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ORIGINAL ARTICLE

Occurrence of secondary insults during endovascular treatment of acute ischemic stroke and impact on outcome: the SIR-STROKE prospective observational study

Anna Teresa Mazzeo[1,2] · **Simone Cappio Borlino**[1,3] · **Stefano Malerba**[1] · **Giulia Catozzi**[1,3] · **Claudia Filippini**[1] · **Vincenzo Francesco Tripodi**[2] · **Andrea Naldi**[4] · **Paolo Cerrato**[4] · **Mauro Bergui**[5] · **Luciana Mascia**[6]

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Abstract

Background Neurological outcome after endovascular treatment (EVT) of acute ischemic stroke (AIS) may depend on both patient-specific and procedural factors. We hypothesized that altered systemic homeostasis might be frequent and affect outcome in these patients. The aim of this study was to analyze secondary insults during EVT of AIS and its association with outcome and anesthesiologic regimen.

Methods This was a single-center prospective observational study on patients undergoing EVT for AIS under local anesthesia (LA), conscious sedation (CS), or general anesthesia (GA). Altered systemic parameters were recorded and quantified as secondary insults. The primary endpoint was to evaluate number, duration, and severity of secondary insults during EVT. Secondary endpoints were to analyze association of insults with modified Rankin Scale at 90 days and anesthesiologic regimen.

Results and conclusions One hundred twenty patients were enrolled. Overall, 78% of patients experienced at least one episode of hypotension, 21% hypertension, 54% hypoxemia, 16% bradycardia, and 13% tachycardia. In patients monitored with capnometry, 70% experienced hypocapnia and 21% hypercapnia. LA was selected in 24 patients, CS in 84, and GA in 12. Hypotension insult was more frequent during GA than LA and CS ($p = 0.0307$), but intraprocedural blood pressure variation was higher during CS ($p = 0.0357$). Hypoxemia was more frequent during CS ($p = 0.0087$). Proportion of hypotension duration was higher in unfavorable outcome but secondary insults did not remain in the final model of multivariable analysis. Secondary insults occurred frequently during EVT for AIS but the main predictors of outcome were age, NIHSS at admission, and prompt and successful recanalization.

Keywords Secondary insult · Acute ischemic stroke · Endovascular treatment · Posterior occlusion · Anterior occlusion · Anesthesia

✉ Anna Teresa Mazzeo
annateresamazzeo@unime.it

1 Anesthesia and Intensive Care, Department of Surgical Sciences, University of Turin, Turin, Italy

2 Anesthesia and Intensive Care, Department of Human Pathology, University of Messina, Via Consolare Valeria, Messina, Italy

3 Department of Health Sciences, University of Milan, Milan, Italy

4 Department of Neuroscience Rita Levi Montalcini, University of Turin, Turin, Italy

5 Department of Neuroradiology, University of Turin, Turin, Italy

6 Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

Introduction

Early treatment of acute ischemic stroke (AIS) aims to restore blood perfusion in the ischemic penumbra to achieve the recovery of neurological functions. Endovascular treatment (EVT) is the standard of care for stroke caused by large vessel occlusion [1], increasing reperfusion rate and improving outcome over intravenous thrombolysis alone [2, 3]. Nevertheless, less than 50% of patients treated with EVT experience a good neurological outcome (modified Rankin Score, mRS, ≤ 2 at 90 days) despite a recanalization rate > 70% [3]. Multiple factors can affect outcome: age, pre-stroke disability, frailty, comorbid conditions, chronic brain damage, collateral flow status, blood pressure [4]. In traumatic brain injury (TBI), secondary insults are important mechanism responsible for worse outcome, and scales to grade their severity have been proposed and validated [5, 6]. Conversely, no study has systematically addressed secondary insults during EVT of AIS so far. Besides, the anesthesiologic regimen during EVT, such as conscious sedation (CS), general anesthesia (GA) or, more recently, local anesthesia (LA), might play a role in affecting outcome. Although several non-randomized studies and their metanalysis [7–11] demonstrated better outcomes in patients treated with CS, four recent randomized control trials (RCTs) [12–15] and their metanalysis [16] suggested that GA is accompanied by higher recanalization rate and better neurological outcome.

The hypothesis of this study was that derangement of physiological parameters may occur frequently during EVT for AIS and represent secondary insults responsible for further brain damage. The aim of this study was to quantify secondary insults during EVT for AIS and to evaluate their association with neurological outcome and anesthesiologic regimen.

Methods

Patients population and ethics

This prospective observational study was approved by the ethical committee of the AOU Città della Salute e della Scienza of Turin, Italy (CS2/905). At enrolment, patients signed consent form to participate into the study. If patients were unconscious and unable to give consent, the family was informed of the study, and consent was delayed. Permission for using collected data was then obtained from the patient or from the family (if the patient remained incompetent or died).

From November 2017 to July 2019, patients with AIS undergoing EVT at our University hospital were consecutively enrolled. Inclusion criteria were age ≥ 18 years, AIS caused by large vessel occlusion, meeting guidelines criteria to undergo EVT [17]. Exclusion criteria were ASPECTS score < 6, cerebral vascular occlusion unrelated to embolic or thrombotic mechanisms.

Clinical management

Patients were treated according to current guidelines for the management of patients undergoing EVT for AIS [17]. All enrolled patients underwent non-contrast computed tomography (CT) and CT angiography in the spoke or in our hub hospital. EVT was performed with a thrombus aspiration system (Penumbra System®), stentriever (Solitaire System®), or a combination of both. The angiographic results of recanalization were evaluated with the modified thrombolysis in cerebral ischemia (mTICI) score [18]. Successful recanalization was defined as mTICI 2b-3.

During the procedure, the anesthesiologist in charge was responsible for selecting anesthesiologic regimen in relation to patient's clinical needs and individual preference. LA was performed by the instillation of a local anesthetic at the arterial puncture site, without the use of other sedative or analgesic drugs. CS consisted of a light analgo-sedation to maintain spontaneous breathing. GA consisted of deep analgo-sedation, endo-tracheal intubation, and mechanical ventilation.

Intraprocedural monitoring consisted of non-invasive blood pressure (BP), heart rate (HR) by continuous ECG monitoring, peripheral oxygen saturation (SpO2), and end-tidal CO2 via the sampling port of tracheal tube for GA or of nasal cannula for LA and CS.

Study design

Upon the activation of the stroke team, 7 am to 10 pm, our research group was activated and participated to the EVT procedure, recording pre- and intra-procedural data. Intraprocedural monitoring parameter data were sampled every 5 min and each derangement in the monitored variables was checked for erroneous recording (e.g., pulse oximeter displacement). The amount of secondary insult was calculated as the time spent within the insult threshold level divided by the good monitoring time (GMT) for that patient and presented as proportion of GMT. Recorded data were verified and validated by principal investigator before being entered in database. Derangements of monitored physiologic parameters were defined as secondary insults and classified in three severity grades, by tailoring to AIS the Edinburgh University secondary insult grades (EUSIG) system, originally elaborated for TBI [5] (Supplementary Table I). Each derangement of physiological parameters had to be sustained for at least 5 min to be deemed a secondary insult. Baseline values of systolic arterial pressure (SAP), mean arterial pressure (MAP), HR, SpO2, and etCO2 were defined as the average of first three measurements recorded on arrival in neuroradiological suite, before drug administration. Delta SAP and delta MAP have been defined as the difference between each measurement and the mean of the first three available values at arrival in endovascular suite. All secondary insults have been analyzed according to grade of severity. Mean value of each monitored parameter is shown. For each secondary insult, occurrence has been calculated as number and percentage of patients exhibiting the insult. Furthermore, mean proportion of insult duration is presented. Proportion of insult duration is calculated as proportion of GMT spent below insult threshold.

Occurrence of secondary insults stratified for anterior or posterior stroke localization and for anesthesiologic regimen has also been analyzed.

The primary endpoint of this study was to evaluate number, duration, and severity of secondary insults during EVT for patients with AIS. The secondary endpoint was to evaluate association of insults with neurological outcome and anesthesia.

Measures of outcome

Neurological outcome was evaluated by neurologists of stroke unit unaware of the study procedure, at 24 h, at hospital discharge and at 90 days. Modified Rankin Scale (mRS) at 90 days has been used as measure of outcome (range 0 to 6). Occurrence of insults has been stratified according to unfavorable (mRS 3–6) or favorable (mRS 0–2).

Statistical analysis

Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) according to data distribution, while categorical data are presented as frequency and proportion.

Comparisons of continuous data between groups are performed using Wilcoxon–Mann–Whitney and Kruskal–Wallis for two and for more than two groups, respectively; for categorical data, we used chi-square or Fisher exact test as appropriate.

Clinical characteristics, procedural data, and insults were evaluated in univariate analysis according to neurological outcome. In multivariable logistic regression model, we entered in the model variables which reached 0.1 level of significance. Odds ratio and relative confidence interval at 95% level were estimated.

In the power analysis, a sample size of 120 produced a two-sided 95% confidence interval with a width equal to 0.185 (from 0.674 to 0.833).

The level of statistical significance was set at 0.05. All statistical analyses were performed using SAS ® 9.4 software (SAS Institute Inc. Cary N.C. USA).

Results

One hundred ninety-two patients were screened for eligibility. Thirty-seven were excluded because occurring at nighttime, 10 for unavailability of research team, and 25 for not meeting inclusion criteria. One hundred twenty patients have been enrolled in this study, mean age was 72 (SD 13), 45% were male. Occlusion site for AIS was anterior in 99 patients (83%). Neurological outcome was missing for one patient.

Patients' characteristics and clinical data stratified for outcome are presented in Table 1. Patients with unfavorable outcome were older, with a more severe neurologic impairment at admission or in the clinical history and had a smoking history. Successful recanalization together and a faster access to treatment were associated with better outcome. Unfavorable mRS was not different with respect of anterior versus posterior circulation site of occlusion ($p = 0.7759$).

Occurrence of secondary insults

Secondary insults are presented in Table 2, overall and stratified for anesthesiologic regimen. Overall ($n = 120$), 78% of patients experienced at least one episode of SAP ≤ 140 mmHg, 70% of MAP ≤ 90 mmHg, 21% of SAP ≥ 180 mmHg, 16% of MAP ≥ 130 mmHg, 54% of SpO2 ≤ 94%, 16% of HR ≤ 50 bpm, and 13% of HR ≥ 120 bpm. In patients in whom EtCO2 monitoring was available during EVT ($n = 53$), 70% had at least one episode of EtCO2 ≤ 29 mmHg and 21% of EtCO2 ≥ 42 mmHg.

Mean proportion of GMT spent with hypotension (SAP) of any grade was 63%, of hypotension (MAP) 55%, of hypoxemia 34%, of hypocapnia 42%, and of hypercapnia 15%.

Occurrence of secondary insults stratified for outcome

Secondary insults stratified for mRS at 90 days are presented in Fig. 1a and b. When *hypotension* (*ΔSAP*) was considered, the mean proportion of duration of grade 2 insult was significantly higher in unfavorable outcome group (7.2 vs 3.7%, $p = 0.0269$). This was also confirmed by mean proportion of duration of *hypotension* (*ΔMAP*) grade 2 insult (9 vs 3.5%, respectively in unfavorable vs favorable mRS, $p = 0.0399$).

Hypertension was found to be a beneficial factor: mean proportion of *hypertension* (*MAP*) of any grade was higher in favorable vs unfavorable outcome (49 vs 14%, $p = 0.0163$), and this difference was evident also for grade 1 (41 vs 12%, $p = 0.0404$).

Hypoxemia, hypercapnia, and hypocapnia insult were not significantly associated with outcome.

Mean proportion of grade 1 *tachycardia* was higher in favorable outcome (39.2 vs 7.2%, $p = 0.0153$).

Occurrence of secondary insults stratified per anesthesiologic regimen

Selected anesthesiologic regimens were LA in 24 patients, CS in 84 patients, and GA in 12 patients. Procedure duration was not different among the regimens, 61.2 vs 70.5 vs 61.3 min in LA, CS, and GA, respectively ($p = 0.2701$). In anterior and posterior circulation occlusion, LA, CS, and GA were applied in 79% vs 21%, 91% vs 10%, and 33% vs

Table 1 Patient characteristics and procedural data stratified for neurological outcome

	Unfavorable outcome (mRS 3–6) at 90 days *n* = 74	Favorable outcome (mRS 0–2) at 90 days *n* = 45	*p*-value
Age, years, mean (SD)	75.2 (11.1)	66.9 (14.1)	0.0003
BMI, mean (SD)	26.3 (4.5)	27.1 (5.1)	0.5110
Male sex, *n*. (%)	29 (39.7)	23 (51.1)	0.2263
NIHSS on ED admission, median (IQR)	19 (14–21)	15 (10–18)	0.0031
NIHSS > 17 on ED admission, *n*. (%)	42 (57.5)	12 (27.3)	0.0021
GCS on ED admission, mean (SD)	13 (10–15)	14 (12–15)	0.0143
Pre-stroke mRS			0.0332
mRS 0, *n*. (%)	27 (39.1)	26 (60.5)	
mRS 1, *n*. (%)	23 (33.3)	12 (27.9)	
mRS 2, *n*. (%)	13 (18.8)	4 (9.3)	
mRS 3, *n*. (%)	6 (8.7)	0 (0)	
mRS 4, *n*. (%)	0 (0)	1 (2.3)	
Comorbidities			
Previous stroke or TIA, *n*. (%)	7 (9.5)	6 (13.3)	0.5534
Atrial fibrillation/flutter, *n*. (%)	31 (41.9)	12 (26.7)	0.1166
Hypertension, *n*. (%)	56 (75.7)	27 (60)	0.0992
Coronary syndrome/MI, *n*. (%)	11 (15.1)	8 (17.8)	0.7978
Diabetes mellitus type II, *n*. (%)	17 (23)	5 (11.1)	0.1446
Smoking, *n*. (%)	15 (20.3)	18 (40)	0.0337
Occlusion site			
Anterior circulation, *n*. (%)	61 (82.4)	38 (84.4)	0.7759
Posterior circulation, *n*. (%)	13 (17.6)	7 (15.6)	
Anterior circulation occlusion *n*. = 99			0.1502
M1, *n*. (%)	44 (72.1)	25 (65.8)	
ICA and M1 *n*. (%)	3 (4.9)	0 (0)	
M2, *n*. (%)	5 (8.2)	9 (23.7)	
Intracranial ICA occlusion, *n*. (%)	8 (13.1)	4 (10.5)	
Extracranial ICA occlusion, *n*. (%)	1 (1.64)	0 (0)	
Posterior circulation occlusion *n*. = 20			
Basilar (medium and superior, including posterior art.), *n* (%)	8 (61.5)	6 (85.7)	0.3544
Vertebral and inferior basilar, *n*. (%)	5 (38.5)	1 (14.3)	
Intervention			
Intravenous rtPA, *n* (%)	40 (54.1)	26 (57.8)	0.7084
Stroke to ED arrival time, min, median (IQR)	200 (106–258)	175 (62–235)	0.0885
ED arrival to groin puncture time, min, median (IQR)	48 (34–121)	59.5 (30–125)	0.9219
Groin puncture to reperfusion time, min, median (IQR)	48 (32–80)	37 (32–48)	0.0568
Stroke to reperfusion time, min, median (IQR)	323 (274.5–369)	261 (216–303)	0.0007
Stroke to groin puncture time, min, median (IQR)	263 (148–315)	181 (99–259)	0.0126
Procedure duration, min, median (IQR)	72.5 (50–100)	51 (40–60)	0.0005
Grade of revascularization			
mTICI 0, *n*. (%)	10 (14.7)	1 (2.3)	0.0006
mTICI 1, *n*. (%)	0 (0)	0 (0)	
mTICI 2a, *n*. (%)	10 (14.7)	1 (2.3)	
mTICI 2b, *n*. (%)	16 (23.5)	5 (11.3)	
mTICI 3, *n*. (%)	32 (47.1)	37 (84.1)	
Successful recanalization (TICI 2b-3), *n*. (%)	48 (70.6)	42 (95.5)	0.0012
Anesthesiological regimen, *n*. (%)			
Local anesthesia	13 (17.6)	11 (22.4)	0.6514
Conscious sedation	53 (71.6)	30 (6.7)	
General anesthesia	8 (10.8)	4 (8.9)	
Length of stay in hospital, days, mean (SD)	10.0 (17.2)	7.2 (7.6)	0.6281

SD, standard deviation; *BMI*, body mass index; *ED*, emergency department; *IQR*, interquartile range; *TIA*, transient ischemic attack; *MI*, myocardial infarction; *M1*, M1 part of mean cerebral artery; *M2*, M2 part of mean cerebral artery; *ICA*, internal carotid artery; *NIHSS*, National Institutes of Health stroke scale; *GCS*, Glasgow coma scale; *mRS*, modified Rankin Scale; *rtPA*, recombinant tissue plasminogen activator; *mTICI*, modified thrombolysis in cerebral infarction scale

67%, respectively ($p<0.0001$). Admission NIHSS score was 16 (13–21) in LA, 16 (12–20) in CS, and 30 (20–42) in GA ($p<0.0001$).

Hypotension Mean (SD) of SAP was 145 (25), 140 (21), and 135 (20) mmHg, in LA, CS, and GA, respectively. MAP was 99 (17), 95 (14), and 94 (16) mmHg, in LA, CS, and GA, respectively. Differences were not significant.

The number of patients experiencing at least one hypotension insult (SAP ≤ 140 mmHg) was significantly higher in GA (100%) vs LA (62.5%) and CS (79.8%) ($p=0.0307$). When variation of intraprocedural BP was considered, patients with ΔMAP ≥ 10% were 71% in CS, 50% in LA, and 42% in GA ($p=0.0357$). This difference was maintained also for grade 1 ΔMAP ($p=0.0233$). The proportion of duration of hypotension (ΔMAP) of all grades was not different in LA, CS, and GA (38.8 vs 33.9 vs 30.2%, $p=0.7545$) while the proportion of grade 3 was higher in LA (14.6%) than CS (2.3%) or GA (0%) ($p=0.0281$).

Hypertension Proportion of grade 2 hypertension (MAP) was higher in LA (10.5%) than CS (0.9%) and GA (0%) ($p=0.0207$).

Hypoxemia SpO2 was significantly higher in GA than LA and CS (99, 97, and 97%, respectively) ($p=0.0038$). The number of patients experiencing at least one hypoxemia insult (SpO2 ≤ 94%) was higher in CS than in LA and GA (62 vs 46, and 17%, respectively) ($p=0.0087$). This difference was observed in all grades and remained significant for grade 1 ($p=0.0353$). Proportion of duration of hypoxemia of any grade was higher in LA than CS and GA (59 vs 29 and 18%, respectively, $p=0.0338$) and this difference remained significant also for grade 1 (49, 20.7, and 18.4%, respectively, $p=0.0211$).

Bradycardia and tachycardia insults Mean and SD of HR were 74 (15), 75 (16), and 77 (22) beat/min in LA, CS, and GA, respectively. No significant difference in this insult occurrence was evident among anesthesiologic regimens.

Hypocapnia and hypercapnia EtCO2 monitoring was available in 53 patients, 11, 35, and 7 in LA, CS, and GA, respectively. Mean and SD of EtCO2 were 28 (6), 29 (7), and 31 (4) mmHg in LA, CS, and GA, respectively ($p=0.5244$). The number of patients experiencing at least one hypocapnia insult was higher in LA (73%) and CS (74%) than in GA (43%), but this difference was not significant. Only patients in CS group experienced hypercapnia insult, measured as EtCO2 ≥ 42 mmHg (31% vs 0 in LA and GA) ($p=0.0234$).

MRS at 90 days stratified for anesthesiologic regimen is presented in Supplementary Fig. 1. Favorable outcome (mRS 0–2) was more frequent in LA than CS and GA, but differences were not significant ($p=0.6514$).

Secondary insults stratified for stroke localization

Ninety-nine patients underwent EVT for occlusion in the anterior circulation and 21 in vertebral-basilar territory (Table 3). Hypotension was more frequent in patients with EVT for anterior than posterior circulation occlusion, and this was significant for ΔMAP (72 vs 29%, $p=0.0002$).

Multivariable analysis

In the multivariable analysis age, NIHSS at admission, smoke habit, stroke to reperfusion time, recanalization success rate and, among secondary insults, hypotension (ΔSAP) grade 2, hypertension (MAP) all grades, and tachycardia grade 1 were entered in the final model, being in the univariate analysis associated with outcome with $p<0.1$. Age, NIHSS at admission, and prompt and successful recanalization remained as strong predictors of outcome (Table 4).

Discussion

In this prospective observational study, we demonstrated that secondary insults, measured both as number of patients experiencing insults and proportion of GMT spent with an insult, occur frequently during EVT for AIS, with hypotension, hypoxemia, and hypocapnia being the insults more frequently recorded.

Duration of hypotension measured as intraprocedural variation was significantly longer in unfavorable than in favorable outcome. Conversely, hypertension revealed to be beneficial, being more frequent in patients with favorable than unfavorable outcome. In multivariable analysis, the most powerful outcome predictors were age, NIHSS at admission, and prompt and successful recanalization.

When anesthesiologic regimen was considered, the number of patients experiencing at least one hypotension insult was significantly higher in GA than LA or CS. Nevertheless, when variation of intraprocedural BP with respect to baseline was considered, this occurred more frequently in patients undergoing CS. Notably, the number of patients experiencing at least one hypoxia insult was higher in CS than LA and GA.

Even if it is still unclear which is the best anesthesiologic management for AIS undergoing EVT, anesthesiologic regimen may have relevant effects on systemic variables, particularly on hemodynamic and respiratory parameters [19].

Blood pressure is an important modifiable parameter to ensure proper cerebral perfusion in stroke patients, and final

Table 2 Clinical characteristics and occurrence of secondary insults stratified for anesthesiologic regimen

	All ($n=120$)	Local anesthesia ($n=24$)	Conscious sedation ($n=84$)	General anesthesia ($n=12$)	*p*-value
Age, years, mean (SD)	72.1 (12.8)	72.8 (11.6)	72.5 (13)	67.9 (14.2)	0.3355
Male sex, *n*. (%)	53 (44.5)	10 (41.7)	39 (46.4)	4 (33.3)	0.6403
Occlusion site					
Anterior circulation, *n*. (%)	99 (82.5)	19 (79.2)	76 (90.5)	4 (33.3)	< 0.0001
Posterior circulation, *n*. (%)	21 (17.5)	5 (20.8)	8 (9.5)	8 (66.7)	
NIHSS on ED admission, median (IQR)	17 (12–20)	16 (12.5–20.5)	16 (12–20)	30 (20–42)	< 0.0001
Procedure duration, *mean* (*SD*), *min*	67.7 (31.4)	61.2 (32.7)	70.5 (31.8)	61.3 (24.2)	0.2701
Secondary insults					
Hypotension (SAP)					
Time of reliable monitoring, *mean* (*SD*), *min*	65.1 (30.2)	59 (31.4)	67.9 (30.4)	57.9 (24.9)	0.1891
SAP during procedure, *mean* (*SD*), *mmHg*	140.6 (21.9)	145 (25.2)	140.2 (21.2)	135.1 (20.4)	0.4407
Patients with SAP ≤ 140 mmHg, *n* (%)	94 (78.3)	15 (62.5)	67 (79.8)	12 (100)	0.0307
Proportion of hypotension of all grades, *mean* (*SD*)	63.3 (34.2)	64.4 (32.5)	64.7 (34.1)	55.8 (38.4)	0.7362
Hypotension (MAP)					
MAP during procedure, *mean* (*SD*), *mmHg*	95.9 (14.4)	98.8 (16.7)	95.4 (13.5)	93.5 (15.6)	0.4400
Patients with MAP ≤ 90 mmHg, *n* (%)	84 (70)	16 (66.7)	59 (70.2)	9 (75)	0.8728
Proportion of hypotension of all grades, *mean* (*SD*)	54.5 (33.3)	51.5 (31.7)	55.8 (36.2)	51.2 (37.1)	0.8872
Hypotension (ΔSAP)					
Patients with ΔSAP ≥ 10%, *n* (%)	78 (65)	14 (58.3)	58 (69.1)	6 (50)	0.3229
Proportion of hypotension of all grades, mean (SD)	33.3 (21.5)	29.9 (22.6)	35.4 (21.6)	21.5 (13.6)	0.2913
Hypotension (ΔMAP)					
Patients with ΔMAP ≥ 10%, *n* (%)	77 (64.2)	12 (50)	60 (71.4)	5 (41.7)	0.0357
Proportion of hypotension of all grades, *mean* (*SD*)	34.5 (22.2)	38.8 (26.1)	33.9 (21.4)	30.2 (24.7)	0.7545
Hypertension (SAP)					
Patients with SAP ≥ 180 mmHg, *n* (%)	25 (20.8)	6 (25)	17 (20.2)	2 (16.7)	0.8200
Proportion of hypertension of all grades, *mean* (*SD*)	28.1 (28.7)	36.9 (31.3)	27.4 (29.1)	7.1 (1.8)	0.1144
Hypertension (MAP)					
Patients with MAP ≥ 130 mmHg, *n* (%)	19 (15.8)	4 (16.7)	14 (16.7)	1 (8.3)	0.8521
Proportion of hypertension of all grades, *mean* (*SD*)	21.1 (24.3)	41.5 (48.2)	16.4 (10.5)	5.8 ()	0.3410
Hypoxemia					
Time of reliable monitoring, *mean* (*SD*), min	66 (30.1)	59.6 (31.5)	68.4 (30.5)	62.1 (23.4)	0.2390
SpO2 during procedure, *mean* (*SD*), %	96.9 (2.8)	96.7 (3.3)	96.7 (2.7)	99 (1.3)	0.0038
Patients with SpO2 ≤ 94%, *n* (%)	65 (54.2)	11 (45.8)	52 (61.9)	2 (16.7)	0.0087
Proportion of hypoxemia of all grades, *mean* (*SD*)	33.9 (28.6)	59.2 (37.6)	29.1 (24)	18.4 (12.2)	0.0338
Bradycardia					
Time of reliable monitoring, *mean* (*SD*), min	66 (30.1)	59.6 (31.5)	68.4 (30.5)	62.1 (23.4)	0.2390
HR during procedure, *mean (SD),* mmHg	75.3 (16.5)	74.1 (14.9)	75.3 (16.3)	76.9 (21.8)	0.9609
Patients with HR ≤ 50 bpm, *n* (%)	19 (15.8)	3 (12.5)	15 (17.9)	1(8.3)	0.7827
Proportion of bradycardia of all grades, *mean* (*SD*)	32.1 (28.6)	48 (17)	29.5 (30.7)	23.3()	0.4471
Tachycardia					
Patients with HR ≥ 120 bpm, *n* (%)	15 (12.5)	2 (8.3)	11 (13.1)	2 (16.7)	0.6731
Proportion of tachycardia of all grades, *mean* (*SD*)	24 (25.2)	9.1 (5.7)	23 (22.9)	44.2 (48.4)	0.5971
Hypocapnia					
Time of reliable monitoring, mean (SD), min	59.2 (31.7)	51.8 (29.9)	60 (33.8)	67.1 (24)	0.4047
EtCO2 during procedure, *mean* (*SD*), mmHg	29.4 (6.5)	28.3 (5.6)	29.4 (7.1)	31.4 (4.1)	0.5244
Patients with EtCO2 ≤ 29 mmHg, *n* (%)	37 (69.8)	8 (72.7)	26 (74.3)	3 (42.9)	0.3172
Proportion of hypocapnia of all grades, *mean* (*SD*)	41.5 (25.5)	47.1 (26.8)	38.3 (23.7)	53.6 (41.2)	0.4819
Hypercapnia					
Patients with EtCO2 ≥ 42 mmHg, *n* (%)	11 (20.8)	0	11 (31.4)	0	0.0234
Proportion of hypercapnia of all grades, *mean* (*SD*)	14.7 (6.9)	0	14.7 (6.9)	0	-

SAP, systolic arterial pressure; *MAP*, mean arterial pressure; Δ*SAP*, delta systolic arterial pressure; Δ*MAP*, delta mean arterial pressure; *HR*, heart rate; SpO_2, peripheral oxygen saturation; *EtCO2*, end-tidal carbon dioxide. EtCO2 monitoring was available in 53 patients. Severity grade stratifications are presented in text when significant

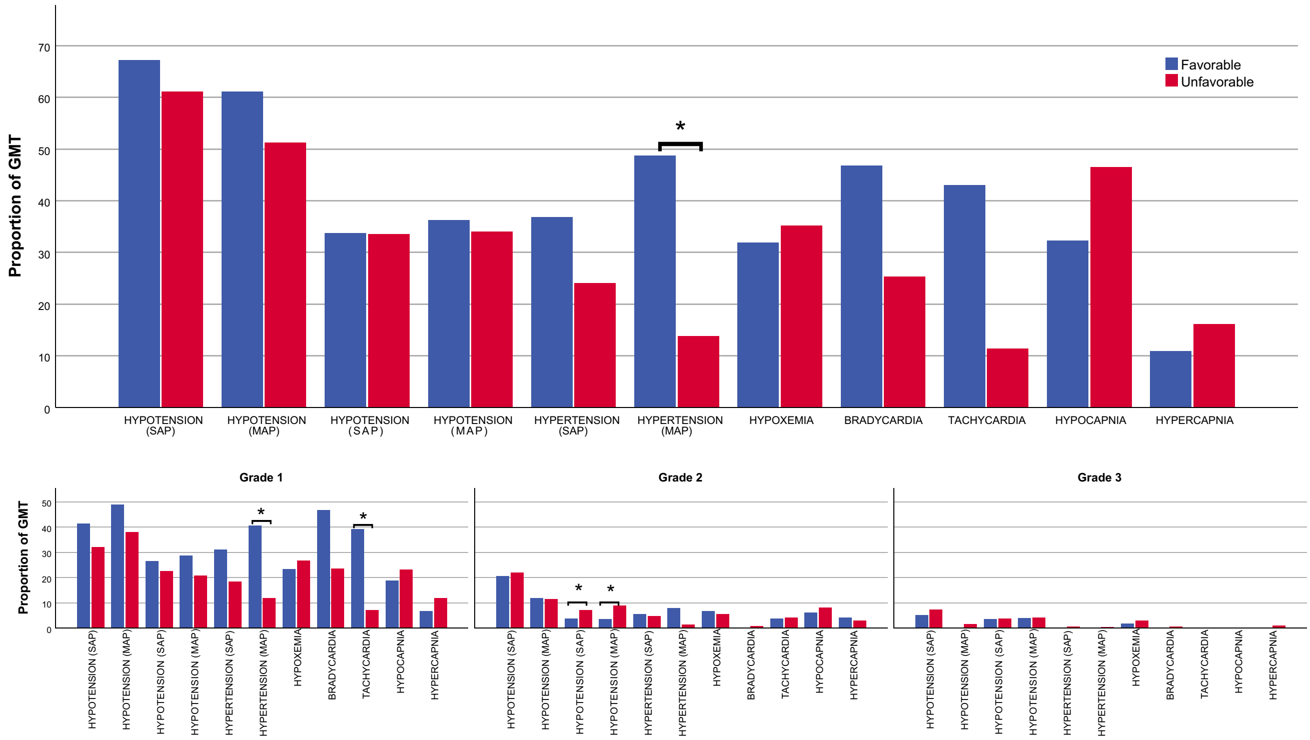

Fig. 1 Occurrence of secondary insults, expressed as proportion of good monitoring time (GMT), stratified for outcome. The figure shows proportion of duration of secondary insults, in patients with favorable and unfavorable neurological outcome, overall (panel a) and for each grade of severity (panel b). *$p < 0.05$

Table 3 Secondary insults stratified for stroke localization

Secondary insults, *n* of patients (%)	Anterior circulation *n* = 99	Posterior circulation *n* = 21	*p*-value
Hypotension			
SAP	79 (79.8)	15 (71.4)	0.3935
ΔSAP	68 (68.7)	10 (47.6)	0.0660
MAP	72 (72.7)	12 (57.1)	0.1569
ΔMAP	71 (71.7)	6 (28.6)	0.0002
Hypertension			
SAP	21 (21.2)	4 (19.0)	1.0000
MAP	15 (15.2)	4 (19.0)	0.7423
Hypoxemia	56 (56.7)	9 (42.9)	0.2521
Bradycardia	18 (18.2)	1 (4.8)	0.1901
Tachycardia	12 (12.1)	3 (14.3)	0.7254
Hypocapnia*	28 (68.3)	9 (75)	0.7366
Hypercapnia*	10 (24.4)	1 (8.3)	0.4209

SAP, systolic arterial pressure; *MAP*, mean arterial pressure; Δ*SAP*, delta systolic arterial pressure; Δ*MAP*, delta mean arterial pressure; *HR*, heart rate; SpO_2, peripheral oxygen saturation; *EtCO2*, end-tidal carbon dioxide. EtCO2 monitoring was available in 53 patients. Severity grade stratifications are presented in text when significant

Table 4 Multivariable logistic regression model for association of secondary insults to neurological outcome measured by modified Rankin Scale at 90 days

	OR (95% *C.I.*)	*p*-value
Age	1.049 (1.004–1.095)	0.0318
NIHSS at admission	1.088 (1.008–1.174)	0.0311
Smoke	0.517 (0.157–1.705)	0.2787
Stroke to reperfusion time	1.005 (1.000–1.009)	0.0331
Successful recanalization	13.804 (1.273–149.647)	0.0309
Hypotension (ΔSAP, grade 2)	1.010 (0.951–1.073)	0.7453
Hypertension (MAP, all grades)	1.066 (0.972–1.169)	0.1748
Tachicardia (grade 1)	0.909 (0.790–1.046)	0.1845

NIHSS, National Institutes of Health stroke scale; *OR*, odds ratio; *CI*, confidence interval; *MAP*, mean arterial pressure; Δ*SAP*, delta systolic arterial pressure

infarct volume mainly depends on the ability to maintain perfusion above the threshold for infarction. Effects of anesthesiologic regimen on hemodynamics have been increasingly investigated in stroke literature, even if there are still limited data to guide blood-pressure management during EVT. The difference between admission MAP and lowest MAP during endovascular thrombectomy until recanalization was independently associated with worse mRS scores at discharge and at 90 days [19]. The same authors demonstrated that 87% of patients experienced reductions in MAP during EVT and every 10 mmHg reduction in MAP before reperfusion increased the risk of worse outcome by 22% [19]. Others showed that single MAP drops < 60 mmHg are independently related to unfavorable outcome [20]. Conversely, in two post hoc analysis of a RCT [21] and a single-center prospective study [22], intraprocedural BP reductions were not associated with functional outcome, whereas higher SBP and MAP at baseline and pre-recanalization were associated with an unfavorable outcome [22]. Known the U-shaped nonlinear relationship of BP and outcome during EVT, and considering the interindividual differences, site of occlusion, size of penumbra, and collateral status, it may be difficult to identify hemodynamic threshold during EVT [22]. It has been suggested that both extremely high and low BP should be avoided in this setting.

The main novel aspect of our study is the precise description of the occurrence, severity, and duration of secondary insults during EVT for AIS. For the first time, we applied to AIS the secondary insults model earlier applied in TBI setting, modified according to pathophysiological differences, with detailed quantitation of hemodynamic ad respiratory variables. Furthermore, we investigated the occurrence of secondary insults stratified for outcome and for the three types of anesthesia used for EVT.

The optimal respiratory targets during EVT for AIS are unknown and data on the effect on outcome are scarce. Hypoxemia is common after AIS and adversely affects outcome. Furthermore, hypocapnia is associated with poor outcomes after stroke, and thus normocapnia has been proposed as a reasonable target in the intubated patient.

Opioid-induced respiratory depression should be carefully avoided in patients receiving CS. In our study, patients receiving CS showed a higher risk of secondary insults even if this did not affect outcome, probably because other factors are still more intensively related to outcome in AIS. The number of patients experiencing at least one hypoxia insult was 62% in CS, 46% in LA, and 17% in GA, and this difference was observed in all grades of insult severity. Even if EtCO2 was measured only in a small number of patients, hypocapnia insult occurred frequently, being recorded in 70% of patients.

Notably, for the first time, we described in detail the occurrence of secondary insults according to anterior or posterior occlusion localization. Hypotension was more frequent during EVT for anterior than posterior stroke, but no difference in outcome was evident according to stroke localization.

Recent literature is addressing the role of mechanical thrombectomy for primary posterior circulation vessel occlusion [23, 24] which had been excluded from previous trials on the effect of anesthesia on outcome, for possible worse outcome related to stroke localization. In our study, patients undergoing EVT for occlusion in posterior circulation were mainly treated with GA and hypotension was less frequent than in anterior circulation stroke, probably for the more controlled intraoperative setting offered by GA than CS or LA. Outcome was not significantly different in the two groups of stroke localization.

Limitations of this study are the single-center nature of the investigation, within a center having a larger propensity to LA and CS than GA, so that the numbers of the three anesthesiologic regimens were quite different. Furthermore, we left at the discretion of anesthesiologist the selection of anesthesiologic regimen, as clinically appropriate. Nevertheless, this limit can make the results easily transferable and generalizable in daily clinic activity. Strengths of this study are the extensive and detailed intraprocedural monitoring data recorded, which allowed a detailed study of secondary insults and the analysis of its association with outcome and anesthesia.

Conclusions

Secondary insults occur frequently during EVT of AIS. Optimization of hemodynamic and respiratory variables and careful maintenance of systemic homeostasis is an important target of treatment in AIS. The ideal anesthesiologic technique remains a topic of great debate and increasing research in the arena of AIS undergoing EVT is required with multicenter studies, larger sample sizes, and a multidisciplinary approach.

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Author contribution ATM: study conception and design, analysis and interpretation of data, and writing the paper. SCB, SM, and GC: patient recruitment, data collection, and analysis and interpretation of data. CF: conception and design, statistical analysis, and interpretation of data; AN, PC, and MB: data collection, analysis and interpretation of data, and revising the manuscript critically for important intellectual content; LM: study design, analysis and interpretation of data, and revising the article critically for important intellectual content. VFT revising the article critically for important intellectual content. ATM, SCB, SM GC, CF, VFT, AN, PC, MB, and LM: final approval of the version to be published and agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data Availability All relevant data are within the paper.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Ethical Committee of the AOU Città della Salute e della Scienza of Turin (Italy) approved (CS2/905).

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