Reducing Mortality in Critically Ill Patients

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Contents

Decision Making in the Democracy-based Medicine Era: The Consensus Conference Process

1

Massimiliano Greco, Marialuisa Azzolini, and Giacomo Monti

Randomized controlled trials (RCTs) are considered the gold standard in evidence-based medicine. However, their efficacy in producing reliable findings has been recently criticized in the field of critical care medicine [1]. While an increasing number of RCTs on critically ill patients have been published over the last few years, a large part of these trials failed to find significant effects [2]. Moreover, when an intervention produced an effect on mortality, it was frequently contradicted by further trials that showed no effect for the same intervention or even opposite results ("the pendulum effect") [1]. Lack of reproducibility or external validity, underpowered studies, or methodological flaws created a blurred picture on the available evidence in critical care medicine. Given these premises, the task of driving clinical practice according to the updated literature has become a tough job for the clinician.

Consensus conference and guidelines were designed to simplify this task [3]. However, their approach has been criticized, due to the priority given to experts' opinion and the possibility of introducing expert-related bias [4].

A new method has been recently proposed and already employed in neighboring fields to answer these drawbacks: democracy-based medicine [5–8].

Following this pathway, a new democratic consensus conference was conducted to identify all the randomized controlled trial with a statistical significant effect on mortality ever published in the intensive care setting.

The entire process of consensus building has been described elsewhere [5] and is summarized in this chapter.

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1.1 Systematic Review

We performed a systematic review searching several scientific databases (MEDLINE/PubMed, Scopus, and Embase) to identify all multicenter RCTs on any intervention influencing mortality in critically ill patients (research updated to June 20, 2013).

Inclusion criteria were:

- Multicenter RCT published in a peer review journal reporting a statistical significant difference on unadjusted mortality between cases and controls at any time
- Focusing on critically ill patients, defined as all patients with acute failure of at least one organ or need for intensive treatment or emergency treatment, regardless of where the admission ward is
- Assessing nonsurgical interventions (but including any other drugs, strategy, or techniques)

The literature research identified more than 36,000 papers that were screened at title/abstract level, of these 200 were retrieved in full text and analyzed. Sixty-three were finally identified in this preliminary phase.

1.2 Reaching Consensus in Democracy-based Medicine

The process of democray-based medicine was based on two distinct worldwide surveys and on an international meeting held between them. The first survey explored the opinions on the strength of the evidence on the articles identified by the systematic review and included a platform where colleagues could also propose other articles allegedly missed by the systematic review.

The international meeting was held on June 20, 2013, at the Vita-Salute San Raffaele University in Milan. The 63 earlier identified articles were analyzed considering the results of the first web survey. Several papers were then excluded because of methodological flaws or exclusion criteria. Nineteen interventions influencing mortality were finally identified during the consensus meeting.

For each of them, a statement was proposed by the consensus meeting to synthetize the participants' opinion on the available evidence on each topic. The external validity of this process was explored by the second web survey, which collected the vote of colleagues worldwide on each statement proposed by the consensus.

The second web survey had the possibility to exclude other studies when there was low agreement among voters.

1.3 The 15 Identified Topics and the Diffusion of the Results to the International Community of Colleagues

Fifteen topics were thus finally identified and reported in Table 1.1 [9–32]. They are extensively described, along with the evidence to support them, in this book, where the reader will find a chapter dedicated to each one of these 15 topics.

Table 1.1 The 15 interventions influencing mortality identified by the consensus conference

Increasing survival	Increasing mortality
Albumin in hepatorenal syndrome [9]	Supranormal elevation of systemic oxygen delivery [25]
Daily interruption of sedatives [10]	Diaspirin cross-linked hemoglobin [26]
Mild hypothermia [11]	Growth hormone [27]
Noninvasive ventilation [12–19]	Tight glucose control [28]
Prone position [20]	IV salbutamol [29]
Protective ventilation [21–23]	Hydroxyethyl starch [30]
Tranexamic acid [24]	High-frequency oscillatory ventilation [31]
	Glutamine supplementation [32]

They were identified through a democratic process by a total of 555 physicians from 61 countries that chose to participate in the first democracy-based consensus conference on randomized and multicenter evidence to reduce mortality in critically ill patients.

Given these premises and the large amount of information collected and generated through the whole process, the authors had the ethical duty to disseminate consensus results so as to reach the widest audience of peers. In addition to this book, the main article regarding the consensus is published in Critical Care Medicine [33], and further articles will be published to describe other unpublished findings of the consensus.

1.4 A Common Shell for a Flexible Process

The process above described in detail was the same with small difference among all the four consensus conferences [6–8, 33]. The first three consensus conferences focused on cardiac anesthesia and intensive care (6), on the perioperative period of any surgery (7), and on patients with or at risk for acute kidney injury (8). The perioperative consensus process and results have already been described in details on a Springer book [34].

The four consensus conferences included between 340 and 1,090 participants from 61 to 77 countries. All were based on a systematic review of literature, on two web-based surveys that preceded and followed, respectively, an international meeting. Each time we published a manuscript on the consensus results on an international journal. There were only a small difference related to the systematic review (according to the broadness and complexity of the subject) and some variance in the question posed by the web survey [5]. However, the five-step process for democratic consensus building is now well tested and to our knowledge is the only method employed to democratically share the decision process with a global audience and to allow to reach an agreement among a population of colleagues in a worldwide horizon.

Conclusions

This consensus conference identified the 15 interventions with the strongest evidence of a positive or negative effect on mortality in the critical care setting. This summary of evidence may serve as a fundamental guide for clinicians worldwide

to orientate their clinical practice, as this is the largest and global survey of intensivists' opinion on ICU treatment reported so far.

This conference is the fourth to be based on the new concept of democracy-based medicine. This process enhances the possibilities of communication and consensus building between pairs, allowing for a global debate of colleagues on the published evidence. The more and more frequent updates in evidence-based medicine will probably benefit from the diffusion of new information technologies and from the methods made available by the new democracy-based medicine. A dedicated web site has recently been created to perform updates of these consensus conferences and create new ones, www.democracy-basedmedicine.org.

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Part I

Interventions that Reduce Mortality

Noninvasive Ventilation

2

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2.1 General Principles

Noninvasive ventilation (NIV) refers to the delivery of positive pressure to the airways and lungs in the absence of an intratracheal tube or an extra-glottic device. Within "NIV" we include both continuous positive airway pressure (CPAP) and any form of noninvasive inspiratory positive-pressure ventilation (NPPV), in which an expiratory positive airway pressure is almost always present [1].

The main benefits of NIV in the prevention or treatment of acute respiratory failure (ARF) include conservation or restoration of lung volumes, reduction of the work of breathing, avoidance or reduction of complications associated with tracheal intubation, greater ease of use of NIV compared to invasive mechanical ventilation, and application even in patients unfit for intubation or outside the ICU [1, 2]. On the other hand, NIV can be contraindicated in some conditions as the inability to manage secretions or the need to protect the airway.

In the last two decades, the use of NIV has continuously increased. A large number of studies have evaluated its efficacy and its limits in acute care settings [3].

2.2 Pathophysiological Principles

Most underlying pathophysiological mechanisms involved in ARF concern imbalances between respiratory system mechanical work and neuromuscular competence and disorders in gas exchange and increased cardiac preload and afterload.

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By using expiratory and inspiratory positive pressures, NIV allows the respiratory muscles to rest, reducing respiratory work as well as cardiac preload and afterload, improving alveolar recruitment, and thus increasing lung volume. As a consequence, pulmonary compliance and oxygenation are commonly improved [4].

2.3 Main Evidences and Clinical Indications

So far ten multicenter randomized trials (mRCTs) evaluated NIV in different conditions. Characteristics of these mRCTs are summarized in Table 2.1.

2.3.1 Noninvasive Ventilation in Hypercapnic Patients

Three mRCTs evaluated NIV in the treatment of hypercapnic respiratory failure.

In the first, Brochard et al. enrolled 85 patients with COPD exacerbations in five hospitals in three countries (France, Italy, and Spain). Patients were randomized to standard oxygen therapy or NPPV (at least 6 h/day). Hospital mortality was 29 % in the control group vs 9 % in the NIV group ($p = 0.02$), thanks to the lower rate of intubation in the NIV group [5].

Plant et al. conducted a mRCT in 14 hospitals in UK, enrolling 236 patients with mild to moderate respiratory acidosis during COPD exacerbations. NPPV was compared to oxygen therapy. Noninvasive ventilation was applied for as long as tolerated on the first day and then progressively suspended on day 4. In the NIV group, the mortality rate was half that of the standard group (12/118 vs 24/118) [6].

More recently, Nava et al. evaluated NIV efficacy in patients with chronic pulmonary disease and acute hypercapnic respiratory failure aged over 75 years. The study enrolled 82 patients in three respiratory intensive care units in Italy and Switzerland. Noninvasive ventilation (as NPPV) was compared to standard treatment. Survival was significantly better in the NIV group at hospital discharge (1/41 vs 6/41 deaths), after 6 and after 12 months [7].

Another nine single-center RCTs evaluated NIV efficacy on mortality for exacerbation of COPD [8–16]. Three noteworthy trials were conducted on respiratory or general wards [12, 13, 15]; only one trial randomized severely ill patients comparing NIV to tracheal intubation [16]. Meta-analysis of the results found a marked beneficial effect on mortality [17].

State of the Art

Noninvasive ventilation is considered a first-line intervention for exacerbation of COPD, with a 1A grade of evidence [3, 18]. The benefit on survival was demonstrated under various conditions in mRCTs and single-center RCTs. In this setting, NPPV should be adopted, as it supports the increased work of breathing of COPD patients. No trial evaluated CPAP in this context.

Table 2.1 Characteristics of multicenter randomized controlled trials that evaluate noninvasive ventilation

First author	Year	N° centers	NIV application	Setting	Mask	Patients in NIV group	Patients in control group	Mortality NIV	Mortality control
Brochard [5]	1995	5	Hypercapnic	ICU	Face	43	42	4 (hospital)	12 (hospital)
Plant [6]	2000	14	Hypercapnic	Ward	Face/full face/nasal	118	118	12 (hospital)	24 (hospital)
Nava [7]	2011	3	Hypercapnic after T-piece trial failure	Ward	Full face	41	41	16 (1 year)	25 (1 year)
Ferrer [19]	2003	3	Hypoxemic	ICU	Face/nasal	51	54	10 (90 days)	21 (90 days)
Nava [47]	1998	3	Earlier extubation (failed T-piece trial)	ICU	Face	25	25	18 (90 days)	23 (90 days)
Ferrer [48]	2003	2	Earlier extubation (failed T-piece trial)	ICU	Face/nasal	21	22	6 (90 days)	13 (90 days)
Collaborating Research Group for Noninvasive Mechanical Ventilation of Chinese Respiratory Society [49]	2005	11	Earlier extubation (accelerated, in pulmonary infection)	ICU	Face	47	43	1 (hospital)	7 (hospital)
Ferrer [50]	2009	2	Prevention of post-extubation ARF (high risk)	ICU	Face	54	52	6 (hospital)	11 (hospital)
Ferrer [58]	2006	2	Prevention of post-extubation ARF (high risk)	ICU	NA	79	83	13 (hospital)	19 (hospital)
Esteban [62]	2004	8	Post-extubation ARF	ICU	Full face	114	107	28 (90 days)	15 (90 days)

2.3.2 Noninvasive Ventilation to Treat Acute Respiratory Failure: Hypoxemic Patients

One mRCT evaluated NIV in hypoxemic patients.

Ferrer et al. enrolled 105 patients with severe hypoxemia (pO_2 <60 mmHg with Venturi mask at 50 % of oxygen) in three ICUs in Spain. Noninvasive ventilation (such as NPPV), applied as long as tolerated, was compared to standard oxygen therapy. Intensive care unit (18 % vs 39 %) and 90-day mortality were lower in the NIV group; the difference was prominent if pneumonia was the cause of ARF, while ARDS was a predictor of 90-day decreased survival. Only two patients in the standard group received NIV as rescue treatment [19].

Hypoxemic ARF can have various etiologies, whose responsiveness to NIV can markedly differ [3, 18, 20–22]. Several single-center RCTs [23–38] demonstrated that NIV significantly reduces mortality in cardiogenic pulmonary edema, and it is currently considered a first-line, grade-of-evidence 1A intervention. The benefit was present both for CPAP and NPPV and also for prehospital use. Noninvasive ventilation also proved effective in reducing mortality in RCTs conducted in hypoxemic ARF in immunocompromised patients [39] and chest trauma patients [3, 18, 40]. On the contrary, the advantage on survival is controversial in the case of pneumonia or ARDS, due to a high failure rate [3, 18, 41]. In this setting, some authors found NIV potentially dangerous (i.e., associated with worse survival) when applied for too long despite its failure, as it delays tracheal intubation [42]. Finally, three single-center RCTs evaluated NIV in asthma, and no death was reported in any of the studies [43–45].

State of the Art

Noninvasive ventilation application in hypoxemic patients should be guided by the etiology of ARF. Noninvasive ventilation improves survival in cardiogenic pulmonary edema, chest trauma, and ARF in immunocompromised patients. However, evidence comes only from single-center RCTs (sRCTs). When pneumonia or ARDS are present, NIV should be applied cautiously and in highly monitored settings. In the case of failure, tracheal intubation should not be delayed [3, 18, 41]. Nevertheless, a recent mRCT showed a trend of better survival with NIV compared to oxygen when applied early during mild ARDS [46]. So far, the NIV effect on mortality in asthma is unknown.

2.3.3 Noninvasive Ventilation in the Weaning from Mechanical Ventilation

2.3.3.1 Noninvasive Ventilation in the Weaning of Hypercapnic and Mixed Patients

Multicenter Randomized Evidence

Several mRCTs with different aims evaluated NIV in the weaning of hypercapnic patients from mechanical ventilation.

Noninvasive Ventilation in Patients After T-Piece Trial Failure

Nava et al. compared standard weaning to immediate extubation followed by NIV (as NPPV) in 50 patients intubated because of COPD exacerbations; the authors enrolled only patients suitable for extubation but who had failed a T-piece weaning trial after 48 h of intubation. The study took place in three Italian centers. Noninvasive ventilation was applied as often as was tolerated during the first 2 days in the intervention group. Mortality at 60-days was significantly higher in the standard group (7/25 vs 2/25 deaths), with 4 cases of fatal pneumonia (while further three cases of pneumonia were not fatal) in the standard group and no case of pneumonia in the NIV group [47].

Ferrer et al. [48] compared extubation followed by NIV (such as NPPV) to standard weaning in two Spanish hospitals in 43 intubated patients who failed a spontaneous breathing trial for 3 consecutive days. Noninvasive ventilation was applied for at least 4 h continuously. Almost half of the patients had been intubated because of COPD exacerbation. ICU and 90-day mortality were significantly reduced in the NIV group; nosocomial pneumonia and septic shock were significantly more common in the control group.

Noninvasive Ventilation to Shorten Standard Weaning

A collaborating research group in eleven Chinese ICUs conducted a mRCT in 90 intubated COPD patients with hypercapnic failure triggered by pulmonary infection: the aim was to evaluate NIV as a tool to hasten extubation. Once the patients reached the "pulmonary infection control (PIC) window," defined by several criteria suggesting a control of the infection, they were randomized to standard weaning or to extubation (without a preliminary weaning trial) immediately followed by NIV (such as NPPV). Mortality rate (1/47 vs 7/43) and incidence of pneumonia were significantly better in the NIV group [49].

Noninvasive Ventilation to Prevent Post-extubation Failure

Ferrer et al. evaluated NIV in preventing ARF after extubation. The mRCT enrolled 106 patients with chronic respiratory disorders in two Spanish hospitals: patients were randomized to NIV (such as NPPV, applied for a maximum of 24 h post extubation) or oxygen therapy after a standard weaning if they passed a T-piece weaning trial but were hypercapnic on spontaneous breathing. The trial had been preceded by a previous study from the same authors (see below) suggesting a potential benefit in this population. In the NIV group, 90-day mortality (but not hospital and ICU mortality) was significantly lower in the NIV group (6/54 vs 16/52); a trend toward lower incidence of pneumonia was also present (6 % vs 17 %, $p = 0.12$). It should be noted that 20 of the 25 patients who developed post-extubation ARF in the control group received rescue NIV, and rescue NIV was also applied to 7 of the 8 patients developing post-extubation ARF in the NIV group [50].

Other Single-Center Randomized Trials

Noninvasive Ventilation in Patients After T-Piece Trial Failure

A sRCT [51] conducted in hypercapnic patients suitable for extubation but who had failed a T-piece weaning trial found no difference in mortality between standard

weaning and early extubation followed by NIV. More recently, in a similar trial the same authors [52] confirmed the absence of difference in mortality rate, even if a trend toward improved survival was present in the NIV group. With regard to NIV use in mixed patients who failed T-piece trial, a sRCT did not found a beneficial effect on mortality [53].

Noninvasive Ventilation to Shorten Weaning

An Italian sRCT enrolled 20 hypoxemic patients in which a standard weaning protocol was compared to an "accelerated" extubation followed by NIV. No difference in mortality was observed [54].

Noninvasive Ventilation to Prevent Post-extubation Failure

Two further RCTs evaluated NIV when applied to prevent post-extubation ARF in mixed patients who passed a T-piece trial. In one trial [55] NIV improved survival, while the other [56] found no difference.

State of the Art

When compared to standard weaning, NIV used in the weaning process significantly decreased the mortality rates, where the benefit seems maximal in COPD patients [57].

Hypercapnic patients are among the most responsive to NIV in most conditions. While findings are still controversial, early extubation followed by NIV seems to be a promising strategy for hypercapnic patients after a failed T-piece trial and could be attempted in expert units. Little data is available regarding non-hypercapnic patients.

Noninvasive ventilation might be a valuable tool to accelerate weaning and therefore reducing the complications associated with tracheal intubation. Intubated COPD patients who have reached the PIC window could be the most promising population, but additional studies are needed.

The routine use of NIV to prevent post-extubation ARF in unselected patients who passed a T-piece trial is still controversial. Even if it was discouraged until recently [3, 18], the study by Ornico questioned the point of reporting a survival benefit. Further research is warranted.

2.3.3.2 Noninvasive Ventilation in the Weaning of Patients at Risk of Post-Extubation ARF

Ferrer et al. evaluated NIV in preventing post-extubation ARF in patients at higher risk, defined by at least one of the following criteria: age >65 years, cardiac failure as the cause of intubation, or increased severity (APACHE score >12 the day of extubation). The authors enrolled 162 patients in two Spanish hospitals; the patients were extubated after they had passed a T-piece trial and were randomized

to standard oxygen therapy or NIV (as NPPV, applied for a maximum of 24 h post extubation). The reintubation rate and ICU mortality were lower in the NIV group (2/79 vs 12/83 deaths); hospital and 90-day mortality were not different, except for patients who were hypercapnic during spontaneous breathing by T-piece, in which both survival rates were better in the NIV group. Rescue NIV was applied to 19 of the 27 developing post-extubation ARF in the control group and in 4/13 in the NIV group [58].

One further trial was performed in patients at high risk of post-extubation failure [59]: the authors found a significant improvement of survival in the NIV group.

State of the Art
Noninvasive ventilation (as NPPV, CPAP was never evaluated) should be considered after planned extubation in patients at high risk of post-extubation failure to prevent ARF [3, 60, 61].

2.3.4 Noninvasive Ventilation to Treat Post-extubation Respiratory Failure: Evidence of Increased Mortality with NIV

Esteban et al. conducted a multicenter trial in 37 centers in eight countries (mainly in Europe and North and South America). The authors enrolled 221 patients who were electively extubated after at least 48 h of mechanical ventilation and who developed ARF within the subsequent 48 h. Noninvasive ventilation (such as NPPV, applied continuously for at least four hours) was compared to standard therapy, which included supplemental oxygen, bronchodilators, respiratory physiotherapy, and any other indicated therapy. Rescue NIV was applied in 28 patients in the control group (three died). ICU mortality rate was higher in the NIV group (25 % vs 14 %). The difference appeared to be due to a different rate of death (38 % in the NIV group vs 22 %) among reintubated patients (whose rate was not different between the two groups); moreover, the interval between the development of ARF and reintubation was significantly longer in the NIV group. A potential logical explanation proposed by the authors was that the delay in reintubation negatively affected survival, by various mechanisms like cardiac ischemia, muscle fatigue, aspiration pneumonia, and complications of emergency reintubation. A trend toward better outcomes was observed for COPD patients treated with NIV [62].

So far, only one further sRCT evaluated NIV in this setting reporting data on mortality. Keenan et al. [63] compared NIV (such as NPPV) with standard oxygen treatment in 81 patients, only a low percentage of whom had COPD. The authors did not find any difference in ICU and hospital survival.

State of the Art

Noninvasive ventilation appears to be neither effective nor harmful when applied to treat established post-extubation failure: its use in this condition is discouraged. At a minimum, NIV failure should be promptly recognized and intubation not delayed. Patients affected by hypercapnic disorders might be more responsive [60, 61, 64].

2.4 Three Issues to Be Considered

First, even though many mRCTs on NIV are available, most fields of NIV application lack mRCTs: in particular, no mRCT evaluated NIV efficacy in one of the most common indications, which is cardiogenic pulmonary edema, and in one of the most promising fields, that is, the prevention and treatment of postoperative ARF [61, 65, 66].

Second, the large majority of mRCTs took place in few European countries: Italy, France, and Spain. Moreover, most evidence on this topic comes from very few highly expert centers and authors. In other words, the possibility of generalizing the findings of these mRCTs could be questionable, despite the fact that mRCTs are usually considered to offer the best generalizable data.

Finally, even if several mRCTs suggested a positive effect using NIV, more research is needed in many fields of application that are still unexplored. Moreover, given its beneficial impact in many areas, investigation should go into why NIV is still underused and which educational and organizational interventions would be most effective in bringing (safely, effectively, and containing costs) NIV to all the patients who could benefit from it.

Conclusions

Several mRCTs showed that NIV could have a beneficial effect on survival. Noninvasive ventilation should be considered to treat ARF, mainly in hypercapnic patients and at an early stage. Noninvasive ventilation could also reduce mortality when applied in the weaning process, particularly in hypercapnic patients after a failed T-piece trial or after control of pulmonary infection. Noninvasive ventilation can improve survival when applied to prevent post-extubation failure in patients at high risk of failure. On the contrary, NIV could be harmful if applied to treat an established post-extubation ARF.

More research is warranted to evaluate NIV in other fields and in controversial areas; furthermore, authors should evaluate the best way to offer safe and cost-effective NIV to all those who could benefit.

Clinical summary

Intervention	Indication	Cautions	Side effects	Way of delivery	Notes
Noninvasive ventilation	Hypercapnic respiratory failure (e.g., exacerbation of COPD) Hypoxemic respiratory failure (cardiogenic pulmonary edema, chest trauma) Accelerate weaning in hypercapnic intubated patients	NIV should be avoided in post-extubation ARF Close monitoring is needed in pneumonia and early ARDS; invasive ventilation should not be delayed Effect on asthma and to prevent post-extubation ARF is unclear	CO_2 rebreathing, noise, patient-ventilator dyssynchrony, skin lesion, discomfort, claustrophobia, failure, aspiration pneumonia, barotrauma, and hypotension	Continuous positive airway pressure Noninvasive inspiratory positive-pressure ventilation (usually with an expiratory airway pressure) The optimal settings have not been defined yet	mRCT to evaluate the effect of NIV in pulmonary edema and to prevent postoperative ARF is needed The possibility to generalize mRCT results out of highly specialized centers is questionable

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Lung-Protective Ventilation and Mortality in Acute Respiratory Distress Syndrome

3

Antonio Pisano, Teresa P. Iovino, and Roberta Maj

3.1 General Principles

Nearly 50 years since its first description [1, 2], acute respiratory distress syndrome (ARDS) remains a major critical care issue: it is relatively common within the intensive care unit (ICU) population, affecting about 5 % of hospitalized mechanically ventilated patients [1], and its current mortality is greater than 40 %, with high long-term morbidity [2, 3]. Moreover, several aspects of its treatment are still controversial or not yet clearly defined [2, 4, 5].

Both pathophysiology and clinical management of ARDS are linked to the mechanisms of ventilator-induced lung injury (VILI), firstly, because the risk of VILI is increased in ARDS patients due to a disruption of lung architecture, which leads to poorly compliant and heterogeneously aerated lungs [2, 4], and, secondly, because mechanical ventilation itself may act as a second "hit" that causes ARDS (according to the so-called multiple hit theory) in the presence of pulmonary or extrapulmonary predisposing inflammatory insults [6, 7].

Lung-protective ventilation may prevent or attenuate VILI [2, 4, 6], and it has been widely shown to reduce mortality in ARDS patients [8–11]. Due to its strong beneficial effects, this practice is generally regarded as the standard in ARDS patients, and it is becoming increasingly used also in mechanically ventilated patients without ARDS [6, 7, 12]. It involves the use of low tidal volumes (V_T), moderate-to-high levels of positive end-expiratory pressure (PEEP), and, sometimes, recruitment maneuvers (i.e., a transitory increase in transpulmonary pressure aimed at opening atelectatic alveoli).

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Different elements of the procedure itself, however, are still a matter of debate. For instance, evidence about the use of PEEP is not as conclusive as that about low V_T [13, 14] probably because tailoring PEEP levels on the single patient is a rather more complex intervention than reducing V_T. In this regard, the use of esophageal pressure to set PEEP [15] seems to be a promising approach [2, 4], but clearer evidences will be provided eventually by an ongoing multicenter study [5]. Some uncertainty remains also for the low-V_T strategy itself. In fact, while it seems clear that a lower V_T is generally better than a higher one, in most clinical contexts, how to choose the best V_T in the single patient is still a matter of debate, as well as the role of protective ventilation in prevention, rather than treatment, of ARDS [4, 6, 7, 16]. Finally, the use of extracorporeal support in combination with protective mechanical ventilation, allowing a further reduction in V_T, and its impact on ARDS outcome have to be better defined [2, 4, 17].

3.2 Main Evidences

Protective ventilation is one of the two interventions – the other being noninvasive ventilation (see Chap. 2) – best proven to have an impact on mortality in critically ill patients [18]. In fact, as many as three multicenter randomized controlled trials (mRCTs) found a significant reduction in mortality with protective ventilation in ARDS patients. They were conducted following the first observational findings [8], that is, the two relatively small investigations by Amato et al. [9] and Villar et al. [11] and the large milestone ARDS Network study [10].

In 1998, Amato and colleagues [9] randomly assigned 53 patients with early ARDS to receive conventional ventilation or protective ventilation. Conventional ventilation consisted in $V_T = 12$ mL/kg of body weight with a target arterial partial pressure of carbon dioxide (P_aCO_2) of 35–38 mmHg and the lowest PEEP allowing acceptable oxygenation, while protective ventilation was intended as $V_T < 6$ mL/kg with permissive hypercapnia (P_aCO_2 up to 80 mmHg) and PEEP above the lower inflection point (P_{flex}) on the static pressure-volume curve. A dramatic reduction in 28-day mortality in the latter group (38 % vs 71 %, $p < 0.001$) was reported, together with significantly lower rates of barotrauma (7 % vs 42 %, $p = 0.02$).

The ARDS Network trial [10], published 2 years later, enrolled 861 patients (from 10 ICUs) with acute lung injury (ALI) or ARDS ($PaO_2/FiO_2 \leq 300$ mmHg and $PaO_2/FiO_2 \leq 200$ mmHg, respectively, according to the definitions at that time). Patients were randomized to receive low-V_T ventilation (432 patients) or "traditional" ventilation (429 patients) ventilation. In the former group, V_T was initially set at 6 mL/kg of predicted body weight (PBW) (Fig. 3.1) [2, 10, 11] and was subsequently reduced, if necessary, in order to maintain a plateau pressure (P_{PLAT}; i.e., the airway pressure measured after a 0.5 s inspiratory pause) ≤ 30 cmH_2O. The control group received an initial V_T of 12 mL/kg PBW, subsequently reduced if necessary, to maintain a $P_{PLAT} \leq 50$ cmH_2O. Unlike the previous study, PEEP was similar in the two groups. Mortality before home discharge without ventilatory assistance was significantly less in the low-V_T group (31 % vs 39.8 %, $p = 0.007$). No differences in the incidence of barotrauma were found.

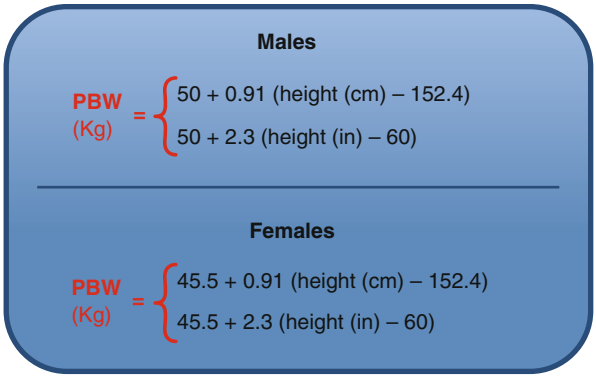

Fig. 3.1 Calculation of predicted body weight (PBW). *cm* centimeters, *in* inches (Modified from Silversides et al. [2] Copyright © 2013 BioMed Central Ltd)

Finally, Villar and colleagues [11] enrolled 103 patients (from 8 ICUs) with persistent, established ARDS (PaO_2/FiO_2 ≤200 mmHg for ≥24 h) and showed a significant reduction in mortality (32 % vs 53.3 %, $p=0.04$) among patients ventilated with $V_T=5–8$ mL/kg PBW and initial PEEP 2 cmH_2O above P_{flex}, compared to the higher V_T (9–11 mL/kg PBW) and lower PEEP (≥5 cmH_2O) group. No difference in the incidence of barotrauma was found in this study as well.

Despite the fact that two of the three aforementioned mRCTs included higher levels of PEEP as part of a protective ventilatory strategy, two recent meta-analyses of mRCTs comparing higher PEEP (with or without recruitment maneuvers) versus lower PEEP, with similar (low) V_T in both groups, failed to show a clear benefit of higher PEEP on survival of ARDS patients [13, 14]. Briel and colleagues [13] found that higher PEEP levels were not associated with improved survival in ALI/ARDS patients, even though a 5 % absolute reduction in hospital mortality (34.1 % vs 39.1 %, $p=0.049$) was observed among the subgroup of patients with ARDS (currently defined as moderate to severe ARDS) [19]. Santa Cruz et al. [14] also found no difference in mortality in relation to PEEP levels but reported a high degree of clinical heterogeneity among the included studies.

3.3 Physiopathological Principles: Mechanism of Reduced Mortality

Acute respiratory distress syndrome is characterized by diffuse alveolar-capillary membrane disruption that results in increased permeability and subsequent pulmonary edema and atelectasis. ARDS may be due to pulmonary (pneumonia, aspiration of gastric content, toxic inhalation, lung contusion, near drowning) or extrapulmonary (sepsis, trauma, burns, pancreatitis, blood transfusion, cardiopulmonary bypass) inflammatory factors [1, 2, 20]. Alveolar damage however is not homogeneously distributed, as atelectasis mainly affects the dependent lung regions (namely, those most subjected to hydrostatic pressure), while nondependent regions remain better aerated [2, 4]. For these reasons, also the volume that needs to be ventilated decreases (hence the term “baby lung”) [21].

Although barotrauma (e.g., pneumothorax) may occur as a consequence of mechanical ventilation with high volumes, the main determinant of VILI is thought to be alveolar overdistension (volutrauma) rather than airway pressure [4]. Therefore, it would be reasonable that low-V_T ventilation could potentially prevent or minimize VILI in ARDS patients, by avoiding overinflation of the decreased normally aerated regions. However, VILI can occur even during a low-V_T ventilation, due to cyclic alveolar opening and closure (atelectrauma), which leads to epithelial sloughing, hyaline membranes, and pulmonary edema [2, 4]. Since atelectrauma is intensified in presence of broad heterogeneities in ventilation [4], as in ARDS, higher levels of PEEP may contribute to minimize VILI by reducing alveolar collapse during expiration [2, 4].

3.4 Therapeutic Use

Low-V_T ventilation (with $P_{PLAT} \leq 30$ cmH_2O) is indicated in patients with ARDS of any severity (mild to severe) [19]. However, probably not all ARDS patients (e.g., those with stiff chest wall and, consequently, high pleural pressure) really need a very low P_{PLAT} (and V_T) in order to avoid alveolar overdistension [4].

Data are also accumulating to support the prophylactic use of low V_T in mechanically ventilated patients without lung injury, in order to prevent ARDS [7]. For instance, in abdominal surgical patients ventilated with $V_T \leq 8$ mL/kg PBW, Futier and colleagues [12] reported a reduction in major pulmonary and extrapulmonary complications, as well as a reduction in hospital length of stay (LOS), while Severgnini et al. [22] found an improved pulmonary function and a reduced modified Clinical Pulmonary Infection Score [23], but no differences in hospital LOS. A recent meta-analysis of RCTs [6] corroborated partially the finding of the previous studies (which were also included in the meta-analysis) showing that low V_T in patients without lung injury is associated with a reduced incidence of ARDS and of pulmonary infection but not associated with a reduced hospital LOS or mortality. Accordingly, the extensive use of prophylactic protective ventilation in all mechanically ventilated patients cannot be recommended at the time, but it is advisable in patients with risk factors for ARDS [7, 16, 24].

Low-V_T ventilation often results in hypercapnia and acidosis, with possible metabolic complications such as acute hyperkalemia [2, 7]. These abnormalities can be counteracted by increasing respiratory rate (RR), but it should be considered that high RR (usually >30 breaths/min) may lead to dynamic hyperinflation and auto-PEEP [7]. However, since low-V_T ventilation was shown to reduce mortality despite hypercapnia [9, 10], it may be speculated that the latter itself may be beneficial due to rightward shift of the oxyhemoglobin dissociation curve, systemic and microcirculatory vasodilation, and inhibitory effects on inflammatory cells. Moreover, mean pCO_2 levels of 66.5 mmHg or higher and a pH up to 7.15 can be tolerated unless specific contraindications exist, such as increased intracranial pressure [2].

The use of extracorporeal arteriovenous CO_2 removal, allowing "ultraprotective" ventilation ($V_T \approx 3$ mL/kg PBW), has been investigated in severe ARDS patients, but its impact on survival remains to be determined [17].

According to current evidences, higher levels of PEEP should be reserved for moderate to severe forms of ARDS [19]. Maybe, in patients with mild ARDS, the potential adverse effects of higher PEEP levels (e.g., impairment of venous return, circulatory depression, lung overdistension) may overcome the advantages [4, 13]. On the other hand, it is also possible that clinical trials failed to show a clear benefit of higher PEEP levels [13, 14] due to the difficulty in tailoring PEEP on the single patient [5]. In fact, lung inflation is strictly dependent on transpulmonary pressure (P_{TP}), that is, the difference between alveolar and pleural pressure [4, 5]. Since pleural pressure is broadly and unpredictably variable among ARDS patients, it is difficult to determine which level of PEEP is needed to prevent alveolar collapse and, therefore, atelectrauma in the individual patient.

As already mentioned, a promising approach would be to use esophageal pressure, which provides (with some important limitations) an estimation of pleural pressure useful to set PEEP [2, 4, 5, 15]. Talmor and colleagues [15] used this approach in a small, single-center trial and reported, in addition to improved oxygenation, a trend toward reduced 28-day mortality. A large mRCT is currently underway [5] and could clarify the impact of such an approach on the outcome of ARDS.

Finally, the impact of recruitment maneuvers on clinical outcomes is still unclear, and some concerns about their complications, including transient desaturation, hemodynamic impairment, pneumothorax, and even worsening of VILI, exist [2, 4].

Clinical summary

Technique	Indications	Cautions	Side effects	Dose	Notes
Protective ventilation (low tidal volume with or without high PEEP and recruitment maneuvers)	All ARDS patients (low V_T) Moderate to severe ARDS patients (low V_T + high PEEP)	Hypercapnia may be hazardous in patients with increased intracranial pressure Excessive respiratory rate may lead to dynamic hyperinflation and auto-PEEP	Low V_T: Hypercapnia Acidemia Acute hyperkalemia High PEEP and recruitment maneuvers: Hemodynamic impairment Lung overdistension Pneumothorax	Initial V_T of 6 mL/kg of predicted body weight (adjusted to maintain $P_{PLAT} \leq 30$ cmH_2O) Initial PEEP 2 cmH_2O above P_{flex} (adjusted according to oxygenation)	Future directions: The role of PEEP has to be further clarified Esophageal pressure could guide PEEP setting Extracorporeal CO_2 removal may provide an additional contribution to the prevention of VILI

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Prone Positioning to Reduce Mortality in Acute Respiratory Distress Syndrome

4

Antonio Pisano, Luigi Verniero, and Federico Masserini

4.1 General Principles

As discussed in Chap. 3, the key objectives of mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) are to prevent ventilator-induced lung injury (VILI) while maintaining acceptable gas exchanges [1, 2]. However, despite the wide use of protective ventilatory strategies, which improve survival significantly, ARDS mortality remains high (up to 45 %) [1, 3, 4].

Improved oxygenation following prone positioning (PP) in ARDS patients was first described about 40 years ago and was subsequently confirmed by several investigations [3, 5]. Nevertheless, it was unclear, until recently, whether such a maneuver resulted in better outcomes [6], since none of the major investigations on PP in ARDS patients [7–10] had shown a significant reduction in mortality. Moreover, PP in critically ill and mechanically ventilated patients requires a careful, out-of-the-ordinary management, as well as a skilled team, and it is not without risks [3, 5, 6, 11]. Accordingly, in many intensive care units (ICUs), PP has been relegated, for many years, to the role of "rescue" treatment for severe hypoxemia [2, 5].

However, two meta-analyses [12, 13] have recently suggested that PP in patients with severe ARDS may provide a significant survival benefit. Most remarkably, these results have been lately confirmed by a landmark prospective study by Guérin et al. (PROSEVA) [14], and they were also consistent with the increasing evidence that prone positioning, in addition to improving oxygenation, could prevent VILI as

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well [2, 5, 14]. Finally, the latest meta-analyses, besides confirming the indication of PP for reduction of mortality in the more severe forms of ARDS [4, 11], provide new insights about its safety [3, 11].

4.2 Main Evidences

The investigation by Guérin and colleagues [14] is the only randomized controlled trial (RCT) reporting a significant reduction in mortality with PP in ARDS patients [15]. Nonetheless, the evidence provided acquires strength when considering the progressive refinements that the study design has undergone over time, through the previous large RCTs [7–10] and, then, in the PROSEVA trial [14]. In particular, the duration of PP was far higher (17–18 h per day, on average) in the newer studies [9, 10] than in the two older studies (<10 h per day) [7, 8]. Moreover, only the most recent of the previous RCTs [10] limited enrollment to the most severe ARDS patients ($PaO_2/FiO_2 \leq 200$ mmHg with PEEP ≥ 5 cmH_2O) and employed a strict protocol of protective ventilation.

The PROSEVA trial, finally, features a more homogeneous population, in terms of ARDS severity, and a longer duration of PP, which can both explain the differences in the results compared to the older trials [2, 11, 16].

The PROSEVA trial [14] included 466 patients (from 27 ICUs) with severe ARDS, defined as $PaO_2/FiO_2 < 150$ mmHg in patients receiving protective mechanical ventilation with a tidal volume (V_T) of about 6 mL/kg of predicted body weight, a PEEP ≥ 5 cmH_2O, and a $FiO_2 \geq 0.6$ (with these criteria persisting after a stabilization period of 12–24 h, in order to select the most severe cases) [16]. Patients were randomized to either undergo early prone positioning (within 1 h after randomization; 237 patients) or to be left supine (229 patients). Additionally, the study included, among others [16], PP sessions of at least 16 h per day, with prefixed criteria to stop them (on average, 17 h per day for 4 days); an experience >5 years with PP management in all centers involved; a minimized crossover between the two groups; and more time overall spent on prone position, as compared with the investigation by Taccone and colleagues [10].

Mortality at 28 days was 16 % in the prone group and 32.8 % in the supine group ($p < 0.001$). A significant reduction in the 90-day mortality (23.6 % vs. 41 %, $p < 0.001$) was also found in the prone group.

These results are consistent with those of both patient-level [12] and study-level [13] meta-analyses of the previous RCTs: in fact, Gattinoni et al. [12] found an absolute mortality reduction of about 10 % in the subgroup of patients with $PaO_2/FiO_2 < 100$ mmHg, while Sud et al. [13] reported a statistically significant improved survival among patients with $PaO_2/FiO_2 < 140$ mmHg.

In addition, all the updated meta-analyses, including the PROSEVA trial, confirm these findings [3, 4, 11]. Particularly, Hu and colleagues [4] reported a reduced 28- to 30-day mortality in the subgroup of patients with $PaO_2/FiO_2 \leq 100$ mmHg (risk ratio (RR) = 0.71, 95 % confidence interval (CI) = 0.57–0.89; $p = 0.003$) and in the subgroup

of patients with a PP duration >12 h per day (RR = 0.73, 95 % CI = 0.54–0.99; $p = 0.04$). Moreover, they found a reduction in both 60-day and 90-day mortality in ARDS patients ventilated with PEEP ≥10 cmH_2O (RR = 0.82, 95 % CI = 0.68–0.99; $p = 0.04$ and RR = 0.57, 95 % CI = 0.43–0.75; $p < 0.0001$, respectively). Consistently, Lee et al. [11] reported that the effect of PP on overall mortality (only detectable in patients with $PaO_2/FiO_2 < 150$ mmHg) was more pronounced in the subgroup with a PP duration >10 h per day, as compared with a shorter duration of PP (odds ratio = 0.62, 95 % CI 0.48–0.79; $p = 0.039$). Finally, Sud and colleagues [3] found that PP reduced mortality among ARDS patients receiving protective ventilation (RR = 0.74, 95 % CI = 0.59–0.95, $I^2 = 29$ %), with a high overall quality of evidence.

4.3 Physiopathological Principles: Mechanisms of Reduced Mortality

Prone positioning improves oxygenation, often considerably, due to a reduction in intrapulmonary shunt: while blood flow distribution remains essentially unchanged (thus prevailing into dorsal regions), the conversion from the supine to prone position induces an increase in aeration in those dorsal regions that exceeds ventral derecruitment [2, 5, 16]. As a consequence, in addition to lung ventilation and ventilation-to-perfusion ratio [17], also transpulmonary pressure and lung densities are more homogeneously distributed along the ventral-to-dorsal axis.

The primary determinant of these effects is the shape matching between the conically shaped lungs and the cylindrically shaped chest wall (Fig. 4.1) [2], adaptation that implies a greater distention in the ventral lung regions [5]. Since the hydrostatic pressure (i.e., the forces due to gravity) is always greater in the regions that lie below (the so-called "dependent" regions), in the prone position, it mainly acts on ventral regions, where it is counteracted by regional expansion. In other words, there is a larger volume of dependent lung in supine position as compared to prone [17]. Other factors, such as the reduced compression of lung tissue by the heart, contribute to the more homogeneous distribution of lung density/inflation in the prone position [2, 5, 17].

Improvement in oxygenation however does not seem to be the primary mechanism of mortality reduction by PP. Indeed, a retrospective analysis of data from the PROSEVA trial has shown that the reduction in mortality observed in ARDS patients receiving prone ventilation was not dependent on whether PP improved gas exchange [18].

The survival benefit may be rather attributed to the prevention of VILI [2, 5, 6, 16, 18, 19], whose major determinants are lung overdistension (volutrauma), pertaining to increase in transpulmonary pressure (lung stress), and cyclic opening and closing of the small airways (atelectrauma) [1, 16]. Accordingly, the aforementioned more uniform distribution of the gravitational transpulmonary pressure gradient, as well as of both V_T and end-expiratory lung volume, results in a homogenization of the strain (i.e., the V_T to end-expiratory lung volume ratio) imposed by mechanical ventilation and, consequently, in a reduction of the resulting

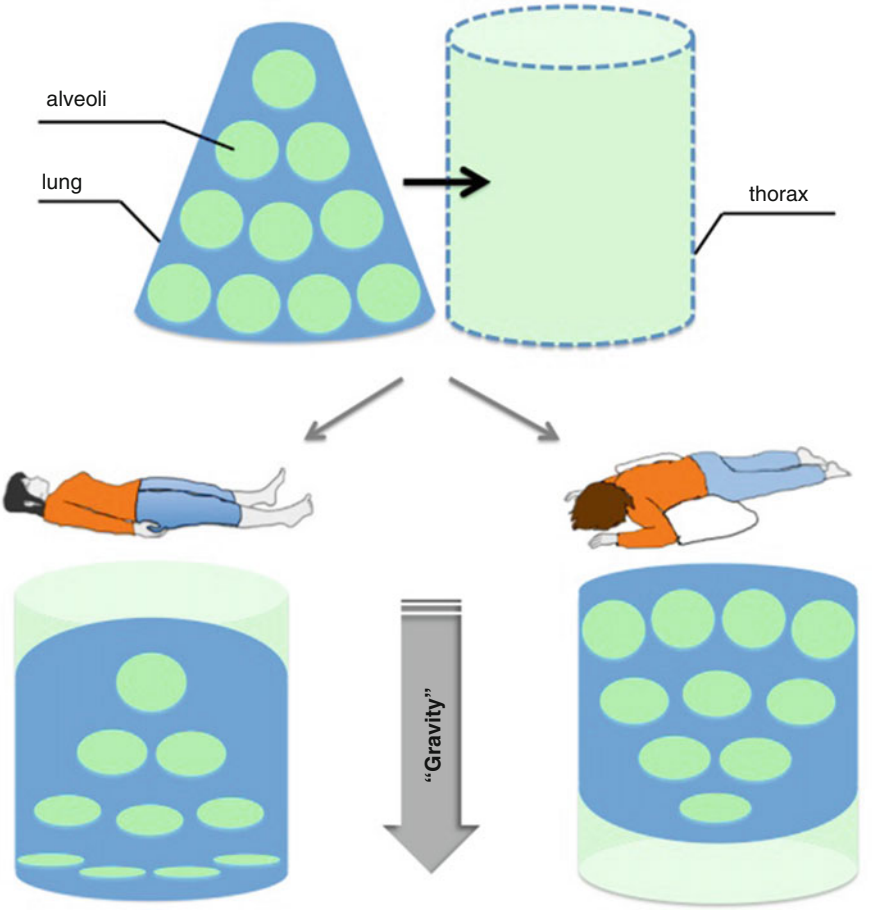

Fig. 4.1 The greater lung expansion in ventral regions, due to shape matching between the lung and thorax, counteracts the gravitational forces when they act on those ventral regions, as in the prone position. This leads to a more homogeneous inflation of alveoli along the ventral-to-dorsal axis in the prone position, as compared to supine (Adapted from Gattinoni et al. [5] with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society)

stress [2, 5, 16]. Finally, a more uniformly distributed V_T translates into a reduced atelectrauma [18], and improvements in PaO_2/FiO_2 ratio resulting from PP may itself indirectly contribute to the prevention of VILI by reducing the need for iatrogenic interventions to sustain oxygenation [5].

4.4 Therapeutic Use

There is now clear evidence that PP, together with protective ventilation, is indicated as first-line therapy in severe ARDS. Probably, its use should be also extended to patients with moderate ARDS (according to the Berlin definition [20]) when PaO_2/FiO_2 ratio is below 150 mmHg.

In order to be effective in reducing mortality, PP should be initiated early and maintained for at least 10–12 h per day (even if maybe >16 is better) until stable improvement in oxygenation is achieved (optimal duration of PP has yet to be established [11]). In fact, since the presumed mechanism of improved survival is the prevention of VILI, PP should start before the onset of structural damage due to mechanical ventilation, and a longer daily time spent in prone position may result in a lower injury [5].

Contraindications are few and not well defined: conditions such as spinal instability, open wounds/burns on the ventral body surface, nonstabilized fractures, increased intracranial pressure, hemodynamic instability, serious cardiac arrhythmias, and pregnancy should preclude PP or, at least, impose a careful evaluation of the risks/benefits balance [5, 6].

The technical features of PP are quite complex. Thus, a skilled and well-coordinated team is needed in order to avoid major complications [3, 5, 6, 11, 14]. Adequate patient preparation (e.g., check the correct positioning of the distal end of the tracheal tube 2–4 cm above the carina in order to prevent extubation or mainstem bronchus intubation) and direct visual monitoring of devices (primarily, endotracheal tube and central lines) are pivotal [6]. In fact, the most common potentially serious complications involve airway problems, such as endotracheal tube displacement, kinking or obstruction, and vascular lines kinking/removal [5, 16].

Despite both Sud et al. [3] and Lee et al. [11], in line with what was said before, reported an increased risk of airway complications with PP, no difference between the two groups was found in the PROSEVA trial [14], maybe due to the high experience with PP of all centers involved in that study. Moreover, none of the previous RCTs reported death from airway problems [11]. Regarding vascular access, PP seems to be safe even during extracorporeal membrane oxygenation (ECMO) [21–23]. Finally, a higher risk of pressure ulcers was reported by previous trials, as well as by the latest meta-analyses [3, 11], and was also confirmed in an ancillary study of the PROSEVA trial [24]. However, it is not clear whether such increase in the incidence of pressure ulcers is due to PP itself or to the greater survival that results from PP [16, 24].

Clinical summary

Drug/technique	Indications	Cautions	Side effects	Dose	Notes
Prone positioning	Severe ARDS Moderate to severe ARDS (PaO_2/FiO_2 < 150 mmHg)	Possible contraindications: Spinal instability Increased intracranial pressure Open wounds/burns on the ventral body surface Nonstabilized fractures Hemodynamic instability/ serious arrhythmias Pregnancy	Major airway problems: Endotracheal tube kinking/ obstruction Endotracheal tube displacement (unplanned extubation or selective mainstem bronchus intubation) Pressure ulcers (debated)	At least 10–12 h per day (maybe >16 h/day could be better, but the optimal daily duration is unknown)	Must be associated with protective ventilatory strategies Requires high experience and specifically trained personnel Feasible during ECMO

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Tranexamic Acid in Trauma Patients

5

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5.1 General Principles

Traumatic injuries are a considerable public health burden with significant personal and social costs. Hemorrhage is responsible for a third of in-hospital trauma deaths and contributes to deaths due to multiorgan failure [1].

The hemostatic system helps to maintain circulation after severe vascular injury, whether traumatic or surgical in origin. Major surgery and trauma trigger similar hemostatic responses, and in both situations, severe blood loss presents an extreme challenge to the coagulation system, resulting in a stimulation of clot breakdown (fibrinolysis) that might become pathological. Hyperfibrinolysis is demonstrated in severely injured trauma patients contributing to an early coagulopathy associated with increased mortality [2].

Antifibrinolytic agents reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, without apparently increasing the risk of postoperative complications [3]. In a large multicenter placebo-controlled trial (CRASH-2), early administration of a short course of tranexamic acid (TXA), an inhibitor of fibrinolysis, was proved to have positive effect on survival, leading to validation of its use in trauma patients [4, 5].

5.2 Main Evidences

Reliable evidence that TXA reduces blood transfusion in surgical patients has been available for many years. Several systematic reviews of randomized trials in patients undergoing elective or emergency/urgent surgery treated with TXA identified a

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reduction in blood transfusion by 30 % without serious adverse effects but with no significant reduction in mortality. Although the effect on thromboembolic events remains uncertain, the use of TXA in cardiac surgery did not increase the risk of myocardial infarction (MI), stroke, deep venous thrombosis, pulmonary embolus, or renal dysfunction [3, 6, 7] (Table 5.1).

Since the hemostatic responses to surgery and trauma are similar, the effects of TXA on death, vascular occlusive events, and the receipt of blood transfusion on adult trauma patients with significant hemorrhage or at risk of significant hemorrhage were evaluated by a large multicenter, placebo-controlled trial, the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2). Tranexamic acid was administrated within eight hours from injury, with a loading dose of 1 g over 10 min followed by infusion of 1 g over 8 h. The trial included 20,211 patients, and treatment with TXA was associated with a reduction in all-cause mortality with no apparent increase in vascular occlusive events, in the number of patients receiving blood products, and in the amount of blood transfused within the two groups (1.7 % vs. 2.0 %, 50.4 % vs. 51.3 %, 6.06 vs. 6.29, respectively). The relative risk (RR) of death with TXA was 0.91 (95 % confidence interval [95 % CI] 0.85–0.97, $p = 0.0035$) [4].

Although the reduction of fibrinolysis is a plausible mechanism, no measure on fibrinolytic activity has been performed in the trial. Alternative plausible hypotheses that may explain the effects take into account the reduction of the pro-inflammatory effects of plasmin, hemostasis improvement, or other mechanisms [5].

A further analysis of the CRASH-2 results showed that TXA treatment within three hours of injury reduced the risk of death due to bleeding by nearly 30 % ($p < 0.0001$), and the effect was even greater if the time of administration was less than 1 h from injury (5.3 % vs. 7.7 %; RR 0.68, 95 % CI 0.57–0.82; $p < 0.0001$). Moreover, there were fewer vascular occlusive deaths with TXA and a significant reduction in fatal and nonfatal MI. Treatment given more than 3 h after injury, on the other hand, significantly increased the risk of death due to bleeding (4.4 % vs. 3.1 %). The hypothesized mechanisms are antithrombotic or anti-inflammatory effects together with the effect on myocardial oxygen demand and oxygen supply, secondary to the reduction of bleeding [5, 8–10].

5.3 Pharmacologic Properties and Physiopathological Principles

Tranexamic acid is trans-4-aminomethylcyclohexane carboxylic acid, a lysine-like drug. It is a competitive inhibitor of plasminogen activation and, at higher concentrations, a noncompetitive inhibitor of plasmin that prevents dissolution of the fibrin clot. With reduction in plasmin activity, TXA also has an anti-inflammatory effect reducing activation of complement and consumption of C1 esterase inhibitor. Since fibrinolysis normally acts in hours or days, while there is a quick clinical effect of TXA, other mechanism should be involved.

Tranexamic acid activates thrombin generation by contact phase and acts on factor XII and prekallikrein. It also shows some modulatory effect on thrombin: it

Table 5.1 Results of the main meta-analysis comparing tranexamic acid to placebo or no intervention in surgical and trauma patients

Meta-analyses	Size		Mortality		Blood transfusion		Myocardial infarction		Stroke		Pulmonary embolism	
	RCT	pts	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI
Henry et al. [3][a]	252	25,000	0.60	0.33–1.10	0.61	0.53–0.70	0.79	0.41–1.52	1.23	0.49–3.07	0.67	0.23–1.99
Ker et al. [11][a]	129	10,488	0.61	0.32–1.12	0.63	0.58–0.68	0.68	0.43–1.09	1.14	0.65–2	0.61	0.25–1.47
Ker et al. [6][a]	104	NR	NR	NR	0.66	0.65–0.67	NR	NR	NR	NR	NR	NR
Perel et al. [7][a]	5	372	1.01	0.14–7.3	0.7	0.52–0.24	[b]	[b]	2.79	0.12–67.10	[b]	[b]
Roberts et al. [9][c]	4	20,548	0.9	0.85–0.97	0.98[d]	0.96–1.03	0.64[d]	0.42–0.97	0.86[d]	0.61–1.23	1.01[d]	0.73–1.41

RCT randomize controlled trial, *pts* patients, *RR* relative risk, *CI* confidence interval, *NR* not reported

[a]Surgical setting

[b]No cases of myocardial infarction or pulmonary embolism reported in this meta-analysis

[c]Traumatic injury setting

[d]Only the CRASH-2 trial reported

inhibits competitively the activation of trypsinogen by enterokinase, it inhibits non-competitively the trypsin and weakly the thrombin, it activates thrombin generation by contact phase, and it acts on factor XII and prekallikrein. Tranexamic acid at usual doses has no effect on blood coagulation parameters (coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects), platelets count, and in vitro aggregation [11, 12].

Although further studies are needed to understand the way TXA reduces the risk of death in bleeding trauma patients, on the basis of evidence, different mechanism should be involved:

- Reduction in perioperative bleeding, transfusion requirements, and risk of post-operative complications. In the CRASH-2 trial, the lack of transfusion reduction could be related to the difficulty to estimate blood loss in the emergency evaluation together with the greater opportunity to receive a blood transfusion by the patients who survived (competing risks).
- Activity on hyperfibrinolysis which is associated with increased mortality [2, 13].
- Reduction in inflammatory response (17 % vs. 42 %; $p<0.05$) and in incidence of vasoplegic shock (0 vs. 27 %; $p<0.01$) [6].

5.4 Therapeutic Use

5.4.1 Pharmacokinetics

After i.v. administration of TXA, the plasma concentration showed three monoexponential decays: the first very rapid, the second with half-life of 1.3–2 h, and the third with half-life of 9–18 h. About half of the dose was recovered unchanged in the urine during the first 3–4 h, 90–95 % within 24 h, and 95–99 % within 72 h. The half-life of elimination was about one-fourth of the half-life related to availability of the compound (3 h). Tranexamic acid is eliminated by glomerular filtration, and neither tubular excretion nor absorption takes place. Impairment of renal function prolongs the biological half-life of the compound with consequent increased plasma concentrations. Tranexamic acid is delivered in the cell compartment and the cerebrospinal fluid with delay. The distribution volume is about 33 % of the body mass.

Moreover, TXA is minimally bound to plasma proteins (≈3 %) at therapeutic plasma concentrations (5–10 mg/L) [14].

5.4.2 Practical Application: Dosage and Timing

Tranexamic acid use is unlabeled in most fields (hemorrhage associated to trauma, surgery, and fibrinolysis), but large reliable evidence has demonstrated its benefit in these circumstances.

In trauma-associated hemorrhage, clinical trial included patients with significant hemorrhage (systolic blood pressure <90 mmHg, heart rate >110 bpm, or both) or those at risk of significant hemorrhage. According to studies in surgical patients that

showed no significant difference between high and low doses, an i.v. loading dose of 1,000 mg over 10 min was recommended for administration, followed by a continuous i.v. infusion of 1,000 mg over the next 8 h. In children, the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group Joint Committee recommended an initial loading dose of 15 mg/kg (maximum 1 g) over 10 min followed by 2 mg/kg/h [15]. In elderly patients, no reduction in dosage is necessary unless there is evidence of renal failure.

Every effort should be made to treat patients as soon as possible. In the CRASH-2 trial, treatment began within 8 h of injury [4], but further analysis demonstrated a higher benefit with an administration within 3 h from injury and preferably within 1 h. There is the possibility, moreover, that late treatment might increase the risk of death due to bleeding, although there was no evidence of any increase in all-cause mortality in patients treated after 3 h [5, 8, 16, 17].

5.4.3 Indications and Contraindications

The recommendation in the European guideline on management of bleeding and coagulopathy following major trauma includes the early administration of TXA (Grade 1A), preferably within 3 h after injury (Grade 1B), considering the administration of the first dose en route to the hospital (Grade 2C) [18].

Waiting for the new clinical guideline of the National Institute for health and Care Excellence (NICE) on major trauma (publication estimated in June 2015), the NICE evidence summary on unlicensed or off-label medicine document allows off-label use of TXA in trauma patients, considering its significant use for the National Health System [19].

Moreover, the 18th Expert Committee on the Selection and Use of Essential Medicines was successful to get TXA included in the World Health Organization list of essential medicines for use in adult trauma patients with hemorrhage within 8 h of injury [20].

In the evidence statement "Major Trauma and the Use of Tranexamic Acid in Children," the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group Joint Committee recommended a pragmatic dosage schedule, but further prospective trials are needed to better define the best dose scheme and the safety profile of these drugs. Administration of TXA or epsilon-aminocaproic acid could potentially be helpful in other settings, such as transplantation, trauma, or massively bleeding children [15].

Contraindications are hypersensitivity to TXA or any of the other ingredients, history of venous or arterial thrombosis, or history of convulsions.

Conclusion

The evidence collected strongly endorses the importance of early administration of TXA in bleeding trauma patients and suggests that trauma systems should be configured to facilitate this recommendation. In patients presenting late (several hours after injury), the clinician should be more cautious and make an assessment of the individual benefits and risks of this treatment, since the drug is likely to be much less effective and possibly even harmful.

Clinical summary

Drug	Indications	Cautions	Side effects	Dose	Notes
Tranexamic acid	Trauma patient with evidence or at risk of significant hemorrhage	Pregnancy and lactation DICs (only with acute severe bleeding), renal impairment: reduction of the dose Upper urinary tract bleeding Subarachnoid hemorrhage Uncorrected cardiovascular or cerebrovascular disease Concomitant use of procoagulant agents (e.g., anti-inhibitor coagulant complex/factor IX complex concentrates, fibrinogen concentrate, oral tretinoin, hormonal contraceptives) *Contraindicated in active thromboembolic disease*	Hypersensitivity reactions Retinal venous and arterial occlusion Seizure Thrombotic events (venous and arterial thrombosis or thromboembolism, including central retinal artery/vein obstruction) Ureteral obstruction Gastrointestinal disorders (nausea, vomiting, and diarrhea)	Loading dose of 1 g infused over 10 min, followed by a continuous intravenous infusion of 1 g over 8 h	Before use of TXA, when possible, risk factors of thromboembolic disease should be investigated

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Albumin Use in Liver Cirrhosis

6

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6.1 General Principles

Albumin is an abundant plasma protein, representing about 50 % of the total protein content, with numerous diverse functions. It is synthesized by the liver and released directly into the circulation without storage. Its production is regulated by osmolarity and metabolic factors, including hormones (stimulation) and acute phase cytokines (inhibition). Under certain circumstances, the human serum albumin (HSA) production can increase three- to fourfolds. The half-life of albumin is 12–19 days in healthy subjects but is altered in disease [1–4].

Hypoalbuminemia is a common complication of liver failure and is associated with a worsened prognosis. Besides the decreased synthesis and increased catabolism, the low HSA concentration results from the dilution of the intravascular fluid protein content, due to plasma volume expansion consequent to renal sodium and water retention, and from the increased transcapillary escape rate toward the extravascular compartment [1, 3, 5–7].

Progression of liver cirrhosis inevitably leads to several devastating complications, including hemodynamic imbalance with dysregulation of compensatory mechanisms, hepatorenal syndrome (HRS), ascites, spontaneous bacterial peritonitis (SBP), malnutrition, ammonia intoxication with encephalopathy, and bleeding diathesis [2–8].

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6.2 Main Evidences

Albumin has been used in critically ill patients for over seven decades. Human serum albumin in cirrhosis was primarily limited to treatment of hypoalbuminemia in patients with advanced ascites and as a volume expander in effective hypovolemia caused by splanchnic vasodilatation. Clinical indications for intravenous administration of HSA have changed during recent years (Table 6.1) [2–8].

It is vital to underline that there is no evidence to use HSA for nutritional interventions, for the correction of hypoalbuminemia per se (without hypovolemia), or as a first-line volume expander in hypovolemic shock of patients with HSR.

6.2.1 Large-Volume Paracentesis

Approximately 10–20 % of patients with ascites have adequate natriuresis and clinical response to dietary sodium restriction (50 mEq per day), and about 70–80 % of subjects respond satisfactorily to diuretics (spironolactone 400 mg per day and furosemide 160 mg per day). Large-volume paracentesis is the treatment of choice for the management of patients with massive or refractory ascites, i.e., in the remaining 10 % of patients. Hemodynamic disturbances that may follow evacuation of large volume of fluid are known as the post-paracentesis circulatory dysfunction (PPCD) or paracentesis-induced circulatory dysfunction (PICD), which is defined as an increase of more than 50 % in the basal plasma renin activity 4–6 days after the procedure. It predisposes to rapid re-accumulation of ascites, hyponatremia, renal dysfunction, and increased mortality [5–7].

There are several randomized trials regarding impact of HSA on the outcome in patients undergoing large-volume paracentesis. All of them were summarized in a meta-analysis by Bernardi et al. It has been confirmed that albumin is effective in preventing the development of PPCD and hyponatremia and in reducing mortality, when compared with alternative treatment (odds ratio (OR) = 0.39; 95 % confidence interval (CI) 0.27–0.55, OR = 0.58; 95 % CI 0.39–0.87 and OR = 0.64; 95 % CI 0.41–0.98, respectively). Across 16 included trials with PPCD data, albumin was not superior to vasoconstrictors (OR = 0.79; 95 % CI 0.32–1.92) but was more effective than other volume expanders (OR = 0.34; 95 % CI 0.23–0.51). Similar results were found for hyponatremia in 16 controlled trials (OR = 0.37; 95 % CI

Table 6.1 Clinical indications for albumin use in liver cirrhosis

Proven applications	Possible applications
Strong evidence	Lack of strong evidence but physiological rationale
Large-volume paracentesis	Recurrent ascites (as a long-term treatment)
Spontaneous bacterial peritonitis (SBP) with ascites	Non-SBP-related sepsis and infections
Hepatorenal syndrome (concomitantly with diuretics and/or vasoconstrictors)	Hypervolemic hyponatremia
	Hepatic encephalopathy
	Detoxification (as extracorporeal blood purification)

0.09–1.49 for vasoconstrictors and OR = 0.61; 95 % CI 0.40–0.93 for other volume expanders). Also in 11 studies with mortality data comparing albumin with alternative treatments, albumin was superior compared to other volume expanders (OR = 0.65; 95 % CI 0.42–1.01) but not to vasoconstrictors (OR = 0.45; 95 % CI 0.08–2.60) [9].

In a second nice meta-analysis with more strict inclusion criteria, albumin transfusion was associated with a significant reduction of PPCD (OR = 0.26; 95 % CI 0.08–0.93) but did not prevent hyponatremia (OR = 0.47; 95 % CI 0.13–1.66) nor reduce mortality (OR = 1.36; 95 % CI 0.61–3.04) [10].

6.2.2 Spontaneous Bacterial Peritonitis

Patients with cirrhosis are susceptible to bacterial translocation from the bowel to the ascetic fluid. Spontaneous bacterial peritonitis is diagnosed when the neutrophil count in the fluid exceeds 250 per ml. Spontaneous bacterial peritonitis may precipitate hemodynamic dysfunction with acute liver failure followed by toxemia and encephalopathy, and HRS, with all their clinical consequences [5–7].

In a meta-analysis of four randomized trials by Salerno et al., albumin infusion in patients with SBP statistically significantly reduced the risk of renal impairment (OR = 0.21; 95 % CI 0.11–0.42) and overall mortality (OR = 0.34; 95 % CI 0.19–0.60) [11].

Similar results were found in a meta-analysis by Kwok et al. (OR = 0.34; 95 % CI 0.15–0.75 for renal impairment and OR = 0.46; 95 % CI 0.25–0.86 for mortality) [10].

6.2.3 Hepatorenal Syndrome

Hepatorenal syndrome is defined as the occurrence of renal failure in patients with advanced liver disease without another identifiable cause of renal insufficiency. In cirrhotic patients, type 1 HRS is usually diagnosed. It is a rapidly progressive acute renal injury with the serum creatinine concentration increase of >100 % from baseline to a final value >2.5 mg/dl in less than 2 weeks. Hepatorenal syndrome is due to an extreme reduction in the effective blood volume, caused by a marked vasodilatation and/or an impairment of cardiac function related to cirrhotic cardiomyopathy, combined with a decrease in the mean arterial pressure. As a result, morbidity and mortality ratios are increased [5–7].

In a meta-analysis including ten randomized trials for HRS treatment in cirrhotic patients, vasoconstrictors used alone or with albumin reduced mortality compared with no intervention or albumin (relative risk (RR) = 0.82; 95 % CI 0.70–0.96) [12]. In subgroup analyses, the effect on mortality was seen at 15 days (RR = 0.60; 95 % CI 0.37–0.97) but not at 30 days (RR = 0.74; 95 % CI 0.40–1.39), 90 days (RR = 0.89; 95 % CI 0.66–1.22), or 180 days (RR = 0.83; 95 % CI 0.65–1.05) [12]. Further subgroup comparisons stratified by the treatment strategy revealed that terlipressin plus albumin reduced mortality compared to albumin (RR = 0.81; 95 % CI 0.68–0.97) [12]. It needs to be underlined that the effect was seen in subgroup analyses of type 1 but not type 2 HRS.

The same scientific team, in a meta-analysis published in 2012, found that terlipressin alone (one trial) or terlipressin plus albumin (four trials) reduced mortality (RR = 0.76; 95 % CI 0.61–0.95) [13].

6.3 Pharmacologic Properties

Albumin has multiple properties (Table 6.2), which are dependent on its total plasma concentration and functional capacity [1–8]. Sole HSA content in circulation is a poor marker of its biological properties. All albumin functions are reduced or disrupted in liver failure. Transfusion is aimed to restore functionally active HSA.

Table 6.2 Albumin functions

Main property	Its relation to albumin structure	Mechanism description
Regulation of oncotic pressure	Constitutes 50 % of total plasma proteins Has net negative charge at physiological pH	Represents 70–80 % of the plasma oncotic pressure Increases intravascular blood volume
Transportation and metabolism	Has net negative charge at physiological pH Has complex flexible tertiary structure with binding sites	Has capacity to bind various endo- and exogenous substances and molecules (bilirubin, metals, ions, hormones, amino acids, fatty acids, bile acids, nitric oxide, drugs, endotoxin)
Additional property		
Capillary permeability stabilization	In 50 % is present in extravascular compartment	Influences vascular integrity
Antioxidative effect	Contains sulfhydryl (thiol) groups	Scavenges free radicals Neutralizes ionic catalyzers (copper and iron)
Hemostatic effect	Has complex flexible tertiary structure with binding sites	Binds and inactivates nitric oxide and arachidonic acid Interferes platelet aggregation Neutralizes factor Xa by AT
Acid-base regulation	Has net negative charge at physiological pH	Buffers plasma
Immunomodulation	Has complex flexible tertiary structure with binding sites Contains sulfhydryl (thiol) groups	Binds and inactivates endotoxin Inhibits and regulates production of TNF-α, NF-κB, complement factor C5a Interferes neutrophil adhesion
Endothelial stabilization	Has complex flexible tertiary structure with binding sites Contains sulfhydryl (thiol) groups Has net negative charge at physiological pH	Regulates metabolic function of substances released to circulation Modulates inflammation and oxidative stress Inhibits apoptosis
Pleiotropic effect	Has complex flexible tertiary structure with binding sites	Prevents myocardial damage Stabilizes endothelial cells

6.4 Therapeutic Use

Albumin can be administrated via the transfusion of plasma products or HSA, which is preferred. There are several albumin solutions in the market: 4 %, 5 %, 20 %, and 25 %, containing 0.04 g, 0.05 g, 0.2 g, and 0.25 g of albumin per ml, respectively.

In healthy subjects, approximately 66 % of the extracellular albumin is in the interstitial space and only 1/3 in the intravascular space. The transfer from the intravascular to interstitial space is 4–5 % per hour, and approximately a parallel transfer exists from the interstitial compartment into the lymphatic system. In patients with liver cirrhosis who undergo albumin transfusion, those ratios are difficult to estimate because of a much more complex albumin metabolism which depends on the degree of organ failure and systemic inflammation. The therapeutic action of HSA in cirrhosis is believed to arise not only from the plasma volume expansion but also from the modulation of systemic and organ inflammation [6].

As the removal of large volumes of fluid has been associated with an increased risk of PPCD, it is recommended to administrate 6–8 g of HSA per 1 l of ascites removed, if paracentesis exceeds 4–5 l [5–8]. Half of the dose should be given in the first one hour (maximum 170 ml/h) and the rest in the next six hours [5].

In patients with SBP, it is also suggested to give high dose of HSA (usually 1.5 g/kg on day 1 and 1 g/kg on day 3), together with broad-spectrum antibiotics [5–8]. The treatment is particularly effective in subjects with liver failure (bilirubin concentration >4 mg/dl) and renal impairment (serum creatinine concentration >1 mg/dl) [8].

In patients with type 1 HRS, the current recommendations endorse the administration of both HSA and vasoconstrictors, to improve renal perfusion and effective volemia. The suggested dose of HSA is 1 g/kg/day, up to a maximum of 100 g/day for at least 2 days [5–8]. The dose should be decreased to 20–40 g/day in the following days [5]. Among vasoconstrictors, terlipressin is the most frequently described, but other drugs, including noradrenaline or midodrine plus octreotide, are also used.

Recognized contraindications to albumin therapy include a known allergy to albumin and states with fluid overload in patients with decompensated congestive heart failure, untreated and/or resistant hypertension, or severe anemia [2].

Possible adverse effects of albumin infusion include allergic reactions (usually due to contamination of solutions or albumin polymerization during long storage), drug interactions (due to albumin-binding properties), fluid overload (plasma volume increases linearly with albumin dose), myocardial depression (perhaps related to the binding of calcium ions), and, very rarely, vanadium contamination [1, 2]. Last, HSA infusion may exacerbate interstitial edema in critically ill patients (e.g., sepsis, trauma, cardiac surgery), because albumin capillary leakage in this condition can be higher than the lymphatic return to the intravascular compartment; therefore, its infusion cannot increase the intravascular albumin concentration [1].

Prudent transfusion should also take into account an economic balance between expected and realistic effects and costs of HSA solutions.

Clinical summary

Drug	Indications	Cautions	Side effects	Dose	Notes
Human serum albumin solution	1. Large-volume paracentesis 2. Spontaneous bacterial peritonitis 3. Hepatorenal syndrome	Expensive therapy Often used "off evidence"	Allergic reactions Drug interactions Fluid overload Myocardial depression	1. 6–8 g/l fluid removed (for paracentesis of at least 4–5 l) 2. 1.5 g/kg at day 0 + 1 g/kg at day 3 + broad-spectrum antibiotic 3. 1 g/kg (max. 100 g) then 20–40 g/day + vasopressin or noradrenalin	Other possible scenarios for albumin use require further randomized studies

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Daily Interruption of Sedatives to Improve Outcomes in Critically Ill Patients

7

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7.1 General Principles

Critically ill patients frequently experience pain, agitation, and delirium, any of which may be promptly treated with sedating analgesics and sedative medications. Thus, intensive care unit (ICU) patients are often deeply sedated either because complicated pharmacokinetics and pharmacodynamics during acute illness contribute to unintended oversedation or because intended deep sedation is perceived to facilitate other aspects of clinical care and provide psychological benefit to patients. A large and growing body of evidence, however, has shown that deep sedation is harmful, increasing the risk of infection, delirium, and death and prolonging the time on mechanical ventilation in the ICU and hospital [1–3]. This evidence has led clinicians and investigators alike to identify and employ safe

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methods to avoid oversedation in the ICU: recent evidence-based clinical practice guidelines recommended "a light rather than a deep level of sedation" for adult ICU patients [1].

Numerous studies have examined strategies that decrease sedative exposure in the ICU. Both randomized trials and observational studies have found that standardized sedation regimens decrease sedative exposure and improve clinical outcomes [4–6]. In general, these protocols have relied on one or both of two key methods to reduce the use of sedatives: daily interruption of sedatives and targeting light levels of sedation. The general principle underlying daily interruption of sedatives is that the best source of information about a patient's need for sedatives is the patient: during a period of sedative interruption, the patient is observed for symptoms indicating whether or not they need sedatives. Alternatively, the general principle underlying targeting light levels of sedation is that ICU patients should be nearly always managed with light sedation, and a validated sedation scale provides an objective method to achieve light sedation. Whereas both of these methods have improved patient outcomes in randomized trials and are recommended in clinical practice guidelines [1], daily interruption of sedatives was employed in the only sedation protocol found to improve mortality in the ICU and is thus the subject of this chapter.

7.2 Main Evidences

7.2.1 Daily Interruption of Sedatives

Kress and colleagues conducted the seminal randomized controlled trial of daily interruption of sedatives, comparing this approach with usual care in a single-center trial of 128 mechanically ventilated medical ICU patients receiving continuous sedative infusions [7]. Once a day in the intervention group, sedatives were interrupted until patients were either awake or demonstrated signs of discomfort, which were treated by restarting sedatives. Compared with sedation via usual care, which was employed in the control group, daily interruption of sedatives decreased the duration of mechanical ventilation (4.9 vs. 7.3 days, $p = 0.004$) and length of ICU stay (6.4 vs. 9.9 days, $p = 0.02$). No difference was seen between groups with regard to complications, and less neuroimaging was required in the intervention group ($p = 0.02$). In long-term follow-up evaluations, patients in the intervention group had fewer psychiatric symptoms [8].

7.2.2 Daily Interruption of Sedation Coordinated with Spontaneous Breathing Trials

Since protocols that use spontaneous breathing trials to determine readiness for liberation from mechanical ventilation have been shown to improve outcomes for mechanically ventilated ICU patients [9, 10], Girard and colleagues coordinated

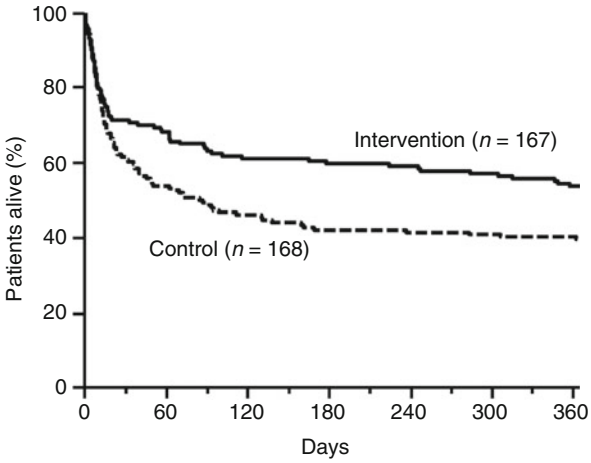

Fig. 7.1 Survival benefit of daily interruption of sedatives paired with spontaneous breathing trials. In the Awakening and Breathing Controlled Trial, patients in the intervention group were managed with daily interruption of sedatives paired with spontaneous breathing trials and were 32 % less likely to die at any instant during the year following enrollment than patients in the control group (hazard ratio for death, 0.68; 95 % CI, 0.50–0.92; $p=0.01$) (From Girard et al. [11], with permission)

spontaneous breathing trials with daily interruption of sedatives—also known as spontaneous awakening trials—in a multicenter, randomized controlled trial of 335 mechanically ventilated medical ICU patients [11]. The intervention group was managed with daily interruption of sedatives plus subsequent daily spontaneous breathing trials—the so-called wake up and breathe protocol—whereas the control group received sedation via usual care plus daily spontaneous breathing trials. In addition to an improvement in ventilator-free days (14.7 days vs. 11.6 days, $p=0.02$) and a reduction in ICU (9.1 days vs. 12.9 days, $p=0.01$) and hospital length of stay (14.9 days vs. 19.2 days, $p=0.04$), patients managed with daily interruption of sedatives benefited from improved survival rates at 1 year (hazard ratio for death 0.68, $p=0.01$; Fig. 7.1). In addition, no long-term adverse cognitive, psychological, or functional outcomes were associated with this coordinated intervention [12].

7.2.3 Combining Daily Interruption of Sedatives with Targeting Light Sedation

Whereas the two aforementioned trials demonstrated the safety and efficacy of daily interruption of sedatives for mechanically ventilated ICU patients, several other trials have shown that targeting light levels of sedation yields similar benefits. Both Brook et al. [5] and Treggiari et al. [13], for example, randomized mechanically ventilated medical and surgical ICU patients to receive either deep sedation or

targeted light levels of sedation and found that less time was spent on mechanical ventilation and in the ICU by patients managed with light sedation. Strom and colleagues [14] took light sedation further by randomizing ICU patients requiring mechanical ventilation to a protocol of no sedation (relying instead on morphine to treat pain and haloperidol to treat agitation) versus sedation with propofol and midazolam. Patients in the intervention group (only 18 % of whom required continuous sedation) benefited from reduced ventilator time and shorter ICU and hospital stays compared with those in the control group.

Given evidence that both daily interruption of sedatives and targeted light sedation improve outcomes in the ICU, several randomized trials were conducted to determine whether combining these two strategies would have additional benefit. An early trial by de Wit et al. [15] was stopped prematurely due to concerns that daily interruption of sedatives was harming patients with alcohol withdrawal, and another by Mehta et al. [16] was not powered to compare clinical outcomes. The third, also by Mehta and colleagues [17], was a large, multicenter, randomized controlled trial of 430 mechanically ventilated medical and surgical ICU patients. This study compared a sedation protocol combining targeted light levels of sedation with daily interruption of sedatives with targeted light sedation alone. Unlike earlier trials of daily interruption of sedatives, the trial by Mehta et al. failed to consistently implement daily sedative interruption in the intervention group, which had sedatives interrupted on only 72 % of eligible days. In fact, patients in the intervention group received significantly higher doses of sedatives ($p = 0.04$) and opioids ($p < 0.001$) than patients managed without daily interruption of sedatives. Furthermore, the sedative doses administered were consistent with those expected to cause moderate to deep levels of sedation rather than light sedation according to pharmacologic models [18], and mean sedation scores did indicate moderate sedation levels in both groups. Overall, no difference was found between groups in time to extubation or in duration of ICU and hospital stay.

7.3 Therapeutic Use

7.3.1 Safety Screens

A critical step in successful daily interruption of sedatives protocols is the daily use of a safety screen to identify circumstances during which sedatives may not be safely withdrawn. In their early trial, Kress and colleagues relied on a very simple safety screen: patients on paralytics did not undergo interruption of sedatives. Girard and coworkers subsequently expanded the safety screen to include six elements: (1) active seizures, (2) alcohol withdrawal, (3) ongoing agitation, (4) paralysis, (5) active myocardial ischemia, and (6) elevated intracranial pressure. The presence of any of these safety screen items should prompt the ICU team to refrain from interruption of sedatives at that time and rescreen later (typically the following morning).

Table 7.1 Benzodiazepine exposure in trials of sedation in the ICU

Trial	Control	Intervention	*P*	Effect of intervention
Daily interruption of sedative trials				
Kress et al. [7]	58 mg/day	47 mg/day	0.05	↓ duration of MV ↓ ICU LOS
Girard et al. [11]	84 mg/day	54 mg/day	0.02	↑ ventilator-free days ↓ ICU and hospital LOS ↑ survival
Mehta et al. [17]	82 mg/day	102 mg/day	0.04	No difference
Targeting light levels of sedation trials				
Bucknall et al. [19]	67 mg/day	64 mg/day	0.49	No difference
Treggiari et al. [13]	54 mg/day	7 mg/day	NR	↓ duration of MV ↓ ICU and hospital LOS
Strom et al. [14]	6 mg/day	0 mg/day	<0.001	↑ ventilator-free days ↓ ICU and hospital LOS

All values converted to and expressed as midazolam equivalents
Abbreviations: *LOS* length of stay, *MV* mechanical ventilation, *NR* not reported

7.3.2 Reduction of Sedative Exposure

Taken together, randomized trials of daily interruption of sedatives as well as targeted light sedation make it clear that clinical outcomes in the ICU are improved when exposure to sedatives, especially benzodiazepines, is reduced; in contrast, outcomes are unchanged by sedation protocols that do not reduce exposure to sedatives (Table 7.1). Whereas patients in these trials were primarily sedated with benzodiazepines, which were the most commonly used class of sedatives at the time the trials were performed despite their association with longer ICU length of stay and duration of mechanical ventilation [20], a recent observational study found that early deep sedation was associated with delayed extubation and higher mortality regardless of which sedatives were used [21].

7.3.3 Barriers to Sedative Reduction in the ICU

Despite evidence showing that daily interruption of sedatives improves outcomes, many clinicians are still reluctant to implement sedative reduction protocols in their ICUs. Commonly cited barriers include concerns about lack of nursing acceptance, patient discomfort or respiratory compromise, and device removal or self-extubation [22]. Despite these barriers, a large number of hospitals, both community- and university-based, are reporting successful incorporation of protocols that include daily interruption of sedatives. Often, this approach to reduce sedative exposure is implemented as part of a larger set of protocols that seek to increase patient arousal, interaction, and mobility. One recent study, for example, reported that patients managed with an ABCDE program (Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Exercise/

Mobility) spent more days breathing without ventilator assistance ($p=0.04$) and had fewer days with delirium ($p=0.004$) than did patients managed at the same institution prior to implementation of ACBDE management [23]. Furthermore, the 2013 Pain, Agitation, and Delirium Clinical Practice Guidelines from the Society of Critical Care Medicine describe an integrated approach to intensive care and advocate for sedative reduction using either daily interruption of sedation or targeted light sedation strategies [1].

Conclusions

Deeply sedating critically ill patients creates a significant barrier to optimizing their patient outcomes. In contrast, protocols that improve pain management and minimize sedative exposure enable ICU patients to actively participate in ventilator weaning and early mobility and can significantly improve outcomes, including duration of mechanical ventilation and ICU and hospital length of stay. Daily interruption of sedatives, especially when combined with spontaneous breathing trials, is safe and effective and has been shown to improve long-term survival for mechanically ventilated medical ICU patients. Key to the success of daily interruption of sedatives is avoiding deep sedation by reducing sedative exposure.

Clinical summary

Technique	Indications	Cautions	Side effects	Dose	Notes
Daily interruption of sedatives	Ongoing treatment with sedating medications via continuous infusion and/or intermittent boluses	Do not interrupt sedatives during: (1) active seizures, (2) alcohol withdrawal, (3) ongoing agitation, (4) paralysis, (5) active myocardial ischemia, or (6) elevated intracranial pressure	Restart sedatives if the following are observed during interruption: (1) anxiety, agitation, or pain, (2) respiratory rate >35/min, (3) $SpO_2<88$ %, (4) other signs of respiratory distress, or (5) acute cardiac arrhythmia	Hold all sedatives and analgesics used for sedation	Efficacy is greatest when daily interruption of sedatives reduced overall sedative exposure, so restart sedatives only if signs of intolerance are noted

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Part II

Interventions that Increase Mortality

Tight Glycemic Control

8

Cosimo Chelazzi, Zaccaria Ricci, and Stefano Romagnoli

8.1 General Principles: Stress-Induced Hyperglycemia

Stress-induced hyperglycemia is common in critically ill and surgical patients, with an incidence of 50 % and 13 %, respectively [1]. Critical illness is associated with alterations in homeostasis, i.e., the ability of the organism to keep a physiologic balance [2]. When environmental/endogenous stimuli challenge this balance, a shift to a state of "allostasis" occurs, whose target is to reach a new steady state involving all systems, including metabolism. During acute critical illness, this response is adaptive, while in prolonged/chronic critical illness is seen as maladaptive [2, 3].

Circulating tumor necrosis factor-α (TNF-α), secreted by macrophages in response to infection, passes the hematoencephalic barrier and activates the hypothalamic-pituitary-adrenal axis (HPA) with increased secretion of cortisol, which in turn promotes hepatic glycogenolysis and gluconeogenesis. TNF-α inhibits gene transcription for glucose transporter family 4 (GLUT-4), inhibiting intracellular insulin-dependent glucose uptake in adipocytes and myocytes [4]. Other metabolic features include decreased levels of insulin-like growth factor-1, reduced peripheral T4-T3 conversion, and suppression of testosterone secretion. Endogenous catecholamines increase as well. This neurohormonal response progressively drives the metabolism toward hypercatabolism and peripheral insulin resistance in order to preserve energy production in tissues directly involved in acute stress responses, such as white blood cells [2]. Hepatic glycogenolysis and

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protein breakdown are enhanced in order to promote hepatic gluconeogenesis and synthesis of acute phase proteins, e.g., C-reactive protein and fibrinogen. Clinically, a progressive hyperglycemia is observed ("stress hyperglycemia"/"stress diabetes") whose severity is related to extent and severity of the causing event (see below). In case of prolonged critical illness, insulin resistance, hypercatabolism, and deleterious consequences of acute hyperglycemia become relevant. These include: increased susceptibility to infections, mitochondrial dysfunction, persistent inflammation, immune paralysis, anemia, and, possibly, increased mortality [3].

8.2 Clinical Associations of Stress-Induced Hyperglycemia

Stress-induced hyperglycemia is associated with worse outcomes in many clinical scenarios, i.e., stroke, traumatic brain injury, myocardial infarction, cardiothoracic surgery, trauma, and burns [5–8]. Among 1,826 critically ill patients, those who died had significantly higher glycemia at admission in intensive care unit (ICU) and during their stay [9].

Patients with acute myocardial infarction and stroke are particularly susceptible to acute hyperglycemia [5, 7, 8, 10–12]. Hyperglycemic trauma patients had increased ICU/hospital length of stay and higher mortality rates, possibly related to increased nosocomial infections and duration of mechanical ventilation (MV) [13]. In patients with traumatic brain injury, hyperglycemia at admission was independently related to worse neurological outcomes [14]. After coronary artery bypass, the association between hyperglycemia and poor outcome is even stronger, including higher rates of mortality and sternal wound infections, longer ICU length of stay, and increased risk for stroke, myocardial infarction, sepsis, or death [15, 16]. Among noncardiac surgical patients, hyperglycemia is associated with higher risk of overall and cardiovascular 30-day mortality.

This evidence prompted researchers to implement strategies to control hyperglycemia in critically ill patients. Although initial results were promising, safety concerns arose about hypoglycemia during continuous insulin infusion. The optimal blood glucose target, the ideal method for glucose monitoring, and insulin protocols are still a matter of debate.

8.3 Tight Glycemic Control: Main Lines of Evidence

In 2001 the Leuven trial, a single-center randomized study, by Van Den Berghe et al., enrolled 1,548 surgical patients to receive intensive insulin therapy (IIT) with continuous intravenous insulin infusion or conventional blood glucose management [17]. Targeted blood glucose for IIT patients was 80–110 mg/dL, while for controls was 180–200 mg/dL. In all patients, a mix of glucose infusion and parenteral/enteral nutrition was used to reach the caloric intake and prevent hypoglycemia. The results of this study were a significant reduction in ICU (−42 %) and in-hospital mortality (−34 %) in the IIT group compared with controls. Intensive

insulin therapy was associated with reduced incidence of acute renal failure (−41 %) and blood stream infections (−46 %). Transfusion requirements and incidence of polymyoneuropathy were lower in the IIT group. Only 3 % of the enrolled patients were diabetic. The incidence of hypoglycemia was significantly higher in the IIT group. The strikingly positive results of this study fostered great interest around glycemic control. The results were partially reproduced in diabetic patients undergoing coronary artery bypass and treated with IIT to target a blood glucose of 100–150 mg/dL, with a reduction in mortality rate and mediastinitis when compared to historical controls [18]. In 2003, Krinsley confirmed better survival rates for patients receiving IIT to target a glycemia of <140 mg/dL [9].

In 2006 the same investigators of Leuven trial performed a similar study enrolling 1,200 medical critically ill patients. In this study, ITT was associated with an absolute 10 % reduction in mortality rates for long-staying patients; IIT was associated with reduced ICU and hospital length of stays, duration of MV, and incidence of acute renal failure. Hypoglycemia was more common among patients undergoing IIT [19]. However, in 2008 the VISEP trial compared the effects of IIT (blood glucose 80–110 mg/dL) versus conventional therapy (180–200 mg/dL) in 537 septic, critically ill patients and did not show any difference in MV, severity of organ failure, and 28-day mortality [20].

Recently, two large trials have challenged the initial results of IIT. In 2009, the GluControl trial randomized 1,101 medical/surgical critically ill patients to IIT (blood glucose 80–110 mg/dL) or conventional glucose control (140–180 mg/dL). The study was interrupted for protocol violations, and although IIT was associated with increased risk of hypoglycemia and a trend toward increased mortality, blood glucose levels were poorly controlled [21]. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, including 6,104 medical/surgical patients, compared IIT (81–108 mg/dL) with conventional treatment (<180 mg/dL). Patients undergoing IIT showed higher rates of hypoglycemia and 90-day mortality (+2.6 %) [22]. Finally, in 2010, the COITISS study on 509 patients with septic shock did not show difference in in-hospital mortality comparing strategies to keep blood glucose levels at 80–110 mg/dL and below 150 mg/dL [23].

8.4 The Risk of Hypoglycemia: Role of Nutrition and Diabetes

Despite a clear increase in mortality was shown only in the NICE-SUGAR trial, the risk for hypoglycemia was constantly higher in patients undergoing ITT. Some issues need to be underlined. In the two Leuven trials, a mean nonprotein daily caloric intake of 20 kCal/kg was achieved mostly with glucose administration; median daily infused insulin was about 71 units. In the NICE-SUGAR, the median daily caloric intake was 11.04 ± 6.08 kCal/kg, with a median daily dose of insulin of 50.2 units. This observation prompts the need to associate an appropriate nutrition protocol with IIT. Indeed, the importance of caloric intake in developing ITT protocols was recently underlined by a meta-analysis by Marik and Preiser [24].

In 2011 the Leuven group demonstrated that early administration of parenteral nutrition is associated with increased infections and cholestasis [25]. In the experimental group, a median daily dose of 58 units of insulin was administered, lower than the dose administered in the original Leuven trials of 2001 and 2006. These results point out that the concomitant infusion of glucose and insulin, rather than the sole tight glycemic control, can be beneficial for critically ill patients [26]. Concomitant administration of high-dose insulin and nutrition may help to prevent hypoglycemia and oppose the inflammatory-induced hypercatabolism, due to the anabolic and anti-inflammatory properties of insulin [27]. Since stress-induced glycogenolysis and hepatic gluconeogenesis are associated with muscle energy depletion and hepatic hypoxic injury, insulin-mediated increased expression of GLUT-4/GLUT-2 on muscles cells and hepatocytes may restore ATP levels and inhibit wasting for neoglucogenic processes [28–32]. Infused insulin may exert immune-modulatory effects, preventing the apoptosis of activated macrophages and promoting a shift toward a T-helper 2 phenotype, contributing to inflammation control and tissue repair [33]. Clinically, these effects may translate in the observed reduced incidence of neuromuscular weakness, need for MV, incidence of infections, length of stay, and, ultimately, mortality.

Finally, the ideal blood glucose target may be different for nondiabetic and diabetic patients, with the latter being more prone to develop hypoglycemia, hypokalemia, and electrocardiographic alterations when treated with IIT [34–36]. On the other hand, previously euglycemic patients may suffer larger injury from acute, stress-induced hyperglycemia. There is strong evidence for the association of hyperglycemia with mortality in nondiabetic critically ill patients: Krinsley et al. found higher mortality rates in 5,365 nondiabetic patients, and Graham found that diabetic ICU survivors had higher levels of blood glucose [9–37]. In addition, ICU hyperglycemia and low preadmission glycosylated hemoglobin were associated with higher risk of mortality in diabetic patients [38]. Interestingly, Van Den Berghe et al. performed a post hoc analysis of both their medical and surgical cohorts of patients treated with IIT and found that reduced mortality was evident only in nondiabetic patients [39]. Thus, tight glycemic control in ICU would bring advantage particularly for previously nondiabetic patients or for diabetic patients with good preadmission glycemic control; for poorly controlled diabetic patients, blood glucose control should be less tight.

Definite evidence about this issue is lacking, and experts recommend to use a general, liberal blood glucose target of 140–160 mg/dL, for both nondiabetic and diabetic patients in good metabolic control [40, 41].

8.5 Areas of Uncertainty: Glucose Variability and Methods for Glucose Monitoring

Interestingly, glucose variability rather than stable hyperglycemia is associated with worse outcomes in critically ill and surgical patients [42]. Todi and Bhattacharya showed that in 2,208 patients, those who were euglycemic but with higher glucose standard deviation had a higher risk of mortality compared with those who were hyperglycemic, irrespective of hypoglycemia [43]. Indeed, there is evidence that

fluctuations of blood glucose levels are associated with increased oxidative stress and neurologic injury [44, 45]. In a retrospective study on 276 mixed medical/surgical ICU patients undergoing parenteral nutrition, glucose variability, expressed by the glycemic standard deviation, was higher among deceased patients, independently from severity scores or hypoglycemia [46]. This association was evident only for patients without history of diabetes. These results suggest that concomitant administration of calories and insulin, aiming at glycemic stability rather than a fixed glycemia, may be protective in critically ill patients and that, the effect of nutrition-insulin coadministration may be particularly relevant for previously nondiabetic patients.

Dynamic protocols of insulin infusion may be more efficacious and safer than the simpler IIT. In these protocols the infusion of insulin is not regulated by the absolute levels of glycemia, but rather on the basis of changes from previous readings. Surgical patients enrolled in the DeLiT trial were managed with a dynamic protocol of insulin infusion [47]. By applying this protocol, the investigators showed a low incidence of hypoglycemia, lower glucose variability during surgery, and longer periods of glycemia within the desired levels. A contribution to efficacy and safety of these protocols may come from implementation of automated softwares and new glycemic monitoring tools. In cardio-surgical patients, automated algorithm of insulin infusion resulted in higher rates of time-in-range glycemias when compared to paper-based algorithm (49 % vs. 27 %, respectively) [48]. Software-based insulin infusion achieved tighter glycemic control and better glycemic stability also in non-cardio-surgical patients [49]. Boom et al. randomized 87 ICU patients needing insulin therapy to the use of a subcutaneous continuous glucose monitoring system (with a sensor inserted in the arm or abdomen) versus point-of-care glucose determinations and concluded that continuous monitoring is a promising tool to implement strategies of glycemic controls [50]. Another proposed method is based on microdialysis technology: a continuous on-line intravenous glucose measurement was tested in a cohort of critically ill patients [51]. The study showed this technology to be effective: the combination of continuous monitoring tools with a computer-based algorithm proved to be efficacious, safe, cost effective, and time saving. Obviously, however, experience of nurses and physicians is also pivotal in warranting a safe glycemic management. To date, closed-loop, automated systems for insulin therapy are under investigation [52].

Conclusions

As stated in our Consensus Conference, acute, stress-related hyperglycemia is associated with adverse outcomes in surgical and nonsurgical critically ill patients [53]. After initial enthusiasm for the positive results of the Leuven trials, concerns were raised about the incidence of hypoglycemia and extra-mortality in patients undergoing IIT. The best target level of blood glucose, particularly for previously nondiabetic patients, is still debated. In addition, concomitant administration of insulin and nutrition seems to be beneficial, but further studies are necessary to confirm the initial encouraging findings. Dynamic protocols and automated insulin infusion may help to achieve a more stable and safer glycemic control.

Clinical summary

Intervention	Indications	Cautions	Side effects	Protocol	Notes
Intensive insulin therapy (or tight glycemic control)	Critically ill patients with stress-induced hyperglycemia (sepsis, stroke, traumatic brain injury, myocardial infarction, trauma, burns, cardiothoracic surgery, and major noncardiac surgery)	Adequate caloric support must be provided Diabetic patients are more prone to develop hypoglycemia, hypokalemia, and electrocardiographic alterations	Severe hypoglycemia	Still debated. A general blood glucose target of 110–140 mg/dL for both nondiabetic and diabetic patients in good metabolic control; unclear for poorly controlled diabetic patients	Intensive insulin therapy (blood glucose target of 81–110 mg/dL) is associated with higher mortality due to a greater incidence of severe hypoglycemia, especially in diabetic patients Furthermore, glucose variability rather than stable hyperglycemia is associated with worse outcomes in critically ill and surgical patients, and glucose stability should be sought whenever treating these patients The effect of nutrition and insulin coadministration may be particularly beneficial for previously nondiabetic patients

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Hydroxyethyl Starch in Critically Ill Patients

9

Rasmus B. Müller, Nicolai Haase, and Anders Perner

9.1 General Principles

Many critically ill patients are hypovolemic, which may impair cardiac output and organ perfusion leading to poor outcome. Therefore, fluid therapy is a mainstay in the resuscitation of these patients. The colloid hydroxyethyl starch (HES) has through decades been widely used as resuscitation fluid for hypovolemic critically ill patients. The rationale for the use of HES vs. crystalloid is the belief that the large starch molecules of colloids will increase the intravascular osmotic pressure leading to better hemodynamics with less use of fluid. However, the first generations of HES, having high molecular weight and substitution ratio, were refined due to safety concerns including tissue deposition and kidney and hemostatic impairment. The manufacturers developed HES solutions with lower molecular weight and substitution ratio in an attempt to reduce toxicity and marketed these starches as having overall beneficial effect. However, the evidence supporting this notion was limited to lower-quality trials on HES (limited sample size, short follow-up time, and high risk of bias) [1], and a large proportion of the data supporting HES was retracted due to scientific misconduct [2]. Now there are data from large randomized clinical trials (RCTs) [3–5] and meta-analyses [6–10] to inform clinicians on the choice of fluid therapy in critically ill patients.

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9.2 Main Evidence

9.2.1 Evidence from Randomized Clinical Trials

The Crystalloids Morbidity Associated with Severe Sepsis (CRYSTMAS) trial was the first RCT with sufficient number of patients to allow some estimation of the benefits and harms of low-molecular-weight HES [11]. The aim of this industry-sponsored trial was to determine the volume needed to obtain hemodynamic stabilization with either 6 % HES 130/0.4 or isotonic saline in patients with severe sepsis. In the 174 of 196 randomized patients in which hemodynamic stabilization was achieved, less volume of HES was needed (mean difference of 0.3 L favoring HES). However, increased use of renal replacement therapy (RRT) and mortality indicated harm from HES, although the confidence intervals (CI) of the point estimates crossed the no-difference point (Table 9.1) [12].

The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial [3] was powered to detect potential differences in mortality in patients with severe sepsis resuscitated with either 6 % HES 130/0.42 or Ringer's acetate. The 6S trial had a simple pragmatic design aiming at reflecting clinical practice and included 798 patients in 26 Scandinavian ICUs. At 90 days patients in the HES group had increased mortality (Table 9.1). Also, more patients in the HES group received renal replacement therapy and blood products, and they had more bleeding events as compared to those in the Ringer's group.

The 6S trial was shortly followed by the larger Crystalloid vs. Hydroxyethyl Starch Trial (CHEST) [4]. Also pragmatic, CHEST randomized 7,000 general ICU patients to resuscitation using either 6 % HES 130/0.4 or normal saline. The trial confirmed kidney impairment with HES as increased use of RRT (Table 9.1) and showed a higher incidence of adverse events, mainly pruritus, and use of blood products with HES vs. saline. Deaths at day 90 did not differ statistically significant between the intervention groups (Table 9.1), but the trial had lower mortality rate than expected and hence lower power.

Table 9.1 The largest trials investigating the effect of HES on mortality and renal replacement therapy

	Mortality with HES		Use of RRT with HES	
RCTs	RR	95 % CI	RR	95 % CI
CRYSTMAS[a]	1.23	0.76–2.01	1.83	0.89–3.89
6S[b]	1.17	1.01–1.36	1.35	1.01–1.80
CHEST[c]	1.06	0.96–1.18	1.21	1.00–1.45
FIRST[d]	1.89	0.71–5.41	0.63	0.08–4.53

Abbreviations: *HES* hydroxyethyl starch, *RRT* renal replacement therapy, *RR* relative risk, *CI* confidence interval

[a]HES 130/0.4 vs. normal saline in patients with severe sepsis [11]

[b]HES 130/0.42 vs. Ringer's acetate in patients with severe sepsis [3]

[c]HES 130/0.4 vs. normal saline in ICU patients [4]

[d]HES 130/0.4 vs. normal saline in severe trauma patients. The mortality data are from the intention-to-treat population, which was not presented in the main paper [12]

The results of the Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients (CRISTAL) trial differed from those in the above trials [5]. In a 9-year period, 2,857 ICU patients with shock were randomized to open-label resuscitation with colloids (mainly HES) vs. crystalloids (mainly saline). The primary outcome measure, a 28-day mortality, did not differ between the groups, and RRT was used at equal rates in the two intervention groups. However, 90-day mortality, which was a post hoc added secondary outcome, was lower in the colloid group. In contrast to the trials mentioned above, CRISTAL had high risk of bias in several domains including open-label design, uncertain allocation concealment, and marked baseline imbalance [13]. The use of different fluids in both intervention groups further hampers the interpretation of the results.

The Fluids in Resuscitation of Severe Trauma (FIRST) trial randomized trauma patients for resuscitation with 6 % HES 130/0.4 vs. normal saline, but was stopped early after the inclusion of 115 patients due to low inclusion rates [14]. The investigators reported faster lactate clearance and decreased kidney impairment in the subgroup of patients with penetrating trauma receiving HES, but more blood products were given to the patients with blunt trauma receiving HES. The trial was criticized for selective outcome reporting [15], and subsequent reporting of mortality (intention-to-treat) revealed a marked increased risk of death at 30 days with HES, but the low sample size precludes firm conclusions from these data (Table 9.1).

9.2.2 Systematic Reviews and Meta-Analyses

A Cochrane review assessed the effect of resuscitation with colloids vs. crystalloids on all-cause mortality in critically ill patients [9], and HES was found to increase mortality compared to crystalloids (Table 9.2).

Zarychanski et al. compared any kind of HES solution with crystalloid, albumin, or gelatin in critically ill patients [7]. After exclusion of retracted trials [2], the investigators also found increased risk of death with HES in addition to increased use of RRT (Table 9.2).

Table 9.2 Meta-analyses investigating the effects of HES on mortality and renal replacement therapy

	Mortality with HES		Use of RRT with HES	
Meta-analyses	RR	95 % CI	RR	95 % CI
Perel et al.[a]	1.10	1.02–1.19	–	–
Zarychanski et al.[b]	1.09	1.02–1.17	1.32	1.15–1.50
Gattas et al.[c]	1.08	1.00–1.17	1.25	1.08–1.44
Haase et al.[d]	1.11	1.00–1.23	1.36	1.08–1.72

Abbreviations: *HES* hydroxyethyl starch, *RRT* renal replacement therapy, *RR* relative risk, *CI* confidence interval

[a]HES vs. crystalloids in critically ill patients. Subgroup analysis of patients receiving HES [9]

[b]HES vs. crystalloids, albumin, or gelatin in critically ill patients [7]

[c]HES 130/0.4–0.42 vs. crystalloids or colloids in acutely ill patients [8]

[d]HES 130/0.4–0.42 vs. crystalloids or albumin in patients with sepsis. Subgroup of trials having low risk of bias [6]

Other systematic reviews assessing the effects of the new generation of HES, tetrastarch, excluded any clinical benefit and found increased risk of death and renal replacement therapy with these new starches both in patients with and without sepsis [6, 8].

In a systematic review, Bellmann et al. [16] identified studies reporting plasma and urine levels of HES residues after HES infusion. Even in healthy volunteers, HES accumulation was as high as 40 % after 24 h and was independent on molecular weight and substitution ratio. Rather modern HES 130/0.4–0.42 seemed to be deposited in the tissue to an even larger extent than the older HES solutions. Wiedermann and Joannidis followed with a systematic review including necropsy and biopsy studies of patients who had received HES formulations [17]. They confirmed that there is a profound and frequently long-lasting deposition of HES residues in a broad spectrum of cells in the human body which consequently may impair, e.g., kidney function.

9.3 Pharmacologic Properties

Hydroxyethyl starch products are colloids derived from potatoes or maize contained in a crystalloid carrier solution. They are defined by their average molecular weight, their substitution ratio, and their pattern of hydroxyethylation (C2/C6 ratio). Several variations of HES exist, but today the so-called tetrastarches with a molecular weight around 130 kDa and a substitution ratio between 0.38 and 0.45 is the most commonly used HES worldwide. Hydroxyethyl starch is almost entirely excreted by glomerular filtration after hydrolysis by amylase [18], but tissue uptake is pronounced regardless of subtype [16], and elimination of this part has not been clarified.

9.4 Therapeutic Use

After the recent injunctions by European and American authorities [13, 19], HES solutions are solely indicated for hypovolemia due to acute blood loss where crystalloids are insufficient. They are to be used in the least necessary dose and for no more than 24 h. Maximum dose is 50 ml/kg in adults. In children the safety profile is not fully established, and HES solutions should be avoided. Kidney function should be monitored for at least 90 days after administration due to risk of kidney injury.

Contraindications comprise critically ill patients, including those with sepsis and burn injuries. Hydroxyethyl starch should also be avoided in patients with severe liver disease, congestive heart failure, clinical signs of fluid overload, kidney failure, and preexisting or ongoing coagulation or bleeding disorders. The side effects of HES are pruritus, coagulation disorders, and kidney failure [20] and those associated with the carrier solution (e.g., electrolyte disturbances).

Conclusion

The data from high-quality RCTs with low risk of bias consistently show that HES causes harm in critically ill patients, including renal and hemostatic impairment and increased mortality. Although the systematic reviews on HES are hampered by the fact that the majority of data are derived from the 6S and CHEST trials, they confirm these findings. They also showed that there is no evidence that differences in molecular weight, substitution ratio, trial design, or carrier fluid influence clinical outcome. Further, the beneficial effects of HES appear negligible, if present at all, and HES products – in any formulation – are therefore not to be used in critically ill patients.

Clinical summary

Drug	Indications	Contraindications	Dose	Side effects	Notes
Hydroxyethyl starch 130/0.4–0.42/ intravenous use	Acute blood loss where crystalloids are considered insufficient	Critically illness Burn injury Sepsis Kidney injury Hemostatic impairment Hypervolemia Intracranial bleeding Children	Lowest possible dose to a maximum of 50 ml/kg. Not to be used for more than 24 h Adverse effects are seen in trials with <10 ml/kg/day	Acute kidney injury Acute bleeding Long-lasting pruritus Tissue deposition	Kidney function should be monitored for 90 days after administration

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Growth Hormone in the Critically Ill

10

Nigel R. Webster

10.1 General Principles

Increased protein turnover with negative nitrogen balance is a common feature of critical illness, particularly in those where the stay in intensive care unit (ICU) is prolonged. This results in skeletal muscle wasting, prolonged requirement for mechanical ventilation, and delayed return to full mobility. It appears that resistance to growth hormone (GH) and decreased production and activity of insulin-like growth factor 1 (IGF-1) also develop in the critically ill.

Small clinical trials of supraphysiological growth hormone supplementation (typically 5–20 times the dose required for replacement therapy in growth hormone-deficient adults in prolonged critical illness) in patients receiving adequate nutrition support demonstrated nitrogen conservation and increased serum levels of IGF-1 and insulin-like growth factor-binding protein 1 (IGFBP-1). Whether these biochemical changes were associated with improved outcome was unknown, and a much larger trial was required to evaluate the effect of treatment with high-dose GH in patients who were in the more chronic phase of ICU treatment.

10.2 Main Evidence

A large study was therefore undertaken to answer the question and the results published in 1999 [1]. This double-blind randomized controlled trial studied the effect of GH supplementation on mortality in patients who were expected to remain in ICU for at least 10 days. Treatment with GH or placebo continued for the duration

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of the ICU stay or for up to 21 days. The dose varied depending on the actual weight of the patient: patients weighing less than 60 kg received 5.3 mg, while those weighing 60 kg or more received 8.0 mg. The published report of the trial combined two similar although not identical studies conducted in parallel – the Finnish study and the European study – with 247 and 285 patients recruited respectively. In both, the in-hospital mortality was higher in the patients receiving GH (39 % versus 20 % in the Finnish study; 44 % versus 18 % in the European study; $p<0.001$ for both). Morbidity was also higher in the survivors who received GH with a prolonged ICU stay and duration of mechanical ventilation than in the placebo groups. The conclusion was that in patients with chronic critical illness, high doses of GH are associated with increased morbidity and mortality.

10.3 Pharmacologic Properties/Physiopathological Principles

Muscle wasting is an important component of chronic critical illness and a major cause of disability following ICU care. The results of this large study were therefore very surprising. It is worth considering the possible effects of GH, which can be both direct and indirect making interpretation of the results of the study more difficult [2].

Growth hormone is released from the anterior pituitary gland under regulation by three factors:

1. Growth hormone-releasing hormone (GHRH)
2. Somatostatin, the inhibitor
3. Ghrelin

Circulating GH acts directly on the skeletal muscle and fat via a specific GH receptor leading to lipolysis, enhanced amino acid uptake into the skeletal muscle, and hepatic gluconeogenesis. The major effects of GH on the skeletal muscle appear to be mediated through stimulated production of IGF-1, which in turn has an effect through a different receptor linked to the GH pathway. Insulin-like growth factor 1 circulates bound primarily to IGF-binding protein-3 (IGFBP-3) and IGFBP-5 and also to acid-labile subunit (ALS). Insulin-like growth factor 1 exerts feedback inhibition on its own response to GH in the liver and also on the release of GH by the pituitary. In the acute situation in ICU, the acute-phase response inhibits the GH axis, through the effects of a number of cytokines; GH receptor density is downregulated, GH secretion is increased, and IGF-1 production is decreased. With the transition to a more chronic phase of critical illness, adaptation occurs, and GH levels decline with a pronounced loss of its pulsatile release (pulse amplitude is reduced, and inter-pulse through GH levels are lower than in the acute phase of critical illness but remain elevated compared with the normal state). This results in

further decreases in IGF-1, IGFBP-3, and ALS production and further promotes skeletal muscle wasting.

The large randomized trial of recombinant human GH in critically ill patients showed improvement in markers of GH activity such as improved nitrogen balance and increases in IGF-1 and IGFBP-3. However, mortality in the treatment group was increased, and this was attributable to a preponderance of refractory septic shock and multiple organ failure. Suggested reasons were a possible effect on the immune system or failure of glutamine release from the muscle. It is now known that GH, IGF-1, and IGF-1 receptor act to coordinate many aspects of the immune response [3].

Another relevant difference between cases and controls was blood glucose level. The intervention group showed significantly higher values as well as an increased use of insulin, as expected. The trial did not include a glycemic control protocol. At the time this trial was conducted, the impact of hyperglycemia on ICU patients was not a matter of concern yet, and careful glycemic control was not a standard of care [4]. Interestingly, reviewing the data from the trial, we observed that the patients who died had the highest blood glucose concentrations and also the highest levels of insulin.

In light of the results of the GH trial, focus has shifted to other agents modulating the GH axis. It is suggested that intensive insulin treatment with careful control of blood glucose can restore circulating GH levels but does not seem to alter IGF-1, IGFBP-3, or ALS [5]. Treatment of chronic critically ill patients with GHRH restored pulsatile GH secretion as well as the production of IGF-1, IGFBP-3, and ALS and restored feedback inhibition.

Another study investigated the use of low-dose GH administered in i.v. pulses every 3 h to see whether this approach was able to normalize IGF-1 levels in subjects in the chronic phase of critical illness following multiple trauma [6]. Although the study was relatively small ($n = 30$), GH treatment resulted in increased IGF-1 and IGFBP-3 and in decreased IGFBP-1. In this study blood glucose control was protocoled, and although the GH group required more insulin than did the control group, median blood glucose concentration was only 0.5 mmol/L higher in the GH group (6.5 mmol/L) than in the control group (6.0 mmol/L).

It is interesting to speculate what the results of the same trial would be if performed today. I would suggest that the protocol of the trial would contain a clause to target blood glucose levels within a fairly tight range. It could well be that this approach, or perhaps one that used pulsed administration of GH, would result in an improved patient outcome.

Conclusions

Despite initial promising results, a large multicenter randomized controlled trial showed that supranormal GH supplementation in critically ill patients increases mortality and morbidity. Therefore, the use of GH in ICU in adult patients who are not known to be severely deficient in GH is still considered inappropriate.

Clinical summary

Drug	Indications	Cautions	Side effects	Dose	Notes
Growth hormone	Growth hormone deficiency Prolonged intensive care unit stay	Diabetes mellitus Chronic renal failure Steroids Critically ill	Appears safe Water retention In critically ill patients, it worsen septic shock and multiorgan failure Hyperglycemia	Up to 8 mg/day (1 IU = 0.33 mg)	It increases mortality in non-deficient critically ill patients

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Diaspirin Cross-Linked Hemoglobin and Blood Substitutes

11

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11.1 General Principles

Oxygen delivery (DO_2) to organs and tissues depends on flow generated by the heart (cardiac output, CO) and arterial oxygen content. Arterial oxygen content depends on oxygen partial pressure (PaO_2) and hemoglobin (Hb) concentration and saturation. In case of hypoxemia and/or low CO states, Hb concentration may play a key role in preventing tissue hypoxia and cellular dysfunction.

Although Hb concentration in perioperative settings and in critical care is a crucial aspect for almost all patients, the optimal values are still a matter of debate [1]. Nonetheless, current guidelines and recommendations suggest lower "transfusion triggers" than in the past, encouraging blood-saving techniques following a multidisciplinary, multi-procedural approach [2]. The difficulties of supplying red blood cells (RBCs), the need to overcome problems of storage and transfusion (refrigeration and crossmatching), the aim to avoid potential transfusions' harming effects (infection, transfusion reactions, transfusion-related acute lung injury, immunomodulation) [3, 4], and the need for alternatives to biological blood for religious reasons (e.g., Jehovah's Witnesses) [5, 6] have led scientists and companies, over the past three decades, to synthesize and test artificial blood solutions. Oxygen carrier (OC) is a generic definition for blood substitutes, blood surrogates, artificial Hb, or artificial blood. These substances mimic oxygen-carrying function of the RBCs (Table 11.1) and are characterized by a long shelf life. In other words, OCs are pharmacological substances that aim to improve DO_2 independently from RBCs.

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Table 11.1 The ideal oxygen carrier

Always available without temperature limitations
Long shelf life
Effective oxygen-carrying capacity
Effective volume expander
Absent scavenging effect on nitric oxide
No side effects
No infectious carrier
No crossmatching necessity
Cost-effective
Usable for cardioplegia priming and preservative fluid for transplant organs

However, OCs only transport oxygen and do not share with whole blood all its other functions (e.g., coagulation and immunological functions). Over the years, various different solutions divided into two main categories have been created and studied: hemoglobin-based oxygen carriers (HBOC) and perfluorocarbon-based oxygen carriers (PFBOC) (Table 11.2).

Both kinds of transporters bind and transport O_2, but their characteristics are totally different. During the decade 2000–2010, great enthusiasm came from the possibility to replace blood transfusions in many clinical situations and led to a number of experimental applications of these new molecules. Some of these products reached phase III in clinical trials, but unfortunately their path toward a final approval was hampered by reports on side effects and regulatory concerns about safety. As a consequence, the lacking of regulatory approval and investor supports led to the withdrawal of many products from the market.

11.2 Main Evidences

The first attempts of substituting Hb as an extracellular substance date back over 100 years ago [11–13]. Considerable side effects, with the so-called stroma-free Hb, were mainly related to renal impairment due to vasoconstriction and led to abandon these potential blood substitutes.

Hemoglobin-like oxygen carriers can be of allogeneic (from outdated red blood cells), xenogeneic (bovine), or recombinant (*E. coli*) origin [14]. Unmodified Hb solutions cannot be used because of the inherent instability of the tetrameric structure ($\alpha 2\beta 2$), which dissociates to $\alpha\beta$-dimers [15]. To stabilize the product and prevent extravasation and renal filtration, after extraction from red blood cells (stroma-free Hb), Hb molecules are modified by cross-linkage, polymerization, pyridoxylation, pegylation, or conjugation to prolong retention time and provide colloidal osmotic pressure [16, 17]. Cross-linking and polymerization appeared to have largely solved some of the problems associated with unmodified stroma-free Hb: longer half-life, limited nephrotoxicity, and improved oxygen transport [16–18].

Table 11.2 Oxygen carriers [7–10]

HBOC product	Company	Availability
Hemopure® Glutaraldehyde-polymerized bovine Hb	OPK Biotech	South Africa and Russia Expanded Access Study of HBOC-201 (*Hemopure®*) for the Treatment of Life-Threatening Anemia is currently recruiting patients *Hemopure* has not been approved yet by the FDA pending safety review
PolyHeme® Pyridoxal-50-phosphate cross-linked and glutaraldehyde-polymerized human Hb	Northfield Laboratories, Inc.	On May 9, 2009, after being informed by the FDA, the product's risks outweighed the benefits; the company shut down any research operation
HemAssist® Bis-3,5-dibromosalicyl fumarate cross-linked human Hb	Baxter Healthcare Corporation	Product withdrawn
rHb 1.1 Optro®; r Hb 2.0 Recombinant hemoglobin	Baxter Healthcare Corporation	Product withdrawn
Hemolink® Open-chain raffinose cross-linked and polymerized human Hb	Hemosol, Inc.	Abandoned due to the cardiac toxicity observed during the clinical trials
PFBOC product	*Company*	*Availability*
Oxygent® PFBOC	Alliance Pharmaceutical Corp.	European phase III in noncardiac surgery concluded in 2002 Not currently approved by the US FDA for safety reasons

Abbreviations: *HBOC* hemoglobin-based oxygen carriers, *PFBOC* perfluorocarbon-based oxygen carriers, *FDA* Food and Drug Administration, *US* United States

Although HBOCs have been shown to be effective in enhancing cellular oxygenation and improve outcome in trauma in preclinical studies [19, 20], they are no longer considered for clinical use since experimental and clinical trials have failed to prove any benefit, while severe concerns about safety have been raised. Among the HBOCs, only one, *Hemopure®* (or HBOC-201 – 13 g/dL glutaraldehyde-polymerized bovine hemoglobin), is currently available for clinical use in South Africa and Russia (Table 11.2).

11.2.1 Diaspirin Cross-Linked Hemoglobin

Sloan et al., over 15 years ago, tested the diaspirin cross-linked hemoglobin (DCLHb), a purified and chemically modified human Hb solution (*HemAssist®*, 10 g/dL diaspirin cross-linked human hemoglobin in balanced electrolytes solution) [21]. Their randomized multicenter study had the primary objective of reducing 28-day mortality for hemorrhagic shock trauma patients. The study design included

Table 11.3 Reported side effects with HBOCs in experimental and human studies [17, 23–26]

Vasoactivity-hypertension (systemic and pulmonary)	NO scavenging
Gastrointestinal	Pancreatic injury, hepatocellular injury, esophageal spasm,↑ AST, ↑ CPK, ↑ amylase, ↑ bilirubin
Renal	Heme-mediated oxidative events
Hemostasis	Coagulation defects, thrombosis, thrombocytopenia
Cardiac	Myocardial infarction

Abbreviations: *NO* nitric oxide, *AST* aspartate aminotransferase, *CPK* creatine phosphokinase

the addition of 500–1,000 mL DCLHb to standard treatment during initial fluid resuscitation. In the 58 treated patients, death rate was higher than in the 53 controls (46 % vs. 17 %; $p=0.003$). It is likely that DCLHb might have worsened outcomes by scavenging nitric oxide (NO) with worsening of hemorrhage and reduction of tissue perfusion due to vasoconstriction. Nitric oxide, an endothelial-derived relaxing factor, is a strong heme ligand, and its reduction results in systemic and pulmonary vasoconstriction, decrease in blood flow, release of proinflammatory mediators, and loss of platelet inactivation, predisposing conditions for vascular thrombosis and hemorrhage [17, 22] (Table 11.3). Nitric oxide scavenging causing microvascular vasoconstriction and reduction in functional capillary density is the major side effect for many of the HBOCs (Table 11.3). Endothelin-1, a strong vasoconstrictor produced by endothelial cells, has also been suggested to be involved in vasoconstrictor effects of HBOCs [27] together with sensitization of α-receptors [28].

In 2003, a randomized controlled study was performed by Kerner et al. [29] in trauma patients with hypovolemic shock. The study population was sorted into the standard care group ($n=62$) or into the *HemAssist*® group (1,000 mL) ($n=53$) during transport from the scene of trauma to the hospital and until definitive control of bleeding source. The trial was interrupted prematurely for futility after an interim evaluation. In fact, no difference in either 5- or 28-day organ failure or mortality between the two groups was found.

11.2.2 Other Hemoglobin-Based Oxygen Carriers

PolyHeme® (hemoglobin glutamer-256 [human]; polymerized hemoglobin, pyridoxylated; Table 11.2) was produced starting from human purified Hb, then pyridoxylated (to decrease the O_2 affinity), and polymerized with glutaraldehyde. In 1998, Gould et al. [30] first compared, in a prospective randomized trial, the therapeutic benefit of *PolyHeme*® with that of allogeneic RBCs in the treatment of acute blood loss in 44 trauma patients. *PolyHeme*® was designed to avoid the vasoconstriction issues observed with tetrameric Hb preparations, probably due to endothelial extravasation of the molecules and binding of NO. The patients were randomized to receive either RBCs ($n=23$) or up to 6 U (300 g) of *PolyHeme*® ($n=21$) as their initial blood replacement after trauma and during emergent operations. The first

results were encouraging since no serious or unexpected adverse events were related to *PolyHeme*®, which maintained total Hb concentration, despite the marked fall in RBCs Hb concentration. This led to reduction in the use of allogeneic blood [30]. In 2002, the same group of authors performed a study in massively bleeding trauma and urgent surgery [31]. A total of 171 patients received a rapid infusion of 1–20 units (1,000 g, 10 L) of *PolyHeme*® instead of RBCs as initial oxygen-carrying replacement, simulating the unavailability of RBCs. Forty patients had a nadir RBC [Hb] ≤3 g/dL. However, total [Hb] was adequately maintained because of plasma [Hb] added by *PolyHeme*®. The 30-day mortality (25 %) was compared with a similar historical group (64.5 %; $p<0.05$). On the basis of these results, the authors concluded that *PolyHeme*® should be useful in the early treatment of urgent blood loss and resolve the dilemma of unavailability of red cells. These first encouraging results led to a multicenter phase III trial performed in 2009 in the United States [32]. The study was designed to assess survival of patients resuscitated with *PolyHeme*® starting at the scene of injury. The patients were randomized to receive either up to 6 U of *PolyHeme*® during the first 12 h post-injury before receiving blood or crystalloids. After 714 patients were enrolled and randomized, 30-day mortality was higher in the *PolyHeme*® arm than in the crystalloid arm (13.4 % vs. 9.6 %), although this difference was not statistically significant. The incidence of multiple organ failure was similar (7.4 % vs. 5.5 % in *PolyHeme*® and controls, respectively). Total adverse events instead were higher in intervention vs. control group (93 % vs. 88 %; $p=0.04$); this was similar to serious adverse event, including myocardial infarction (MI) (40 % vs. 35 %; $p=0.12$).

Hemospan® (Table 11.2) is an oxygenated, polyethylene glycol-modified hemoglobin: it showed some promising results in clinical trials [15, 23]. Olofsson et al. conducted a safety phase II study in patients undergoing major orthopedic surgery. The authors compared Ringer's lactate with *Hemospan*® given before the induction of anesthesia in doses ranging from 200 to 1,000 mL. *Hemospan*® mildly elevated hepatic enzymes and lipase and was associated with less hypotension and more bradycardic events. Nausea was more common in the patients receiving *Hemospan*®, without correlation with the dose [23]. A "Phase III Study of *Hemospan*® to Prevent Hypotension in Hip Arthroplasty" has been completed, but the results have never been published [33]. Moreover, due to the lack of investor interest, this product is not currently used in clinic [34].

In the mid-1990s, recombinant technology for hemoglobin production (use of *E. coli* transfected with human hemoglobin genes; *rHb1.1*, *Optro*®) gave some promising results [35]. Nevertheless, when tested in animal models, vasoconstriction due to NO scavenging and increase in amylase and lipase levels led to project abandonment [35]. Further modification of *rHb 1.1* (*rHb 2.0*), which aimed at mitigating the vascular response [24], did not reach the desired objective, and consequently, due to the hemodynamic side effects, synthesis of recombinant product was discontinued [36].

Hemopure® (bovine hemoglobin, polymerized by glutaraldehyde-lysine) is the only available HBOC, and it is nowadays licensed in South Africa and Russia: it was tested in some clinical trials including cardiac, vascular, and surgical patients [37–39]. The largest study was a randomized controlled multicenter phase III trial

performed in 2008 in the United States. 688 patients were randomized to receive either *Hemopure*® ($n=350$) or RBCs ($n=338$) at first transfusion decision in orthopedic surgery [40]. The investigators reported that 59.4 % of the patients receiving *Hemopure*® were able to avoid allogeneic RBC transfusions; adverse events (8.47 % vs. 5.88 %; $p<0.001$) and serious adverse events (0.35 % vs. 0.25 %; $p<0.01$) were higher in *Hemopure*® in comparison with controls; mortality was comparable in the two treatment groups [40].

Hemolink® is an open-chain raffinose cross-linked and polymerized human Hb that was used in patients undergoing cardiac surgery (Table 11.2). Treatment with *Hemolink*® allowed a reduction in RBCs compared with pentastarch [41, 42]. However, hypertension, MI, increase in pancreatic enzymes, and raised bilirubin were observed [25, 41, 42]. Consequently, *Hemolink*® has been abandoned due to the toxicity observed during the clinical trials.

In 2008, Natanson et al. published a meta-analysis [17] counting 16 randomized controlled trials (3,711 patients) focusing on the safety evaluation of 5 OCs (*HemAssist*®, *Hemopure*®, *PolyHeme*®, *Hemospan*®, *Hemolink*®) in surgical, stroke, and trauma patients. Overall analysis showed a significant increase in risk of death in treated patients (relative risk (RR), 1.30; 95 % confidence interval [CI], 1.05–1.61) and risk of MI (RR, 2.71; 95 % [CI], 1.67–4.40). Although some limitations can be acknowledged (some details on study protocols were unavailable, and control groups received different treatments), this meta-analysis addressed important safety concerns as far as all five different types of OCs are concerned.

11.2.3 Perfluorocarbon-Based Oxygen Carriers

Perfluorocarbon-based oxygen carriers are inert organofluorine compounds containing only carbon and fluorine. They are chemically and biologically inert, have low viscosity, and have a high gas-dissolving capacity. Plasma half-life is approximately 12 h, and when refrigerated at 4 °C for storage, they last up to 2 years [43]. Differently from HBOCs, in PFBOC, the relationship between PaO_2 and PFC-transported O_2 is linear. Therefore, they are efficient solvents, and their oxygen-carrying capacity is relevant in patients receiving high concentrations of supplemental oxygen [43, 44]. The only product based on perfluorocarbon ever approved by the Food and Drug Administration (FDA) was *Fluosol*® in 1989, for perfusion during percutaneous coronary angioplasty [45]. In 1994 the product has been withdrawn from the market due to its insufficient applicability in clinical practice. During the following years, *Oxygent*®, a new PFBOC (Table 11.2), was tested by Spahn et al. [46] in a European phase III trial in noncardiac surgery patients, with expected blood loss of 20 mL/kg or greater, and used in conjunction with acute normovolemic hemodilution (1.8 g/Kg). The administration of *Oxygent*® as fluid for PFBOC normovolemic hemodilution reduced transfusion needs. Adverse event rates were similar in the PFBOC (86 %) and the control (81 %) groups, and the overall mortality was not statistically significant. However, more serious adverse events were reported in the PFBOC group than in the control (32 % vs. 21 %; $p<0.05$).

Conclusions

Clinical evidence, recommendations, and guidelines suggest that RBC transfusion indications should be much more restrictive than in the past and the decision to transfuse or not transfuse must be tailored on an individual basis for each patient. Nonetheless, there is an undisputed need for an oxygen-carrying product with reduced risk of transfusion harming effects, universal compatibility, infinite availability, and long-term storage capability. Perioperative settings, trauma scenes, military battlefield casualties, disaster scenarios, remote settings, and religious issues are conditions suitable for alternatives to blood administration. During the last decades, much research has been done to develop products to substitute blood transfusion: so far, randomized controlled trials have raised questions about safety and have failed to demonstrate clinical benefits of the available substitutes. Thus, new and safer alternative products are absolutely needed before transfusion medicine can be profoundly modified.

Clinical summary

Drug	Indications	Side effects	Dose	Notes
Hemoglobin-based oxygen carriers	Prehospital treatment of severe trauma Major orthopedic surgery Cardiac surgery	Vasoconstriction Pancreatic and hepatic injury Nausea Kidney oxidative injury Coagulopathy Myocardial infarction	*Hemopure®*, 1 unit = 30 g, tested to a maximum dose of 300 g	Hemoglobin-based oxygen carriers appear to increase mortality and morbidity. None of these drugs are available in Europe or the United States *Hemopure®* is available in South Africa and Russia

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Supranormal Elevation of Systemic Oxygen Delivery in Critically Ill Patients

12

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12.1 General Principles

The perceived benefits of elevating systemic oxygen delivery (DO_2) in the critically ill have been a source of debate since the 1970s. Since then much work has been devoted to assessment, monitoring, and optimization of the microcirculation to avoid multiple organ dysfunction syndrome (MODS).

Multiple organ dysfunction syndrome remains the lead cause of morbidity and mortality in intensive care patients [1]. The etiology of MODS is multifactorial and is likely precipitated by a combination of tissue hypoperfusion, hypoxia, metabolic derangement, and mitochondrial dysfunction [2]. As a result optimization of oxygen delivery (to supranormal levels) was adopted in an effort to avoid and reverse tissue hypoxia and resultant organ damage.

Research has demonstrated that improved survival is associated with the ability to achieve survivor levels of cardiac index and oxygen delivery and consumption. However, studies that randomized critically ill patients to protocolized supranormal oxygen delivery failed to demonstrate any benefit on outcome and moreover may have caused harm. As a result of this, the European Consensus Conference in Intensive Care recommended that efforts to increase DO_2 were not warranted in this patient group [3].

In health oxygen extraction increases in organs that have greater oxygen demand, and blood is preferentially distributed to those organs accordingly.

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Once physiological reserve has been reached, demand is no longer met by supply, resulting in an "oxygen debt," which is normally reversible. In the critically ill, however, despite efforts to increase oxygen delivery, there is an impaired ability to extract oxygen as a result of bioenergetic failure (mitochondrial dysfunction). This inability to reverse the "oxygen debt" may lead to MODS [2]. The greater this "oxygen debt," the more likely a patient is to develop MODS, and the more prolonged or pronounced this oxygen deficit, then the more detrimental the outcome [4].

In landmark observational studies on high-risk surgical patients, Shoemaker and colleagues demonstrated that patients who were able to generate a high cardiac output, oxygen delivery, and oxygen consumption had a significantly higher survival rate than those who did not [5, 6]. The same group proceeded to test the hypothesis that early, aggressive, prophylactic therapy designed to achieve the median maximum values of survivors (CI > 4.5 L/min/m^2, DO_2 > 600 ml/min/m^2, VO_2 > 170 ml/min/m^2) would improve outcome [7]. The subsequent prospective, randomized study demonstrated a reduction in mortality from 33 to 4 %. Although these results were impressive, the protocol group received twice as much fluid as the control group suggesting that the control group was inadequately fluid resuscitated.

A UK group later studied the effects of a management protocol designed to maintain high levels of oxygen delivery and consumption in patients with septic shock. This was clearly a different approach as treatment was commenced after septic shock was established and after admission to the intensive care unit. The overall survival rate of the 32 patients was 48 %. Unfortunately this was an uncontrolled study and claims that this management plan reduced mortality relied on retrospective comparisons [8].

Tuchschmidt et al. later conducted a prospective randomized trial whereby increased cardiac index (CI) and hence oxygen delivery were targeted in patients with septic shock. When results were analyzed on an intention to treat basis, there was no significant difference in overall mortality between those who received normal treatment (CI 3 L/min/m^2, $n = 25$) when compared with those who had their cardiac output and oxygen delivery significantly augmented (6 L/min/m^2, $n = 26$). Subgroup analysis of those treatment group patients who achieved a CI >4.5 L/min/m^2, compared to controls that did not, showed a reduced mortality which may indicate that ability to achieve such goals predicts survival. In addition they noted those patients who had had their treatment optimized and survived had shorter stays in the intensive care unit (ICU) [9].

Yu et al. similarly studied the effects of increasing DO_2 but in a mixed group of critically ill patients. They found no significant difference in outcome between the control and treatment groups with regard to mortality, organ failure, ICU days, and hospital days. Once again, however, mortality rates were lower in those in the subgroup who generated a supranormal level of DO_2 either spontaneously or via active treatment [10].

Although these studies were difficult to interpret owing to heterogeneous patient groups, differing study design, and small numbers, the premise of optimizing oxygen delivery was at that time very appealing. Subsequent evidence, however,

discussed below, indicated quite clearly that attempts to achieve supranormal levels of oxygen delivery and utilization were not beneficial and might even have been detrimental to patient outcome.

12.2 Main Evidences

To date, numerous groups have sought to investigate the effects of goal-directed therapy in a variety of surgical and critical care cohorts. However, two key large randomized trials have investigated this in patients with established critical illness.

Hayes et al. aimed to increase cardiac index, oxygen delivery, and oxygen consumption in the critically ill with intravenous dobutamine to achieve supranormal levels [11].

Initially 109 patients were fluid resuscitated to achieve three goals: cardiac index above 4.5 L/min/m^2 of body surface area, oxygen delivery above 600 ml/min/m^2, and oxygen consumption above 170 ml/min/m^2. If these goals were not achieved with fluids alone, they were then randomized into treatment ($n=50$) and control groups ($n=50$). Of note, those that responded to fluids alone (who were therefore not randomized) all survived to discharge from hospital. Results of the study showed that while oxygen delivery ($p<0.0012$) and cardiac index ($p<0.001$) were both increased in the treatment group, oxygen extraction decreased, and therefore there was no significant difference in overall oxygen consumption between treatment and control groups. Furthermore outcomes were worse in the treatment group, with both in-unit and in-hospital mortality being higher ($p<0.04$). However, the higher doses of dobutamine that were needed in the treatment group may have increased the maldistribution of flow within the microcirculation, leading to impaired organ perfusion, multiple organ failure, and increased overall mortality. Excessive efforts to boost oxygen consumption may also have been detrimental, as cardiovascular side effects that were recorded included tachycardias, electrocardiographic ischemic changes, hypertension, and tachyarrhythmias [11].

This work was followed by a large multicenter trial undertaken by Gattinoni and his group, which included 762 patients from 56 units. They hypothesized that by increasing cardiac index and oxygen delivery to supranormal levels or by increasing mixed venous oxygen saturations to normal levels, there would be a reduction in morbidity and mortality. In this study, patients were randomly assigned into three groups: control group (CI 2.5–3.5 L/min/m^2), cardiac index group (CI >4.5 L/min/m^2), and oxygen saturation group (≥70 %). Outcome measures were ICU mortality and 6-month morbidity (number of dysfunctional organ systems) and mortality. As with the Hayes study, not all patients reached their therapeutic targets. The hemodynamic goals were achieved by 94.3 % of the control group, 66.7 % of the oxygen saturation group, but only 44.9 % of the cardiac index group. Those who did not reach the assigned target required a greater amount of treatment and were older and sicker. There were no differences in mortality rates between the three groups studied, or at 6 months after entry to the study, as well as no difference in the number of impaired organ systems at the end of the study period. Again as with Hayes et al.,

Gattinoni et al. found no overall benefit in attaining supranormal targets as there was no observed reduction in mortality and morbidity [12].

The following year the European Society of Intensive Care Medicine published the results of their consensus conference with the Societé de Reanimation de Langue Française and the American Thoracic Society on tissue hypoxia. The following sentence is fine following a comprehensive literature review and 2-day conference, it was concluded that despite subset data supporting improved survival following DO_2 optimization, no beneficial effect could be demonstrated. Furthermore they noted that the ability of patients to achieve supranormal goals may predict improved survival and a reduced likelihood of multiple organ failure [3]. While this phenomenon has been used as evidence to support maximizing DO_2 in the critical care population, it may instead only represent a group of patients who have greater physiological reserve. They reinforced the finding that intention to treat analysis showed no improvement in mortality and concluded that DO_2 maximization was unwarranted in intensive care patients (although prompt resuscitation was still essential).

A meta-analysis performed in 1996 on the effect on mortality of maximizing oxygen delivery in the critically ill identified seven relevant studies and included 1,016 patients. The group concluded that achieving supraphysiological goals (CI, DO_2, and VO_2) did not significantly reduce mortality rates [13]. Others, however, considered the usefulness of comparing such diverse groups of patients treated at different time points to be limited.

The unanticipated negative effects of supranormal oxygen delivery may be linked to dysfunction at the mitochondrial level. Several studies have indicated that septic patients exhibit high tissue oxygen tension, implying impaired utilization and thus multiple organ failure [14, 15]. Furthermore work by Brealey et al. positively correlated various measures of mitochondrial dysfunction to mortality in septic patients [16]. On reviewing this more recent literature, Montgardon et al. proposed the mitochondria to be both the "victim and the player" in MODS, with decreased mitochondrial activity leading to organ "hibernation" and a poor outcome [17].

Of note patients seen to achieve goals with fluids alone all survived in the Hayes study, supporting that this in itself may have prognostic value. This is echoed by the previous work by Vallet et al., who found septic patients responding to a dobutamine trial had a lower mortality (8.7 %) than those that did not (44.4 %) [18]. These studies highlight the importance of timing of resuscitation, and in spite of negative data from critically ill patients, goal-directed resuscitation still remains an attractive concept. Certainly work in the perioperative patient groups supports hemodynamic optimization, at an early stage. For example, Boyd et al. showed protocolized optimization with fluid administration and dopexamine treatment to be beneficial in high-risk surgical patients (75 % reduction in mortality), although the effect on outcome may have been unrelated to optimization of DO_2 [19]. Support for early intervention was also provided by a trial demonstrating increased mortality rates when care (intravenous fluids and vasoactive medications) was delayed in general wards in comparison to in ICU (70 % versus 39 %) [20]. Similar work was done by Wilson et al., whereby patients randomized to hemodynamic monitoring and

vasoactive therapy had significantly improved mortality rates to those receiving standard postoperative care following major elective surgery [21]. However, in both cases, critics pointed out the need to be cautious about interpreting results when comparing such contrasting patient groups.

Following on from these studies, Rivers et al. assessed early initiation of treatment (before admission to intensive care), in patients with sepsis and septic shock. They found that early goal-directed therapy significantly improved in-hospital mortality rates in those randomized to treatment (with targeted fluid, red cell, and dobutamine infusion, $p = 0.009$). However, they aimed for normal rather than supranormal physiological targets, based on targeting central venous oxygen saturation, CVP, MAP, and urine output [22]. Although this paper has been subject to much scrutiny over the years, it does provide evidence that early identification, interventions, and treatments in septic shock patients lead to a more favorable outcome, and as such this early goal-directed therapy became a cornerstone of the surviving sepsis campaign [23].

Importantly there is also a suggestion from these studies that less aggressive therapy may be potentially more beneficial. Similar to many other trends in intensive care, protocolized care such as supranormal oxygenation is likely to have been initiated on the basis of expert opinion. While this is not necessarily incorrect, it may demonstrate a need to gather more evidence before there is widespread adoption of protocols that lead to negligible beneficial or even harmful effects [24].

The perceived benefits of supranormal oxygen delivery hinge on the theory that with optimization of DO_2 and VO_2, survival is improved through prevention of "oxygen debt" and subsequent MODS. However, optimization of the macrocirculation in the above fashion does not necessarily correlate with beneficial effects on the microcirculation. There may be no improvement in tissue hypoxia as a result of mitochondrial or endothelial dysfunction. It is hypothesized that bioenergetic failure at the mitochondrial level is an important mechanism in multiple organ failure, as 90 % of total oxygen consumption occurs in the mitochondria [16]. Both the Hayes and Shoemaker studies aimed to prevent oxygen debt through maximization of oxygen flux through fluid loading, transfusion, and vasoactive agent use. However, causes of the increased mortality in the treatment group from the Hayes et al. study may have resulted from the use of higher doses of dobutamine that although increased macrocirculatory flow did not improve microcirculatory perfusion. This may have resulted in increased vasopressor requirements increasing the risk of gut ischemia, exacerbation of tissue hypoxia, and MODS. The latter was the leading cause of death in the treatment group [11].

Conclusions

Supranormal elevation of oxygen delivery and consumption does not improve overall outcome in critically ill patients. Furthermore, it is often difficult to achieve targets of increased oxygen consumption with attempts to do this proving detrimental. Early resuscitation, however, appears to be beneficial, and a favorable response to hemodynamic optimization may predict survival.

Clinical summary

Intervention	Indications	Cautions	Side effects	Protocol	Notes
Supranormal elevation of oxygen delivery	Critically ill patients at increased risk of death	Patients not responding to initial challenge have a worse prognosis Older and sicker patients tend not to reach therapeutic goals	Extensive use of dobutamine is associated with increased incidence of tachyarrhythmias and ischemic electrocardiographic findings	Supranormal targets: cardiac index ≥4.5 L/min/m^2, oxygen delivery ≥600 mL/min/m^2, oxygen consumption ≥170 mL/min/m^2, and mixed venous oxygen saturation ≥70 %	Aiming to increase oxygen consumption is demonstrated to increase mortality

Box 12.1. Definitions

Oxygen content

The oxygen content of blood is determined by several factors with the major proportion provided by the saturation of hemoglobin in the blood.

$$CaO_2 = (SaO_2 \times Hb \times 1.34) + 0.003(PaO_2)$$

Hb = hemoglobin concentration in g/l
SaO_2 = oxygen saturation
PaO_2 = arterial oxygen partial pressure

Oxygen delivery

Oxygen delivery is simply a product of the arterial oxygen content and cardiac output.

$$DO_2 = CO \times CaO_2$$

CO = cardiac output (heart rate x stroke volume)

Oxygen consumption

Oxygen consumption can be calculated from the product of the cardiac output and the difference between the arterial and venous oxygen content.

$$VO_2 = CO(CaO_2 - CvO_2)$$

CO = cardiac output
CaO_2 = arterial oxygen content
CvO_2 = venous oxygen content

Oxygen extraction ratio

The ability to extract oxygen from the blood is determined by the ratio of oxygen consumption to oxygen delivery.

$$_{O2}ER = VO_2 / DO_2$$

VO_2 = oxygen consumption, DO_2 = oxygen delivery

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Does β_2-Agonist Use Improve Survival in Critically Ill Patients with Acute Respiratory Distress Syndrome?

13

Vasileios Zochios

13.1 General Principles

Acute respiratory distress syndrome (ARDS) is characterized by inflammatory pulmonary edema that can be precipitated by pulmonary or extrapulmonary factors and confers substantial in-hospital mortality in critically ill patients [1]. Although advances in supportive care such as lung protective ventilation have resulted in significant mortality benefit, ARDS-specific pharmacologic therapies remain elusive [2]. Edema clearance is a key component of care in critically ill patients with ARDS and has been the subject of a substantial number of experimental studies. In human cells and animal models, stimulation of β_2-adrenergic receptors leads to an increase in the vectorial transport of sodium across the alveolar epithelium to facilitate edema clearance [3, 4]. Despite this important effect of β_2-adrenergic stimulation, several studies have failed to demonstrate that intravenous infusion or inhalation of short- or long-acting β_2-agonists is effective in improving or preventing ARDS. In fact, the use of β_2-agonist in the treatment of ARDS could potentially worsen outcomes, and its routine use is not recommended [5–10].

13.2 Main Evidences

It has been demonstrated that prophylactic inhalation of the long-acting β_2-agonist salmeterol, during exposure to high altitude, reduced the incidence of high-altitude pulmonary edema [5]. A retrospective chart review of 86 consecutive mechanically ventilated patients with ARDS showed that inhaled albuterol

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(salbutamol) use was associated with shorter duration and lower severity of ARDS [6]. These findings were the basis for further clinical trials of β_2-agonist use in ARDS. In a small phase II trial [7], Perkins et al. showed that sustained treatment for 7 days with intravenous albuterol compared with placebo reduced extravascular lung water in ARDS patients with improvement in gas exchange and respiratory mechanics, although outcome benefits were not shown. However, two successive large-scale randomized control trials were terminated due to safety concerns and futility [8, 9]. In the Beta-Agonist Lung injury TrIal-2 (BALTI-2) [8], 326 mechanically ventilated ARDS patients were randomized to receive either intravenous infusion of albuterol (at a maximal dose) or placebo. The study was terminated due to increase in 28-day mortality in the group of patients treated with albuterol compared with placebo (34 % vs. 23 %). In the Albuterol to Treat Acute Lung Injury (ALTA) study [9], 282 patients with ARDS were randomized to receive either nebulized albuterol or placebo. Clinical outcomes tended to be worse in the albuterol-treated group: ventilator-free days and mortality favored the placebo-treated group, in particular patients with shock. The study was terminated on the grounds of futility. In a recent randomized trial, Perkins et al. tested the hypothesis that β_2-agonists might be useful in preventing the development of ARDS in high-risk patients undergoing elective esophagectomy [10]. Patients were randomized to receive either inhaled salmeterol or placebo in the first 72 postoperative hours. Treatment with salmeterol did not prevent early ARDS; secondary outcomes (organ failure, survival, health-related quality of life) were similar irrespective of β_2-agonist use.

13.3 Pharmacological Properties and Pathophysiology

13.3.1 β_2-Adrenoreceptors: Molecular Structure and Activation

Beta$_2$-adrenoreceptors are G protein-coupled receptors that have seven transmembrane-spanning α-helices. Intracellular signaling after β_2-adrenoreceptor activation is largely affected through cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). Activation of β_2-adrenoreceptor by β_2-agonist causes increased production of cAMP and stimulation of PKA [11]. Beta$_2$-receptors are the most common adrenoreceptor subtype in the pulmonary tree, mostly present in the distal airway and alveoli, expressed on the surface of alveolar type I and II cells [12]. The potential therapeutic effects of β_2-agonists in ARDS are outlined in Fig. 13.1.

13.3.2 Effects on Excess Alveolar Fluid

The absorption of excess alveolar fluid is an ATP-dependent process involving vectorial Na^+ transport out of the alveoli via the apical Na^+ and Cl^- channels and

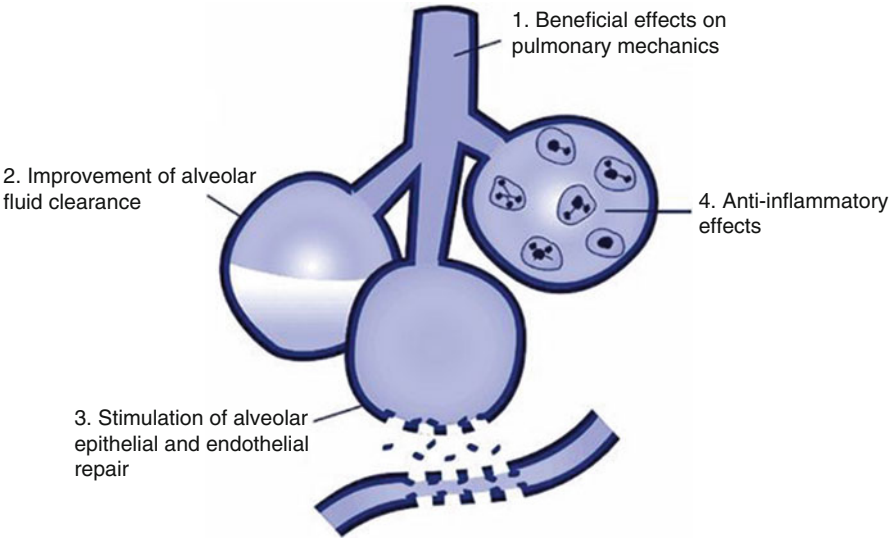

Fig. 13.1 Schematic diagram showing the scientific rationale and potential role of β_2-agonists in ARDS (Adopted from: Bassford et al. [13]. Permission to reproduce granted under BioMed Central's general terms)

basolateral Na^+-K^+ ATPases in the alveolar epithelium [14]. It has been demonstrated, in experimental models, that Na^+ and Cl^- transport is "upregulated" by β_2-agonists via an increase in intracellular cAMP caused by β_2-adrereceptor stimulation leading to an osmotic gradient across the alveolar epithelium and subsequent movement of fluid [14, 15].

13.3.3 Effects on the Injured Alveolar Epithelium

In ARDS there is a damage to alveolar barrier with subsequent alveolar flooding leading to refractory hypoxemia. It has been shown that β_2-agonists reduce neutrophil sequestration, activation, and production of inflammatory cytokines. There is some in vivo evidence of reduced permeability of alveolar capillaries and in vitro evidence of enhanced wound repair in epithelial monolayers [15, 16]. These findings suggest that β_2-agonists could potentially maintain alveolar-capillary integrity and therefore decrease alveolar flooding and degree of hypoxemia [15, 16].

13.3.4 Anti-inflammatory Effects

At the onset of ARDS, there is an increased neutrophil activation and recruitment suggesting a possible correlation between neutrophil activation and development

of the syndrome [15, 16]. The interaction between β_2-agonists and inflammatory response is not fully understood. It has been shown that β-agonists-induced elevation in intracellular cAMP in neutrophils inhibits stimulated neutrophil adhesion to bronchial epithelial cells [17]. Treating ARDS patients with intravenous β_2-agonist, although it increases the number of circulating neutrophils, has no effect on alveolar neutrophil number, neutrophil activation, or alveolar inflammation [18].

13.3.5 Failure of β_2-Agonists to Improve Clinical Outcomes

Recent evidence suggests that routine use of β_2-agonists in mechanically ventilated ARDS patients is unlikely to be beneficial and in fact could worsen outcomes and leaves us wondering why β_2-agonist therapy has been ineffective in improving or preventing ARDS [8–10].

One potential explanation is that the myocardial stimulation caused by β_2-agonists could lead to increased myocardial oxygen demand with adverse effects on cardiac function, especially in ARDS patients with refractory hypoxemia. It is also possible that critically ill patients with underlying coronary artery disease experience adverse cardiac events, including occult ischemia [13]. The cardiovascular effects of β_2-agonists may therefore offset their potential benefit on alveolar edema clearance.

The vasodilatory effect of some β_2-agonists (e.g., albuterol), especially when administered via intravenous route, and the increase in cardiac output cause an increase in ventilation/perfusion mismatch and could potentially have an adverse effect on outcomes [13].

Finally, β_2-agonists may have adverse off-target effects including β_2-adrenergic receptor-mediated increase in cytokines and pro-inflammatory effects [19].

13.4 Therapeutic Use

Beta$_2$-agonists produce smooth muscle relaxation and bronchodilation caused by activation of adenyl cyclase that will produce cAMP. Of note, β_2-adrenoreceptors are also present in submucosal glands, vascular endothelium, mast cells, circulating

inflammatory cells such as eosinophils and lymphocytes, type II pneumocytes, and cholinergic ganglia [11]. They are the mainstay of current management of airflow obstruction (chronic obstructive pulmonary disease and asthma) and are divided into three groups: short acting (e.g., albuterol, fenoterol, terbutaline), long acting (e.g., formoterol, salmeterol), and ultra-long acting (e.g., indacaterol, olodaterol, vilanterol, carmoterol) [20]. Short-acting β_2-agonists have a 3–6 h duration of action, whereas that of the long-acting β_2-agonists can exceed 12 h. These agents also differ significantly in their intrinsic efficacy which depends on their affinity and potency [20].

β_2-agonists can be administered via oral, parenteral, or inhalational route. Gut absorption is incomplete and subjected to a significant first-pass effect, while after inhalation or intravenous administration, short-acting β_2-agonists have rapid onset of action (e.g., 1–5 min for albuterol, 30–45 min for salmeterol). The onset of action is related to the lipophilicity of these agents and their ability to activate β_2-adrenergic receptors in their aqueous phase (albuterol and formoterol) [11, 20].

Albuterol, the most frequently prescribed agent in the critical care setting, is 10 % protein bound and has a half-life of 4–6 h. It is metabolized in the liver to the inactive 4-O-sulfate, which is excreted along with albuterol in the urine [11, 20, 21].

Adverse effects associated with β_2-agonists use include: tachyarrhythmias, transient hypoxemia despite bronchodilation (due to ventilation/perfusion mismatch), hyperglycemia, hypokalemia, fine tremor of skeletal muscles, headaches, nausea, and sleep disturbances [20].

The pharmacology and therapeutics of β_2-agonists are summarized in the clinical summary.

Conclusions

Although preliminary data suggested that the use of β_2-agonist in the context of ARDS could potentially accelerate alveolar edema clearance and have beneficial anti-inflammatory and immunomodulatory effects, robust prospective clinical trials demonstrated that the use of β_2-agonists in ARDS patients is unlikely to be beneficial and could worsen outcomes. Routine administration of β_2-agonists in mechanically ventilated critically ill patients with ARDS should therefore be avoided.

Clinical summary

Drug	Indications	Cautions	Side effects	Dose (adults)[a]	Notes
SABAs (*albuterol, fenoterol, terbutaline*) LABAs (*formoterol, salmeterol*)	Reversible lower airway obstruction (COPD, asthma) Occasionally in premature labor (relaxes the gravid uterus)	Known cardiovascular disease Hyperthyroidism Arrhythmias Susceptibility to QT interval prolongation Hypertension Diabetes (risk of DKA especially, when given intravenously) Known hypokalemia Mild to moderate preeclampsia	Fine tremor (hands) Nervous tension Headaches Tachyarrhythmias (especially in the presence of hypokalemia) Myocardial ischemia Sleep disturbances Paradoxical bronchospasm Hypokalemia/ hyperglycemia Hypoxemia (V/Q mismatch)	*Albuterol (salbutamol):* By mouth: 4 mg (2 mg in the elderly), 3–4 times daily By intramuscular or subcutaneous injection: 500 mcg repeated every 4 h if needed By slow intravenous injection: 250 mcg repeat if necessary By intravenous infusion: initially 5 mcg/min adjusted according to response and heart rate usually in range 3–20 mcg/min By aerosol inhalation: 100–200 mcg (1–2 puffs) up to four times daily By inhalation of nebulized solution: 2.5–5 mg repeated up to four times daily or more frequently in severe cases In uncomplicated premature labor: initially 10 mcg/min increase gradually according to response (maximum rate 45 mcg/min) *Salmeterol:* −By inhalation: 50 mcg (2 puffs or 1 blister) twice daily	*Avoid* routine use of β_2-agonists in mechanically ventilated critically ill patients with ARDS, unless there is clinical evidence of airflow obstruction (current evidence suggests a tendency of β_2-agonists to cause harm when routinely used in ARDS patients)

SABA short-acting β_2-agonist, *LABA* long-acting β_2-agonist, *COPD* chronic obstructive pulmonary disease, *DKA* diabetic ketoacidosis, *V/Q* ventilation/perfusion ratio, *ARDS* acute respiratory distress syndrome

[a]Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press http://www.medicinescomplete.com [Accessed on 28/08/2014]

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High-Frequency Oscillatory Ventilation

14

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14.1 General Principles

Acute respiratory distress syndrome (ARDS) remains one of the major causes of morbidity and mortality in the critically ill population. There is a complete disruption of normal pulmonary architecture during ARDS as well as loss of functioning units and the development of high lung permeability and edema, resulting in clinically low-compliant, stiff lungs [1].

Conventional mechanical ventilation with high tidal volumes was shown to be associated with ventilator-induced lung injury (VILI), a feared phenomenon that often contributes to exacerbate lung damage. Ventilator-induced lung injury was first described in animal studies [2–4] and later confirmed in humans [5, 6] and seems to be promoted by the high alveolar pressures resulting from high tidal volume ventilation. The mechanisms of VILI have already been described in Chap. 3.

Although new protective ventilation strategies have improved outcome of critically ill patients, mortality rate in ARDS continues to remain high. Current in-hospital mortality of patients with ARDS is reported to be above 40 % [7].

Nowadays, lung-protective mechanical ventilation with low tidal volumes is considered the standard of care for patients suffering from ARDS [8–10]. Historically extracorporeal membrane oxygenation, high-frequency oscillatory ventilation (HFOV), and prone positioning have been suggested as "unconventional" strategies for improving oxygenation in life-threatening severe hypoxemia in ARDS patients.

High-frequency oscillatory ventilation was developed by Lunkenheimer et al. in 1972 [11]. It is characterized by a very low tidal volume (frequently less than

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anatomical dead space), delivered at a very high-frequency rate. Gas exchange occurs, and potential adverse effects of conventional ventilation, such as overdistension (volutrauma) and the repetitive opening and closing of collapsed lung units (atelectrauma), are mitigated. Therefore, it theoretically meets all the main principles of lung-protective ventilation and has been widely studied in the last decade.

14.2 Main Evidences

Several observational studies and a small number of randomized trials supported the safety of HFOV and its role in improving oxygenation in patients with ARDS, limiting further lung injury. Several reviews and meta-analysis have been published on this topic, but probably due to previous limited evidence, the role of HFOV in improving outcome of patients with ARDS remained unclear for a long time [12].

In 2013, Ferguson et al., in a large multicenter randomized clinical trial, proved that early application of HFOV in patients with moderate to severe ARDS was associated with higher mortality rate when compared with a ventilation strategy that used small tidal volumes and high positive end-expiratory pressure (PEEP) levels (with HFOV applied only in the subgroup of patients with severe refractory hypoxemia) [13]. In-hospital mortality was 47 % (129 patients) in the HFOV group, while only 35 % (96 patients) of the patients died in the control group (HFOV relative risk (RR) of death 1.33; 95 % confidence interval (CI), 1.09–1.64; $p = 0.005$). Moreover, HFOV strategy was associated with a higher mean airway pressures and with a larger use of vasoactive drugs, neuromuscular blockers, and sedatives. Such an unattended, impressive difference in mortality between groups led to earlier termination of the trial due to safety reasons [13].

The discrepancy of these results with previous trials is probably due to the inadequacy of ventilation strategies in the control group. Accordingly, another large randomized clinical trial performed by Young et al. did not find any difference in 30-day mortality between patients undergoing either HFOV or conventional ventilation (41.7 % versus 41.1 %, $p = 0.85$ %). In this trial, patients in the conventional ventilation group were treated according to local practice; as a result, the mean tidal volume was 8 mL/kg, higher than recommended [14].

A trend in increased mortality (RR 1.04, 95 % CI 0.83–1.31) was also confirmed by Haung et al., in a meta-analysis pooling only randomized controlled trials. Moreover, two out of five included trials were stopped early due to safety reasons. A trend toward increased risk of barotrauma (RR 1.19; 95 % CI 0.83–1.72) and unfavorable hemodynamics (RR 1.16; 95 % CI 0.97–1.39) was also observed [15].

14.3 Physiopathological Principles

High-frequency oscillatory ventilation is characterized by extremely small tidal volumes (1–4 mL/kg) and high respiratory frequencies (3–15 Hz), generated by an oscillatory pump. This extremely low tidal volume, usually lower than anatomical

dead space, is not a real tidal volume, but rather an amplitude of oscillations (delta pressure). This ventilation technique can be described as a sort of "vibrating CPAP machine": it keeps alveoli open at a constant, less variable, and relatively high mean airway pressure, avoiding tidal overstretch and the cyclic alveolar collapse and recruitment, thus preventing further lung damage [16].

Moreover, HFOV may improve gas exchange and ventilation/perfusion (V/Q) matching. Mechanism of gas exchange during HVOF is complex and involves several factors such as turbulence, laminar flow with Taylor dispersion, membrane diffusion, "pendelluft effect," and convection. Each of these factors, except for membrane diffusion, results in the generation of convective fluid flow and is influenced by the impedance of the tracheal tube, circuit, ventilator and respiratory system as well as by ventilatory setting.

Different mechanisms have been hypothesized to explain the detrimental effect of HVOF compared with current protective lung ventilation reported by Ferguson et al. [13]. First of all, higher mean airway pressure may decrease venous return or directly affect the function of the right ventricle resulting in severe hemodynamic impairment. Moreover, the increased need of sedative drugs may cause systemic vasodilation, worsening the hemodynamic impairment. Furthermore, an increased barotrauma associated with the use of HFOV cannot be excluded.

14.4 Therapeutic Use

High-frequency oscillatory ventilation is usually considered for all ARDS patients with refractory hypoxemia despite optimal conventional mechanical ventilation. Best timeline and criteria for starting HFOV are not supported by strong evidence.

In Ferguson's trial, according to the results of a pilot study and consensus guidelines, patients randomized to HFOV underwent, first, a recruitment maneuver, performed applying a continuos pressure of 40 cm H_2O for 40 s. Then HFOV was started with a mean airway pressure of 30 cm H_2O, later adjusting the pressure in order to maintain a PaO_2 ranging from 55 to 80 mmHg [17, 18]. Therefore, HFOV tidal volumes were reduced using the highest frequency ensuring an arterial blood pH above 7.25 [19, 20]. If mean airway pressure was $\leq$24 cm H_2O for at least 12 h, conventional ventilation could be restarted after 24 h of HFOV. On the contrary, conversion to conventional ventilation was mandatory when airway pressure achieved 20 cm H_2O.

Over the next 48 h, HFOV was resumed if a $FiO_2 > 0.4$ or a PEEP level >14 cm H_2O was needed for more than 1 h in order to maintain the desired target of oxygenation.

Positive end-expiratory pressure or mean airway pressure could be reduced to a lower level according to clinical physicians' judgment, in case of persisting hypoxemia or when lungs appeared radiographically over distended.

Prone positioning, inhaled nitric oxide, or other strategies not interfering with ventilation protocols could be instituted in case of severe hypoxemia ($FiO_2 > 0.9$).

Alternative therapies (including HFOV in the control group) could be started in case of refractory hypoxemia ($PaO_2 < 60$ mmHg despite $FiO_2 = 1.0$ and neuromuscular

blockade), refractory barotrauma (persistent pneumothorax or increasing subcutaneous emphysema despite double thoracic drainage), or refractory acidosis (pH of ≤7.05).

The application of HFOV has been shown to be associated with higher mean airway pressures and with a larger use of vasoactive drugs, neuromuscular blockers, and sedatives [13]. Moreover, recent meta-analyses proved that the application of HFOV was associated with a trend toward an increased risk of barotrauma and unfavorable hemodynamics [15].

Conclusions

According to the most recent data, HFOV does not offer any real advantage compared to current protective lung ventilation, but it is associated with a major need of sedative and neuromuscular blocker drugs, unstable hemodynamics, and lung barotrauma. The OSCILLATE trial demonstrates an increased risk of death in patients undergoing HFOV. As stated in our Consensus Conference [21], HFOV should therefore be avoided as a first-line treatment in ARDS.

Clinical summary

Technique	Indications	Contraindications	Side effects	Protocol	Note
High-frequency oscillatory ventilation (HFOV)	Acute respiratory distress syndrome with hypoxemia refractory to conventional protective ventilation	Recent lung surgery, lung disease characterized by airway narrowing or air trapping, intracranial hypertension	Increased mean airway pressures, use of vasoactive drugs, neuromuscular blockers, and sedatives	Initial mean airway pressure of 30 cm H_2O, later adjusted to maintain PaO_2 55–80 mmHg. HFOV tidal volumes reduced using the highest frequency for maintaining pH >7.25	Increases mortality compared to protective lung ventilation, avoid first-line use

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Glutamine Supplementation in Critically Ill Patients

15

Laura Pasin, Pasquale Nardelli, and Desiderio Piras

15.1 General Principles

Providing artificial nutrition is a key part of the care of intensive care unit (ICU) patients.

Critically ill patients are highly hypermetabolic and have increased nutrient requirements, but almost all of them, especially those receiving mechanical ventilation, are unable to provide their own sustenance. As a result, malnourishment is frequently observed in intensive care unit, and most critically ill patients receive specialized nutrition therapy to prevent the development of malnutrition. Large observational studies suggest that malnutrition is associated with increased morbidity and mortality, regardless of patient's body mass index [1, 2]. Therefore, providing appropriate artificial nutrition may contribute to improve outcome of critically ill patients. Consequently, clinical research in critical care nutrition has been a hot topic in the last decade, and many randomized clinical trials have been published on this argument [3]. Among them, the potential benefit of glutamine supplementation in critical care setting has been extensively studied.

Glutamine is the most abundant human conditionally essential amino acid, mostly stored in skeletal muscle tissue. Through glutamate, it is a precursor of glutathione and plays a crucial role in different stress-response pathways by modulating

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inflammatory response, by preventing organ injury, by modulating glucose metabolism, and by inducing cellular protection pathways in critical illness [4].

Low blood glutamine levels have been associated with a poor outcome and have been demonstrated to be independent predictors of mortality in critically ill patients [5, 6].

15.2 Main Evidences

Heyland et al. provided evidence that glutamine supplementation increases mortality in critically ill patients in a large, multicentric randomized clinical trial published in 2013 in the *New England Journal of Medicine* [7].

On the contrary, previous meta-analysis of randomized clinical trials suggested that glutamine and antioxidant supplementation could be associated with improved survival in this population [8, 9]. However, most of the studies included in these meta-analyses were at high-risk of bias, and large, subsequent, randomized studies did not confirm such beneficial effects [10, 11].

The high-quality, blinded 2-by-2 factorial trial of Heyland et al. included 1,223 patients from 40 different intensive care units in Canada, United States, and Europe [7].

Mechanically ventilated patients with multiorgan failure were randomly assigned to receive either intravenous and enteral glutamine supplementation or matching placebo solutions. In addition, patients were randomly assigned to receive 500 μg of selenium intravenously plus different enteral vitamins and minerals (selenium, zinc, beta-carotene, vitamin E, and vitamin C) or placebo.

The primary outcome of the study was 28-day mortality. Secondary outcomes were length of ICU and hospital stay, development of infectious complications and antibiotic use, multiple organ dysfunction, duration of mechanical ventilation, and survival up to 6 months.

The trial showed that antioxidants did not affect outcome, whereas glutamine supplementation was associated with an increased 28-day mortality (32.4 % vs. 27.2 %; adjusted odds ratio, 1.28; 95 % CI, 1.00–1.64; $p = 0.05$). Moreover, both in-hospital mortality and mortality at 6 months were significantly higher among patients who received glutamine.

A later meta-analysis confirmed that glutamine supplementation was associated with a significant increase in mortality when included trials were limited to multicenter, randomized trials: 35 % (434 of 1,232 patients) for those receiving glutamine versus 31 % (385 of 1,231 patients) for controls ($p = 0.015$ for the comparison). On the contrary, when pooling together only single-center randomized trials, glutamine supplementation was associated with a significant decrease in mortality: 20 % (160 of 819) for those receiving glutamine versus 23 % (189 of 826 patients) for controls ($p = 0.019$ for the comparison). The authors attributed these contrasting results to a single-center study bias bringing further evidence to confirm that glutamine supplementation increases mortality in critically ill patients [12].

15.3 Pharmacological Properties

15.3.1 Physiological Considerations

Glutamine is the most abundant amino acid in the body since it represents approximately 30 % of plasmatic free amino acids, with a concentration ranging between 500 and 900 μmol/L [13].

It is produced in the cytoplasm from glutamate and ammonia, due to the action of the enzyme glutamine synthetase that replaces the side-chain hydroxyl of glutamic acid with an amine functional group. Different enzymes can use glutamine as a substrate, but glutamine synthetase is the only enzyme responsible for de novo glutamine synthesis.

Glutamine is commonly known as a nonessential amino acid because of the capacity of most human cells to produce it. Most glutamine in the body is synthesized by skeletal muscle mass, which is responsible for about 90 % of its production, while the brain and the lungs synthesize the rest [14].

Glutamine plays a main role in many metabolic functions and serves as an energy substrate for most cells, particularly for lymphocytes and enterocytes. Moreover, it is a precursor for purine nucleotides and glutathione, one of the most important cellular antioxidant [15]. It is involved in nitrogen transport and is the most important substrate for renal ammoniagenesis.

It also serves as a metabolic intermediate, providing nitrogen and carbon for the synthesis of nucleic acids, proteins, fatty acids, and other amino acids [16].

Although it is a nonessential amino acid in the diet of healthy subjects, endogenous glutamine biosynthesis may be inadequate to meet the needs of critically ill patients. In fact, during extreme stress, such as sepsis, critical illness, trauma, major surgery, and other catabolic conditions, glutamine demand and consumption exceed the normal supply. In case of increased requirement, glutamine is rapidly released from muscle stores, but, despite this compensatory mechanism, low blood glutamine levels are frequently observed in severely ill patients and have been associated with a poor outcome [5, 6]. All these observations led researchers to think that glutamine supplementation could represent a successful strategy to improve outcome in critically ill patients. However, quite unexpectedly, Heyland et al. showed that glutamine supplementation was associated with an absolute increase in mortality of 6.5 % points at 6 months. The mechanism underlying this unexpected result is not clear. Authors speculated that glutamine may have been administered too early or drug doses may have been too high, but it seems unlikely since the rationale for timing and dosing was based on previous published evidence. Probably, as Greet Van den Berghe stated in the accompanying editorial, “If low glutamine levels during acute critical illness reflect an adaptive and beneficial stress response rather than a conditional deficiency, interfering with such adaptation could be deleterious” [17].

The detected amino acid toxicity could be related to direct or indirect effects of glutamine or its metabolites and/or to the higher total amount of amino acids administered to the study group patients.

15.3.2 Pharmacokinetics Proprieties

After infusion, the dipeptide N(2)-L-alanyl-L-glutamine is quickly divided into alanine and glutamine. Half-life in humans is relatively short, being approximately 2.4–3.8 min (4.2 min in severe renal failure), while the plasmatic clearance is between 1.6 and 2.7 L/min. Hydrolysis probably occurs in the extracellular space only. Renal elimination of constant infusion of N(2)-L-alanyl-glutamine is less than 5 %.

15.4 Therapeutic Use

Glutamine supplementation has been evaluated both as enteral and parenteral nutrient in different clinical trials. Usually, intravenous supplementation is more likely to increase nitrogen balance, while enteral administration is less likely to improve the plasma glutamine level.

Glutamine is an unstable amino acid in solution since it undergoes cyclization to create the neurotoxin pyroglutamate [18]. This reaction takes place at room temperature, but it is promoted by heat [19]. For this reason, only glutamine-containing dipeptides (alanyl- or glycyl-glutamine) and not free glutamine are added to enteral or parenteral nutrition solutions.

As a rule, a maximum dosage of 2 g/kg/day of amino acids or proteins supplementation should not be exceeded in parenteral or enteral nutrition.

In the trial of Heyland et al., patients randomized to glutamine received 0.35 per kg of ideal body weight per day of the amino acid supplementation (provided as intravenous 0.50 g/kg/day of the dipeptide alanyl-glutamine plus 42.5 g/day of enteral alanyl-glutamine and glycine-glutamine dipeptides, which provide 30 g of glutamine). Moreover, some of them were randomized to receive 500 μg of intravenous selenium plus enteral 300 μg of selenium, 20 mg of zinc, 10 mg of beta-carotene, 500 mg of vitamin E, and 1,500 mg of vitamin C [7].

According to pharmaceutical industry recommendations, glutamine dipeptide should not be administered to patients with severe liver dysfunction, renal insufficiency (creatinine clearance <25 mL/min), or severe metabolic acidosis.

Parenteral dipeptide solutions are widely used in European countries, while their use in the United States is currently not approved by the Food and Drug Administration.

Previous clinical trials on enteral supplementation of glutamine did not report adverse events.

Heyland et al. reported a total of 52 serious adverse events in 46 of the 1,223 randomized patients, four of which potentially related to study supplements. Moreover, a higher frequency of high urea levels (>50 mmol/L) in patients who received glutamine was recorded (13.4 % vs. 4.0 %, $p<0.001$) [7]. Overall, they found no significant differences in rates of major adverse events among groups. Nonetheless, mortality rate was significantly higher among patients who received glutamine.

Conclusions

Glutamine supplementation in ICU patients is supposed to improve outcome by modulating inflammatory response, preventing organ injury, modulating glucose metabolism, and inducing cellular protection pathways. Trials showed conflicting results on mortality. Heyland et al. demonstrated a significant increase of death risk in ICU patients receiving glutamine supplementation, and their results were confirmed by a subsequent meta-analysis considering only high-quality evidence. Therefore, glutamine supplementation should be avoided in this setting.

Clinical summary

Drug	Indications	Contraindications	Side effects	Dose	Note
Glutamine (alanyl-glutamine and glycine-glutamine)	Critically ill patients (intensive care unit patients, burns, surgical patients) Bone marrow transplant Weight loss in patients with AIDS	Cirrhosis or severe liver disease with hepatic encephalopathy Metabolic acidosis Renal insufficiency (creatinine clearance <25 mL/min) Monosodium glutamate sensitivity Seizures	Increased frequency of high urea levels (>50 mmol/L)	0.35 g/kg intravenously plus 30 g per day enterally	In critically ill patients it increases mortality

AIDS acquired immunodeficiency syndrome

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Part III

Updates

Reducing Mortality in Critically Ill Patients: A Systematic Update

16

Marta Mucchetti, Livia Manfredini, and Evgeny Fominskiy

Evidence-based medicine (EBM) is a form of medicine that aims to optimize decision-making by implementing the use of evidence from well-designed and conducted research.

Unfortunately, available literature on critically ill patients appears to be wide, but conflicting and inconclusive. Vincent [1] identified several reasons for this. First, intensive care unit (ICU) population is extremely heterogeneous. Second, most of the randomized controlled trials (RCT) are characterized by weak statistics and poor design (small sample size and inadequate power, rare blinding). As a consequence, EBM rarely can give strong recommendations to guide the intensivists' practice.

The Consensus Conference process that has been described in this book [2] and its "Democracy Based Medicine" are meant to integrate EBM and potentially give some indications when EBM has to stay silent [3]. The consensus process is made up of three fundamental components: (1) a systematic literature search, (2) the evaluation of the selected papers by a Consensus Conference of experts, (3) and the validation of consensus statements by international web vote (see Chap. 1).

Scientific literature is growing every day, and continuous updates are needed to confirm or challenge the validity of selected interventions and to evaluate new ones.

A clear example of this is the use of hypothermia after out-of-hospital cardiocirculatory arrest (CCA). When the Consensus Conference was held, on June 20, 2013, the American Heart Association recommended that "comatose (i.e. lack of meaningful response to verbal commands) adult patients with return of spontaneous circulation after out-of-hospital ventricular fibrillation cardiac arrest should be

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cooled to 32–34 °C (89.6–93.2 °F) for 12–24 h (Class I, LOE B)" [4]. Six months later, Nielsen et al. published a large multicenter randomized controlled trial (mRCT) that did not find any difference in mortality in patients treated with mild hypothermia (33 °C) compared with normothermia (36 °C) [5]. The implications of these findings are discussed in depth in Chap. 17.

In this chapter we report briefly the mRCT published from June 21, 2015, to January 31, 2015, focusing on interventions that showed a significant effect on mortality in adult critically ill patients. We searched PubMed, Medline, and EMBASE databases using the same search strategy (Box 16.1) and inclusion/exclusion criteria (Table 16.1) chosen for the Consensus Conference [6].

Box 16.1. Full Search Strategy

(dead[tiab] or death[tiab] or die[tiab] or died[tiab] or mortality[tiab] or fatalit*[tiab] or exitus[tiab] or surviv*[tiab]) and ("anesthesia"[tiab] OR "cardiac arrest"[tiab] or "critical care"[tiab] or sepsis[tiab] or "critical illness"[tiab] or "critically ill" [tiab] or "ARDS"[TIAB] or "acute respiratory distress syndrome"[tiab] OR "ecmo"[tiab] OR "intensive care"[tiab] or emergen[tiab]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]))

Table 16.1 Inclusion and exclusion criteria during literature screening

Inclusion criteria
1. Published in peer-reviewed journal
2. Multicenter randomized design
3. Dealt with a nonsurgical intervention (drug/technique/strategy)
4. Involving adult critically ill patients
5. Showing a statistically significant reduction or increase in crude mortality at least at one time point
Exclusion criteria
1. Used a quasi-randomized methodology
2. Dealt with surgical interventions
3. Involved pediatric population
4. Dealt only with the perioperative period
5. Showed a mortality effect only in a subgroup of the studied population
6. Showed a mortality effect only in adjusted mortality analysis

Only four mRCTs that fulfill our inclusion criteria were found. One intervention, hypothermia in bacterial meningitis [7], increased mortality. Three interventions – colloids [8], vasopressin and steroids in cardiocirculatory arrest (CCA) [9], and ulinastatin in severe sepsis [10] – seem to have a beneficial effect on survival. The main characteristics of these trials are summarized in Table 16.2.

16.1 Colloids

One large mRCT on the impact of colloids on survival in critically ill patients was published after the Consensus Conference [8]. The CRISTAL trial (Colloids versus Crystalloids for the Resuscitation of the Critically Ill) involved 57 ICUs from five different countries and enrolled 2,857 patients. Patients with hypovolemic shock were randomized to receive fluid resuscitation by either colloid or crystalloids. There was no blinding, and clinicians could choose to administer whichever fluid was available in their institution. Most of the patients in the crystalloid group received normal saline; most of the patients in the colloid group received hydroxyethyl starches. Enrolment was stopped early due to futility at an ad interim analysis; therefore, no significant difference was found in 28-day mortality (primary end point). The need of renal replacement therapy did not differ between the two groups. Ninety-day mortality was investigated as a secondary post hoc endpoint, and a statistical significant difference was found: relative risk (RR) 0.92 (95 % confidence interval (CI) 0.86–0.99), $p = 0.03$. The authors themselves highlighted the weakness of this result that should be considered as explorative. Nevertheless, this trial started a vivacious debate on the impact of colloids on mortality and on renal impairment. Perner noted that the CRISTAL trial had a high risk of bias, as it was open-label and allocation might have been inadequate [11]. The open-label design imposes to demonstrate equal-quality resuscitation and continuous monitoring of renal function, but both of these points were suboptimal in Annane's work, according to Bellomo and colleagues [12]. Moreover, the use of different fluids in each intervention group makes the interpretation of these results difficult [11]. The implications of Annane's work are discussed in Chap. 9, dedicated to the detrimental effect of colloids.

16.2 Vasopressin and Steroids in In-Hospital Cardiac Arrest

Heart diseases still rank as United States first cause of death. Out-of-hospital CCA has an overall incidence of 126 cases per 100,000 inhabitants/year. Survival till hospital discharge is less than 5 % and doubles in case of treatment by the emergency medical services. In case of in-hospital CCA, survival increases up to 24 % [13]. Moreover, among CCA survivors, the prevalence of severe cerebral disability or vegetative state ranges from 25 to 50 %.

Mentzelopoulos and colleagues designed a double-blinded mRCT to investigate the effect on survival with good neurological outcome (cerebral performance

Table 16.2 Characteristics of the selected trials

	Intervention	Setting	Effect on survival	No. of centers	No. of patients	RR/OR	*p*-value	Blinded	Interruption	ITT
Annane D [8]	Colloids	Hypovolemic shock	Increase survival	57	2,857	0.92(0.86–0.99)[a]	0.03	No	Yes, for futility	Yes
Mentzelopoulos S [9][b]	Vasopressin + steroids	In-hospital CCA	Increase survival	3	300	3.28 (1.17–9.29)[c]	0.02	Yes	No	No
Karnad DR [10]	Ulinastatin (human urinary trypsin inhibitor)	Severe sepsis	Increase survival	7	122	0.26(0.07–0.95)[c]	0.04	Yes	No	No
Mourvillier B [7]	Hypothermia (32–34 °C for 48 h)	Severe bacterial meningitis	Increase mortality	49	98	1.99(1.05–3.77)[a]	0.04	No	Yes, for safety	Yes

RR relative risk, *OR* odd ratio, *ITT* intention to treat, *CCA* cardio circulatory arrest

[a]RR and 95 % confidence interval

[b]In this case, the tested outcome is survival with favorable neurological outcome until hospital discharge

[c]OR and 95 % confidence interval

category score of 1 or 2) of epinephrine, vasopressin, and steroids in "vasopressor-requiring, in-hospital CCA" [9]. The intervention group received vasopressin (20 UI/CPR cycles, till return to spontaneous circulation or up to 100 UI) and methylprednisolone (40 mg) on top of standard cardiopulmonary resuscitation (CPR) with epinephrine; hydrocortisone was given to the intervention group patients that survived more than 4 h (300 mg die, for 7 days). Three hundred patients were enrolled in three centers. Compared with patients in the control group, patients in the experimental group were more likely to be alive at hospital discharge with favorable neurological recovery (18/130 [13.9 %] vs. 7/138 [5.1 %]; odd ratio (OR) = 3.28; 95 % CI, 1.17–9.20; $p = 0.02$). Overall survival was not analyzed by the authors, but it could be calculated from the reported data, and the difference was significant (Fischer's exact test, $p = 0.034$). Data was analyzed according to the per-protocol principle.

This is the first mRCT showing positive neurological outcomes with pharmacotherapy in ACC. A major limitation of this study is the use of multiple interventions, making it difficult to discern which one of these interventions caused benefit. Previous literature on vasopressin alone [14] or with epinephrine [15] compared to epinephrine alone did not show definitive results. Further trials to assess the benefits of this multiple-agent combination and to delineate the precise role of each individual agent are needed.

16.3 Ulinastatin in Severe Sepsis

The incidence of sepsis is increasing, and fatality rate for severe sepsis ranges between 20 and 50 % [16]. Urinary trypsin inhibitor or ulinastatin is a protease inhibitor found in human blood and urine, believed to inhibit a wide variety of pro-inflammatory serine protease enzymes. Therefore, it may attenuate the inflammatory response by acting at multiple sites. Karnad et al. conducted a pilot, double-blinded, placebo-controlled mRCT involving seven Indian ICUs [10]. The primary outcome was 28-day survival. This trial was founded by the Bharat Serums and Vaccines Limited, the pharmaceutical company that produces the medication.

A total of 122 patients were randomized. According to a modified intention-to-treat principle, 114 were analyzed, and 28-day mortality was significantly reduced in the intervention group (OR 0.26, 95 % CI 0.07–0.95, $p = 0.042$), but significance was lost with the intention-to-treat analysis.

This trial shows a relatively small sample size, it is probably underpowered, and statistical significance is lost when a more conservative approach is used. Besides, when other protease inhibitors acting on inflammatory response (e.g., activated protein C) have been studied, they failed to provide substantial clinical benefit in large non-sponsored-driven clinical trials [17]. The interesting results of this trial advocate for further investigations.

16.4 Moderate Hypothermia in Severe Bacterial Meningitis

The popularity of moderate hypothermia to improve survival and neurological outcome after out-of-hospital CCA has induced various authors to study this technique in other clinical settings that might benefit from neuroprotection, such as traumatic brain injury and severe meningitis.

Mourvillier et al. conducted an unblinded mRCT in 49 French ICUs to assess the effect of moderate hypothermia on neurological outcome in patients affected by severe bacterial meningitis [7]. The primary outcome was 3-month score on the Glasgow Outcome Scale (GOS). Good neurological outcome was defined as GOS = 5 (i.e., mild or no neurological disability). Patients in the hypothermia group were cooled down to 32–24 °C by infusion of 1,500 mL of cold (4 °C) saline, hypothermia was maintained for 48 h, and rewarming phase was strictly passive. The data and safety monitoring board stopped the enrollments after only 98 patients were enrolled due to safety reasons. The intervention group showed an increased risk of mortality (RR 1.99, 95 % CI 1.05–3.77, $p = 0.04$). The primary outcome did not significantly differ between the two groups.

As discussed by the authors, the early stopping precludes a firm conclusion about the effect on mortality of moderate hypothermia in comatose patients with bacterial meningitis. Truncated trials systematically overestimate treatment effects [18].

Literature on this topic is poor and consists in just few case series [19] that suggested a favorable outcome. Moreover, the setting where hypothermia seemed a well-established practice (i.e., after out-of-hospital CCA) has now been greatly challenged by Nielsen trail [5] (see Chap. 17).

Conclusions

The consensus process needs continuous updates. We found four recent mRCTs that show a statistically significant effect on survival in critically ill adult patients. Hypothermia in severe bacterial meningitis was the only intervention that increased mortality. Three treatments showed an improvement in survival. One of these, colloids for volume resuscitation, seems in contrast with previous literature (and it was discussed in a dedicated chapter). The other two interventions were ulinastatin in severe sepsis and the combination of vasopressin and steroids on top of standard CPR.

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Is Therapeutic Hypothermia Beneficial for Out-of-Hospital Cardiac Arrest?

17

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17.1 General Principles

Cardiovascular mortality is the leading cause of death in the United States and developed countries. A proportion of cardiac deaths are due to out-of-hospital cardiac arrest (OHCA). Among the total resident population of the United States, 318,248,024 (www.census.gov, accessed June 15, 2014), approximately 424,000 experience emergency medical services (EMS) – assessed OHCA yearly [1], out of which 92 % die [2]. One fourth of OHCA cases shows shockable rhythms due to ventricular tachycardia (VT) or ventricular fibrillation (VF) [3]. Among those transported to the hospital, many remain comatose due to hypoxic brain damage, which is the leading cause of death, and poor neurological function after cardiac arrest. Over the past decade, mild therapeutic hypothermia (TH) to 32–34 °C for 12–24 h has been utilized in VF OHCA, especially after two landmark studies in 2002 showed an increased rate of favorable neurological outcome [4, 5] and a reduction in mortality [5]. For these reasons, TH was recommended by international resuscitation guidelines, and its use has been extended to all victims of cardiac arrest, regardless of the shockability of initial rhythm or whether the arrest was in or out of the hospital. The optimal timing for induction of hypothermia remains controversial. In animal models of cardiac arrest, the benefit of hypothermia rapidly declines if it is started 15 min after reperfusion [6]. Experimental data suggest superiority of

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intra-arrest compared with post-resuscitation cooling [7]. However, these variables were not reproduced among the 234 patients resuscitated from prehospital VF and randomized to early field cooling [8] nor were reproduced by other studies [9]. In a recent multicenter trial, TH did not improve survival or neurological outcome [10], casting some doubt on earlier studies. Herein, we review the available evidence for the benefit of targeted temperature management for OHCA victims.

17.2 Main Evidences

17.2.1 Randomized Trials for TH in OHCA with Shockable Rhythms

Several randomized trials compared TH with standard care in improving survival and neurological outcome after VF/VT OHCA (Table 17.1). Initial studies were small in size and inadequately powered with random errors; therefore, the quality of evidence was low. The main evidence for the value of TH was generated by two studies performed a decade ago [4, 5] that comprised 352 patients with VF/VT OHCA. In the study by Bernard et al., 77 patients were randomized within 2 h of return of spontaneous circulation (ROSC) to surface cooling (core body temperature reduced to 33.5 °C for 12 h) or to receive passive rewarming, as control group [4]. In the second trial, 275 patients were randomized to a temperature of 32–34 °C or normothermia. Cooling began in a median time of 105 min, and target temperature was achieved in 8 h and continued for 24 h [5]. Both studies showed an increase in rate of favorable neurological outcome [4, 5] and reduction of mortality [5].

The insufficient evidence from these two trials, together with expert recommendations for the need for larger trials [11–13], stimulated further research. A recent randomized multicenter trial showed no survival benefit nor neuroprotective effect with TH. Nielsen et al. randomized 939 patients with OHCA to targeted temperature management at either 33 or 36 °C [10]. Fifty percent of patients in the 33 °C group versus 48 % in the 36 °C group died ($p=0.51$). At 180-day follow-up, 54 % of the patients in the 33 °C group had died or had poor neurological function as compared with 52 % of patients in the 36 °C group ($p=0.78$). The modified Rankin scale was also comparable between both groups. In this study there was a window of 240 min between ROSC and randomization.

A study by Kim et al. with a different objective evaluated if prehospital cooling was beneficial compared with standard in-hospital cooling. Two hundred and twenty-four adults with VF OHCA were assigned to either prehospital cooling (through receiving 2 L of 4 °C saline) or standard in-hospital cooling (224 patients) [14]. The core body temperature decreased by >1 °C on arrival to the hospital, and the interval required to reach target temperature decreased to 4.2 h with prehospital cooling, compared with 5.5 h with in-hospital cooling in cases with VF OHCA, suggesting that prehospital cooling reduced time to goal temperature by more than 1 h. However, early cooling was not translated to better outcome. Survival to hospital discharge was similar among the intervention and control groups in patients with

Table 17.1 Summary of main randomized trials of TH in OHCA due to cardiac causes

1st author/year	*N*	Duration of study	Participants	Therapeutic intervention	Control intervention	Follow-up time	Conclusion
HACA/2002 [5]	275	65 m	Unconscious OHCA patients, cardiac cause of arrest (initial rhythm VF or non-perfusing VT)	Air cooling-induced hypothermia to 32–34 °C for 24 h, passive rewarming for 8 h	Standard ICU care, no temperature control	6 m	Therapeutic mild Hypothermia increase the rate of favorable neurological outcome and reduce mortality in VF OHCA
Bernard/2002 [4]	77	33 m	Unconscious OHCA patients, cardiac cause of arrest (initial rhythm VF or VT)	Air cooling-induced hypothermia to 32–34 °C for 24 h, passive rewarming for 8 h	Standard ICU care, no temperature control	Hospital discharge	TH improve outcome after OHCA
Nielsen/2013 [10]	939	26 m	Unconscious OHCA patients due to cardiac cause	Ice-cold fluids, ice packs, or surface temperature management devices for 36 h. Target temperature 33 °C	Target temperature control of 36 °C	256 d	TH at 33 °C did not confer benefit compared with 36 °C

h hour, *d* day, *m* month, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *OHCA* out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, *ICU* intensive care unit

VF ($p=0.69$) or without VF ($p=0.30$), and there was no improvement in neurological status despite early cooling.

17.2.2 Is TH Beneficial for Non-VF/VT Cardiac Arrest?

VF and VT account for only 25 % of OHCA cases [3]. For the remaining 75 % who experience non-VF/VT rhythms, the indications for receiving TH after ROSC are less clear. Although earlier randomized trials [4, 5] only examined OHCA due to VF, it can be reasonable to think that the effect of TH on brain injury after circulatory arrest would be the same regardless of the cause. This hypothesis was tested in 15 observational and two randomized studies. Regarding the randomized trials, both were not dedicated to study benefit of TH (one was a feasibility study on a helmet device for inducing hypothermia [15], and the other assessed whether high volume hemofiltration alone or with TH improve survival after cardiac arrest [16]). These trials included only 44 patients with non-VF/VT rhythms and found a nonsignificant survival benefit in the hypothermia group.

Among the 15 observational studies [17–31], the majority showed a nonsignificant trend toward better outcome with mild TH, but statistically significant survival benefit was shown only in few studies. In a multicenter observational study that included data from 19 centers, among which 197 developed non-VF/VT cardiac arrest and 124 received mild TH, the rate of survival to hospital discharge was significantly higher in mild TH-treated patients ($p=0.023$) [18]; however, only univariate analysis was performed. Also, selection bias was a concern, because decision of hypothermia treatment was at the discretion of the treating physician. A meta-analysis evaluated these 17 studies (two randomized and 12 observational) that included 1,336 non-VF/VT patients, out of which 30.8 % were treated using mild TH [32]. The quality of evidence in all studies was low with a substantial risk of bias and high degree of imprecision due to small sample size, and therefore the results should be interpreted cautiously.

Some studies showed benefit of implementing TH in OHCA due to VF/VT, but not in non-shockable rhythms. In a retrospective study that included 491 patients with OHCA (of whom 74 % had non-VF/VT cardiac arrest), there was no significant improvement in patients resuscitated from non-VF/VT rhythms, but there was a significantly higher rate of survival and favorable neurological outcome in the VF/VT group who received TH [19].

17.3 Therapeutic Application: Criticism Raised After Recent Studies on the Value of TH in VF OHCA

Several questions were raised after a recent trial showed no benefit for TH in VF OHCA. In the study by Nielsen et al. [10], the median time for ROSC was 25 min, with a wide range from 18 to 40 min. One may expect that the reduction of

neurological metabolism by hypothermia will not benefit the already damaged neurons by prolonged cardiac arrest. Also, up to 4 h were permitted to start the cooling process after OHCA, and four more hours were allowed to achieve a mean temperature of <34 °C. The delay in starting hypothermia protocol and achieving target temperature might have affected the outcome. The neurological outcome was determined by the cerebral performance category and modified Rankin scale, which assess the patient's capability of daily activity but does not evaluate for fine cognitive impairment. Also, the rapid rate of rewarming from 33 to 36 °C in a 6 h period can be harmful and may abolish a potential benefit from hypothermia. It should be noted that in this study by Nielsen et al., the TH group was compared with a group of normothermic patients with a targeted temperature of 36 °C, while in the earlier studies [4, 5] the control group did not receive thermal control. There is evidence for the negative effect of hyperthermia in the 72–96 h post-ROSC, as it was found to be associated with increased mortality and poor neurological outcome [33].

Regarding the value of prehospital compared with in-hospital cooling, Kim et al. [14] found less than 1 °C temperature difference at hospital admission between both groups. One can assume that the small difference in temperature did not allow for an expected change in outcome. Moreover, the use of cold fluids to achieve hypothermia can be associated with pulmonary edema. In a review of experimental studies, the utilization of cold fluids to achieve intra-arrest hypothermia was associated with a poorer outcome compared with other cooling strategies [34]. In the same study, there was an 11 % higher absolute rate of pulmonary edema on arrival to the emergency department in the interventional group. The 2 L of saline given rapidly after ROSC caused negative hemodynamic effects. This conforms to prior animal studies that demonstrate a reduction in coronary perfusion pressure when saline load is given to achieve cooling [35]. This adverse outcome was not observed when cooling was achieved with other methods. Therefore, the outcome of this study might be an effect of the method used rather than an effect of hypothermia. The trial was powered to show a 30 % improvement in outcome, so a modest treatment effect may have been missed. Also, the quality of cardiac arrest care is very high in Seattle (site of study conduction), which might have masked a subtle benefit of hypothermia.

Conclusion

In conclusion, the benefit of TH in OHCA demonstrated initially by the two studies in 2002 was not reproduced by the recent larger trial. How should this influence our current practice? First, many questions still need to be answered. What is the ideal target temperature? Is intra-arrest cooling superior to later cooling? How fast should the target temperature be reached? How long should hypothermia continue? Does cooling work for patients with asystole or pulseless electrical activity? Is intravascular cooling or surface cooling more effective? Therefore, before abandoning TH for OHCA, further rigorous randomized trials should be performed targeting possible concerns that might have attenuated its benefit in recent studies.

Clinical summary

Technique	Indication	Protocol	Side effects	Notes
Mild hypothermia	Comatose adult patients with return of spontaneous circulation after out-of-hospital ventricular fibrillation cardiac arrest (Class I, LOE B) or after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole (Class IIb, LOE B)	Patients' core body temperature is cooled to 32–34 °C (89.6–93.2 °F) for 12–24 h Cooling techniques include surface cooling devices and iced isotonic fluid injection	Cooling by infusion of iced crystalloids seems to be associated to pulmonary edema and worse hemodynamics	Current data does not show enough evidence for targeting a body temperature of 33 °C compared to a body temperature of 36 °C. Literature does not allow to state: specific indications and populations, timing and duration of therapy, and methods for induction, maintenance, and subsequent reversal of hypothermia

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