BRIEF REPORT

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Cerebral Vasospasm After Subarachnoid Hemorrhage: Respective Short-Term Effects of Induced Arterial Hypertension and its Combination With IV Milrinone: A Proof-of-Concept Study Using Transcranial Doppler Ultrasound

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OBJECTIVES: It is unclear whether IV milrinone relaxes spasmed cerebral arteries and therefore reduces cerebral blood mean velocity (V_{mean}). In patients treated for cerebral vasospasm, we aimed to assess and delineate the respective impacts of induced hypertension and its combination with IV milrinone on cerebral hemodynamics as assessed with transcranial Doppler.

DESIGN: Observational proof-of-concept prospective study.

SETTING: ICU in a French tertiary care center.

PATIENTS: Patients with aneurysmal subarachnoid hemorrhage who received induced hypertension (mean arterial blood pressure [MBP] of 100–120 mm Hg) and IV milrinone (0.5 µg/kg/min) for moderate-to-severe cerebral vasospasm. We excluded patients who underwent invasive angioplasty or milrinone discontinuation within 12 hours after the diagnosis of vasospasm.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: V_{mean} was measured at vasospasm diagnosis ($T_{DIAGNOSIS}$), after the induction of hypertension (T_{HTN}), and 1 ($T_{HTN+MILRINONE\_H1}$) and 12 hours after the adjunction of IV milrinone ($T_{HTN+MILRINONE\_H12}$). Thirteen patients were included. Median V_{mean} was significantly lower ($p < 0.01$) at $T_{HTN+MILRINONE\_H1}$ (99 [interquartile range (IQR) 89; 134] $cm.s^{-1}$) and $T_{HTN+MILRINONE\_H12}$ (85 [IQR 73–127] cm/s) than at $T_{DIAGNOSIS}$ (136 [IQR 115–164] cm/s) and T_{HTN} (148 [IQR 115–183] cm/s), whereas $T_{DIAGNOSIS}$ and T_{HTN} did not significantly differ. In all patients but one, V_{mean} at $T_{HTN+MILRINONE\_H1}$ was lower than its value at $T_{DIAGNOSIS}$ ($p = 0.0005$). V_{mean}-to-MBP and V_{mean}-to-cardiac output (CO) ratios (an assessment of V_{mean} regardless of the level of MBP [$n = 13$] or CO [$n = 7$], respectively) were, respectively, similar at $T_{DIAGNOSIS}$ and T_{HTN} but were significantly lower after the adjunction of milrinone ($p < 0.01$).

CONCLUSIONS: The induction of arterial hypertension was not associated with a significant decrease in V_{mean}, whereas the adjunction of IV milrinone was, regardless of the level of MBP or CO. This suggests that IV milrinone may succeed in relaxing spasmed arteries.

KEY WORDS: cerebrovascular circulation/drug effects; delayed ischemia; Doppler; intracranial; milrinone; subarachnoid hemorrhage; transcranial; ultrasonography; vasospasm

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KEY POINTS

- **Question:** Does IV milrinone relax spasmed cerebral arteries and therefore reduce cerebral blood mean velocity (V_{mean}) measured with transcranial Doppler?
- **Findings:** In this observational proof-of-concept prospective study among 13 patients with moderate-to-severe vasospasm after aneurysmal subarachnoid hemorrhage, the induction of arterial hypertension was not associated with a significant decrease in V_{mean}, whereas the adjunction of IV milrinone was, regardless of the level of mean arterial blood pressure or cardiac output.
- **Meaning:** These preliminary findings suggest that IV milrinone may have succeeded in relaxing spasmed arteries and encourage the assessment of its use on functional outcomes.

Because it may cause cerebral infarction, cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) should be detected early to timely implement therapies that increase cerebral blood flow in jeopardized brain areas (1). For such detection, transcranial Doppler is helpful, via measurements of blood mean velocity (V_{mean}). The blood flow running through a vessel is the product of its cross-sectional area and the V_{mean}. If the former decreases, during vasospasm, for instance, V_{mean} increases to maintain a sufficient cerebral blood flow. Ischemia occurs when the vessel lumen narrows below a critical level and when the increase in V_{mean} is not sufficient. Hence, a significant increase in V_{mean} is an alert signal that may prompt an imaging procedure (CT angiography, for instance) for vasospasm confirmation before the initiation of specific therapies (1). Conversely, a decrease in V_{mean} may indicate the success of a vasodilatory therapy. Hence, repeated V_{mean} measurements could be an appealing means to monitor the response to therapy at the bedside.

The current standard for vasospasm treatment is the induction of systemic arterial hypertension (to promote blood flow through the narrowed arteries) and endovascular angioplasty (to relax the vessel with intra-arterial vasodilators and/or balloon angioplasty) (1, 2). Induced hypertension may not be sufficient, whereas invasive angioplasty has evident drawbacks: substantial healthcare resource utilization, low availability, catheter-related complications (arterial wall rupture, thrombosis, embolism, hematoma, infection), and complications related to intrahospital transport and anesthesia. Furthermore, balloon angioplasty is contra-indicated or irrelevant when the vasospasm is distal and/or involves several portions of multiple arteries. In addition, a single intra-arterial administration of vasodilators has only transient effects and iterative procedures may be required. IV milrinone—a phosphodiesterase-3 inhibitor with cerebral vasodilatory properties—is increasingly adopted to treat vasospasm although robust evidence about its efficacy is lacking (2–5). It is unclear whether IV milrinone relaxes spasmed cerebral arteries and therefore reduces V_{mean}. The objective of this observational proof-of-concept prospective study in patients treated for moderate-to-severe vasospasm was to assess and delineate the respective impacts of induced hypertension and its combination with IV milrinone on cerebral hemodynamics as assessed with transcranial Doppler (TCD). We compared V_{mean} measured at vasospasm diagnosis ($T_{DIAGNOSIS}$), 1 hour after the induction of hypertension (T_{HTN}), and 1 ($T_{HTN+MILRINONE\_H1}$) and 12 hours after the adjunction of IV milrinone ($T_{HTN+MILRINONE\_H12}$).

MATERIALS AND METHODS

Ethics

This is a post hoc analysis of the Milrispasm study, which assessed the tolerance and impact of IV milrinone on long-term outcomes (4). Procedures were followed in accordance with the ethical standards of the regional responsible committee on human experimentation (Comité de Protection des Personnes Sud-Ouest and Outre-Mer III, March 28, 2018, No. 2017-A03347-46, study title "Milrispasm study") and with the Helsinki Declaration of 1975. Consent to use the data was obtained from all participants (patients or their next-of-kin then the patients themselves if they regained capacity) after oral and written reminding of their rights.

Patients

Patients with aSAH who received IV milrinone for moderate-to-severe cerebral vasospasm between June

2018 and January 2020 were prospectively included. We did not include pregnant women and patients under 18 years old, those with vasospasm unrelated to aSAH, individuals under guardianship, those unaffiliated with any social security scheme (as mandated by French law), patients with no temporal acoustic window, and patients with an incomplete set of V_{mean} measurements (for an unbiased delineation or the effects of hypertension and its combination with milrinone). Patients with nonelevated V_{mean} (< 90 cm/s) bilaterally at $T_{DIAGNOSIS}$, or undergoing invasive angioplasty or IV milrinone discontinuation within the 12 hours after the diagnosis of vasospasm was not included either.

Patients' Management

International guidelines were applied (6). Nimodipine (Nimotop, Bayer Healthcare, Loos, France) was administered for 21 days (enteral route if possible: 60 mg every 4 hr; otherwise IV: 2 mg/hr) and was not discontinued during vasospasm treatment. There was no dose adjustment of nimodipine in the event of systemic hypotension, norepinephrine was then administered with a targeted level of mean arterial blood pressure (MBP) of 100–120 mm Hg during vasospasm treatment or otherwise determined by the attending physician. Vasospasm was detected via iterative clinical examinations and daily transcranial color-coded duplex Doppler (Vivid S5, GE Healthcare, Velizy Villacoublay, France) of middle cerebral arteries (MCAs) (7). CT angiography of all large intracranial arteries was used for vasospasm confirmation and its classification as mild (arterial narrowing of less than 25% as compared with CT angiography performed at SAH diagnosis), moderate (25–50%), or severe (> 50%) (8). CT perfusion was also performed.

The trigger for treatment initiation was angiographic vasospasm, even though it was not always associated with neurologic deterioration (9). Treatment mainstay was induced hypertension, targeting an MBP of 100–120 mm Hg via the avoidance of hypovolemia, the withholding of anti-hypertensive drugs (except for nimodipine), and if needed, the infusion of norepinephrine. In moderate-to-severe vasospasm, IV milrinone (Medac, Lyon, France) was started one hour after the attainment of the MBP target. According to our institutional written protocol, the initial infusion rate was 0.5 µg/kg/min (with no loading dose), before reassessment. IV milrinone infusion was always combined with induced hypertension (4).

Ultrasound Measurements

V_{mean}. MCA was identified, and at a depth of 4–6 cm, a pulsed Doppler sample volume was placed aiming for a clearly delineated Doppler signal with the lowest possible angle of insonation. Of the two MCAs, only the one with the maximal value of V_{mean} measured at $T_{DIAGNOSIS}$ was considered in the default analyses.

Cardiac Output (CO). The velocity–time integral (VTI) of subaortic flow was computed on an apical five-chamber view using pulse Doppler and the angle of insonation was the lowest possible. Cardiac output = heart rate × subaortic VTI × (subaortic diameter)^2 × $\pi/4$. Because the subaortic diameter did not change during the study protocol, its default value was 2 cm.

Statistical Analysis

As a primary objective, we compared V_{mean} measured at $T_{DIAGNOSIS}$, T_{HTN}, $T_{HTN+MILRINONE\_H1}$, and $T_{HTN+MILRINONE\_H12}$ under quasi-experimental conditions: gradual implementation of therapies, unique dosage of IV milrinone at $T_{HTN+MILRINONE\_H1}$. As secondary objectives, comparisons involved the average of V_{mean} measurements at both MCAs, V_{mean}-to-MBP, and V_{mean}-to-CO ratios (an assessment of V_{mean} regardless of the level of MBP or CO, respectively).

Categorical variables were expressed as count (%) and compared using the χ^2 test. Continuous variables were expressed as median (interquartile range [IQR]) and compared using the Mann-Whitney or the Wilcoxon test. A p value of less than 0.05 was considered significant. For multiple testing with regard to three or four timepoints, the Friedman test (a nonparametric analysis, offering an alternative to the one-way repeated measure analysis of variance, used for comparing multiple-related groups) was followed by post hoc tests and adjustments of the p value were made (< 0.025 and < 0.001, respectively). There was no imputation of missing data. Analyses were performed with MedCalc 19.4.1 (Ostende, Belgium).

RESULTS

Thirteen patients were included (**Table 1**; and **Supplemental Fig. 1**, http://links.lww.com/CCX/B249).

TABLE 1.
Patients' Characteristics

Variable	Count (%) or Median (IQR)
Female sex (*n* [%])	7 (54%)
Age (yr)	49 (IQR 43–52)
Tobacco use (*n* [%])	5 (39%)
Causal aneurysm in the anterior circulation (*n* [%])	9 (69%)
Rebleeding prevention within 24 hr (*n* [%]): coiling/clipping	13 (100%)/0 (0%)
World Federation of Neurosurgical Societies grade (a specific scale of subarachnoid hemorrhage initial clinical severity) (*n* [%])	
I	4 (31%)
II	3 (23%)
III	1 (8%)
IV	3 (23%)
V	2 (15%)
Modified Fisher scale (*n* [%])	
I	1 (8%)
II	0 (0%)
III	3 (23%)
IV	9 (69%)
Simplified Acute Physiology Score (a nonspecific severity score calculated 24 hr after the admission in the ICU) II	26 (IQR 15–39)
Time from aneurysm rupture to vasospasm detection (d)	7 (IQR 5–8)
Time from V_{mean} measurement to CT angiography at $T_{DIAGNOSIS}$ (hr)	1:30 (IQR 1:05–2:06)
Vasospasm in the anterior circulation	13 (100%)
Perfusion defects at $T_{DIAGNOSIS}$[a]	4/11 (36%)
Duration of the treatment of vasospasm (d)	10 (IQR 7–11)
Length of stay in the ICU (d)	23 (IQR 21–31)
Hospital length of stay (d)	30 (IQR 24–36)
Modified Rankin scale (6 mo) < 3	10 (77%)
Modified Rankin scale (6 mo) < 2	9 (69%)
Mortality at 6 mo	2 (15%)

IQR = interquartile range, Modified Fisher scale = a specific scale of subarachnoid hemorrhage initial severity on the CT scan, $T_{DIAGNOSIS}$ = time of vasospasm diagnosis, V_{mean} = blood mean velocity measured in the middle cerebral artery with trans-temporal Doppler.
[a]Perfusion defects were assessed with CT.
Categorical variables were expressed as count (%). Continuous variables were expressed as median (interquartile range).

Vasospasm involved the anterior cerebral circulation in all patients.

Median V_{mean} was significantly lower ($p < 0.01$) at both $T_{HTN+MILRINONE\_H1}$ (99 [IQR 89–134] cm/s) and $T_{HTN+MILRINONE\_H12}$ (85 [IQR 73–127] cm/s) than at $T_{DIAGNOSIS}$ (136 [IQR 115–164] cm/s) and T_{HTN} (148 [IQR 115–183] cm/s), whereas V_{mean} at T_{HTN} did not significantly differ from that at $T_{DIAGNOSIS}$ (**Fig. 1**). In all patients but one, V_{mean} was lower at $T_{HTN+MILRINONE\_H1}$ than at $T_{DIAGNOSIS}$ ($p = 0.0005$). The average of the V_{mean} measurements taken bilaterally was lower ($p < 0.01$) after the initiation of IV milrinone: 123 (IQR 105–139), 124 (IQR 101–142), 95 (IQR 70–126), and 83 (IQR 72–113) cm/s at $T_{DIAGNOSIS}$, T_{HTN}, $T_{HTN+MILRINONE\_H1}$, and $T_{HTN+MILRINONE\_H12}$, respectively.

Milrinone dosage was 0.5 µg/kg/min at $T_{HTN+MILRINONE\_H1}$ and 0.7 (IQR 0.5–1) µg/kg/min at $T_{HTN+MILRINONE\_H12}$.

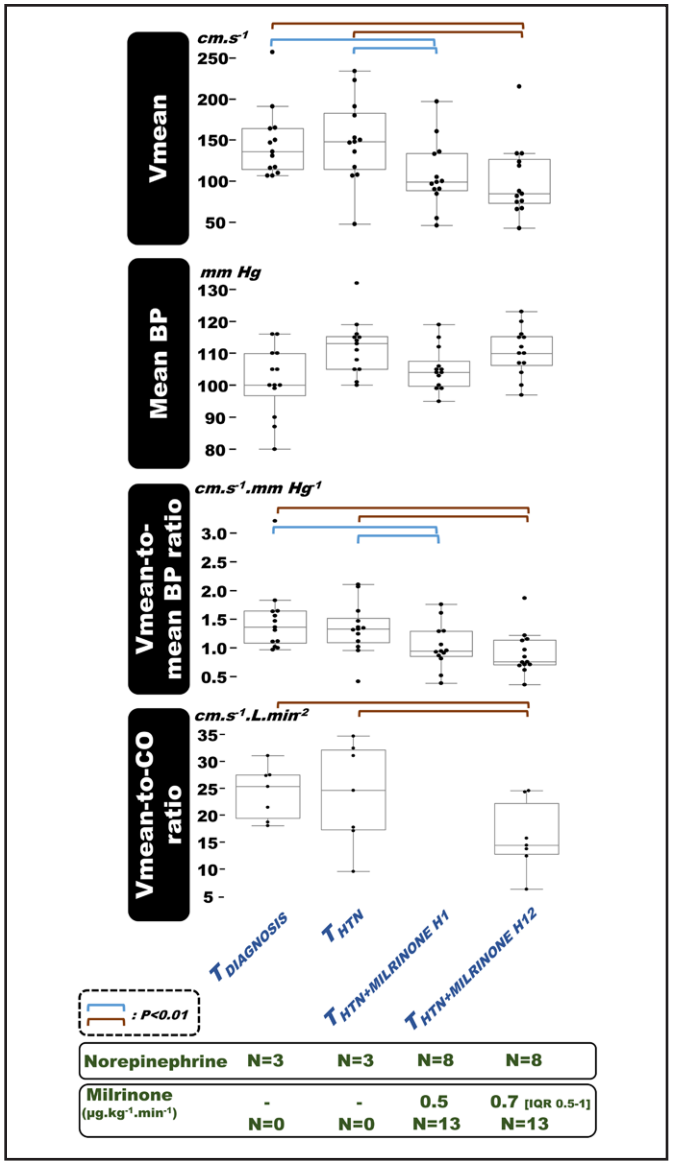

Figure 1. The main message of this figure is that the induction of arterial hypertension did not significantly affect blood mean velocity measured in the middle cerebral artery with trans-temporal Doppler (V_{mean}), whereas the adjunction of IV milrinone was associated with a significant decrease in V_{mean}. This finding was independent of the level of mean BP ($n = 13$) or CO ($n = 7$) as illustrated by the indexation of V_{mean} to these parameters. Respective effects of induced arterial hypertension and its combination with IV milrinone. The interquartile range (IQR) is calculated: IQR = third − first quartile. The *upper inner fence box-and-whisker plots* were constructed as follows: a box is drawn from the first to third quartile, and a horizontal line is drawn at the median, an imaginary line, is drawn at the third quartile + 1.5 × IQR. The *horizontal line* above the box is the highest measurement just below the *upper inner fence*. Similar lines are drawn at the lower side of the plot. A *bracket* indicates a significant difference ($p < 0.01$) between two timepoints. BP = arterial blood pressure, $T_{DIAGNOSIS}$ = at vasospasm diagnosis, T_{HTN} = 1 hr after the induction of hypertension, $T_{HTN+MILRINONE\_H1}$ = 1 hr after the adjunction of IV milrinone, $T_{HTN+MILRINONE\_H12}$ = 12 hr after the adjunction of IV milrinone.

MBP was 100 (IQR 97–110), 113 (IQR 105–115), 104 (IQR 100–108), and 110 (IQR 106–115) mm Hg at $T_{DIAGNOSIS}$, T_{HTN}, $T_{HTN+MILRINONE\_H1}$, and $T_{HTN+MILRINONE\_H12}$, respectively ($p = 0.11$). To attain these MBP levels, norepinephrine was required in 3, 3, 8, and 8 patients, respectively. Norepinephrine dosage was significantly higher ($p < 0.01$) at both $T_{HTN+MILRINONE\_H1}$ (0.30 [IQR 0–0.42 µg/kg/min) and $T_{HTN+MILRINONE\_H12}$ (0.28 [IQR 0–0.64 µg/kg/min) than at $T_{DIAGNOSIS}$ (0 [IQR 0–0.05 µg/kg/min] and T_{HTN} (0 [IQR 0–0.08 µg/kg/min]). Norepinephrine dosage at T_{HTN} did not significantly differ from that at $T_{DIAGNOSIS}$.

V_{mean}-to-MBP ratio was similar at $T_{DIAGNOSIS}$ and T_{HTN} but was significantly lower after the initiation of IV milrinone (Fig. 1). In seven patients, CO was measured at $T_{DIAGNOSIS}$, T_{HTN}, and $T_{HTN+MILRINONE\_H12}$ (5.9 [IQR 4.6–6.3], 5.5 [IQR 4.7–6.3], and 5.5 [IQR 5.0–6.5] L/min, $p = 0.49$). V_{mean}-to-CO ratio was similar at $T_{DIAGNOSIS}$ and T_{HTN} but was significantly lower at $T_{HTN+MILRINONE\_H12}$ (Fig. 1).

DISCUSSION

Contrary to the induction of arterial hypertension alone, the adjunction of IV milrinone was associated with a decrease in V_{mean}, regardless of the level of MBP or CO. This may suggest that IV milrinone succeeded in relaxing the spasmed vessel.

Rouanet et al (10) also reported that V_{mean} did not significantly change after the induction of arterial hypertension (in 6–12 patients), but decreased after the initiation of IV milrinone (in 9–15 mostly different patients). Another study, involving 13 patients, reported a decrease in V_{mean} among those receiving IV milrinone. The effects of induced hypertension were not studied (11). As compared with these previous studies, the present one has strengths: 1) the delineation, in the same population, of the respective effects of induced hypertension and its combination with IV milrinone via an a priori defined stepwise implementation of these therapies, 2) the indexation of V_{mean} to MBP or CO to assess V_{mean} changes regardless of these parameters. Although the two previous studies involved patients whose ruptured aneurysms were predominantly treated surgically, we observed a similar effect of IV milrinone on V_{mean} in our population exclusively treated with endovascular coiling.

It is noteworthy that CO did not increase after the initiation of hypertension and IV milrinone. This

finding, which warrants confirmation in a larger cohort, suggests that milrinone may be more useful for its cerebral vasodilatory properties rather than its inotropic effects aiming to increase CO, and theoretically, thereby cerebral blood flow (12).

This study has limitations. First, it is a single-center observational study of limited size that tested, at $T_{HTN+MILRINONE\_H1}$, the effects of a unique dosage of milrinone (0.5 μg/kg/min). The dose-effect relationship was not studied. Second, as our objective was to delineate the effects of induced hypertension and its combination with IV milrinone, we excluded nine patients with incomplete sets of V_{mean} measurements. The reason for these missing values was not collected. **Supplemental Table 1** (http://links.lww.com/CCX/B249) shows that, as compared with the 13 included patients, these 9 patients were older and had a shorter duration of treatment for vasospasm. Whether these exclusions resulted in a selection bias is uncertain. Third, most patients lacked the measurement of another relevant Doppler parameter, the Lindegaard ratio, which would have allowed discrimination between hyperemia-induced elevated V_{mean} and vasospasm-induced elevated V_{mean} at $T_{DIAGNOSIS}$. However, all patients had an angiographic moderate-to-severe cerebral vasospasm. Furthermore, considering that the combination of induced hypertension and milrinone is more likely to induce hyperemia than reduce it, the observed decrease in V_{mean} was likely due to the relaxation of narrowed arteries. Fourth, we only focused on patients with elevated V_{mean} at the MCAs, and vasospasms always involved the anterior cerebral circulation. Caution should be exercised before extrapolating our findings to other cerebral arteries and/or vasospasm in the posterior circulation. Fifth, we did not study either intra-observer or inter-observer reproducibility of V_{mean} or CO measurements. Sixth, in the absence of advanced imaging (CT angiography for instance) within the very few hours after the adjunction of IV milrinone, we can only assume that the IV milrinone-induced decrease in V_{mean} was related to the relaxation of the narrowed arteries, a finding reported in the few available case series with intra-arterial infusion of milrinone (3). If confirmed, that would indicate that TCD may be a valuable noninvasive tool at the bedside not only to detect vasospasm but also to monitor the response to vasodilatory therapy. Last, assessing the impact of this early IV milrinone-induced decrease in V_{mean} on patients' outcomes would deserve a larger specific study. Indeed, in the present study, only one patient did not respond to IV milrinone, that is, did not experience a decrease in V_{mean}.

CONCLUSIONS

This study suggests that IV milrinone may succeed in relaxing narrowed arteries during vasospasm after aSAH. These preliminary findings encourage the conduction of studies assessing the impact of IV milrinone on functional outcomes.

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Dr. Lakhal substantially contributed to the conception and design of the study, the collection of clinical data, the statistical analysis, the interpretation of data, and the drafting and revision of the article. Dr. Fresco contributed to the collection of clinical data and the drafting and revision of the article. Dr. Hivert contributed to the conception and design of the study, the collection of clinical data, and the drafting and revision of the article. Dr. Rozec substantially contributed to the interpretation of data and the drafting and revision of the article. Dr. Cadiet contributed to the conception and design of the study and the drafting and revision of the article. Authorship requirements have been met and the final article was approved by all authors.

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The work was performed in the Department of Anesthesia and Critical Care, Laënnec Hospital, University Hospital of Nantes, France.

Use of reporting checklist: STrengthening the Reporting of OBservational studies in Epidemiology checklist has been attached.

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Procedures were followed in accordance with the ethical standards of the regional responsible committee on human experimentation (Comité de Protection des Personnes Sud-Ouest and Outre-Mer III, March 28, 2018, No. 2017-A03347-46, study title "Milrispasm study") and with the Helsinki Declaration of 1975. Consent to use the data was obtained from all participants (patients or their next-of-kin then the patients themselves if they regained capacity) after oral and written reminding of their rights.

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