REVIEW

Mean intensity curve on dynamic contrast-enhanced susceptibility-weighted perfusion MR imaging — review of a new parameter to differentiate intracranial tumors

Courbe d’intensité moyenne en IRM de perfusion par susceptibilité magnétique avec injection de contraste — analyse d’un nouveau paramètre pour différencier les tumeurs intracraniennes

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KEYWORDS
MRI; Brain tumors; Perfusion; DSC; Mean perfusion curve

Summary Dynamic susceptibility contrast (DSC) perfusion imaging has been in clinical use for various indications, including characterization and grading of intracranial neoplasms. However, several technical factors can lead to pitfalls in image interpretation. This review discusses the extraction of T1 and T2* information from mean curve analysis of DSC perfusion imaging of various brain tumors, which provides further insights into tumor biology and, thus, may be useful in the differential diagnosis of such tumors. Indeed, by looking at the mean time–signal intensity curve from the tumor bed in addition to the rCBV maps, it is possible to obtain further inferences of capillary density and lesion leakiness. When dynamic contrast enhanced (DCE) T1 perfusion is not available, DSC perfusion with mean curve analysis appears to be a valid alternative for characterizing various brain neoplasms in a routine clinical setting.

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Abbreviations: MPC, Mean perfusion curve; DSC PMRI, Dynamic susceptibility contrast perfusion magnetic resonance imaging; rCBV, Relative cerebral blood volume; EVL, Extravascular leakage; AVS, Arteriovenous shunt; GBM, Glioblastoma multiforme; LGG, Low-grade glioma; SI, Signal intensity; BBB, Blood–brain barrier; TDL, Tumefactive demyelination.

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Introduction

As novel therapies for patients with brain tumors are being developed, the role of imaging has begun to shift towards providing information on tumor physiology in addition to anatomy. Perfusion methods are ideally suited to such physiological imaging. Dynamic susceptibility contrast perfusion magnetic resonance imaging (DSC PMRI) is a novel technique used in the evaluation of intracranial tumors that offers a functional view of in vivo hemodynamics of normal and pathological brain tissue [1—4]. It is based on single-shot echo-planar rapid imaging of the first pass of gadolinium-based contrast through the tumor vasculature [5,6]. This review attempts to correlate patterns of the mean perfusion curve (MPC) with various intracranial tumors to understand tumor hemodynamics.

Tumor angiogenesis and role of dynamic contrast-enhanced susceptibility-weighted perfusion magnetic resonance imaging

The concept of tumor angiogenesis was first explained by Folkman [7], who showed that survival, growth and expansion of a solid tumour is highly dependent on the vascular system recruited by malignant cells. It has now been documented that malignant intracranial tumors have the ability to recruit and synthesize a vascular network for further growth and proliferation, as such a network provides a route for delivery of oxygen and glucose, and removal of metabolic waste products. Vascular morphology and degree of angiogenesis are important parameters in the evaluation of different tumor types, as they determine the biological aggressivity of the tumor. As tumor grows, its metabolic demands increase due to rapid cell growth and increased cell turnover, leading to cellular hypoglycemia and hypoxia that, in turn, lead to the production of angiogenic cytokines, resulting in neoangiogenesis [8]. Histological studies show that tumor vasculature is composed of immature vessels with large endothelial cell gaps, incomplete basement membrane and absence of smooth muscle layers [9]. Tumor vessels are also more tortuous, thus affecting the distance that blood must travel through the tumor. Thus, there is not only an increase in vessels, but also the presence of abnormal vessels that react differently to their environment and which are arranged differently from their normal counterparts.

Dynamic susceptibility contrast MRI provides non-invasive in vivo assessment of normal and diseased microvascular systems [3]. It has been proved that microvascular density is a major prognostic marker for survival in low-grade astrocytomas [10]. Various studies have cited the role of DCS PMRI in the preoperative evaluation and grading of tumors [11—17], and in the determination of recurrent/residual disease in patients with treated tumors [18]. It can also help to guide stereotactic biopsy [19—21], predict clinical response in brain tumors [22,23] and differentiate post-radiation tumor necrosis from residual/recurrent tumor [19,20,24,25]. Indeed, PMRI can replace positron emission tomography (PET) for differentiating necrosis from tumor recurrence [26], assessing tumor responses to new treatment approaches [13,14,19,23,25], predicting malignant transformation in low-grade gliomas [21,27], diagnosing tumor mimics such as demyelinating lesions [28], and differentiating between various intraventricular tumors [29], between two types of gliomatosis cerebri [30] and tubercular ring-enhancing lesions from similar-looking metastases [31]. The effect of angiogenesis on peritumoral tissue was also studied in meningiomas and glioblastomas [32]. Increased tumor vascularity does not necessarily suggest malignancy: extra-axial tumors such as meningeoma and choroid plexus papilloma can be highly vascular tumors, but with benign behaviors, whereas oligodendroglioma can show foci of high cerebral blood volume irrespective of tumor grade [11]. This suggests the importance of studying the MPC as well.

MR measurements of relative cerebral blood volume (rCBV) have been shown to correlate with both conventional angiographic assessments of tumor vascular density and histological measurements of tumor neovascularization [1,14]. It has also been confirmed that there are statistically significant correlations between rCBV and tumor grade [1,11—17]. However, as there is overlapping of rCBV measurements between different glioma grades, the rCBV map can give spurious results, especially in cases of extra-axial lesions, oligodendroglioma, pilocytic astrocytoma and lymphoma.

T2* DSC perfusion imaging is based on the first-pass bolus of intravascular contrast, which results in T2 shortening and a reduction of signal intensity (SI). Extravascular leakage (EVL) of contrast results in a T1 effect, which tends to increase the SI. Thus, the T2* effect indicates a predominant increased vascular density leading to a dip in the MPC, while the T1 effect indicates extravascular leakage, resulting in an increased SI that, in turn, leads to a rise in MPC. The relative dominance of these effects will affect the MPC accordingly: a high-grade tumor associated with increased vascular density will show a predominant T2* effect, while a low-vascular tumor with no significant EVL will demonstrate a mean perfusion curve resembling normal parenchyma and a high-vascular tumor with a significant EVL will demonstrate a T1 effect along with the T2* effect.

Many authors have suggested that rCBV measurement is useful for evaluation of tumor angiogenesis and grading [1,12,14,15], but the role of the MPC has never been stressed. In the proceedings of the ISMR 2007 meeting, different patterns of MPC in intracranial tumors were discussed and categorized into four types by Thomas et al. [33], but no study published so far in the literature has correlated the MPC pattern with various intracranial mass lesions comprehensively.

High-grade gliomas

In glioblastoma multiforme (GBM), the associated angiographic findings include a hypervascular mass with tumor blush, prominent feeding and draining vessels, arteriovenous shunts (AVS), aberrant vessels, vascular pooling, stasis and mass effect [34—36]. The MPC in GBM and other high-grade gliomas tend to have one of the following patterns:

• rapid steep fall in SI with rapid return to baseline;
Mean intensity curve to differentiate intracranial tumors

Figure 1 Four patterns of mean perfusion curve (MPC) observed in glioblastoma multiforme (GBM): (A) rapid steep fall in signal intensity (SI) with rapid return to baseline due to arteriovenous shunt; (B, C) rapid SI drop with variable recovery but not reaching baseline, depending on interactions between T1 and T2* effects of contrast; and (D) rapid SI drop with a tendency towards rapid return followed by a second, smaller dip due to recirculation.

Note: the mean perfusion curves (MPC) in continuous lines indicate in the region of interest (ROI) in the tumor, and the MPCs in dotted lines indicate in the corresponding contralateral normal tissue. The x axis shows time, while the y axis shows mean signal. Quantitative evaluation was not carried out; however, the rCBV was considered high when it was 1.5—1.8 times greater than the contralateral white matter.

- rapid steep fall in SI with a tendency to return to baseline, but not reaching it;
- rapid steep fall in SI with little tendency to return to baseline;
- rapid steep fall in SI with rapid return to baseline, immediately followed by a second, smaller dip (Fig. 1).

The first pattern can be explained by marked AVS resulting in a decreased mean transit time, leading to a rapid fall in SI. The shunt results in early contrast drainage into the veins with a rapid return of SI to baseline. Sometimes, the angiographic findings in GBM may, in fact, resemble an arteriovenous malformation (AVM) [37,38].

The second and third patterns can be explained by the degree of abnormalities such as aberrant vessels, vascular pooling and stasis. There is also a fall in SI at intravascular entry of contrast. However, intravascular pooling and stasis of contrast prevents the return of SI to baseline. In addition, a second dip has been noted in some cases of GBM that represents rapid recirculation of contrast due to AVS (Fig. 1). Peak height and SI recovery, as reflected by the MPC, have been used to differentiate between GBM and single metastases [39].

Low-grade gliomas

These gliomas (WHO grades I/II) usually show a low rCBV map and an MPC with one of the following characteristics:

- same MPC as that of normal contralateral white matter (Fig. 2B);
- moderate fall in SI with return to baseline;
- moderate fall in SI with return of SI to above baseline (as seen in mural nodules of some pilocytic astrocytomas);
- rapid fall in SI with a tendency to return to baseline, but not reaching it (in some pilocytic astrocytomas).

The lower vascularity explains the relatively smaller drop in signal with a return to baseline. In the mural nodules of some pilocytic astrocytomas, the return of SI tends to rise to above baseline secondary to a predominance of EVL over intravascular contrast. An ultrastructural study by Soto et al. [40] confirmed a defective blood–brain barrier (BBB) in mural nodules of pilocytic astrocytoma. However, some pilocytic astrocytomas resemble higher-grade gliomas, with tumor blush on angiography [37], and have been described as tumors with rich vascularity [40,41]. These show the fourth pattern due to stasis of contrast within the mural nodule, resulting in the return of SI, but without reaching baseline. Sugahara et al. [15] showed that perfusion-sensitive MR imaging findings correlated with digital subtraction angiography (DSA) findings in patients with glioma. A similar study comparing perfusion MRI and DSA in various other intracranial masses was conducted by Wetzel et al. [42]. However, both these studies considered rCBV maps and not the MPC. More recently, the MPC and perfusion pattern were well described in pilocytic astrocytoma [43].

Lymphomas

These are relatively avascular masses on angiography [34–36]. However, due to the lack of BBB, they demonstrate contrast enhancement [44]. Thus, the combined characteristics of low vascularity and EVL (T1 effect) can explain the characteristic MPC in lymphoma. These tumors also usually show a low rCBV with an MPC showing a minimal fall in SI with return to and above baseline (Fig. 3).
Figure 2  Primary CNS lymphoma with poorly defined T2 iso/hypointense lesion (A) in right thalamocapsular region showing intense homogenous contrast enhancement (B). RCBV map shows low rCBV (C). MPC shows minimal fall in SI, with return of the SI to and above the baseline due to predominant T1 effect.

or histopathology, but appear as intrinsically normal vessels with no neovascularization [45].

Enhancement in TDL correlates with the degree of macrophage infiltration and BBB breakdown. The absence of increased vascularity and the presence of EVL are responsible for the predominant T1 effect. This results in the MPC resembling that of lymphoma: a minimal fall in SI with return to and above baseline (Fig. 2A).

**Meningioma**

The characteristic angiographic appearances of these tumors include:

- increased size and tortuosity of feeding arteries and trunks;
- homogeneous and sharply margined contrast cloud;
- persistence of the contrast cloud that is most prominent during the middle-to-late venous phase;
- sluggish circulation with delayed filling of veins [34–36].

The malignant type of meningioma is characterized on angiography by the presence of AVS with early filling of veins, and tumor vessels that are usually more irregular in their course and in an arrangement with marked variations in caliber, often with small sinuses [34–36]. The rCBV in meningioma is usually high.

The MPC of meningioma may show either a rapid steep fall in SI with little tendency to return to baseline (Fig. 2C), or a rapid steep fall in SI with rapid return to baseline. The first pattern arises because of the sluggish circulation within the tumor with relative intravascular stasis. There is also marked EVL, resulting in the T1 effect, although the T2 effect still predominates. This results in a curve with little tendency to return to baseline. Such a pattern can also be observed in GBM and pilocytic astrocytoma, metastases and
Choroid plexus papilloma. Malignant meningiomas show the second pattern of MPC secondary to AVS.

Metastases

Tumor vascularity may depend on the primary malignancy. However, there is no evidence that the primary malignancy determines the vascularity of the metastatic lesion. Four patterns of abnormal vascularity have been described on angiography:

- more or less homogeneous opacification of the tumor, as with meningioma;
- many irregular vessels with AVS, a finding mimicking GBM;
- a network of thin and tortuous vessels, often in a regular arrangement;
- a ring-like appearance, with a relatively avascular central portion of tumor and a vascular periphery [34–36].

Metastatic lesions also usually show a high rCBV, and two patterns of MPC may be seen: a rapid steep fall in SI with little tendency to return to baseline (Fig. 2D); and a rapid steep fall in SI with rapid return to baseline. These patterns are similar to those observed in meningioma, and their occurrence may also be similarly explained.

Hemangioblastoma

These tumors show AVS on angiography [34–36], and are usually lesions with high rCBV. They can show: a rapid steep fall in SI with rapid return to baseline; and a rapid steep fall in SI with rapid return to baseline, followed immediately by a second, smaller dip (Fig. 4). It has also been shown that, depending on rCBV values, hemangioblastoma and pilocytic astrocytoma can be differentiated with confidence [46].

Conclusion

Intracranial tumors demonstrate relatively predictable patterns of MPC on T2* DSC PMRI. Tumor vascular dynamics and EVL are the main determinants of the MPC patterns that, along with perfusion maps and conventional cross-sectional...
Depending on the relative cerebral blood volume (rCBV) maps, intracranial masses are grossly divided into low rCBV or high rCBV lesions. In the low rCBV group, Tumefactive demyelination (A) shows poorly defined contrast enhancement. MPC from lesion shows minimal fall in signal intensity and rapid signal overshoot above the baseline. Signal recovery is the result of T₁ effect due to EVL of contrast. Low grade glioma (B) showing poor and minimal contrast enhancement, low rCBV with MPC showing SI fall and recovery just like that of contralateral white matter. In the high rCBV category, intra ventricular meningioma (C) shows well defined intense contrast enhancement, with a rapid fall in signal intensity followed by signal up shoot, but fails to reach the baseline. Intracranial metastasis (D) shows heterogenous strong contrast enhancement and high rCBV. MPC shows rapid steep fall in SI with tendency to return to the baseline, but late.

Note: In figures 2—4, the mean perfusion curve (MPC) in red indicates in the region of interest (ROI) in the tumor, and the MPC in yellow indicates the corresponding contralateral normal tissue. The x axis shows time, while the y axis shows mean signal. Quantitative evaluation was not carried out; however, the rCBV was considered high when it was 1.5—1.8 times greater than the contralateral white matter, as indicated by the color map.

imaging, can help in the characterization of intracranial tumors. However, a larger prospective and more inclusive study group is necessary to validate their usefulness as a diagnostic parameter.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.
Appendix A. Intracranial mass lesion evaluation on mean perfusion curve

![Diagram of perfusion curve with rCBV and signal recovery]

- **LOW rCBV**
  - Recovery of signal
  - Below baseline
  - Reaching baseline rapidly
  - Above baseline

- **HIGH rCBV**
  - Recovery of signal
  - Below baseline with slow recovery
  - Reaching baseline rapidly
  - Above baseline
  - Rapid second dip

<table>
<thead>
<tr>
<th>Mass Lesion Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Low-grade glioma</td>
<td>Recovery below baseline, slowly rising</td>
</tr>
<tr>
<td>Lymphoma, demyelination, low-grade glioma</td>
<td>Recovery below baseline, rapidly rising</td>
</tr>
<tr>
<td>GBM with necrosis, menigioma, metastasis, pilocytic astrocytoma</td>
<td>Recovery above baseline, slow dip</td>
</tr>
<tr>
<td>GBM with no necrosis, menigioma, metastasis, hemangioblastoma, AVM</td>
<td>Recovery above baseline, rapid second dip</td>
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<tr>
<td>Pilocytic astrocytoma, hemangioblastoma</td>
<td>Recovery above baseline</td>
</tr>
<tr>
<td>GBM, hemangioblastoma</td>
<td>Recovery above baseline</td>
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