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# Cerebral perfusion measurement in brain death with intravoxel incoherent motion imaging

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## Abstract

**Background:** The assessment of brain death can be challenging in critically ill patients, and cerebral perfusion quantification might give information on the brain tissue viability. Intravoxel incoherent motion perfusion imaging is a magnetic resonance imaging technique, which extracts perfusion information from a diffusion-weighted sequence, and provides local, microvascular perfusion assessment without contrast media injection.

**Methods:** Diffusion weighted images were acquired with 16 b-values (0–900 s/mm$^2$) in the brain in two patients with cerebral death, confirmed by clinical assessment and evolution, as well as in two age-matched healthy subjects. The intravoxel incoherent motion perfusion fraction maps were obtained by fitting the bi-exponential signal equation model. 8 regions of interest were drawn blindly in the brain neocortex (in the frontal, temporal, parietal, and occipital lobes on both sides) and perfusion fractions were compared between patients with cerebral death and healthy control. Statistical significance was assessed using two-sided Wilcoxon signed rank test, and set to $\alpha < 0.05$.

**Results:** Intravoxel incoherent motion (IVIM) perfusion fraction was vanishing in the brain of the two patients with cerebral brain death compared to the healthy controls. Mean (± standard deviation) cortex perfusion fraction was $0.016 \pm 0.005$ respectively $0.005 \pm 0.008$ in the cerebral death patients, compared to respectively $0.052 \pm 0.021$ ($p = 0.02$) and $0.071 \pm 0.042$ ($p = 0.008$) in the age-matched controls.

**Conclusion:** Intravoxel incoherent motion perfusion imaging is a promising tool to assess local brain tissue viability in critically ill patients.

**Keywords:** Perfusion, IVIM, Brain, Cerebral death

## Background

The diagnosis of brain death, as adopted by most countries, is based on clinical criteria that include coma, absence of brain-stem reflexes, and apnea [1]. Nevertheless, additional non-invasive quantitative methods to assess brain tissue viability are of interest, in particular in critically ill patients under anesthesia, in whom clinical assessment is difficult. In this context, perfusion imaging is of particular interest [2].

Intravoxel Incoherent Motion (IVIM) MR perfusion imaging [3] is a method that extracts perfusion information (using a bi-exponential signal equation model) from diffusion-weighted images acquired at multiple b-values, including low b-values < 200 s/mm$^2$ (which is the threshold under which perfusion effects are the most prominent). The percentage of "diffusion signal" arising from the microvascular compartment is called the perfusion fraction f, and should be understood as an "effective" cerebral blood volume (in the sense of participating to the "diffusion signal"). While the method can be seen as technically challenging, improvements in hardware and pulse sequences have caused a regain in interest in IVIM perfusion imaging in recent years [4], in particular in the brain [5], mainly because it permits to obtain local cerebral perfusion information without intravenous contrast injection. We applied the IVIM perfusion method in two cases of cerebral brain death, and compared the

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results to two healthy age-matched controls, as well as to the conventional Dynamic Susceptibility Contrast (DSC) perfusion imaging.

## Methods

### IVIM and DSC sequence parameters

A monopolar diffusion-weighted spin-echo EPI sequence was acquired with 16 b-values (0, 10, 20, 40, 80, 110, 140, 170, 200, 300, 400, 500, 600, 700, 800, 900 s/mm$^2$) in 3 orthogonal directions, from which the trace was calculated. Further acquisition parameters were TR 4000 ms, TE 99 ms, in-plane resolution 1.2x1.2 mm$^2$, slice thickness 4 mm, parallel imaging acceleration factor 2, 75 % partial Fourier encoding, receiver bandwidth 1086 Hz/pixel. Total acquisition time was 3 min 7 s. IVIM perfusion fraction maps were obtained as previously described [6]. DSC acquisition parameters were: TR/TE = 1950/43 ms; voxel size 1.8 x 1.8 x 6 mm$^3$); injection dose 0.2 mL/kg; injection rate 3 mL/s.

### Quantitative perfusion fraction assessment in cortical regions

Standardized regions of interest of 1 cm$^3$ were placed blindly by an experienced neuroradiologist on the b0 images, in frontal, temporal, partial, occipital cortex, bilaterally, in the patients and aged matched healthy controls. Statistical significance was assessed using two-sided Wilcoxon signed rank test, and set to $\alpha < 0.05$. Ethic committee approval of the Canton de Vaud, Switzerland, has been obtained for this study.

### Patient 1

This 52-year-old patient was transferred from an outside hospital to our emergency department after swallowing 10 g of aconite root extract in suicidal attempt. Starting during the transfer and for 12 h following hospitalization, the patient had multiple episodes of tachycardia and ventricular fibrillation that were treated with multiple electric cardioversions and cardiac massages. A treatment with an intravenous fat emulsion was attempted, with the rational that the structure of aconitine resembles local anesthetics. On hospital day 2, the patient returned to sinus rhythm, but developed acute renal failure, probably on tubular necrosis following the multiple cardiac arrests. The neurologic evolution was unfavorable. The patient never regained consciousness and developed progressively bilateral mydriasis. On hospital day 5, an MRI with IVIM was obtained. On hospital day 7, a clinical examination confirmed cerebral death. External support was withdrawn and his viable organs donated to other patients.

### Patient 2

This 7 month-old patient, without history of any known disease, was found with a blue skin tone on the back without spontaneous respiration, 20 min after being seen sleeping normally. Cardiac massage was started immediately and the patient was transferred to our institution. The patient received a total of 600 μg adrenaline intraosseously, and normal cardiac rhythm was re-established 45 min after the start of the reanimation. On neurological examination, the patient presented with a non-reactive bilateral mydriasis, no spontaneous movements and no brain stem reflexes. Images were obtained the day of the admission. The patient presented with multi-organ failure the day after admission, and died.

## Results

### Patient 1

The MRI obtained demonstrated a diffuse brain edema, bilateral necrotic pallidi and severe swelling of the brain stem and cerebellum, with compression of the mesencephalon and tonsillar herniation through the foramen magnum (Fig. 1a and b). DSC imaging demonstrated a lack of brain perfusion, but preserved perfusion of the scalp, which belongs to the external carotid artery territory (Fig. 1c). Similarly, IVIM perfusion imaging demonstrates no brain perfusion, and similarly to dynamic susceptibility contrast, preserved perfusion of the scalp (Fig. 2). There is some limited residual IVIM signal visible in some posterolateral sulci, which arise probably from incoherent motion of cerebrospinal fluid induced by scanner vibration. Mean (± standard deviation) cortex perfusion fraction in the 8 cortical regions of interest was 0.016 ± 0.005, compared to 0.052 ± 0.021 in the aged-matched healthy ($p = 0.02$).

### Patient 2

The MRI showed a diffusely edematous brain, with compression of the brain stem, and herniation through the foramen magnum, with no brain perfusion visible with DSC (Fig. 3). The absence of brain perfusion is well seem on IVIM as well (Fig. 4), and interestingly in this patient, the conserved scalp perfusion is better visible on IVIM compared to DSC, which might be due to slow flow. Mean (± standard deviation) cortex perfusion fraction was 0.005 ± 0.008, compared to 0.071 ± 0.042 in the aged-matched healthy ($p = 0.008$).

## Discussion

In these two patients with cerebral brain death, we showed that IVIM could demonstrate lack of cerebral perfusion similarly to DSC. The demonstration of a lack of cerebral circulation can be used as a marker of cerebral death, in addition to neurologic examination. Although cerebral angiography is considered the standard method, CT-angiography [7] and CT perfusion [2] have

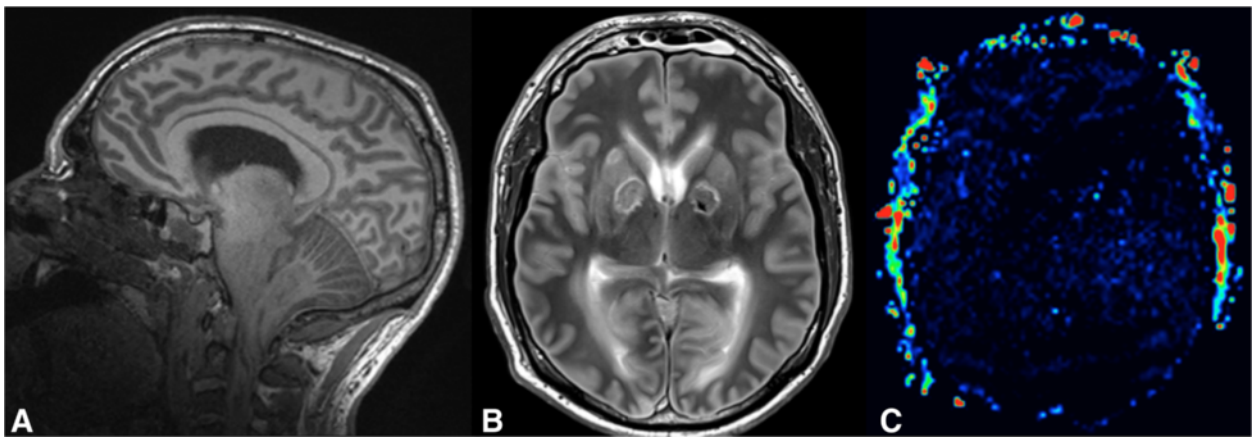


**Fig. 1** Patient 1. **a** Sagittal T1-weigthed images demonstrating severe cerebellar edema with brainstem compression and foramen magnum herniation. **b** The T2-weighted axial brain slice shows bilateral basal ganglia necrosis. **c** The dynamic susceptibility contrast MRI cerebral blood volume map shows a lack of brain perfusion, but preserved perfusion of the scalp, which belongs to the perfusion territory of the external carotid artery

also been proposed. IVIM might be of additional interest, because it generates essentially local perfusion maps of microvascular origin, (i.e. from the incoherent motion of blood due to it passage through the microvasculature), therefore using a different paradigm than inflow techniques such as arterial spin labeling or DSC MRI. In other words, IVIM might add complementary perfusion information to currently used perfusion technics. IVIM might add perfusion information of particular interest in the context of slow flow, which may be particularly relevant in cases of brain death, but also, importantly, in the assessment of acute stroke [8, 9].

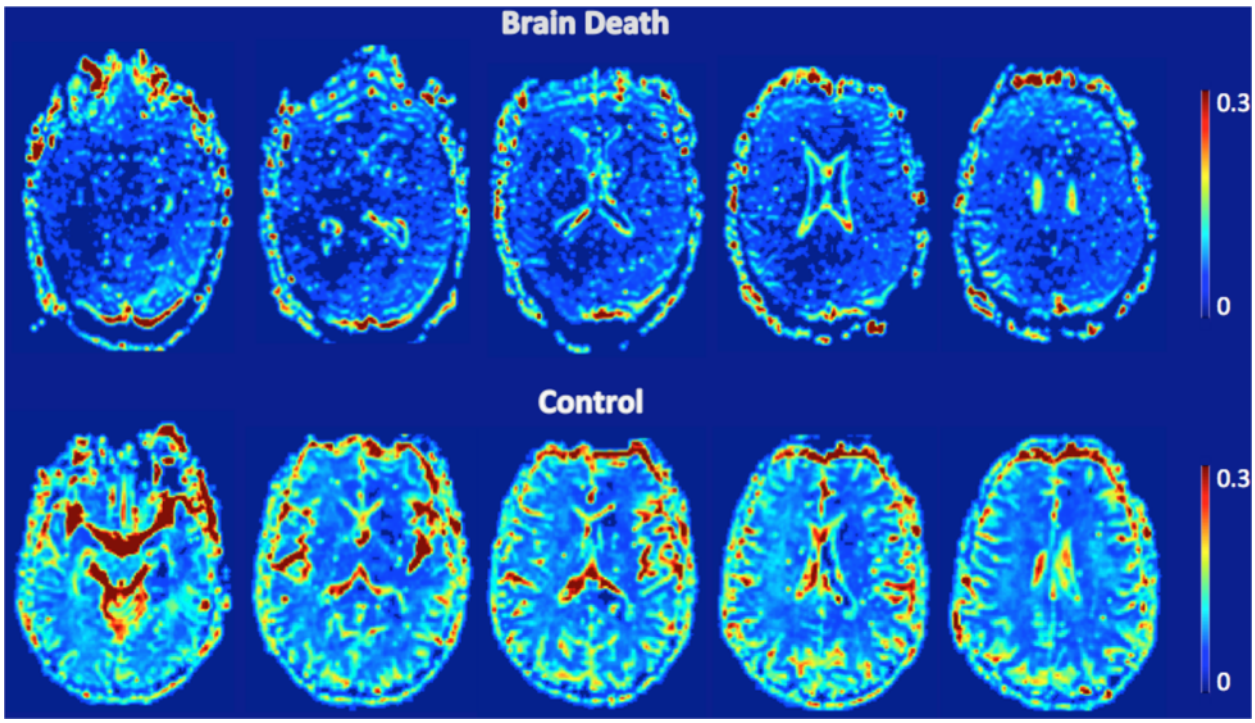


**Fig. 2** Patient 1. IVIM perfusion fraction color maps (colorbar unitless), showing a lack of brain perfusion, but preserved perfusion of the scalp, which belongs to the perfusion territory of the external carotid artery. The lower row shows the normal IVIM perfusion fraction in a 25-year-old healthy control

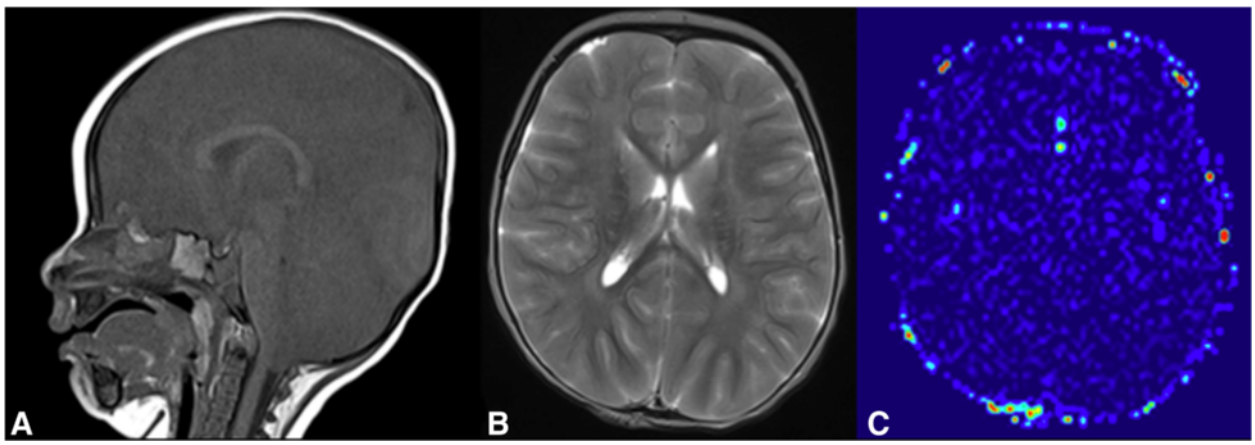


**Fig. 3** Patient 2. **a** Sagittal T1-weigthed images demonstrating severe brain edema, compression of the brain stem, and foramen magnum herniation. **b** T2-weighted axial brain slice showing edematous brain tissue. **c** The dynamic susceptibility contrast MRI cerebral blood volume map shows a lack of brain perfusion. The perfusion of the scalp is less well visible compared to patient 1, as well as compared to the IVIM perfusion maps visible on Fig. 4

In addition, no exogenous contrast agent is required with IVIM, and can therefore be used without concerns in critically ill patients, who often have impaired renal function. Nevertheless, the production of high quality IVIM brain perfusion images remains challenging, because the relatively low cerebral perfusion fraction in the brain requires high signal-to-noise-ratio of the raw diffusion-weighted images. In addition, images can be degraded by cerebrospinal fluid pulsations [10], susceptibility artefacts, or the dependence of the IVIM parameters on the cardiac cycle [11].

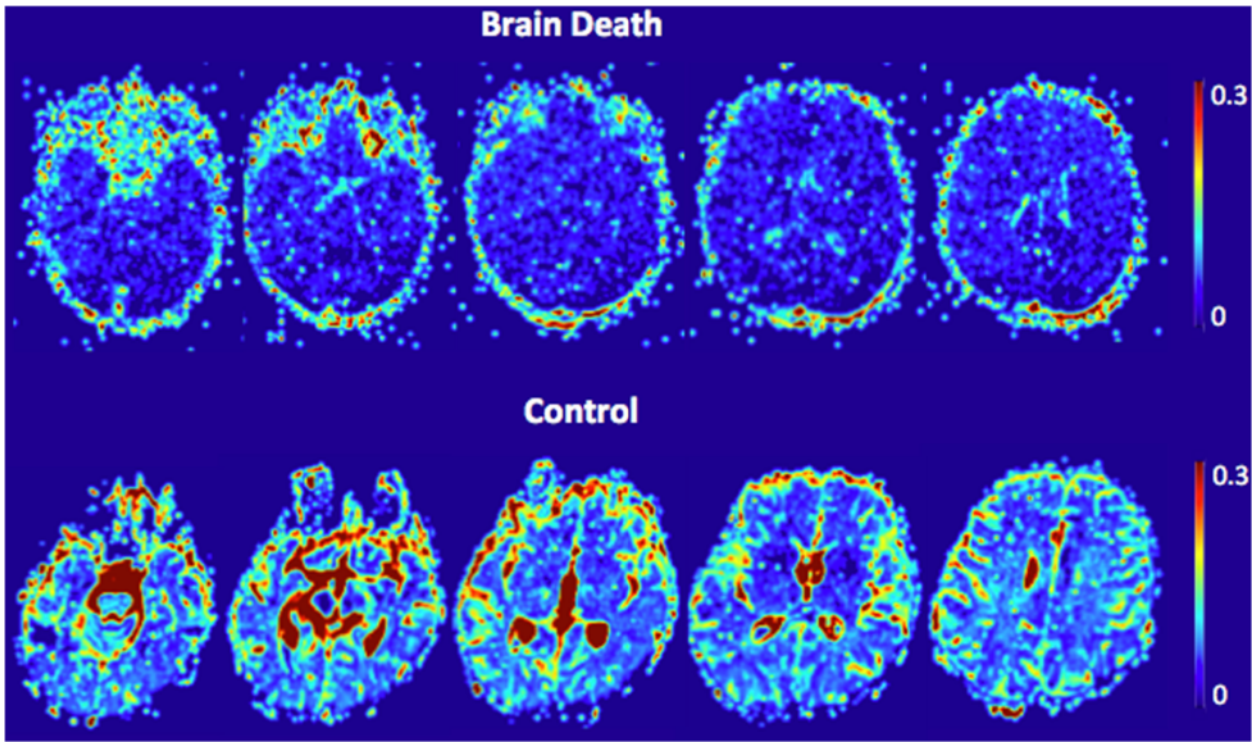


**Fig. 4** Patient 2. IVIM perfusion fraction color maps (colorbar unitless), showing a lack of brain perfusion, but preserved perfusion of the scalp, which is better visible than on the DSC belongs to the perfusion territory of the external carotid artery. The lower row shows the normal IVIM perfusion fraction in a 1-year-old healthy control

## Conclusion

This report demonstrates that global brain viability can be probed using IVIM perfusion MRI.

## Consent

Patient consent was waived by the ethical committee.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

CF acquired the data, reconstructed the images, analyzed the data, and wrote the manuscript. AN participated in images reconstruction and edited the manuscript. SC participated in data analysis and edited the manuscript. LS and MW participated in the design and coordination of the study. All authors read and approved the final manuscript.

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### References

1. Wijdicks EF. The diagnosis of brain death. N Engl J Med. 2001;344(16):1215–21. doi: 10.1056/NEJM200104193441606. [published Online First: Epub Date]|.
2. Shankar JJ, Vandorpe R. CT perfusion for confirmation of brain death. AJNR Am J Neuroradiol. 2013;34(6):1175–9. doi: 10.3174/ajnr.A3376. [published Online First: Epub Date]|.
3. Le Bihan D, Breton E, Lallemand D, et al. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology. 1988; 168(2):497–505. doi: 10.1148/radiology.168.2.3393671. [published Online First: Epub Date]|.
4. Iima M, Le Bihan D. Clinical Intravoxel Incoherent Motion and Diffusion MR Imaging: Past, Present, and Future. Radiology. 2016;278(1):13–32. doi: 10.1148/radiol.2015150244. [published Online First: Epub Date]|.
5. Federau C, O'Brien K, Meuli R, et al. Measuring brain perfusion with intravoxel incoherent motion (IVIM): initial clinical experience. J Magnetic Resonance Imaging. 2014;39(3):624–32. doi: 10.1002/jmri.24195. [published Online First: Epub Date]|.
6. Federau C, Maeder P, O'Brien K, et al. Quantitative measurement of brain perfusion with intravoxel incoherent motion MR imaging. Radiology. 2012; 265(3):874–81. doi: 10.1148/radiol.12120584. [published Online First: Epub Date]|.
7. Frampas E, Videcoq M, de Kerviler E, et al. CT angiography for brain death diagnosis. AJNR Am J Neuroradiol. 2009;30(8):1566–70. doi: 10.3174/ajnr.A1614. [published Online First: Epub Date]|.
8. Federau C, Sumer S, Becce F, et al. Intravoxel incoherent motion perfusion imaging in acute stroke: initial clinical experience. Neuroradiology. 2014;56(8): 629–35. doi: 10.1007/s00234-014-1370-y. [published Online First: Epub Date]|.
9. Suo S, Cao M, Zhu W, et al. Stroke assessment with intravoxel incoherent motion diffusion-weighted MRI. NMR Biomed. 2016;29(3):320–8. doi: 10.1002/nbm.3467. [published Online First: Epub Date].
10. Federau C, O'Brien K. Increased brain perfusion contrast with T(2)-prepared intravoxel incoherent motion (T2prep IVIM) MRI. NMR Biomed. 2015;28(1):9–16. doi: 10.1002/nbm.3223. [published Online First: Epub Date]|.
11. Federau C, Hagmann P, Maeder P, et al. Dependence of brain intravoxel incoherent motion perfusion parameters on the cardiac cycle. PLoS One. 2013;8(8):e72856. doi: 10.1371/journal.pone.0072856. [published Online First: Epub Date]|.