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INVITED COMMENTARY

Incremental Versus Immediate Induction of Hypertension in the Treatment of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage: Invited Commentary

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In the context of cerebrovascular accidents, subarachnoid hemorrhage is a less frequent, but very often dramatic, occurrence that mainly affects young and productive-age patients. It is a complex disease that the clinician tends to delegate, in most cases, to a specialist environment. It is a complex pathology with various types of complications: cerebral and systemic, early and late. The precocious ones can be strictly cerebral, can be grouped in the concept of early brain injury, and can include endothelial damage, vasospasm, microspasm, alteration of the blood–brain barrier, hydrocephalus. They can also be systemic, such as in the stress cardiomyopathy of Takotsubo or the neurogenic pulmonar edema. Among the later complications, cerebral conditions fall within a symptom complex called delay cerebral ischemia (DCI), which can include phenomena such as spreading depolarization, cerebral tissue oxygenation deficits, and cerebral infarction. The treatment of this pathologic condition is greatly influenced by the health resources available, and only in a relatively few centers in the world is it possible to diagnose and treat these complications in the best possible way, beyond the initial golden hour and interventional treatment. In settings in which complications are not promptly diagnosed and treated, patients die or have a much worse outcome.

The new article written by Michael Veldeman et al. [1] focuses on the treatment of DCI. In the two previous articles, from the same series collected in 8 years, the same authors were able to establish that the introduction of neuromonitoring for the treatment of DCI can improve outcome at 12 months and also reduces the number of tomography scans and cerebral infarcts [2].

Once DCI is diagnosed, induced arterial hypertension is one of the few tools, with level B evidence in most of the guidelines, is supported almost exclusively by observational studies.

This study compares two modalities of induction of hypertension: incremental and immediate, on the onset of symptoms. However, induced systemic hypertension is not without cerebral and systemic side effects. There are no guidelines on the timing in which to undertake induced hypertension, the drugs to be used, and how to define a patient's refractory to treatment. There is a lot of heterogeneity in the literature on application protocols. This study seeks to define the efficacy and complications of hypertensive treatment.

Raising blood pressure of a patient in an intensive care unit is not a standard method; every intensivist, in most cases, tries to do exactly the opposite or, at most, in shock conditions, is forced to use drugs to maintain pressure at physiological levels. Stroke is one of the few cases in which hypertension represents a cure, a therapeutic goal.

But how do you diagnose DCI? The great difficulty in a critically ill patient in intensive care is caused by the state of consciousness. Usually, after an initial wake up test, the physician decides whether to continue to sedate the patient. If the patient is neurologically "explorable," the onset of new focal neurologic deficit or a decrease in Glasgow Coma Scale of ≥ 2 for at least 1 h, not ascribable to other diagnoses, is defined as DCI. If, on the other hand, the patient remains sedated, and therefore "not

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explorable," multimodal neuromonitoring is necessary: a complex of diagnostic technologies, such as computer tomography (CT) perfusion scan, tissue brain oxygenation ($PtO_2 < 10$ mm Hg), transcranial Doppler, and microdialysis (lactate/pyruvate ratio ≥ 40). Honestly, not even in the hub center where I work are all these technologies available or put together, and the analysis of the data extracted, if any, are not of univocal interpretation.

Therefore, there is a space, a time, between the clinical/instrumental manifestation of DCI and its irreversible radiological consequence: the DCI infarction (new region of hypodensity on CT imaging).

Once the DCI alarm bell is triggered, the clinician activates the treatment considered effective: induced euvolemic arterial hypertension by means of intravenous norepinephrine. Unlike previous studies, which compared populations of patients treated with induced hypertension and without induced hypertension [3], this study compares the two different ways of inducing hypertension. In the incremental treatment group, systolic blood pressure goals were raised in 20–mm Hg increments. In case no improvement of clinical, radiological, or invasively detected DCI was observed, the systolic pressure goal was increased by 20 mm Hg. This process was repeated until a systolic pressure above 180 mm Hg was considered necessary.

In the immediate elevation group, the systolic blood pressure was immediately raised to reach systolic levels above 180 mm Hg. At this point, the patients without clinical or radiological improvement during hypertensive treatment, persisting brain hypoxia, or anaerobic metabolism as measured in invasive monitoring were considered for endovascular rescue treatment.

If symptoms reoccurred during weaning, norepinephrine was restarted. But is 180 mm Hg a default target? In both treatment groups, further pressure augmentation above 200 mm Hg was considered if DCI symptoms persisted under systolic pressures more than 180 mm Hg, but only in the absences of hypertension induced complications.

In the study results, in the incremental treated group, 37.8% of patients remained refractory to hypertensive treatment compared with 53.9% of patients in the immediate treatment group ($p = 0.094$). Thus, there are fewer refractory patients in the incremental group than in the immediate group. Complications were comparable in the two groups. Favorable outcome was reached in 43.1% of patients in the immediate versus 27.0% of patients in the incremental treatment group ($p = 0.076$), but only age and Hunt and Hess grading were identified as an independent predictor variable of clinical outcome.

The interesting thing about this article is that none of the study's aims have been proven: the type of hypertension induced in this study was not independently associated with the occurrence of a DCI-related infarction, nor with the favorable outcome rate or with the need for an endovascular rescue treatment.

This study includes some limitations: the main sources of anticipated bias are the lack of randomization and selection bias that is introduced by the per preference treatment allocation. Furthermore, of the population examined with DCI, only 139 entered the study, and the two groups are numerically inhomogeneous: 37 with incremental management versus 102 immediately induced to hypertension.

In light of these results, in addition to accepting the challenge for a larger multicenter study, we believe it is useful for the clinician to try as much as possible to awaken the patient to explore them neurologically and, if able, to diagnose the appearance of DCI and use arterial hypertension, induced following the incremental modality and guided by the clinic, step by step, to minimize the complications deriving from hypertension itself.

Author contributions
R.A. contributed to the article conception and design. The author read and approved the final manuscript.

Conflicts of interest
The author declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval/informed consent
The study was conducted in accordance with the declaration of Helsinki and the principles of good clinical practice.

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