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ORIGINAL ARTICLE

Effect of norepinephrine on spinal cord blood flow and parenchymal hemorrhage size in acute-phase experimental spinal cord injury

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Abstract
Purpose In the acute phase of spinal cord injury (SCI), ischemia and parenchymal hemorrhage are believed to worsen the primary lesions induced by mechanical trauma. To minimize ischemia, keeping the mean arterial blood pressure above 85 mmHg for at least 1 week is recommended, and norepinephrine is frequently administered to achieve this goal. However, no experimental study has assessed the effect of norepinephrine on spinal cord blood flow (SCBF) and parenchymal hemorrhage size. We have assessed the effect of norepinephrine on SCBF and parenchymal hemorrhage size within the first hour after experimental SCI.
Methods A total of 38 animals were included in four groups according to whether SCI was induced and norepinephrine injected. SCI was induced at level Th10 by dropping a 10-g weight from a height of 10 cm. Each experiment lasted 60 min. Norepinephrine was started 15 min after the trauma. SCBF was measured in the ischemic penumbra zone surrounding the trauma epicenter using contrast-enhanced ultrasonography. Hemorrhage size was measured repeatedly on parasagittal B-mode ultrasonography slices.
Results SCI was associated with significant decreases in SCBF ($P = 0.0002$). Norepinephrine infusion did not significantly modify SCBF. Parenchymal hemorrhage size was significantly greater in the animals given norepinephrine ($P = 0.0002$).
Conclusion In the rat, after a severe SCI at the Th10 level, injection of norepinephrine 15 min after SCI does not modify SCBF and increases the size of the parenchymal hemorrhage.

Keywords Spinal cord injury · Spinal cord blood flow · Norepinephrine · Contrast-enhanced ultrasonography

A. Dubory and E. Laemmel have equally contributed to this work.
E. Vicaut and J. Duranteau have equally contributed to this work.

M. Soubeyrand (✉) · A. Dubory · E. Laemmel · E. Vicaut · J. Duranteau
"Microcirculation, Bioénergétique, Inflammation et Insuffisance Circulatoire Aiguë", Equipe Universitaire 3509 Paris VII-Paris XI-Paris XIII, Paris, France
e-mail: soubeyrand.marc@gmail.com

A. Dubory
e-mail: arnauddubory@hotmail.fr

E. Laemmel
e-mail: elisabeth.laemmel@univ-paris-diderot.fr

E. Vicaut
e-mail: eric.vicaut@univ-paris-diderot.fr

M. Soubeyrand · A. Dubory · C. Court
Service de Chirurgie Orthopédique, Hôpital de Bicêtre, Hôpitaux Universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris, 78 Rue Général Leclerc, Le Kremlin-Bicêtre, France
e-mail: charles.court@bct.aphp.fr

J. Duranteau
Département d'Anesthésie Réanimation, Service d'Anesthésie Réanimation, Hôpital de Bicêtre, Hôpitaux Universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris, Université Paris Sud-11, 78 Rue Général Leclerc, Le Kremlin-Bicêtre 94275, France
e-mail: jduranteau@bct.aphp.fr

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Introduction

Spinal cord injury (SCI) leads to impairments of motor, sensory, and autonomic functions. Immediately after SCI, a cascade of molecular and cellular events known as the secondary injury contributes to worsen the primary lesions [1].

Ischemia is among these events and increases lesion size via two mechanisms, namely, necrosis and apoptosis [2]. Moreover, SCI induces parenchymal hemorrhage that aggravates the ischemia [3] and whose extent at the acute phase correlates closely to the size of the necrotic fluid-filled cavity seen at the chronic phase [4]. There is considerable interest in limiting both the ischemia and the hemorrhage with the goal of improving the neurological outcomes. Even a small effect may be clinically valuable, as a study by Blight et al. [5] in a cat model established that the persistence of only 10 % of myelinated axons was sufficient to allow locomotion.

After SCI, ischemia is most severe at the epicenter of the injury, which is surrounded by an area of decreased spinal cord blood flow (SCBF) [6, 7]. This area is similar to the penumbra zone surrounding the necrotic core in ischemic stroke [8]. In the penumbra zone, a further decrease in SCBF results in the death of neural and glial cells, whereas an increase in SCBF may allow cell recovery. A widely recommended method for increasing SCBF consists in maintaining the mean arterial blood pressure (MABP) above 85 mmHg for 1 week after the injury. However, published evidence supporting this recommendation is scant [9–12]. All the clinical studies were level III or IV and, for ethical reasons, none included a control group. Moreover, only two studies evaluated the impact of aggressive hemodynamic management on neurological outcomes, and their validity is limited by the lack of a control group.

To maintain MABP above 85 mmHg after SCI, norepinephrine (NE) is considered a vasopressor of choice [10, 11]. However, we are aware of no experimental studies assessing the effect of NE on SCBF or hemorrhage size. A few experimental studies evaluated epinephrine, another catecholamine, and found no improvement in posttraumatic SCBF, as well as a trend toward larger parenchymal hemorrhage size [13–16]. Recently, our team has shown that contrast-enhanced ultrasonography (CEU) is a valuable tool to assess real-time and in vivo both the spinal cord ischemia and the parenchymal hemorrhage in the settings of experimental spinal cord injuries [17].

The present study was carried out to address both following questions: (1) does NE administration affect SCBF? (2) Does NE influence parenchymal hemorrhage size?

Materials and methods

All methods used in this experimental animal study were approved by the bioethics committee of the Lariboisière School of Medicine (CEEALV/2011-08-01). The animals were housed in individual quarters with a 12-h light/dark cycle and had free access to food and water.

Surgical preparation and experimental protocol

We used male Wistar rats weighing 380–470 g. A subcutaneous injection of buprenorphine (0.05 mg/kg) was given 30 min before an intraperitoneal (IP) injection of sodium pentobarbital (60 mg/kg). Body temperature was maintained at 37 °C with a heating blanket and monitored continuously using a rectal probe. A tracheotomy allowed spontaneous ventilation. MABP was recorded continuously using Student Lab Pro® software (Biopac Systems, Goleta, CA, USA) and a catheter inserted into the left carotid artery. The same catheter allowed continuous hydration with 0.9 % saline (10 mL/kg/h). A catheter was inserted in each external jugular vein for the injection of NE and of microbubbles for contrast-enhanced ultrasonography (CEU), respectively. With the animal in the prone position, a midline incision was performed to expose the thoracic (Th) vertebras from Th7 to Th13 and laminectomy was performed from Th9 to Th11.

A stereotaxic frame was clamped to the spinous processes of Th7 and Th13 with the thorax elevated from the heating blanket to eliminate any influence of respiratory movements on spine position (Fig. 1). The ultrasound probe of an Aplio™ ultrasound system (Toshiba, Tokyo, Japan) was positioned 5 mm from the spinal cord in a parasagittal plane with 20° of left obliquity. This position allowed access to the posterior aspect of the dura mater for positioning of the impaction device. An acoustic gel was carefully applied at the posterior aspect of the dura mater (Fig. 2). This gel acted as a coupling medium to transmit the ultrasound pulses emitted by the transducer and the echo returned from the animal. Throughout the experiment, the ultrasound machine was alternatively set on "harmonic" mode or on "B" mode. The "harmonic" mode allows to measure SCBF, thanks to the CEU technique described below while the "B" mode (i.e., "Brightness mode") provides morphological grayscale slices and allows to visualize the parenchymal hemorrhage [17]. The ultrasound slice remained constant throughout the experiment, as the spine and ultrasound probe were locked into the stereotaxic frame.

At the end of the surgical preparation, a 30-min hemodynamic stabilization phase was started. The end of this phase was taken as the baseline. Five minutes after baseline (defined as t_0), in the experimental SCI groups, a 10-g

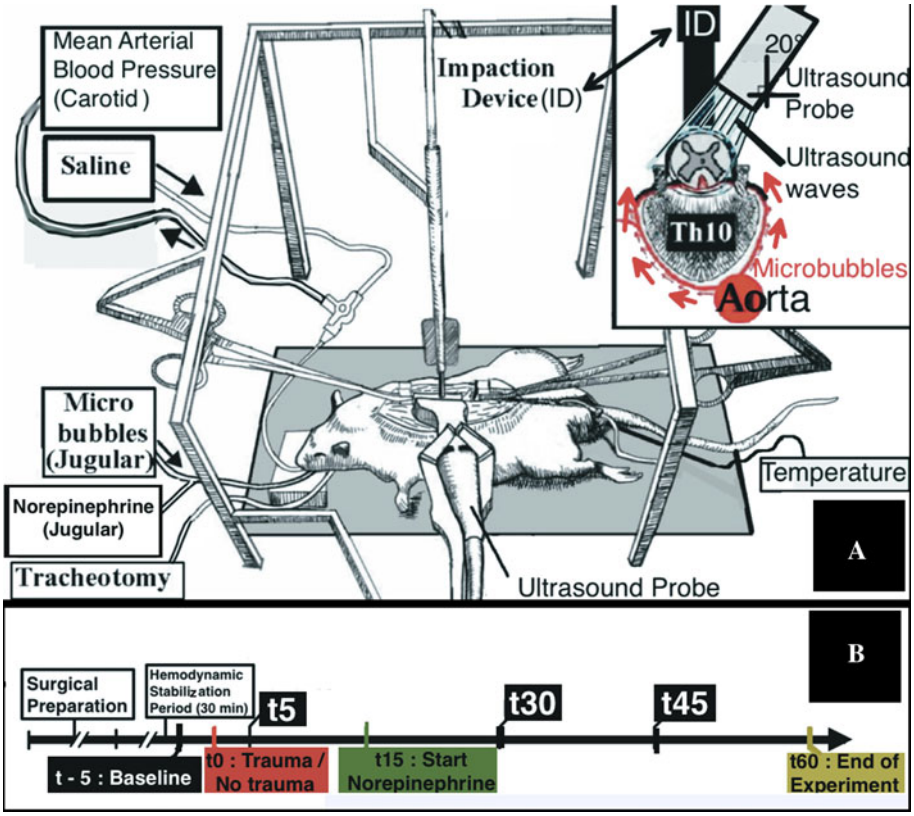

Fig. 1 Description of the experimental protocol. **a** Animal stabilization in the stereotaxic frame. The probe orientation (relative to the spinal cord) is illustrated in the *box on the right*. **b** Timeline of the experimental protocol. Norepinephrine is infused 15 min after the injury (post-SCI). *ID* impaction device

weight was dropped on the spinal cord at Th10 from a height of 10 cm to induce severe SCI. The impaction device used in the present study was custom-made in our lab and previously described [18].

SCBF was measured 5 (t_5), 15 (t_{15}), 30 (t_{30}), 45 (t_{45}), and 60 (t_{60}) min after t_0 with the CEU technique. At 5-min intervals, parenchymal hemorrhage size was measured in mm^2 on the conventional "B" mode images using OsiriX software (Pixmeo, Geneva, Switzerland). The size of the parenchymal haemorrhage was measured twice by the same observer and the mean value was calculated. To assure that the observer was blind to the status of the animal (i.e., whether he received norepinephrine or not), the files were first anonymized by another investigator.

Four experimental groups were defined. Sham animals underwent a sham operation without SCI induction and either received no NE ("Control" group) or received NE from t_{15} to t_{60} ("Control + NE" group). The animals subjected to SCI at t_0 either received no NE ("Trauma" group) or received NE from t_{15} to t_{60} ("Trauma + NE" group). In the animals given NE, the injection was performed using a power syringe from t_{15} to t_{60}. The injection rate was 5 µg/kg/min initially and was adjusted repeatedly as needed to maintain MABP between 20 and 30 % of the t_{15} value.

At the end of the experiment, each animal was euthanized with a lethal injection of pentobarbital IV.

Contrast-enhanced ultrasonography (CEU)

The CEU technique relies on injection of a contrast agent composed of microbubbles filled with sulfur hexafluoride and ranging in size from 1 to 10 µm [17]. The microbubbles reflect the ultrasound waves emitted by the probe, thereby increasing tissue echogenicity. They can be destroyed by the high-frequency ultrasound waves used in conventional "B" mode, but are not affected by the lower-frequency waves used in "harmonic" mode. Therefore, SCBF can be quantified via computer analysis of "harmonic" mode images. For each CEU acquisition, the ultrasound machine was set on "harmonic" mode and raw data were recorded automatically for 2 min while a 400-µL bolus of Sonovue® (Bracco Imaging, Milan, Italy) was injected intravenously through the jugular vein. Each acquisition was analyzed using Ultra-Extend® software (Toshiba, Tokyo, Japan). The SCBF was quantified in two circular regions of interest (ROIs) adjacent to the epicenter, which centers were, respectively, located 1 mm rostrally and 1 mm caudally to the epicenter (Fig. 2). Indeed, we have previously shown that both these regions correspond to the penumbra zone where SCBF is decreased [17]. The ROIs were positioned identically for each acquisition. For each ROI and each acquisition from baseline to t_{60}, the software generated a perfusion–deperfusion curve and calculated the area under the curve

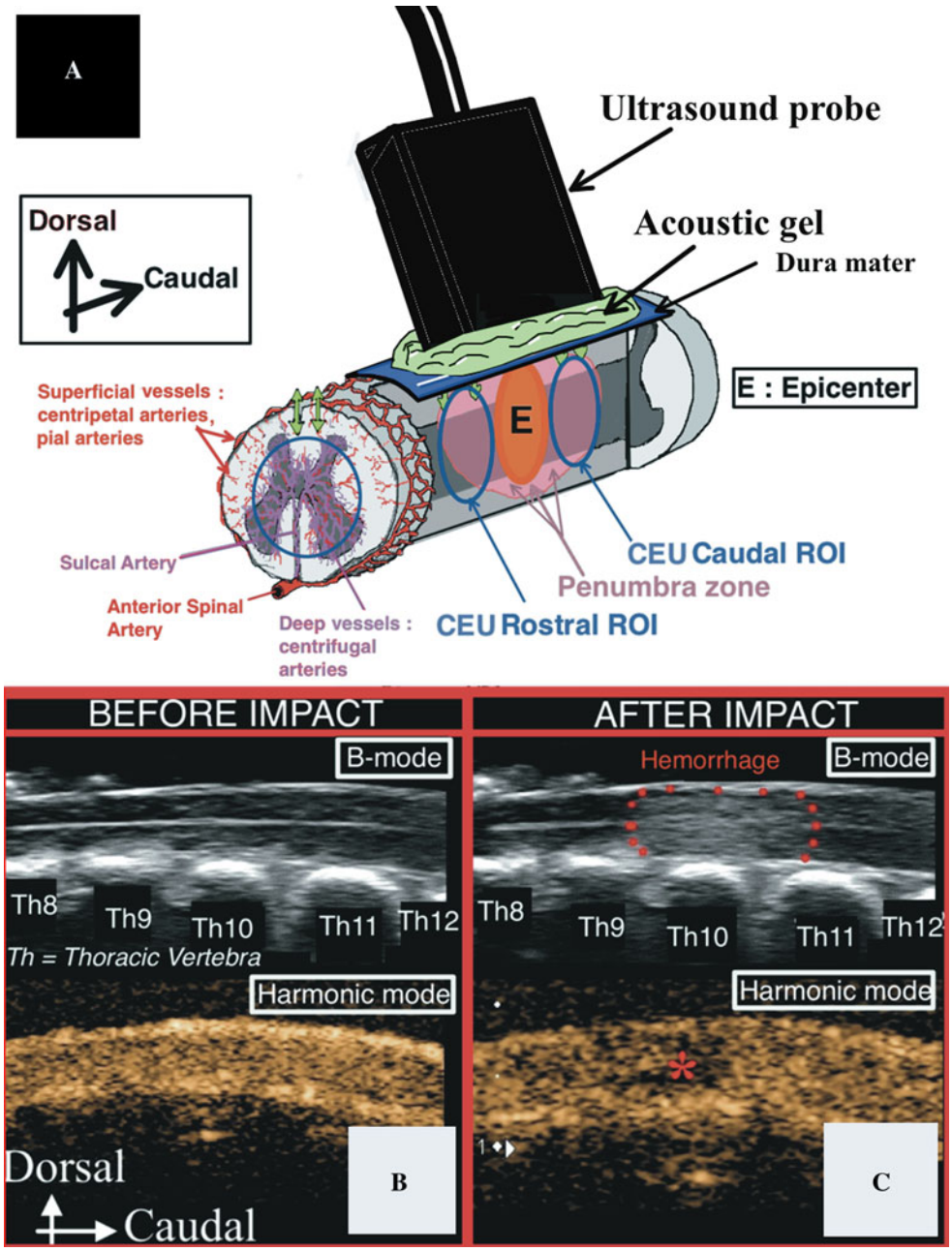

Fig. 2 Description of the ultrasound imaging experimental approach. **a** The probe is at the posterior aspect of the dura mater and an acoustic gel is applied to transmit the ultrasound pulses emitted by the transducer and the echo returned from the animal. Spinal cord blood flow is measured in two regions of interest (*ROI*) adjacent to the epicenter (*E*). **b** The intact spinal cord in "B" mode and in "harmonic mode". Note that the central canal appears as a longitudinal bright line in the middle of the cord and that the bodies of the vertebras (Th8–Th12) are well visible as well as the intervertebral disks. The orange pixels correspond to the microbubbles circulating in the microcirculation. **c** The spinal cord after injury in "B" mode, a hyperechoic lesions appears in the spinal cord (*red dot lines*) corresponding to the parenchymal hemorrhage. Visualized by the "harmonic" mode, the injured spinal cord appears as a dark area devoid of microbubbles, illustrating the ischemia. The maximum of ischemia is at the epicenter (*red asterisk*). Beyond the image, the software allows to quantify the blood flow in the ROIs

(AUC) directly correlated to SCBF. Between each CEU acquisitions, the ultrasound system was switched to conventional "B" mode in order to measure the parenchymal hemorrhage and to destroy the circulating microbubbles. Values of SCBF were expressed as percentages of the baseline values.

Animals meeting any of the following predefined criteria were excluded from the study: death before t_{60},

technical failure during SCI induction, and technical failure during norepinephrine injection.

Statistical analysis

Statistical analysis was performed using Statview 5.0 software (SAS Institute, Cary, NC, USA). All results are reported as mean ± SEM. Baseline MABP values were compared between groups using two-way ANOVA (presence/absence of trauma and presence/absence of NE) and baseline SCBF values using three-way ANOVA (presence/absence of trauma, presence/absence of NE, and rostral/caudal location relative to the trauma epicenter). MABP changes over time were compared between groups using three-way ANOVA (time, presence/absence of trauma, and presence/absence of NE) and SCBF changes over time using four-way ANOVA (time, presence/absence of trauma, presence/absence of NE, and rostral/caudal location relative to the trauma epicenter). To assess parenchymal hemorrhage size, we used two-way ANOVA (time and presence/absence of NE). *P* values smaller than 0.05 were considered significant.

Results

The number of animals was 10 in the "Control" group, 8 in the "Control + NE" group, 10 in the "Trauma" group, and 10 in the "Trauma + NE" group. Two animals were excluded from the "Control" group because an accidental parenchymal hemorrhage was induced by the laminectomy procedure.

Mean arterial blood pressure (Fig. 3)

Baseline MABP was comparable in all four groups: 109 ± 3 mmHg in "Control", 95 ± 6 mmHg in "Control + NE", 109 ± 3 mmHg in SCI, and 104 ± 4 mmHg in SCI + NE. SCI was associated with a significant decrease in MABP versus baseline, of −10 ± 2 % in the "Trauma" group and −13 ± 2.7 % in the "Trauma + NE" group at t_5. NE injection at t_{15} significantly increased MABP versus baseline ($P < 0.0001$), by 27 % (from 0 ± 2 % at t_5 to 27 ± 6 % at t_{30}) in the "Control + NE" group and 34 % (from −13 ± 3 % at t_5 to 21 ± 6 % at t_{30}) in the "Trauma + NE" group.

SCBF measured using contrast-enhanced ultrasonography (CEU) (Fig. 4)

The SCBF did not differ significantly between the rostral and caudal ROIs.

SCI induced a significant decrease in SCBF ($P = 0.0002$): at t_{15}, SCBF in both ROIs was 24 ± 13 % of baseline in the "Control" group and −26 ± 11 % in the "Trauma" group, a 50 % SCI-related decrease.

NE injection in the "Control + NE" and "Trauma + NE" groups did not significantly modify SCBF.

Parenchymal hemorrhage size (Fig. 5)

Parenchymal hemorrhage size was significantly larger in the "Trauma + NE" group than in the "Control" group ($P = 0.0002$). From t_0 to t_{15}, hemorrhage size was similar in these two groups as shown by Fig. 5. The curves of both groups become separate when injection of NE is started in the "Trauma + NE" group.

Discussion

We found that, after SCI at the Th10 level in rats, SCBF decreased in the ischemic penumbra zone surrounding the

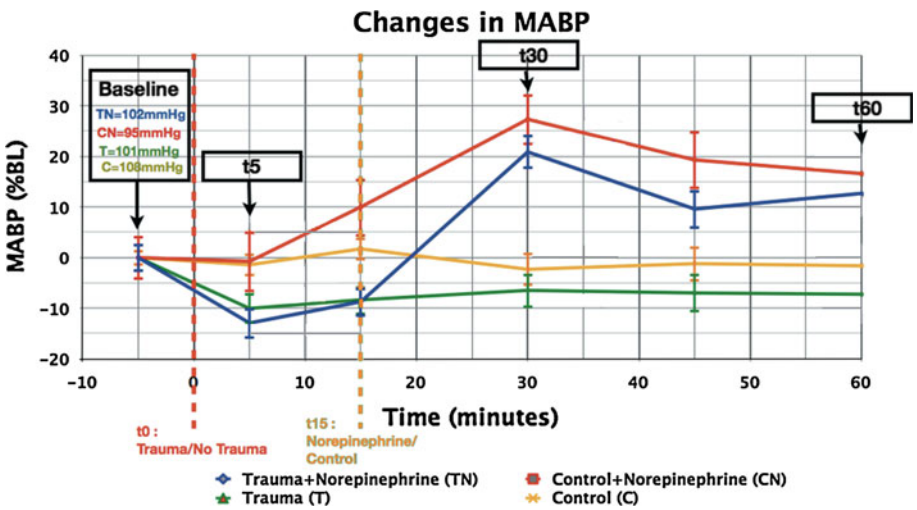

Fig. 3 Changes in mean arterial blood pressure (*MABP*) in the four study conditions. The spinal cord injury induced a significant decrease in MABP in both injured groups. Infusion of norepinephrine induced a significant increase in MABP in injured and non-injured animals

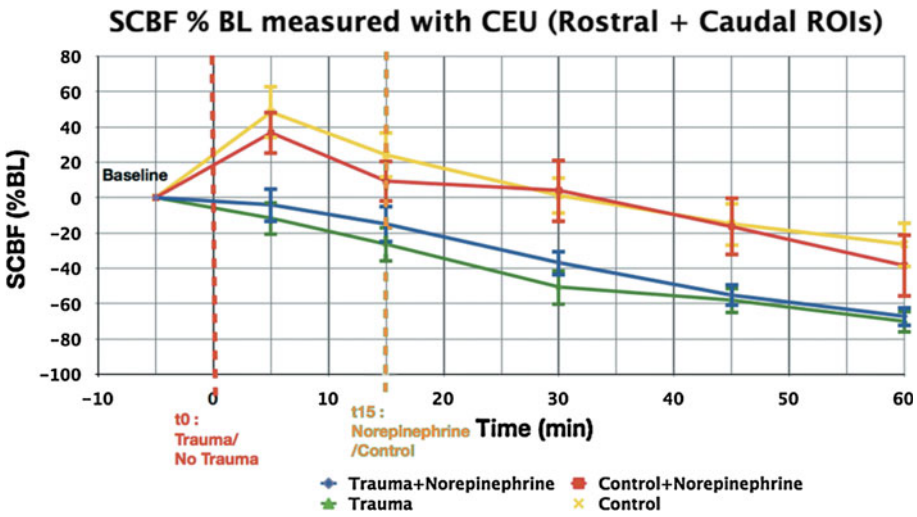

Fig. 4 Changes in spinal cord blood flow (*SCBF*) expressed as percentages of the baseline (*BL*). Since there was no statistical difference in SCBF between the rostral and caudal regions of interest (*ROI*), SCBF of both ROIs are merged to improve clarity of the graph. The experimental SCI induced a significant decrease in SCBF. Infusion of NE did not modify SCBF, whether there was a spinal cord injury or not

trauma epicenter and after NE injection, SCBF showed no significant change. However, NE given 15 min after SCI significantly increased the size of the parenchymal hemorrhage.

Preserving SCBF at the acute phase of SCI is considered crucial to limit the posttraumatic ischemia, thereby improving the neurological outcomes. In experimental settings, axonal conduction impairment in the spinal-cord motor and somatosensory tracts after SCI correlated significantly with the SCBF decrease [19] and, conversely, higher posttraumatic SCBF values were associated with better axonal function [20]. A recent literature review [10] identified only 25 experimental studies assessing the use of vasoactive agents in SCI. Only one of these studies used NE, and it did not include SCBF measurements [21]; the authors concluded that, despite MABP maintenance at normotensive or hypertensive levels, NE did not improve functional recovery of the animals. The other studies assessed the effect of other drugs and fluid replacement on SCBF and/or functional recovery [15, 20, 22–26]. To the best of our knowledge, the present study is the first that specifically assesses the influence of NE on SCBF while

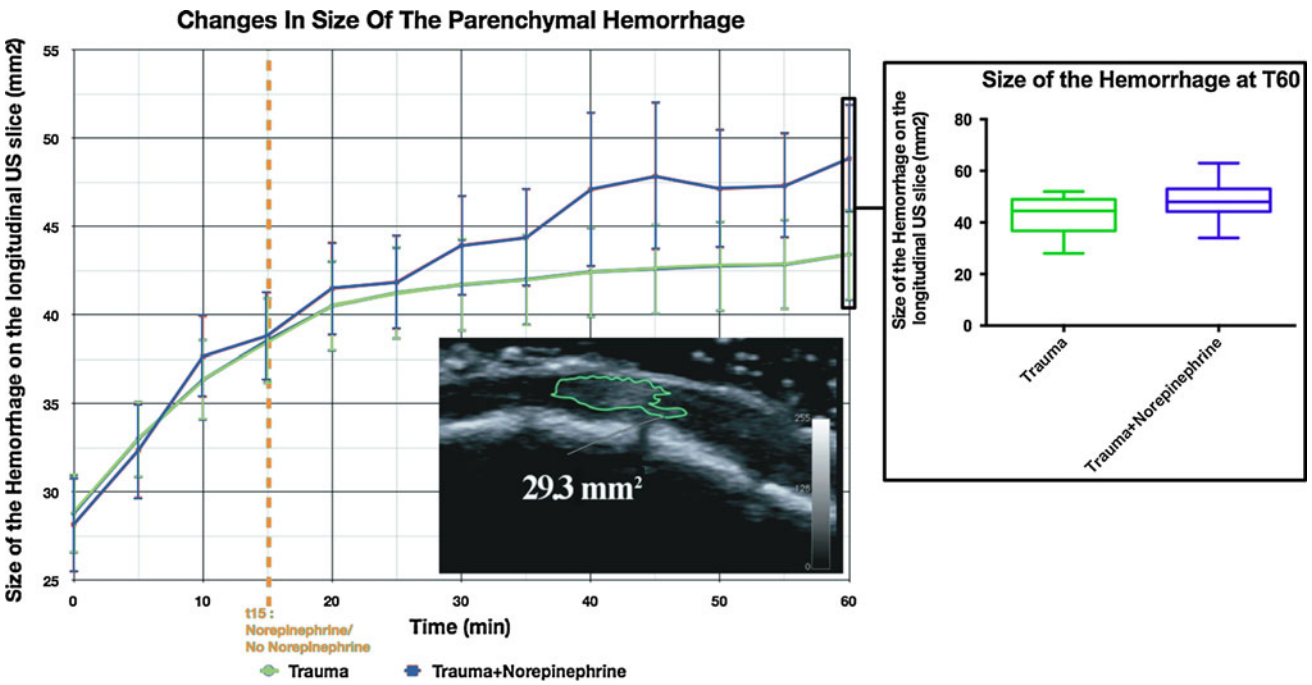

Fig. 5 Evolution of the parenchymal hemorrhage in injured animal receiving norepinephrine or controls. Starting from norepinephrine infusion, the size of the parenchymal hemorrhage is significantly more important in animals receiving norepinephrine

NE is considered a vasopressor of choice to maintain MABP after SCI. Interestingly, our results are similar to those obtained by Guha et al. [13, 14] with epinephrine, another catecholamine that closely resembles NE in terms of biochemical structure and circulatory effect. Guha et al. measured SCBF in rats using the hydrogen clearance technique and found that epinephrine alone failed to improve SCBF after experimental SCI at Th1. Concomitant nimodipine therapy was needed to improve SCBF [13, 14]. A key hypothesis for explaining the absence of an SCBF response to epinephrine alone involves the intrinsic autoregulatory capabilities of the spinal cord. Some arteriovenous glomeruli located in the gray matter can open, shunting blood from the arteries to the veins and therefore bypassing the capillary bed and regulating the parenchymal blood flow [16, 27]. These glomeruli may be devoid of receptors for catecholamines, thereby explaining the absence of effect of NE and epinephrine on SCBF.

We found that size of the parenchymal hemorrhage was significantly larger in the group given an NE injection 15 min after SCI. Similarly, a previous experimental study showed a trend towards greater bleeding by histological examination in animals given epinephrine at the acute phase of SCI [14]. These findings are of concern, for at least two reasons. First, based on studies using magnetic resonance imaging, it is admitted that extent of parenchymal hemorrhage is correlated with the severity of neurological outcomes in human patients with SCI [28]. Second, in a rat model, initial hemorrhage size correlated with the size of the fluid-filled cavity devoid of neurological function that developed within the cord parenchyma at the chronic phase of SCI [4]. The adverse effect of NE on hemorrhage size is probably ascribable to mechanical counteraction of hemostasis by the NE-induced increase in MABP. An analogy can be drawn with the association between MABP elevation in patients with hemorrhagic stroke and larger hematoma size [29]. If NE promotes bleeding by preventing efficient hemostasis, then a waiting period would be in order before NE initiation, to allow the hemostatic process to unfold, thereby limiting hemorrhage size. However, further experimental studies are needed to confirm this hypothesis. Our data combined with those of the literature suggest that SCI has both an ischemic component and, at the very early phase, a hemorrhagic stroke component.

In an extensive review of literature, Ploumis et al. [10] found only seven clinical studies in humans relevant to vasopressor support in patients with acute SCI. All seven studies were level III or IV. The main evaluation criterion was the ability to maintain MABP above the study target (i.e., 85–90 mmHg) and, paradoxically, only two of these studies evaluated the neurological outcomes [30, 31]. Unfortunately, given the absence of a control group, whether aggressive resuscitation improves neurological outcomes remains unproven. Despite the paucity of supporting evidence [10], guidelines issued by the Consortium for Spinal Cord Medicine and others [9–12] recommend that MABP be kept above 85 mmHg for at least 1 week after SCI. Because the heart receives its sympathetic supply from T1–T4, the use of inotropic and chronotropic vasoactive agents such as NE is recommended in patients with cervical and upper thoracic SCI.

The main limitation of our study is that we aimed at highly increasing the MABP (i.e., 20–30 % of the baseline) which is superior to what is recommended by the guidelines. Indeed, the latter do not attempt to make hypertensive the patients with SCI as previously suggested by the experimental findings of Guha and Tator [15].

The second experimental limitation of our study is the non-linear time-course of SCBF measured using CEU in the "Control" group, with an increase between t_0 and t_{15} then a decrease to about 30 % of baseline between t_{15} and t_{60}, in the absence of changes in MABP. This time pattern may be ascribable to the repeated injection and destruction of microbubbles as well as to the prolonged exposition of the spinal cord inside the dura mater after the laminectomy. Similar findings were obtained by Anderson et al. [32] who used an isotope-labeled microsphere technique and found that isolated laminectomy was followed by a significant decrease (22–45 %) in SCBF within the first few minutes. They suggested temperature-induced vasoconstriction as a possible explanation. Despite this limitation, at least three arguments support the reliability of our CEU measurements. First, the time-course of deep SCBF was highly reproducible across animals. Second, the time-dependent changes observed in the "Control" group were taken into account in the statistical analysis. Third, the post-SCI changes in SCBF were fully consistent with previous studies. For example, at t_{15}, SCBF values were diminished by about 60 %, in keeping with the results obtained by others in various experimental settings. Thus, a study of SCBF using the hydrogen clearance method after severe clip compression trauma in rats showed a 70 % decrease at the epicenter [15]. Similarly, SCBF decreased by 60 % after severe weight-dropping SCI in a canine model [33].

Two other limitations of the present study are to be mentioned. On the one hand, the animals were killed 90 min after SCI, thereby impeding the comparison of the effect of NE on neurological outcomes. On the other hand, NE was injected 15 min after SCI and longer delays may modify the effect of NE on SCBF and on the size of the parenchymal hemorrhage. A further study is already planned to investigate the influence of these parameters on SCBF and on the size of parenchymal hemorrhage.

Conclusion

In the rat, after a severe SCI at the Th10 level, injection of NE 15 min after SCI does not modify SCBF and increases the size of the parenchymal hemorrhage.

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Conflict of interest The ultrasound device was lent by the society Toshiba, but none of the authors received fundings from Toshiba.

Bioethic committee All the methods used in this experimental animal study were approved by the bioethics committee of the Lariboisière School of Medicine, Paris, France. Reference = CEEALV/2011-08-01.

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