Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial

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Disclosures: This study was funded by institutional funds only and carried out at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. The company Covidien-Medtronic, Italy donated the BIS, INVOS and probes used for neuromonitoring during the study.

Conflict of interest: The authors certify that they have no affiliations with, or involvement in any organization or entity with any financial or non-financial interest in the subject matter discussed in this manuscript. The company Covidien-Medtronic had no role in data acquisition, interpretation and analysis.

Trial registration number: NCT02428062 www.clinicaltrials.gov

Word count: Abstract 289; **Introduction** 382; **Discussion** 1345; **Total** 3614.

Submission includes: Manuscript Body, Table 1, Table 2, Table 3, Table 4, Figure 1, Figure 2, Figure 3 and Online Supplementary Material.

Running title: Intraoperative blood pressure and POCD

Keywords: anesthesia, general; blood pressure; cognitive dysfunction; delirium; frail elderly.

Abstract

Background: The role of intraoperative blood pressure on the development of postoperative cognitive dysfunction (POCD) is debated. This pilot randomized controlled trial assessed the effect of different intraoperative blood pressure targets on the development of POCD and the feasibility of a larger randomized controlled trial.

Methods: 101 patients aged ≥75 years, scheduled for elective, non-cardiac surgery under general anesthesia were randomized to a personalized intraoperative blood pressure target, mean arterial pressure (MAP) ≥ 90% of preoperative values (*Target-group)*, or to a more liberal intraoperative blood pressure management (*No-Target-group)*. Strategies to reach intraoperative blood pressure target were at discretion of anesthesiologists. An experienced neuropsychologist performed a validated battery of neurocognitive tests preoperatively and 3 months after surgery. Incidence of POCD at three months and postoperative delirium were assessed. Intraoperative time spent with MAP ≥ 90% of preoperative values, recruitment and drop-out rate at 3 months were feasibility outcomes.

Results: The Target-group spent a higher percentage of intraoperative time with MAP ≥ 90% of preoperative values (65±25% *vs.* 49±28%, p<0.01). Incidence of POCD (11% *vs*. 7%, relative risk 1.52; 95% CI, 0.41 to 6.3; p=0.56) and delirium (6% *vs*. 14%, relative risk, 0.44; 95% CI, 0.12 to 1.60; p=0.21) did not differ between groups. No correlation was found between intraoperative hypotension and postoperative cognitive performance (p=0.75) or delirium (p=0.19). Recruitment rate was of 6 patients/month, (95% confidential interval (CI), 5 to 7) and drop out rate at 3 months was 24% (95% CI, 14 to 33%).

Conclusions: Intraoperative hypotension did not correlate with postoperative cognitive dysfunction or delirium occurrence in elderly patients undergoing general anesthesia for non-cardiac surgery. A multicentre randomized controlled trial is needed in order to confirm the effect of intraoperative blood pressure on the development of POCD. (NCT02428062)

1. INTRODUCTION

The world population is both growing and aging, causing a steady increase in surgical procedures performed in elderly patients [1]. In these patients, postoperative complications are more common [2] and correlate with age [3]. Postoperative cognitive dysfunction (POCD) is a frequent, often under-recognized complication posing elderly patients at higher risk for long-term disability and, possibly, mortality [4,5]. The pathophysiology of POCD is complex and multifactorial [6,7]. Non-modifiable risk factors, such as age, educational level [5,8] and type and duration of surgery [9] have been identified. On the other hand, any cerebral insult possibly encountered during the perioperative period is a potentially modifiable risk factor. The major *intraoperative* cerebral insults could be pharmacological neurotoxicity and cerebral tissue hypoxia. Indeed, general anesthetics are associated, both in experimental and neonatal literature, with neurotoxicity [10] and impaired neurological development [11]. On the other side, intraoperative cerebral tissue hypoxia can be the consequence of systemic hypoxemia and/or hypotension. While intraoperative hypoxemia is a relatively rare event [12], hypotension is frequent [13] and more often observed in elderly and hypertensive patients [14]. Few studies have explored the role of intraoperative hypotension on POCD development. Gold et al [15] randomly assigned patients to two absolute pressure targets, during on-pump cardiac surgery, without finding any difference in cognitive function between the two groups. Moller et al. found no association between intra- and postoperative hypotension and POCD [8]. Several factors, including the use of absolute rather than relative values for the definition of hypotension in the study by Gold et al, and the observational nature of Moller's study, do not allow us to draw conclusions on the hemodynamic hypothesis of POCD pathogenesis. Especially for hypertensive patients, in which a rightward shift of cerebral autoregulation has been documented [16], absolute pressure values, adequate for healthy subjects, could lead to cerebral hypoperfusion [17].

Another cognitive disorder frequently encountered in surgical patients is postoperative delirium [18]. Also for this complication a role for intraoperative blood pressure has been hypothesized [19,20].

The aim of the present pilot randomized controlled trial was to assess the effect of an individualized intraoperative blood pressure target (≥90% of baseline mean arterial pressure, MAP) on the incidence of POCD and postoperative delirium in elderly patients undergoing elective non-cardiac surgery under general anesthesia, as compared to usual practice (no target specified).

2. MATERIALS AND METHODS

2.1 Study design

This prospective, single center, pilot randomized controlled trial was approved by the ethics committee (N°336/2013) of the Policlinico Ca' Granda Hospital in Milan, Italy and registered at ClinicalTrials.gov (ID NCT02428062, PI Luciano Gattinoni). Patients were recruited between November 2014 and April 2016, inclusive, and each participant gave written informed consent. Patients were randomly assigned in a 1:1 ratio on the day of surgery with a dedicated software using the minimization technique [21] to balance groups for (i) age, (ii) expected duration of surgery and, (iii) educational level. The anesthesiologists in the operating rooms were necessarily aware of group assignment, while patients and research personnel were blinded to the study-group assignment.

An age-matched Control group was also recruited from patients' and staff members' relatives to gather normative material for POCD definition (see below). Every control subject gave written informed consent to the study and underwent the same multidimensional geriatric assessment and neuropsychological evaluation (see *Data collection*) of the enrolled patients.

This manuscript adheres to the applicable CONSORT guidelines.

2.2 Study patients

Inclusion criteria were age ≥ 75 years and scheduled general anesthesia for elective non-cardiac surgery. Exclusion criteria consisted of a pre-existing cognitive impairment (preoperative

mini-mental state examination (MMSE) < 24), neurologic or vascular surgery and general anesthesia in the previous 6 months. Furthermore, patients with metastatic cancer, American Society of Anesthesia (ASA) physical status classification ≥ 4, or patients with difficult geographical accessibility were excluded.

Inclusion criteria for the Control group was age ≥ 75 years. General anesthesia in the previous 6 months, scheduled surgery/hospitalization in the subsequent 3 months and pre-existing cognitive impairment (MMSE < 24) constituted exclusion criteria.

2.3 Study treatment

Study patients were assigned either to a targeted intraoperative blood pressure management (*Target group*), in which the anesthesiologist was provided with a personalized intraoperative blood pressure target (90% of baseline MAP, *see* below), or to a liberal intraoperative blood pressure management (*No-Target group*), in which no target was specified. In the *Target group*, the strategy to reach the hemodynamic target was at the discretion of the anesthesiologist.

2.4 Data collection

2.4.1 *Preoperative Phase*

The preoperative evaluation was performed at the pre-anesthesia outpatient clinic before the scheduled surgery.

An anesthesiologist recorded baseline demographic/medical data and vital parameters. Blood pressure was measured with an automated device and the average MAP of three recordings was considered the patient's baseline MAP, subsequently employed for intraoperative blood pressure target definition.

A multidimensional geriatric assessment was performed, including MMSE and physical frailty [22] measurements. The definition of physical frailty considers five items: unintentional weight loss, weakness (grip strength), self-reported exhaustion, slow walking speed and low physical activity. Patients were defined as Non-frail (0 items), Pre-frail (1-2 items) or Frail (≥3 items).

Finally, an experienced neuropsychologist (S.I.) performed a neuropsychological evaluation, including the Trail Making Test (TMT) part A and B, the Stroop test (time and errors), the Symbol Digit Modalities Test (SDMT), the Free and Cued Selective Reminding Test (FCSRT), immediate and delayed recall, the Verbal Phonemic Fluency Test (VPFT) and the Denomination test. Time measurements (TMT A and B and Stroop time) were transformed to a logarithmic scale as suggested by Rasmussen [23].

2.4.2 *Intraoperative phase*

In patients in which a radial artery catheter was placed for clinical reasons, blood pressure was measured using disposable transducers and recorded every minute. In the remaining patients, blood pressure was non-invasively measured and recorded every three minutes. Other

cardiorespiratory variables and administered drugs were recorded every thirty minutes. When available, the non-invasive cerebral regional oxygen saturation, i.e., rSO_2 (INVOS 5100C, Covidien, Mansfield MA, USA), and the depth of anesthesia based on the Bispectral index (BIS VISTA, Covidien, Mansfield MA, USA), were monitored every minute. Since these monitoring techniques are not routinely used in our hospital, the anesthesiologist was blinded to both values to avoid any change in current clinical practice.

2.4.3 *Postoperative phase and follow-up*

For the first postoperative week, or until discharge (whatever came first), patients were evaluated daily. The post-discharge follow-up visit, consisting of the same evaluations of the preoperative phase, was performed 3 months ± 2 weeks after surgery at the outpatient clinic by the same experienced neuropsychologist.

All abovementioned evaluations were performed twice, 4 months apart from each other, also in the age-matched Control group. Neuropsychological test results of these subjects were used as normative material to define POCD as previously reported [8,9].

2.5 Outcome measures

The occurrence of POCD at three months was defined using the reliable change index [23,24] Briefly, for each patient and each test, baseline scores are subtracted form scores obtained at 3-months. From these results, the average change in score of the control subjects is subtracted (corrected score). This is done to account both for the learning effect (repetition of the same tests)

and for physiologic cognitive decline in an elderly population. To express the resulting corrected score in standard deviation units (Z-score), the value is divided by the standard deviation of the change in score of the control subjects. In addition, to summarize the global change in cognitive function, the combined Z-score is calculated as the sum of the Z-scores of the single tests divided by the standard deviation of the sum of the Z-scores of the control subjects [20].

An individual was diagnosed with POCD if the Z-score was below -1.96 on at least 2 neuropsychological tests and/or the combined Z-score was below -1.96.

A member of the research team, blinded to group assignment, evaluated patients once daily for delirium. Assessment was performed in the late afternoon, using the CAM-ICU scale [25]. This screening tool assesses the presence of delirium according to the following four features: acute onset or fluctuating course; inattention; disorganized thinking and/or altered level of consciousness [26]. In addition, medical and nursing records were reviewed [27]. In case of clinically documented postoperative delirium, the patient was considered positive for delirium, regardless of the results of the CAM-ICU.

Additionally, regardless of group assignment, the association between intraoperative hypotension and postoperative cognitive function/delirium was assessed. To summarize quantitatively both duration and degree of hypotension, we multiplied time and percent reduction in MAP below 90% of baseline MAP and termed this value *hypotension index* (Figure 1E).

Additional clinical outcomes included mortality; length of hospital stay; unscheduled intensive care unit (ICU) admission; and any other postoperative complication (neurologic, cardiovascular, infectious, respiratory, renal or hemorrhagic) [28].

Feasibility outcomes of the study were: (i) feasibility of the proposed intervention, assessed as difference in intraoperative time spent with MAP ≥ 90% of preoperative values between the two groups; (ii) overall recruitment rate; (iii) overall drop-out rate at 3 months.

2.6 Statistical analysis

We conducted this pilot study on 100 randomized and operated patients. Baseline characteristics and intraoperative procedures were summarized as mean ± standard deviation or as median (interquartile range), in case of numerical variables, and as frequency (percentage), in case of categorical variables. Binary outcomes (POCD, delirium, postoperative complications) were compared with chi-square test, and continuous outcomes (average MAP, time spent at target, hospital length of stay) with Student t-test or Wilcoxon rank-sum test, as appropriate. The association of hypotension index with combined Z-score at 3 months, and with postoperative delirium, was assessed with linear and logistic regression analysis, respectively. The recruitment rate was calculated dividing the number of enrolled patients by the number of months in which recruitment took place, with 95% confidence interval (CI). The drop-out rate was calculated as number (percentage) of patients lost to follow-up at 3 months, with 95% CI. P-value < 0.05 was defined as statistically significant. Stata statistical software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP), was used for analysis.

3. RESULTS

3.1 Study population

Figure 1 shows the study flow diagram. Of 187 patients assessed for eligibility, 127 were enrolled at the pre-anesthesia outpatient clinic. After enrollment, 11 patients had a change in anesthetic strategy, i.e. general anesthesia was not performed, and were therefore excluded. In 15 cases the therapeutic plan was changed and these patients never underwent surgery at our Institution. Therefore, 101 patients were randomized, on the day of surgery, and operated under general anesthesia. On average, 3±2 weeks elapsed between the outpatient visit and the day of surgery. Seventy-seven patients (76%) completed the 3-month follow-up and were included in the explorative outcome analyses. Baseline characteristics and type of surgery of patients of the Target and No-Target group are reported in Table 1. Except for older age (81±5 *vs.* 79±4, p = 0.03) recorded baseline characteristics of the 24 randomized patients not completing the follow-up were similar to those completing the study (Table 1E).

Furthermore, 33 age-matched controls, i.e. non-hospitalized subjects not scheduled for surgery, were enrolled. Table 2 summarizes the characteristics of this population and provides a comparison with surgical patients completing the follow-up.

3.2 Outcomes

On average, intraoperative mean (92±9 *vs.* 85±11, p<0.01) and systolic arterial pressure (130±15 *vs.* 120±13, p<0.01) were significantly higher in the Target group (Table 3). In the Target group, a

higher percentage of intraoperative time was spent with MAP ≥ 90% of preoperative values (65±25% *vs.* 49±28%, p<0.01). Specifically, the Target group spent more intraoperative time with MAP between 91 and 120 % of baseline values, while it spent less time in each category of hypotension below 80% of baseline (Figure 2).

Three months POCD incidence in patients completing the follow-up was of 7 patients out of 77 (9.1%, 95% CI, 4.5% to 17.6%): 4 (11%) randomized to the Target group and 3 (7%) to the No-Target group (relative risk 1.52; 95% CI, 0.41 to 6.3; p = 0.56). Data regarding baseline and 3 months scores of the single neuropsychological tests, including a comparison between treatment groups and data from the 33 age-matched controls are reported in Table 12E of the Online Supplementary Material.

Delirium occurred in 10 out of 101 patients (9.9%, 95% CI, 4.9% to 17.5%) undergoing surgery: 3 (6%) patients in the Target group and in 7 (14%) patients in the No-Target group (relative risk, 0.44; 95% CI, 0.12 to 1.60; p = 0.21). No between-group difference was observed in any other secondary outcome (Table 4). No correlation was found between intraoperative hypotension, expressed as hypotension index, and either the composite Z-score (p=0.75, Figure 3), or delirium (p=0.19, Figure 2E).

The recruitment rate was of 6 patients/month (95% confidential interval, 95% CI, 5 to 7), with a drop-out rate of 24% (95% CI, 14% to 33%), yielding a recruitment rate of 4 patients/month (95% CI, 3 to 5) completing follow up.

3.3 Intraoperative procedures

Table 3 compares the intraoperative procedures in the two study groups. Additional intraoperative variables are reported in the Online Supplementary Material (Table 3E). More patients in the Target group received an intraoperative vasoconstrictor. Neither the average vasoconstrictor dose, nor amount of intraoperative fluids administered differed between the groups (Table 3). Furthermore, the Target group was characterized by a lower time-weighted end-tidal sevoflurane concentration (1.08±0.31 *vs*. 1.26±0.32, $p<0.001$), while no difference in other anesthetic drugs was observed. Average intraoperative BIS was higher in the Target group (54±8 *vs.* 50±6, $p<0.01$). Patients randomized to the Target group spent less time with BIS values between 30 and 50, while no significant difference was observed for the time spent within other BIS categories (Figure 3E). No difference in intraoperative regional cerebral oxygen saturation was observed between patients of the Target and No- Target group (65± 9 *vs.* 64± 5, $p=0.50$).

4. DISCUSSION

We conducted a pilot, single center, randomized controlled trial to evaluate the effect of intraoperative blood pressure on the development of POCD at three months after surgery. Patients were randomized to a personalized intraoperative blood pressure target (MAP ≥ 90% of preoperative values) or to a more liberal hemodynamic approach (usual practice). Intraoperative time spent at target was significantly higher in patients randomized to the Target group, demonstrating the efficacy of the proposed intervention. No significant difference in POCD and delirium incidence was observed between the two treatment arms. Furthermore, intraoperative hypotension did not correlate with postoperative cognitive performance or development of postoperative delirium.

In the Target group we provided the anesthesiologist with a personalized blood pressure target (90% of baseline MAP) with the aim of maintaining intraoperative blood pressure close to the patient's preoperative values, likely within her/his cerebral autoregulation range. Given the explorative and pragmatic nature of the present study, no hemodynamic protocol was provided and strategies to achieve the target were at discretion of the anesthesiologist. Despite that, patients assigned to the Target group spent, on average, significantly more time with intraoperative MAP ≥ 90% of preoperative values (Figure 2). Furthermore, average intraoperative MAP and average systolic arterial pressure were significantly higher in the Target group (Table 3). Of note, these differences are comparable, or even higher than those recently reported in a randomized controlled trial employing a strict hemodynamic protocol based on the use of vasopressors [29]. In our study the higher intraoperative MAP was achieved through both a more frequent use of vasopressors and a reduction in administered hypnotic agents (Table 3). As a result, the Target group spent less intraoperative time with low BIS values (Figure 2E). A non-significant increase in time spent with

BIS values above 60 was observed. In the subset of patients in whom regional cerebral oxygen saturation was monitored, no difference was observed between groups. This could suggest that our very old and hypertensive population had preserved cerebral autoregulation, effectively limiting cerebral hypoperfusion during hypotension.

Our pilot study does not suggest an effect of treatment assignment on POCD development. Furthermore, when analyzing outcomes irrespective of group assignment, no correlation was observed between intraoperative hypotension and cognitive function, expressed as combined Z-score of the battery of neuropsychological tests (Figure 3). However, the great confidence interval of the relative risk of developing POCD (2-fold decrease up to 6-fold increase) does not allow to exclude definitively a clinically significant effect of treatment assignment. Similarly, intraoperative hypotension was not correlated with delirium development, in line with other studies on the subject [19,20]. Also in this case, the wide confidence interval (10-fold decrease up to 0.5-fold increase) underlines the need for a larger study. Given the observed incidence of POCD, approximately 1000 patients would be needed to detect a clinically relevant reduction (50%). This sample size would also allow to detect a similar reduction in delirium occurrence. A larger, more definitive, adequately powered, multicenter prospective randomized trial is therefore warranted.

The incidence of POCD at three months after surgery in the International Study of PostOperative Cognitive Dysfunction-1 (ISPOCD-1) trial in patients aged >70 years was 14% [8]. We enrolled patients aged 75 years and more and thus expected a higher incidence (20%). However, we observed in our population of very old patients an incidence of only 9%. There are several possible explanations for this finding. First, we studied any type of surgery under general anesthesia, therefore including also minor surgery. On the contrary, the ISPOCD study enrolled patients scheduled to major abdominal, non-cardiac thoracic and orthopaedic surgery. However, in other studies a similar incidence of POCD was observed in patients undergoing major

cardiac/orthopaedic surgery and patients undergoing procedural sedation [30,31]. Second, it is conceivable that patients experiencing a postoperative cognitive decline are less prone to return to the follow-up, leading to a falsely reduced incidence of POCD. For instance, the likelihood of returning to follow-up was significantly lower in patients experiencing postoperative delirium as compared to patients without delirium (50% *vs.* 79%, p = 0.05). Finally, it is possible that the steady improvement in anesthesia, surgery and postoperative care over the past 20 years led to a reduction in postoperative complications, including POCD.

4.1 Limitations and Strengths

The design of the trial, not providing an intraoperative treatment protocol, resulted in variable therapeutic choices made by the anesthesiologists. The results in terms of intraoperative MAP were however comparable or even better than recently published trials using a standardized hemodynamic protocol [29]. The more frequently employed strategy was a reduction in the administration of anesthetic agents. As a result, the Target group differed from the No-Target group for two factors potentially affecting POCD development. On the one hand, a reduction in intraoperative hypotension, on the other reduced doses of anesthetic drugs, leading to a lighter level of anesthesia (BIS). It is therefore not possible to separate the hemodynamic from the pharmacologic hypothesis. Moreover, as reported in Table 2, our control group had a slightly higher educational level as compared to patients (10 [8-13] years *vs.*8 [5-13] years, p = 0.05). This fact could theoretically lead to an overestimation of the reported incidence of POCD. However, this seems unlikely, given the small difference in educational level and the overall low incidence of POCD.

We had a 24% drop-out rate, which, while being in line with other studies on the topic, could be explained by our inability to perform home visits for follow-up. This strategy should be

considered for future larger studies, in order to reduce the drop-out rate and thus increase the clinical relevance.

In addition, delirium assessment presented two weaknesses: 1) delirium screening was performed only once daily; 2) the CAM-ICU scale was employed in all patients. These two aspects could have led to an underestimation of delirium incidence. Indeed, given the fluctuating nature of delirium, its punctual evaluation could miss the diagnosis. We therefore reviewed medical and nursing records looking for a clinical diagnosis of delirium [27], to increase sensitivity of our evaluation. Regarding the CAM-ICU scale, this tool is validated only for critically ill patients and has lower sensitivity outside the ICU. The choice to use this scale was of practical nature, since all research members were trained for CAM-ICU administration. Both these limitations could have contributed to the lower than expected incidence of delirium. However, the underestimation should affect equally the two groups. Finally, no systematic assessment of intraoperative awareness was performed and no data regarding postoperative hypotension were available.

Some strengths of this study need to be mentioned. First, this is one of the very few randomized controlled trials on the subject and the first study exploring the hemodynamic hypothesis using a personalized, rather than an absolute blood pressure target. Second, we chose a very old population, not well characterized in the literature, and performed the preoperative evaluation in the outpatient clinic, i.e. 3±2 weeks before the scheduled surgery, therefore limiting the effect of stress and anxiety on both cognitive performance and blood pressure. Third, this is one of the few studies extensively reporting intraoperative data including depth of anesthesia and non-invasive cerebral regional oxygen saturation. Additionally, the extensive neuropsychological evaluation of both patients and control subjects was performed before surgery, at the outpatient clinic and 3 months after surgery, always by the same, experienced neuropsychologist, allowing to use the reliable change method to define POCD [8,24].

The extreme organizational effort needed to accomplish this design needs to be acknowledged. Performing the neuropsychological evaluation in the immediate postoperative period, as frequently performed in literature, results in a higher incidence of POCD at a significantly lower organizational cost. However, several cases of transient cognitive dysfunction likely attributable to medications and post-operative pain would be included, limiting the possibility to make long-term inferences on cognitive function [23].

In conclusion, our results in elderly surgical patients do not suggest a major role of intraoperative hypotension on the development of POCD and postoperative delirium. Results of the present study, including incidence of POCD and postoperative delirium observed in this particular population could be helpful in the design of future trials on the topic.

Online Supplementary Material

Supplemental digital content is available online.

Acknowledgements

Assistance with the study: The authors are grateful to the staff of the outpatient anesthesia clinic, operating rooms and surgical wards for their fundamental support during the study; to Martina Dansi M.D., Silvia Prolo M.D. and Federica Romano M.D. (Geriatric Unit, Department of Medical Sciences and Community Health, University of Milan, Italy; Fondazione Ca' Granda, IRCCS Ospedale Maggiore Policlinico, Milan, Italy) for assistance with the geriatric evaluations; to Elisa Cipriani M.D. (Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy) for assistance in intraoperative data collection; to Paolo Cadringher M.Sc. (Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy) for providing the software for randomization; to Prof. Paolo Pelosi M.D., F.E.R.S. and Dr. Lorenzo Ball M.D. (Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Italy) for revising the manuscript and providing useful suggestions for its improvement; to the patients and control subjects that accepted to participate in the study.

Presentation: The manuscript was presented in form of abstract, and won the best abstract award at the 28th Smart Meeting Anesthesia Resuscitation and Intensive Care held in Milano, Italy between the 10th and 12th of May 2017 (www.smartonweb.org).

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Table 1. Baseline characteristics of randomized patients.

	No-target group (n=51)	Target group (n=50)
Age, years	80 ± 4	80 ± 4
Female sex, no. (%)	22 (43)	26 (52)
Body mass index, kg/m^2	24.7 ± 3.2	24.8 ± 4.5
Education, years	8 [5-13]	8 [5-13]
Mini-mental state evaluation	28 [27-30]	28 [27-30]
Baseline Mean arterial pressure, mmHg	94 ± 14	94 ± 13
Hypertensive patients, no. (%)	35 (69)	31 (62)
Diabetic patients, no. (%)	11 (22)	6 (12)
Charlson comorbidity index	2 [1-4]	2 [0-3]
ASA physical status, no. (%)		
1	1 (2)	0 (0)
2	33 (35)	31 (62)
3	17 (33)	19 (38)
Physical Frailty, no. (%)	(n=44)	(n=45)
Non - frail	14 (32)	14 (31)
Pre - frail	24 (55)	19 (42)
Frail	6 (14)	12 (27)
Type of surgery, no. (%)		
General	27 (53)	30 (60)
Urologic	8 (16)	9 (18)
Thoracic	6 (12)	6 (12)
Head-neck	9 (18)	5 (10)
Orthopedic	1 (2)	0 (0)
Cancer surgery, no. (%)	34 (67)	28 (56)
Expected duration of surgery above 2 hours, no. (%)	22 (43)	18 (36)

Table 1. Baseline characteristics of randomized patients.

Data are expressed either as mean ± standard deviation or as median [interquartile range]. Reported baseline mean arterial pressure refers to values measured at the outpatient anesthesia clinic approximately 2-4 weeks prior to the scheduled surgical procedure. Please see the Materials and Methods section for the definition of physical frailty.

Table 2. Baseline characteristics of patients completing follow-up and control subjects.

	Patients (n=77)	Controls (n=33)	p value
Age, years	79 ± 4	79 ± 5	0.36
Female sex, no. (%)	34 (44)	20 (61)	0.11
Body mass index	25.0 ± 3.7	23.7 ± 3.6	0.09
Education, years	8 [5-13]	10 [8-13]	0.05
Mini-mental state evaluation	28 [27-30]	28 [27-30]	0.75
Baseline Mean arterial pressure [mmHg]	95 ± 14	93 ± 10	0.46
Hypertensive patients, no. (%)	53 (69)	24 (54)	0.68
Diabetic patients, no. (%)	14 (18)	3 (9)	0.19
Charlson comorbidity index	2 [1-3]	0 [0-1]	<0.001
Physical Frailty, no. (%)	(n=67)	(n=33)	
Non - frail	24 (36)	16 (49)	
Pre - frail	30 (45)	13 (39)	
Frail	13 (19)	4 (12)	0.42

Table 2. Baseline characteristics of patients completing follow-up and control subjects.

Data are expressed either as mean ± standard deviation or as median [interquartile range]. The definition of physical frailty considers 5 items: unintentional weight loss, weakness (grip strength), self-reported exhaustion, slow walking speed and low physical activity. Patients were defined as Non-frail (0 items), Pre-frail (1-2 items) or Frail (≥3 items).

Table 3. Intraoperative variables, drugs and monitoring of randomized patients.

	No-Target group (n=51)	Target group (n=50)	p value
Duration of intervention, minutes	193 ± 117	198 ± 108	0.84
Average mean arterial pressure, mmHg	85 ± 11	92 ± 9	< 0.01
Average systolic arterial pressure, mmHg	120 ± 13	130 ± 15	< 0.01
Any vasoconstrictor, no. (%)	22 (43)	32 (59)	0.04
Ephedrine, mg	5 [3-10]	8 [5-13]	0.10
n	11	13	
Ethylephrine, mg	2 [1-4]	3 [1-7]	0.26
n	11	19	
End-tidal Sevoflurane, %	1.26 ± 0.32	1.08 ± 0.31	< 0.01
n	51	50	
Propofol, induction dose, mg/kg	2.0 ± 0.6	1.8 ± 0.7	0.09
n	51	50	
Midazolam, mg	2.1 ± 1.2	1.9 ± 0.8	0.46
n	29	34	
Remifentanil, mcg/kg/min	0.07 ± 0.03	0.06 ± 0.03	0.22
n	34	41	
Fentanyl, mcg	136 ± 93	99 ± 37	0.06
n	31	27	
Crystalloids, liters	1.5 [1.0 – 2.5]	1.8 [1.3 – 2.5]	0.27
Any hemocomponent, no. (%)	5 (10)	6 (12)	0.72
Average Bispectral index	49 ± 6	54 ± 8	<0.01
n	45	47	
Average left rSO_2, %	64 ± 5	65 ± 9	0.50
Average right rSO_2, %	65 ± 7	67 ± 9	0.29
n	38	43	
ICU admission, no. (%)	17 (33)	14 (28)	0.47

Table 3. Intraoperative variables, drugs and monitoring of randomised patients.

Continuous variables are expressed either as mean ± standard deviation or as median [interquartile range] and comparisons are performed via Student's t-test or rank sum test, respectively. Comparison between proportions are performed via chi-square or Fischer's exact test, as appropriate. For drugs, the mean dose was calculated considering as denominator only patients receiving the specific drug. Of note, all patients received both propofol and sevoflurane. Neuromonitoring was performed using the BIS Vista in 70 patients (36 in the No-Target group and 34 in the Target group) and using the INVOS 5100C in 60 patients (29 in the No-Target group and 31 in the Target group). *Definition of abbreviations:* rSO_2 cerebral regional oxygen saturation; ICU = intensive care unit.

Table 4. Secondary outcome measures in the overall study cohort.

	No-Target group (n=51)	Target group (n=50)	p value
Delirium, no. (%)	7 (14)	3 (6)	0.19
Unscheduled ICU admission, no. (%)	3 (6)	1 (2)	0.32
Any post-operative complication, no. (%)	9 (18)	8 (16)	0.83
Mortality, no. (%)	1 (2)	1 (2)	0.99
Hospital length of stay, days	5 [3-7]	5 [2-8]	0.93

Table 4. Secondary outcome measures in the overall study cohort.

Hospital length of stay is expressed as median [interquartile range] and comparison was performed via Rank sum test. Post-operative complications were defined as previously described[21] and comparisons between proportions were performed via chi-square or Fischer's exact test, as appropriate.

FIGURE LEGENDS

Figure 1. Study Flow chart

Screening, randomization, and follow-up of study patients.

Figure 2. Intraoperative mean arterial pressure

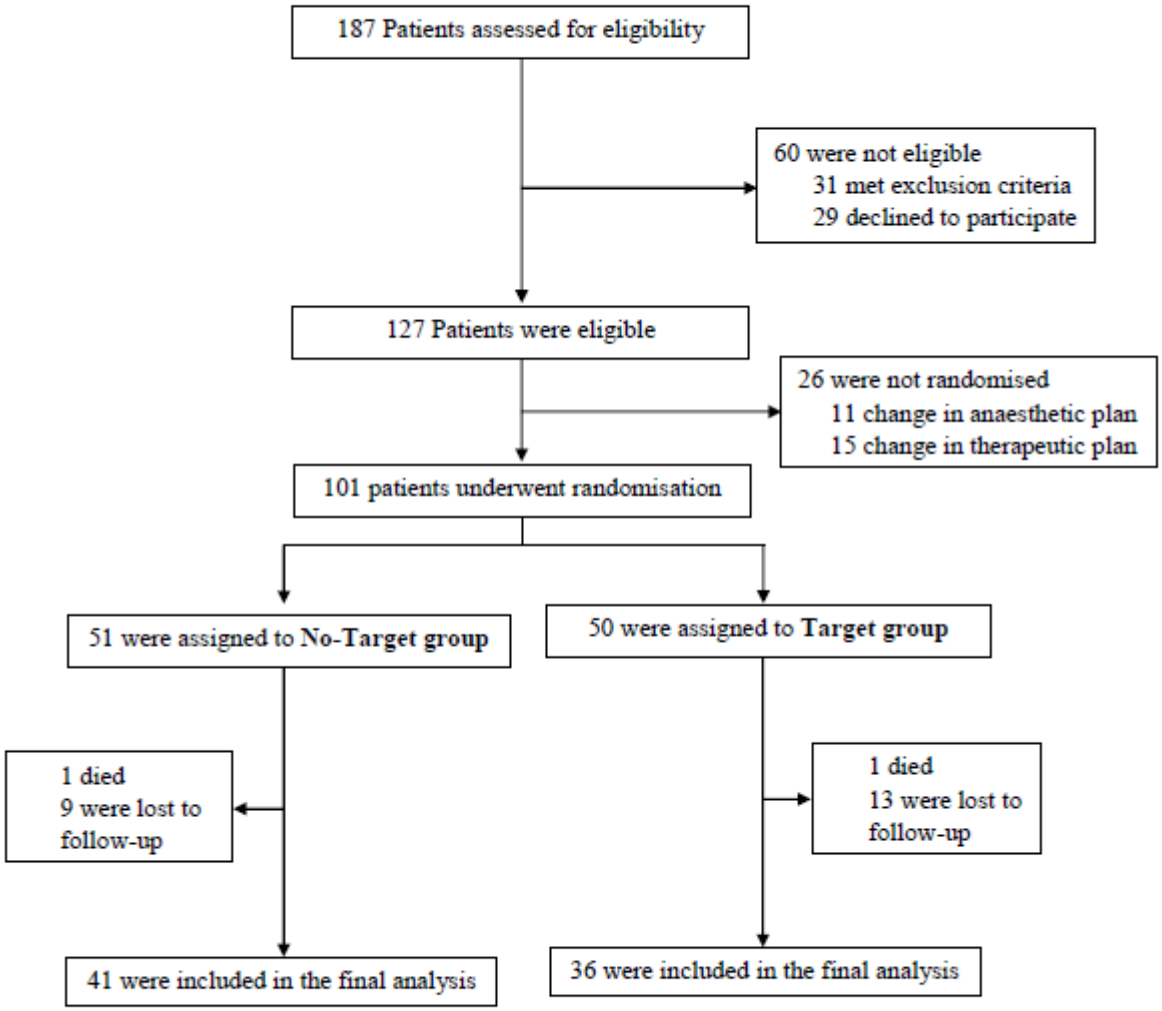
Intraoperative time (% of total anesthesia time) spent within ranges of mean arterial pressure, expressed as percent of preoperative values. Grey box plots represent data from the No-Target, while white box plots represent data from the Target group. For each of the pressure categories data were compared using the Wilcoxon rank-sum test.* $p<0.05$ vs Target group.

Figure 3. Hypotension index and postoperative cognitive performance

Association between intraoperative hypotension, expressed as hypotension index and postoperative cognitive impairment, expressed as combined Z-score (negative values represent cognitive decline). Squares represent patients randomized to No-Target group, while circles represent patients randomized to the Target group. Pink symbols (circles and squares) represent patients developing POCD at three months.

1

Figure 1. Study Flow chart



2

3

4

5

6

7

Figure 2

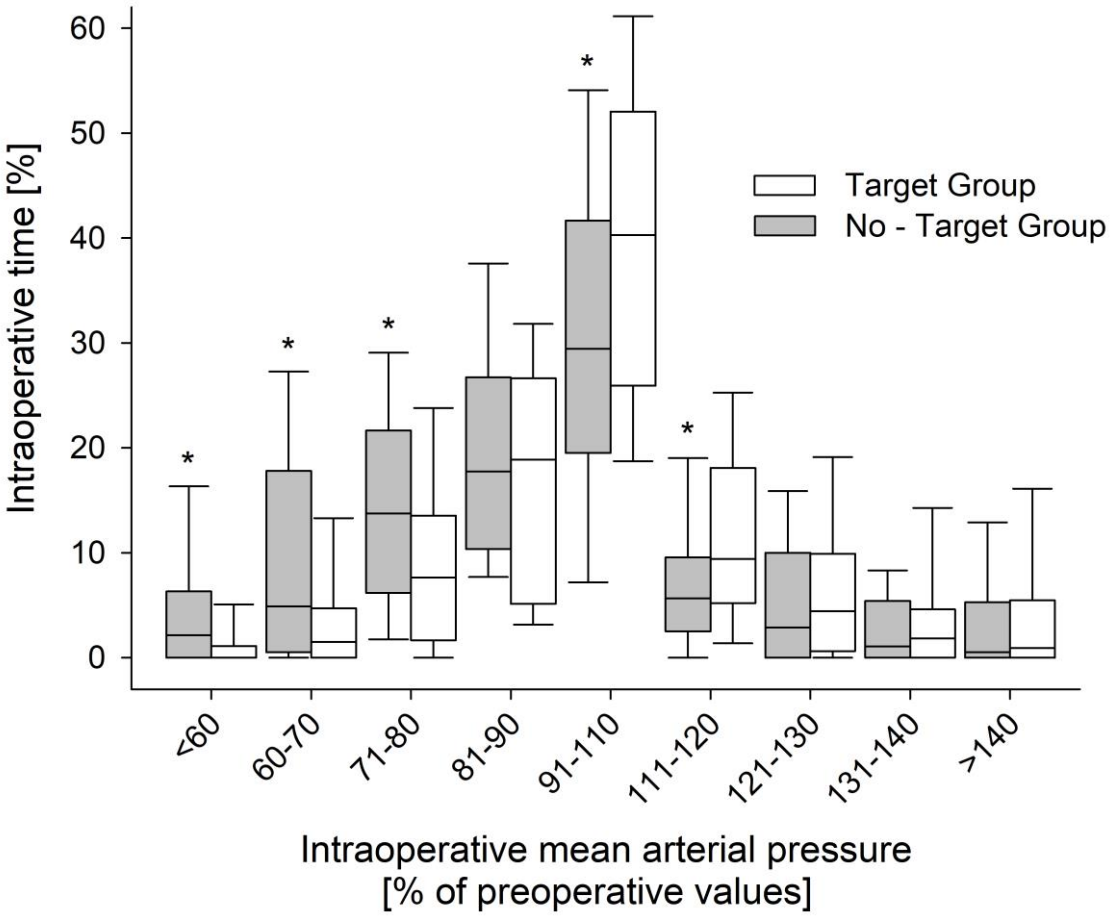
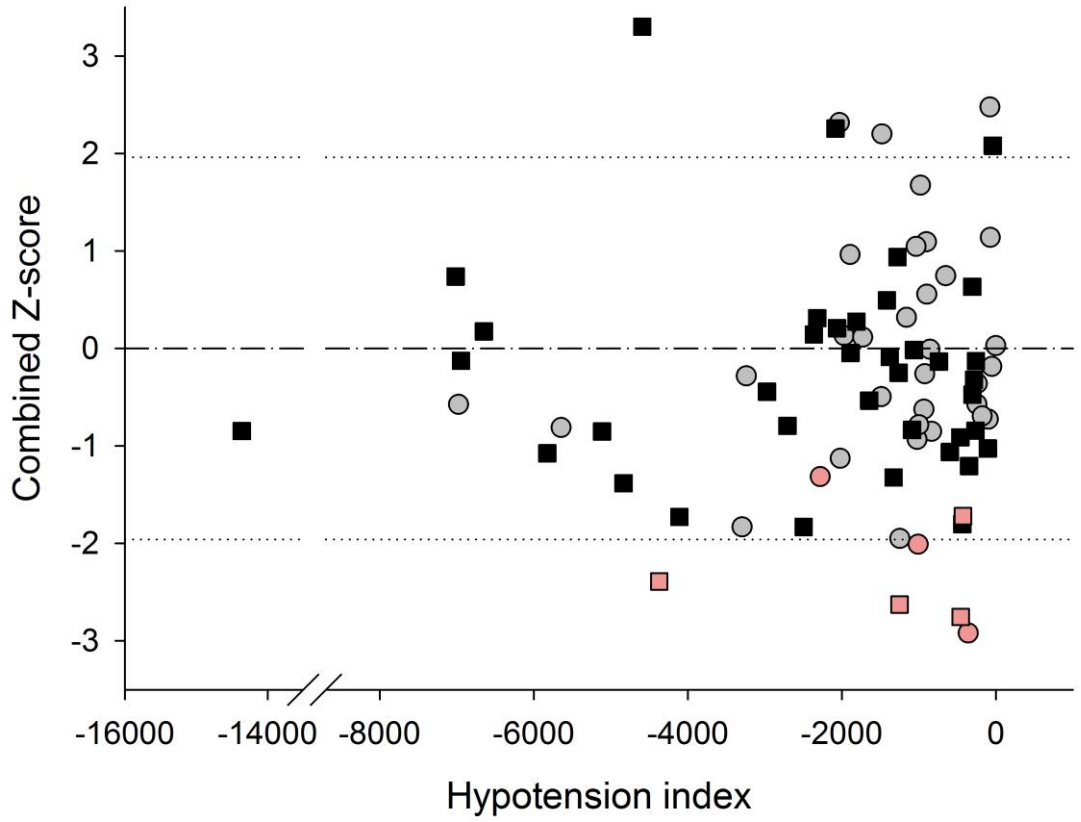

Intraoperative time [%]
60
50
40
30
20
10
0
*
*
*
*
*
Target Group
No - Target Group
<60
60-70
71-80
81-90
91-110
111-120
121-130
131-140
>140
Intraoperative mean arterial pressure
[% of preoperative values]

Figure 3


Combined Z-score
3
2
1
0
-1
-2
-3
-16000
-14000
-8000
-6000
-4000
-2000
0
Hypotension index

1