Neurocrit Care (2021) 34:1047–1061
https://doi.org/10.1007/s12028-020-01072-5

NEUROCRITICAL CARE SOCIETY

REVIEW ARTICLE

Multimorbidity and Critical Care Neurosurgery: Minimizing Major Perioperative Cardiopulmonary Complications

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Abstract

With increasing prevalence of chronic diseases, multimorbid patients have become commonplace in the neurosurgical intensive care unit (neuro-ICU), offering unique management challenges. By reducing physiological reserve and interacting with one another, chronic comorbidities pose a greatly enhanced risk of major postoperative medical complications, especially cardiopulmonary complications, which ultimately exert a negative impact on neurosurgical outcomes. These premises underscore the importance of perioperative optimization, in turn requiring a thorough preoperative risk stratification, a basic understanding of a multimorbid patient's deranged physiology and a proper appreciation of the potential of surgery, anesthesia and neurocritical care interventions to exacerbate comorbid pathophysiologies. This knowledge enables neurosurgeons, neuroanesthesiologists and neurointensivists to function with a heightened level of vigilance in the care of these high-risk patients and can inform the perioperative neuro-ICU management with individualized strategies able to minimize the risk of untoward outcomes. This review highlights potential pitfalls in the intra- and postoperative neuro-ICU period, describes common preoperative risk stratification tools and discusses tailored perioperative ICU management strategies in multimorbid neurosurgical patients, with a special focus on approaches geared toward the minimization of postoperative cardiopulmonary complications and unplanned reintubation.

Keywords: Neurocritical care, Perioperative complications, Neurosurgery, Cardiopulmonary complications, Multimorbidity, Risk stratification

Introduction

Multimorbid patients are commonplace in the neurosurgical intensive care unit (ICU), as a consequence of prolonged life expectancy with rise in the prevalence of chronic diseases [1, 2]. Comorbidities decrease physiological reserve, thereby increasing the risk of progressive organ failure in instances of physiologic stress, such as hypoxemia, extreme changes in blood pressure, hypovolemia, acute blood losses and conditions of heightened sympathetic activity. Therefore, they may adversely affect postoperative ICU care and outcomes through major medical complications. This appreciation has spurred early efforts in developing scoring systems for the assessment of a patient's frailty and reduced tolerance to surgical interventions, such as the American Society of Anesthesiologists physical status (ASAPS), the Revised Cardiac Risk Index (RCRI), the Acute Physiology And Chronic Health Evaluation (APACHE) scores and even a grading system for patients with aneurysmal subarachnoid hemorrhage (SAH) that incorporates medical comorbidities to improve prognostic prediction [3–6].

It is important to appreciate how the interaction among multiple comorbidities has a compounding effect with respect to the risk of postoperative

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in-hospital mortality and major complications—especially cardiopulmonary complications—which parallels an increase in the number of comorbidities, as shown by several, mostly retrospective studies in the neurosurgical literature [7–19]. Recently, a preoperative frailty score has been retrospectively developed by Thomson et al. to predict this enhanced vulnerability in multimorbid patients undergoing cranial neurosurgery [19].

Given such premises, the successful management of this difficult patient population hinges on perioperative optimization and thorough understanding of the effects of surgery, anesthesia and neurocritical care interventions on comorbidity pathophysiology. Our review addresses these principles and aspects of ICU care geared toward minimizing postoperative cardiopulmonary complications.

Anticipating Potential Perioperative Pitfalls

Certain comorbidities, regularly encountered in the neurosurgical ICU, require specific considerations in order to formulate an individually tailored perioperative plan premised upon the anticipation, and geared toward the minimization, of potential medical complications stemming from a patient's poor physiological reserve. This appraisal may guide preoperative medical optimization and the appropriate use of perioperative resources such as neurocritical care. Criteria for intensive neuro-ICU observation remain poorly defined for elective neurosurgical patients [20]; a clinical care pathway entailing perioperative ICU stay for high-risk but stable patients has not currently met uniform adoption, perhaps due to concerns over its cost-effectiveness, the significant institutional commitment that would be required to implement it and the lack of sufficient data to support the necessary cultural change. However, when the combination of multimorbidity with complex neurosurgery is identified, the challenging needs of these patients are arguably better met by a thorough evaluation, medical optimization and careful monitoring that begins preoperatively in the neuro-ICU. Indeed, according to some retrospective studies analyzing various surgical settings, respiratory and hemodynamic instability due to suboptimal preoperative preparation are not infrequently observed upon patient presentation in the operating room and may lead to canceling the elective operation or performing it with a high probability of an untoward outcome [21–23]. Certainly, important pieces of the management puzzle are good mutual understanding and ongoing communication between neurosurgeons, anesthesiologists and neurointensivists regarding a multimorbid patient's needs.

Cardiac Risk Stratification

The above premises bring up the importance of cardiac risk stratification in multimorbid neurosurgical patients, aimed at the individualization of perioperative strategies for reducing major adverse cardiac events (MACE) [24, 25].

For elective cases, this risk assessment is generally performed by an anesthesiologist [26, 27]. It also benefits from the input of the patient's internist, who can endeavor to contribute to the optimization of medical issues and should be engaged in an interdisciplinary communication with all teams involved [28]. For high-risk patients, the participation of the neurointensivist in this evaluation is ideal, as it provides an early opportunity for heightened scrutiny.

An aging population and growing rates of obesity, type II diabetes and chronic kidney disease imply that a greater number of neurosurgical patients will have ischemic heart disease and heart failure and thus an increased MACE risk. Surgery may result in a significant degree of physiological stress that can lead to myocardial dysfunction via volume shifts, acute blood loss, enhanced oxygen demand and increases in blood pressure, heart rate and postoperative platelet reactivity. Cardiovascular perturbations (blood pressure fluctuations, arrhythmias, myocardial ischemia and neurogenic cardiac stunning) may also occur in patients with intracranial lesions as a result of central neurogenic effects on the myocardium [29]. These effects are poorly tolerated in those with a compromised cardiac reserve.

The American College of Cardiology and American Heart Association (ACC/AHA) guidelines stratify non-cardiac surgery into high (> 1%) and low (< 1%) risk categories for MACE [30, 31]. Relevant factors that affect surgery-specific estimates of risk, by influencing hemodynamic stress, include surgery duration and urgency, anticipated blood losses and fluid shifts, and vascular intervention. By these criteria, major neurosurgery (especially complex spine surgery) and carotid endarterectomy are perceived to have an inherently high (> 1%) cardiac risk. However, such high risk has not always been confirmed in large retrospective neurosurgical studies, or has been concluded by interpolating surgery and patient characteristics [32–39]; thus, it cannot be correctly assigned to an individual patient independently of factors such as age and comorbidities.

Known ischemic heart disease, congestive heart failure, insulin-dependent diabetes, chronic kidney disease and cerebrovascular disease are all independently documented to be associated with an increase in postoperative

Table 1 ASA Physical Status Classification System

Classification	Description
ASA I	Healthy patient
ASA II	Mild systemic disease
ASA III	Severe systemic disease
ASA IV	Severe systemic disease that is a constant threat to life
ASA V	Moribund, not expected to survive without the operation
ASA VI	Declared brain dead

Table 2 Revised cardiac risk index (RCRI)

Clinical predictor	Point
H/o cerebrovascular disease	1
H/o heart failure	1
H/o coronary artery disease	1
Preoperative creatinine ≥ 2 mg/dl	1
Insulin-dependent diabetes mellitus	1
High-risk surgery (vascular surgery, any open intraperitoneal or intrathoracic procedure)	1

Rate of myocardial infarction, pulmonary edema, ventricular fibrillation, cardiac arrest and complete heart block, according to the number of predictors [36]

0 = 0.5%; 1 = 1.3%; 2 = 3.6%; ≥ 3 = 9.1%

untoward cardiac events and death. This heightened vulnerability can be captured by the ASAPS classification system [40], where increasing ASA class is associated with a higher risk of complications (Table 1). However, it is more precisely assessed by the RCRI (Table 2), a widely validated tool according to which the presence of two or more risk factors, among six independent predictors of cardiac morbidity, is associated with an elevated risk of MACE [3, 41]. Additionally, a well-validated online surgical risk calculator has been developed using the National Surgical Quality Improvement Program (NSQIP) database and affords a more accurate estimation of cardiac risk, as well as prediction of other perioperative morbidities and mortality [42]. In a recent large retrospective study by Quinn et al., using said database to explore cardiac arrest (CA) rates in non-traumatic emergent and elective craniotomy and spine surgery, an increased risk of CA was documented in patients with ASA class > 3, chronic kidney disease or congestive heart failure [38]. Moreover, patients who suffered CA were more likely to incur additional adverse postoperative outcomes, such as acute kidney injury, dialysis, failure to wean from mechanical ventilation, myocardial infarction, venous thromboembolism and sepsis. The authors therefore suggested that the clinical insight into patient and surgery-specific characteristics afforded by these NSQIP data may prompt therapeutic initiatives aimed at minimizing morbidity and mortality in the neurosurgical patient population, as discussed below.

Intensive Perioperative Management to Reduce Cardiac Risk

The knowledge that factors such as sustained tachycardia, anemia and extreme BP changes increase the risk of myocardial ischemia dictates that the perioperative ICU care includes aggressive pain management, tight BP control and hemodynamic optimization as a standard approach. More controversial issues are the perioperative use of beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs) and the optimal blood transfusion threshold in these high-risk patients.

Perioperative Beta-Blockade and ACEIs/ARBs

Meta-analyses of randomized controlled trials (RCTs) have found a potential for increased mortality and ischemic stroke when beta-blockade is initiated de novo within 24 h of non-cardiac surgery, likely due to beta-blockers' side effects of hypotension as well as their possible interference with cerebral vasodilation [25, 41–46].

In particular, the POISE study (a multicenter placebo-controlled trial of fixed metoprolol dosing for patients undergoing intermediate- and high-risk surgery with at least a RCRI of 1) concluded that a significant reduction in supraventricular arrhythmias and acute myocardial infarction comes at the cost of perioperative hypotension and is offset by a significant increase in 30-day stroke and all-cause mortality [47].

These findings indicate that careful patient selection for perioperative β-blockade is paramount, especially when major surgical blood loss is anticipated. Undoubtedly, discontinuation of chronic β-blocker therapy preoperatively may lead to poorer outcome and is therefore ill-advised [48]. However, equally harmful is the indiscriminate β-blockade of noncardiac surgical patients without strong indications. Most of the patients enrolled in POISE had an RCRI of 1 or 2, but observational studies and a retrospective analysis suggest that perioperative beta-blockers might be beneficial only in patients with an RCRI ≥ 3 and increase the chance of death in patients with RCRI 0 [49–51].

In agreement with this evidence and the recommendations in the ACC/AHA guidelines, one can conclude the following: (1) beta-blockers should be continued in patients who are already receiving them, and (2) it may be reasonable to begin perioperative beta-blockade only in patients in whom a preoperative risk assessment

identifies ≥ 3 RCRI risk factors. However, in the latter instance, de novo initiation of beta-blockade immediately preoperatively remains controversial and should generally be avoided given the above-outlined risk of harm. Conversely, it may be considered postoperatively, with careful titration, as soon as the patient is hemodynamically stable. In such scenario, consultation with a cardiologist is advised to obtain input on the optimization goal.

Controversy surrounds the perioperative management of ACEIs/ARBs, the most commonly prescribed antihypertensive medications in higher-risk surgical patients. Current ACC/AHA guidelines provide a class IIa recommendation for continuing ACEIs/ARBs in the setting of noncardiac surgery. However, a large international prospective cohort study suggested that withholding ACEIs/ARBs in the 24 h before major noncardiac surgery is associated with lower risks of death, intraoperative hypotension, postoperative stroke or myocardial injury [52]. Nevertheless, while confirming the risk of intraoperative hypotension, a 2018 meta-analysis failed to demonstrate an association between perioperative administration of ACEIs/ARBs and mortality or MACE [53]. A large randomized trial is needed to shed more light on this issue. In the interim, withholding ACEIs/ARBs 24 h before surgery is reasonable for most patients (especially when large fluid shifts are anticipated), but their timely postoperative resumption (ideally within 48 h) is arguably important to minimize postoperative MACE risk and mortality [54].

Transfusion Triggers for Neurosurgical Patients with Cardiovascular Diseases

Maintenance of an adequate balance between oxygen supply and demand entails appropriate treatment of anemia. Most studies examining general ICU cohorts favor a restrictive transfusion threshold of hemoglobin 7 g/dl, but conclusive evidence to guide practices in neurosurgical patients remains lacking [55–58].

Anemia has been associated with increased postoperative mortality after noncardiac surgery, as well as poorer outcomes after acute brain injury [59, 60], but so is the use of blood transfusion, which appears to parallel an increased risk of intra-hospital mortality, infections, cerebral vasospasm, worsened cerebral autoregulation and other adverse events in neurosurgical patients [61–71]. The proposed mechanisms for these adverse outcomes are related to a number of changes in red blood cells (RBC) that occur with the aging of refrigerated blood (stored up to 42 days), collectively referred to as the "RBC storage lesion." These include: (1) depletion of intraerythrocytic energy sources and development of membrane structural alterations, which lead to impaired RBC deformability and increased fragility; the latter results in release of breakdown products able to induce pro-oxidant effects, cytotoxicity and increased nitric oxide (NO) consumption; (2) decrease in levels of 2,3-diphosphoglycerate (DPG), which reduces tissue oxygen delivery by shifting the oxyhemoglobin dissociation curve to the left; and (3) deficiency of blood NO synthase activity, which may contribute to microvascular perturbations by reducing NO bioavailability [72]. Findings of adverse outcomes from transfusions have been, however, inconsistent in the literature; moreover, methodological weaknesses of pertinent studies make it difficult to separate the detrimental effects of anemia and transfusions from those related to the severity of the underlying disease [73].

The ideal transfusion strategy in neurosurgical patients remains thus a clinical conundrum, and an individualized risk–benefit analysis is encouraged. In this respect, a systematic review of RCTs revealed an increased risk of acute coronary syndrome in patients with cardiovascular diseases randomized to a restrictive threshold, thereby suggesting the benefit of a more liberal transfusion strategy (> 9) in this group [74]. Additionally, in a retrospective study of noncardiac surgical patients, acute surgical anemia, with a hemoglobin drop exceeding 35% of the preoperative value, increased the risk of MACE, especially in beta-blocked patients, suggesting that transfusion triggers should be higher for this group of patients [75].

Advanced Hemodynamic Monitoring

Precise hemodynamic monitoring and management, with the goal of preventing both hypovolemia and hypervolemia, is important for maintenance of adequate cerebral blood flow (CBF) and minimization of systemic complications in patients with vasospasm after SAH. Either inadequate or overly aggressive intravascular fluid administration may result in excess morbidity and mortality from delayed cerebral ischemia (DCI) or cardiopulmonary complications, respectively. These considerations are especially relevant to multimorbid neurosurgical patients with poor cardiac reserve or renal compromise, who are at risk of development or aggravation of pulmonary edema after even a modest preload augmentation. The ability to monitor CO may also better guide efforts aimed at avoidance of cerebral hypoperfusion. Indeed, the potential existence of a direct CO-CBF connection, emerging in specific situations of physiologic stress, has been highlighted in a recent editorial by Drummond, arguing that therapeutic ameliorations of low CO might stimulate mechanisms responsible for cerebral vasodilation (e.g., decreased output from the cervical sympathetic chain, which provides vasoconstrictor innervation of cerebral extracranial and proximal

intracranial vessels; endothelial NO release in response to increased arterial pulsatility). Albeit limited and not widely acknowledged, the physiological evidence available on these mechanisms is clear enough, the author argues to support the suggestion that augmenting MAP by means of vasopressors in the face of decreased CO may further compromise CBF via additional reduction of CO, which would promote the aforementioned sympathetic-mediated vasoconstriction of cerebral vessels. In such context, CO restoration with an inotrope would represent a more physiologically sound approach to CBF preservation [76].

Several available systems for minimally invasive advanced hemodynamic monitoring (e.g., PiCCO™, LiDCO™, FloTrac™/Vigileo™ and VolumeView™/EV1000™) can provide continuous estimates of CO and volume responsiveness, obviating the inadequacies and risks of these determinations using a pulmonary artery catheter (PAC) [77–79]. These devices require the insertion of an arterial catheter for beat-to-beat analysis of the contour of the arterial pulse pressure waveform, which is then related to stroke volume (SV: proportional to the area under the curve of the systolic portion of the arterial waveform). Some of these methodologies (PiCCO™, VolumeView™/EV1000™) allow for calibration of the pulse contour analysis via intermittent transpulmonary thermodilution (TTD) measurements of CO. This non-automated process requires a central venous catheter (CVC), for injection of a small cold saline bolus, and the insertion of a thermistor-tipped central arterial catheter, which records aortic pressure waveforms and senses the decrease in blood temperature following the cold bolus. The analysis of the aortic TTD curve is then used to intermittently calculate CO (inversely proportional to the area under this curve) based on the Stewart-Hamilton equation [80]. Evidence suggests that TTD measurements compare well with PAC measurements of absolute CO values (PATDCO) [81–83], with the basic difference being that PATDCO changes in blood temperature are recorded by a thermistor located in the PA, with an earlier and higher peak compared with the TTD curve [77]. TTD also allows determination of certain intrathoracic volumetric variables of pathophysiological interest, as later discussed. Calibration of the pulse contour analysis via a transpulmonary lithium dilution technique (i.e., LiDCO™ system, which calculates CO from an injected minimal dose of lithium and the area under the concentration–time curve prior to recirculation) is an alternative strategy that does not require a CVC or specialized central arterial catheter, but does not calculate the aforementioned intrathoracic volumetric variables [77, 84].

Other useful provided parameters are stroke volume variation (SVV), pulse pressure variation (PPV), global end-diastolic volume index (GEDVI, normal range 680–800 ml/m^2) and extravascular lung water index (EVLWI, normal range 3–7 ml/kg).

SVV and PPV (the percentage of variation in SV and PP, respectively, in response to preload changes during a single mechanical respiratory cycle) have been proved to be far better predictors of fluid responsiveness than static indices of ventricular preload, such as central venous pressure (CVP) and pulmonary artery occlusion pressure [85–88]. Under controlled mechanical ventilation, SVV and PPV are dynamic reflections of a patient's position on the Frank–Starling curve and can reliably predict preload responsiveness, provided that patients are ventilated with tidal volumes of at least 8 ml/kg, not spontaneously breathing, with normal right ventricle function and without arrhythmias [89]. A low SVV or PPV correlates with a patient operating on the flat part of the curve, denoting SV insensitiveness to cyclic changes in preload induced by mechanical inspiration, and thus a lack of fluid responsiveness. Conversely, a greater SVV or PPV indicates that the patient is operating on the steep portion of the curve and hence fluid responsive [90–95].

GEDVI and EVLWI are volumetric variables measured by TTD. GEDVI is a static index of cardiac preload, representing the combined end-diastolic volumes of the four cardiac chambers. However, it does not distinguish between left and right cardiac preloads: In the setting of right ventricular dilation, GEDV may be increased in the face of normal left ventricular preload. EVLWI informs the amount of water present in the lungs, making it a useful parameter to monitor the onset and evolution of pulmonary edema [96–102].

Published treatment thresholds for these variables are heterogeneous, but in general a SVV > 10%, PPV > 13% or GEDVI < 680 ml/m^2 are predictors of fluid responsiveness; SVV < 10% and PPV < 13% indicate lack of fluid responsiveness; GEDV > 921 ml/m^2 and EVLW > 10 ml/kg represent warning parameters for pulmonary edema [93, 103–105].

These tools have been applied for pre- and intraoperative fluid optimization in intracranial surgeries, as neurosurgical patients often experience significant intravascular volume changes owing to volatile anesthetics and vasodilators during anesthesia [93, 106]. Additionally, they have been studied in postoperative SAH patients. In a prospective randomized trial of 100 consecutive SAH cases, patients undergoing early goal-directed hemodynamic management guided by the PiCCOplus system experienced reduced incidences of TCD vasospasm, DCI, pulmonary edema and arrhythmias, compared with those managed with traditional therapy guided by CVC or PAC-derived preload measures [103]. In a multicenter prospective observational study of 180 SAH patients

monitored with the PiCCO system, a GEDVI < 822 ml/m^2 during the first week after SAH best correlated with DCI, suggesting that maintaining GEDVI slightly above normal levels could minimize this complication. In contrast, values greater than 921 ml/m^2 independently and best correlated with severe pulmonary edema [104]. In addition, a single-center prospective observational study of ten consecutive patients with poor-grade SAH demonstrated a strong relationship between brain tissue oxygen pressure amelioration and CI augmentation in response to fluid challenges, which was predicted by an SVV ≥ 9% [105].

This evidence suggests that goal-directed hemodynamic management via these tools can offer a therapeutic advantage for improving the functional outcome of SAH patients with vasospasm [106], as well as reducing cardiopulmonary complications from volume overload in neurosurgical patients with poor cardiac or renal function.

All pulse contour analysis monitors, however, suffer from sources of potential error and clinical limitations (Table 3), described in detail elsewhere [77, 96, 107–117]. It is also important to keep in mind that SSV and PPV are not indicators of volume status, but dynamic markers of the position on the Frank–Starling curve, reflecting LV responsiveness to preload changes. The slope of such curve, however, depends upon inotropy and afterload, which determine the LV performance. For a given LV preload, decreasing inotropy or increasing afterload (vasopressors) decreases the slope of the Frank–Starling curve (i.e., decreased LV performance), resulting in a lower SV, and hence a decreased SVV and PPV. Conversely, increasing inotropy (inotropes) or decreasing afterload (e.g., sepsis, vasodilators) increases the slope (improved LV performance), resulting in greater SV, SVV and PPV. Vasopressors may also decrease the magnitude of SVV and PPV (thereby masking true intravascular volume deficit) by increasing venomotor tone, which enhances venous return (and thus SV) by shifting blood from unstressed to stressed volume [118–120]. By contrast, vasodilators can decrease SVV and PPV by increasing unstressed circulating blood volume, thus creating a relative hypovolemic state [121]. The implication is that significant variations in inotropy or vasomotor tone can influence both PPV and SVV independently of true volume status, potentially leading to misinterpretation of these indicators for fluid management [122–131]. For instance, fluid therapy guided by ideal cutoff values for SVV and PPV may lead to volume overload in patients with increased contractility or decreased afterload, and occult hypovolemia in those with either decreased contractility or vasopressor-induced increases in afterload and venomotor tone. While the decision to administer fluids should not be based on these dynamic indices in the early phase of septic shock or in the setting of overt fluid/blood losses (where fluid administration is obviously beneficial), the assessment of the need for further volume expansion after initial resuscitation can be appropriately guided by SVV and PPV only when influenced by the knowledge that the aforementioned confounding interactions may hinder the ability of these variables to indicate an intravascular volume shift. Moreover, even if preload responsiveness is detected, the decision of fluid administration should not be automatic, but based on a risk–benefit analysis that takes into consideration the absence of a high risk of fluid overload and the presence of tissue hypoperfusion/hypoxia [132–134]. It is thus important to implement a thoughtful approach integrating CO and dynamic indices of volume responsiveness

Table 3 Limitations of pulse contour analysis systems

Method	Major limitations
All methods (calibrated and uncalibrated)	Rely on an optimal arterial signal to estimate flow from pressure: lack accuracy if *over- or under-damped traces, arrhythmias, significant aortic regurgitation, use of intra-aortic balloon counterpulsation* SVV and PPV are not reliable if *spontaneous breathing, arrhythmias, mechanical ventilation with low tidal volume, low lung compliance, increased abdominal pressure, open chest* SVV accuracy affected by the 30-*degree head-up or prone position*, which are associated with decreased SV
Uncalibrated methods (e.g., FloTrac®/Vigileo®; LiDCOrapid®/pulseCO®)	Estimate dynamic characteristics of the arterial vasculature (impedance, compliance and resistance) by integrating analysis of the geometrical properties of the arterial pressure waveform with mean arterial pressure and patients' biometric data (e.g., age, sex, height and weight): *in patients with significant changes in arterial compliance and vasomotor tone, such model lends itself to an incorrect estimation of the resistive component of the cardiovascular system and thus inaccuracies in CO measurement* (*calibrated devices preferable in those circumstances*, as they provide an accurate determination of aortic impedance and compliance by calibration against a measure of CO obtained from transpulmonary dilution)
Calibrated methods (external calibration) Transpulmonary thermodilution (PiCCO®; VolumeView®/EV1000®) Transpulmonary lithium dilution (LiDCO®)	TTD methods: (1) Regular external calibration needed every 6 h to confirm continued accuracy: its *intermittent nature precludes detections of short-term changes* (2) Need for specialized central arterial catheter and central venous line: *increased risk of infection, bleeding* LiDCO: Decreased accuracy compared to thermodilution methods; intrathoracic volume quantification not available; measurements affected by muscle relaxants; expensive

with "downstream" markers of organ perfusion (e.g., venous oxygen saturation, lactate, capillary refill and troponin), which better reflect the need and adequacy of resuscitation [135].

Postoperative Pulmonary Complications in Multimorbid Patients

Multimorbid neurosurgical patients are at increased risk of postoperative pulmonary complications (PPCs: atelectasis, pneumonia, pulmonary embolism, postoperative respiratory depression and prolonged mechanical ventilation), which are a significant source of morbidity and mortality [136].

COPD, in particular, emerges as the most consistent predictor for PPCs across studies: COPD patients are more sensitive to the respiratory depressant effects of sedatives, opioids and residual anesthetic agents, which increase their risk of unplanned intubation. Additionally, exacerbation of bronchial inflammation at the time of preoperative intubation, chronic bacterial airway colonization and surgery-induced immunosuppression may all promote pulmonary infections and acute respiratory failure in this population. COPD patients also tend to have coexisting coronary artery disease and congestive heart failure, with inherent increased risk of pulmonary edema. Finally, they display an increased propensity for fatal pulmonary embolism [137–141].

Similarly, morbidly obese neurosurgical patients are at a substantially increased risk of postoperative respiratory dysfunction, extubation failure and ventilator weaning difficulty. The neurointensivist must keep in mind the altered respiratory mechanics of these patients, with reduced chest wall compliance in relation to the massive adiposity of the chest wall, diaphragm and abdomen, which restricts chest wall mobility and diaphragmatic excursion into the abdominal cavity. Such alterations can be exacerbated by: supine or prone positioning, which allows the elevated pressure of the massive abdominal compartment to displace the diaphragm upward reducing the capacity of the chest; postoperative pain, leading to restrictions on ventilation; general anesthesia and residual anesthetic effects, causing a loss of diaphragmatic tone with unopposed intra-abdominal pressure; and administration of sedatives or opioids [142–149]. This deranged physiology leads to a reduction in lung volumes, specifically functional residual capacity (FRC) and expiratory reserve volume (ERV), which in turn predisposes obese patients to: 1) atelectasis in the basal lung regions (alveolar and small airway collapse due to the FRC falling within the range of the closing capacity), with ensuing ventilation-perfusion (V/Q) mismatch (a frequent cause of hypoxemia in obese patients); (2) increased airway resistance with expiratory flow limitation (EFL) due to early airway closure, resulting in air trapping and thus higher intrinsic positive end-expiratory pressure ("auto-PEEP"); and (3) increased work of breathing, as inspiratory muscles are loaded by the task of overcoming both reduced chest wall compliance and auto-PEEP [150–153]. In this respect, it must be emphasized that, in order to facilitate diaphragmatic excursion and prevent expiratory flow limitation, spontaneously breathing morbidly obese patients should never be allowed to lie completely flat. Conversely, the reverse Trendelenburg position can unload the weight of the intra-abdominal contents from the diaphragm, thereby increasing chest compliance, FRC and oxygenation [154–159].

Obese patients also exhibit a high rate of obstructive sleep apnea (OSA), an additional risk factor for unplanned reintubation after even trivial insults. Even minimal concentrations of residual anesthetics, or low doses of sedatives and opioid analgesics may worsen OSA by decreasing pharyngeal muscle tone (via decreased neural input through the hypoglossal nerve) and blunting the ventilatory and arousal responses to hypercapnea, hypoxia and upper airway obstruction [160–164].

Minimizing the Risks of Postoperative Reintubation in Neurosurgical Patients with Obesity or COPD

Several strategies have the potential to minimize the high risk of unplanned reintubation in patients with morbid obesity and/or COPD, in turn associated with higher mortality, longer ICU course, increased incidence of nosocomial pneumonia and increased risk of transfer to long-term care facilities [165–168]. Incentive spirometry and aggressive chest physiotherapy should be instituted in the immediate postoperative stage [169]. Additionally, avoidance of benzodiazepine and minimization of long-acting opioids are important factors to decrease the risk of respiratory depression. Although the judicious use of opioids remains the mainstay of postoperative pain management after neurosurgery, multimodal analgesia sedation that relies of non-opioids agents, such as acetaminophen, dexmedetomidine, ketamine and gabapentinoids, should be strongly considered to minimize the requirement for opioids in these high-risk patients and is best implemented with the collaboration of a pain specialist.

In particular, dexmedetomidine (α2-adrenoceptor agonist) is an attractive agent increasingly used after neurosurgery because of its properties of inducing sedation and analgesia without causing significant respiratory depression or obstructive breathing, as well as its sympatholytic effects that help maintain a stable blood pressure and heart rate [170].

Due to its opioid-sparing effects, ketamine (non-competitive NMDA antagonist) may also have a place in ICU analgo-sedation regimens for neurosurgical patients at high risk of respiratory depression, being especially well suited for patients with chronic pain and opioid dependence undergoing major spine surgeries [171–175].

Gabapentinoids are additional options that appear beneficial in patients undergoing major spine surgery, since they block calcium channels, which are upregulated in dorsal root ganglia and contribute to neuropathic pain. They may also have anxiolytic properties, decreasing postoperative anxiety scores [175–177]. It is worth noting, however, that, according to several case reports and two randomized trials, a higher risk of respiratory depression seems to exist when gabapentinoids are either combined with CNS depressants (e.g., opioids, benzodiazepines, antidepressants, antipsychotics and antihistamines) or administered in COPD and elderly patients [178–187].

Other opioid-sparing strategies that may be considered for these high-risk patients include: (1) regional scalp block using local anesthetics (e.g., lidocaine, bupivacaine or ropivacaine) before incision in craniotomy surgery [188] and (2) combined epidural/general anesthesia with postoperative epidural analgesia in patients undergoing major spine surgery. According to a prospective, randomized study, this latter approach may lead to better pain control, less bleeding and a lower surgical stress response than conventional general anesthesia with postoperative opioid analgesia [189]. However, this strategy is not widely adopted. Moreover, patients undergoing epidural analgesia require careful postoperative monitoring and management in consultation with a pain specialist, given the potential significant side effects of sympathetic blockade.

Several authors have also documented the benefits of the immediate, prophylactic post-extubation application of either continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV), in order to minimize the risk of reintubation in high-risk patients [190–194]. Evidence for the postoperative implementation of noninvasive ventilatory support, as a preventative measure in recently extubated patients, is lacking in the neurosurgical literature; however, this strategy is supported by randomized trials and meta-analyses which have examined its use in various other surgical settings, documenting improved arterial blood gases, decreased reintubation rate and lower mortality if it is applied soon after extubation and before the onset of respiratory failure [194–198]. In contrast, NIV appears ineffective in reducing the need for reintubation, and potentially harmful, if it is delayed until after the onset of post-extubation respiratory failure [199].

Post-extubation high-flow nasal cannula (HFNC), which delivers heated and humidified oxygen at a rate of up to 60 l/min, is a reliable alternative to NIV to reduce reintubation rates in patients at high risk of hypoxemic respiratory failure, according to RCTs and meta-analyses [200–203]. In properly selected patients, HFNC may be considered to avoid potential issues with the use of NIV, such as skin damage, eye irritation, interface intolerance, diet and expectoration interruption. The mechanisms underlying the efficacy HFNC in decreasing reintubation rate include: (1) the generation of a low PEEP level in the pharynx (2.7–7.4 cm H_2O, based on flow rate, nasal prongs size and mouth position), which reduces airway collapse, maintains alveolar recruitment and improves the ventilation–perfusion mismatch; (2) the ability to deliver constant inspired oxygen concentrations of up to 100% while also providing heated humidification of the airway, which in turn improves comfort and facilitates secretion clearance; (3) the decrease in work of breathing related to a CO_2 washout of pharyngeal dead space, as HFNC creates an oxygen reservoir within the pharynx by virtue of a high oxygen flow; this results in reduced CO_2 rebreathing and thus improves the efficiency of ventilation [204–213]. However, as a form of continuous positive airway pressure, HFNO shares certain potential contraindications with NIV, including skull base fractures or surgeries and recent transsphenoidal surgery, where the delivery of such pressure may result in breakdown of the operative repair or pneumocephalus [214].

Mechanical Ventilation of Morbidly Obese Patients: Optimization of Body Position, Application of Higher PEEP and Careful Interpretation of Plateau Pressures

The deranged respiratory mechanics related to extreme obesity have important implications for the extended mechanical ventilation, when required, of this group of neurosurgical patients. Their predisposition to EFL, auto-PEEP and basal lung atelectasis, and often coexisting obesity hypoventilation syndrome, all pose particular challenges to the maintenance of adequate oxygenation and the process of liberation from mechanical ventilation.

Since the reverse Trendelenburg position, as opposed to the supine one, has been shown to ameliorate respiratory system compliance, it can be inferred that ventilating hemodynamically stable, morbidly obese patients in such position may be part of a successful strategy aimed at decreasing their work of breathing and facilitating weaning from mechanical ventilation [215]. A modification of this position that can equally improve respiratory mechanics is a “cardiac chair position” obtained by raising the upper half of the bed by 70° while the patient’s back is kept straight and the buttocks lean on the back of

the bed. Such posture in obese patients requiring invasive mechanical ventilation was associated with a partial or complete reversal of EFL resulting in a reduction of auto-PEEP compared to the supine position [216].

The application of a higher PEEP of 10 cm H_2O, to prevent basal atelectasis from small airway and alveolar collapse, has been found to lead to significant improvements in respiratory compliance, inspiratory resistance and oxygenation in morbidly obese patients compared to non-obese subjects [217, 218].

Finally, in the modern era of lung-protective ventilation, using low tidal volumes and targeting a plateau pressure < 30 cm H_2O is recommended to minimize ventilation-induced lung injury (VILI), which recognizes in regional lung overdistension its key promoter [219]. Because of the reduced chest compliance in morbid obesity, plateau pressures should be interpreted, however, with caution: A high value does not necessarily imply alveolar overdistension, since these patients have elevated pleural pressures resulting in a lower transpulmonary pressure. Thus, when using lung-protective ventilation in morbidly obese patients, a plateau pressure of 35–40 cm H_2O may be acceptable in some instances [220]. One option to monitor lung inflation pressures is via indirect measurements of transpulmonary pressures using the esophageal balloon technique (esophageal pressure monitoring), which can assist the intensivist in the optimization of the ventilator strategy to limit VILI in the physiologically complex obese patients [221, 222].

Conclusions

The critical care management of multimorbid neurosurgical patients is often challenging, but a thorough understanding of their comorbidities and physiopathology enables the neurocritical care team to minimize and appropriately manage major perioperative hemodynamic and pulmonary complications.

De novo postoperative initiation of beta-blockade, with careful titration, should be considered in selected neurosurgical patients with three or more RCRI factors, in order to minimize the risk of perioperative myocardial ischemia and cardiac death.

Blood transfusion triggers remain elusive; however, a more liberal hemoglobin threshold may benefit neurosurgical patients with a history of cardiovascular disease.

Several minimally invasive systems for advanced hemodynamic monitoring may be useful for guiding precise volume management in neurosurgical patients with cardiopulmonary and renal comorbidities, which render them prone to acute pulmonary edema from overzealous fluid administration, especially during cerebral vasospasm treatment.

A number of strategies can reduce the risk of unplanned reintubation in high-risk populations, such as (1) avoidance of the supine position and use of the reverse Trendelenburg position in morbidly obese patients, (2) immediate post-extubation application of either NIV or HFNC (in selected patients with no contraindications to positive pressure) and (3) implementation of opioid-sparing multimodal analgesia in either obese or COPD patients.

Further, a higher PEEP of 10 cm H_2O is beneficial to minimize basal atelectasis in mechanically ventilated morbidly obese patients.

Last but not least, frequent communication between the neurosurgical and neurocritical care teams is crucial for delivering optimal care to multimorbid neurosurgical patients.

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RA was involved in the literature search and writing of the manuscript. AM was involved in the conception of the manuscript, literature search, writing and editing of the manuscript.

Source of Support
None.

Conflict of interest
The authors declare that they have no conflicts of interest.

Ethical approval/Informed consent
This article does not contain any studies with human participants performed by any of the authors.

Publisher's Note

Received: 3 March 2020 Accepted: 28 July 2020
Published online: 13 August 2020

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