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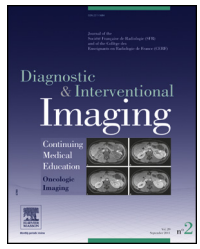

CONTINUING EDUCATION PROGRAM: FOCUS...

Can we justify not doing liver perfusion imaging in 2013?

M. Ronot[a,b,*], S. Lambert[a,b], J.-L. Daire[a,b], M. Lagadec[a,b], S. Doblas[a,b], P. Garteiser[a,b], A. Kerbaol[a,b], R. Sinkus[a,b], B.E. Van Beers[a,b], V. Vilgrain[a,b]

[a] *Service de Radiologie, Hôpital Beaujon, 100, boulevard du Général-Leclerc, 92110 Clichy, France*
[b] *Université Paris Diderot, Sorbonne Paris Cité, Inserm U773, Centre de Recherche Biomédicale Bichat-Beaujon, CRB3, Paris, France*

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Abstract Liver perfusion imaging is a quantitative functional investigation. Liver perfusion imaging is complicated because of the liver's dual vascular supply, artefacts due to respiratory movements and the fenestrated sinusoidal capillaries which allow the contrast medium to diffuse out. Liver perfusion can be examined by ultrasound, CT or MRI: each technique has its limitations and specific features. The major indications in hepatology are oncology (detection, characterization and tumor response) and non-invasive investigation of patients with chronic liver disease. Work is needed to standardize acquisition and modeling methods to allow wider use of results and more widespread use of the technique.

The liver is a large, richly vascularized, subcutaneous solid organ. It is therefore easily accessible for various imaging modalities (ultrasound, computed tomography [CT] and magnetic resonance imaging [MRI]), despite the fact that it moves with the diaphragm and can deform. Various contrast media, each of which is specific to these individual methods, are also extremely useful and explain the key role of imaging in diagnostic and therapeutic hepatology.

Perfusion imaging provides information about the tissue microcirculation, in other words the movement of water and solutes at levels far below the spatial resolution of the instrument. It is not, therefore, a dynamic qualitative analysis of what is typically described as tissue enhancement, but a quantitative extraction of descriptive parameters of the

* Corresponding author. Service de Radiologie, Hôpital Beaujon, 100, boulevard du Général-Leclerc, 92110 Clichy, France.
E-mail address: maxime.ronot@bjn.aphp.fr (M. Ronot).

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liver's perfusion physiology (Table 1). It is based on the principle of injecting an iodinated contrast medium (called a tracer) and recording curves showing the change in its tissue concentration over time by rapid temporal samplings. These curves provide information on the concentration of the tracer at each point in time and for each image voxel. The parameters required are extracted from these curves by adjusting them to mathematical perfusion models. The difficulty in the case of the liver is the fact that it has a dual vascular supply, that the acquisition is hindered by respiratory movements and that the organ deforms. In addition, the sinusoidal capillaries are fenestrated and the tracer therefore readily diffuses out of them.

The basic hypothesis on which liver perfusion imaging is based is that local or diffuse pathological processes lead to measurable changes in these perfusion parameters. Quantifying these changes therefore provides information about the presence or progression of disease processes. There are two indications for studying perfusion in hepatology: oncology and investigation of chronic liver diseases. We shall start from a simple paradigm based on the relationship between the radiologist and clinician being organized around four major questions:

- is a lesion present, and if so is it an abnormality, a variant or a pathological process?
- if the imaging is performed for detection purposes, what is the type of process or pathology in question and is it related to the underlying disease?
- what treatment can be considered depending on the imaging results?
- and what is the response to treatment and can complications be diagnosed?

After examining the relevant theoretical and methodological questions, we will examine the use of perfusion imaging in detecting focal hepatic lesions, characterizing the lesion and studying tumor response.

General principles

Physiology of the liver

The liver has a dual blood supply, approximately 25% of which comes from the hepatic artery and the remaining 75% from the portal vein. There is no hepatic capillary network as such and this is replaced by fenestrated sinusoids. Both afferent vascular systems communicate with each other through trans-sinusoidal and transvasal communications and through the peribiliary plexuses. A fundamental concept that allows us to fully understand the adaptatory mechanisms involved in vascular abnormalities is the existence of an arterio-portal balance in human beings called a ''buffer effect'' which is characterized by a compensatory increase in arterial blood supply if the portal supply falls, although the reverse does not occur [1].

Theoretical bases for studying liver perfusion

Pandharipande et al. [2] described a list of requirements for an ideal study of liver perfusion:

- accurate quantification of overall or regional arterial and portal perfusion in order to assess focal or diffuse abnormalities;
- high spatial resolution which enables small lesions to be examined;

Table 1 The main perfusion parameters and their significance.

Parameter	Definition	Significance	Units
Time to peak	Time between arrival of the tracer in the large afferent vessels and maximum enhancement	Perfusion pressure	Seconds
Blood flow or perfusion	Volume of blood passing into a region studied per unit of time	Tumor vascularization and grade	mL/100 g/min
Blood volume	Volume of blood in a region studied (vascular, extravascular)	Tumor vascularization, vascular or extracellular volume	mL/100 g
Mean transit time	Mean time the tracer takes to cross the region studied	Perfusion pressure	Seconds
Permeability	Plasma flow leaking from the vascular compartment into the interstitium	Abnormal vessels	mL/100 g/min
Arterial/venous perfusion index	Amount of blood entering the region studied through the arterial/venous network	Type of vascularization	%
K trans	Transfer constant between the vascular compartment and the extracellular space	Equivalent to the permeability × perfusion product	mL/100 g/min

- high temporal resolution to correctly identify the kinetic properties of tracers which may differ within tissue lesions;
- measuring the concentrations of reliable tracers for an accurate quantitative study;
- robust modeling of liver perfusion physiology;
- ''whole-liver'' imaging;
- compatibility with morphological imaging modalities to allow complementary perfusion studies alongside more conventional investigations.

The above list highlights the difficulties in specifically studying the liver. Apart from the known classical limitations of the various instruments (such as accessibility, cost, irradiation, variability and dependence on the operator and type of contrast medium), perfusion imaging itself has other limitations and advantages depending on the approaches and instruments used. These are summarized in Table 2.

The problem of modeling liver perfusion

Modeling relies entirely on an analysis of the signal-time curve which is obtained, the shape of which depends on the tissue properties studied (the perfusion parameters measured, the properties of the tracer bolus injected [volume, injection rate] and the patient's cardiovascular parameters [cardiac output, ejection fraction]).

It should be stressed that this study is focused on tracer concentrations rather than the signal. Therefore, the signal has to be converted into a concentration. In ultrasound, specific software can process the video-intensity obtained and separate the signal due to contrast from the background noise (see details below). In a CT, the relationship between tracer concentration and density is linear. In MRI, extraction of concentration from the signal is more complicated and is based on calibrating a sequence with tubes containing increasing doses of tracer and the use of multiple angle tilting gradients [3].

There are two main mathematical approaches to studying liver perfusion:

- descriptive methods of signal/time curve morphology are not based on any physiological hypothesis (free models) which enable semi-quantitative parameters (such as enhancement gradient, time to peak, area under the curve) to be extracted. These are used in ultrasound (see below) and in CT and MRI [4,5]. However, this analysis varies considerably depending on the acquisition method used for each individual investigation and according to the imaging instrument used;
- pharmacokinetic models incorporate the specific restrictions of liver perfusion to a greater or lesser extent. These models are based on determining the relationship between arterial input function alone (in the tumor application) and the arterial-portal input functions (in diffuse disease), obtained from the enhancement curve from afferent blood vessels. Deconvolution algorithms [6] and compartmental models [3,7] belong to this category. These models assume that there are several hepatic compartments in which the contrast medium is present, mixed in a uniform concentration throughout the compartment, that flow is linear between compartments (passive exchange only) and that the parameters which describe the compartments are invariant during the data acquisition. Depending on the model, the parameters of interest are then extracted (Table 1). The CT models vary depending on the number of compartments and afferent blood vessels. The Tofts model (or modified Tofts) is often used in MRI clinical research. It circumvents the arterial input function and considers the whole vascular compartment.

As shown in the CT sample by Kanda et al. and Goh et al. [8,9], the data obtained are not independent from the model used. The choice of model depends on the organ being studied and the experience of the users and makes it difficult to generalize findings.

Table 2 Advantages and limitations of imaging modalities used to study liver perfusion.

	Ultrasound	CT	MRI
Spatial resolution	++	+++	+
Temporal resolution	+++	++	++
Measurement of tracer concentration alone	++	+++	+
''Whole-liver'' imaging	+	+	+++
Modeling	+/−	+/−	+/−
Compatibility with morphological imaging	++	+++	++

+: average; ++: good; +++ excellent; +/−: problematic.

Different study models in perfusion imaging

Isotopic imaging

Scintigraphic methods to calculate liver perfusion parameters were first described in the 1970s. Images are generally acquired every 1 to 2 seconds after intravenous injection of a radiopharmaceutical (technetium 99m pertechnetate, albumin or sulfur-based colloids). Liver enhancement is analyzed by regions of interest (ROI) and the arterial and portal components are separated, working on the principle that the renal enhancement peak represents the beginning of portal enhancement of hepatic parenchyma [10—16]. The important parameter is the hepatic artery perfusion index defined as A/(A+P) where A is the arterial enhancement gradient and P is the portal enhancement gradient.

Scintigraphic studies based on positron emission tomography (PET) have recently assessed the feasibility of studying hepatic perfusion [17]. Isotopic imaging, however, is hindered by poor spatial and temporal resolution.

Ultrasound

Doppler ultrasound quantifies flows rather than perfusion. In order to examine perfusion, mean flow velocity is multiplied by the diameter of the blood vessel. An alternative approach is to calculate the difference between the time

taken for an ultrasound beam to travel a defined distance in the direction of flow and counterflow. Trans-abdominal measurement of hepatic arterial (A) and portal (P) flow and the hepatic Doppler perfusion index can be calculated from the equation A/(A+P). The major disadvantages of these approaches are inter- and intra-observer variability and the inability to obtain regional findings.

Contrast-enhanced ultrasound (CEUS) with microbubble contrast agents is a more recent technique which is used to quantify tissue perfusion. CEUS has several advantages over other imaging modalities in measuring tissue perfusion: it uses purely endovascular agents which circumvent the issue of extravascular leakage, are readily available and do not involve exposure to X-rays or radionuclide tracers.

Dynamic image sequences are obtained after injection of the contrast medium, which then varies in local concentration over time. These images represent the changes in intensity over time, which can then be modeled in order to obtain parameters describing the microcirculation. Microcirculation is based on a precise distinction between the backscatter signals from the microbubbles and from the surrounding native tissue. Specific software is needed to quantify signal intensity and allow tissue contrast uptake to be calculated.

In practice, if uncompensated attenuation effects are assumed to be negligible, grey scale (from 0 to 255) image intensity quantification (videodensitometry) is the most widely available technique to measure the response to the contrast medium in clinical practice. The signal is generally compressed logarithmically and image intensity is then broadly similar to the logarithm of the backscatter coefficient value and therefore to the logarithm of the number of microbubbles present. However, this technique does not theoretically provide an accurate measurement without bias from the diffusion coefficient because of the many signal processing stages required.

In order to more closely reflect the direct relationship between signal and the backscatter coefficient, some ultrasound manufacturers now offer quantification software that is called 'linear of the signal', using the principle of studying the signal value in a region of interest (ROI) defined from raw image data before processing the video signal. These software solutions therefore circumvent the final stages of logarithmic compression and extrapolation.

The three main methods for ultrasound measurement of tissue perfusion are measurement of organ transit time, analysis of tissue reperfusion kinetics and analysis of enhancement intensity curves [18].

Measurement of organ transit time

In the liver, the time between injection or arrival in the hepatic artery of the contrast medium and the first appearance of contrast medium in a hepatic vein can be measured. To do this, a hepatic vein is targeted and kept within the field of vision before injection. The acquisition is taken with the subject breathing slowly and freely. The time taken for the contrast to arrive is generally over 30 seconds in normal subjects (the lower limit of the normal has been reported to be 25 seconds) [19,20]. This technique is particularly useful for investigating patients with diffuse liver disease, but has also been studied in patients with liver metastases.

Reperfusion methods

A state of equilibrium is reached after 2—3 minutes when the microbubbles are administered as a continuous infusion. At steady state, microbubble arrival and departure from any microcirculatory unit is constant and proportional to the fractional blood volume in this unit. It only depends on the speed of microbubble flow. Local tissue perfusion can then be calculated by analyzing the reconstitution kinetics of the volume of microbubbles after they have been destroyed by high initial power insonation [21,22]. After the microbubbles have been destroyed, the system switches to a low emission power in order to study the microbubble filling rate. One of the main limitations of the technique is that the perfusion data are obtained from a single tissue plane, a situation which is not particularly useful in accurately reflecting overall perfusion of the tissue or organ during the investigation. 3D volumetric and reperfusion studies are complex and have not yet been completely modeled. Analysis of the filling process provides semi-quantitative data linked to tissue perfusion values: the time to peak, initial slope of reperfusion, maximum refilling curve amplitude, area under the curve (related to blood volume) and mean transit time [23,24].

Analysis of enhancement intensity curves

After a bolus of contrast has been injected, changes in intensity over time during the filling phase (wash-in) and elimination phase (wash-out) of the bolus are studied to estimate the microcirculation. Different imaging modalities use identical methods, the most widely used, as described above, being compartmental modeling. This requires access to an arterial input which is used as the input function, that is often difficult obtain on CEUS. Deconvolution and behavioral models are therefore difficult to use. As a result, solely the descriptive parameters are extracted from the bolus kinetics. The most widely used are the maximum intensity peak (i.e. maximum intensity), the time to maximum intensity peak, the width of the maximum intensity peak, mean transit time and the area under the curve.

Computed tomography

The tracer used in CT is a concentrated iodinated contrast medium injected at high flow. In principle, CT has many advantages. It is readily accessible, inexpensive, quick and highly reproducible. It offers good spatial and temporal resolution and quantification of the tracer is straightforward as the density concentration relationship is linear (Figs. 1—3) and it also provides morphological information. Its disadvantages are well known and classic: radiation and injection of iodinated contrast. The additional radiation, however, is low and can be reduced by optimizing the acquisition settings, improving detectors and using reconstruction algorithms [25,26].

The acquisition settings vary depending on the author. As a guide, in our experience with a 64-slice instrument the acquisition settings are: 80 kV, 100 mAs, 512 × 512 square matrix, 1 second rotation time, simultaneous acquisition of eight transverse sections (8 sections per rotation), each with a thickness of 5 mm. In order to reduce radiation, the images are acquired each second for 30 seconds and then every 3 seconds up to 2 minutes. The total number of images per

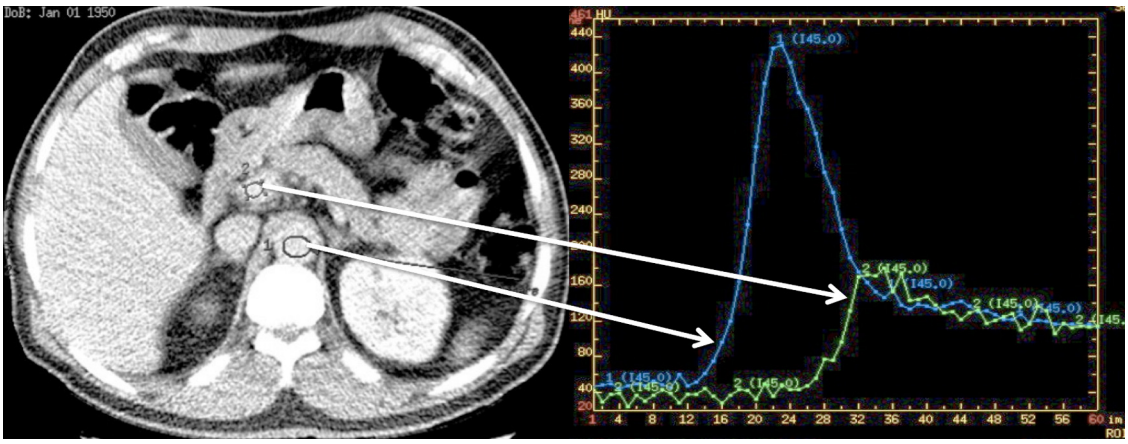


Figure 1. Example of signal to time curve obtained on CT. On the left, axial section passing through the gallbladder. The signal to time curve (image on the right) is obtained after positioning the regions of interest in the afferent vessels (aorta and portal vein). The change in tracer concentration over time is obtained by rapid signal sampling (in this case density). The perfusion parameters are extracted from an analysis of these curves.

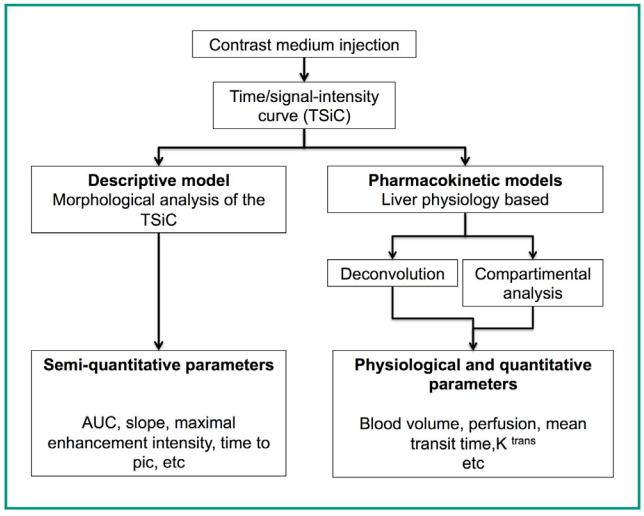


Figure 2. Diagram showing the models used to analyze the signal-time curve.

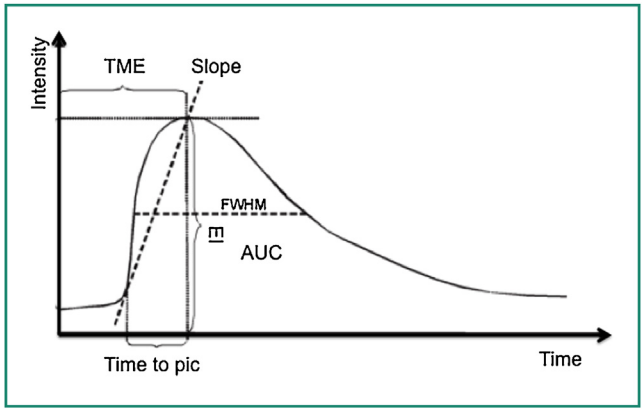


Figure 3. A display of semi-quantitative parameters obtained from a descriptive analysis of the morphological properties of the signal-time curve. EI: enhancement intensity; TTP: time to peak enhancement; AUC: area under the curve; Gradient: gradient of the entry phase; FWHM: full width at half maximum.

patient is 400 and the total acquisition time is 2 minutes. The iodinated contrast (containing 350 mg of iodine/mL) is administered as 40 mL into an antecubital vein at a rate of 4 mL/s. In order to reduce respiratory artefacts during the investigations, patients are asked to breathe slowly and superficially and are told about the possible flush sensation they may experience after the injection. The investigation takes an average total time of 15 minutes. The radiation dose delivered under these conditions is in the region of 10—15 μSv.

MRI

In 1999, Scharf et al. described a significant correlation between MRI and thermal dilution probe flow measurements in pigs using 1.0 T T1-weighted sequences [27]. MRI has good spatial and temporal resolution and does not necessitate radiation.

The most common methods used for MRI measurement of perfusion are dynamic contrast-enhanced MRI (DCE-MRI) after injection of a gadolinium chelate, arterial spin labeling and dynamic contrast susceptibility MRI (DCS-MRI) [28]. The first of these approaches is by far the most commonly used. Unlike CT, in which the tracer concentration curve over time is proportional to changes in attenuation measured in Hounsfield units, the curve is more difficult to obtain in MRI as the relationship between signal intensity and tracer concentration is not linear. Concentration is related to the relaxivity of the medium and requires measurement of T1 which can be performed using samples of increasing gadolinium concentration. Whilst most groups use conventional gadolinium chelates, some very recent studies have used liver specific contrast media and have reported similar results [29].

Finally, the sequences which are affected by molecular diffusion (diffusion MRI) are influenced by the microperfusion. This is the IVIM (intravoxel incoherent motion) model, the concept of which was initially introduced and developed by Le Bihan et al. [30] to quantitatively measure all microscopic movements which could contribute to the diffusion MRI signal. These movements in biological tissues are mostly

due to molecular diffusion of water and to microcirculation of blood in the capillary network (perfusion). The concept introduced by Le Bihan et al. was that water circulating in randomly oriented capillaries (at a voxel level) imitates random motion (''pseudodiffusion''). This leads to attenuation of the diffusion MRI signal which depends on the speed of the circulating blood and the vascular architecture. As with true molecular diffusion, the effect of pseudodiffusion on signal attenuation depends on the *b* value. The amount of signal attenuation occurring as a result of pseudodiffusion, however, is of an order of magnitude greater than molecular diffusion in tissues and, as a result, the relative contribution to the diffusion-weighted signal only becomes significant at very low *b* values, theoretically allowing the diffusion and microperfusion components to be separated. An initial experimental study showed that rats suffering from liver fibrosis had reduced in vivo ADC (apparent diffusion coefficient) values compared to controls, although that this difference disappeared ex vivo [31]. A clinical study published by Luciani et al. in patients suffering from cirrhosis compared to volunteers confirmed the fall in ADC in cirrhotic patients and showed that the restriction in diffusion which was seen was due, in large part, to changes in microperfusion components and, to a lesser extent, to a reduction in pure hepatic diffusion [32]. Several areas of research have since opened as a result of this approach, particularly in tumor imaging.

The liver: a large mobile organ

The liver is a mobile organ

Radiographic studies using fixed landmarks, radioscopy and even CT [33] have shown that the liver is an organ which moves considerably with respiration, shifting approximately 20 mm along its cranio-caudal axis, 10 mm along its antero-posterior axis and 5 mm laterally. This raises major questions for infusion imaging, the aim of which is to obtain a quantitative pixel scale assessment. Several CT and MRI techniques have been described to compensate for these movements, including respiratory monitoring when the acquisition is taken with a belt or a dedicated sequence and adjustment of images acquired manually, semi-automatically, rigidly or non-rigidly. The results obtained vary. However, comparisons between different adjustment methods have shown that the non-rigid semi-automated methods appear to be more robust [34]. Attempts to introduce image adjustment methods are currently being evaluated for ultrasound, although in most studies no method is available to correct for respiratory movements.

The liver is a large organ

Ideally, a perfusion study should examine the whole organ, although in practice the acquisition is often limited to a thick section, as in our CT protocol example. This does not raise many problems for investigations focused on tumors close to the large vessels but does raise an issue when the lesions are located in the dome, when it is very difficult to obtain acquisitions of the lesion and the portal vessels within one acquisition.

Recent CT and MRI studies have taken account of this issue. Authors of CT studies describe the use of machines with wide area coverage (128 to 320 slice) [35] or dynamic spiral techniques (Jog mode) based on a short forward and return of the table past the detectors to obtain the equivalent to wide area coverage (240 slice detectors), but using 64- or 128-slice instruments [36]. Rapid dynamic 3D sequences have been described for MRI which require a compromise to be made vis-à-vis the instrument's temporal resolution [37,38].

The reproducibility problem

The combination of variable results depending on the instruments, patient respiration problems and total liver perfusion leads to different results being obtained both between patients and in the same patient. Ng et al. [39] showed that the variation for some parameters could be as great as 75% and concluded that absolute perfusion parameters are not available and that the results obtained from perfusion data need to be interpreted, paying particular attention to the acquisition protocols and analytical methods.

A few studies have also attempted to compare the results obtained with the different imaging modalities. Lefort et al. [40] and Goetti et al. [41] compared contrast ultrasound and perfusion CT and showed a modest correlation (*r* ranged from 0.45 to 0.75).

Liver imaging applications

Detection of liver metastases

The presence of established metastases in the liver produces hemodynamic changes, with an increase in arterial perfusion and reduction in portal perfusion. These were first reported on scintigraphy and CT [5,42—44] and then confirmed in MRI [45]. However, these changes are of limited use as the tumors are already established.

Studies which show similar results for occult metastases [6,46,47] are of more interest, although these have not been confirmed in human beings. A multicentre French PHRC (hospital clinical research program) study which included over 400 patients and finished in 2012 will attempt to establish the prognostic value of perfusion indices in terms of development of liver metastases in people suffering from colonic cancer.

Tumor characterization

Perfusion has been studied mostly as an indicator in hepatocellular carcinoma (HCC), to assess tissue differentiation (Fig. 4) and to distinguish between a dysplastic nodule and HCC. The imaging appearances of HCC typically include intense arterial enhancement and a portal or late stage wash-out. Perfusion imaging shows an increase in blood volume, blood flow and permeability although a lower mean transit time compared to the adjacent liver. A relationship has been found between tumor differentiation and perfusion parameters [48,49]. In addition, because of the arterial supply to the tumor, differences in perfusion have been shown in the presence or absence of portal vein thrombosis [49].

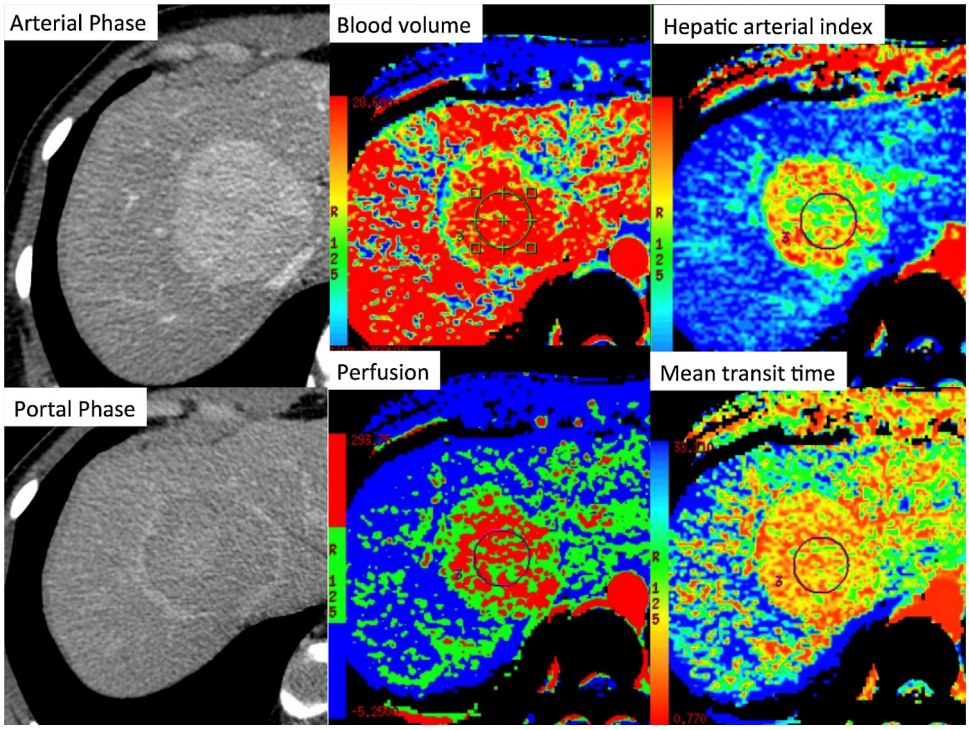


Figure 4. Hepatocellular carcinoma (HCC) in a 54-year-old patient with viral hepatitis C cirrhosis investigated by liver perfusion CT. The lesion is clearly demarcated and hypervascular with wash-out (left column). The four images on the right show four parameter charts (vascular volume, arterial index, perfusion and mean transit time). In this case, the lesion is preferentially supplied by the hepatic artery and has a greater vascular volume and perfusion than the adjacent liver. The mean transit time is prolonged, which is unusual in these tumors before treatment.

Assessing response to treatment

Locoregional therapy: the example of chemo-embolization

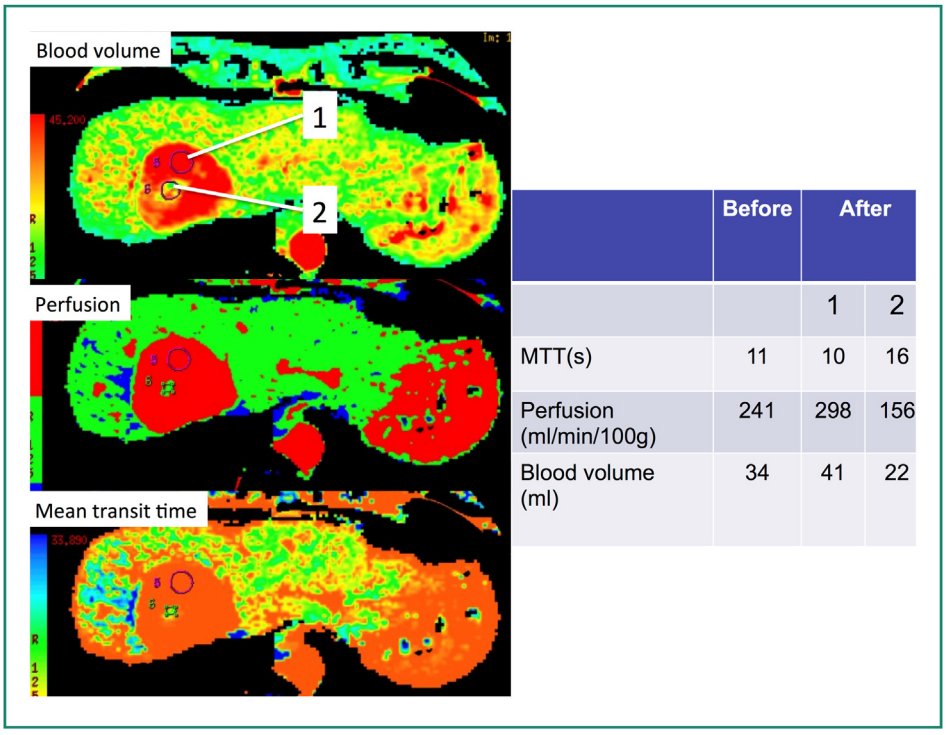
Perfusion investigations in locoregional therapies for liver tumors, particularly HCC, have little to offer in percutaneous ablation (such as radiofrequency or microwave) as the response and relapse criteria are well described and robust [50,51]. However, a study by Meijerink et al. [52] did conclude that investigation of hepatic vascular volume appeared to be useful in detecting and locating recurrences in contact with the ablation impact sites.

Many studies have been published on chemo-embolization. Results from a rabbit model have validated the use of perfusion CT [53] and MRI [54] to quantify tumor perfusion after several successive embolization sequences. More recently, Choi et al. carried out a prospective assessment of the feasibility of perfusion CT as a follow-up method after hepatic artery chemo-embolization and showed early perfusion changes (at 1 week) which were different in the treated areas compared to untreated areas. They concluded that perfusion CT is useful in assessing rapid response and in detecting tumor recurrence early, after treatment [55].

There are, however, only a few studies in human beings. Ippolito et al. examined perfusion parameters in tumor residues following treatment and showed, as Choi did in animals, differences from the successfully treated areas [56]. These findings show the direction of current research: early identification of responders and non-responders for prompt change in management. Other groups have shown perfusion changes on MRI during the procedure [57,58]. Perfusion is therefore considered to be a prognostic biomarker. Finally, Michielsen et al. studied perfusion's capacity to predict disease-free progression (DFP) in patients suffering from inoperable hepatocellular carcinoma treated with chemo-embolization and concluded that the parameters studied (area under the curve [AUC], initial slope [IS], and time to peak [TTP]) were predictive indicators for disease-free survival which were independent of the size and number of lesions. In this case, the role of the biomarker was examined as a predictive indicator of response [59].

Systemic chemotherapy and targeted therapies

This research is based on the principle of studying early perfusion changes in treated tumors, particularly in patients treated with anti-angiogenics (such as anti-VEGFR) (Figs. 5 and 6). This is an extremely interesting area, although at present there is a lack of large published series and radiopathologic correlation. Most of the published ultrasound studies are limited to descriptive analyses of changes in ultrasound enhancement curves. Lassau et al. [60,61] showed that early changes (D0 to D3) in several parameters were associated with tumor response (particularly the area under the curve and the intensity of the enhancement peak) and that some even had prognostic value in terms of disease-free progression (intensity



	Before	After	
		1	2
MTT(s)	11	10	16
Perfusion (ml/min/100g)	241	298	156
Blood volume (ml)	34	41	22

Figure 5. Hepatocellular carcinoma (HCC) in a 54-year-old patient with viral hepatitis C cirrhosis investigated by hepatic perfusion CT (same lesion as in Fig. 4) after 1 month of treatment with sorafenib. Two regions are seen within the tumor. Region 1 has similar perfusion features to those of the tumor before treatment (table on the right). Region 2 shows a fall in perfusion and vascular volume with increase in mean transit time in relation to local response to treatment.

of enhancement peak) or overall survival (area under the curve).

MRI studies based on the same analytical methods are described [62], and the first studies using Bloomley free models [63] or pharmacokinetic models [64—66] have been published. The aim of these studies was again to use perfusion as a prognostic biomarker by correlating early response with long-term survival, or as a response biomarker by demonstrating differences in the parameters before treatment in future responders compared to future non-responders, as reported in the recent study published by Hsu [66].

Chronic diffuse diseases

The development of liver fibrosis and progression of fibrosis to cirrhosis is associated with vascular and perfusion micro-architectural changes: the sinusoids are gradually converted into continuous non-fenestrated capillaries demarcated by an organized basal membrane containing laminin, with an increase in vascular resistance and fall in portal perfusion which is partly compensated by an increase in arterial perfusion (buffer effect) and later by an overall fall in perfusion. These findings have been obtained from scintigraphic studies.

In echography, the ultrasound organ transit time method showed a decreased contrast bolus arrival time (< 24 s) in cirrhosis, with a left shift in the time intensity curve due to the increased arterial supply and intrahepatic shunts. The same approach has been used to assess the severity of diffuse liver disease [67], and to distinguish between mild and moderate/severe fibrosis in patients with chronic hepatitis [68].

Miles et al. and Blomley et al. [4,5] have demonstrated the buffer effect via the gradient method in perfusion scanning and Van Beers et al. reported an increase in the arterial fraction and mean transit time in a compartmental model in a group of cirrhotic patients compared to a control group ($41 \pm 27\%$ compared to $17 \pm 16\%$ and 51 ± 79 s compared to 16 ± 5 s). They also highlighted the fall in overall perfusion compared to livers in the control group (0.67 ± 0.23 mL/min/mL compared to 1.08 ± 0.34 mL/min/mL) [69]. The increase in mean transit time was attributed to reducing mobility of the low molecular weight tracer molecules in the Disse space of the fibrotic livers, as mobility was preserved and the volumes at distribution were unchanged. More recently, we have described the use of perfusion CT to distinguish the early stages of fibrosis [70].

The MRI studies which have been published have mostly been on animal models [3,71,72], and have confirmed the earlier studies which reported similar results with albumin. There have been few MRI studies on chronic liver disease in human beings. Annet et al. described a reduction in portal perfusion and an increase in arterial perfusion and the mean transit time in established cirrhosis [73]. We have also shown changes in these parameters with progression of fibrosis before the development of cirrhosis in an unpublished study whose data have been corroborated by Hagiwara et al. [37]. No studies have been carried out in this area in the different stages of fibrosis classified in routine clinical practice by the METAVIR score.

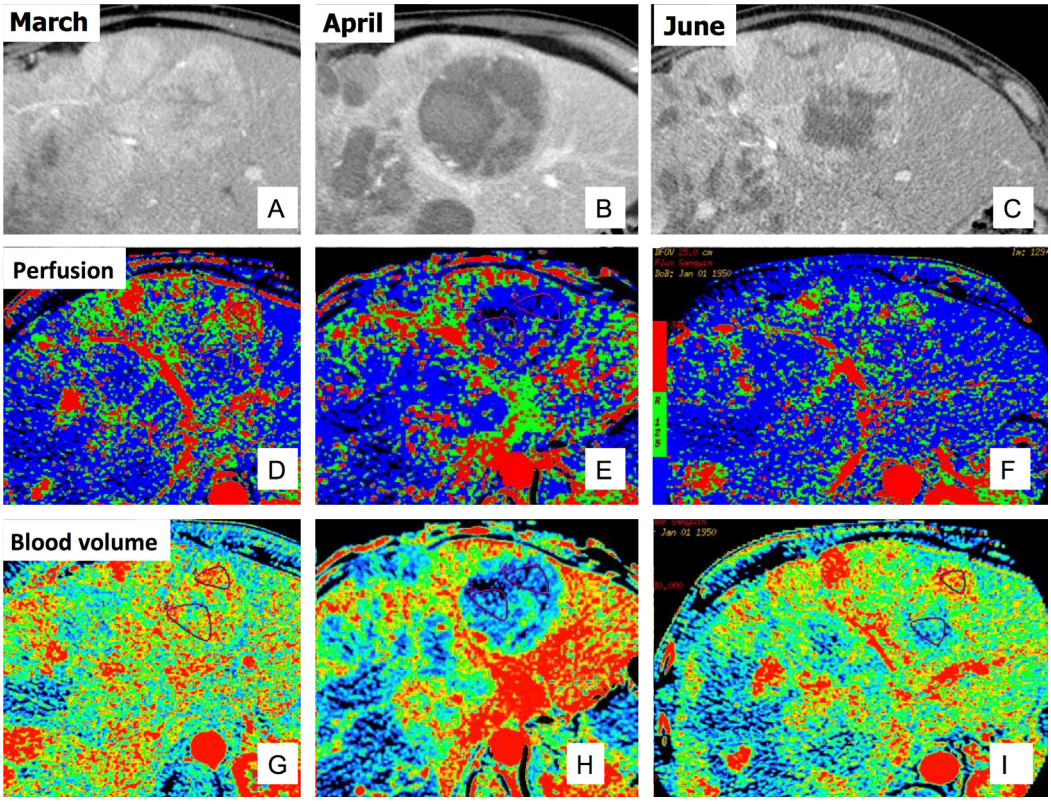


Figure 6. Infiltrating hepatocellular carcinoma (HCC) in viral hepatitis C cirrhosis treated with an anti-angiogenic (sunitinib), investigated by liver perfusion CT. The figure is read by line and column. The upper line (A—C) shows three arterial phase sections taken in March, April and June of the same year. The HCC is an infiltrating hypervascular mass. The second line (D—F) shows perfusion parameter charts voxel by voxel on the same three dates. High flow is shown in red and low flow in blue. The lower line (G—I) shows blood volume parameter charts voxel by voxel on the same three dates. High flow is shown in red and low flow in blue. The first column (A, D and G) shows the investigation before starting treatment. The middle column (B, E and H) is the investigation after starting treatment. Tumor response is reflected by necrosis, seen as a hypodense area on CT (B), and a fall in tumor perfusion (E) and tumor blood volume (H). The last column (C, F and I) shows the tumor failing to respond to treatment with further lesional growth on the periphery (C), and an increase in perfusion (F) and tumor blood volume (I).

Conclusion

Perfusion studies are a useful tool in liver imaging, although many methodological problems need to be resolved before it is implemented. Whilst the use of perfusion is currently largely limited to research, encouraging results have been published. Findings from perfusion studies, however, suffer from a lack of standardization as the models and the machines vary and the series are small and single-centred. A group effort is required to harmonize practices and incorporate perfusion into a multiparameter approach.

TAKE-HOME MESSAGES

General points
- Liver perfusion imaging is the study of descriptive quantitative parameters of liver perfusion physiology.
- The liver has a dual blood supply. Approximately 25% of total blood supply comes from the hepatic artery and the remaining 75% from the portal vein.
- The basic hypothesis on which liver perfusion imaging is based is that focal or diffuse pathological processes lead to measurable changes in these perfusion parameters.

Difficulties with modeling
- Perfusion parameters are extracted from an analysis of the signal to time curve.
- There are two major mathematical approaches to studying liver perfusion: descriptive signal to time curve methods and pharmacokinetic models.
- The descriptive approach is not based on any physiological hypothesis and is used to extract semi-quantitative parameters from the morphology of the time-signal curve (enhancement gradient, time to peak, area under the curve).
- The pharmacokinetic models incorporate the specific limitations of liver perfusion. These mostly involve deconvolution models and the compartmental approach.
- The data obtained are not independent of the model used.

Different imaging methods for studying perfusion
- Perfusion can be studied by isotopic, ultrasound, CT and MR imaging.
- Contrast agents containing microbubbles are used to quantify tissue perfusion in ultrasound.
- The three main methods used to evaluate tissue perfusion by contrast-enhanced ultrasound are measurement of the organ transit time, analysis of tissue reperfusion kinetics and analysis of the enhancement intensity curves. The last of these is the most widely used.
- The tracer used for CT is a concentrated iodinated contrast medium injected at high flow. The curve of tracer concentration against time is proportional to changes in attenuation measured in Hounsfield units (density).
- The most widely used MRI method to measure perfusion is dynamic contrast-enhanced MRI (DCE-MRI) after an injection of gadolinium chelate.
- In MRI, the intensity relationship between the signal and concentration of the tracer is non-linear although it is related to the relaxivity of the environment and requires calibration.
- The IVIM MRI model (intravoxel incoherent motion) can be used in diffusion imaging to assess the microperfusion.

Liver imaging applications
- The major indications are detection of liver metastases, characterization of tumors, assessing tumor response and studying diffuse liver disease.
- Established metastases in the liver cause hemodynamic changes, with an increase in arterial perfusion and a fall in portal perfusion. Studies to assess the role of perfusion in occult metastases are ongoing.
- In HCC, there is a relationship between tumor differentiation and perfusion parameter values.
- Studies of tumor response have mostly been carried out in HCC with the aim of using perfusion imaging as a biomarker for response or prognosis by demonstrating early changes in perfusion parameters in responders.
- In chronic liver disease, perfusion parameters change as the fibrosis progresses.
- In established cirrhosis, perfusion imaging shows a reduction in portal perfusion and an increase in arterial perfusion and the mean transit time.

Clinical case report

This 53-year-old man has chronic viral hepatitis C with histologically proven cirrhosis. A focal right posterior lesion was found on ultrasound monitoring and as a result this CT was performed (Fig. 7).

Questions

1. Based on the findings from the CT (Fig. 7), what would your diagnosis be? How would you confirm it?

A liver resection was organized and the patient was included in a clinical trial with a targeted neo-adjuvant therapeutic molecule. Perfusion imaging before beginning treatment and after starting the targeted therapy was organized as part of the trial (Fig. 8).

2. Describe the perfusion parameters of the lesion on Fig. 8.

3. Looking at the images on Fig. 8, can you tell which analytical model was used?

4. The baseline investigation (pre-treatment) showed an increase in perfusion and vascular volume and a low mean transit time. What is your conclusion on the perfusion imaging after treatment (Fig. 8)?

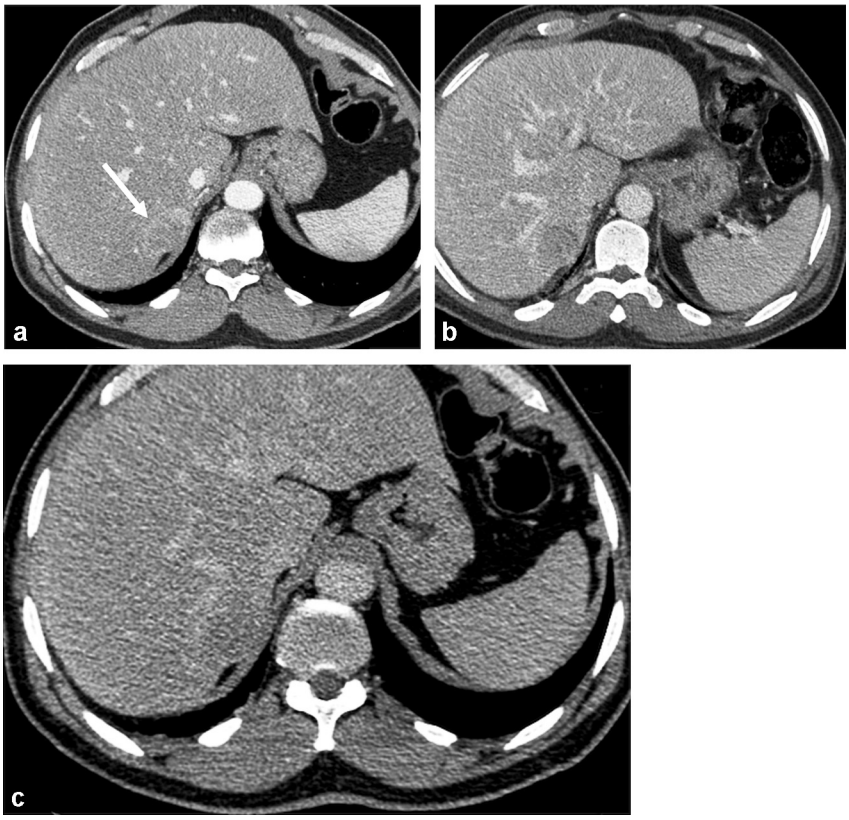


Figure 7. Abdominal CT passing through the liver after iodinated contrast enhancer injection with triphasic acquisition in the arterial (a), venous (b) and late (c) phases.

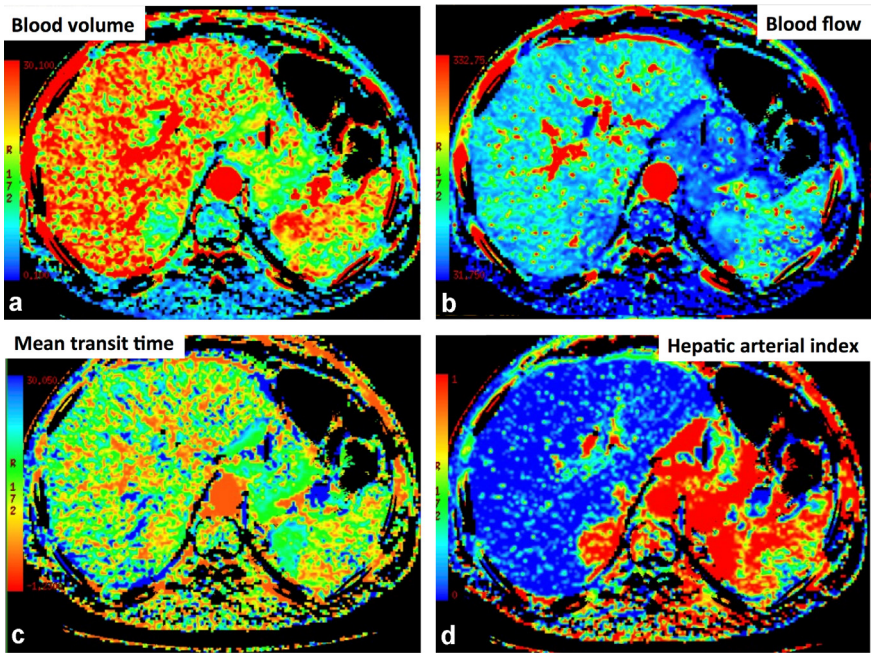


Figure 8. Perfusion CT centered on the right posterior lesion. Four parameter charts are shown: vascular volume (a), vascular flow (b), mean transit time (c), and arterial index (d).

Answers

1. The CT shows a single subcapsular lesion located in the lower part of segment VII. The lesion is hypervascular and exhibits wash-out in the late venous phase. As it has developed in the cirrhotic liver and is more than 10 mm in diameter, it meets all of the criteria for a non-invasive diagnosis of hepatocellular carcinoma and

the diagnosis therefore requires no further investigations.

2. The four images show four parameter charts: vascular volume (a), arterial blood flow (b), mean transit time (c) and arterial index (d). The lesion is supplied preferentially by the hepatic artery (d) and has a lower vascular volume and perfusion than the adjacent liver (a and b). The mean transit time is identical to that of the adjacent liver (c).

3. As the parameters shown are quantitative and based on liver physiology, this is not a descriptive analysis of the signal to time curve morphology and the model used is therefore a pharmacokinetic model. However, the parameter charts alone do not show us which specific model has been used. We can see that this model incorporates two vascular supplies (artery and portal vein) in order to calculate the arterial index (d) and that it includes a calculation of the volume of the vascular compartment. For information purposes, in this case, this is a deconvolution model.

4. By comparing the baseline investigation and Fig. 8, we can see that the lesion's volume and vascular flow have reduced and the mean transit time has increased after treatment. These appearances reflect a change in vascularization of the lesion and probably represent an early response to starting targeted therapy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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