1–4 days), yielding 60 measurements in total.

**Compartmental model**

A dual-input one-compartmental model with first-order rate constants (Figure 2) was used to reflect the fact that the liver receives its blood supply from both the aorta (through the hepatic artery) and the portal vein, and therefore has two inflow $k_1$ rate constants [15]. The mathematical equation for the compartmental model shown in Figure 2 is:

$$\frac{dC_i(t)}{dt} = k_{1a} C_a(t) + k_{1p} C_p(t) - k_2 C_i(t)$$  \hspace{1cm} (1)

where $C_i(t)$, $C_a(t)$ and $C_p(t)$ represent the concentration from the aorta, portal vein and liver compartments respectively, $k_{1a}$ represents the aortic inflow rate constant, $k_{1p}$ the portal venous inflow rate constant and $k_2$ the outflow rate constant.

Solving for $C_i(t)$, and adding two delay parameters, $\tau_a$ and $\tau_p$, which represent the transit time from the aorta and portal vein regions respectively to the liver ROI, we obtain:

$$C_i(t) = \int_0^\infty \left[ k_{1a} C_a(t' - \tau_a) + k_{1p} C_p(t' - \tau_p) \right] e^{-k_2(t'-t)} \, dt'$$  \hspace{1cm} (2)

assumptions $C_i(0) = 0$; $t'$ is a dummy integration variable. Since iodinated contrast media do not enter into red blood cells, the time series values $C_a(t)$ and $C_p(t)$ were divided by 1 minus the large-vehicle haematocrit, which either was measured in the patients or was assumed to be 0.45 in the rabbits [30]. The delays $\tau_a$ and $\tau_p$ were defined to be equal, and were fixed to the delay between the first non-zero value of the $C_a(t)$ curve and the first non-zero value of the $C_p(t)$ curve. The median time delays were 3.3 s in the rabbits (range 2.7–4.5 s) and 3 s in the patients (range 3–6 s).

Two models were tested. In the first model, the concentration of the contrast agent in the liver ROI was considered to be equal to the concentration in the liver compartment:

$$C_{\text{ROI}}(t) = C_i(t)$$  \hspace{1cm} (3)

Substituting eqn (2) into eqn (3), we obtain:

$$C_{\text{ROI}}(t) = \int_0^\infty \left[ k_{1a} C_a(t' - \tau_a) + k_{1p} C_p(t' - \tau_p) \right] e^{-k_2(t'-t)} \, dt'$$  \hspace{1cm} (4)

An unweighted least-squares fit using the Levenberg–Marquardt method [31,32] for the three parameters $k_{1a}$, $k_{1p}$ and $k_2$ was then performed. All data points, i.e. the number of acquired images, were used in the fitting procedure.

In the second model, the concentration of the contrast agent in the liver ROI was considered to be a linear combination of the three compartments $C_a$, $C_p$ and $C_i$:

$$C_{\text{ROI}}(t) = f_a C_a(t - \tau_a) + f_p C_p(t - \tau_p) + (1 - f_a - f_p) C_i(t)$$  \hspace{1cm} (5)

where $f_a$ is the relative volume fraction of the arterial
plasma and \( f_p \) is the relative volume fraction of the portal-venous plasma. Substituting eqn (2) into eqn (5), we obtain:

\[
C_{t0}(t) = f_s C_a(t - \tau_s) + f_p C_p(t - \tau_p) + (1 - f_s - f_p) \int_0^t [k_{1s} C_s(t' - \tau_s) + k_{1p} C_p(t' - \tau_p)] e^{-k_f(t-t')} dt'
\]

(6)

In this case, an unweighted least-squares fit was performed for the five parameters \( k_{1s}, k_{1p}, k_s, f_s \), and \( f_p \).

With both models, total liver plasma perfusion was calculated as \((k_{1s} + k_{1p})/E\), where \( E \) is the extraction fraction of the contrast agent in the liver, which is assumed to be 1 in the normal liver, i.e. the contrast agent has free access to the extravascular interstitial space of Disse through the endothelial fenestrae. The extraction fraction \((E)\) has no units, and the units of \( k_{1s} \) and \( k_{1p} \) (s\(^{-1}\)) are converted into the more familiar perfusion units ml\(\cdot\)min\(^{-1}\)\cdot100 ml\(^{-1}\) by multiplying by 60 s/min and by 100 ml (of blood)/ml (of tissue), where we assume a specific tissue gravity of 1.0. Similarly, arterial plasma perfusion was calculated as \( k_{1s}/E \), and portal plasma perfusion as \( k_{1p}/E \). In addition, whole-blood perfusion values were calculated by dividing plasma perfusion measurements by 1 minus the small-vessel haematocrit, which was assumed to be 0.25 [29].

**Statistical analysis**

Numerical variables are expressed as means \( \pm \) S.D. Comparisons between hepatic perfusion parameters measured with microspheres in the experimental and control groups were performed with the unpaired Student’s t test. Correlation between CT- and microsphere-derived liver perfusion parameters was assessed by Pearson correlation coefficients and by linear regression. Intra- and inter-observer reproducibility was studied by two-way ANOVA. All statistical tests are two-tailed, and a \( P \) value of < 0.05 was considered statistically significant.

**RESULTS**

In the rabbits, the microsphere distribution was homogeneous. Indeed, the right and left renal perfusion values were 304 \( \pm \) 138 and 304 \( \pm \) 146 ml \( \cdot \) min\(^{-1}\) \cdot100 g\(^{-1}\) respectively, and they were linearly related \((r = 0.98; \ P < 0.001)\). In the three rabbits receiving adenosine, the mean arterial pressure was 83.2 \( \pm \) 6.5 mmHg before adenosine infusion, and 64.6 \( \pm \) 5.8 mmHg after perfusion. Comparison between liver perfusion measurements obtained before and after vasodilation showed that total hepatic perfusion was increased by 36\% and 29\% for the CT and microsphere techniques respectively.

The total-liver, arterial and portal perfusion values measured with microspheres and with CT are summarized in Table 1. The perfusion values obtained with microspheres did not differ significantly between the experimental and control groups \((P > 0.09)\). The plasma perfusion values obtained with the three-parameter fit \((k_{1s}, k_{1p}, k_s)\) by CT correlated well with the microsphere perfusion values. Correlation coefficients were \( r = 0.92 \) for total liver perfusion \((y = 61.9 + 1.1x; \ P < 0.001)\), \( r = 0.81 \) for arterial perfusion \((y = 31.8 + 0.8x; \ P = 0.002)\) and \( r = 0.85 \) for portal perfusion \((y = 39.3 + 1.2x; \ P = 0.001)\) (Figure 3). When the small-vessel haematocrit was taken into account (i.e. when whole-blood perfusion rather than plasma perfusion was calculated at CT), the \( r \) values did not change; only the slopes and intercepts of the regression lines changed. Indeed, correlation coefficients were \( r = 0.92 \) for total liver perfusion \((y = 82.6 + 1.5x)\), \( r = 0.81 \) for arterial perfusion \((y = 42.4 + 1.0x)\) and \( r = 0.85 \) for portal perfusion \((y = 52.3 + 1.6x)\). In contrast, the plasma perfusion values obtained with the five-parameter fit \((k_{1s}, k_{1p}, k_s, f_s\) and \(f_p)\) at CT did not correlate significantly with the microsphere data \((r = 0.28 - 0.32; \ P > 0.3)\).

The CT perfusion measurements were performed successfully in all patients. In particular, no patients were excluded because of excessive movement during the CT acquisition. As a consequence of the results obtained in

<table>
<thead>
<tr>
<th>Method</th>
<th>Total liver perfusion</th>
<th>Arterial perfusion</th>
<th>Portal perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microspheres (ml ( \cdot ) min(^{-1}) \cdot100 g(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>178 ( \pm ) 56</td>
<td>38 ( \pm ) 11</td>
<td>140 ( \pm ) 49</td>
</tr>
<tr>
<td>Experimental group</td>
<td>134 ( \pm ) 47</td>
<td>29 ( \pm ) 18</td>
<td>105 ( \pm ) 34</td>
</tr>
<tr>
<td>CT (ml ( \cdot ) min(^{-1}) \cdot100 ml(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-parameter fit</td>
<td>216 ( \pm ) 58</td>
<td>54 ( \pm ) 18</td>
<td>162 ( \pm ) 47</td>
</tr>
<tr>
<td>Three-parameter fit (with correction for small-vessel haematocrit)</td>
<td>288 ( \pm ) 78</td>
<td>72 ( \pm ) 23</td>
<td>216 ( \pm ) 63</td>
</tr>
<tr>
<td>Five-parameter fit</td>
<td>382 ( \pm ) 319</td>
<td>67 ( \pm ) 47</td>
<td>314 ( \pm ) 332</td>
</tr>
</tbody>
</table>

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Figure 3 Correlations of perfusion measurements obtained with dynamic CT and microspheres

The hepatic (top), arterial (middle) and portal (bottom) perfusion measurements obtained with dynamic CT (three-parameter fit, without correction for small-vessel haematocrit) and microspheres are well correlated.

in the rabbits, liver perfusion measurements were calculated in patients only with the three-parameter fit. Total liver plasma perfusion was 112 ± 28 ml min⁻¹ 100 ml⁻¹, arterial plasma perfusion was 18 ± 12 ml min⁻¹ 100 ml⁻¹, and portal plasma perfusion was 93 ± 31 ml min⁻¹ 100 ml⁻¹. The corresponding whole-blood perfusion values were 149 ± 38, 25 ± 16 and 124 ± 42 ml min⁻¹ 100 ml⁻¹ respectively. The plasma perfusion measurements are detailed in Table 2. ANOVA showed no significant differences (P > 0.1) between the three observers or between the two measurements performed by each observer.

**DISCUSSION**

The aim of the present study was to validate the use of dynamic CT and compartmental modelling for the non-invasive quantification of liver perfusion. Quantification of liver perfusion is relevant, as changes in liver perfusion are observed in various circumstances, including liver metastases, chronic liver diseases and liver graft rejection [1–10]. It is also relevant to use CT for this quantification, as CT examinations are often performed in patients with liver lesions. The method would thus provide an opportunity to obtain functional and anatomical information about liver diseases during the same examination. Several authors have reported the use of hepatic perfusion measurements with CT in clinical practice [1,2,7,8,16]. In these studies, perfusion was calculated using the gradient method. With this method, perfusion is quantified by dividing the maximal slope of the organ-density curve (i.e. the liver-density curve) by the peak density of the vascular input. The gradient method relies on the assumption that the contrast agent remains intravascular and intrahepatic when the slopes are measured. This method is difficult to use in the liver, because this organ has two vascular inputs, the hepatic artery and the portal vein. This means that the arterial and portal-venous phases of the liver-density curve have to be separated. This separation is often impossible to perform directly on the liver time–density curve. For this reason, the splenic or renal blood flow has been used as a template for hepatic arterial blood flow, introducing an additional assumption. The dual-input supply can be modelled with a compartmental model if the two inputs can be measured adequately. CT can be used for this purpose, since this technique has high spatial and temporal resolution.

<table>
<thead>
<tr>
<th>Plasma perfusion (ml min⁻¹ 100 ml⁻¹)</th>
<th>Total liver</th>
<th>Arterial</th>
<th>Portal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Session 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer 1</td>
<td>108.3 ± 28.7</td>
<td>18.4 ± 12.9</td>
<td>89.9 ± 31.1</td>
</tr>
<tr>
<td>Observer 2</td>
<td>118.0 ± 28.8</td>
<td>19.2 ± 14.2</td>
<td>98.8 ± 31.2</td>
</tr>
<tr>
<td>Observer 3</td>
<td>110.5 ± 30.2</td>
<td>18.5 ± 12.8</td>
<td>91.9 ± 31.2</td>
</tr>
<tr>
<td><strong>Session 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer 1</td>
<td>106.5 ± 27.5</td>
<td>17.6 ± 11.8</td>
<td>88.9 ± 30.0</td>
</tr>
<tr>
<td>Observer 2</td>
<td>113.0 ± 29.8</td>
<td>18.4 ± 12.5</td>
<td>94.6 ± 34.6</td>
</tr>
<tr>
<td>Observer 3</td>
<td>114.2 ± 33.2</td>
<td>18.5 ± 12.5</td>
<td>95.7 ± 35.8</td>
</tr>
</tbody>
</table>

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Our results validate the use of dynamic CT and a compartmental model to quantify liver perfusion, and demonstrate the feasibility and reproducibility of the method in humans. The compartmental model we employed derives from the single-compartmental model reported by Kety [33], and was modified to account for the dual blood supply of the liver through the hepatic artery and the portal vein. In this model, the inflow rate constant \( k_i = F \cdot E \) was measured, and liver perfusion \( F \) was considered to be equal to \( k_i \) by assuming that the extraction fraction \( E \) of the contrast agent in the liver is equal to 1. Although the hepatic extraction of iodinated contrast agents has not yet been defined in vivo, the assumption that the extraction fraction equals 1 is reasonable in the healthy liver, where the sinusoids are fenestrated, allowing instantaneous lateral diffusion of small and even large molecules [20].

By using a three-parameter model in which the signal arising from the arterial and portal-venous plasma in the liver ROI was considered to be negligible (i.e. \( f_0 = f_i = 0 \) ), the results correlated well with microsphere measurements. In contrast, a five-parameter perfusion model, which took into account \( f_a, f_p, k_{1a}, k_{1p} \), and \( k_2 \), showed poor correlation with microsphere measurements. This can be explained by the use of too many parameters, resulting in non-unique fits.

Perfusion values obtained with CT and the three-parameter fit were higher than those obtained with microspheres. If we consider whole-blood perfusion rather than plasma perfusion, the CT values were even higher, but this did not decrease the excellent correlation between CT and microsphere perfusion values. Whole-blood perfusion is obtained by dividing plasma perfusion by 1 minus the small-vessel haematocrit. The haematocrit in the small vessels is known to be significantly lower than the systemic haematocrit [23,34]. Low regional values have been reported, ranging between 0.20 and 0.48 [35]; in the present study it was assumed to be 0.25 [29]. However, the capillary haematocrit is heterogeneous and, to the best of our knowledge, has not yet been defined in the liver. Therefore we preferred to use plasma perfusion values rather than whole-blood perfusion values.

There are several limitations in the comparison of perfusion measurements obtained with CT and microspheres. First, blood flow is measured with microspheres, whereas with the CT compartmental model an inflow rate constant is actually what is measured. Secondly, our three-parameter fit did not take into account the vascular fraction of the liver density measurements. This led to an overestimation of hepatic perfusion with CT. It may be argued that with the five-parameter model (i.e. taking into account the vascular fraction of the liver density measurements), the perfusion results were even higher than with the three-parameter model, but the very large standard deviations obtained with the five-parameter model, and the fact that there was poor correlation with the microsphere perfusion data, show that this model is not valid. In addition, the portal vein lies at a shallow angle to the image plane and is the most affected by respiration, and therefore the concentration measured in terms of HU is likely to be underestimated due to the partial volume effect. A simple computer simulation showed that if the portal vein time curve was 60% of its true value (i.e. 40% partial vowing), this would lead to an approx. 50% overestimation of liver perfusion, which was what we saw in our data. Finally, it should be remembered that hepatic perfusion is unlikely to be homogeneous throughout the entire liver, and that marked temporal variations have also been found [15,36,37]. For these reasons, the comparison between CT and microsphere data may be hampered by spatial and temporal variations. In the present study, we were particularly careful to minimize the time interval between CT and microsphere experiments. This may be one reason why our correlation between CT and microsphere measurements was better than that reported between positron emission tomography and microsphere data by Ziegler et al. [15].

The inclusion in our study of a control group of rabbits that did not receive iohexol allowed us to study the effect of a bolus of a low-osmolar contrast agent on liver perfusion. Indeed, intravenous administration of iodinated contrast media produces both vasodilation and vasoconstriction [38]. These effects are very complex, depending on the osmolality and the chemical structure of the contrast agent, and also on the organ and the species involved [39]. In our study, the perfusion values measured with microspheres were lower in the rabbits receiving 1 ml/kg iohexol than in the control group, but this difference was not statistically significant. Our rabbit study thus suggests that intravenous injection of a small volume of a low-osmolar contrast agent such as iohexol has no significant effect on liver perfusion. This is an important prerequisite for the use of iodinated contrast agents as perfusion tracers in the liver.

In the second part of the study, the feasibility and the reproducibility of measuring liver perfusion with dynamic CT and a dual-input one-compartmental model was assessed in patients without liver disease. Because of the results in rabbits, only the three-parameter model was used in humans. No patients were excluded from the study because of excessive movement during the CT acquisition, despite their breathing. Moreover, reproducibility studies showed no significant intra- or inter-observer differences, suggesting that CT perfusion measurements can be readily and reliably performed in humans.

Some limitations of the CT technique must be outlined. First, as already mentioned, the CT protocol we used acquired only one section level through the liver at a time, and heterogeneity of hepatic perfusion in the longitudinal...
axis was not taken into account [36,37]. For this reason, multi-row detector CT scanners should be considered in further studies. Another limitation is related to patient respiratory movement during the CT acquisition. Movements can be minimized by decreasing patient discomfort by the use of low-osmolality contrast agents [7], and by carefully instructing the patients to breathe as quietly as possible during the whole acquisition. Finally, radiation exposure is another limitation for measuring liver perfusion with CT. As reported previously in a similar setting, we used a tube current of 100 mA and a scanning time of 1 s [1]. However, strategies to further decrease the dose should be considered.

As already mentioned, measurement of liver perfusion has the potential to be useful in the study of various hepatic diseases. In patients with chronic liver disease, perfusion measurements obtained with CT should be compared with Doppler ultrasound and portal pressure measurements. Quantification of liver perfusion is also important for the study of the systemic availability of drugs in health and disease [40–43]. Finally, compartmental analysis of liver perfusion might also provide important information on altered capillary permeability in liver disease by using various contrast agents of different molecular mass. This should be assessed in further experimental studies.

In conclusion, liver perfusion can be studied with CT and compartmental modelling. Our results show that dynamic CT combined with a dual-input one-compartmental model is a reproducible method that provides perfusion values that correlate with microsphere data in the normal liver. Arterial and portal-venous perfusion can be determined separately. This method provides non-invasive functional information and may be useful in various liver diseases in which the hepatic microcirculation is altered.

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