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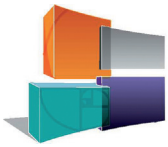

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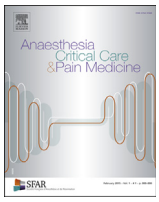

Editorial

Consider brain perfusion imaging rather than just the delay from symptoms onset to indicate reperfusion strategies after stroke: Implications for perioperative care☆

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Brain infraction (BI) results from the occlusion of a cerebral artery. Downstream of this occlusion, brain tissue may evolve into necrosis, or to a reversible state defined by an impaired neuronal function, the ischemic penumbra. The ischemic penumbra may recover if an acute revascularisation of the occluded vessel is performed or progress into necrosis if the vessel stays occluded. Over the past 25 years, revascularisation treatments using thrombolysis with recombinant tissue plasminogen activator (rtPA), and more recently mechanical thrombectomy (MT), have demonstrated their efficacy to improve the rate of functional recovery after an acute BI, and both became standard treatments. Over the past 10 years, the development of automated software has allowed physicians to assess the presence of salvageable penumbra, independently of the delay from BI onset. Imaging selection has been, until last year, limited to non-contrast computed tomography (CT) scan and CT angiography. Based on this imaging selection, thrombolysis was recommended up to 4.5 hours and MT up to 6 hours after stroke onset. In 2018, two randomised controlled trials demonstrated the benefit of MT up to 16 (DEFUSE-3 study) [1] and even 24 hours (DAWN study) [2] after onset in selected patients. Selection criteria were based on the presence of a salvageable penumbra on multimodal imaging: diffusion-perfusion weighted magnetic resonance imaging (DWI-PWI MRI) or CT perfusion.

In a recent randomised controlled trial (EXTEND study) [3], the potential benefit of late thrombolysis (between 4.5 and 9 hours) guided by brain perfusion imaging (CT scan or MRI) was tested. The hypothesis was a 15% increase in good neurological outcome, defined by a modified Rankin scale at 90 day of 0 (no symptom) or 1 (no significant disability despite symptoms; patient able to carry out all usual duties and activities) in the intervention group (rtPA 0.9 mg/kg between 4.5 to 9 hours) vs. placebo. Patients were considered for inclusion if they presented an ischemic stroke of moderate severity (National Institutes of Health Stroke Scale between 4 to 26 at admission) from 4.5 to 9 hours from onset, and hypo-perfused but salvageable region on initial imaging (CT perfusion scan or perfusion-diffusion MRI). In case of unknown time of onset (stroke during sleep), the inclusion was possible if within 9 hours from the midpoint of sleep. Three hundred and twenty inclusions were planned, but the study was prematurely stopped after 225 inclusions due to the concomitant publication of the WAKE UP study [4]. WAKE UP used a DWI/FLAIR mismatch to identify patients experiencing a wake-statistical up stroke evolving for less than 4.5 hours. In EXTEND, inclusion was possible in case of wake-up stroke within 9 hours from the midpoint of sleep, and persistent salvageable penumbra on perfusion imaging. Interestingly, in this study, more than 60% of the inclusion was wake-up stroke. In the intervention group (rtPA), good neurological outcome was significantly more frequent than in the placebo group (35 vs 29.5%, $P = 0.04$). Mortality at day 90 was similar between groups (11.5 vs 8.9%, $P = 0.53$). Symptomatic intracranial haemorrhage within 36 hours after thrombolysis tends to be more frequent in the rtPA group without reaching statistical significance (6.2 vs 0.9%, $P = 0.07$).

In addition, the same month, the Lancet published the results of a meta-analysis of 3 randomised controlled studies (EXTEND, EPITHET and ECASS 4) using multimodal imaging at enrollment, but with a different mismatch definition [5]. The results of this meta-analysis confirmed the benefit of rtPA in comparison to the best medical treatment in the subgroup of patients who did have a significant penumbra on multimodal imaging, while this benefit was not observed in the one who did not.

These new data have major implications for the anaesthesiologist and critical care physicians. The overall incidence of perioperative stroke after general surgery is less than 1%, but can reach 10% after cardiac valve surgery or carotid endarterectomy [6,7]. Perioperative strokes are mainly ischemic from embolic origin [8] and their management is often challenging [9]. The exact time from onset is often unknown, as stroke can occur during surgery and general anaesthesia, under sedation in intensive care

☆ Comments on: Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. N Engl J Med 2019;380:1795–803 and Campbell BC V, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, et al. Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. Lancet 2019. doi:10.1016/S0140-6736(19)31053-0.

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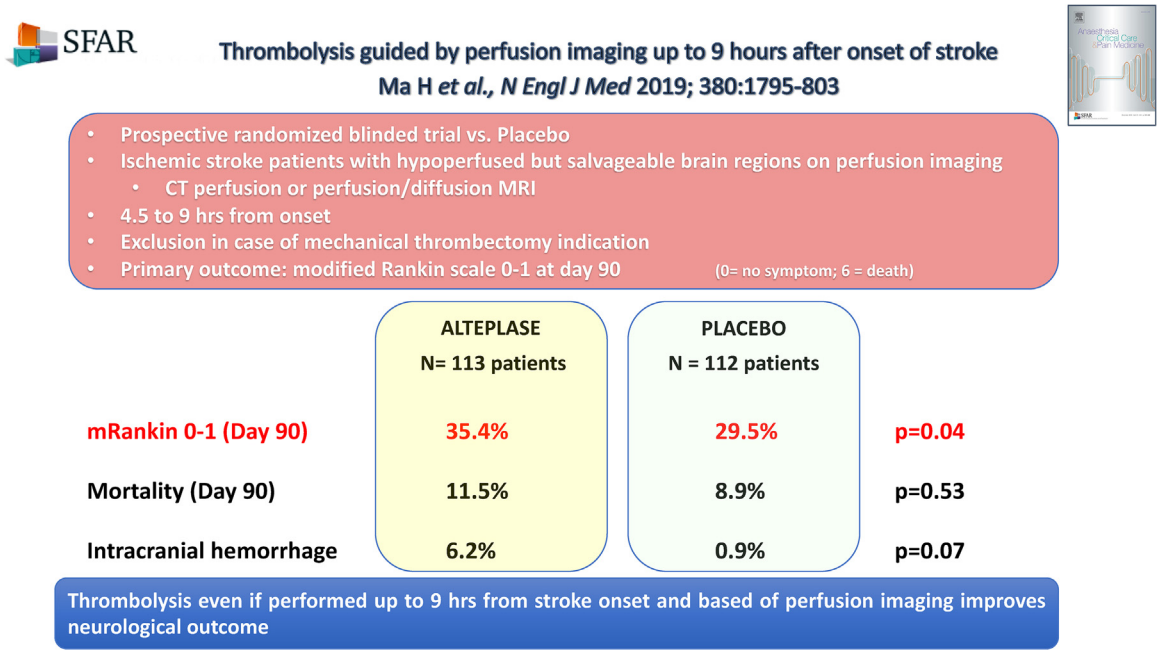

Fig. 1.

unit or during sleep. Stroke recognition can be delayed due to confounding factors, such as difficult neurological examination in the recovery room after general anaesthesia. Perioperative stroke is associated with infrequent interventions, and significant rate of morbidity and mortality [10]. Reperfusion strategies are often not performed due to excessive delay when considering the "historical" cut-off of 4.5 hours for thrombolysis and 6 hours for mechanical thrombectomy. Moreover, haemorrhagic complications are often feared in the postoperative period. A recent cohort study found an incidence on surgical site haemorrhage after thrombolysis for postoperative stroke of 4.2% after minor surgery [11]. If thrombolysis is administrated very early in the postoperative period (within 24 hours), the incidence of surgical bleeding can reach up to 25%, although most of them were considered as minor [12]. rtPA is therefore considered to be contra-indicated in case of major surgery in the early postoperative period, and patients are more likely to receive MT if indicated. Considering brain perfusion imaging rather than the sole delay from clinical symptoms onset it is probably of major interest to select patients who could benefit from reperfusion strategies (thrombolysis or mechanical thrombectomy) and to better estimate the benefit/risk ratio of thrombolysis in the postoperative period. Perfusion imaging should be used in case of postoperative stroke to quantify the salvageable brain and indicate the best reperfusion possibilities (thrombolysis if possible (minor surgery), and/or mechanical thrombectomy in case of proximal arterial occlusion). As "time is brain", reperfusion strategies should obviously be considered as early as possible. Anaesthesiologist and critical care physicians should however be aware that reperfusion can be performed up to 9 hours for thrombolysis and 24 hours for mechanical thrombectomy based on perfusion imaging to improve neurological outcome (Fig. 1).

1. How to select patient who could benefit from reperfusion strategies?

EXTEND, DEFUSE-3 and DAWN studies used the same software (RAPID) to estimate hypoperfused but salvageable brain regions.

Table 1
Mismatch definition in EXTEND [3], DEFUSE-3 [1] and DAWN [2] studies.

	Delay	CORE volume	Mismatch definition
EXTEND	4.5–9h from onset If wake-up stroke, possible if within 9 h from the midpoint of sleep	< 70 mL	Mismatch Volume > 10 mL Ratio > 1.2
DEFUSE 3	Wake-up 6–16h	< 70 mL	Mismatch Volume > 15 mL Ratio > 1.8
DAWN	Wake-up 6–24h	< 50 mL < 30 mL < 20 mL	NIHSS > 20 NIHSS > 10 if age > or = 80 year.

Abbreviation: NIHSS: National Institutes of Health Stroke Scale.

The critical hypoperfusion was defined as a time to maximum threshold of more than 6 sec with perfusion CT or MRI. The ischemic core was defined by a relative cerebral blood flow (CBF) of less than 30% of normal CBF for CT perfusion, or by an apparent diffusion coefficient of less than 620 μmÇ/sec for DWI MRI. The presence of penumbra was then estimated by the mismatch ratio and volume between critical hypoperfusion and core lesion volume. The DAWN study used the mismatch between the core size and the neurological deficit assessed by the NIH stroke scale. Finally DAWN and DEFUSE-3 only enrolled patients with proximal internal carotid/middle cerebral artery occlusion. The Table 1 summarises delays, core volumes and mismatch definitions used in these studies.

Disclosure of interest

Thomas Geeraerts, Ségolène Mrozek and Clément Monet declare that they have no conflict of interest. Jean-Marc Olivot has received speaker fees Boehringer Ingelheim, Bristol Myers Squibb, and consulting for Medtronic, Astra-Zeneca. The other authors declare that they have no competing interest.

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Thomas Geeraerts[a,*], Ségolène Mrozek[a], Clément Monet[b], Jean-Marc Olivot[c]

[a]*Anaesthesiology and Critical Care Department, University Hospital of Toulouse, University Toulouse 3-Paul Sabatier, Toulouse, France*

[b]*Intensive Care Unit and Anaesthesiology Department, University of Montpellier Saint-Eloi Hospital, Montpellier, France*

[c]*Neurology Department, University Hospital of Toulouse, University Toulouse 3-Paul Sabatier, Toulouse, France*

[*]Corresponding author at: Coordination d'anesthésie, CHU Toulouse, Hôpital Pierre Paul Riquet, 31059 Toulouse cedex 9, France
E-mail address: geeraerts.t@chu-toulouse.fr (T. Geeraerts).