# Practical Issues Updates in Anesthesia and Intensive Care

Davide Chiumello
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*Editor*
Davide Chiumello
Dipartimento di Anestesia, Rianimazione e
Terapia del Dolore
Ospedale Maggiore Policlinico Fondazione
IRCCS Ca' Granda
Milano
Italy

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# Al Nostro Maestro
# Biagio Allaria

Cambiare la vita degli altri è un dono concesso a pochi,
Ai maestri, ad esempio.
Ma i veri maestri diventano sempre più rari e incontrarli è un privilegio per pochi.
Noi che abbiamo vissuto con te quei che il poeta chiamò
"I migliori anni della nostra vita" siamo qui a ricordare che ne è valsa la pena viverli insieme con te, intensamente, caro Maestro!

*… the physician without physiology practices a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which. William Osler*

Professor Biagio Allaria left us suddenly on May 3, 2014, the victim of a devastating heart attack, the illness he spent his life fighting against but which hit him from behind, in a cowardly manner, during the nighttime.

Many of the readers and some of the authors of this book will have had Biagio Allaria as Director and Mentor during their clinical careers and will have been fired by his enthusiastic, modern and smart medical approach. But we all have Biagio as a Maestro, in the full meaning that the Italian word deserves.

From the very beginning of his involvement in the field of care of the critically ill, Biagio taught his pupils to go deeper into each single case encountered in everyday medical practice, never to be convinced by the first explanation or the first glance, and never to be afraid of challenging what is considered fact. This is why the gift of changing the course of others' lives is reserved for the few, and among them are those we consider true masters, or Maestri. Unfortunately, Maestri are becoming increasingly rare. We had the privilege and the unique, invaluable opportunity to be guided by a Maestro in our first medical steps (and beyond…), during times often remembered as "the best years of our lives".

This book offers the opportunity to have Biagio with us once again.

On behalf of all the alumni who were nurtured and inspired by Professor Biagio Allaria and who have been and will continue to be involved in the care of critically ill patients.

Milano, Italy

Furio Zucco
Marco Dei Poli
Andrea De Gasperi

# Contents

# The Prone Position in the Treatment of Patients with ARDS: Problems and Real Utility

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Davide A. Chiumello, Ilaria Algieri, Matteo Brioni, and Giovanni Babini

## 1.1 Introduction

Prone positioning during mechanical ventilation is a type of treatment used in severe ARDS patients when conventional ventilation with low tidal volume and high positive end-expiratory pressure (PEEP) is not able to improve gas exchange and exposes lungs to high risk of ventilation-induced lung injury (VILI). In this chapter we will discuss the pathophysiological rationale of this procedure and current evidences in literature regarding improvement in clinical outcomes, indications, contraindications, and any complications.

## 1.2 Background

Prone positioning as a treatment for acute respiratory failure was first described in the mid-1970s. In these years Piehl et al. investigated the effects of posture changing in patients with acute respiratory failure, describing a significant improvement in oxygenation during prone ventilation [1].

However, the clinical application of prone positioning in ARDS patients became popular in the mid-1980s. During this time, the first reports on the use of computed tomography (CT) in ARDS patients were published, demonstrating the nonhomogeneous nature of the disease: ventral lung regions (non-dependent) were spared and maintained good aeration and instead dorsal lung regions (dependent) appeared

D.A. Chiumello (✉)
Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolore, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan, Italy
e-mail: chiumello@libero.it

I. Algieri • M. Brioni • G. Babini
Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy



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damaged [2, 3]. Further observations showed that normally aerated lung parenchyma maintains normal mechanical properties and were the basis in shaping the concept of "baby lung": in ARDS patients the part of lung parenchyma available for gas exchange is not "stiff," but instead as "small" as the lung of a 6-year-old child [4]. Since "baby lung" was located on CT scans in ventral regions, prone ventilation was used in order to redistribute flow to normally aerated lung regions, thus improving perfusion, reducing shunt, and improving oxygenation. Later, CT images of ARDS patients during prone position showed that pulmonary atelectasis shifts from dorsal to ventral regions and the dorsal lung parenchyma retrieves normal or near-normal aeration [5, 6]. These findings changed the concept of baby lung from an anatomical to a functional entity and brought to the development of a pathophysiological model known as "sponge lung" [7].

## 1.3 Epidemiology and Etiology

To date, the epidemiology of ARDS remains hard to define because the incidences are extremely different between various trials, probably due to the heterogeneous global epidemiology in different geographical areas and to the lack of common diagnostic criteria. Only recently a consensus conference defined these criteria in a new definition of ARDS known as the "Berlin definition"; [8] it will, anyway, be necessary to wait for a new perspective study that employs these new criteria. From data based on the most recent literature [9, 10], the incidence varies from 15 to 80/100,000 person-years; this finding highlights that ARDS is not a rare syndrome, and it has a high impact on public health. Based on the etiopathogenetic mechanism of the disease, we recognized two forms of ARDS: the first one where the lung is directly damaged (pulmonary ARDS) and the second one where the lung is indirectly damaged by acute systemic inflammatory responses such as sepsis, severe extrathoracic trauma, massive transfusion of blood products, burns, and cardiopulmonary bypass (extrapulmonary ARDS). Between extrapulmonary ARDS patients, those with septic etiology have the highest mortality [11]. In pulmonary ARDS the alveolar epithelium is primitively damaged, whereas in extrapulmonary ARDS the main mechanism of disease seems to be the formation of interstitial edema associated with the systemic inflammatory response. Extrapulmonary ARDS patients develop pulmonary edema because of inflammatory mediators originated in extrapulmonary inflammatory outbreaks; the gain in lung weight causes compression atelectasis in dependent lung regions. On the other hand, pulmonary ARDS patients present less homogeneous alterations characterized by the presence of parenchyma consolidation, not by lung collapse. Potential for lung recruitment is higher in patients with extrapulmonary ARDS than pulmonary ARDS. As a consequence, there are two different treatments for these two different forms of ARDS: extrapulmonary forms seem to better respond to recruitment maneuver, PEEP, and prone positioning [12]. This could be explained by the fact that increased airway pressure recruits alveoli previously closed when lung is collapsed, but it causes hyperinflation of well-inflated lung regions when alveoli are closed due to lung consolidation.

## 1.4 Pathophysiological Rational of Prone Positioning

In ARDS, diffuse alveolocapillary interface injury causes onset of inflammatory edema in the interstitium and, partially, in the alveoli. Gain in lung weight amplifies hydrostatic pressure (the so-called superimposed pressure) that lies on dependent lung parenchyma, causing pulmonary atelectasis (dependent lung regions are dorsal regions in supine position and ventral regions in prone position) [13]. Redistribution in aeration during prone position shows that improvement in gas exchange is not simply a result of redistribution in blood flow, as previously believed, but it is a much more complex mechanism, as shown by in-depth pathophysiological studies.

### 1.4.1 Respiratory Mechanics

CT studies in healthy lungs during an end-expiration hold demonstrated that there is an increase in lung radiological densities starting from ventral regions toward dorsal regions when the patient is in supine position. This means that gas/tissue ratio and consequently parenchyma aeration is maximum in ventral regions and slowly decreases when proceeding to the most dependent lung regions. This aeration gradient from non-dependent to dependent regions seems to be the result of gravitational forces acting on the lung (and of the resulting superimposed pressure acting on dependent regions) in addition to the nonhomogeneous expansion of alveolar units due to the different shape existing between the lung and the chest wall. The isolated lung with homogeneously expanded alveoli has a roughly conical shape (with the dorsal side bigger than the ventral side), whereas the chest wall has a cylindrical one [14]. Nevertheless, in vivo they have the same volume (pleural space is a virtual space); consequently the lung parenchyma will have a greater gain in volume and greater aeration of ventral lung regions compared to dorsal regions ("shape matching" model). These two different mechanisms cooperate to create a gradual decrease in alveolar aeration from ventral to dorsal zones of the lung. In prone position ventral regions shift to dependent dorsal regions and the pressure gradient is inverted. However, the compression generated from gravitational forces in ventral regions is counterbalanced by alveolar expansion due to "shape matching." The two mechanisms act in opposite ways, resulting in a much more homogeneous aeration of alveolar units [15]. A further factor is the compression of lung parenchyma caused by heart weight. In supine position a large part of the lung parenchyma is compressed by the heart (especially the inferior left lobe), whereas in prone position this effect is negligible [16]. However, the superimposed pressure can increase four or five times compared to its normal value, so the effect of "shape matching" and cardiac compression on gas/tissue gradient is negligible. In prone position, ventral regions became atelectasic as dorsal regions are recruited and regain aeration. From an anatomical perspective, there is more lung tissue in the dorsal regions and consequently the recruitment in this zone tends to be higher than the derecruitment that happens in ventral regions, resulting in increased parenchyma aeration and lung compliance (Fig. 1.1). The greater the potential for lung recruitment, defined as the

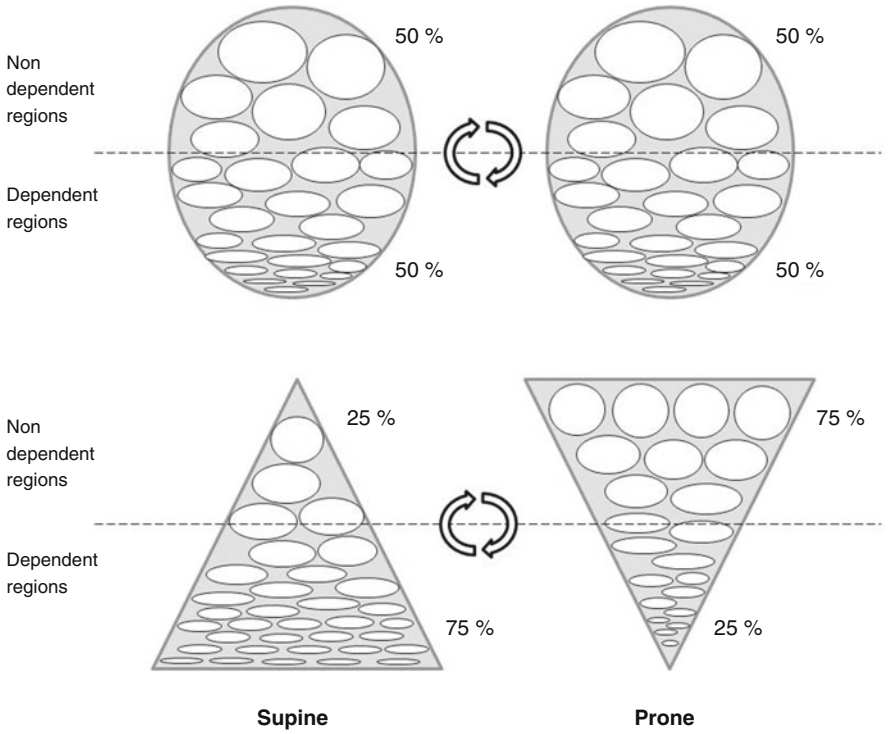


**Fig. 1.1** The figure illustrates a simplified model that shows the influence of lung shape on the distribution of aeration in the parenchyma during supine and prone position. If we consider an elliptical-shaped lung, the portion of well-aerated tissue in non-dependent regions is similar between supine and prone position. As the amount of open and closed parenchyma will be the same in both positions, the aeration distribution will remain the same. If we consider a triangle-shaped lung, the portion of well-aerated tissue in non-dependent regions increases during the turning process as the result of recruitment in dorsal zones is higher than the derecruitment in ventral zones. As a consequence, parenchyma aeration will increase and lung compliance will improve

amount of atelectasic lung that could be re-opened, the greater this effect. In regard to the chest wall, compliance decreases during prone positioning because the ventral regions' expansion is limited by the bed surface and by the fact that dorsal regions are stiffer; furthermore, there is an increase in intra-abdominal pressure. However, the increase in lung compliance counterbalances the decrease in chest wall compliance, and the result is a respiratory system compliance that remains nearly unchanged or even improves [15].

### 1.4.2 Blood Flow Distribution

Historically, pulmonary perfusion has been described using a gravitational model in which uneven distribution of blood flow can be explained by the hydrostatic pressure difference between blood vessels in dependent and non-dependent lung regions.

In non-dependent regions, intravascular pressure (in pulmonary arterioles and venules) falls below alveolar pressure (zone 1 according to West). If this occurs, capillaries are squashed flat and no flow is possible, resulting in ventilated but not perfused alveoli (alveolar dead space). In intermediate regions (zone 2 according to West), alveolar pressure is lower than arteriole pressure, but higher than venule pressure and blood flow is dependent on pressure difference between arterioles and venules. In the most dependent regions (zone 3 according to West), intravascular pressure is always greater than alveolar pressure, both in arterioles and venules, so these are the best perfused lung regions [17]. According to the West model, lung segments that are at the same height should receive the same perfusion. However, studies on pulmonary perfusion performed with the radioactive microsphere emboli technique showed that the craniocaudal perfusion gradient is maintained both in supine and lateral body position [18, 19]. Further studies using the same technique pointed out that differences in perfusion between lung segments at the same height may be even ten times greater than the differences existing between lung segments at different heights [20]. It follows that gravitational forces are minor determiners of nonhomogeneous pulmonary perfusion distribution and that blood vessel architecture might be the leading cause of regional perfusion differences; [21] this last model gives a more complete picture of what might happen during prone positioning. In supine position pulmonary perfusion is distributed along a ventral-dorsal gradient; however, in prone position, this gradient doesn't shift and dorsal regions remain well perfused. Between all the body positions that were tested, prone position is the one associated with the best distribution of pulmonary perfusion.

### 1.4.3 Gas Exchange

As previously described, in ARDS patient, prone positioning is associated with increased arterial oxygenation. This data was confirmed by countless clinical trials and by experimental animal models of acute respiratory failure. This increase is justified by the pathophysiological mechanisms previously described: in ARDS prone positioning causes a recruitment of dorsal lung regions that is greater than the derecruitment of ventral lung regions; also, recruited dorsal regions are better perfused than the ventral regions and this induces an improvement in ventilation/perfusion relationship and reduces blood shunt, the major cause of hypoxemia [15]. However, an increase in dead space and a resulting decrease in $CO_2$ elimination seem to be the major determiner of patient outcome in ARDS [22]. In prone positioning the greater recruitment of dorsal lung regions compared to the ventral region collapse reduces dead space, improves $CO_2$ elimination at even total ventilation, and reduces overdistension of ventral lung regions that are inclined to overinflation and inadequate ventilation [15]. Prone positioning is not always associated with a decrease in arterial $CO_2$ because the presence of aerated alveoli (and the associated improved oxygenation) doesn't necessarily mean that they are well ventilated. It has been described that the variations in arterial $CO_2$ after pronation are independent from oxygenation response and a decrease in $PaCO_2$ is associated with a greater lung recruitment and a better outcome [23, 24].

## 1.5 Prone Positioning and Ventilator-Induced Lung Injury

Many trials demonstrated that there is a greater homogeneity in ventilation during prone position than during supine position, and experimental studies showed that prone position has a role in modulating ventilator-induced lung injury (VILI). VILI originates from the repeated application to lung tissue of forces generated and amplified between consolidated and ventilated zones and from cyclical opening-closing of ventilated alveoli (atelectrauma). These areas are prevalent in dependent lung regions; for this reason dorsal regions are mainly exposed to the risk of VILI in supine position and consequently more protected from it in prone position. The mechanism involved in reducing lung injury implies the reduction of interfaces between consolidated and ventilated areas and the decrease and better distribution of transpulmonary pressure (the driving force distending the lung) due to increase in compliance that follows lung recruitment. So if prone positioning is successful in recruiting lung parenchyma, mechanical ventilation should be less harmful, thanks to the reduction in global "stress" (transpulmonary pressure) and "strain" (tidal volume/functional residual capacity ratio) of overinflated areas. Atelectrauma (injury due to opening-closing of lung units) seems to be reduced particularly in patients with high potential for lung recruitment ventilated with high PEEP. Also, prone position reduces the injury due to inflammation (a significant reduction in pro-inflammatory cytokine concentration has been indeed shown) and the development of hemorrhagic pulmonary edema [25]. It also improves transpulmonary pressure distribution and contributes in preventing VILI thanks to mechanical factor and to the simple gas exchange improvement (particularly $PaO_2$), reducing in this way iatrogenic intervention to sustain oxygenation. In fact, all common procedures that enhance oxygenation or improve ventilation induce lung injury; so oxygenation improvement allows to reduce $FiO_2$ and mean airway pressure, both determinants of VILI progression. Another important factor is that prone positioning potentially increases drainage of oropharyngeal and airways secretions: this can improve gas exchange and reduces incidence of ventilator-associated pneumonia (VAP) [26]. The main determiner in reducing mortality, besides maneuver per se (considered a life-saving treatment in the most severe cases of hypoxemia), is probably related to the reduced incidence of VILI.

## 1.6 Patient Selection

### 1.6.1 Indication

Prone positioning has to be considered a life-saving treatment in severe hypoxemia, especially when the procedure is standardized and performed by a skilled team. As is known, prone positioning is indicated in patients with "severe ARDS"; however the definition of "severe ARDS" has been formalized only recently in the Berlin definition of ARDS [8]. In clinical practice the severity of ARDS is established by

$PaO_2/FiO_2$ ratio, but it's obvious that it might change on the base of the ventilator strategy (i.e., PEEP level) or applied $FiO_2$. Despite this variability, based on existing literature from randomized trials and meta-analysis, long-term pronation in severe ARDS (defined by a $PaO_2/FiO_2$ ratio < 100 mmHg) is recommended. Instead, it is not recommended in mild ARDS ($PaO_2/FiO_2$ 300–200 mmHg) because it doesn't provide any benefit in terms of survival. The use of prone positioning in moderate ARDS ($PaO_2/FiO_2$ 200–100 mmHg) is still debated: recent meta-analysis suggests that prone positioning should be considered in moderate ARDS with $PaO_2/FiO_2$ lower than 150 mmHg, with PEEP level set on 5 $cmH_2O$ or higher and $FiO_2$ set on 0.6 or higher. This is why it is reasonable to use prone positioning in ARDS patients with $PaO_2/FiO_2$ lower than 150 mmHg measured at least with a PEEP level of 5 $cmH_2O$ [15, 27]. It is important to highlight that the efficacy of prone positioning is maximum when performed in an early stage of the disease in which edema, lung recruitability, and absence of structural alterations of the lung are most represented. This means that the benefits of prone positioning in minimizing VILI in early stage of ARDS are probably greater than those obtained in late stage when lung injury is already induced.

### 1.6.2 Contraindications and Complication

There are only few absolute contraindications to prone positioning and they are mainly represented by spinal instability and unmonitored intracranial hypertension, because the procedure may require to turn the head leftward or rightward and this might cause compression of jugular veins and reduce cerebral venous outflow; it is possible to overcome the problem by using specifically designed beds to prone patients, maintaining the head in neutral position. Relative contraindications include severe hemodynamic instability, open abdominal wounds, multiple unstabilized fractures, pregnancy, difficult airway management, and presence of invasive line monitoring (included dialysis catheter), even though the latter should not be considered a real contraindication to the maneuver since firmly securing them to the patient and monitoring them during the procedure should be sufficient. Regarding the decision whether to pronate or not the patient, it is important to consider the team expertise and to balance risks and benefits associated with a life-saving procedure not free from potential complications. Complications, such as extubation, catheter displacement, and transient hypotension or desaturation, mainly related to the proning maneuver itself, have been described in literature. Another series of complications, such as pressure ulcers, vomiting, and need for increased sedation, are associated with the duration of staying prone. Particularly harmful although extremely rare is the compression of optic nerve and retinal vessels and the resulting blindness. The incidence of adverse effects decreases with experience gained by a team routinely using this intervention and with the use of preventive measures or special devices that facilitate the mechanics of safe proning and prevent duration-related complications.

## 1.7 Application

### 1.7.1 Positioning

Prone positioning requires the cooperation of more people from the intensive care unit staff. A standardized procedure does not exist; hence a lot of centers apply prone position based on sequence of movements used for log-rolling maneuver (by the way, materials that facilitate the procedure and beds specifically designed to facilitate prone positioning in intensive care unit and minimize associated risks are available (Table 1.1)). Independently from the technique used, it is essential for the staff performing the procedure to be adequately skilled to avoid injuries to the patients and central catheter dislocation. It is necessary that support zones are protected to avoid bedsore formation. The number of people it takes to safely prone the patient depends on the size of the patient itself, on the number and the position of invasive lines, and on the choice of material that will be used. An accurate preparation of the patient before prone positioning and a special attention to endotracheal tube and vascular lines are crucial issues; we recommend having, during the turning process, one person assigned only to do nothing more than monitoring the endotracheal tube and central lines (if placed on upper thorax). Because of the accidental extubation risk, the endotracheal tube must be secured and it is always recommendable to have promptly available all the materials for an emergency re-intubation of the patient before starting the procedure. Another issue is represented by the position of the endotracheal tube compared to the carina; during prone positioning, the endotracheal tube might move and be displaced, so it is important for the distal tip of the tube to be placed 2–4 cm above the carina in order to avoid extubation or right mainstem bronchus intubation. Regarding airway management, prone positioning can result in such copious drainage of airway secretions that ventilation becomes impaired; hence we recommend to have promptly available endotracheal suction equipment. During prone positioning the presence of tracheostomy may represent a major problem; however, various devices allow full support to the patient, avoiding any contact of tracheostomy cannula to the bed or to the foam pads and sparing excessive head and neck rotation. The head is usually rotated leftward or rightward to minimize any orbital or facial pressure and to avoid lip or nasal trauma caused by endotracheal tube. This lateral rotation may be difficult to accomplish in elderly patients who have stiff cervical spines or in those with cervical disk disease. In this case it is possible to use foam donuts that suspend the head off of the bed without any lateral rotation. However these devices may result in greater facial trauma. Furthermore, it is important that any pillow or device potentially useful to support the head or other body parts during prone positioning is promptly available before beginning the procedure [28]. Regarding vascular line management, the patency of all catheters should be monitored before and after the turning process, especially when vasopressor agents are being administered.

**Table 1.1** Prone positioning checklist

| |
|---|
| *Preparation* |
| 1. Check for contraindications (spinal instability, intracranial hypertension, cranked fractures) |
| 2. Consider possible adverse effects of pronation on invasive line monitoring and chest tube drainage |
| 3. If possible, explain the procedure to parents and relatives |
| 4. Assess endotracheal tube position (through bronchoscopy or fluoroscopy), making sure that the distal tip of the tube is placed 2–4 cm above the tracheal carina |
| 5. Assess that both endotracheal tube and venous and arterial catheters (peripheral and central) are firmly secured to the patient; protect support zones, i.e., applying hydrocolloid dressing; protect corneas, keeping eyelids closed during prone positioning |
| 6. Consider exactly which position the head, neck, and shoulders will assume after prone positioning |
| 7. Assemble all the material (pillows, foam pads, supports) that could be necessary to accurately position the patient |
| 8. Stop tube feeding and fully evacuate the stomach |
| 9. Prepare endotracheal suction equipment and check its functioning |
| 10. Decide whether the turn will be rightward or leftward (we suggest as clinical practice to turn the patient always in the direction of the ventilator in order to avoid pulling the tubes and leaving them on the back of the patient) |
| 11. Assure sufficient tubing length (ventilator, infusion line, arterial catheter, chest tubes, vesical catheter, etc.) and eventually move drainage bags to the opposite side of the bed; place vesical catheter bag between the legs of the patient |
| *Pronation* |
| 1. Position two people on both sides of the bed and another one at the head of the bed (to assure the central lines and the endotracheal tube do not become dislodged or kinked) |
| 2. Increase $F_iO_2$ to 100 % until the end of the procedure |
| 3. Move the patient to the edge of the bed furthest from whichever lateral decubitus position will be used (we suggest the side opposite to the ventilator), pulling the bedsheet, and later position the patient side-lying |
| 4. Place a clean bedsheet on the side of the bed that the patient will face when in this lateral decubitus position, removing at the same time the old one |
| 5. Gently pronate the patient, keeping the arm in dependent position tucked slightly under the thorax. While prone positioning proceeds, the non-dependent arm can be raised in a cocked position over the patient's head, avoiding brachial plexus sprain; alternatively, log-rolling procedure could be used |
| 6. Relocate ECG leads and patches on the back (to not cause bedsores on thorax). Suction mouth, nasal cavities, and endotracheal tube if necessary |
| 7. Use the new bedsheet to relocate the patient at the center of the bed |
| 8. Rotate the head of the patient to the ventilator side, making sure that the endotracheal tube is not obstructed or kinked, the eyes are not compressed, and the eyelids remain closed |
| 9. Auscultate the thorax, verifying that both lungs are ventilated (rule out right mainstem bronchus intubation) |
| 10. Adjust all tubes (catheter, infusion lines) and verify that they are not kinked or excessively strained |

### 1.7.2 Duration

In all the trials assessing pronation benefits, prone position duration varies from a minimum of 6 h to a maximum of 20 h. However, it is important to highlight that most recent trials succeeded in demonstrating a relationship between prone duration and benefits on the patient outcome [28, 29]. The PROSEVA trial, designed with prolonged prone-positioning sessions (the mean duration per session was 17 ± 3 h) [30], demonstrated a decrease in mortality in patients with severe ARDS. Also, in this study prone-positioning sessions were repeated up to 28 days. Mortality reduction was probably obtained by decreasing VILI. Even though in many trials the criteria to discontinue prone treatment were quantitatively different, the common points were the random interruption after few days or the achievement of a preset oxygenation level in supine position (after the end of the last prone session).

It is feasible to maintain prone position even for shorter period of time; in this case the procedure is effective in improving drainage of airway secretions and in expanding atelectasic lung regions not responding to recruitment maneuvers in supine position. These benefits are particularly evident in the left inferior lung lobus because prone position relieves dorsal lung regions from cardiac compression.

### 1.7.3 PEEP Management

Ventilator settings and PEEP level influence oxygenation during prone position. Experimental studies demonstrated that prone positioning improves the effect of PEEP by enhancing recruitment maneuver and in the meantime reducing alveolar overdistension. Also, the more homogeneous ventilation and transpulmonary pressure distribution promote ventilator/perfusion matching, preventing redistribution of blood flow from ventilated to atelectasic zones that occurs when high PEEP level or high mean airway pressure are applied. The improvement in ventilation/perfusion relationship increases oxygenation [31].

## 1.8 How to Evaluate Patient Response to Prone Positioning

It is essential to assess the effectiveness of prone positioning in terms of lung recruitment by the improvement in gas exchange, the appearance of crackles in the region of interest, and the imaging, even at the patient bedside such as lung ultrasonography.

### 1.8.1 Lung Recruitment and Ventilation

After prone positioning, patient respiratory functions should be monitored: mean airway pressure and plateau pressure should be assessed during volume-control ventilation, while tidal volume should be checked during pressure-control ventilation. The decrease in chest wall compliance could increase plateau pressure (during volume-control ventilation) or reduce tidal volume (during pressure-control

ventilation). These potentially harmful effects are neutralized if the patient responds to prone positioning and the recruitment of dorsal lung regions is greater than the derecruitment of ventral lung regions, resulting in significantly increased lung compliance and functional residual capacity (FRC). In this last scenario, mean airway pressure and plateau pressure will decrease (during volume-control ventilation) and tidal volume will increase (during pressure-control ventilation).

### 1.8.2 Gas Exchange

Oxygenation: an increase in $PaO_2$, soon after prone positioning, could be explained by the anatomical recruitment and by the ventilation of not inflated lung regions normally perfused or by the improvement in ventilation/perfusion matching in dorsal zones of the lung. An improvement in oxygenation does not necessarily correspond to an anatomical recruitment of the lung parenchyma or to an improvement in ventilation; indeed, oxygenation increases when perfused lung regions are inflated, not necessarily ventilated.

$CO_2$ elimination: in ARDS, impaired $CO_2$ elimination is the result of structural alteration in the lung parenchyma such as emphysema, microthrombosis, cysts, bullae, and edema. Dead space and $PaCO_2$ do not always change in shifting from supine to prone position. However, independently on the ventilator setting, the patients who reacted to prone positioning with a decrease in $PaCO_2$ have a better outcome than the patients who do not [23]. This effect is probably a result of the lung recruitment or of the decrease in overdistension of overinflated ventral regions and brings to the improvement in lung ventilation. Both these mechanisms are involved in reducing VILI, and this might explain why the decrease in $PaCO_2$, but not the increase in $PaO_2$, is related to the patient outcome.

### 1.8.3 Outcomes

Four randomized trials and two meta-analyses showed that prone position significantly improves survival rate (16 % decrease in relative risk of death) in patients with severe hypoxemia ($PaO_2/FiO_2 < 100$ mmHg) at the moment of randomization [32]. Thus, the procedure is strongly recommended in case of severe hypoxemia. However, prone position should be reserved to "responder" patients, in which the maneuver produces a real benefit, in order to minimize adverse effects in "nonresponder" ones. It is necessary to highlight that an exact method to predict modification in gas exchange due to prone positioning does not exist, as well as the relationship between improvement in gas exchange and patient outcome remains unclear.

**Conclusion**

Prone positioning improves oxygenation by optimizing lung recruitment and ventilation/perfusion matching. Furthermore, prone positioning helps to protect against VILI by distributing ventilation and transpulmonary pressure more homogeneously throughout the lung parenchyma. These beneficial effects appear

to confer a survival advantage in patients with severe ARDS. Its long-term use is not indicated for mild to moderate form of ARDS ($PaO_2/FiO_2 > 150$ mmHg) as it may expose the patient to unnecessary risk of complications in the absence of proven benefits.

## References


1. Piehl MA, Brown RS (1976) Use of extreme position changes in acute respiratory failure. Crit Care Med 4(1):13–14
2. Gattinoni L, Presenti A, Torresin A et al (1986) Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imaging 1(3):25–30
3. Maunder RJ, Shuman WP, McHugh JW, Marglin SI, Butler J (1986) Preservation of normal lung regions in the adult respiratory distress syndrome. Analysis by computed tomography. JAMA 255(18):2463–2465
4. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. Am Rev Respir Dis 136(3):730–736
5. Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D (1991) Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. Anesthesiology 74(1):15–23
6. Langer M, Mascheroni D, Marcolin R, Gattinoni L (1988) The prone position in ARDS patients. A clinical study. Chest 94(1):103–107
7. Gattinoni L, Pesenti A (2005) The concept of "baby lung". Intensive Care Med 31(6): 776–784
8. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD et al (2012) Acute respiratory distress syndrome: the Berlin Definition. JAMA 307(23):2526–2533
9. Rubenfeld GD, Herridge MS (2007) Epidemiology and outcomes of acute lung injury. Chest 131(2):554–562
10. Lewandowski K, Lewandowski M (2006) Epidemiology of ARDS. Minerva Anestesiol 72(6):473–477
11. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP (2005) Causes and timing of death in patients with ARDS. Chest 128(2):525–532
12. Gattinoni L, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J (2010) Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. Minerva Anestesiol 76(6):448–454
13. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L (1994) Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med 149(1):8–13
14. Hubmayr RD (2002) Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story. Am J Respir Crit Care Med 165(12):1647–1653
15. Gattinoni L, Taccone P, Carlesso E, Marini JJ (2013) Prone position in acute respiratory distress syndrome. Rationale, indications, and limits. Am J Respir Crit Care Med 188(11): 1286–1293
16. Albert RK, Hubmayr RD (2000) The prone position eliminates compression of the lungs by the heart. Am J Respir Crit Care Med 161(5):1660–1665
17. West JB (1977) Ventilation-perfusion relationships. In: Respiratory physiology. Wolter e Kluwer Lippincott Williams & Wilkins, Philadelphia, US, pp 55–74
18. Greenleaf JF, Ritman EL, Sass DJ, Wood EH (1974) Spatial distribution of pulmonary blood flow in dogs in left decubitus position. Am J Physiol 227(1):230–244
19. Reed JH, Wood EH (1970) Effect of body position on vertical distribution of pulmonary blood flow. J Appl Physiol 28(3):303–311

20. Glenny RW, Bernard S, Robertson HT, Hlastala MP (1999) Gravity is an important but secondary determinant of regional pulmonary blood flow in upright primates. J Appl Physiol Bethesda Md 1985 86(2):623–632
21. Galvin I, Drummond GB, Nirmalan M (2007) Distribution of blood flow and ventilation in the lung: gravity is not the only factor. Br J Anaesth 98(4):420–428
22. Nuckton TJ, Alonso JA, Kallet RH et al (2002) Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 346(17):1281–1286
23. Gattinoni L, Vagginelli F, Carlesso E et al (2003) Decrease in PaCO2 with prone position is predictive of improved outcome in acute respiratory distress syndrome. Crit Care Med 31(12):2727–2733
24. Protti A, Chiumello D, Cressoni M et al (2009) Relationship between gas exchange response to prone position and lung recruitability during acute respiratory failure. Intensive Care Med 35(6):1011–1017
25. Broccard A, Shapiro RS, Schmitz LL, Adams AB, Nahum A, Marini JJ (2000) Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. Crit Care Med 28(2):295–303
26. Li Bassi G, Torres A (2011) Ventilator-associated pneumonia: role of positioning. Curr Opin Crit Care 17(1):57–63
27. Sud S, Friedrich JO, Adhikari NKJ et al (2014) Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ 186(10):E381–E390
28. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK (2002) The pragmatics of prone positioning. Am J Respir Crit Care Med 165(10):1359–1363
29. Taccone P, Pesenti A, Latini R et al (2009) Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA 302(18): 1977–1984
30. Guérin C, Reignier J, Richard J-C et al (2013) Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 368(23):2159–2168
31. Richard J-C, Bregeon F, Costes N et al (2008) Effects of prone position and positive end-expiratory pressure on lung perfusion and ventilation. Crit Care Med 36(8):2373–2380
32. Guérin C (2014) Prone position. Curr Opin Crit Care 20(1):92–97

# Therapeutic Hypothermia in the Intensive Care Unit

2

Massimo Girardis and Emanuela Biagioni

## 2.1 Introduction

The idea that low temperatures could be "useful" in the medical field is anything but modern. Since the ancient times, Hippocrates had observed a beneficial effect of low temperatures on the bleeding of the wounds. Galen described in his "Opera Omnia" some treatments based on hypothermia [1]. In relatively more recent era, Napoleon's general of armies, Larrey, described a higher percentage of survivors among the hypothermic injured in respect to the soldiers who were warmed near the fire [2]. But the first job with scientific approach on this issue is due to a neurosurgeon named Temple Fay and dates back to the mid-twentieth century. Fay applied hypothermia in patients with pain for advanced intracranial neoplasia and patients undergoing craniotomy, using devices of his own invention as a cooling blanket and an irrigation system through invasive metal capsules. These systems can be considered rudimentary prototypes of modern invasive and superficial equipment for patients' cooling [3]. In 1945, Botterel et al. described hypothermia in patients undergoing surgery for brain aneurysm [4]. In 1950, a cardiac surgeon named Bigelow applied hypothermia in order to ensure a degree of neuroprotection in interventions with circulatory arrest [5]. The first study in critically ill patients was published in 1959 by Benson et al. [6] who successfully used hypothermia in 12 patients after cardiocirculatory arrest (CCA) [6]. Later, Rosomof and Safar (father of modern cardiopulmonary resuscitation) published other experiences on small numbers of patients treated with hypothermia after CCA [7]. Despite the promising results, the technique was abandoned due to the high incidence of side effects and the difficult management of these patients. For about 20 years, works and publications on hypothermia disappeared from the international scene. The Russian

M. Girardis (✉) • E. Biagioni
Department of Anesthesia and Intensive Care Medicine, University Hospital of Modena, L.go del Pozzo, 71, 41100 Modena, Italy
e-mail: girardis.massimo@unimo.it



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philosopher and essayist Petr Kropotkin wrote: "Science is not real progress until a new truth finds an environment ready to accept it." Indeed the story of "modern" therapeutic hypothermia is strongly linked to technological progresses and to the birth of intensive care and monitoring departments.

## 2.2 Clinical Indications

According to the World Health Organization, the incidence of out of hospital cardiac arrest is between 56 and 138 cases per 100,000 population per year. From 20 to 50 % of these are successfully resuscitated and anoxic brain damage remains the major cause of morbidity and mortality. To better understand the extent of the problem, only 10–20 % of the patients who were admitted to the hospital after return of spontaneous circle (ROSC) will return to home without neurological sequels [8]. In this field, two observational prospective studies published in the 1990s [9, 10] opened the way for two large randomized controlled clinical trials conducted at the beginning of the new century in Australia and in Europe. Both trials showed that TH provides a significant improvement in the neurological outcome of patients with ROSC after CCA [11, 12]. After the publication of these two studies, the Advanced Life Support Task Force of the International Liaison Committee on Reanimation (ILCOR) published an Advisory Statement on the basis of new evidence by defining first hypothermia's therapeutic indications. A core temperature between 32 and 34° Celsius must be applied for a period of 24 h in all patients who experienced a return of cardiac activity after ACC and presenting a state of coma. The evidence for this recommendation was high for patients with the ACC and early defibrillating rhythm [13]. Two years later, the European Resuscitation Council (ERC) introduced in its guidelines the same recommendations. Although in recent years the trend of application of the method in the ICU increased sharply, a recent survey indicated that in Italy only 50 % of the patients with ROSC receive an appropriate TH management [14].

A large debate about the application of TH is related to the lack of evidence regarding the definition of target temperature. In 2013, Nielsen et al. have published the results of a large multicenter trial (TTM-Trial) in which more than 900 patients with ROSC post ACC in 36 intensive care units in Europe and Australia have been enrolled. Patients have been assigned to the hypothermia (33 ° C) or to the normothermia groups (36 ° C) and the 6-month mortality and neurological outcome have been assessed. The study showed no difference in the two groups with regard to the main outcome, leaving many doubts about the best choice of treatment in these patients [15].

Large randomized controlled trials showed also the beneficial effects of TH in neonates with hypoxic-ischemic encephalopathy, and the use of this strategy has spread throughout the world [16, 17].

The use of TH has been also evaluated in neurological vascular disease, namely, in ischemic stroke, in order to reduce extension of brain damage. Unfortunately, at this time there is no evidence to justify the inclusion of therapeutic hypothermia in the international guidelines for the treatment of ischemic stroke [18].

## 2.3 Mechanisms of Action

The exact mechanisms by which hypothermia would be able to provide neuroprotection are still unclear. Historically, the protective effects of hypothermia have been attributed to the reduction of cerebral metabolism with consequent reduction of the oxygen and glucose's consumption. Indeed, cerebral metabolism is reduced by about 7 % for each degree of body temperature.

In the last few years, the mechanisms related to the death of neuronal cell and to the damage reported by it after reperfusion have been studied in more details. The ischemic cells after CAA may undergo necrosis or may trigger processes of programmed cell death (apoptosis). Apoptosis is achieved by mitochondrial dysfunction with alteration of cellular metabolism and release of lytic enzymes called caspases. Some studies on animals have shown that hypothermia is able to act in the early stages of the same apoptotic mechanism inhibiting its activation [19]. Several recent studies showed also the key role of hypothermia in the homeostasis of calcium. The sudden decrease of intracellular adenosine triphosphate concentration occurring during ischemia triggers the anaerobic pathway that leads to intra- and extracellular acidosis with impairment of all the ATP-dependent ionic pumps present on the cell membrane. The consequence is the loss of the cell gradient for sodium associated to accumulation of intracellular calcium which is the primary cause of mitochondrial dysfunction. Moreover, rapid and uncontrolled cell depolarization is due to the release of glutamate, the excitatory neurotransmitter normally reabsorbed by the presynaptic terminals with energy consumption. In the conditions of low-energy substrates, glutamate accumulates in the extracellular environment and stimulates specific membrane receptors, in turn increasing the influx of intracellular calcium. Many studies on animals have shown that hypothermia is able to reduce the accumulation of excitatory neurotransmitters [20, 21]. Therapeutic hypothermia seems also able to reduce and modulate the production of free radicals and superoxide dismutase [20].

Increasing evidences in animal and human models indicate that inflammatory response following an ischemic event may have an important role in the post-cardiac arrest syndrome. In fact, both ischemia and reperfusion stimulate production and release of inflammatory cytokines, prostaglandins and leukotrienes. The activation of this cascade causes endothelial dysfunction with increased permeability and oedema formation. Hypothermia may reduce the inflammatory response by limiting the production of leukotrienes and by exerting an inhibitory effect on lipid peroxidation and on the production of nitric oxide.

## 2.4 Systemic Effects

It is a common opinion among intensivists and nurses that therapeutic hypothermia represents an easy and safe procedure. A doubt towards this very simplistic approach would be suggested by the history of the method itself which has always been

closely related to the possibility of high-level monitoring. In fact, hypothermia may produce a series of systemic effects whose majority is not completely predictable.

In the ventilated patient, hypothermia is able to reduce the production of CO2, favouring the portion dissolved in the blood. This principle has inspired a series of studies that have supposed a help of hypothermia in the management of patients with ARDS [22, 23]. Furthermore, in animal models, it has been shown that hypothermia is able to reduce the production of oxygen free radicals by inhibiting the damage at the level of the respiratory tree mediated by specific enzymes. Other works suggest that hypothermia is able to act on the lung injury, maintaining higher concentrations of surfactant.

A decrease of urine output associated to TH has been documented. However, the effects of TH on renal function are still uncertain because in the studied population, cardiac arrest itself may have contributed to kidney damage [24]. A review published in 2012 including 19 randomized trials did not show any sound correlation between hypothermia and renal function [25].

In trauma and surgical patients, hypothermia induces a significant impairment in the haemostatic processes. However, in patients undergoing controlled therapeutic hypothermia, only a modest dysfunction of platelet activity without an increased risk of bleeding has been observed [26].

Hypothermia has also an immune-modulatory effect acting on the cascade of inflammatory cytokines (IL-1 and IL-6) and activation of neutrophils. This action seems to be able to reduce the accumulation of granulocytes in the tissues and the production of free radicals in the central nervous system (SNC) after cerebral stroke. On the other hand, some studies have demonstrated an increased risk of infections in patients undergoing hypothermia [27, 28], but a recent review concluded that, although there is an association between onset of hypothermia and pneumonia/sepsis in the ICU, it is not yet demonstrated a causal link between hypothermia and overall increase of infectious episodes [29].

## 2.5 Devices

In the last decades, we observed an extraordinary development in the medical technology, particularly in critical care medicine where sophisticated equipment and interfaces have been provided by using innovative materials. As refers to TH, we moved from the ancillary methods based on infusion of large amounts of cold solutions or ice cubes on the skin surface to the actual intravascular catheters and/or external cooling methods. The use of intravascular systems requires the use of large catheters that may be complicated by mechanical and thrombotic complications. Surface cooling systems for the adult patients are characterized by bands and blankets that are generally positioned on the trunk and pelvic regions. The major side effect of the external cooling is the occurrence of cold burns beneath the cooling surfaces, and the constant check of these areas is mandatory. The data reported from clinical experiences have not yet clarified whether internal or external cooling is preferable. The latest-generation devices are able to provide hypothermia to the

target temperature and also to implement a phase of controlled re-warming that should be as linear as possible.

## References


1. Galenus C (129–199 AD) Opera Omnia
2. Larrey DJ (1814) In: Cushing J. (ed.) Memoirs of military service and campaigns of the French armies, vol. 2. Baltimore, MD, pp 156–164
3. Fay T (1959) Early experiences with local and generalized refrigeration of the human brain. J Neurosurg 16:239–260
4. Botterel EH, Lougheed WM, Scott JW et al (1945) Hypothermia and interruption of carotid, or carotid and vertebral circulation, in the management of intracranial aneurysms. J Neurosurg 13:1–42
5. Bigelow WC (1950) Methods for inducing hypothermia and rewarming. Ann N Y Acad Sci 13:522–532
6. Benson DW, Williams GR Jr, Spencer FC et al (1959) The use of hypothermia after cardiac arrest. Anesth Analg 38:423–438
7. Rosomoff HL, Safar P (1965) Management of the comatose patients. Clin Anesth 1:244–258
8. Kern KB (2012) Optimal treatment of patients surviving out-of-hospital cardiac arrest. JACC Cardiovasc Interv 5(6):597–605
9. Sterz F, Zeiner A, Kurkciyan I et al (1996) Mild resuscitative hypothermia and outcome after cardiopulmonary resuscitation. J Neurosurg Anesthesiol 8(1):88–96
10. Bernard SA, Jones BM, Horne MK (1997) Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 30(2):146–153
11. Bernard SA, Gray TW, Buist MD et al (2002) Treatment of comatose survivor of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346(8):556–563
12. Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346(22):1756
13. Nolan JP, Morley PT, Vanden Hoek TL et al Members of the Advanced Life Support Task Force (2003) Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. Circulation 108:118–121
14. Gasparetto N, Scarpa D, Rossi S et al (2014) Therapeutic hypothermia in Italian Intensive Care Units after 2010 resuscitation guidelines: still a lot to do. Resuscitation 85(3):376–380
15. Nielsen N, Wetterslev J, Cronberg T et al (2013) Target temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 369:2197–2206
16. Azzopardi D, Strohm B, Linsell L et al (2012) Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK – analysis of national data. PLoS One 7(6):e38504
17. Gunn AJ, Batin M, Gluckman PD et al (2005) Therapeutic hypothermia: from lab to NICU. J Perinat Med 33:340–346
18. Lakhan SE, Pamplona F (2012) Application of mild therapeutic hypothermia on stroke: a systematic review and meta-analysis. Stroke Res Treat 2012:295906
19. Xu L, Yenari MA, Steinberg GK et al (2002) Mild hypothermia reduces apoptosis of mouse neurons in vitro early in the cascade. J Cereb Blood Flow Metab 22:21–28
20. Globus MY-T, Busto R, Lin B et al (1995) Detection of free radical activity during transient global ischemia and recirculation: effects of intraischemic brain temperature modulation. J Neurochem 65:1250–1256
21. Dietrich WD, Busto R, Globus MY et al (1996) Brain damage and temperature: cellular and molecular mechanism. Adv Neurol 71:177–194
22. Ball MK, Hillman NK, Kallapur SG et al (2010) Body temperature effects on lung injury in ventilated preterm lambs. Resuscitation 81(6):749–754

23. Duan M, Berra L, Kumar A et al (2011) Use of hypothermia to allow low-tidal-volume ventilation in a patient with ARDS. Respir Care 56(12):1956–1958
24. Guluma KZ, Liu L, Hemmen T et al (2010) Therapeutic hypothermia is associated with a decrease in urine output in acute stroke patients. Resuscitation 81(12):1642–1647
25. Susantitanphong P, Alfayez M, Bucay AC et al (2012) Therapeutic hypothermia and prevention of acute kidney injury: a meta-analysis of randomized controlled trials. Resuscitation 83(2):159–167
26. Polderman KI (2012) Hypothermia and coagulation. Crit Care 16(2):A20
27. Frink M, Flohè S, van Griensven M et al (2012) Facts and fiction: the impact of hypothermia on molecular mechanism following major challenge. Mediators Inflamm 2012:762840
28. Ishikawa K, Tanaka H, Shiozaki T et al (2000) Characteristics of infection and leucocyte count in severely head-injured patients treated with mild hypothermia. J Trauma 49:912–922
29. Geurts M, Macleod MR, Kollmar R et al (2014) Therapeutic hypothermia and the risk of infection: a systematic review and meta-analysis. Crit Care Med 42(2):231–242

# Which Among Septic Patients Are the Best Candidate for Immunoglobulins?

3

Giorgio Berlot, Perla Rossini, and Federica Turchet

## 3.1 Introduction

The recent guidelines on the treatment of sepsis and sepsis-related conditions, published on behalf of the "Surviving Sepsis Campaign" (SSC) [1], consider the use of intravenous immunoglobulin (IvIg) with a certain degree of ambiguity: on the one hand, a series of papers and meta-analysis that demonstrates their efficacy in terms of mortality reduction of both adult and child/infant are quoted, but on the other hand, the use of IvIg is strongly discouraged as it is considered not supported enough by studies satisfying the evidence-based medicine (EBM) requirements, that claim for randomized, controlled, double-blind, multicenter trials, involving an adequate number of patients who are subjected to the same entry criteria in terms of diagnosis and timing of the studied treatment. This ambiguity can make the clinician facing a septic patient doubt about the opportunity to use IvIg despite the vast majority of published studies reporting a better outcome in patients given IvIg. This situation is further complicated by the consideration that the number of patients involved in the studies on IvIg quoted in the SCC largely exceeds those enrolled in the investigations chosen to support the hemodynamic management of the resuscitation bundle, which basically relies on only two studies, of which one has been published in Chinese without English translation.

With these limitations in mind, it must be admitted that, in the everyday practice, we still lack a method able to identify the patients in which the administration of IvIg can represent a precise therapeutic choice, comparable, for example, to measurement of cardiac enzymes for the primary angioplasty in acute myocardial infarction.

G. Berlot (✉) • P. Rossini • F. Turchet
U.C.O Anestesia, Rianimazione e Terapia Antalgica,
Azienda Ospedaliero-Universitaria "Ospedali Riuniti di Trieste",
Strada di Fiume 447, Trieste 34149, Italy
e-mail: berlot@inwind.it



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Several causes can account for this lack of certainty deriving from the published studies, including:

(a) The use of IvIg preparation containing different classes of Ig: actually, the biological characteristics of each of them and the chemical reactions with different antigens which they are directed against make impossible to compare their effect and can justify the somehow conflicting results deriving from studies in which different preparations have been used.
(b) The heterogeneity of the treated patients, in terms of causes of sepsis (e.g., surgery or medical), age (adults vs. infants and/or pediatrics), and concomitant diseases (e.g., burns, cancer, etc.).
(c) The absence of cheap and immediately available laboratory tests that could indicate whether the administration of IvIg is warranted
(d) The uncertain relationship between the timing of IvIg administration and the onset of sepsis: it is likely that, likewise antibiotics, their use is more effective in the initial stage of sepsis than in the more advanced ones, where a full-blown multiorgan dysfunction syndrome (MODS) is established. Conversely, an indiscriminate treatment extended also to patients with less severe conditions who do not really need them could elevate costs without gaining any benefit. In both conditions, the informations derived from their use are hard to understand.

Then it is clear how that, independently from the SCC recommendations, several factors contribute to confound the clinician that considers IvIg as a reasonable therapeutic option. This can determine either an unjustified negative attitude toward substances that can be considered as drugs and biological agent in the same time, or, conversely, the choice to treat all patients with expensive medication whose use could be reserved to more severe cases.

The final aim of this chapter is to give some useful indications to the practitioner facing a patient with severe sepsis and/or septic shock in order to identify the circumstances in which the maximum advantage of administration of IvIg can be expected.

## 3.2 Structure and Biologic Role of Ig

Before examining the issues related to the clinical use of IvIg, it is necessary to consider some basic concepts in order to show how the host reacts to an infection.

Briefly, the immune system has been developed during the evolution to recognize and neutralize the extraneous substances invading the organism [2, 3].

The reaction is based on two different but strictly related systems:

(a) The natural immunity, mostly based on the cells belonging to the reticuloendothelial system (SRE) cells, on the SRE-produced mediators, and on the complement system: in functional terms, the natural immunity is a fast-reacting and is an unspecific system which is immediately available and does not require any sophisticated procedure for the recognition of extraneous substances.

In an immunological mature and competent organism, the natural immunity acts concomitantly with:

(b) The adaptive immunity, which is based on the production of immunoglobulins by the plasma cells, which, in turn, are obtained by the exposure of B lymphocytes to the antigens (Ag) moving and localized on the immune cells surface under the stimulus provided by the T lymphocytes belonging to the CD4 class. In evolutionary terms, it can be supposed that the adaptive immunity has evolved since the number of the receptors on the SRE cells that form the natural immunity is genetically limited and, regardless of its relevancy, it is not able to recognize all the extraneous molecules which could interact with the organism throughout its life span.

Depending on their chemical and physical characteristics and the dimensions, geometric shape, and their antigen-binding capabilities, the molecules of Ig can be subdivided in five classes (G, A, M, D, E) (Fig. 3.1).

The G class is considered prototypical and is formed by two heavy chains (H) with variable weight between 50 and 70 kDa and two light chains (L) weighing around 20–25 kDa (Fig. 3.2). Electrostatic bonds and bisulphurate bridges keep the single chains together.

Both chains have a variable (V) region which interacts with the antigen and a constant one (C) which activates the immune system functions like the complement system, the phagocytosis, the cell's mediated lysis, etc.

The interconnection region between V and C components undergoes three-dimensional arrangements in order to adapt its structure to the Ag surface. Each variable region is formed by other three hypervariable subregions where their shape

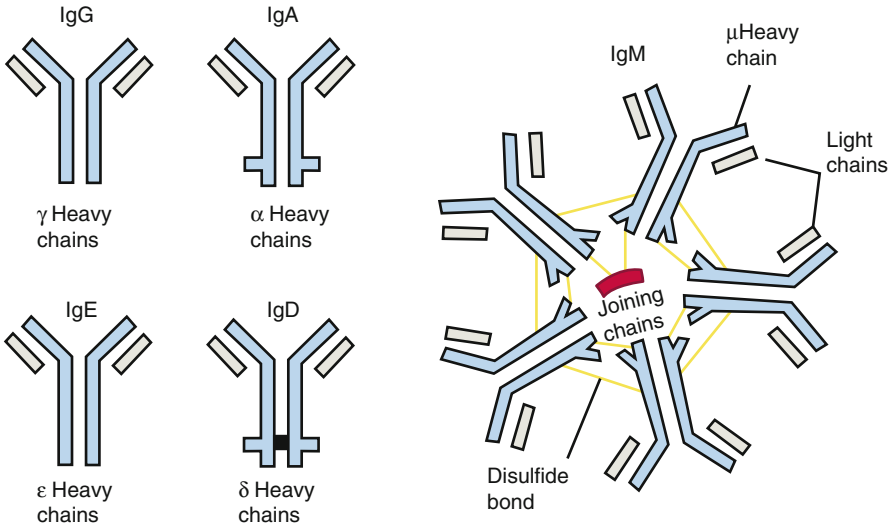


**Fig. 3.1** Different molecules of Ig

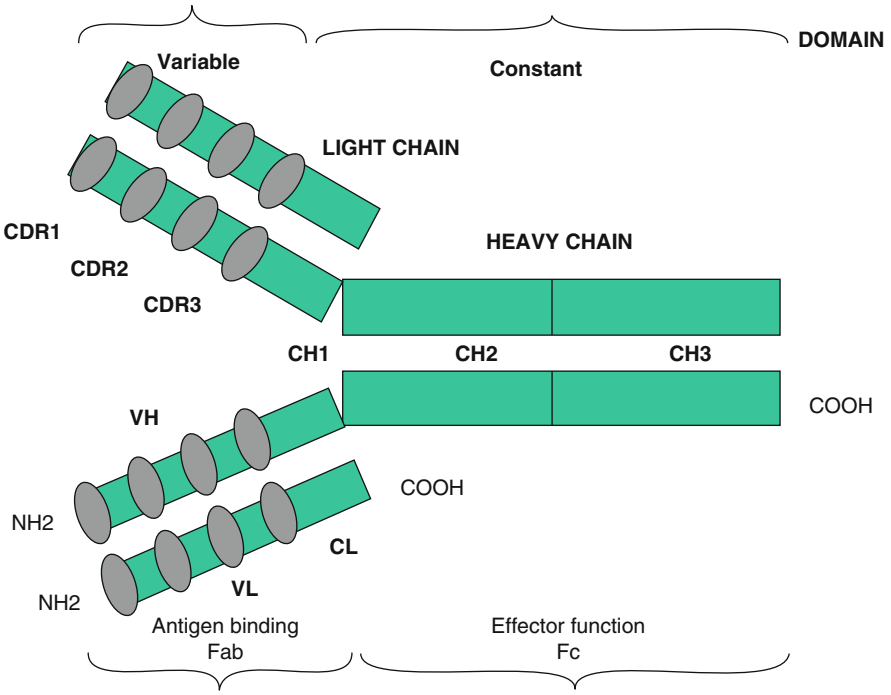


**Fig. 3.2** Schematic two-dimensional structure of an IgG molecule. VH and VL indicate the variable regions of the heavy and light chains, respectively. The different epitopes are recognized by the variable regions located on both the light and heavy chains (Fab region). The CDR segments are hypervariable domains located in the Fab regions, which are separated from each other by relatively constant polypeptide chains. The Fc region binds to the complement and to the receptors located on the surface of the RES cells and triggers their activation

defines the specificity of the molecule. Both variable and fixed regions on the chains L and H are arranged on of Fab region, which binds the Ag.

In general terms, the Ig molecules can be considered biochemical transducers able to (Table 3.1):

- Recognize and neutralize infective germs and their derived substances
- Opsonize extraneous molecules in order to facilitate their elimination by the reticulum-endothelial system
- Recognize and inhibit early and late-released sepsis mediators, by a direct effect on the cell nucleus which produces and facilitates their scavenging by the SREs
- Activate the complement system
- Influence the death of the immunitary cells via apoptotoc and non-apoptotic pathways

Then, it appears that the Ig can modulate the inflammatory response, and this capability can be useful in the different phases of sepsis, which are characterized by a different arrangement of the immune response. Actually, sepsis and its related

**Table 3.1** Mechanisms of action of immunoglobulins

| |
|---|
| *Toxin inactivation* |
| Neutralization of endotoxin and exotoxins |
| Increase clearance of endotoxin |
| Reduction of bacterial cell adherence, invasion, and migration |
| *Stimulation of the leukocyte and serum bactericidal action* |
| Enhancement of endotoxin-induced neutrophilic oxidative burst (7S-IvIgG); intact |
| Reduction of endotoxin-induced neutrophilic oxidative burst (5S-IvIgG; F(ab′)2 fragments and IgM) |
| Enhancement of serum opsonic activity |
| *Modulation of cytokine effect* |
| Modulation of the release of cytokine and their antagonists |
| ↓ Proinflammatory mediators |
| ↑ Anti-inflammatory mediators |
| Infusion of cytokines and antagonists contained in the Ig preparations |
| Cytokine neutralization by anti-cytokine antibodies |
| *Modulation of the complement cascade* |

conditions as severe sepsis and septic shock can be considered as a complex and articulated response to an infection, which is characterized by (at least) two different phases. In the first one, whose features are the classical signs of fever, leucocytosis, hemodynamic instability, metabolic acidosis, etc., there is a predominant secretion of proinflammatory mediators (TNF, various interleukins, etc.) that can cause the derangement of organs different from the one in which the infective process and immunity response have started. This reaction is mainly determined by the action of the indicated proinflammatory mediators, whose qualitative and quantitative properties are genetically determined and thus vary from an individual to another; the subsiding of this initial response is determined either by reduction of the production of proinflammatory substances and by the contemporaneal release of mediators with anti-inflammatory capabilities [3].

If the patient survive the initial insult, a second phase ensues, which is characterized by the reduction and progressive disappearance of the above described proinflammatory response due to the overwhelming action of anti-inflammatory mediators ultimately leading to a state of immunoparalysis; this condition is characterized by a profound alteration of both natural and adaptive immunity mechanism, and the consequent immunitary state can be compared to that present in advanced neoplastic conditions [4, 5]. This state, which is difficult to diagnose due to the lack of suitable biological markers, is particularly frequent in patients affected by multiple chronic conditions, who can survive the infection and/or its related conditions causing the intensive care unit admission (surgery, lung infection, etc.) but who cannot be weaned from the mechanical ventilation and are prone to multiple infections, thus becoming critically ill chronic patients.

The above described clinical aspects can justify the use of IvIg both in the early phase of sepsis, in which they can modulate an excessive systemic inflammatory

response, and in the more advanced phase, during which their antibacterial action can restore the adaptive immune response. These actions are only partly shared by other immunomodulatory substances recommended by the SSC guidelines, like steroids with glucocorticoid activity: indeed, if their use has a rationale in the early inflammatory phase, in the later one, their use can contribute at the occurrence of immunoparalysis. Anyhow, the use of IvIg does not replace the other therapies indicated by the SSC, including the early administration of appropriate antibiotics and the surgical drainage of infective sources. Even if it is probable that in the next future some other immunomodulatory and immunostimolatory molecules can be introduced in clinical practice, actually their application has to be considered only experimental.

## 3.3 The Administration of IvIg in Sepsis

Although the IvIg use has long anticipated the first edition of the SSC, their administration in septic patients has been initiated long before and was based for long time more on the intuition of their utility than on robust scientific bases. In general, the different IvIg preparation currently used in clinical practice can be divided into two principal categories. The first one is formed by monoclonal antibodies directed versus one single antigen (e.g., the antitetanic toxin Ig), and the other is compounded by polyclonal antibodies directed against different antigens.

On the other hand, the application's modality in the sepsis treatment is based essentially on two different strategies [6]:

(a) The administration of polyclonal antibodies directed versus Ag expressed on the surface of the infection responsible bacteria and/or versus bacteria's produced substances like endotoxin, peptidoglycans, etc., that are released when the antibiotics cause cellular lysis; the IvIg actually in use belongs from this category, and it is composed by mixtures of IgG, IgM, and IgA in concentrations different than in plasma (Table 3.2). Independently of single composition, the IvIg solutions derive from a plasma pool of 1.000–10.000 donators and so contain a great variety of antibodies directed versus a myriad of different antigens that can vary with the different geographic donator origins and with their exposure on different antigens. The main preparation's process consists on the extraction and cold fractionation in ethanol, instead, whereas the inactivation of any blood donator virus involves the use of solvents, detergents, the pH reduction to 4, the incubation, the nanofiltration, and the chromatography

**Table 3.2** Concentrations of the different classes of IgG in the available preparations

| | Ig G (%) | IgM (%) | IgD (%) |
|---|---|---|---|
| Normal serum | 80 | 7 | 13 |
| IgM and IgA IvIg preparations | 76 | 12 | 12 |
| Other IvIg preparations | ≥97 | Traces | <3 |

(b) The administration of monoclonal antibodies in order to neutralize a single mediator that is produced and released from different immune system cells during the interaction between the bacteria and the host or, alternatively, versus its receptors on the target cells. Even though this strategy is based on clear pathophysiological and experimental assumptions, a wide number of clinical trials conducted with antibodies directed against different sepsis mediators (tumor necrosis factor, platelet-activating factor, etc.) carried results largely inferior to the expectations so that no one of this substances is used for the treatment of septic patients [7]. The causes of these results are not clear; it is likely, however, that the antagonism of only one of the many mediators that are released during sepsis and that are connected to each other with numerous negative or positive feedback cannot be sufficient per se to reduce the systemic inflammation process typical of the early phase of sepsis. Moreover, as the production of septic mediators is genetically determinate, the administration of a specific Ig directed versus one determinate molecule does not take into account this peculiarity. Anyway, these substances find extensive application in treatment of diseases characterized by chronic and/or relapsing inflammation state (e.g., rheumatoid arthritis, Crohn's disease, etc.).

Currently, only preparations containing polyclonal antibodies belonging from the IgG, IgM, and IgA classes are clinically used in the treatment of sepsis. The rationale for their use, as well as the pathophysiological premises exposed before, is based on the results of different studies and meta-analysis that have demonstrated that (a) the administration of polyclonal IvIg is associated with the reduction of mortality in different populations of septic patients [8–11] and that (b) the preparations containing IgM are more effective as compared with those containing IgG [12–15]. These results cannot be applied to all septic patients, because other studies have demonstrated that the IvIg administration does not improve the surviving of neutropenic patients and/or patients with hematology malignancy [16, 17]. The skepticism expressed by the SSC guidelines is principally derived from a number of causes, including the relatively poor number of patients enrolled in each single study, the heterogeneity of the underlying clinical conditions, the difference in pharmacological preparation used, and the different IvIg doses used [1, 14].

## 3.4 The Choice of the Patient

According to the authors of the SSC guidelines, the administration of IvIg cannot be recommended mainly due to lack of EBM criteria in the published studies and the consequent difficult identification of one or more categories of septic patients who likely could take advantage from their use. Presently, as stated above, this treatment is based more on the experience of the single centers than on sound biological and/or pathophysiological criteria, leaving a great probability of subjective decisions. The lack of precise indications is a relevant clinical issue as this relatively expensive treatment should be reserved to patients who could take maximum

benefit from it, thus maximizing the risk/benefit ratio; despite the lack of a biological or clinical marker (as troponin in the case of ischemic cardiopathy) that can be suited to start and/or to continue for the administration of IvIg, it is possible to present some findings derived from different studies that could be considered as a possible starting point for the identification of the patient in which the treatment is effective:

(a) In a group of patients with severe sepsis or septic shock, Maury et al. have demonstrated that the most elevated spontaneous IgM concentration has associated with a better outcome [18].
(b) Reduced spontaneous anti-endotoxin IgM antibodies concentration was associated with the increase in number of infective complications in a group of cardiosurgery patients [19].
(c) In septic shock patients, Venet et al. have demonstrated that the IgM and IgG concentrations were decreased at the beginning but increased in the following days [20]; the reduction of both classes was more nonsignificantly more pronounced in dead patients.
(d) Conversely, in another study, plasmatic IgM levels in patients with septic shock were significantly lower than in patients with systemic inflammatory response syndrome or severe sepsis; the IgM concentrations gradually increased in the survivor patients, whereas in nonsurvivors, they remained unchanged or decreased [21].
(e) Several meta-analyses in adult, pediatric, or neonatal patients demonstrate that IgM and IgA preparation are more effective than IgG in terms of mortality reduction [12–15].
(f) The IgM administration is more effective in the early phase of septic shock or severe sepsis [22], but the improvement in the clinical condition monitored with SOFA score does not increase before 48 h from the beginning of the treatment [23].
(g) The administration IgM did not decrease the mortality of neutropenic patients with leukemia or lymphoma but was associated with a decreased rate of MODS [16, 17]. This observation probably reflects the impossibility to restore the immune competence by reinforcing only one arm of its components.

In conclusion, despite the caution derived from the absence of one or more biological marker to monitor the effectiveness, the ideal patient candidate to IvIg treatment could be considered as a subject with severe sepsis or septic shock of both medical and surgical origin, with at least one organ dysfunction [16], caused by either gram − and gram + germs [19], treated in the early phase of illness [22], and without advanced cancer disease or other conditions that could reduced his/her life expectation. The monitoring of plasmatic IgM and IgG concentrations could be useful to early identify the patient to treat, even if the waiting for the result should not delay the beginning of the treatment.

In order to have a more precise idea about the biological effects of the IvIg administration, it could be useful to measure repeatedly the concentration of each Ig

class concentration in order to understand the causes of their variations and to identify the dose needed for every single patient [24].

**Conclusions**

Despite a number of experimental and clinical evidences demonstrated that the sepsis and its derived conditions are characterized in the early phases by excessive inflammatory response and in the later phases by a state of depression of both natural and adaptive response, the IvIg treatment that can modulate both conditions is often chosen on a subjective basis and not on indications derived from international guidelines that, instead, advise against this approach.

This situation derives from the lack of studies based on EBM criteria and of data about the Ig kinetics during sepsis. However, despite these relevant limitations, it is possible to identify with clinical and time criteria the kind of patient who could have their prognosis improved by the administration of IvIg.

## References

1. Dellinger P, Levy MM, Rhodes A et al (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
2. Cohen J (2002) The immunopathogenesis of sepsis. Nature 420:885–891
3. Hotchkiss RS, Karl IE (2003) The pathophysiology and treatment of sepsis. N Engl J Med 348: 138–150
4. Späth PJ (1999) Structure and function of immunoglobulins. Sepsis 3:197–218
5. Hotchkiss RS, Monneret G, Payen D (2013) Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis 13:260–268
6. Darabi K, Abdel-Wahab O, Dzik WH (2006) Current usage of intravenous immune globulins and the rationale behind it. The Massachusetts General Hospital data and a review of the literature. Transfusion 47:741–753
7. Deans KJ, Haley M, Natanson C et al (2005) Novel therapies for sepsis: a review. J Trauma 58:867–874
8. Rodriguez A, Rello J, Neira J et al (2005) Effects of intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. Shock 23:298–304
9. Dominioni L, Dionigi R, Zanello M et al (1991) Effects of high-dose IgG on survival of surgical patients with sepsis score of 20 or greater. Arch Surg 126:236–240
10. Cafiero F, Gipponi M, Bonalimi U et al (1992) Prophylaxis of infection with intravenous immunoglobulins plus antibiotics for patients at risk for sepsis undergoing surgery for colorectal cancer: results of a randomized, multicentre clinical trial. Surgery 112:24–31
11. Schedel I, Dreikhausen U, Newtig B et al (1991) Treatment of gram negative septic shock with immunoglobulin preparation: a prospective, randomized clinical trial. Crit Care Med 19: 1104–1113
12. Alejandra MM, Lansang MA, Dans LF et al (2002) Intravenous immunoglobulin for treating sepsis an septic shock. Cochrane Database Syst Rev (1):CD001090
13. Turgeon AF, Hutton B, Fergusson DA et al (2007) Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. Ann Intern Med 146:193–203
14. Pildal J, Goetzshe PC (2004) Polyclonal immunoglobulins for the treatment of bacterial sepsis: a systematic review. Clin Infect Dis 39:38–46
15. Norby-Teglund A, Haque KN, Hammarström L (2006) Intravenous polyclonal IgM-enriched immunoglobulin therapy in sepsis: a review of clinical efficacy in relation to microbiological aetiology and severity of sepsis. J Intern Med 260:509–516

16. Hentrich M, Fehnle M, Ostermann H et al (2006) IgMA-enriched immunoglobulin in neutropenic patients with sepsis syndrome and septic shock: a randomized, controlled multiple-center trial. Crit Care Med 34:1319–1325
17. Tugrul S, Ozoan PE, Akinci O et al (2002) The effects of IgM-enriched immunoglobulin preparations in patients with severe sepsis (ISRCTN28863830). Crit Care 6:357–362
18. Maury E, Blanchard HS, Cahuvin P et al (2003) Circulating endotoxin and antiendotoxin antibodies during severe sepsis and septic shock. J Crit Care 18:115–120
19. Bennet Guerrero E, Ayuso L, Hamilton-Davies C et al (1997) Relationship of preoperative antiendotoxin core antibodies and adverse outcomes following cardiac surgery. JAMA 277: 646–650
20. Venet F, Gebeile R, Bancel J et al (2011) Assessment of plasmatic immunoglobulin G, a and M levels in septic shock patients. Int Immunopharmacol 11:2086–2090
21. Giomarellos-Bourboulis E, Apostolidou E, Lada M et al (2013) Kinetics of circulating immunoglobulin M in sepsis: relationship with final outcome. Crit Care 17:R 247
22. Berlot G, Vassallo MC, Busetto N et al (2012) Relationship between the timing of administration of IgM and IgA enriched immunoglobulins in patients with severe sepsis and septic shock and the outcome: a retrospective analysis. J Crit Care 27:167–171
23. Berlot G, Dimastromatteo G (2004) Impiego delle immunoglobuline arricchite con IgM e IgA nel trattamento della sepsi severa e dello shock settico. Esperienza clinica. Minerva Anestesiol 70:739–745
24. Shanka-Hari M, Spencer J, Sewell WA, Rowan KM, Singer M (2012) Bench-to-bedside review: immunoglobulin therapy for sepsis: biological plausibility from a critical care perspective. Crit Care 16:206–280

# The Role of Noradrenaline, Vasopressin, and Terlipressin in Septic Shock

4

Biagio Allaria

The spirit in which this subject has been addressed is not in the style of a series of recommendations that are valid for the general treatment of the hemodynamic imbalance that is typical of septic shock.

Every patient is different. Frequently the guidelines and results of randomized, controlled trials that form the backbone of them are poorly adapted to the clinical reality of individual patients, and the results of treatment are very often disappointing even if this has been performed according to what is commonly defined as the "state of the art." The high mortality rate from septic shock, which even in a very recent study was almost 40 % [1] but which has also reported at much higher percentages up to 60 %, bears witness to this.

I read with interest and a certain amount of enthusiasm an editorial by J. L. Vincent published 2 years ago in Critical Care Medicine under the title "*We should abandon randomized controlled trials in the intensive care unit*" [2].

According to the author, we should abandon this type of study because it is too often characterized by what he defines as the "pendulum effect." In simple terms, when a study shows a positive and beneficial effect from a drug or therapeutic strategy, it is often followed by another study that concludes the opposite, causing upset. Unfortunately there are many reasons for this "pendulum effect," some of which are linked to commercial interests and others to incorrect imaging methods, whereas others still are related to insufficient numbers to reach general conclusions, but the most important factor is that critical patients are so diverse that it is particularly

Prof. Biagio Allaria, former Director of the Critical Patient Department of the National Institute for the Study and Treatment of Tumors, Milan. Currently consultant in Clinical Risk Management at the same Institute.

B. Allaria
Critical Patient Department,
National Institute for the Study and Treatment of Tumors, Milan, Milan, Italy
e-mail: info@int-service.it



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difficult to create homogeneous groups for comparison. Moreover, case studies from single wards with limited beds are small in scale and lead necessarily to multicenter reports, which may be even carried out in very diverse geographic areas that subsequently highlight the nonhomogeneity of samples. For these reasons, it seems to me that to address the problem of serious hypotension and septic shock, it is not of great importance, as has been said, to compile general recommendations but to give an overview of the information on mechanisms that are at the basis of vasodilation and the pharmacological and pharmacodynamic characteristics of drugs that are currently available in order to carry out a comparison. The goal is that at the end of this chapter, intensive care staff are helped in their therapeutic choices when faced with considerable variability in the patients they have to manage.

Any of us who are faced with patients of this type know how often we see extremely complex situations characterized by the need to infuse large quantities of fluids in the conviction that a large part of these fluids will rapidly end up in the interstitium without expanding the circulating volume as much as needed. This reality is clearly shown by serious hypotension that is resistant to infusions and requires the use of amines. But which amines? At what dose? And what pressure values should we aim for?

This is the reality we are faced with, and there are no general criteria that apply to all patients and therefore no treatment that is equal for everyone. In these moments we need to be clear about the mechanism that sustains vasodilation and the characteristics of drugs available to counter it. One of the questions we need to understand is the use of amines.

For years, we have preferred dopamine since we are convinced that it is the most effective and least dangerous amine; later we included noradrenaline (which for years was demonized because of alleged negative effects on the perfusion of noble organs); gradually we reduced the use of dopamine in favor of noradrenaline on the basis of important studies that attributed more adverse cardiovascular events to amine [1]; finally, faced with the frequent failures of this amine, we resorted to vasopressin or its synthetic analog, terlipressin, choosing between the two based on its availability in different geographic areas (in the USA only vasopressin is available and in Europe only terlipressin), often underestimating the considerable difference between the two drugs. Therefore, even in the use of amines, the "pendulum effect" of ambiguous studies has made it difficult to make reasoned decisions.

## 4.1 General Information on Mechanisms That Susta in Vasodilation

Noradrenaline (NE) is released from the postganglionic sympathetic nerve fibers and produced directly by the adrenal medulla, stimulating the endothelial alpha receptors of the arterioles and, via a series of mechanisms, promoting the introduction of calcium into the smooth muscle cells of vessels and the passage of calcium into the sarcoplasmic reticulum of the cytosol. The result is that calmodulin (a cytoplasmic protein) binds to four calcium molecules and activates the process of

connection between actin and myosin and thus contraction of the smooth muscle fibers of vessels.

The vasoconstrictor effect of NE is therefore not direct but the result of a series of processes triggered by the increase in calcium in the cytosol and culminating in activation of the actin-myosin complex.

At the end of contraction, the expulsion of calcium from smooth muscle cells in the vessels and/or the binding of calcium to the sarcoplasmic reticulum are at the basis of the release process. Sepsis is characterized by specific resistance to NE, and hyperproduction of nitric oxide (NO) is considered the most important cause of this resistance and of the vasodilation that occurs thanks to the production of cyclic GMP. But the increased production of prostacyclin, peroxynitrite, and superoxide anion and the excessive activation of ATP-dependent potassium channels are also clearly relevant in determining the reduced sensitivity of NE and vasodilation. For the above reasons, septic patients require much higher doses of NE than those which are usually capable of causing vasoconstriction in normal subjects. It is therefore not surprising that doses of more than 4 μg/kg/min of NE have been used to obtain mean arterial pressure (MAP) levels that are acceptable in septic shock. Since NO is considered the most important cause of vasodilation and reduced sensitivity to amines in patients with septic shock and since NO is produced from arginine thanks to an enzyme, nitric oxide synthase (NOS), it was expected in the 1980s that vasodilation could be reduced by using an NOS blocker such as N-nitro L-arginine methyl ester (L-NAME). After some apparently favorable experiments, phase III studies were interrupted following evidence of high mortality among treated patients [3]. In fact, the blocker of NO production caused a series of negative effects including impaired microcirculation, reduced bactericidal activity of NO, reduced neutralizing activity of $O_2$ radicals, reduced modulation of the coagulation cascade, and deterioration of the supply/demand balance in tissues in which oxygenation was already precarious. In conclusion, NO is certainly the largest cause of vasodilation and the poor response to amines in septic patients, but its blockage with L-NAME is not only not advantageous but also dangerous.

Another vasodilator involved in septic shock is prostacyclin (PGI2), which is produced from the interaction with arachidonic acid and cyclooxygenase (COX) and prostacyclin synthase (PGTIS).

PGTIS acts on receptors present in the smooth muscle cells of the vessels resulting in an increase in cyclic MAP which in turn causes vasodilation. Even in this case, it seems acceptable to block the synthesis of prostacyclin with an anti-COX such as ibuprofen, but this approach has also not been effective in humans [4]. Another hyperproduced substance during sepsis is superoxide anion. This anion finds NO (even if it is hyperproduced) and colloids with it without any need for enzyme activation. This results in the production of peroxynitrite [5]. Peroxynitrite is involved in the mechanism that causes reduced sensitivity to amines but is also the only superoxide anion to be involved in this mechanism. This information could open new routes to block the low sensitivity to amines caused by superoxide anion and peroxynitrite by blocking their production. General experiments have been conducted in endotoxinic shock in animals [6], but although they are certainly

interesting, no studies of this type in humans have begun yet, at least as far as I know. Another mechanism involved in vasodilation which is typical of septic shock is that of the ATP-dependent potassium channels. When these channels open, potassium (K) leaves the cells causing hyperpolarization of them, resulting in relaxation of the smooth muscle fibers of the vessels and therefore vasodilation. Both NO and peroxynitrite (as well as hyperlactacidemia) can activate the KAPT channels producing vasodilation and a reduced response to amines. An action that contrasts with this mechanism has been demonstrated experimentally by glibenclamide. Even this method of contrasting vasodilation has nevertheless been ineffective in humans [7]. It is useful to remember the possibility of inhibiting the vasodilator effect of NO and the production of it with a substance that has already been used in the past in the treatment of methemoglobinemia: methylene blue. One study in particular drew attention to this substance [8]. This study, the fruit of cooperation between Russian and Norwegian researchers, showed that the administration of a 2 mg/kg bolus of methylene blue, followed 2 h later by a continuous infusion of 0.5–1 mg/kg/h was capable of reducing the vasodilator effect of NO and improving the response to amines. The adverse effects at the doses they used were irrelevant except for a bluish-gray color to the skin that persisted for a few days. The problem is that the effect of this substance does not last long in time, and the authors of the study, afraid of unpredictable accumulative effects, interrupted the study after 6 h. The result was that, eventually, in addition to the very comforting short-term hemodynamic results, the duration of hospitalization and mortality were not statistically affected by the use of methylene blue. This does not mean that in critical moments with a poor response to the infusion of amines and fluids, methylene blue could be attempted at least to address situations that are difficult to manage. To conclude this introductory section, it is clear that for septic shock, although noradrenaline is the amine of choice in the treatment of hypotension, it is often not very effective, especially in terms of its resistance.

As we have seen, antagonizing the mechanisms that are at the basis of vasodilation is anything but simple, and many attempts to apply therapeutic strategies to humans that have been successful in animals have been in vain. It is therefore understood how the use of two drugs that can replace NE or be used alongside it to obtain sufficient pressure value levels can be regarded with interest. They are the two drugs that appear in the title of this chapter: vasopressin and terlipressin. This must not, however, be interpreted as alternative treatment to NE in serious cases of hypotension in septic patients. NE remains the drug of choice that is to be used as first-line treatment in these patients, and even the amine used as an alternative for many years, dopamine, is losing its consensus recently. In fact, the most recent study [8] has shown that, apart from hemodynamic effects, dopamine has more cardiovascular adverse events than NE. In particular there is a greater incidence of arrhythmias and atrial fibrillation, which undoubtedly make the management of these patients even more difficult, by enhancing hemodynamic imbalance. The particular utility of NE is reaffirmed by studies that have been published in recent years [9, 10]. These studies have shown that in patients with *preload dependency* (demonstrated by positive tests upon raising the lower limbs), NE improves venous return by increasing

*global end-diastolic volume* (GEDV), cardiac output, and CVP. NE, probably by increase mean systemic pressure (*mean circulatory filling pressure*, MCFP), which is the most important factor in venous return, improves cardiac filling and therefore output. This shows that in patients with *preload dependency*, cardiac filling can be improved not only with fluid administration but also with early use of NE. These observations confirm what has already been said for hemorrhagic shock, namely, that NE is able to reduce PPV in patients with artificial ventilation [11]. The important clinical implication that arises from these observations is that NE has the same effects as fluid infusion and that there can therefore be savings with infusions, which, as we all know, are a double-edged sword: on the one hand, they are helpful if used early to counter the imbalance between the dilated circulatory bed and the circulating mass, but on the other hand, they promote interstitial edema, which is one of the greatest problems for septic patients. Confirmation of this possible therapeutic strategy is found in the study by Sennoun [12], which, by using an animal model of endotoxic shock and combing fluid reanimation alone with fluid reanimation accompanied by early use of NE, has demonstrated the possibility of reducing fluids without systemic, regional, or tissue damage with NE. Another advantage of NE is in its effects on the heart. By increasing MAP and diastolic arterial pressure (DAP), it improves both the perfusion pressures of the left ventricle (DAP) and right ventricle (MAP). In particular, DAP is considerably reduced in septic shock, and therefore maintaining it with NE is a clear advantage and makes it possible to prevent ischemic events and contractility disorders that are anything but rare in septic patients, especially if they also suffer from coronary stenosis [13]. If, therefore, we take into account the fact that NE also has beta-adrenergic activity, a positive effect on myocardial contractility can also be expected. Considering the positive effect that NE has on preloading, coronary perfusion, and myocardial contractility, a constant increasing effect on cardiac output can also be deduced. In reality this effect is not highly expected, and along with studies that show an increase in cardiac output with NE [14], there are others that do not show it [15]. This apparent discrepancy may depend on the difference between the patients studied. Based on the above, it can be presumed that patients with preload dependency in particular are those who benefit most from NE, at least in terms of cardiac output, whereas those with high levels of filling with infusions are likely to respond less. This observation is right for the effects of NE on regional fluids and microcirculation. According to Monnet and Teboul [13], it is necessary to distinguish between patients with very serious hypotension (e.g., MAP 45–55 mmHg) and high cardiac output and those with moderate hypotension. In the former, MAP recovery with NE can improve renal function, even without any effects on output [16, 17], and it has been shown that it can improve microcirculation examined with *near-infrared spectroscopy* (NIRS) [14]. In patients with moderate hypotension (e.g., MAP 65–75 mmHg), Derundt et al. demonstrated that by increasing MAP to 85–90 mmHg from 65 to 75 with NE can lead to an improvement in microcirculation if the patient has not yet experienced an improvement in the microcirculation with generous early infusions of fluids. This has been demonstrated in the study by Thooft et al. [18], which, by increasing MAP from 65 to 85 mmHg, showed an increase in cardiac output and $SVO_2$ as well a

reduction in lactate and an improvement in microcirculation. In concluding this chapter, we must therefore stress that NE is an extremely valid support in the treatment of hypotension in patients with sepsis; and that, considering the resistance found in this type of pathology, the dosage is variable from patient to patient and is regulated according to the pressure response that reasonably stabilizes around a MAP of 85–90 mmHg; and finally that early use of this drug can enable savings of useful infusions to reduce the trend for interstitial edema. The above, however, should not create the illusion that increasing MAP above 80 mmHg with NE leads to a positive result. Unfortunately, as repeated many times, each septic patient is a separate case, and even in the literature, there are negative opinions on the real possibility of gaining and advantage by increasing MAP to above 65 mmHg. Is this another case of the "pendulum effect"?

I would like to say no. Today a MAP target of 85–90 mmHg is justified, and it is still being debated how to reach this value. With an increasing dose of NE? By supporting NE early with vasopressin or terlipressin? This is the subject of the next chapter.

## 4.2 Role of Vasopressin and Terlipressin in Septic Shock

Vasopressin (an antidiuretic hormone) is a hormone synthesized by the neurons of paraventricular and supraortic nuclei of the thalamus. Transported by an axonal protein (neurophysin) to the nerve part of the pituitary gland, it is viewed here in vesicles from which it is released in response, as we shall see, to various stimuli. The most important stimulus for vasopressin release is plasmatic osmolarity. Only a minimal increase (2 %) in osmolarity is sufficient to stimulate the release of vasopressin, and small increases in plasmatic osmolarity are enough to have an antidiuretic effect and return osmolarity to normal. Even arterial pressure reductions are a stimulus for vasopressin release, but reductions must be of at least 10 % and the vasoconstrictor response tends to restore the pressure value, but this occurs only with an increase of at least ten times the baseline plasma value. Therefore, minimal increases in osmolarity cause vasopressin responses that are already effective with the plasma levels of hormones only moderately increased, while falls in pressure, to activate a vasopressin response, must be substantial and be addressed only with increases in the plasma level of the hormone that are equally substantial. Various factors interact in the release of vasopressin. For example, high doses of NE, such as those used in septic shock, inhibit vasopressin release; acidosis and hypoxia stimulate the release of vasopressin, while nitric oxide reduced it. Considering that in septic shock there are factors that trigger release and those that inhibit it, it is difficult to predict the final result. But it nevertheless seems clear that in the initial phase of shock, there is a transient sharp rise (up to ten times the baseline value) in plasma levels of vasopressin (probably due to the rapid release of stored vasopressin) followed after about 24 h by a stable reduction leading to depletion. It also seems obvious that the mechanism of resistance in play in septic patients is not confirmed with vasopressin either. It seems that in septic shock, the response to vasopressin is

improved. Indeed, while in healthy subjects the administration of exogenous vasopressin does not increase pressure values, hypertension is not in fact a typical symptom of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in patients with septic shock who are not responsive to fluids and amines; the hypertensive response is present. The pressure effect is felt in a few minutes and often enables a reduction in or interruption of amines.

It is possible to reduce the amine dose not only due to the vasoconstrictor effect of vasopressin or terlipressin, but because they seem to be able to restore, at least in part, sensitivity to amines, which is lost the longer the septic shock lasts [19].

The vasoconstrictor action of vasopressin works via the stimulation of $V_1$ receptors, which are particularly present in the smooth muscles of the vessels in the systemic, splanchnic, renal, and coronary circulation. The stimulation of $V_1$ receptors leads to vasoconstriction, mediated above all by the entry of calcium into the cells and the release of calcium from the sarcoplasmic reticulum into the cytosol. The antidiuretic action of vasopressin is, however, maintained by stimulation of $V_2$ receptors located especially in the renal collector tubes. The stimulation of $V_2$ receptors triggers the reabsorption of water and therefore increases urine osmolarity. It is essentially with this mechanism that plasmatic osmolarity is constantly kept normal. There are, however, also extrarenal endothelial $V_2$ receptors which, when stimulated, lead to vasodilation [19], fluid accumulation [20], and procoagulation effects [21], with a clear trend toward deterioration of interstitial edema in septic patients. There are also $V_3$ receptors for vasopressin in the pituitary gland: the stimulation of these receptors triggers a release of ACTH and therefore a rapid increase in plasmatic cortisol. This multifunctional hormone is ultimately able to stimulate existing receptors in the myoepithelial cells of the uterus and breast (so-called OTRs, *oxytocin receptors*). The stimulation of OTRs produces a contraction of the smooth muscles. The use of vasopressin in obstetric practice, however, is beyond our scope. It is clear that the most useful effect of vasopressin in septic shock is that which occurs on $V_1$ receptors that lead to useful vasoconstriction. The antidiuretic effect resulting from stimulation of $V_2$ receptors is not only of minimal use but can also be harmful, just as the stimulation of extrarenal endothelial $V_2$ receptors is harmful, since, as has been said, they aggravate the tendency for interstitial fluid accumulation. A considerable amount of current research into the treatment of septic shock is based on this distinction between the beneficial effect of stimulation of $V_1$ receptors and the damage from stimulation of $V_2$ receptors. It has, for example, been shown that the use of a $V_2$ receptor antagonist is useful in the treatment of experimental septic shock in sheep [22]. In the vasopressin commonly used in English-speaking countries, the ratio between the stimulation of $V_1$ and $V_2$ receptors is 1:1. Terlipressin, which is more frequently used in Europe, has a ratio that is more favorable to $V_1$ receptors: 2.2:1. With terlipressin, therefore, the vasoconstrictor response is greater, and the accumulation of interstitial fluids is of less importance [23]. There are two $V_1$ receptor antagonists (vasoconstrictors) being studied that have no effect on $V_2$ receptors: POV, which has selectivity for $V_1$ receptors that is 220 times higher than that of vasopressin, and FE 2020158, which has selectivity for $V_1$ receptors that is over 1000 higher than that of vasopressin [24]. It is very

interesting in these experimental studies on septic shock treated with highly selective drugs for $V_1$ receptors that they can have an optimal vasoconstrictor effect without causing extravasation of fluids from capillaries to the interstitii, giving rise to a much more favorable fluid balance: by infusing less fluid, better hemodynamic results are therefore obtained.

In this sense terlipressin, even if it does not have the high selectivity of the new molecules we have mentioned, is twice as selected for $V_1$ receptors than vasopressin and should therefore, from this point of view, be preferred. There is a possibility of further improving the safety and efficacy of vasopressin. It involves the concomitant use of hydrocortisone, which increases sensitivity to $V_1$ receptors. In particular, the very recent study by Torgersen in 159 patients with shock seems to show that the addition of hydrocortisone alongside vasopressin leads to a reduction in mortality both during recovery in ICU and at 29 days [25]. What has been demonstrated for vasopressin in this sense has not yet been shown for terlipressin, but I think that, based on the current state of knowledge, even the terlipressin + hydrocortisone combination can be taken into consideration. Basically, a part from the varying selectivity for $V_1$ and $V_2$ receptors and the longer duration of action of terlipressin, vasopressin and terlipressin have identical mechanisms of action, and it is probable that the advantages of combining it with hydrocortisone are common to both. The dosage of hydrocortisone used in Torgersen's study was on average 300 mg per day as a continuous infusion until it was possible to discontinue amines. Initial treatment of shock was made with NE at a dose sufficient to obtain MAP of 60–70 mmHg. In patients in whom this pressure value was not obtained with NE doses of >0.5 μg/kg/min or when NE-related adverse effects occur, vasopressin was added at a dose of between 1 and 6 IU/h. All of Torgersen's patients were in a state of serious septic shock. This study therefore differs from the previous multicenter study (VASST Study 2009) [26], which involved patients who were only partly in serious septic shock, where only those with a mild shock status benefited from the administration of hydrocortisone. In any case, in the light of both studies, it seems appropriate to add a continuous infusion of 300 mg/day of hydrocortisone in the treatment of serious hypotension in septic shock. From what has been stated above, it seems evident that the international literature in recent years is increasingly demonstrating the validity of combination treatment with NE + vasopressin/terlipressin in serious hypotension during shock, supported by a continuous infusion of hydrocortisone. Naturally this strategy is awaiting confirmation of much wider clinical practice and, in particular, we can agree, at least in terms of the combination with hydrocortisone, with Lauzier that this proposal confirms that, "… vasopressin and corticosteroids are currently officially engaged but not yet married …" [28].

Now, how must we use vasopressin and terlipressin? As boluses? As a continuous infusion? At what dose? And when?

One of the first studies to show an advantage in the combination of NE + vasopressin/terlipressin in patients in whom NE alone did not lead to satisfactory MAP levels was that of O'Brien et al. in The Lancet 10 years ago. Referring to various English authors, this study investigated the use of terlipressin, which, as we have seen, is the form available in Europe.

The authors used boluses of 1–2 mg terlipressin, obtaining a pressure response in 10–20 min with a duration of effect of at least 5 h and the possibility of reducing the NE dose in 7 of the 8 patients [27]. This is, however, the strategy for terlipressin as a "last resort" strategy, used when circulatory filling and NE have not achieved a satisfactory MAP. Today a different strategy is being pursued, which involves low doses as a continuous infusion with early initiation in combination with NE. This applies to both vasopressin and terlipressin. In particular, for terlipressin, the only form available in Italy, Morelli's observation that, " … *less may be the best and the earlier the better*" [29] may be valid. The authors described a very serious case treated successfully by early infusion of a very low dose of terlipressin (0.0013 mg/kg/h), which is equivalent to a 1 mg vial infused over 12 h in a man weighing 70 kg. It is absolutely correct that a single case is not a test, but this observation stands alongside many others in the literature that recommend a similar strategy with vasopressin, which has been more widely tested, with early low-dose administration as a continuous infusion. Even in 2003 Denser et al. demonstrated that a low dose of vasopressin (4 U/h, equivalent to 0.0067 U/min) combined with a low dose of NE led to a lower incidence of tachyarrhythmia compared to treatment with higher doses of NE alone [30]. These results were confirmed by Luckner et al. [31] in 2006 and Torgersen et al. [32] in 2010. But it is above all when NE and vasopressin are combined with corticosteroids that better results are obtained as an obvious consequence of the study cited above by Torgersen et al. in 2011 [24]. The problem in Europe, where vasopressin is not available, is in transferring dosages that are already sufficient and usefully investigated to the same recommended doses for terlipressin. It is currently impossible, unless we want to use a "low dose" of terlipressin in an "early phase" as described by Morelli in his case that was successfully treated in combination with NE equivalent to a 1 mg vial diluted in a physiological solution and infused over 12 h in a man weighing 70 kg (0.0013 mg/kg/h). This dosage is very wise if we think that the initially recommended dose of terlipressin for septic shock was 1–2 mg as an intravenous bolus. In Morelli's case hydrocortisone was not administered. I think that, in light of the above, it would most probably be useful to administer it as combination therapy.

Reports to analyze the state of knowledge on the role of NE, vasopressin, and terlipressin in the treatment of septic shock have ended up broadening the evaluation of the concomitant use of other drugs such as hydrocortisone and methylene blue, each of which may play an important role. So as not to ignore a supporting therapeutic element that is recommended in German guidelines from 2010, we shall finish with a brief look at gamma globulins. While the use of IgG is not currently advised, the use of well-known preparations containing IgG, IgM, and IgA (IgGMA) is still recommended. At doses of 0.25 kg bodyweight every day for 3 consecutive days, IgGMA seems to yield good results, probably due to its high antibody content for the endotoxin and the significant inhibition of the complement. These effects have enabled a reduction of mortality in septic patients by demonstrating a positive effect on the microcirculation too [33]. In conclusion it is comforting to know that in the near future, it will be possible to establish as a priority whether a patient can undergo treatment with vasopressin with a probability of success. A very recent

study by Nokada [32] has, in fact, shown that in septic shock there can be genetic variations of vasopressinase (the enzyme that breaks down vasopressin) and that these genetic variations affect the response to vasopressin. By highlighting these genetic variations, it is already possible to establish the probability of success of the therapy [34]. We hope that this possibility, which is already real in some treatment centers, can become available for us too.

## Conclusions

Septic shock remains a considerable problem for intensive care specialists with very high mortality rates throughout the world that range from 30 to 60 %. The high variability in the final outcome can naturally depend on the different levels of seriousness in patients as well as the different therapeutic approaches. This observation makes us think that there is still a wide margin of possibility to optimize treatment and therefore to improve results of treatment. There is already a certain amount of consensus on the methods of early fluid reanimation in serious hypotensive states that accompany septic shock and which are certainly the most important contributing factor to the high mortality rates. But when fluid reanimation does not achieve satisfactory pressure rebalance (which is currently considered to be 80–85 mmHg MAP), it is inevitably necessary to use amines. This is where the problems begin and the therapeutic approaches differ considerably around the world. While the choice of NE at initially low dosages (5 μg/min, and up to 15 μg/min) is now corroborated, the subsequent approach is still not agreed upon when hypotension does not respond to these doses. An approach that is always based on the use of NE is to increase the dosage, and this decision is supported by the fact that in septic shock NE resistance is experienced and therefore each patient is a separate case and can respond to plasma NE levels that are higher than those up to a specific moment. But when there is the precise feeling of an insufficient response to fluid infusion and it is necessary to continuously increase the dose of NE, we must not hesitate to administer combination with terlipressin very early, using the low dosage recommended by Morelli. The combination of hydrocortisone at this point as a continuous infusion is justified. In particularly critical situations, when traditional procedures do not seem to yield a sufficient response, the use of blue methylene is justified, even for a few hours. As we have seen, there is a great deal of flexibility in the treatment of septic shock, and various strategies can be adopted. By widening our mental framework (which is sometimes even closed to dopamine), more satisfactory results are possible, but since, as we have repeatedly stated, every patient is different, the use of the means available is highly variable from case to case, and there is certainly a greater chance of success if we know the value and limits of these measures as best as possible.

In this chapter we have intentionally omitted the early fluid treatment of septic shock with all the problems relating to the quality of fluids to be administered and the necessary quantity for each individual patient. This is an important area that nevertheless lies outside what we have proposed, highlighting the use of amines. To update knowledge of fluid reanimation in septic shock, we recommend

the recent overview by Puskarich published a few months ago in *Current Opinion of Critical Care* [35].

## References


1. Russel JA, Keith RW, Walley MD et al (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 358:877–887
2. Vincent JL (2010) We should abandon randomized controlled trials in the intensive care unit. Crit Care Med 38(Suppl):S534–S538
3. Vincent JL, Zhang H, Szabo C, Preiser JC (2000) Effects of nitric oxide in septic shock. Am J Respir Crit Care Med 161:1781–1785
4. Bernard GR, Wheeler AP, Russell JA et al (1997) The effects of ibuprofen on the physiology and survival of patients with sepsis. N Engl J Med 336:912–918
5. Pocher P, Beckman JS, Liandet L et al (2007) Nitric oxide and peroxynitrite in health and disease. Physiol Rev 87:315–324
6. Salvemini D, Wang ZQ, Zweier J et al (1999) A unpeptidic mimic of superoxyde dismutase with therapeutic activity in rats. Science 286:304–306
7. Morelli A, Lange M, Estmer C et al (2007) Glibenclamide dose response in patients with septic shock; effects on norepinephrine requirements, cardiopulmonary performance and global oxygen transport. Shock 28:530–535
8. De Baker D, Biston P, Devriendt J et al (2010) Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 362:779–789
9. Hamazoni O, Georger JF, Monnet X et al (2010) Early administration of norepinephrine increased cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care 14:R142
10. Monnet X, Jabot J, Maizel J et al (2011) Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. Crit Care Med 39:689–694
11. Nouira S, Eldrons S, Dimassi S et al (2005) Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. Crit Care Med 35:2339–2343
12. Lennound N, Montemont G, Gibot S et al (2007) Comparative effect of early versus delayed use of norepinephrine in resuscitated endotoxic shock. Crit Care Med 35:1736–1740
13. Monnet X, Teboul JL (2012) Cardiovascular effects of norepinephrine in septic shock. In: Vincent JL (ed) Annual update in intensive care and emergency medicine. Springer, Heidelberg, pp 65–75
14. Georger JF, Hamzaoui O, Chaari A et al (2010) Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. Intensive Care Med 36:1882–1889
15. De Backer D, Creteur J, Silva E, Vincent JL (2003) Effects of dopamine, norepinephrine and epinephrine on the splanchnic circulation in septic shock: which is the best? Crit Care Med 31:1659–1667
16. Albanes J, Leone M, Garnier E et al (2004) Renal effects of norepinephrine in septic and non septic patients. Chest 126:534–539
17. Deruddre S, Cheisson G, Mozart JX et al (2007) Renal arterial resistance in septic shock: effects in increasing mean arterial pressure with norepinephrine on the renal resistive index assessed by Doppler ultrasonography. Intensive Care Med 33:1557–1562
18. Thooft A, Favory R, Ribeira Solgado D et al (2011) Effects of changes in arterial pressure on organ perfusion during septic shock. Crit Care 15:R222
19. Lucinda K, Barrett MA, Singer M et al (2007) Vasopressin: mechanisms of action on the vasculature in health and in septic shock. Crit Care Med 35:33–40
20. Kaufman JE, Bezzi M, Vischer UM (2003) Desmopressin (DDAVP) induces NO production in human endothelial cells on V2 receptors. J Thromb Haemost 1:821–828

21. Traber DL (2007) Selective V1 receptor agonists in experimental septic shock. Crit Care 11:P51, abstract
22. Rehberg S, Laporte R, Enkhbaatar P et al (2009) Arginine vasopressin increases plasma level of Willebrand factor in sheep. Crit Care 13:A182
23. Rehberg S, Ermer C, Lange M et al (2010) Role of selective V2 receptor antagonism in septic shock: a randomized, controlled, experimental study. Crit Care 14:R200
24. Rehberg S, Westphal M, Ertemer C (2012) Vasopressin therapy in septic shock. In: Vincent JL (ed) Annual update in intensive care and emergency medicine. Springer, Heidelberg, pp 76–84
25. Torgersen C, Luckner G, Schroder DC et al (2011) Concomitant arginine-vasopressin and hydrocortisone therapy in severe septic shock: association with mortality. Intensive Care Med 37:1432–1437
26. Russel JA, Walley KR, Gordon AC et al; For the VASST investigators (2009) Interaction of vasopressin infusion, corticosteroid treatment and mortality of septic shock. Crit Care Med 37:611–818
27. O'Brien A, Clapp L, Singer M (2002) Terlipressin for norepinephrine resistant septic shock. Lancet 359:1209–1210
28. Lanzier F (2011) Arginine vasopressin and corticosteroids in septic shock: engaged but not yet married! Intensive Care Med 37:1406–1408
29. Morelli A, Ermer C, Lange M et al (2007) Continuous terlipressin infusion in patients with septic shock: less may be best, and the earlier the better? Intensive Care Med 38:1669–1670
30. Dunser MW, Mayr AJ, Ulmer H et al (2003) Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation 107:2313–2319
31. Luckner G, Mayr VD, Jochberger S et al (2007) Comparison of two dose regimens of arginine vasopressin in advanced vasodilatory shock. Crit Care Med 35:2280–2285
32. Torgersen C, Dunser MW, Wenzel V et al (2010) Comparing two different arginine-vasopressin doses in advanced vasodilatory shock: a randomized controlled, open-label trial. Intensive Care Med 36:57–65
33. Pasler M, Dietr S, Werdan K (2012) Hypogammaglobulinemia in sepsis. In: Vincent JL (ed) Annual update in intensive care and emergency medicine. Springer, Heidelberg, pp 98–108
34. Nakado TA, Russe JA, Wellman H et al (2011) Lencyl/cystinyl aminopeptidase gene variants in septic shock. Chest 139:1042–1049
35. Puskarich MA (2012) Emergency management of severe sepsis and septic shock. Curr Opin Crit Care 18:295–300

# The Most Recent Strategies for VAP (Ventilator-Associated Pneumonia) Prevention

5

Davide A. Chiumello, Silvia Coppola, and Sara Froio

## 5.1 Definition

Ventilator-associated pneumonia (VAP) represents a type of hospital-acquired pneumonia, which occurs in patients who are receiving mechanical ventilation. This nosocomial infection arises more than 48 h after patients have started mechanical ventilation [1, 2]. It is considered a common nosocomial infection in critically ill patients admitted to intensive care units (ICUs).

## 5.2 Introduction

Ventilator-associated pneumonia affects 9–27 % of all mechanically ventilated patients. This variability probably depends on the absence of a gold standard for diagnosis and on the wide heterogeneity of the studied population [3]. At the same time, VAP presents the highest mortality rate among *nosocomial infections* [4].

D.A. Chiumello (✉)
Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolore, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Via F. Sforza 35, Milan 20122, Italy

Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Via F. Sforza 35, Milan 20122, Italy
e-mail: chiumello@libero.it

S. Coppola • S. Froio
Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolore, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Via F. Sforza 35, Milan 20122, Italy
e-mail: silvia_coppola@libero.it; sara.froio@hotmail.it



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Patients affected by VAP reach a mortality rate of 50 % [5]. Then, VAP increases the length of mechanical ventilation itself, as well as the ICU and the overall hospital length of stay. VAP leads to increased antibiotic prescription and administration.

Moving from these considerations and these implications on morbidity, mortality, and healthcare costs, physicians, dealing with critically ill mechanically ventilated patients, need to explore etiology, associated risk factors, and preventive strategy for VAP.

## 5.3 Pathogenesis

Ventilator-associated pneumonia develops following the invasion of the *lower respiratory tract* and lung parenchyma by microorganisms. The pathogenesis of VAP is related to the colonization of the oral cavity by potential respiratory pathogens, which obtain direct access to the lower respiratory tract.

The bacterial flora of the oral cavity colonizes different surfaces, including the teeth, gums, and tongue. In critically ill patients and in patients taking antibiotics or immunosuppressive drugs, the normal microbial flora may change. The antibiotic treatment may select resistant bacteria, resulting in preferential growth of bacterial strains [6].

Studies have shown that the majority of patients present the same bacteria in the oral cavity and in the respiratory secretions, suggesting that the oral flora could be involved in the pathogenesis of respiratory bacterial infections. Samplings were carried out on standard cultures and on gene sequences [7]. Of course, if rapid and cheap techniques could monitor changes in the oral flora, an accurate microbiological surveillance could be obtained and could result in opportunities for preventive interventions and for improvement in treatment of patients who develop VAP.

The type of organism that causes VAP usually depends on the prevalence of specific pathogens that are common in ICUs, on the length of intensive care and hospital stay and on the diagnostic tool applied [8].

Gram-negative bacilli are frequently involved in the pathogenesis of VAP. Studies have reported that aerobic Gram-negative bacilli are responsible for the 60 % of VAP [8].

Other bacteria causing VAP include *Escherichia coli*, *Klebsiella* spp., and *Haemophilus influenzae*.

Less frequently, Gram-positive organisms, such as *S. aureus*, are involved.

Table 5.1 presents pathogens causing VAP [8].

Moreover, it is important to remember that the predominant bacteria in each hospital could develop specific hospital-acquired antibiotic resistances, so that different treatment models can be used according to the local bacterial population.

The use of wrong empiric antibiotic therapy may represent a particular problem especially with the presence of *Pseudomonas aeruginosa*, *Acinetobacter* spp., and methicillin-resistant *S. aureus* (MRSA). These multidrug microorganisms are typically involved in the 60 % of patients that develop a late VAP (after 7 days of mechanical ventilation) and that had previously received an antibiotic treatment.

**Table 5.1** Pathogens causing VAP with their frequencies [8]

| Pathogens | Frequency (%) |
|---|---|
| *Pseudomonas aeruginosa* | 24.4 |
| *Acinetobacter* spp. | 7.9 |
| *Stenotrophomonas maltophilia* | 1.7 |
| *Enterobacteriaceae*[a] | 14.1 |
| *Haemophilus* spp. | 9.8 |
| *Staphylococcus aureus*[b] | 20.4 |
| *Streptococcus* spp. | 8.0 |
| *Streptococcus pneumoniae* | 4.1 |
| Coagulase-negative *Staphylococcus* | 1.4 |
| *Neisseria* spp. | 2.6 |
| Anaerobe | 0.9 |
| Fungi | 0.9 |
| Others (<1 % per species[c]) | 3.8 |

[a]*Klebsiella* spp. (15.6 %), *Escherichia coli* (24 %), *Proteus* spp. (22.3 %), *Enterobacter* spp. (18.8 %), *Serratia* spp. (12.1 %), *Citrobacter* spp. (%5.0 %), *Hafnia alvei* (2.1 %)
[b]*S. aureus* methicillin resistant (55.7 %), *S. aureus* methicillin sensitive (44.3 %)
[c]Includes *Corynebacterium* spp., *Moraxella* spp., and *Enterococcus* spp.

## 5.4 Risk Factors

The presence of an endotracheal tube is considered an important risk factor for the development of VAP. However, some patients have a higher risk than others [9].

Several studies have identified two groups of risk factors for the onset of VAP [1, 10]:

- Factors related to the presence of an endotracheal tube
- Host factors

The presence of the endotracheal tube itself implies an impairment of the mucociliary clearance of secretions, the pooling of subglottic secretions around the cuff, and the development of a biofilm laden with bacteria within the endotracheal tube.

Among patient-related risk factors, it is important to mention the presence of chronic lung disease, the age >70 years, the altered state of consciousness, the aspiration of gastric contents, the elevated gastric pH, and the prior antimicrobial use [9]. Furthermore, surgical patients admitted to ICU are at high risk for VAP. The development of VAP in these patients is related to the presence of preoperative markers of the severity of the underlying disease, such as preoperative nutritional status, serum albumin levels, history of smoke, preoperative length of stay, and more long surgical procedure times. Furthermore, thoracic and upper abdominal surgery could increase the risk of VAP [8].

## 5.5 Preventive Measures

The knowledge of risk factors contributes to the development of *preventive strategies* to reduce the incidence of VAP.

The Institute of Healthcare Improvement (IHI) has developed a set of recommendations for the prevention of VAP called *ventilator bundle* that includes five suggested measures to prevent morbidity related to VAP (Table 5.2) [11].

Three of the five elements of VAP bundle are aimed at the prevention of VAP development, while the remaining two concern stress ulcer prophylaxis and deep venous thrombosis prophylaxis.

The IHI ventilator bundle has been widely adopted by many institutions and ICUs as VAP preventive strategy, and it was erroneously considered a VAP prevention bundle. In fact, stress ulcer prophylaxis with $H_2$ receptor blockers can increase the risk of VAP, while deep venous thrombosis prophylaxis has not been directly associated with the prevention of VAP [12].

The IHI bundle should not be considered for the prevention of VAP but for the prevention of the adverse events associated with mechanical ventilation.

So far, no large randomized controlled study has demonstrated that the application of any measures for the prevention of VAP including the bundle approach can improve relevant clinical outcomes [9].

In this chapter we discuss the latest evidence on VAP preventive measures. Similarly to the risk factors, these preventive strategies can affect the artificial airways or the daily caring of the mechanically ventilated patient (Table 5.3) [3].

**Table 5.2** "Ventilator bundle" – Institute for Healthcare Improvement [11]

| Suggested preventive measure | Goal |
|---|---|
| Elevation of the head of the bed 45° | Prevention of VAP |
| Daily sedation assessment and weaning trials | Prevention of VAP |
| Daily oral care with chlorhexidine | Prevention of VAP |
| Proton pump inhibitors and $H_2$ blockers | Stress ulcer prophylaxis |
| Anticoagulants or leg compression devices | Deep venous thrombosis prophylaxis |

Suggested measures for the prevention of VAP (ventilator-associated pneumonia)

**Table 5.3** VAP (ventilator-associated pneumonia) preventive measures can specifically affect the artificial airways and daily caring of the mechanically ventilated patient

| VAP preventive measures | |
|---|---|
| Management of artificial airways | Management of ventilated patient |
| Reduce duration of intubation<br>Monitoring of endotracheal tube cuff pressure<br>Aspiration of subglottic secretions<br>Endoluminal biofilm prevention<br>Tracheostomy | Oral decontamination<br>Selective digestive decontamination<br>Enteral nutrition and probiotics<br>Patient positioning<br>Kinetic therapy<br>Reduction of sedative administration |

## 5.6 Preventive Measures Related to the Artificial Airway Management

### 5.6.1 Endotracheal Tube Cuff Pressure

Maintaining the internal cuff pressure within the recommended range of 25–30 $cmH_2O$ can reduce the aspiration of *oropharyngeal secretions* [13].

An internal *cuff pressure* less than 20 $cmH_2O$ may promote the drainage of oropharyngeal secretions, while an excessive cuff pressure higher than 30 $cmH_2O$ against the tracheal wall may cause a lesion of the mucosa; in fact, the normal tracheal mucosa capillary perfusion pressure is estimated to be around 30 $cmH_2O$.

Therefore, it is evident that cuff overinflation can produce tracheal ischemia, especially in critically ill patients whose peripheral capillary perfusion may already be impaired. A potential benefit could be to maintain a known constant level of cuff pressure.

Two randomized controlled trials tested two devices for the continuous control of tracheal pressure.

In the trial of Valencia et al., 142 patients, within 24 h of intubation, were randomly allocated to undergo continuous regulation of the cuff pressure with the automatic device or routine care of the cuff pressure. Pressure values were recorded every eight hours in both groups.

Despite the cuff pressure was better controlled using the automatic device, no differences were found between the two groups in terms of the onset of VAP, mortality, and ICU and hospital stay [15].

More recently, Nseir et al. conducted a trial on 122 patients on mechanical ventilation for more than 48 h to evaluate the efficacy of the continuous control of the endotracheal tube (ETT) cuff pressure by a *pneumatic device versus* manual control with a manometer every 8 h. In this study, the microaspiration of gastric contents, defined by the presence of a significant level of pepsin in tracheal aspirates, was significantly lower in the intervention group as well as the tracheal bacterial concentration and the VAP rate compared with the control group [14].

However, it is important to remember that coughing and even slight movements of the endotracheal tube either due to patient moving or caregiver handling the endotracheal tube should require rapid adaptation of pressure cuff by automatic devices in order to limit the risk of microaspiration of overhanging secretions.

### 5.6.2 Aspiration of Subglottic Secretions

The placement of the ETT through the vocal cords and into the trachea promotes the aspiration of oropharyngeal secretions composed of either oral flora and/or *gastric contents*. In intubated patients oropharyngeal secretions accumulate above and below endotracheal cuff facilitating the drainage into the lower airways [13]. In the first case, secretions easily drain into the subglottic space, pooling around the outer superior surface of the ETT cuff, progressively organizing in a thickening layer.

These layers are found early after intubation and are rich in oral pathogens that can leak through the cuff and the tracheal mucosa into the lower airway. Recently, a strategy to prevent this occurrence has been developed consisting in *subglottic secretion drainage* (SSD) obtained by an ETT with a small suctioning port opening on the upper surface of the cuff. The suctioning can be applied in either a continuous or an intermittent fashion.

The effectiveness of this strategy in preventing the incidence of VAP seems to be demonstrated, despite the small number of randomized trials and the concern about the risk of tracheal mucosal damage.

A recent meta-analysis that included 13 randomized clinical trials with a total of 2,243 patients found that the subglottic secretion drainage was associated with a relative reduction in the incidence of VAP in patients requiring more than 24 h of intubation, with a reduction in the duration of mechanical ventilation and ICU length of stay and delayed VAP onset. However, it did not improve intensive care or hospital mortality [16].

Currently, the use of endotracheal tubes with subglottic secretion drainage should be taken into consideration as a VAP preventive strategy, to reduce the duration of mechanical ventilation and ICU stay, although further studies are needed to evaluate the best method of administration (continuous or intermittent) and the real risk of tracheal mucosal damage.

### 5.6.3 Biofilm Prevention

After a few days of mechanical ventilation, the lumen of the endotracheal tube is coated with a thick layer of biological material that is a favorable medium for bacteria adhesion and growth [17].

The most common *nosocomial pathogens* cultured from the lumen of the endotracheal tube are *Staphylococcus aureus* (including methicillin-resistant strains), group A *Streptococcus*, *Acinetobacter*, *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* [18, 19].

Once this *biofilm* has formed, aggregates of bacteria can easily come off into the lower airways during the suctioning maneuvers or bronchoscopy or by gravity or by the effect of the inspiratory gas flow [17].

It was demonstrated that 70 % of VAP patients have the same pathogens in tracheal secretions and endotracheal biofilm that, therefore, represent a potential source of colonization and infection of the lower respiratory tract [20].

Many efforts have been made to prevent the formation of the endotracheal biofilm. Several studies investigated the use of endotracheal tubes coated with antimicrobials or heavy metals, that is, silver, to contrast the formation of the biofilm.

The coating with polymers containing silver ions has bacteriostatic properties as the silver ions penetrate the bacterial membrane and interfere with DNA synthesis and then with bacterial replication.

New kinds of *coatings* seem to have a higher antimicrobial activity, but their clinical use is currently under development [21].

Up to now only silver-coated endotracheal tubes have been tested in clinical trials.

The North American Silver-Coated Endotracheal Tube (NASCENT) Investigation Group conducted a large multicenter randomized controlled clinical trial enrolling 1,509 patients intubated for more than 24 h randomized to receive a standard tube or a silver-coated endotracheal tube. Kollef et al. found that the silver-coated endotracheal tubes reduced the incidence of VAP and delayed the onset of the infection. However, their use was not demonstrated to reduce mortality rates, duration of intubation, or ICU or hospital length of stay [22].

A medical device to retrieve secretions from the lumen of the endotracheal tube is the *Mucus Shaver* that is a concentric inflatable catheter for the removal of mucus and secretions from the interior surface of the endotracheal tube.

In fact, standard *suctioning catheters* cannot remove the secretions on the walls of the endotracheal tube that is the first step for the endoluminal biofilm formation.

The Mucus Shaver is advanced to the distal endotracheal tube tip, inflated, and subsequently withdrawn over a period of 3–5 s to remove the biofilm. Initially, it has been tested in mechanically ventilated sheep [23], and recently it has been studied in a randomized controlled clinical trial. At the extubation, only 8 % of the ETT from the Mucus Shaver Group was internally colonized by pathogens versus 83 % in the control group [24].

### 5.6.4 Tracheostomy

The effect of replacing the endotracheal tube with a *tracheostomy* on the incidence of VAP has been analyzed in several studies. In a meta-analysis of Griffith and colleagues [29], data from 5 randomized controlled trials with a total of 382 enrolled patients showed that early tracheostomy (<7 days) did not reduce the risk of VAP or mortality despite beneficial effects in terms of reduction of mechanical ventilation and hospital and ICU length of stay [25]. Furthermore, in a more recent study, early tracheostomy (<4 days) did not provide any effect on VAP incidence, duration of mechanical ventilation, hospital stay, or mortality [26].

## 5.7 Preventive Measures Related to Management of the Mechanically Ventilated Patient

### 5.7.1 Decontamination of the Oropharyngeal Tract

After a prolonged intubation, a tracheal colonization by the same bacteria often resident in the *oral cavity* has been demonstrated, and the gastric enzyme, pepsin, may be detected in *trachea-bronchial aspirates*.

Bacterial load presented in the teeth, gums, tongue, and oral mucosa is different between healthy patients and patients treated with antibiotic therapy or immunocompromised. In patients affected by VAP, the same bacteria are often present in the distal airways, stomach, and oropharynx [27].

This suggests that the draining of saliva or gastric contents, below endotracheal tube cuff, determines the colonization of the tracheal mucosa, causing pneumonia.

The use of acid-suppressive medications that increase the gastric pH promotes the bacterial growth in the stomach, increasing the risk of tracheal colonization in case of aspiration of gastric contents. A study enrolling 60,000 patients showed an increased risk of nosocomial pneumonia when acid-suppressive medications are administrated [9].

Despite of this, we cannot provide definitive recommendations on the use of antiacids in relation to VAP in the ICU setting. Furthermore, the bundle for VAP prevention published by the Institute for Healthcare Improvement still suggests *stress ulcer prophylaxis* [9, 28].

Given the etiology of VAP, a selective digestive tract decontamination (SDD) with antiseptics has been proposed.

A recent meta-analysis has assessed the effect of oral decontamination with 2 % chlorhexidine or povidone-iodine on the prevalence of ventilator-associated pneumonia versus oral care without these antiseptics in adults [29]. Twelve studies were included, enrolling 2,341 patients. The use of chlorhexidine was associated with a significant reduction in the risk of VAP. Cardiosurgical patients benefited from topical antiseptic use. However, no benefits were found in terms of mortality, ICU length of stay, or duration of mechanical ventilation [9].

Currently, the selective decontamination of the oral cavity with *chlorhexidine* is a preventive measure suggested by the bundle for VAP prevention published by the IHI despite the paucity of evidence to support beneficial effects in most patients [9].

### 5.7.2 Decontamination of Digestive Tract

*Selective digestive decontamination* (*SDD*) has the purpose to eradicate potentially pathogenic microorganisms from the oropharyngeal and gastrointestinal tract, by the administration of nonabsorbable antibiotics against Gram-negative bacilli and various species of *Candida*. Nowadays, the selective digestive decontamination is still a subject of great debate because it can impact on the microflora of the gastrointestinal tract, resulting in the development of *antibiotic resistance*.

After more than 50 randomized clinical trials and 10 meta-analyses, the findings of two meta-analyses, which included studies with different pharmacological SDD strategies, showed that SDD reduced the incidence of VAP and the mortality of 65 % and 15–20 %, respectively [30, 31].

The most recent multicenter trial enrolling 5,939 patients from 13 ICUs randomized patients into three groups: a control group receiving standard therapy; a group undergoing oral selective decontamination (SOD) consisting in 4-day topical antibiotic therapy of tobramycin, colistin, and amphotericin B acting at oropharynx and stomach level; and a group undergoing complete digestive decontamination (SDD) consisting in the same topical antibiotic therapy described above together with the parenteral administration of cefotaxime for 4 days [32].

A significant reduction in mortality was found in both complete digestive decontamination and oropharyngeal decontamination groups with a higher decrease in the digestive decontamination group. However, a relevant limit of the digestive decontamination is the development of antibiotic resistance and the increased risk of nosocomial infections after ICU discharge, as demonstrated by the studies published by De Smet et al. [33].

### 5.7.3 Enteral Feeding

*Enteral feeding* is based on the physiological functions of digestion and absorption. Its beneficial effects in critically ill patients include better substrate utilization, prevention of mucosal atrophy, preservation of gut flora and integrity, and the maintenance of local immune competence [34].

The maintenance of the intestinal integrity thanks to the enteral nutrition can improve the immune response implementing the secretion of immunoglobulin type A. In fact, the gut is the biggest *immunological organ* and produces 80 % of the immunoglobulins of the organism.

Because of these beneficial effects, enteral feeding should be preferred to parenteral nutrition in critically ill patients. It has been demonstrated that the early administration of enteral nutrition, within 36–48 h of mechanical ventilation, can reduce the incidence of infectious complications and the hospital length of stay [35]. Despite the potential benefits of the early enteral feeding, it has been suggested that the use of a *nasogastric tube* may predispose the aspiration of gastric contents and thus the development of VAP. However, the placement of a postpyloric nasogastric tube seems to reduce the risk of aspiration and VAP. Recent studies have shown reduced incidence of VAP and mortality in patients who were fed using a postpyloric tube, but without any statistical significance [36, 37].

The optimal timing of enteral nutrition is controversial. A large multicenter retrospective analysis, published in 2006, reported an increased risk of VAP developing, but also a reduction in ICU and hospital mortality in patients who received early enteral nutrition within 48 h of mechanical ventilation [34].

More recently, a clinical trial did not find any difference in the incidence of VAP in patients receiving enteral versus parenteral nutrition [38].

### 5.7.4 Probiotics

*Probiotics*, according to the definition of the World Health Organization, are "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host." The preparations commercially available consist in live nonpathogenic microorganisms that represent an option to preserve *orointestinal flora* homeostasis [3].

The potential benefit of probiotics in the VAP prevention could be related to a mechanism of competition with the pathogenic microorganisms in the oropharynx and stomach. Probiotics have also immunomodulatory properties.

Recently, Morrow et al. reported the results of a single-center, double-blind study, enrolling 146 mechanically ventilated patients, randomized to receive standard care or enteral probiotics twice a day (*Lactobacillus rhamnosus*). VAP incidence was significantly decreased in patients treated with prophylactic probiotic therapy [39]. Moreover, a decreased incidence of *Clostridium difficile* infections was found.

Although no adverse effects were reported in this trial, further studies on the probiotics safety are required before their widespread use [3].

In fact, patients with severe pancreatitis who received probiotics showed a higher mortality than patients who received standard care, although primarily associated with an increased incidence of intestinal ischemia and therefore probably unrelated to the use of probiotics [40].

### 5.7.5 Patient Position

Different clinical studies using solutions of radiolabeled enteral nutrition have shown that supine intubated patients have a higher risk of aspiration of gastric contents compared to intubated patients in *semirecumbent position* [41, 42]. The semirecumbent patient position is recommended by the VAP bundle approach [11].

However, only two clinical studies have evaluated the role of patient positioning in the onset of VAP. The randomized controlled trial conducted by Drakulovic et al., enrolling 86 patients, showed that the VAP incidence, microbiologically confirmed, was significantly lower in patients in "semirecumbent position" compared to supine patients. This trial was stopped after the planned interim analysis [43].

Supine position and enteral nutrition were considered *independent risk factors* for nosocomial pneumonia.

Potential limitations of this study are that the position of patient in the treatment group was controlled once a day and that patients in the control group were kept completely supine that is not a common practice in the majority of intensive care units.

In the other prospective multicentered trial, critically ill patients undergoing mechanical ventilation were randomly assigned to the semirecumbent position, with a target backrest elevation of 45° or standard care with a *backrest elevation* of 10°. No difference was found in terms of VAP diagnosis although the target semirecumbent position of 45° was not achieved for 85 % of the study time and the mean of backrest elevation in the treatment group was 30° [44].

The findings of these studies suggest that the supine patient position should be avoided, in particular when patients are receiving enteral nutrition, that the semirecumbent position to 45° could be not easy to maintain because the risk of hemodynamic instability and of thromboembolic events, and finally that a position with a backrest elevation between 10° and 30° might be sufficient to reduce the incidence of VAP.

Recently, a new approach on the patient positioning for VAP prevention is developing. Some animal studies suggest that causative VAP pathogens reach the lower

airways primarily driven by gravity; thus, a position opposite to the recommended semirecumbent, that is, lateral with a slight *Trendelenburg*, theoretically could have additional advantages, avoiding pulmonary aspiration of pathogen-laden oropharyngeal secretions and preventing VAP.

Two experimental studies in sheep showed that this new position is safe and can lead to an outward flow of secretions and reduced bacterial colonization of the respiratory tract [45, 46].

In the study conducted by Libassi et al., sheep ventilated for 72 h with a tracheal orientation below the horizontal line did not develop respiratory infections, while the sheep ventilated with the trachea inclined at 40° above the horizontal line developed VAP in 75 % of cases [45].

In the first human clinical trial, 60 infants were randomized to receive mechanical ventilation in the supine position or *lateral position* (with the trachea below the horizontal). After 5 days of mechanical ventilation, tracheal cultures were positive in 26 of 30 children of the supine group and in 9 of 30 in the lateral position group [47].

Subsequently, the lateral horizontal position was demonstrated safe and not correlated with an increased risk of the aspiration of gastric contents [48]. Currently, we are waiting for the results of an ongoing large multicenter trial to assess whether the anti-Trendelenburg position can prevent VAP in adults [49].

### 5.7.6 Kinetic Therapy

In healthy subjects, the mucociliary clearance is one of the most important dynamic mechanisms for the prevention of bacterial colonization of the respiratory tract.

The immobility of the intubated patients may impair mucociliary clearance. The kinetic therapy based on the mechanical rotation of patients with 40° turns may improve respiratory function, facilitating the drainage of secretions and avoiding the accumulation of mucus in the dependent lung zones. Unfortunately, many critically ill patients develop complications that can be associated with the *kinetic therapy*, including intolerance to rotation on each side, arrhythmias, unplanned extubation, and loss of vascular access [28].

The level of *sedation* of mechanically ventilated patients represents a challenge in the clinical management of these critically ill patients.

Continuous and deep sedation, which is often administered in the acute phase of an illness, can delay the physiokinesitherapy resulting in muscle atrophy and delayed weaning from mechanical ventilation.

Daily interruption of sedation allows a daily monitoring of neurological status and the application of weaning protocols favoring the reduction of the duration of mechanical ventilation.

Because the duration of mechanical ventilation directly affects the likelihood of VAP, minimizing the duration of mechanical ventilation is considered a VAP preventive strategy [9].

**Conclusions**

In conclusion, many factors contribute to the development of VAP. Many strategies have been proposed for the prevention of this disease that is associated with significant morbidity in critically ill patients.

However, unfortunately, only few preventive strategies have been demonstrated to be effective, while many others should be evaluated in large randomized trials before becoming part of clinical recommendations.

Among the latter there are both preventive strategies related to the management of the artificial airway, including subglottic secretion drainage systems, antimicrobial-coated endotracheal tubes, continuous maintenance of proper cuff inflating pressure, and endotracheal tube biofilm removal, and preventive strategies related to the management of the ventilated patient including patient positioning in the anti-Trendelenburg lateral horizontal position, kinetic therapy, and administration of probiotics [28]. Although some preventive strategies need to be validated in the context of clinical trials, implementation of preventive measures grouped into bundles can represent the way forward to reduce the rates of VAP.

## References

1. Bouadma L, Wolff M, Lucet JC (2012) Ventilator-associated pneumonia and its prevention. Curr Opin Infect Dis 25:395–404
2. Coppadoro A, Bittner E, Berra L (2012) Novel preventive strategies for ventilator-associated pneumonia. Crit Care 16:210
3. Ramirez P, Bassi GL, Torres A (2012) Measures to prevent nosocomial infections during mechanical ventilation. Curr Opin Crit Care 18:86–92
4. Melsen WG, Rovers MM, Koeman M, Bonten MJ (2011) Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. Crit Care Med 39:2736–2742
5. Arroliga AC, Pollard CL, Wilde CD, Pellizzari SJ, Chebbo A, Song J et al (2012) Reduction in the incidence of ventilator-associated pneumonia: a multidisciplinary approach. Respir Care 57:688–696
6. Flanagan JL, Brodie EL, Weng L, Lynch SV, Garcia O, Brown R et al (2007) Loss of bacterial diversity during antibiotic treatment of intubated patients colonized with Pseudomonas aeruginosa. J Clin Microbiol 45:1954–1962
7. Bahrani-Mougeot FK, Paster BJ, Coleman S, Barbuto S, Brennan MT, Noll J et al (2007) Molecular analysis of oral and respiratory bacterial species associated with ventilator-associated pneumonia. J Clin Microbiol 45:1588–1593
8. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903
9. O'Grady NP, Murray PR, Ames N (2012) Preventing ventilator-associated pneumonia: does the evidence support the practice? JAMA 307:2534–2539
10. Cook DJ, Kollef MH (1998) Risk factors for ICU-acquired pneumonia. JAMA 279:1605–1606
11. Implement the IHI ventilator bundle (2012) Institute for Healthcare Improvement. http://www.ihiorg/knowledge/Pages/changes/ImplementtheVentilatorBundleaspx
12. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L et al (2004) Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med 141:305–313

13. Pinciroli R, Mietto C, Berra L (2013) Respiratory therapy device modifications to prevent ventilator-associated pneumonia. Curr Opin Infect Dis 26(2):175–183
14. Nseir S (2012) Efficiency of continuous control of tracheal cuff pressure: electronic versus pneumatic devices. Am J Respir Crit Care Med 185:1247–1248
15. Valencia M, Ferrer M, Farre R, Navajas D, Badia JR, Nicolas JM et al (2007) Automatic control of tracheal tube cuff pressure in ventilated patients in semirecumbent position: a randomized trial. Crit Care Med 35:1543–1549
16. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK (2011) Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. Crit Care Med 39:1985–1991
17. Inglis TJ, Millar MR, Jones JG, Robinson DA (1989) Tracheal tube biofilm as a source of bacterial colonization of the lung. J Clin Microbiol 27:2014–2018
18. Bousbia S, Papazian L, Saux P, Forel JM, Auffray JP, Martin C et al (2012) Repertoire of intensive care unit pneumonia microbiota. PLoS One 7, e32486
19. Cairns S, Thomas JG, Hooper SJ, Wise MP, Frost PJ, Wilson MJ et al (2011) Molecular analysis of microbial communities in endotracheal tube biofilms. PLoS One 6, e14759
20. Adair CG, Gorman SP, Feron BM, Byers LM, Jones DS, Goldsmith CE et al (1999) Implications of endotracheal tube biofilm for ventilator-associated pneumonia. Intensive Care Med 25: 1072–1076
21. Raad II, Mohamed JA, Reitzel RA, Jiang Y, Dvorak TL, Ghannoum MA et al (2011) The prevention of biofilm colonization by multidrug-resistant pathogens that cause ventilator-associated pneumonia with antimicrobial-coated endotracheal tubes. Biomaterials 32: 2689–2694
22. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD et al (2008) Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. JAMA 300:805–813
23. Kolobow T, Berra L, Li BG, Curto F (2005) Novel system for complete removal of secretions within the endotracheal tube: the Mucus Shaver. Anesthesiology 102:1063–1065
24. Berra L, Coppadoro A, Bittner EA, Kolobow T, Laquerriere P, Pohlmann JR et al (2012) A clinical assessment of the Mucus Shaver: a device to keep the endotracheal tube free from secretions. Crit Care Med 40:119–124
25. Griffiths J, Barber VS, Morgan L, Young JD (2005) Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. BMJ 330:1243
26. Blot F, Similowski T, Trouillet JL, Chardon P, Korach JM, Costa MA et al (2008) Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. Intensive Care Med 34:1779–1787
27. Torres A, el Ebiary M, Gonzalez J, Ferrer M, Puig dB, Gene A et al (1993) Gastric and pharyngeal flora in nosocomial pneumonia acquired during mechanical ventilation. Am Rev Respir Dis 148:352–357
28. Coppadoro A, Bittner E, Berra L (2012) Novel preventive strategies for ventilator-associated pneumonia. In: Annual update in intensive care and emergency medicine 2012. (ed.): Vincent, Jean-Louis, Springer, pp 289–298
29. Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI (2011) Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. Lancet Infect Dis 11:845–854
30. Liberati A, D'Amico R, Pifferi S, Leonetti C, Torri V, Brazzi L et al (2000) Antibiotics for preventing respiratory tract infections in adults receiving intensive care. Cochrane Database Syst Rev 4, CD000022
31. Liberati A, D'Amico R, Pifferi S, Leonetti C, Torri V, Brazzi L et al (2000) Antibiotics for preventing respiratory tract infections in adults receiving intensive care. Cochrane Database Syst Rev 2, CD000022
32. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS et al (2009) Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 360:20–31

33. de Smet AM, Hopmans TE, Minderhoud AL, Blok HE, Gossink-Franssen A, Bernards AT et al (2009) Decontamination of the digestive tract and oropharynx: hospital acquired infections after discharge from the intensive care unit. Intensive Care Med 35:1609–1613
34. Artinian V, Krayem H, DiGiovine B (2006) Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 129:960–967
35. Hise ME (2005) Enteral nutrition in the intensive care unit: an evaluation of timing, quantity, and outcomes. Support Line 27:8–16
36. Marik PE, Zaloga GP (2003) Gastric versus post-pyloric feeding: a systematic review. Crit Care 7:R46–R51
37. White H, Sosnowski K, Tran K, Reeves A, Jones M (2009) A randomised controlled comparison of early post-pyloric versus early gastric feeding to meet nutritional targets in ventilated intensive care patients. Crit Care 13:R187
38. Altintas ND, Aydin K, Turkoglu MA, Abbasoglu O, Topeli A (2011) Effect of enteral versus parenteral nutrition on outcome of medical patients requiring mechanical ventilation. Nutr Clin Pract 26:322–329
39. Morrow LE, Kollef MH, Casale TB (2010) Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med 182: 1058–1064
40. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM et al (2008) Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 371:651–659
41. Orozco-Levi M, Torres A, Ferrer M, Piera C, el Ebiary M, de la Bellacasa JP et al (1995) Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med 152:| 1387–1390
42. Torres A, Serra-Batlles J, Ros E, Piera C, Puig dB, Cobos A et al (1992) Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med 116:540–543
43. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M (1999) Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 354:1851–1858
44. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, Joore HC, van Schijndel RJ, van der Tweel I et al (2006) Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. Crit Care Med 34:396–402
45. Li BG, Zanella A, Cressoni M, Stylianou M, Kolobow T (2008) Following tracheal intubation, mucus flow is reversed in the semirecumbent position: possible role in the pathogenesis of ventilator-associated pneumonia. Crit Care Med 36:518–525
46. Panigada M (2003) Bacterial colonization of the respiratory tract under artificial ventilation: trachea and tracheal tube orientation. Crit Care Med 31:2715
47. Aly H, Badawy M, El Kholy A, Nabil R, Mohamed A (2008) Randomized, controlled trial on tracheal colonization of ventilated infants: can gravity prevent ventilator-associated pneumonia? Pediatrics 122:770–774
48. Mauri T, Berra L, Kumwilaisak K, Pivi S, Ufberg JW, Kueppers F et al (2010) Lateral-horizontal patient position and horizontal orientation of the endotracheal tube to prevent aspiration in adult surgical intensive care unit patients: a feasibility study. Respir Care 55: 294–302
49. Berra L, Sampson J, Fumagalli J, Panigada M, Kolobow T (2011) Alternative approaches to ventilator-associated pneumonia prevention. Minerva Anestesiol 77:323–333

# 6 Hemodynamic Optimization in the Perioperative Period: General Guidelines and a Comparison of Personalized Strategies

Biagio Allaria

In order to address the issue of perioperative fluid management in an informed manner, it is important to remember the proportion of body water since this information is vital if action is required to maintain the balance in various regions of the body.

Total body water (TBW) in adults is approximately 60 % of body weight. Water is held by all tissues but is particularly abundant in muscles and relatively scarce in body fat. A young adult with healthy muscles therefore has a higher TBW than an elderly overweight person with small muscles and a large amount of fat.

This distinction has important practical consequences: for example, medicines with a high distribution level that dissolve in body water will have higher dose-dependent plasma levels in overweight patients compared to young adults.

But this knowledge is also useful in assessing the need for infusions to maintain a circulating mass volume within the limits of normal.

Since water is distributed in two large areas, the intracellular compartment (60–65 % of TBW) and the extracellular compartment (35–40 % of TBW), and, in turn, the extracellular area is divided into interstitial (25–30 %) and intravascular (10 %) regions, it is clear that in a man weighing 70 kg with TBW of 42 l, intravascular water is only 4,200 ml, while interstitial water is much greater, at about 12–14 l. Interstitial water is in close contact with intravascular fluids by means of continual exchange.

When a patient loses a circulating mass (which is made up of about 55 % water), there is a rapid rebalance of the liquid component thanks to the interstitium which

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Prof. Biagio Allaria, former Director of the Critical Patient Department of the National Institute for the Study and Treatment of Tumors, Milan. Currently consultant in Clinical Risk Management at the same Institute.

B. Allaria
Critical Patient Department,
National Institute for the Study and Treatment of Tumors, Milan, Italy
e-mail: info@int-service.it



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has a water content that is three times that of the circulation. This therefore reflects a loss of blood content for which there is no hemodynamic alert and which is due exclusively to a reduction in hematocrit. But this miniscule observation is of great significance in the operating room: the patient has lost a blood mass which is replaced by a similar quantity of plasma from the interstitia.

This is, however, a form of compensation that cannot continue in the long term in the event of persistent blood loss.

Until such compensation is sufficient, arterial pressure, heart rate, CVP, and cardiac output are normal, possible fluid challenge is negative, and dynamic monitoring parameters such as SPV, PPV, and SVV are within the limits of normal. The patient has no need of a circulating mass since this has remained normal due to fluids from the interstitia.

In addition to this compensation mechanism, there is the switching of the blood mass from "less noble" compartments such as the splanchnic compartment to those that would be more affected by a decrease in flow, like the heart, brain, and lungs. Again this is a compensation mechanism that, as with the previous one, is not without limits.

Water recovered from the interstitia is also rapidly replaced from the absorption of $H_2O$ and Na which is activated in the kidneys.

If the blood loss continues, however, venous return (VR) can be maintained as normal thanks to a fall in CVP. In fact, venous return is calculated using the formula

$$VR = MCFP - CVP$$

where MCFP is the mean circulatory filling pressure.

By observing the formula, we can see clearly that if MCFP decreases due to blood loss, venous return remains normal as CVP also falls.

A reduction in CVP is therefore a warning sign, even if arterial pressure and heart rate remain normal. If blood loss continues and therefore the circulating mass, the venous return is reduced and along with it the stroke volume, but cardiac output remains normal thanks to an increase in heart rate. We therefore have three signs of a loss of circulating mass: decreased Htc, decreased CVP, and increased heart rate.

These are wonderful multiple compensation mechanisms that make it possible to overcome any oversight by the anesthetist for a certain amount of time, although he/she must also learn to recognize them early: reduced Htc, reduced daily diuresis (due to tubular reabsorption of $H_2O$ and Na), reduced CVP, and increased heart rate are all signs of a hypovolemic process that is compensated for but at risk of leading to hemodynamic deterioration which is not desirable.

If not equipped, cardiac output decreases along with pulse and $EtCO_2$ (which are closely linked to output).

However, unless this is a substantial acute hemorrhage, this point is not reached quickly. In fact, the body can rely not only on interstitial fluids but also intracellular fluids (which make up the majority of TBW), which amount to 24 l in patients weighing 70 kg. The passage of water from cells to the interstitium when needed is immediate and follows osmotic logic.

The extracellular compartments (interstitium and circulation) have osmotic forces that are in balance with the intracellular compartment, which is made up of concentrations of cations and anions that ensure electroneutrality in various sectors. The most important cation in the extracellular compartment is $Na^+$ followed by cations with less importance such as $K^+$, $Mg^+$, and $Ca^{++}$. Electroneutrality is guaranteed by the presence of anions $Cl^-$ and $HCO_3^-$ and proteins (especially albumin).

In the intracellular compartment, the most important cation is $K^+$, and the anion $PO_4^-$ ensures electroneutrality. Osmolarity is determined by the number of particles dissolved in a solution and is therefore fundamentally determined by $Na^+$ in the plasma and interstitium and $K^+$ in the cells.

These concepts, as far as expected, are very important since they regulate the distribution of water in the body. This can pass freely and rapidly from compartments with low osmolarity to others with greater osmolarity by maintaining identical osmolarity in various compartments.

Why is the intracellular water content much higher than the extracellular content?

This is simply because there is a K salt content in cells that is greater than the Na salt content in extracellular compartments. A change in osmolarity in one area triggers an immediate movement of water to restabilize the balance. This game of water movement applies to the balance between intracellular and extracellular interstitial spaces since the cell membrane is not permeable for ions, and therefore water movement is considerably linked to osmotic forces. In the relationship between capillaries and the interstitium, the mechanism is different since the capillary endothelium is permeable to ions which are therefore no longer part of the osmotic force that can lead to the movement of water. The passage of water is regulated by Starling's law, and the forces at play are mainly the hydrostatic pressure and oncotic pressure of the capillary and interstitium.

Therefore, when a patient experiences rapid blood loss, the lost volume is quickly replaced by fluids from the interstitium. This results in the maintenance of the hemodynamic balance, and the phenomenon is revealed only due to a reduction in Htc, which is nevertheless moderate since autotransfusion of whole blood from the splanchnic reservoir also occurs at the same time.

The tolerance of fluid overloading is just as amazing as the negative effect of blood loss is marvelously "muted." When there is an inappropriate overloading of crystalloids, a kidney response suddenly enters into play, and when the possibility of a diuretic renal response is overcome, the increased hydrostatic pressure in the capillary along with a reduction in oncotic pressure due to dilution thereof pushes excess fluid into the interstitial space, thus maintaining a normal hemodynamic pattern.

These compensation mechanisms (and we have only described some of them) are initially capable of covering up our carelessness.

We have described only some of the forms of compensation activated by the body in the event of volemic imbalance.

In reality we have described those that can most easily be discovered (decreased Htc, decreased CVP, decreased diuresis, increased heart rate). But there are other

more complex mechanisms that require greater acuity and control to demonstrate. I am referring to the renin-angiotensin-aldosterone system (RAAS) and the action of ADH.

At this point it is essential to refer to effective circulating volume (ECV): this is the volume of blood distributed in the arterial system intended for perfusion of the tissues. It is not a measurable parameter and is regulated by baroreceptors in three areas:

1. The carotid sinuses that regulate sympathetic activity and, to a lesser extent, the release of ADH. One of the main functions of this apparatus is the maintenance of cerebral perfusion.
2. The juxtaglomerular apparatus that regulates the activity of the RAAS and therefore glomerular perfusion and glomerular filtration.
3. The atria and ventricles that release natriuretic peptides in response to increases in pressure.

If cardiac output decreases, the regulation systems enter into play to restore it. For example, in a patient with cardiac insufficiency, upon reduction of output the carotid sensors stimulate sympathetic activity, and those of the juxtaglomerular apparatus activate the RAAS. These responses promote an increase in heart rate and sodium retention and therefore an increase in circulating blood volume that causes greater distension of the cardiac chambers and, according to Starling's law, an increase in cardiac output, which is also promoted by the increased heart rate.

The response of these regulation systems is therefore initially favorable, but, if cardiac insufficiency and the Na-sparing mechanism continue, the blood volume increases later on even if the heart is no longer able to empty the venous return: this leads to blocked circulation, edemas, dyspnea, and pulmonary edemas.

In the case of advanced-phase cardiac sufficiency, the blood volume increases, while the ECV decreases.

It is confirmation of the fact that volemia and ECV are two values that are not necessarily correlated.

We have highlighted the concept of ECV and described the example of chronic cardiac insufficiency to draw attention to the fact that volemic overloading may coexist even if ECV is reduced.

The aim of this article is to attract the attention of anesthetists to apparently normal situations which in reality are the result of compensation mechanisms, but providing advice for better diagnosis and management.

## 6.1 Fluid Dynamics in the Capillary

### 6.1.1 The Importance of the Glycocalyx

The mechanism that regulates fluid movement in the capillaries was described by Starling in 1896 and is still largely applicable. Fluids are maintained within the capillaries thanks to oncotic pressure from plasma components. Oncotic pressure

counters hydrostatic pressure which pushes fluids into the capillaries and therefore the interstitium. In the interstitium both hydrostatic and oncotic pressure are lower than in the endocapillary plasma. The net result is a constant moderate passage of fluids from capillaries to the interstitium where any excess fluid is immediately removed from the lymph nodes and rechanneled towards the heart. The endothelial barrier is permeable for water and small molecules such as sodium, potassium, chlorine, and glucose, which pass freely via specialized pathways.

The macromolecules can be transported via larger pores or vesicles. The movement of fluid across the capillaries can be distinguished as two types: Type 1 (physiological) occurs continuously and, as mentioned above, is removed from the lymph nodes and Type 2 (pathological) is seen when the barrier is damaged or does not function properly: this results in the formation of edemas.

If it is true that the physiological basis that regulations of fluid movement across the capillaries are still the old Starling's law, we must, however, include much more recent information that currently provides us with particularly useful data on the perioperative management of fluids.

The new information essentially relates to demonstrating the presence of the glycocalyx system at the endothelial level.

The endothelium is made up of a wafer-thin barrier formed of a single layer of cells (endothelial cells). In the part facing the lumen, the endothelium is covered by a thin, fragile membrane, the glycocalyx, which is the first barrier regulating the transport of macromolecules and cells.

This barrier, which is made up of glycoproteins and proteoglycans and contains glycosaminoglycans, traps red blood cells and protein-rich plasma. We must therefore today consider the intravascular fluid volume as having two distinct parts: that which is noncirculating and is trapped in the glycocalyx system and that which is circulating.

The endothelial wall is therefore made up of endothelial cells and the glycocalyx and is 0.4–1.2 μm in thickness; it is in continuous dynamic balance with the circulating plasma.

To function normally, this barrier requires a normal level of albumin. In hypoalbuminemic states, which are very common in our patients, the barrier does not work properly, and, even with a reduction in oncotic pressure, large quantities of fluid pass from the capillary to the interstitium, and when the lymph nodes are no longer able to empty them, edemas occur.

When we administer iso-oncotic colloids to our patients, we increase capillary hydrostatic pressure, but oncotic pressure remains constant: this situation encourages a more moderate passage of fluids towards the interstitium. When, however, we administer crystalloids, hydrostatic pressure increases, as in the case of colloids, but oncotic pressure falls: this leads to the passage of more fluids from the capillary to the interstitium.

The endothelium and the glycocalyx systems are not only a barrier between intravascular liquids and the interstitium, but play an important role in hemostasis, platelet aggregation, leukocyte adhesion, and permeability of the barrier. In perioperative phases, therefore, it is mandatory to protect the barrier from events that may damage it.

Negative factors are processes of ischemia/reperfusion, hypoxemia/reoxygenation, proinflammatory cytokine, and BNP. In particular we must draw readers' attention to BNP since it is of great significance in anesthesiological practice.

In the case of fluid overloading, whether iatrogenic (excessive administration) or resulting from pathological states (chronic cardiac insufficiency), distention of the cardiac chambers leads to increased BNP release, which has a harmful effect on the glycocalyx system [1].

Fluid overloading therefore does not only increase the hydrostatic pressure of the capillary but damages the barrier, transforming Type 1 transcapillary fluid movement into Type 2 movement and thus promoting the formation of edemas.

There are few protective factors of the endothelial/glycocalyx complex, but one of these is a widely used anesthetic, sevoflurane, which enables better tolerance of possible fluid overloading [2]. The other two protective factors are hydrocortisone and antithrombin [3].

### 6.1.2 The Distribution of Crystalloids and Colloids

The use of a glycosylated solution to expand the circulating volume is destined to be unsuccessful. In fact, glucose is rapidly metabolized by the liver, and therefore administering a glycosylated solution is equal to administering free water.

Water passes through all barriers freely and rapidly, and therefore 1,000 ml of an infused glycosylated solution on 7 % (the equivalent of 70 ml) remains in the circulation, adding to the other 4 l of intravascular water. The remaining water is distributed by balancing itself with other compartments where water totals 24 l and/or is eliminated via diuresis.

The use of 1,000 ml of a 0.9 % saline solution remains confined in the extracellular space (interstitium + circulation) since sodium cannot enter the larger intracellular space. Therefore a greater proportion of the solution compared to the glycosylated solution remains in the bloodstream (approx. 20 % or 200 ml out of 1,000 ml, compared with 7 % or 70 ml out of 1,000 ml for the glycosylated solution).

Colloids – hydroxyethylamides, gelatin, or albumin solutions – remain longer in the bloodstream compared with crystalloids since the dimensions of their molecules do not facilitate transcapillary movement.

This passage nevertheless occurs. It has been shown that a colloid administered in normal volemic situations, whether 6 % hydroxyethylamide or a 5 % albumin solution, enters into the interstitia in a few minutes at a rate of 68 %. If, however, these plasma expanders are administered to a hypovolemic patient, leading to normovolemic hemodilution, the amount of fluid remaining in the circulation in this period is roughly 90 % [4].

This observation is important for clinical practice. If we administer a plasma expander to a patient who needs it, and who is hypovolemic, we have greater persistence in the circulation and less passage into the interstitia. If, however, we administer it to a patient who does not require it, it rapidly enters the interstitia: this mechanism protects the circulation from an excessive rise in hydrostatic pressure but also has negative consequences that trigger pruritus and edema.

Recently a comparison has been made between 0.9 % saline, gelatin, and 6 % hydroxyethylamide in healthy young subjects. After 1 h of infusions, 68 %, 21 %, and 16 % of infused liquids, respectively, left the circulation [5].

The difference between the two colloids used was therefore moderate, but their molecular weight varied greatly: 30 KDa for gelatin and 130 KDa for hydroxyethylamide.

In the same study the response of the RAAS was assessed for the three infusions: all reduced it by depriving the response of renin and aldosterone and by promoting the elimination of $H_2O$ and Na. This observation confirms that it had already been demonstrated in the past that the elimination of $H_2O$ and Na in acute hypervolemia depends essentially on suppression of the RAAS. Even BNP increases iatrogenic hypervolemia, but its diuretic effect in this situation is weaker. As mentioned above, however, the harmful effect of BNP on the glycocalyx is very important.

It is usually thought that the amount of crystalloids to be infused in the case of acute hypovolemia is three to four times that of colloids, which are, however, equal in terms of estimated blood loss.

A systematic review of the issue seems to result in the recommendation of a 2:1 ratio [6].

What is certain is that the administration of colloids enables greater linear recovery of cardiac filling and therefore CO in all patients, whether or not they have sepsis, for saline solutions.

We must not, however, ignore the study recently published in the New England Journal of Medicine which examines the use of hydroxyethylamide in septic patients in whom the use of this drug compared with saline solutions would be greatly burdened by adverse events and mortality [7].

In cases of multiple trauma, however, the use of hydroxyethylamide seems to enable faster clearance of lactate and a lower incidence of renal damage compared with the use of saline solutions [8].

In concluding this short section, it appears possible to say that, in the presence of a perioperative hypovolemic state, it would be preferable to use colloids rather than crystalloids, which would be used exclusively to rebalance the physiological losses (perspiration and diuresis), which are abundantly and rapidly compensated for by fluid movements from extravascular compartments, whether intracellular or extracellular.

## 6.2 Perioperative Management of Fluids: Comparison of Liberal, Restrictive, and Goal-Directed Strategies

The goal of maintaining good organ perfusion is still too often pursued in operating rooms with high levels of crystalloid administration. This approach is supported by the conviction that surgery patients who have fasted for at least 12 h are often prepared for intestinal surgery with enema and have lost fluids through perspiration and diuresis or as a result of hypovolemia. The belief that during surgery an irrelevant quantity of body fluids escapes towards a “third space,” which has never been determined, is just as widespread.

This so-called third space has been discussed since the 1960s [9] when research with techniques based on the use of a tracer in patients undergoing major abdominal surgery demonstrated that in these patients a loss of water from the extracellular compartment is confirmed even without blood loss.

It is believed that an amount of fluid is discharged into a compartment that is then called a "third space" and that it is identified in the gastrointestinal apparatus and tissues that have been damaged during surgery. Based on this assumption, which is fantastical and minimally supported by research, the liberal use of crystalloids has become the standard, not only to compensate for diuresis and perspiration, but also for the amount of fluids discharged into the "third space" and reduced from the intravascular amount. As a result of this perioperative fluid management strategy, a consistent increase in weight (of up to 10 kg!) in patients in the immediate postoperative period has become very common in recent years.

A systematic review of the studies in which the behavior of perioperative extracellular volume has been controlled has very recently discredited the theory of the "third space" [10], and therefore currently in the perioperative phase, it is justified to compensate with crystalloids only during diuresis and perspiration.

Perspiration, among other things, is considered less important than in the past, and forty years ago it was shown by Lamke et al. [11] that it can amount to 0.5–1 ml/kg/h during major abdominal surgery.

Therefore, during a classical intervention of this kind, such as hemicolectomy in a patient weighing 70 kg (lasting 3 h), fluid loss via perspiration fluctuates between 100 and 200 ml. If diuresis occurs during the same period at a rate of 150 ml/h, it can immediately be understood that in a patient like the one described above, replacement with 500 ml crystalloids is justified. Higher doses can lead to episodes of hypervolemia which, even if transitory, cause the release of BNP, which, as we have seen, damages the glycocalyx system leading to the transcapillary passage of fluids into the interstitia with a resulting increase in weight, as described above.

In becoming aware of this reality, there is naturally a comparison with a different perioperative fluid management strategy that has been labeled "restrictive." This strategy has been rapidly embraced in thoracic surgery, in which the advantage in terms of oxygenation and the prevention of respiratory complications is immediately clear.

In abdominal surgery, where the advantages are not particularly evident or resounding, the "restrictive" strategy of fluid therapy has not had such an immediate success.

Even in 2003 it was necessary to conduct a multicenter study, published by Brandstrup et al. in Ann. Surg. [12], to draw attention to the risks of liberal fluid management in the perioperative phase. The authors compared two groups of patients who underwent colorectal surgery: one group was treated liberally with crystalloids, receiving on average 5.4 l of fluids, and the other group, which underwent a restrictive strategy, received 2.7 l.

The postoperative complications were much more common in patients treated with high doses of crystalloids (51 % vs. 33 %), including liver infections, failure of intestinal sutures, and cardiovascular and respiratory damage.

The much-feared renal damage, however, as a result of fluid restriction, was not found. It is sufficient to notice that patients undergoing the restrictive strategy

received more colloids, as a percentage, and those with the liberal strategy more crystalloids, which confirms the comparison between the two different theories: one (the restrictive) that used crystalloids mainly to compensate for diuresis and perspiration and/or as a vehicle for drugs, and colloids to compensate for blood loss, and one that uses crystalloids much more liberally, even to treat any type of hypotension if confirmed during the perioperative phase.

It should be pointed out that hypotension during anesthesia is mostly due to vasodilation and could be treated by reducing anesthesia and/or using vasoconstrictors, which, among other things, are much more effective in such cases.

The liberal use of crystalloids, as we have seen, is also based on the old concept of underlying hypovolemia in surgery patients as a result of fasting and, in the case of intestinal surgery, of enema preparations. This concept has been discredited. In 2008 Jacob et al. published a study in Acta Anesth. Scand. which demonstrated the absolute normality of the circulating volume in surgical patients after nocturnal fasting [13].

The considerations made up to now point towards a constantly restrictive use of fluids in major surgery. In reality things are not as simple as this. Alongside a study that is favorable to this type of strategy, there are others that do not show differences in outcome between liberal and restrictive strategies.

Among other things, it is not easy to compare the various strategies used by different working groups, since a universally accepted restrictive strategy has not yet been codified.

Colorectal surgical interventions with miniscule administration of fluids (800 ml) have been reported, and others, such as the multicenter study by Brandstrup mentioned above, in which the average fluid administration was 2,700 ml.

We therefore have before us studies that demonstrate that liberal fluid administration can be harmful, but it seems we can confirm that a valid restrictive strategy for all patients cannot currently be defined with certainty.

Faced with this uncertainty it is even more beneficial to agree on a personalized perioperative fluid management strategy, the so-called goal-directed fluid therapy (GDT), in order to avoid both hypovolemia leading to organ damage due to hypoperfusion and hypervolemia with cardiac overloading, $O_2$ desaturation, and damage to the glycocalyx system.

GDT has been stressed for more than 20 years, but in order to carry it out in the 1980s, a Swan-Ganz catheter was required, and $DO_2I$ was recommended at above-normal doses (600 ml/m$^2$/min) to ensure perfusion of the organs even in critical moments.

This position was barely acceptable for patients at high risk since such invasive monitoring was not fully justified in large numbers of surgical patients.

Due to this difficulty, GDT did not acquire the consensus that it would conceptually have deserved, but the idea reemerged gradually after several years that other less invasive methods were available for cardiovascular monitoring that, above all, enabled monitoring of the stroke volume and the use of “dynamic” parameters such as SPV, PPV, and SVV.

The instruments currently available for the personalized management of fluid therapy in the perioperative phase are numerous and can be divided up into:

1. Instruments that measure stroke volume (and other parameters) by using esophageal echo Doppler or thoracic impedance graphs.

   These instruments measure stroke volume directly by assessing aortic flow in various ways. The advantage of esophageal echo Doppler lies in the widespread documentation that exists on the validity of its use intraoperatively. The disadvantage is the inability to use it in awake patients and therefore in preoperative and postoperative phases.

   Thoracic impedance graphs have the great advantage of being easy to activate even by the nursing staff by applying two self-adhesive sensors to the skin of the neck and throat.

   This monitoring technique is therefore not at all invasive and can monitor stroke volume without calibration in addition to other useful parameters in the evaluation of circulatory filling and the contractility of the left ventricle such as the preejection period (PEP), peak aortic flow, and flow acceleration. It is the only monitoring system that is not at all invasive that provides information on extravascular lung water (EVLW). The disadvantage is the low level of experience in intraoperative monitoring, while there is generally a good consensus regarding its reliability and sensitivity in measuring stroke volume in other situations
2. Instruments that monitor stroke volume and other useful parameters with invasive methods. One of these is the widely known system based on transpulmonary thermodilution (PiCCO), which requires a catheter with sensors in the superior vena cava and another in the femoral or axillary artery.

   This monitoring system, after directly measuring cardiac output with the transpulmonary thermodilution method, uses the stroke volume obtained as a calibration factor for continual monitoring of the same parameter with the pulse profile analysis method. PiCCO is also able to provide information on the contractility of the left ventricle and EVLW. Since it requires sensors in the central veins and arteries, it cannot be considered a noninvasive monitoring method but can nevertheless be used in preoperative and postoperative phases other than in intensive therapy in conscious patients.

   Another minimally invasive system is based on lithium dilution (LiDCO): after measuring cardiac output method cited above, it uses this value as calibration to carry out continuous monitoring of stroke volume by analyzing the pulse profile.

   As with PiCCO, the cost of the sensors makes this a monitoring method for selected patients. Both methods, along with the continuous assessment of stroke volume, enable the monitoring of dynamic parameters such as SPV, PPV, and SVV. LiDCO can also be used in all perioperative phases.

   The FloTrac/Vigileo system also calculates stroke volume using the pulse profile method but unlike the other systems does not require preliminary calibration, thanks to an IT program activated by inputting biometric data.

   All the monitoring systems described above are so far able to monitor the so-called dynamic parameters (SPV, PPV, SVV), except for thoracic impedance graphs, which, since they do not need an arterial catheter, cannot monitor SPV and PPV but nevertheless monitor SVV, which has a similar meaning.

All the monitoring methods described above make it possible to use GDT through an early understanding above all of hypovolemic states which have not yet given clear signals of their presence and through the observation of the correction of these states.

It should be pointed out that in young, healthy patients with all compensation mechanisms intact, up to 25 % of circulating volume can be lost before a drop in pressure and/or an increase in heart rate is observed [14]. It is true, as we have already said, that less obvious signals such as a fall in CVP, a contraction of hourly diuresis, and a fall in Htc may occur, but there is no doubt that the monitoring systems listed above are an important and easy-to-read tool in understanding these imbalances early and monitoring their correction.

Useful information on the utility or otherwise of mass administration comes from performing the so-called fluid challenge. If the patient's hemodynamic characteristics can be placed on the steep ascending part of Starling's curve, a volume bolus (e.g., 200 cc of a colloid infused in 5 min) causes an increase in stroke volume of at least 15 %. A response of this type favors the administration of fluids. If, however, the hemodynamic status is placed on the horizontal part of the curve, a mass bolus will not lead to a significant increase in stroke volume. A response of this type discourages the subsequent administration of fluids.

The information provided by the "dynamic parameters" is even more immediate: SPV, PPV, or SVV higher than 15 % is indicative of hypovolemia, and a response that tends to lead to normalization after a fluid bolus is indicative of the utility of fluid administration. The most tested hemodynamic parameter in recent years is PPV [15, 16].

The studies relating to this suggest that to implement GDT in the perioperative period using PPV, it must be between 10 and 15 % with the infusion of fluids if it exceeds 15 % for the purpose of reporting the value within the recommended range.

A recent study, however, in 413 patients under general anesthesia and artificial ventilation for various types of surgery at four different study centers [17], has demonstrated a gray zone for PPV between 9 and 13 %, in which it was not possible to predict whether a patient would be a responder or a nonresponder upon administration of fluids. The identification of the gray zone makes it possible to determine with certainty the nonresponders who do not respond favorably to fluid administration (PPV <9 %) and the responders who will almost certainly benefit from the administration of mass infusion (PPV >13 %). Average values are not very indicative in predicting the utility or otherwise of infusions. In this study the responders and nonresponders were identified with a 500 ml fluid challenge and by observing the percentage response of the cardiac index measured with Swan-Ganz catheters or otherwise with transpulmonary thermodilution or esophageal echo Doppler. Patients who responded to the fluid bolus with an increase in the CI of 15 % or more were considered responders.

A monitoring system that is not at all invasive which has recently drawn a consensus in particular for its ease of use is based on continuous control of the variability of the plethysmographic wave and Hb obtained using simple plethysmographic skin sensors.

The controlled parameters are the plethysmographic variability index (PVI) and SpHb. PVI has a similar meaning to the dynamic parameters listed above, and SpHb enables constant information on total hemoglobin and is very useful in monitoring hidden bleeding.

A very recent meta-analysis published in Anesthesia [18] looked at 10 studies in which PVI was used to monitor fluid infusions. If patients were under artificial ventilation and the fluid challenge was performed with colloids, PVI was a very useful parameter to monitor infusions. There are currently no convincing comparisons with other monitoring systems that measure dynamic parameters (SPV, PPV, SVV), but the method is promising and has the great advantage of not even requiring catheterization of a peripheral artery. The cost of the instrument that enables this type of monitoring is not particularly high. The PVI value at which it can reasonably be thought that the patient is hypovolemic and at which a fluid challenge and possible subsequent mass infusion is justified varies from author to author, but it can be considered that variability greater than 15 % is indicative of a hypovolemic state.

PVI has also been used to monitor fluid therapy in patients with spontaneous respiration: in this case, however, the cutoff point is much higher and is determined as 19 % by Keller [19]. The dedicated instrument also provides the continuous value of pulse symmetry, heart rate, and, as mentioned, total hemoglobin, and it can be thought that at least in high-risk patients, it can be substituted with simple pulse symmetry with the advantage of providing much more comprehensive data.

It can be said that this instrument, along with the recent mobile version of thoracic impedance graphs, can be considered extremely useful and not at all invasive in the management of fluids in the perioperative period.

## 6.3 The Specific Case of Fluid Therapy in Day Surgery in a Low-Risk Patient

In this type of patient, a liberal strategy of fluid administration seems much more acceptable.

In fact, in day surgery it is essential to reduce postoperative disorders such as nausea, vomiting, and postural hypotension.

These objectives are achieved with the administration of 20–30 ml/kg of crystalloids [20, 21].

In the case of laparoscopic surgery, even higher infusions (40 ml/kg) are required to achieve the results mentioned above [22].

## 6.4 How to Manage an Asymptomatic Patient with Chronic Anemia Perioperatively?

For over 40 years the hemostatic characteristics of patients with chronic anemia have been well known. Even today the description made by Duke and Abelman in Circulation in 1969 still applies [23].

Patients with chronic anemia have high cardiac output, enhanced left ventricular contractility, tachycardia, low peripheral vascular resistance, and reduced circulating volume.

Thanks to the high cardiac output and increase in tissue extraction of $O_2$, tissue oxygenation is substantially ensured even in the presence of significant anemia. Hemodynamic changes depend on the extent of anemia and become particularly relevant when Hb falls below 7 g/dl.

With this kind of hemodynamic picture, it can easily be understood that patients with chronic anemia are weak. Anesthetists, by depriving the heart of its contractile force, reduce cardiac output and thus $DO_2$ by jeopardizing tissue oxygenation. Hypotensive events are, moreover, more common and subsequently complicate oxygenation. It is therefore vital not to subsequently reduce the circulating mass in these patients and to avoid as far as possible cardiodepressant anesthetics, remembering that tachycardia is a compensation mechanism.

Precisely because tachycardia is a compensation mechanism, it is inadvisable to use beta-blockers. Furthermore, since hypovolemia is compensated for by stimulation of the RAAS, ACE inhibitors and sartanes (which are not very widespread in general anesthesia in all patients) are contraindicated.

If GDT is a useful strategy in all patients at risk, this is particularly true of those with chronic anemia, but, as currently understood, the approach to this type of patient who must undergo surgical intervention is all in the preparation.

The preparation for interventions in patients with chronic anemia rests upon two main points: diagnosis of the type of anemia and correction of it.

To accomplish these two objectives, a large amount of time is required. When the anesthetist is faced with a patient with chronic anemia, who is apparently asymptomatic and has not yet received a precise diagnosis of the cause of anemia, elective surgery must be postponed for 1–2 months. To respond to diagnostic questions, the easiest, but often the longest, way is to refer the patient to a hematologist, asking him/her to correct the anemia. However, apart from very specific situations, the most common causes of asymptomatic chronic anemia are not numerous and can easily be identified and corrected. In young women the most common cause of anemia is iron deficiency linked to menstrual discharge. More complex is sideropenic anemia in men and especially in elderly persons. In these cases, the first question to be asked is whether the patient is losing blood: hemorrhoids, gastric or colonic neoplasia, and hiatus hernia are the most common causes of iron deficiency and are corrected prior to considering planned elective surgery before it is necessary.

Let us imagine a 70-year-old male patient with moderate anemia (Hb 11 g/dl), low iron and ferritin levels, and low MCV of red blood cells, who must undergo a hip replacement. Reports show the presence of an asymptomatic colon tumor. It is clear that hemicolectomy will take precedence over the hip replacement. But, if we have underestimated the moderate anemia, how will we go about things?

In the case of anemia without obvious iron deficiency, attention should be drawn to the low levels of folic acid and $B_{12}$, especially if MCV of red blood cells is higher than 100.

MCV, which is always available, is a determining factor: values higher than 100 require control of plasma levels of $B_{12}$ and folate; MCV values below 80, on the other hand, require a focus on iron deficiency [24].

In patients with a documented deficiency in iron, it is essential to prescribe oral treatment for at least 1 month, which will be decided when Hb is <13 g/dl for women and <14 g/dl for men, along with MCV <80, ferritin <12 mg/dl, or transferrin saturation <15 % [25].

Since oral therapy is often poorly tolerated and the cause of treatment interrupted, it can be useful to remember that a better tolerated medicine is nowadays available in Italy (iron bisglycinate chelate), which therefore results in better patient compliance with the therapeutic plan.

The recommended dose of this medicine is 2 tablets per day (28 mg) for 1 month, possibly continuing with 1 tablet per day if longer periods are available.

It has been shown that at this dosage iron bisglycinate chelate has the same efficacy as ferrous sulfate, which is usually used, but with drastically higher gastric tolerability [26].

In the event of MCV >100 and plasma $B_{12}$ levels below the limits of normal (200–900 pg/ml), it will obviously be necessary to supplement this vitamin.

If MCV is normal, a control of reticulocytes and creatinine will be useful to determine possible hemolysis or a nephrological cause of anemia. In this type of situation, a consultation with a hematologist or nephrologist is important.

A few more words may be said about anemia from chronic disease that is an exclusion diagnosis and is suspected if iron and $B_{12}$ deficiency have been ruled out, if renal function is normal, if hemolysis is not suspected, and if chronic disease is present (such as COPD or rheumatoid arthritis).

In such cases the use of erythropoietin (beta epoetin and similar) is justified, since it is supported by simultaneous oral administration of iron [24].

In concluding this brief chapter on perioperative anemia, it should be specified that, following a diagnosis of anemia without identified causes in a patient who has been proposed for elective surgery, especially if the intervention might involve consistent blood loss, must consider postponing the intervention. Anemia should be seen as a significant pathological condition and not simply as a moderate change in laboratory data. Let us remember the title of the work of an expert in the field, Lawrence T. Goodenough, published 10 years ago in Arch. Int. Med.: “Anemia: not just an innocent bystander?”.

## 6.5 Perioperative Colloids: Angels or Demons?

There is no doubt that colloids, whether proteic (albumin) or nonproteic (hydroxyethylamide, gelatin, dextran), have a capacity for plasma expansion that is more effective and longer lasting for crystalloids. Since the most common determining factor for perioperative hemodynamic imbalance is hypovolemia, it should be deduced that colloids are the better adapted fluids to treat this complication. This is because, as we have said many times in this article, crystalloids should be used to

compensate for losses due to perspiration and diuresis, while blood losses and resulting hypovolemia should be treated with colloids until the transfusion of blood and blood derivatives is no longer useful. Since, however, for many years a restrictive strategy in the use of blood has been increasingly adopted (the critical limit for Hb below which is currently justified is set by most authors as 7–8 g/dl), it is clear that the place of colloids in the perioperative phase is highly important.

But which colloids? To delve further into the topic, let us return to the excellent editorial published by Niem et al. in the Journal of Anesthesia in 2010, which concluded that "… rapidly degradable hydroxyethylamides (hydroxyethylamide 130/0.4) have an excellent hemodynamic effect, and the risk of renal damage and hemostatic imbalance, as well as allergic reactions, is minimal" [27].

Older studies too demonstrate the beneficial effect on inflammatory responses [28], postoperative nausea, and vomiting [29] and more generally on the outcomes of surgical patients [12].

Currently hydroxyethylamide 130/0.4 therefore seems to be the best colloids to recommend in the treatment of perioperative hypovolemia.

We must not, however, confuse this indication with the use of colloids in patients with septic shock.

According to Perner et al., who have recently published what is perhaps the most important study in this field in the NEJM, colloids should not be prescribed to patients with septic shock [30].

The study caused a sensation throughout the world, but also quickly established the erroneous conviction that hydroxyethylamide 130/0.4 is dangerous for all patients. This statement is nowadays untenable. Among other things, a number of authors in the same journal have sent letters to the editor in which they criticize the work of Perner. The criticisms come from prestigious centers such as the University of Berlin, the University of Munich in Bavaria, and the University of Cape Town [31]. These criticisms refer in particular to the fact that in Perner's study colloids were used without a hemodynamic guide, and thus with the risk of plasma hyperexpansion, especially in patients in whom hemodynamic stability had already been achieved.

The hemodynamic status in Perner's study was controlled only with CVP, which alone is certainly an unsafe parameter in the evaluation of circulatory filling. This may have contributed to colloid overloading compared to real needs, with the negative effects we have referred to repeatedly above.

Less recent information about forms of hydroxyethylamide that are now more commonly used may also have played a role in creating a certain amount of skepticism in hydroxyethylamide comparisons.

Not all forms of hydroxyethylamide are equal. There are three different types: the first is the concentration of the solution (e.g., 6 %) and the second and third are the molecular weight and molar substitution (e.g., 130/0.4).

Molar substitution (0.7, 0.6, 0.5, 0.4) gives its name to the hydroxyethylamide, hetastarch, hexastarch, pentastarch, and tetrastarch. The higher the molar substitution (e.g., 0.7) and molecular weight (e.g., 670 Kdaltons), the more the drug remains in the body, which is essentially the reason for complications reported in the past,

predominantly renal damage. Even the concentration is important: 6 % solutions are iso-oncotic, and therefore with 6 % hydroxyethylamide a liter of blood is replaced by a liter of hydroxyethylamide; 10 % solutions are hyperoncotic, and the mass expansion is therefore considerably greater than the infused volume (145 %) [32].

Today the form of hydroxyethylamide most used is 6 % 130/0.4, an iso-oncotic plasma expander, with a low molecular weight and low molar substitution: these are all qualities that guarantee safety if plasma expansion is guided by the patient's real needs.

To be thorough, we must also refer to the $C_2/C_6$ ratio. The hydroxyethylation of glucose subunits that make up the hydroxyethylamide molecular occurs mainly at the $C_2$ and $C_6$ levels. The hydroxyethylation of $C_2$ inhibits amylase access to the substrate in a much more marked way than the hydroxyethylation of $C_6$. Types of hydroxyethylamide with a high $C_2/C_6$ ratio are much more difficult for amylase to attack and therefore are harder to break down. Since we do not need the hydroxyethylamide we use to lead to rapid plasma expansion with low persistence in the body, it is obvious that hydroxyethylamides with a low $C_2/C_6$ ratio are preferable.

In concluding this chapter we must say that the latest generation of hydroxyethylamides (6 % 130/0.4) are, according to current knowledge, efficient and sufficiently safe plasma expanders that can be used in perioperative phases. In particular, compared with gelatin [33] and 5 % albumin [34], 6 % hydroxyethylamide 130/0.4 has not demonstrated a higher rate or extent of renal damage.

But even in various types of critical patient, including cases of severe sepsis, 6 % hydroxyethylamide 130/0.4 was not an independent risk factor in a study that appeared in the Brit. J. Anaesth. involving 3,147 patients [35]. Even if there were "only" 822 patients in this study with severe sepsis and they were therefore much less represented compared with Perner's study in the NEJM in 2012, we cannot ignore it.

A few words should be said about the solutions used as vehicles for hydroxyethylamide. There are basically two that are commercially available: 0.9 % polysaline and a balanced solution that is much more similar to the biochemical composition of plasma. When large amounts of hydroxyethylamide are used, the second option is certainly preferable. With the first, in fact, the risk of hyperchloremic acidosis is real, but it is much less common since most authors use it after saline infusions of at least 3 l [32] and its clinical relevance does not appear to be reduced.

Studies in this field are not unequivocal in the information they provide. Alongside those that confirm that hyperchloremic acidosis is a benign disease that disappears on its own [36–38], there are others that maintain that it is the basis of renal and splanchnic fluid reductions [39] and interference in the passage of electrolytes via membranes [40].

Measurements have been made comparing the effects on coagulation with two types of hydroxyethylamide, one derived from potato plants in a balanced solution and one from maize in a saline solution. The authors of this study concluded that 6 % hydroxyethylamide 130/0.4 derived from potato plants in a balanced solution has less of a negative effect on hemostasis even in the presence of Ringer's acetate alone [41].

This appears to confirm the premise of this chapter that nonproteic iso-oncotic colloids, if used correctly, behave "as angels rather than demons" in perioperative phases.

As regards the most commonly used proteic colloid (albumin), it appears that its use in perioperative phases is not justified as a plasma expander, since this role is usefully taken on by 6 % hydroxyethylamide 130/0.4.

**Conclusions**

Perioperative hemodynamic optimization can be achieved by following the precise rules, even if they vary from one patient to the next, by consciously responding to three questions: When to infuse? How much to infuse? How to infuse?

We answered the first and second questions by recalling the importance of early identification of clinical signs of hypovolemia, which is the most common imbalance in the operating room, and the use of instruments that are easily obtainable today for selected patients, which make it possible not only to recognize hypovolemic states early, but also to correct them accurately. Goal-directed fluid therapy is a strategy that is easy to perform today in operating rooms and is certainly able to improve the outcomes of at-risk patients.

Not using it is increasingly considered a guilty omission. The alibi we have used for years that GDT was possible only with a diagnostic means, the Swan-Ganz catheter, which by itself could constitute an additional risk in nonexpert hands, is no longer tenable. We have monitoring instruments that are increasingly easy to use and less costly, and only a lack of desire and culture is at the heart of their inadequate use.

To the third question (What to infuse?) we have clearly replied that mass filling is undertaken with nonproteic colloids, primarily hydroxyethylamide 130/0.4 when the use of blood is not justified; today blood is used much more restrictively.

Crystalloids are reserved for the filling of fluids lost with perspiration and diuresis, which are nevertheless moderate during operations.

Described in such brief terms, these concepts seem very simple, but to put them into practice, it is necessary to have a deep understanding of everything that has been stated above, including every single detail.

## References

1. Bruegger D, Schwartz L, Chappell D et al (2011) Release of atrial natriuretic peptide precedes shedding of the endothelial glycocalyx equally in patients undergoing on- and off-pump coronary artery bypass. Basic Res Cardiol 106:1111–1121
2. Chappel D, Heindl B, Jacob M et al (2011) Sevoflurane reduced leukocyte and platelet adhesion after ischemia-reperfusion by protecting the endothelial glycocalyx. Anesthesiology 115:483–491
3. Chappel dD, Jacob M, Hoffmann-Kiefer K et al (2007) Hydrocortisone preserves the vascular barrier by protecting the endothelial glycocalyx. Anesthesiology 107:776–784

4. Lobo DN, Macafee DA, Allison SP (2006) How perioperative fluid balance influences postoperative outcomes. Best Prac Res Clin Anaesthesiol 20:439–455
5. Lobo DN, Stanga Z, Aloyrius MM et al (2010) Effect of volume loading with 1 liter intravenous infusions of 0,9% saline, 4% succinylated gelatin and 6% HES on blood volume and endocrine responses. Crit Care Med 38:464–470
6. Hartog CS, Kohl M, Reihart K (2011) A systematic review of third generation HES 130/0,4 in resuscitation: safety not adequately addressed. Anesth Analg 112:635–645
7. Myburgh JA, Finfer S, Bellomo R et al (2012) HES or saline for fluid resuscitation in intensive care. N Engl J Med 367:1901–1911
8. James MF, Michell WL, Joubert IA et al (2011) Resuscitation with HES improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial. Br J Anaesth 107:693–702
9. Shires T, Williams J, Brown F (1961) Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 154:803–810
10. Brandstrup B, Svensen C, Engquist A (2006) Hemorrhage and operation cause a contraction of extracellular space needing replacement-evidence and implication? Syst Rev Surg 139:419–432
11. Lamke LO, Nilsson GE, Reithner KL (1977) Water loss by evaporation from the abdominal cavity during surgery. Acta Chir Scand 143:279–284
12. Brandstrup B, Tonnesen H, Beier-Hegersen R et al (2003) Danish Study Group on perioperative fluid therapy. Effect of intravenous fluid restriction in postoperative complications: comparison of two perioperative fluid regimes: a randomized assessor-blinded multicenter trial. Ann Surg 238:641–648
13. Jacob M, Chappel D, Conzen P et al (2008) Blood volume is normal after preoperative overnight fasting. Acta Anaesthesiol Scand 52:522–529
14. Doherty M, Buggy J (2012) Intraoperative fluids: how much is too much? Br J Anaesth 109:69–79
15. Bens J, Chytra I, Altman P et al (2010) Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. Crit Care 14:R118
16. Mayer J, Boldt J, Mengistu AM et al (2010) Goal directed intraoperative therapy based on autocalibrated arterial pressure wave form analysis reduces hospital stay in high-risk surgical patients: a controlled randomized trial. Crit Care 14:R18
17. Cannesson M, Uannick LM, Christopher K et al (2010) Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a gray zone approach. Anesthesiology 115:231–241
18. Yn JY, Ho KM (2012) Use of plethysmographic variability index derived from the Massimo pulse oximeter to predict fluid or preload responsiveness: a systematic review and meta-analysis. Anaeshtesia 67:777–783
19. Keller G, Cassar E, Desebbe O et al (2008) Ability of pleth variability index to detect hemodynamic changes induced by passive leg raising in spontaneously breathing volunteers. Crit Care 12:R37
20. Maharaj CH, Kallam SR, Malik A et al (2005) Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. Anesth Analg 100:675–682
21. Lambert KG, Wakim JH, Lambert NE (2009) Preoperative fluid bolus and reduction of postoperative nausea and vomiting in patients undergoing laparoscopic gynecologic surgery. AANA J 77:110–114
22. Holte K, Klarskov B, Christensen DS et al (2004) Liberal vs restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: a randomized, double-blind study. Ann Surg 240:892–899
23. Duke R, Abelmann WH (1969) The hemodynamic response to chronic anemia. Circulation 39:503–515
24. Lawrence T, Goodnough T, Shader A et al (2005) Detection, evaluation and management of anemia in the elective surgical patients. Anasth Analg 101:1858–1861

25. Beris P, Munoz M, Garcia-Erce JA et al (2008) Perioperative anaemic management: consensus statement on the role of intravenous iron. Br J Anaesth 100:590–604
26. Ferrari R, Nicolini P, Mancia M et al (2012) Treatment of mils non chemotherapy-induced iron deficiency anemia in cancer patients: comparison between oral ferrous bisglycinate chelate and ferrous sulfate. Biomed Pharmacother 66(6):414–418, Elsevier, Masson
27. Niemi TT, Miyashita R, Yamakage M (2010) Colloid solutions: a clinical update. J Anesth 24:913–925
28. Boldt J, Schölorn T, Mayer J et al (2006) The value of an albumin based intravascular volume replacement strategy in elderly patients undergoing major abdominal surgery. Anesth Analg 103:191–199
29. Moretti EW, Robertson KM, El-Moalem H et al (2003) Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared with crystalloid administration. Anasth Analg 96:611–617
30. Perner A, Haase N, Guttormsem AB et al (2012) HES 130/0,4 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–134
31. Magder S Protocols, physiology and trials of HES. Letters to Editor (2012) N Engl J Med. 367:1265–1267
32. Westphal M, James M, Korek S (2009) Hydroxyethyl starches. Anesthesiology 111:187–202
33. Boldt J, Brosch C, Röhm K et al (2008) Comparison of the effects of gelatin and a modern HES solution on renal function and inflammatory response in elderly cardiac surgery patients. Br J Anaesth 100:457–464
34. Boldt J, Brosch C, Röhm K et al (2008) Is albumin administration in hypoalbuminemic elderly cardiac surgery patients of benefit with regard to inflammation, endothelial activation, and long-term kidney function? Anesth Analg 107:1496–1503
35. Sakr Y, Payen D, Reinhart K et al (2007) Effects of HES administration on renal function in critically ill patients. Br J Anaesth 98:216–224
36. McFarlane C, Lee A (1994) A comparison of Plasmalyte 148 and 0,9% saline for intraoperative fluid replacement. Anesthesia 49:779–781
37. Scheingraber S, Rehm M, Schisch C et al (1999) Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 90:1265–1270
38. Mathes DD, Morell RC, Rohr MS (1997) Dilutional acidosis: is it a real clinical entity? Anesthesiology 86:501–503
39. Williams EL, Hildebrand KL, Mc Cormick SA et al (1999) The effects of intravenous lactate Ringer's Solution vs. 0,9 sodium chloride solution on serum osmolality in human volunteers. Anesth Analg 88:999–1003
40. Prough DS, White RT (2000) Acidosis associated with perioperative saline administration: dilution or delusion? Anesthesiology 93:1167–1169
41. Boldt J, Wolf M, Mengistu A (2007) A new plasma-adapted HES preparation: in vitro coagulation studies using thromboelastography and whole blood aggregometry. Anesth Analg 104:425–430

# 7 Management Strategies in the Postoperative Course, with Particular Attention to Pain Treatment: Revision of the Most Recent Knowledge

Gennaro Savoia and Maria Loreto

The postoperative period is a crucial time for patients. Careful monitoring, integrated with a treatment plan that takes into account the basal pathologies and postoperative peculiarities of specific interventions (surgical site, blood losses, pain intensity, hospitalization duration), is able to reduce the complications and, thus, postoperative morbidity and hospital stay. Recent guidelines on perioperative treatment emphasize the role of simultaneous therapeutic measures, ensuring safe risk-management pathways such as prevention of surgical site infections, thromboembolic prophylaxis, strategies to reduce the incidence of perioperative stroke, and strategies to ensure enhanced techniques integrating postoperative analgesia, nausea and vomiting control, early mobilization, and enteral nutrition [1, 2]. The main integrated recommendations below are derived from the guidelines on the treatment of postoperative pain, characterized by levels of evidence A and B [3–7].

## 7.1 Postoperative Pain

The technique of analgesia adapted to the individual patient plays a key role in the evaluation and management of perioperative pain. Pain must be considered as the fifth vital sign, after heart rate, blood pressure, temperature, and urine output. These vital signs must be periodically evaluated, measured, and transcribed in the clinic database (level A). The evaluation must include not only the pain at rest but also, and especially, the pain "incident" using one of the following scales: numeric rating scal, visual analog scale, or verbal rating scale.

G. Savoia (✉) • M. Loreto
Department of Anesthesiology and Intensive Care, AORN A. Cardarelli, Naples, Italy
e-mail: gennarosavoia@libero.it



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A good model of postoperative pain management must take into account the following parameters:

(a) patient characteristics;
(b) type of surgery and surgical technique;
(c) intensity and duration of postoperative pain and its tendency to become chronic;
(d) organization of existing resources and control through the adoption of tools to "measure" and "assess" pain at rest and during movement;
(e) identification and training of personnel involved.
(f) the process should be sensitive to the clinical context of application

In its 2012 guidelines, the American Society of Anesthesiologists [5] emphasized the role of outcome patient monitoring and of a dedicated service for acute pain management.

The Acute Pain Service (APS) formally is multidisciplinary, involving anesthesiologists, surgeons, nurses, physiotherapists, and other specialists. There is not a single best organizational model, but it must to be adapted to the local environment and its possibilities. The APS improves pain control in surgical wards and seems able to reduce adverse effects such as nausea and postoperative vomiting.

It is recommended to refer to the quality indicators (level C) and to consider the following key points when organizing an APS:

1. institutionalization of the service with identification of a responsible person and the employees (staff assigned);
2. organization for the care of patients during nights and weekends;
3. identification of an referent 24-h anesthesiologist;
4. sharing, drafting, and updating of written treatment protocols;
5. systematic survey of pain;
6. collection of data on the efficacy and adverse effects of the protocols used;
7. carrying out an audit at least annually;
8. continuing education.

In its guidelines, the American Society of Anesthesiologists [5, 6] also stressed the concept of multimodal analgesia with the use of different classes of drugs: COX-2 selective, NSAIDs, acetaminophen, Calcium channel alpha-2-delta antagonists (pregabalin, gabapentin). Drugs must be administered at fixed times, the blocks locoregional with local anesthetics considered as part of a multimodal approach. The regime must optimize the therapeutic efficacy and reduce the risk of adverse events. The choice of drug, administration route, and duration of therapy should be individualized.

## 7.2 Systemic Analgesia

*Paracetamol* has a good analgesic efficacy (NNT for 3.5–3.8 500–1,000 mg) with no significant effects side (Level A). Monitoring of the liver is necessary when paracetamol is used. Its pharmacological profile is not altered in the presence of

alterations of the renal function (Level B). The association of paracetamol and morphine reduces the daily consumption of opioid by a variable percentage of 33–20 % (Level A). The administration of acetaminophen and tramadol is more effective than paracetamol – codeine (Level B).

*NSAIDs* (nonsteroidal anti-inflammatory drugs) are effective drugs for the pain of average intensity. In combination with opioid analgesics they reduce the need for analgesia and are able to control moderate to severe pain (Level A).

The *COXIBs* are contraindicated in patients with ischemic heart disease and/or cerebrovascular disease, congestive heart failure, and aorto-coronary bypass (Level B).

*Opioids* are the drugs of choice for the treatment of moderate to severe POP postoperative pain (Level A). Their epidural, intrathecal, and intravenous (IV) patient-controlled analgesia (PCA) use is preferred over intramuscular injections at fixed hours.

The use of opioids can cause adverse effects in a dose-dependent manner. The use by continuous infusion device may increase the side effects. Vomiting can be reduced with the use of droperidol, dexamethasone, ondansetron, or propofol at minimal doses, thus avoiding nitrous oxide (Level C).

*Tramadol* results in less respiratory depression than morphine (Level B). Its association with morphine is not recommended for an infra-additive effect (Level C). A better association is with NSAIDs (Level D).

*Remifentanil* is the opioid of choice for patients with kidney and liver disease (Level B), and for patients recovering in a protected ward environment.

*Oxycodone* is used in the DPO as analgesia step-down after use of IV PCA (Level D) or opioid premedication if a short half-life opioid is chosen for minor surgery.

*Ketamine* administered perioperatively can reduce the intensity of postoperative pain (Level A), the incidence of postoperative nausea and vomiting (PONV) (Level B), and morphine consumption by 30–50 % (Level A).

### 7.2.1 Epidural Analgesia

Epidural analgesia is recommended for the following reasons: In postoperative pain, it has an analgesic efficacy higher than systemic analgesia with opioids (Level A). With local anesthetics, associated with opioids, it can reduce respiratory complications, lung infections, and paralytic ileus (Level A). The association of thoracic epidural analgesia and early enteral nutrition is able to reduce protein catabolism postoperatively (Level C) and the incidence of peripheral thrombosis (Level C). The association between low doses of local anesthetic and lipophilic opioids represents the best compromise in terms of control of postoperative pain and reduced incidence of side effects (Level A). The risk of epidural hematoma is very low when the recommendations relating to the timing of thromboprophylaxis and the suspension of antiplatelet agents drugs are complied with. Spinal hematoma has an incidence of 0.02 % (Level D). In suspected epidural hematoma, it is necessary to request an urgent check with magnetic resonance imaging (MRI) or a computerized tomography (CT) scan (Level A). A decompression by surgical laminectomy within 6 h

**Table 7.1** Drug, interventional and physical therapy

| **Intravenous route** | **Oral route** | **Rectal route** | **Subcutaneous route** | **Topical** |
|---|---|---|---|---|
| Antiepileptic<br>Ketamine<br>NSAIDs<br>Opioids | Antiepileptic<br>Antidepressants<br>Antihistamines<br>Anxiolytics<br>Cortisone<br>Hypnotics<br>Local anesthetics<br>NSAIDs<br>Opioids | Acetaminophen<br>Aspirin<br>Opioids<br>Phenothiazines | Local anesthetics<br>Opioids | Capsaicin<br>Cold<br>Hot<br>Lidocaine/ prilocaine<br>Local anesthetics |
| **Interventional** | | | | |
| Treatment of pain with the use of local injections or invasive procedures | | | | |
| Consultation preoperatively with a specialist in pain therapy | | | | |
| **Physical therapy** | | | | |
| Biofeedback | | | | |
| Exercise | | | | |
| Hot/cold | | | | |
| Immobilization | | | | |
| Massage | | | | |
| TENS (transcutaneous electrical nerve stimulation) | | | | |
| Relaxation | | | | |

after symptom onset can reduce neurological complications (Level E). The incidence of major neuraxial complications linked to the use of an epidural catheter to deliver postoperative analgesia is approximately 1:1,000. The incidence of epidural abscess is 0.07 % and is associated with high fever and infection site insertion. Early diagnosis is crucial. In most cases, the bacteria responsible are *Staphylococcus aureus* or *S. epidermidis*. The combination of infection of the insertion site and hyperpyrexia are sufficient to investigate with NMR nuclear magnetic resonance, and the addition of local pain or neurological symptoms imposes the need for urgent investigations (Level D). The average time from the insertion of the catheter to the first symptoms can vary from 1 to 60 days. The initial symptoms include back pain, fever, and leukocytosis (Level A) (Table 7.1).

### 7.2.2 Continuous Peripheral Blocks

In recent years, continuous peripheral blocks have been used successfully in the treatment of acute postoperative pain (Level A). After orthopedic surgery of the upper and lower limbs, clinical trials have shown that continuous peripheral blocks are as effective as continuous epidural block, and both are considerably more effective than parenteral opioids (Level A). Studies have shown a remarkable effectiveness of these techniques in reducing pain at rest and during movement, the consumption of opioid analgesics, and nausea and vomiting. This treatment has

improved, especially in orthopedic surgery, functional recovery with adequate analgesia, and reduced side effects (Level A). Regional analgesia should also be used in critically ill patients to reduce the consumption of sedatives and opiates (Level C).

After major orthopedic surgery of the upper and lower limbs, clinical studies have shown that continuous peripheral blocks are as effective as continuous epidural and that both are greatly *more effective than intravenous opioids or infiltration with local anesthetics (Level A).*

Regional analgesia also should be used in critically ill patients to reduce the consumption of sedatives and opiates (Level C).

It has been shown that, in knee surgery, the adductor canal ultrasound-guided block, compared with continuous femoral block, ensures equal analgesia and lower incidence of quadriceps femur motor block, thus preventing accidental falls in the first postoperative days [4, 8]. Likewise, the role of *continuous* thoracic paravertebral block for breast and thoracic surgery has been reaffirmed as an alternative to continuous epidural and TAP (transversus abdominis plane) block (abdominal wall block with continuous infusion of local anesthetic).

### 7.2.3 Infusion Modality

Several studies have shown that PCRA (*patient controlled regional anesthesia)* is a more effective infusion baseline in postoperative pain control and allows a better mobilization of the patient (Level C).

It is recommended to avoid continuous infusion techniques with no flow control devices and to adopt a programmed registration system, including pain level, analgesia effectiveness, and side effects notation (Level A).

### 7.2.4 Patient Controlled Analgesia (PCA)

#### 7.2.4.1 PCA Intravenous

The intravenous PCA is a method for the treatment of postoperative pain that allows the patient to self-administer the needed doses of analgesics. The intravenous PCA opioid guarantees better analgesia (with an average of 5 mm on a scale 0–100 mm for pain) and greater patient satisfaction than conventional treatments with parenteral opioids at fixed hours (Level A).

The intravenous opioid PCA, however, is not associated with a reduction in opioid consumption or reduced incidence of side effects related to opioids compared with conventional treatments with parenteral opioids (Level A). There is no evidence that a basal infusion can improve pain relief or quality of sleep, or reduce the number of doses required by IV PCA. Before starting treatment with PCA, a correct initial titration must be made to reach an adequate level of analgesia.

The incidence of side effects related to opioids, including respiratory depression, is the same for both the IV PCA and the intermittent administration of opioid

analgesics (Level A). The risk factors for respiratory depression associated with IV PCA are divided into those associated with the patient (elderly, children, obesity, obstructive sleep apnea, respiratory failure) and those related to the technique:

- mistakes made by the patient
- errors made by operators (programming errors, accidental boluses during the syringe change, inappropriate prescription drug dose, inadequate dose interval).

### 7.2.5 Day Surgery

#### 7.2.5.1 Anesthetic Approach (Level A)

Whenever possible, general anesthesia should be integrated with preemptive analgesia (acetaminophen/NSAIDs and/or peri-incisional local anesthetic infiltration).

Due to the expected vomiting/pain interactions, the use of nitrous oxide is not recommended. If indicated, peripheral nerve blocks are preferred over general anesthesia (Table 7.2).

#### 7.2.5.2 Early and Late Postoperative Recovery: Analgesia at Discharge (Level D)

The hospital discharge letter must include pain assessment, postoperative drug provision plan, rescue dose commitment, and adverse events prevention suggestions. It is recommended to provide, both orally and in writing, information and clear and precise instructions on where and when prescribed drugs can be taken and how side effects can be controlled. These recommendations relate particularly to the need to clearly inform patients who are discharged with continuous perinervous infusion of local anesthetics, emphasizing the risks of loss of motor function and ambulation.

**Table 7.2** Security intervals between drug administration interfering with coagulation and execution of epidural block

| |
|---|
| ENF 4 h |
| LMWH low doses 12 h |
| LMWH high doses 24 h |
| Fondaparinux 36 h |
| Anti Vitamin K INR <1.5 |
| Ticlopidine 10 days |
| Clopidogrel 7 days |
| Tirofiban 8–10 h |
| Hirudin 8–10 h |
| Abciximab 24–48 h |
| Dabigatran Nc |
| Rivaroxaban 18–22 h |
| Apixaban 24 h |

## 7.3 Specific Groups of Patients

### 7.3.1 Elderly Patients

In elderly patients (>65 years), the following is recommended:

use of a simple semantic scale (absent, mild, moderate, severe) to measure pain in collaborating patients;
use of neuro-behavioral parameter scales in uncooperative patients;
taking account of changes in pharmacokinetics and pharmacodynamics to avoid the risks involved in the choice of NSAIDs/coxibs;
reducing the minimum effective dose of opioids from 1/3 to 2/3;
use of methods of PCA is safe in elderly patients without cognitive deficits;
use of methods of epidural analgesia requires a reduction of the doses of local anesthetics and opioids;
ensure a level of analgesia aimed at early motor rehabilitation and a complete functional recovery plan.

### 7.3.2 Pediatric Patients

An appropriate analgesia plan must be considered over sedation alone. The most used drugs for the procedural analgosedation are nitrous oxide, associated or not to low doses of ketamine and midazolam. For minor procedures (venipuncture, stitches, etc.) the inhalation of nitrous oxide (50 %) and/or the use of topical local anesthetic can be considered an effective and safe procedure (Level A).

For procedures of moderate severity (lumbar puncture, aspiration of bone marrow) the inhalation of nitrous (50 %) and the use of topical or local anesthetic for injection is effective in most patients (Level A).

For other procedures (reduction of fracture), regional IV blocks with local anesthetic are effective in most of children, despite the potential complications and the high incidence of side effects. General anesthesia may be more appropriate in some groups of patients. Cognitive techniques, the presence of family members, behavioral interventions (Level C), and administration of sugar reduce behavioral responses in neonates and infants (Level B).

Paracetamol and NSAIDs are effective for pain with moderate intensity and reduce the opioid requirements after major surgery (Level A). Acetylsalicylic acid should be used with caution in children to reduce the potential risk of Reye's syndrome. In addition, aspirin and NSAIDs increase the risk of postoperative bleeding (Level A). Severe side effects are rare in children above 6 months of age.

Opioids are effective and can be used safely in children of all ages. The initial opioid dose must be established according to weight and age and must be adjusted according to the individual response.

The mode of administration with PCA is very effective and safe; it can be used in children who are able to collaborate, typically 5 years and older.

The caudal block is effective for analgesia after interventions on the lower abdomen, perineum, and lower limbs. Continuous epidural infusion is effective in controlling postoperative pain but requires the collaboration of an experienced team capable of accurate monitoring (cardiovascular and neurological) to identify early complications such as local anesthetic toxicity, more frequent in children due to reduced clearance, and lower protein binding from local anesthetics or intravascular drug injection, more frequent in children because of the low consistency of the sacral ligament. Continuous epidural infusion of local anaesthetics guarantees a level of analgesia equal to intravenous opioids, prolonged by adding clonidine (Level B).

In day surgery, wound infiltration with local anesthetic, caudal block, or peripheral perineural blocks (the dorsal penile nerve block for phimosis, ileoinguinal/ileohypogastric nerve block for hernia) provides suitable analgesia (Level B).

### 7.3.3 Obese Patients

Prolonged hospitalization is often necessary in obese patients to ensure that analgesia is both effective and safe, with close monitoring of the sedation level, respiratory rate, oximetry, and capnometry (Level B).

Frequently, OSA (obstructive sleep apnea) is a syndrome associated with obesity. In these patients, strict monitoring associated with reduction of opiate doses is mandatory. Remifentanil seems to provide greater hemodynamic stability than sufentanil, although these differences vanish when used in TCI (target controlled infusion). The perioperative use of NSAIDs, ketorolac in continuous IV infusion during surgery and within 24 h, compared with the use of the same remifentanil, has been shown to ensure a greater intraoperatory hemodynamic stability, a faster discharge from the PACU (post-anesthesia care unit), and a better outcome. The use of the PCA mode and PCEA are recommended (Level C), even if epidural loco-regional analgesia (PCEA) shows more complications and technical difficulties [2].

### 7.3.4 Chronic Opioids Consumer Patients (CCO)

In these cases the following is recommended:

preoperatively identify CCO patients;
do not reduce the usual daily doses of opiates;
identify a multimodal treatment plan, “proactive” vs postoperative pain;
premedicate with opioids, titrating the dose;
use, if possible, perioperative continuous techniques of regional anesthesia;
administer NSAIDs and/or paracetamol at full doses daily;
assure full daily doses of opiates (>2–3 times the average dose routinely used), possibly titrated using target controlled infusion (TCI) intraoperatively and PCA postoperatively;
avoid both holes in analgesia and oversedation phases, planning for the transition to the oral route in the following days;

provide for the use of adjuvants perioperatively such as alpha-2-agonists, low-dose ketamine, even appealing the rotation of opioids from morphine/fentanyl versus methadone or buprenorphine.

### 7.3.5 Patients Suffering from Sleep Obstructive Apnea (OSA)

The prevalence of OSA is widely underestimated in adults (5 % undiagnosed, mild forms up to 20 %, moderate to severe forms in 7 % of cases).

In the setting of patients with OSA the following is recommended:

preoperative identification of patients at risk (COPD, smoking, chronic snorers, obese) and possible programming of postoperative hospitalization in a protected area;
prefer opioid-sparing analgesic techniques;
monitor the level of sedation, over the respiratory rate;
supplement oxygen also by nasal C-PAP (continuous positive airway pressure);
banish in these patients all forms of baseline opioids infusion;
titrate drug administration by continuous epidural and IV PCA.

## 7.4 Treatment-Related Adverse Events in Postoperative Pain

When using anti-inflammatory drugs, any contraindications should always be ruled out (known allergy to NSAIDs, gastric or duodenal ulcer, thrombocytopenia, renal failure) and it is a good idea to associate gastro-protective drugs (H2 blockers or pump inhibitors).

When using local anesthetics, the possibility of neurotoxicity should be considered (alterations in the level of consciousness, agitation, seizures) and cardiotoxicity of substances (heart arrhythmias).

When using opioids, the following clinical signs should be monitored: nausea, vomiting, skin rash, itching, and blood pressure. Nursing staff should have adequate training to detect early clinical warning signs of possible complications:

clinical signs suggestive of allergy (skin rash, edema, appearance of macules, papules), bruising (indicators of poor platelet function);
contraction diuresis (evaluate azotemia, creatinine).
When using opioids, the most common side effects and the simplest rules for its treatment are:
nausea and vomiting: use antiemetics, modify opioid dose or predict transition to alternative medication;
constipation: always provide a intestinal stimulation plan when using an opioid, avoid fiber-based laxatives to avoid production of gas and abdominal cramps;
itching: change opiate, eventually add antihistamine;

myoclonus: change opiate, use benzodiazepine to treat myoclonus;
respiratory depression: use naloxone 0.4 mg, administer 0.02 mg/min up to the reversion effect.

In patient-controlled analgesia, mistakes can relate to:

mixing drugs (concentration, dilution);
setting of the system (basal infusion, bolus dose, maximum hourly/day dose);
inadequate monitoring of vital signs (blood pressure, heart rate, respiratory rate, $SaO_2$, sedation level);
mismanagement of therapy if analgesia is not effective;
underestimation of the difficult patient.

### 7.4.1 Epidural Infusions

To identify the early appearance of clinical signs of complications, the following should be monitored every three hours: level of consciousness, blood pressure, heart rate, respiratory rate, sensory discrimination and motor block (dermatomeric level of analgesia), $SaO_2$, urine output, nausea, vomiting, and visual analog scale at rest and during movement.

The remote but devastating risks related to the use of the technique can be related to dislocation of the catheter and its migration to the subdural/intraspinal space, spinal cord ischemia, and spinal hematoma.

Opioids, as already said, may induce itching, nausea, vomiting, and respiratory depression and may cause loss of control of metameric sensorial discrimination, variability of respiratory rate, pulse oximetry, and end-tidal $CO_2$, or excessive drowsiness of the patient.

Local anesthetics can induce orthostatic hypotension and motor block which, in turn, could mask a compartmental syndrome (from any surgical hematoma in a closed space). In the presence of ineffective analgesia and in cases of suspected malfunction of epidural infusion, a series of tests must be performed in the ward:

- verify the normal flow of the epidural catheter;
- check the dressing and links;
- inject 5 ml of saline;
- call the anesthesiologist.

The events that should alert the attention of ward staff during the use of the infusion for epidural are:

- onset of respiratory depression (RR < 8/min);
- onset of motor block despite the use of local anesthetic at low concentrations or failure of regression of motor block after central blocks: call the anesthesiologist,

identify clinical warning signs of spinal hematoma, perform spinal MRI, proceed to neurosurgical evacuation within 3h – maximum 6 h – from the onset of symptoms.

It is important to respect the security intervals between last dose of antiplatelet/anticoagulants and execution of the central block. This emphasizes the importance of not suspending antiplatelet agents in patients at risk of clogging metallic coronary stents (30 days) and double antiplatelet therapy in patients with drug-eluting stents (365 days), but in these cases central blocks should be avoided.

### 7.4.2 Peripheral Blocks

Complications may be due to the appearance of:

- infection of the insertion site;
- hematoma in proximity of the block due to vascular injury;
- permanent or transitory nerve injuries;
- systemic toxic manifestations of the use of excessive anesthetic doses or its vascular reabsorption (early treatment with 20 % lipidic solution, administering a bolus of 100 ml, continuing with 400 ml in 20 min until full recovery);
- pneumothorax in thoracic blocks.

## 7.5 Chronicity of Surgical Acute Postoperative Pain (POP)

The risk of postoperative pain chronification can be reduced with minimally invasive surgical techniques and avoiding any direct cuts, inflammation, or scarring to peripheral nerves. Data in the literature on the effectiveness of preventive multimodal analgesia in reducing the chronicity of POP are conflicting.

Several studies have been conducted on the effectiveness of prevention with opioids, demonstrating its ineffectiveness. The most promising results are given by the use of anticonvulsants and multimodal drug plans using anticonvulsants, antidepressants, ketamine, local anesthetics, or any combination of these [7–12].

Postoperative chronic pain (persistent) occurs in 10–50 % of patients undergoing surgery, especially after hernioplasty, breast and thoracic surgery, and limb amputations. In 2–10 % of cases, the pain remaining after surgery is classified as severe. Genetic factors are probably involved because not all patients who suffer from a peripheral nerve injury develop chronic pain. The presence of infection and surgical bleeding, the appearance of compartment syndrome and breakage of internal organs favor the development of chronic pain.

## 7.6 Recent Knowledge

Despite the enormous progress that has been made in anesthetic practice in the last 50 years, the worldwide incidence of intraoperative mortality is estimated at nearly 30 deaths/million uses of anesthetics. A mortality of 20 % is estimated in postoperative critical patients, thus elevated to 50 % in patients with multi organ failure.

Diseases such as stroke, myocardial infarction, ARDS, renal failure, and acute intestinal ischemia are more frequent perioperatively. At the base of the organ damage is ischemic damage that triggers the activation of genes involved in production of inflammatory substances capable of worsening the stability of the membrane and thus increasing cell and tissue damage. There are perioperative strategies for reducing complication such as anemia, tachycardia, hypertension, and hyperthermia (Table 7.3).

**Table 7.3** Perioperative treatments can change the postoperative outcome

| Drug | Advantage postoperative | Level of evidence |
|---|---|---|
| Intraoperative normothermia | Reduced surgical site infection | Level A |
| Regional anesthesia | < surgical site infection | Level B |
| Avoid hyperglycemia | < surgical site infection | Level B |
| Using continuous insulin infusion | < surgical site infection | Level A |
| Regional anesthesia | < frequency of cancer recurrence | Level B |
| Avoid nitrous oxide | < frequency of cancer recurrence | Level C |
| Perioperative use of NSAIDs | < frequency of cancer recurrence | Level C |
| Perioperative use of Propofol | < frequency of cancer recurrence | Level C |
| Avoid heterologous transfusions | < frequency of cancer recurrence | Level C |
| Preoperative treatment with iron and erythropoietin | < transfusion | Level B |
| Intraoperative fluid restriction in cardiopulmonary bypass | < transfusion | Level C |
| Hypotensive anesthesia | < transfusion | Level B |
| Recovery intraoperative blood | < transfusion | Level A |
| Anesthesia with propofol | < transfusion | Level C |
| Antifibrinolytic agents | < transfusion | Level A |
| Epidural anesthesia pre-incisional | < incisional postoperative chronic pain development | Level C |
| Anesthesia without nitrous oxide | < incidence of perioperative myocardial infarct | Level B |
| Using beta blockers in surgery non-cardiac surgery | < postoperative cardiovascular complications | Level B |
| ALR use in children | < neurocognitive side effects of immature brain tissue | Level C |
| ALR use in the elderly | < long lasting postoperative cognitive dysfunction | Level C |

Preoperatively, it is important to check for hyperlipidemia; use of beta blockers, statins, and antiplatelet agents puts patients at risk. Assess the patient carefully and determine which pharmacological treatment should be undertaken, continued, or integrated according to its pharmacokinetics and pharmacodynamics and its interference with the anesthetic technique used [13–15].

## References

1. White P, Kehlet H (2010) Improving postoperative pain management: what are the unresolved issues? Anesthesiology 112(1):220–225
2. Kozek-Langenecker SA et al (2013) Guidelines from the European Society of Anaesthesiology. Management of severe perioperative bleeding. Eur J Anaesthesiol 30:270–382
3. Joeschke R, Jankowski M, Brozek J, Antonelli M (2009) How to develop guidelines for clinical practice. Minerva Anestesiol 75:504–508
4. Savoia G, Alampi D, Amantea B et al (2010) SIAARTI recommendations for the treatment of postoperative pain. Minerva Anestesiol 76(8):657–667
5. An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management (2012) Practice guidelines for acute pain management in the perioperative setting. Anesthesiology 116(2):240–273
6. Paul JE, Buckley N, McLean RF (2014) Hamilton acute pain service safety study. Anesthesiology 120(1):97–109
7. Kuwajerwala NK, Schwer WA. Perioperative medication management. Institute for Clinical Systems Improvement Perioperative Protocol. Fourth Edition/November 2012. www.icsi.org
8. Kim DH, Lin Y, Goytizolo EA (2014) Adductor canal block versus femoral nerve block for total knee arthroplasty. Perioperative medicine. Anesthesiology 120(3):540–551
9. Turan A, Sessler I (2011) Steroids to ameliorate postoperative pain. Anesthesiology 115:457–459
10. Ilfeld BM, Madison SJ, Suresh PJ (2014) Treatment of postmastectomy pain with ambulatory continuous paravertebral nerve blocks. Reg Anesth Pain Med 39(2):89–96
11. Schmidt PC, Ruchelli G, Mackey SC (2013) Perioperative gabapentinoids. Anesthesiology 119(5):1215–1221
12. Memtsoudis SG, Rasul R, Suzuki S (2014) Does the impact of the type of anaesthesia on outcomes differ by patient age and comorbidity burden? Reg Anesth Pain Med 39(2):112–119
13. Kavanagh T, Buggy DJ (2012) Can anaesthetic technique effect postoperative outcome? Curr Opin Anaesthesiol 25(2):184–198
14. Institute for Clinical Systems Improvement. Assessment and management of acute pain. Sixth Edition/March 2008. www.icsi.org
15. Bartels K, Karhausen J, Clambey E, Grenz A, Eltzschig HK (2013) Perioperative organ injury. Anesthesiology 119:1474–1489

# Optimum Management of Perioperative Coagulation in Patients with Spontaneous Intracranial Haemorrhage

8

Patrizia Fumagalli

## 8.1 Introduction

Every year about 70,000 new cases of spontaneous intracranial haemorrhage (SICH) are recorded in the USA, with a 30-day mortality that may reach 50 %. Associated coagulation alterations are quite frequent.

The incidence of SICH associated with oral anticoagulants has been growing since the early 1990s, and today it is almost as high as that of subarachnoid haemorrhage (SAH), which is 6.6/100,000 inhabitants. From 1988 to 1999 the incidence of SICH rose from 0.8 to 4.4/100,000, matching the increasing use of anticoagulant treatment with *warfarin* in patients with atrial fibrillation over the same period. The increment – from 13 % in 1990 to 41 % in 2000 – is even more remarkable in patients aged >80 years (48 %) [1, 4].

A comparable study carried out in a Finnish population in 2011 found an increased prophylactic use of *warfarin*, even though the association with SICH was not as linear as in the US study. The less severe course may be related to a more careful management of anticoagulant therapy and, above all, to early treatment of the haemorrhage itself [3].

A more recent study of a Danish population confirmed the rising trend and found that SICH is actually overtaking SAH, with 8.7/100,000 cases of patients receiving oral anticoagulants [5, 6].

Spontaneous (non-traumatic) intracranial haemorrhage is therefore a highly significant cause of morbidity and mortality worldwide. Correct management of coagulation is clearly a key aspect in SICH prevention and especially in the perioperative period.

P. Fumagalli
Neurorianimazione, Ospedale A. Manzoni, Lecco, Italia
e-mail: p.fumagalli@ospedale.lecco.it



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A large number of patients present with a modest haemorrhage that is amenable to medical treatment. Standardising an effective, early therapy may thus have beneficial effects on mortality and morbidity.

## 8.2 Treatment

First of all, treatment requires early diagnosis and evaluation of the causes of the haemorrhage. Interventions include:

- Haemostasis
- Cardiovascular and respiratory support
- Monitoring of blood pressure (BP)
- Monitoring of intracranial pressure (ICP) and tissue oxygenation
- Surgery
- Treatment of the intra-ventricular haemorrhage
- Prevention of further haemorrhage
- Rehabilitation, as appropriate

SICH is a medical emergency, and early diagnosis and close observation are thus crucial, as the condition of most patients deteriorates over the first few hours. At least 20 % of patients lose two or more points on the Glasgow Coma Scale (GCS – Table 8.1) from symptom onset to their arrival at the emergency department (ED); a fall by more than 6 points before arrival at the hospital is associated with a mortality rate >75 %.

**Table 8.1** Glasgow Coma Scale (GCS)

| | | | |
|---|---|---|---|
| E | Eye opening | Spontaneously | 4 |
| | | To speech | 3 |
| | | In response to pain stimulus | 2 |
| | | None | 1 |
| V | Verbal response | Oriented | 5 |
| | | Confused | 4 |
| | | Inappropriate words | 3 |
| | | Incomprehensible sounds | 2 |
| | | None | 1 |
| M | Best motor response | Obeys commands | 6 |
| | | Localises to pain (purposeful movements towards painful stimuli) | 5 |
| | | Normal flexion (rapidly withdraws from pain) | 4 |
| | | Abnormal flexion (slow, dystonic) | 3 |
| | | Extension (becomes stiff) | 2 |
| | | None | 1 |
| **Total score** | | **3/15** **15/15** | |

## 8.3 Prehospital

The main goal in this phase is to provide adequate cardiovascular and respiratory support. It is essential to establish the timing of symptom onset and especially to gain information about current medications. Transfer to the ED should be under the *Code Stroke* to obtain immediate triage and minimise the waiting time for CT scanning.

## 8.4 In Hospital: ED

Activation of the *Code Stroke* protocol involves immediate evaluation by a specialised team, which comprises a neurologist, a resuscitation specialist, a neuroradiologist, and a neurosurgeon. A cranial CT scan is the gold standard diagnostic imaging approach to acute haemorrhage. Emergency management may involve neurosurgery, but any clotting disorder should be treated first.

The *Code Stroke* protocol is usually reserved for patients with ischaemic stroke, but the ED should predispose a fast, standardised protocol for patients with cerebral haemorrhage.

## 8.5 In Hospital – ICU

Patients with intracranial haemorrhage (ICH) should be treated in a neurological intensive care unit (ICU) and managed according to the protocol for neurological patients:

- Airway management: intubation and ventilation to ensure correct oxygenation and normocapnia. Hyperventilation and hypocapnia may be harmful and require careful monitoring of ICP and cerebral perfusion.
- ICP monitoring: guidelines recommend ICP monitoring in sedated and ventilated patients for whom close monitoring of consciousness is not possible and for all patients with a GCS score <9, hydrocephalus or extensive haemorrhage.
- If intra-ventricular haemorrhage is also present, an external ventricular drain is indicated: this allows simultaneous ICP monitoring and liquor and blood drainage to reduce ICP. Associated risks are infection and catheter obstruction due to clotting. Administration of intra-ventricular thrombolytic agents has been advocated to accelerate haemorrhage clearance. The study "Clot Lysis Evaluating Accelerated Resolution of Intra-ventricular Haemorrhage III" (CLEAR III) is still ongoing, but preliminary evidence indicates that intra-ventricular administration of recombinant tissue plasminogen activator (rTPA) is safe [7].
- Support therapy: control of blood glucose and temperature, treatment of anaemia as appropriate.

- Control of epilepsy seizures: clinical seizures should be treated with anticonvulsants. Careful EEG monitoring is indicated, especially in sedated patients; therefore, even electrical seizures should be treated. Anticonvulsants should not be used prophylactically [2].
- BP control: BP should be under continuous monitoring. Systolic BP (SBP) values >200 mmHg or average values >150 mmHg should be managed by continuous infusion of antihypertensive drugs. It is considered safe to treat SBP values >150 mmHg in any case [2].
- Prevention of deep vein thrombosis (DVT): application of intermittent pneumatic compression devices. In patients with reduced mobility, after documenting the cessation of bleeding, prophylactic low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) may be considered from the fourth up to the tenth day of the ICH [2].
- Prevention of further haemorrhage: it is based essentially on close BP control, especially in patients where the ICH has the typical localisation of hypertensive vasculopathy. Once the acute phase is over, the goal should be to maintain BP in the 140/90 mmHg range.
  In patients with lobar ICH and non-valvular atrial fibrillation, withdrawal of anticoagulants should be considered given the high risk of recurrence.
  Anticoagulant therapy in smaller haemorrhages and antiplatelet therapy after ICH of all types may be considered when there are well-defined indications for their administration [2].

## 8.6 Pathophysiology of the Coagulation Cascade

The development of a clot can be schematically subdivided into three phases:

- Platelet activation
- Actual activation of the coagulation cascade
- Fibrinolysis

### 8.6.1 Platelet Phase

The first response to a vascular insult is the contraction of the smooth muscles of the vessel wall itself and platelet adhesion to the wall. Antiplatelet therapy, which inhibits platelet activation, adhesion and aggregation, is used to prevent vessel occlusion.

*Acetylsalicylic acid* is the most widely used antiplatelet. It acetylates platelet cyclooxygenase-1 (COX-1) irreversibly; it prevents platelet activation by inhibiting the release of thromboxane (TxA2).

The active metabolites of thienopyridines (*ticlopidine*, *clopidogrel* and *prasugrel*), produced by cytochrome P450 metabolism, bind to receptor $P_2Y_{12}$ with a covalent, irreversible bond during the platelets' whole life. The new receptor $P_2Y_{12}$

inhibitors (*cangrelor* and *ticagrelor*) change receptor conformation, inducing an irreversible block. All $P_2Y_{12}$ receptor blockers act by stopping the platelet activation induced by adenosine diphosphate (ADP).

Platelet activation alters the conformation of glycoprotein IIb/IIIa receptors, favouring fibrinogen binding and subsequent platelet aggregation. The glycoprotein IIb/IIIa receptor antagonist, *abciximab*, prevents fibrinogen binding and platelet aggregation.

### 8.6.2 The Coagulation Cascade

The event triggering the initiation of the coagulation cascade is exposure of tissue factor (TF, thromboplastin) from the microvascular bed. The TF-factor VII complex generates activated factor VII (extrinsic pathway), favouring the initiation, amplification and propagation of subsequent coagulation phases [8, 9]. Activation of coagulation factors II, VII, IX and X requires γ-carboxylation in the liver in the presence of the reduced form of vitamin K. Vitamin K antagonists (VKA) inhibit the enzyme vitamin K epoxide reductase, thus blocking the formation of reduced vitamin K and limiting the activity of coagulation factors [10]. The response to VKA is influenced by several factors such as polymorphisms altering the metabolism of the cytochrome P450 system, other medications, diet and other conditions.

Both UFH and LMWH are administered to reduce the risk of thromboembolism. Binding to heparin accelerates the effects of the inhibitor antithrombin; the heparin-antithrombin complex inactivates thrombin (factor IIa) and other proteases involved in clotting, especially factor Xa, but also factors IXa, XIa and XIIIa. Owing to their low molecular weight, LMWH have modest anti-factor IIa activity, and their anticoagulant activity is mostly exerted as anti-factor Xa activity, whereas UFH acts on both targets.

Direct thrombin inhibitors inactivate thrombin by binding it directly; bivalent inhibitors (*bivalirudin*, *hirulog*) bind thrombin both on the active site and on exosite1; monovalent inhibitors (*argatroban*, *melagatran* and *dabigatran*) bind only to the active site. (*Dabigatran* is a prodrug for oral administration).

The new factor X-antagonists (*rivaroxaban*, *apixaban*, *endoxaban*) are also administered orally.

No efficient inhibition strategies have yet been developed for the new oral anticoagulants [11].

### 8.6.3 Fibrinolytic Agents

Fibrinolysis is an enzymatic process that involves dissolution of fibrin clots by plasmin. Plasmin is generated from plasminogen by the action of an activator (tissue plasminogen activator, TPA) synthesised by endothelial cells and secreted locally following stimulation of the endothelium. Recombinant TPA (rTPA) is so powerful that it can reduce the concentration of fibrinogen in vitro (Fig. 8.1).

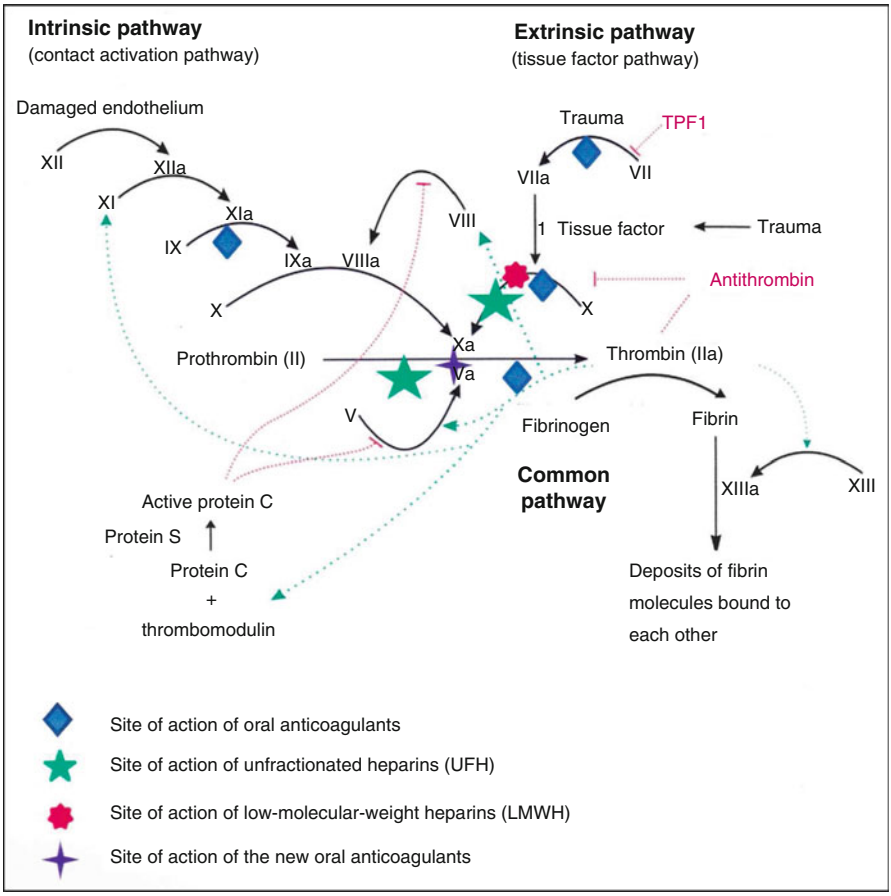


**Fig. 8.1** Coagulation cascade

## 8.7 Treatment

About 12–14 % of patients with ICH take oral anticoagulants [12, 13]: thus, a crucial goal in their treatment is to inhibit their effect to stem the haemorrhage and make subsequent treatment possible, be it medical or surgical.

The decision about surgical treatment is a complex one and should be weighed carefully, case by case, especially in relation to the patient's neurological conditions and the site of the haemorrhage. The American Heart Association published its most recent guidelines in 2010 [2].

- Patients with cerebellar haemorrhage, whose neurological condition is deteriorating and those suffering from brainstem compression and/or hydrocephalus

from ventricular obstruction, should undergo surgical decompression as soon as possible; ventricular drainage alone is insufficient.

- Supratentorial haemorrhage involving the cerebral hemispheres with a volume >30 ml and within 1 cm of the surface: surgical decompression with standard craniotomy may be considered. Currently there is no clear evidence indicating that very early haematoma removal can improve functional outcome or mortality rate.
- Patients taking anticoagulants: they need to be inhibited in the shortest time possible. If surgery is required, the goal is to obtain international normalised ratio (INR) ≤1.5, platelets ≥100,000 and partial thromboplastin time (PTT) in the normal range.

### 8.7.1 Vitamin K Antagonists

The action of these anticoagulants alters prothrombin time (PT) and INR. In the past they used to be antagonised by infusion of fresh plasma, which involved a prolonged procedure, the risk of transfusion reaction and, above all, a high volume of fluids for correction. The European guidelines recommend the use of prothrombin complex concentrate (PCC) together with vitamin K.

Factor VIIa infusion as the sole antagonist is not recommended: its action lasts only a few hours, and not all factors are replaced (Table 8.2).

### 8.7.2 Antiplatelet Therapy

Although transfusion of platelet concentrates is envisaged, it requires further investigation.

### 8.7.3 Heparins

The anticoagulant activity of UFH is measured by PT and antagonised by slow intravenous infusion of protamine sulphate (PS), whose dosage is calculated on the basis of the heparin dose administered and the time elapsed from its administration.

LMWH activity is measured by dosing factor Xa. LMWH cannot be antagonised completely, because PS inhibits no more than 50 % of its effect; repeat administration may thus be needed.

**Table 8.2** Ricoagulation flow chart

| INR | PCC dose (IU/kg) |
|---|---|
| <2 | 25 |
| 2<INR<4 | 35 |
| INR>4 | 50 |

### 8.7.4 New Oral Anticoagulants

The activity of *dabigatran* can be measured with thrombin time (TT). Commercial kits that assess *apixaban* and *rivaroxaban* activity indirectly are available, although there are no specific data on the actual degree of anticoagulation achieved during treatment.

Oral activated carbon may be administered if *dabigatran* was ingested less than 2 h earlier. It does not bind to plasma proteins and is eliminated by renal clearance; therefore, it can be removed by haemodialysis. Activated carbon has also been proposed to counter *rivaroxaban* and *apixaban*, but few data are available.

There are only in vitro data confirming the action of factor VIIa used as an antagonist [11].

### 8.7.5 Fibrinolytic Agents

Fibrinogen depletion is induced by rTPA administration and can be antagonised by antifibrinolytics such as *tranexamic acid* and *aprotinin*. Administration of fibrinogen, coagulation factors, and platelets has been suggested, but the guidelines do not provide conclusive data.

PCC preparations containing 3 (IX, X, II) or 4 (IX, X, II, VII) coagulation factors are available on the market. A possible scheme for their use with simultaneous slow intravenous infusion of vitamin K 5–10 mg is reported in Table 8.3:

If the INR target has not been reached in 20–30 min, administration can be repeated.

Only if PCC is not available may the infusion of fresh plasma (15 ml/kg) be considered, given the risk associated with the fluid overload (Table 8.3).

## 8.8 Thromboelastography (TEG)

TEG measures the dynamics of clot formation and resolution and may be useful in determining the risk of haemorrhage.

The TEG device consists of a cuvette and a thin wire probe suspended within it. Blood is added to the cuvette, which gently rotates every 10 s. As the blood clots, a fibrin network forms between the cuvette and the pin, connecting the freely suspended pin to the oscillating cuvette. The mechanical oscillation signal is translated into an electric signal, decrypted and integrated by a software. The values provided by the method include the velocity of clot formation (in minutes) measured by the following parameters [15]:

- R, time until the first evidence of a clot is reached (amplitude, 2 mm)
- K, speed of clot formation to reach an amplitude of 20 mm
- Delta, interval from initial clot formation to maximum velocity
- MA, clot strength measured as mm of maximum amplitude
- G, derived from MA and measured as dynes/cm$^2$

**Table 8.3** Anticoagulant – antiaggregant agents

| Agent | Route of admn. | Half-life | Duration of action | Metabolism | Lab test | Antidote |
|---|---|---|---|---|---|---|
| *Aspirin* | Oral | 20 min | 7 days | Hepatic | None | None/platelet transfusion |
| *Ticlopidine* | Oral | 4 days | 10 days | Hepatic | None | None/platelet transfusion |
| *Clopidogrel* | Oral | 7 h | 5 days | Hepatic | None | None/platelet transfusion |
| *Prasugrel* | Oral | 4 h | 5–9 days | Hepatic | None | None/platelet transfusion |
| *Ticagrelor* | Oral | 7 h | 12 h | Hepatic | None | None/platelet transfusion |
| *Abciximab* | Oral | 30 min | 72 h | Renal | None | None/platelet transfusion |
| *Warfarin* | Oral | 2–4 days | 2–4 days | Hepatic | INR | PCC + vitamin K |
| *UFH* | IV/SC | 1.5 h | 6 h | Hepatic | PTT | PS |
| *LMWH* | SC | 4–6 h | 12–24 h | Renal | Xa | PS (partial) |
| *Dabigatran* | Oral | 12 h | 1–2 days | Renal | Thrombin time | None/haemodialysis (activated carbon) |
| *Apixaban* | Oral | 8–12 h | 24 h | Hepatic | Assessment of action | None (activated carbon) |
| *Rivaroxaban* | Oral | 9–12 h | 24 h | Hepatic | Assessment of action | None (activated carbon) |
| *rTPA* | IV | 5 min | 1 h | Hepatic | INR-PTT | Antifibrinolytics/platelet transfusion/PCC |

Adapted from Roberts et al. [9] – Degos et al. [14]

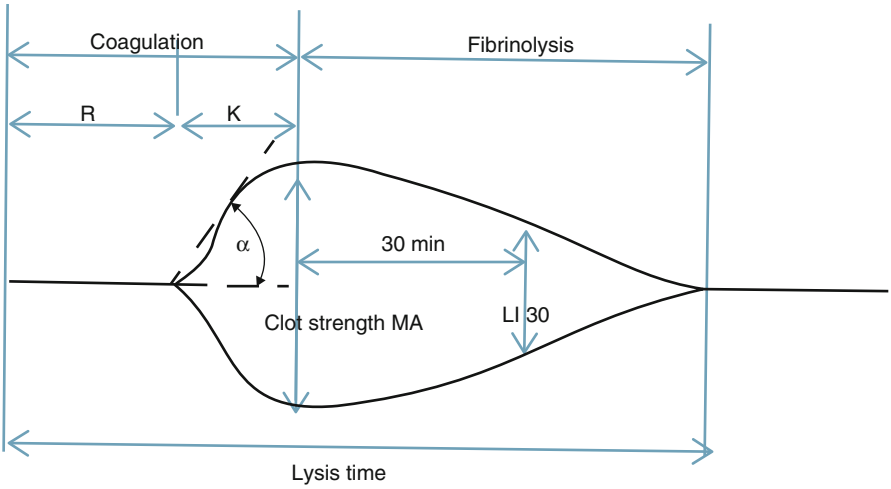


**Fig. 8.2** TEG

- **R** clot formation reaction time, it is the latency period until fibrin formation (normal value [N.V.] 5–10 min). It is a measure of the coagulation factors, i.e. the substances that induce fibrin formation. There may be congenital abnormalities (e.g. haemophilia) or acquired deficits (hepatopathy). In surgery, heparin administration is the most powerful inhibitor of thrombin formation (it potentiates ATIII and acts on its cofactor). An extended R typically means that the heparin administered has not been completely antagonised by PS, whereas a reduction is found in hypercoagulability states.
- **α** angle indicates clot extent at the beginning of its formation and measures the velocity of fibrin network formation and binding to platelets (N.V. 53–72°). It is a measure of fibrinogen-platelet interactions: it declines in hypofibrinogenemia and hypocoagulability states and is a result of excessive anticoagulant administration. It evaluates fibrin polymerisation.
- **K** clot hardening velocity, fibrin binding to platelets (N.V. 1–3 min).
- **MA** stabilised clot, it measures clot strengthening by platelets (N.V. 50–70 mm). MA is the maximum strength exerted by the clot; it decreases in case of hypocoagulability.
- **LI 30** lysis caused by clot firmness measured 30 min after it has reached MA. It measures clot reduction by plasmin after 30 min (N.V. 0–8 %).
- **CI** coagulation index, it is a derived parameter based on R, α and MA; it measures clotting ability as a whole and ranges from –3 to +3 (Fig. 8.2).

TEG can show coagulation alterations that are important in patients with ICH. However, it is operator dependent, and its reliability decreases when it is performed by multiple operators. It should be carried out by dedicated and adequately

trained staff; the device should be calibrated and subjected to quality control tests every day.

**Conclusions**

ICH is a very serious event whose incidence is continuously rising both due to the ageing of the population and to the increasing use of prophylactic anticoagulants and antiplatelet therapy.

Awareness of the mechanisms and time of action of the main medications and of the available lab tests can be very useful in the early management of patients with ICH.

The fairly recent introduction of new oral anticoagulants is improving compliance, but also exposes patients to a high risk of haemorrhage, since neither validated tests to measure the level of anticoagulation nor wholly efficient antagonists are available.

TEG provides precise data on the coagulation phases, improving treatment, if any, and reducing antagonist use. However, it is still poorly reproducible if performed by multiple operators: dedicated and well-trained staff and daily device calibration and quality control testing would partially address these limitations, even though the main goal should be to prevent haemorrhages by careful monitoring of anticoagulant therapy and BP control, which remains the main risk factor.

## References

1. Flaherty ML et al (2007) The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology 68:116–121
2. Morgernstern IB et al (2010) American Heart Association Stroke Council and Council on Cardiovascular Nursing: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for health care professionals from the American Heart Association/ American Stroke Association. Stroke 41:2108–2129
3. Huhtakangas J et al (2011) Effect of increased warfarin use on warfarin-related cerebral hemorrhage - A longitudinal population-based study. Stroke 42:2431–2435
4. Van Walraven C et al (2002) Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient metanalysis. JAMA 288:2441–2448
5. Witt DM et al (2013) Effect of warfarin on intracranial hemorrhage incidence and fatal outcomes. Thromb Res 132:770–775
6. Schols Angel MR et al (2014) Incidence of oral anticoagulant-associated intracerebral hemorrhage in the Netherlands. Stroke 45:268–270
7. Morgan T et al (2008) Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. Acta Neurochir Suppl 105:217–220
8. Adams RI, Bird RJ (2009) Coagulation cascade and therapeutics update: relevance to nephrology. Part I: overview on coagulation, thrombophilias and history of anticoagulants. Nephrology (Carlton) 14:462–470
9. Roberts HR, Monroe DM, Escobar MA (2004) Current concepts of hemostasis: implication tor therapy. Anesthesiology 100:722–730

10. Ansell J et al; American College of Chest Physician (2008) Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133(6 suppl):160–988
11. Kaatz S et al (2012) Guidance on the emergent reversal of oral thrombin and factor X inhibitors. Am J Hematol 87(Suppl 1):S141–S145
12. Radberg JA, Olsson JE, Radberg CT (1991) Prognostic parameters in spontaneous intracerebral hematomas with special reference to anticoagulant treatment. Stroke 22:571–576
13. Nilsson OG et al (2000) Incidence of intracerebral and subarachnoid hemorrhage in southern Sweden. J Neurol Neurosurg Psychiatry 69:601–607
14. Degos V et al (2013) Perioperative management of coagulation in nontraumatic intracerebral hemorrhage. Anesthesiology 119–1:1–10
15. Kawano-Castillo J et al (2014) Thromboelastography detects possible coagulation disturbance in patients with intracerebral hemorrhage with hematoma enlargement. Stroke 45:683–688

# Postpartum Haemorrhage (PPH): Diagnosis, Prevention and Treatment

9

Giorgio Tulli

## 9.1 Introduction

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality, responsible for approximately 25 % of almost 300,000 maternal deaths estimated to occur every year [1, 2]. It is also the major cause of maternal morbidity, i.e. anaemia [3].

Whereas the countries with lower economic resources are bearing the highest burden of postpartum haemorrhage, it is still a significant cause of maternal deaths in the more developed countries [4].

Deaths caused by PPH occur every thousand births in developing countries against one every hundred thousand in those with greater economic resources [5]. On average, PPH causes 100,000 maternal deaths per year [1] or a death every five minutes.

The sequelae of PPH include:

- Infertility
- Hysterectomy
- Neurological impairment
- Persistent organ failure

PPH causes 15 million cases of severe acute maternal morbidity. In Canada, for 25 % of severe acute maternal morbidity, 1 out of 1,000 live births is attributed to PPH [6]. In Great Britain, severe PPH complicates 0.1 % of live births, and two thirds of these suffer from severe acute maternal morbidity.

PPH is an authentic paradigm of the extreme inequality in health worldwide. Compared with western Europe or the United States, maternal mortality from PPH

G. Tulli
Department of Intensive Care Units and Perioperative Medicine,
Azienda Sanitaria Fiorentina (ASF), Florence, Italy
e-mail: gtulli@anicusgd.org



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is around 100 times more frequent in developing countries and sometimes even 200 times [7, 8], meaning that 99 % of deaths occurs in these countries. In the higher-income countries, PPH is significantly more frequent among members of ethnic or racial minorities [9] or in circumstances of social and economic disadvantage [10].

Nevertheless, the global trend of maternal mortality is favourable and has fallen by a third since 1990 [1], following efforts by the United Nations and many other organisations (*Millennium Development Goal 5 A*).

Overall it is estimated that PPH occurs in 1 to 5 % of births [11, 12], but the incidence reported varies with the definition of PPH. Calvert et al. [12] have recorded a prevalence of 10.8 % (95 % CI: 9.6–12.1) worldwide with a wide regional variation ranging from 7.2 % (95 % CI: 6.3–8.1) in Oceania to 25.7 % (95 % CI: 13.9–39) in Africa [13]. Severe PPH resulted lower at 2.8 % (95 % CI: 2.4–3.2) with a similar pattern, ranging from 1.9 % (95 % CI: 1.2–2.8) in Asia up to 5 % (95%CI: 0.3–15.3) in Africa.

The variability in PPH prevalence is referred to the blood loss measuring method (objective vs. subjective), to the treatment of the third stage of labour (active vs. waiting) and to region. The data over the last ten years suggest an increase in the prevalence of PPH, highlighted by various studies in Australia, Canada, the United States and Great Britain [14]. Joseph and colleagues [14] report that the increase observed in Canada was mediated by an increase in uterine atony despite the time adjustment for risk factors. Wu et al. [15] describe an increase in the incidence of placenta accreta compared to past decades, leading to an increase in caesarean sections. It is thus surprising that in recent years the percentage of PPH has grown in developed countries, almost exclusively caused by a growth in atonic PPH [10, 11, 13, 16, 17]. The reasons for this growth are still unclear. It has partly been attributed to an increase in risk factors, such as caesarean section, repeated caesareans (doubling the risk compared to the first), age, obesity and multiple gestations following assisted reproductive techniques [13].

It must however be stressed that death from PPH seems to be preventable in many if not most cases, and not least in high-income countries [18, 19]. And yet this phenomenon is one of those most affected by substandard care, according to the three-yearly report published in the UK.

## 9.2 Physiopathological Considerations and Definition of Postpartum Haemorrhage

The pregnant uterus receives approximately 350 ml/min of maternal blood [20], meaning that postpartum haemorrhage can be extremely serious but is easily diagnosed, while it can be very difficult to diagnose during the initial stages of PPH or for less serious bleeding.

To get an idea of the changes in the uterus blood flow, some physiological data have to be considered. In the ascending uterine artery before pregnancy, there is a 94.5 ml/min flow that reaches 342 ml/min at term (3.5 times greater); the percentage of the cardiac output in the uterine artery is 3.5 % in the initial gestation and 12 %

at term; the artery diameter widens from 1.6 to 3.7 mm at term, and the resistance to flow (flow velocity/systolic-diastolic peak ratio) is 5.3 in early pregnancy and 2.3 at term. These changes reflect the continuous growth and development of the uteroplacental circulation that guarantees the metabolic requests of the growing foetus.

There are many different definitions of PPH, but the majority refer to *arbitrary thresholds* in terms of millilitres of blood loss considered separately for vaginal and caesarean delivery or combined as in the case of the Royal College of Obstetrics and Gynaecology in Great Britain, statistically associating the increasing percentages of caesarean section with a greater incidence of PPH.

There are also different definitions of severe PPH in many countries, mainly based on functional thresholds, such as the need to transfuse more than 4 units of concentrated red blood cells or on haemodynamic values enabling a haemorrhagic shock diagnosis. However, the majority of the PPH thresholds are not well defined since they refer to imprecise blood loss estimates [21]. The World Health Organisation (WHO) recommends defining PPH as the loss of ≥500 ml of blood within 24 h after birth, with severe PPH defined as a blood loss of ≥1,000 ml (*WHO Recommendations for prevention and treatment of postpartum haemorrhage*, *2012*). Other definitions indicate a blood loss for PPH of >15 % of the total blood volume or 10 % decrease in the haemoglobin levels measured during peripartum [22]. It is essential however that blood loss is measured with objective methods such as collecting sacs for the blood lost in postpartum.

Recent definitions highlight the importance of symptoms (light-headedness, weakness, palpitations, sweating, restlessness, confusion, air hunger and/or syncope) and signs of hypovolaemia (hypotension, tachycardia, oliguria, low oxygen saturation). The majority of healthy women do not show signs or symptoms of haemodynamic instability until a 1,200 ml blood loss. Some PPHs might not be recognised before the appearance of obvious hypovolaemia because the loss of blood is often underestimated, bleeding can be intra-abdominal, and furthermore a minor loss of blood is enough to develop PPH when women are already compromised by anaemia, preeclampsia or other comorbidities [23–25].

It is important to reflect on the miscalculation of the mother's real blood loss. Even an expert gynaecologist or midwife can seriously underestimate this [26] since during pregnancy coagulation factors increase, including fibrinogen, and although this can be considered as a protection, it can also be confusing if the physiology of the coagulation system during pregnancy is not clear. More scientifically, the real intrapartum blood loss is greater than 500 ml when it is measured with Cr 51 tagged erythrocytes [27], so that in clinical setting we should be considering that the majority of vaginal deliveries are followed by an authentic PPH. It is thus not surprising that the PPH rates reported vary according to the blood loss method of assessment [28, 29]. It was clear that a global consensus was needed on the definitions of blood loss, and an international database has now been set up [13].

Another general point to make is that the term PPH suggests a diagnosis, which it definitely is not. Quite the opposite, if the PPH syndrome occurs, then a diagnosis must be made with clinical assertiveness [30], and it is essential for it to be prompt with equally prompt treatment to permit a conservative approach. The definition of

intrapartum haemorrhage must be preferred to a postpartum haemorrhage since the former does not semantically exclude bleeding before delivery and its sub-terms open the way to differential diagnoses on the basis of the underlying causes of the haemorrhage:

- Antepartum haemorrhage (APH)
- Primary PPH
- Secondary PPH

These PPHs usually have different pathophysiological causes and consequently distinct treatments. Before examining the different types of intrapartum haemorrhage, let us see how blood loss during vaginal or caesarean section is calculated. The estimate can be visual and therefore very approximate, for example, calculating the haematocrit value and also other variables before and after delivery. Otherwise the blood volume can be calculated during pregnancy (cEBL) {0.75 × [(mother's height in inches × 50) + (mother's weight in pounds × 25)]} [31] (Nadler's formula for calculating blood volume for non-pregnant females: 0.3561 x height in $m^3$ + 0.03308 × weight in kg + 0.1833). The blood volume calculated is multiplied by the percentage of blood lost indicated by the ratio [(Hct pre-delivery – Hct post-delivery)/Hct pre-delivery] (vEBL). This estimate is related to the type of delivery and perineal laceration in a study on 677 pregnant women. It was seen that vEBL is statistically different from cEBL. This study demonstrates how visual methods can underestimate blood loss [26].

### 9.2.1 Antepartum Haemorrhage

The most common causes of antepartum haemorrhage (bleeding after the 24th week up to expulsion) are:

- Placenta previa
- Placental abruption
- Uterine rupture

All these conditions can be very serious with a mortality rate of between 22 and 37 % for placenta previa and for placental abruption [32, 33]. Uterine rupture after uterine scarring or obstructed labour often results in catastrophic foetal outcome, and in developing countries, it is the greatest cause of maternal mortality [34], while in Europe it more often contributes to maternal morbidity with a high hysterectomy rate [35].

Naturally the most important issue for these patients is that they have not given birth, meaning that two lives are at risk; the well-known difficulties in resuscitation in pregnancy have recently been the subject of a critical review [36]. Another important issue is that placental abruption can be chronic, with a progressive process of coagulation and fibrinolysis in the laceration between the placenta and decidua, starting up a disseminated intravascular coagulation in over 50 % of cases [37].

### 9.2.2 Primary Postpartum Haemorrhage

It is defined as a haemorrhage within the first 24 h after delivery and is the most common subtype of PPH. This is because the most frequent cause of PPH, uterine atony, appears as primary PPH.

Other differential diagnoses include:

- Placental retention
- Lacerations of the cervical tract or genitals
- Uterine inversion consequent to severe atony or vigorous umbilical cord traction
- More rarely:
- Pre-existing coagulation disorders such as HELLP syndrome (haemolysis, elevated liver enzymes, low platelets syndrome), acute fatty liver of pregnancy and congenital defects

The reason coagulation disorders play a lesser role in primary PPH is because the uterine contractions play a greater role in the haemostasis of the initial stages. Myometrium fibres spread in all directions, and this mechanical action clamps the spiral arteries; the coagulation only becomes important later on.

### 9.2.3 Secondary Postpartum Haemorrhage

Bleeding appearing later than the 24 h up to 6 weeks after birth is called secondary postpartum haemorrhage. Besides coagulopathy, as previously described, other factors develop only after birth, such as intrauterine sepsis.

The appearance of PPH before or immediately after birth or even later already provides the first important elements for the differential diagnosis that anaesthetists in the emergency team or in intensive care must bear in mind.

## 9.3 Aetiology

The aetiology of PPH is traditionally indicated by the four Ts: tone, trauma, tissue and thrombin. Tone describes uterine atony, when the uterus fails to contract sufficiently. This is the primary cause of PPH, responsible for some 70 % of cases [38].

Trauma of the genital tract or uterus is responsible for around 20 % of PPH and includes perineal, cervical and vaginal lacerations as well as the spontaneous or iatrogenic rupture of the uterus caused by surgical or instrumental delivery [38].

Aetiologies linked to tissue include placental retention and abnormal placentation and are responsible for 10 % of cases [39]. These aetiologies operate through three primary mechanisms: uterine atony caused by tissue retention that prevents the uterus from contracting effectively, erroneous placentation in a less contractile tissue in the lower part of the uterus or invasive placentation with various levels of

attack on the myometrium and potential extension to other organs (e.g. rectum or bladder) [39]. Thrombin refers to congenital or acquired coagulation disorders that include dysfunction of the coagulation cascade or platelets and disseminated intravascular coagulation (DIC causing around 1 % of PEs) [40].

## 9.4 Diagnosis of PPH

The majority of PPHs occur without a definite warning; a consistent use of prevention measures such as the rapid detection of PPH, its prompt identification and treatment of the haemorrhage aetiology are essential for reducing maternal mortality and morbility [23]. A frequent monitoring of vital signs and palpation of the fundus after delivery are strongly recommended to identify the development of PPH, and doctors, nurses and midwives must always be on the alert for any blood loss and changes in vital signs.

The "track and trigger" clinical signs that include definite threshold values for haemodynamic instability are used to indicate patients at risk of an adverse event. The California Maternity Quality Care Collaborative (CMQCC) has proposed definite values for warning and action (e.g. heart rate $\geq$ 110 beats/min, systolic blood pressure $\leq$ 85/45 mmHg and oxygen saturation $<$ 95 %), and the Confidential Enquiry into Maternal and Child Health (CEMACH) has developed an Obstetric Early Warning Chart for health professionals with numeric and visual suggestions for taking action, currently in use in the National Health Service [41, 42].

The CEMACH chart prompts healthcare professionals to carry out an urgent medical assessment when either one markedly abnormal finding is observed or a combination of two abnormal but less severe findings among the vital signs considered (e.g. breathing rate, oxygen saturation, temperature, heart rate, systolic blood pressure). The validation study on this tool has revealed a high sensitivity and a reasonable specificity, but it also requests a further refining of the blood pressure threshold values [42].

The British Royal College of Obstetricians and Gynaecologists recommends the use of MEOWS for the early detection of continuous bleeding [43]. The shock index, a combined pulse and pressure measurement (pulse/blood pressure), has been seen to have a certain clinical utility for the early diagnosis of haemorrhage in a recent systematic review [44]. However, a more in-depth research among an obstetric population is necessary [45].

The effectiveness of the trigger tools to reduce intensive care admissions or for severe medical outcomes has not yet been established, and there is as yet no complete evidence. The timely detection of PPH by carefully monitoring blood loss during delivery and in the postpartum stage is especially critical in low-income contexts, but it is also very useful in the developed world. The gold standard for estimating blood loss, i.e. photospectrometry or the colorimetric measurement of alkaline haematin in blood, is impracticable in many clinical settings (*low-cost mobile platform for real-time monitoring of blood loss 2013*: *May 10*, *2011*).

As said earlier, although visual estimation is the most common method for quantifying blood loss worldwide, it tends to underestimate it by 30–50 %, with a still greater inaccuracy when the blood loss increases. A dedicated clinical training improves the accuracy of the visual estimation of blood loss, and written and illustrated guidelines can assist the delivery room staff. Specific devices designed to assist measuring, such as a plastic sheet under the hips closed at one end to collect the blood, can also help the estimation. Doctors today can also use mobile phone cameras to estimate blood loss and construct an algorithm; other low-cost applications for a real-time monitoring of blood loss are also being developed (*National Institute for Health and Clinical Excellence CG 55 Intrapartum Care*: *Care of healthy women and their babies during childbirth*; *2007*).

## 9.5 Identifying PPH Risk

A logical way to reduce maternal morbidity and mortality from PPH should be to identify patients at risk of PPH and notify their delivery to a hub equipped with the appropriate facility for efficiently treating severe PPH in secure conditions. Unfortunately this approach is not entirely possible at the moment. Great efforts have been made to identify the risk factors (Table 9.1 and Fig. 9.1), to develop scores and nomograms for PPH risk [7, 29, 46–48], but although an odd ratio of 18.4 has been demonstrated for certain risk patterns [47], 90 % of PPHs are still unpredictable [48], and in parturients with programmed vaginal delivery (that is

**Table 9.1** Risk factors for development of postpartum haemorrhage (PPH)

| | Prepartum | Peri/postpartum |
|---|---|---|
| Placenta/foetus | **Anomalous insertion of the placenta**<br>Hypertensive diseases of pregnancy<br>Chorioamnionitis | **Pathological adherent placenta/retained placenta**<br>**Macrosomy**/large for gestational age baby |
| Uterus/birth channel | History of surgery of the uterus, including caesarean section<br>Myoma<br>Uterine overdistension (poly-hydramnios, **multiple gestations**, non-cephalic presentation)<br>Multiparity (>5) | Induced/**prolonged labour**<br>Instrumental birth<br>Trauma of the birth channel (**uterine rupture, cervical laceration**, vaginal trauma) |
| Coagulation | Innate or acquired coagulopathy, including HELLP syndrome and pregnancy-associated thrombocytopenia<br>**Thrombocytopathy** | Amniotic fluid embolism |
| Other | **Antenatal bleeding**<br>**History of PPH**/retained placenta<br>Nicotine abuse<br>Age <20/>35<br>Anaemia | Elective caesarean section<br>**Emergency caesarean section**<br>Inhaled anaesthetics |

In **bold** type more frequent risk factors

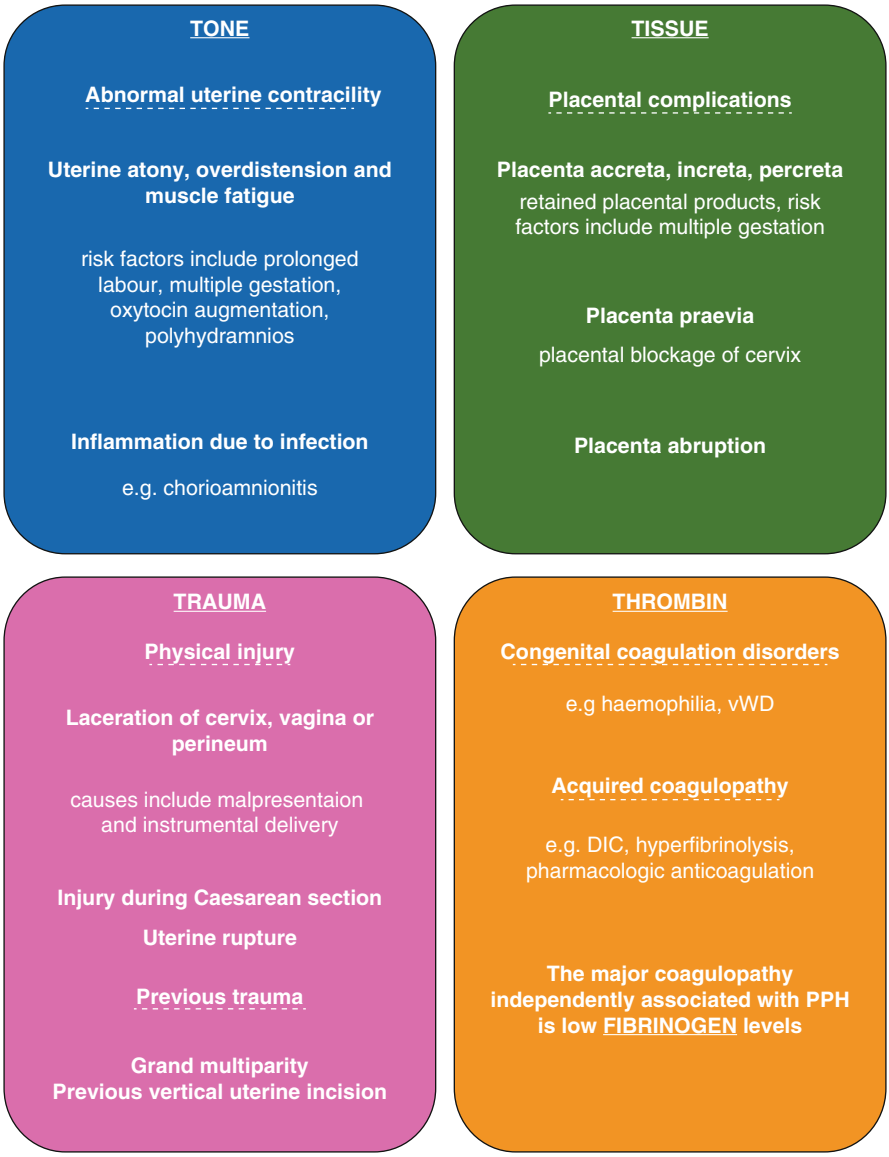


**Fig. 9.1** Major risk factors associated with PPH. Conditions are classified according to pathophysiology. *DIC* disseminated intravascular coagulation; *vWD* von Willebrand's disease; *PPH* postpartum haemorrhage

without abnormal placentation, anomalous foetal position, etc.), the aforesaid probability of PPH in the presence of all the remaining risk factors is under 1 % [29]. The main reason for this is that the well-known antepartum risk factors are more frequent than the incidence of PPH, hence their low probability of being predictive.

Greater risk factors, such as a prolonged labour or placental retention, develop only during the labour and delivery, and it is thus impossible to rapidly send the patient to a specialised centre.

PPH will thus continue to occur in contexts with less than optimal facilities. The aim should be to develop and validate protocols for preventing PPH morbidity and mortality that can be used in clinical contexts outside the big medical centres (and possibly also in low-resource countries), such as the AMTSL (*active management of the third stage of labour*), a bundle of low-cost measures easily applicable for the management of a parturient after birth and until the placenta is expelled:

- Administration of an uterotonic agent (oxytocin is mostly preferred) within a minute of the baby's birth
- Controlled traction of the umbilical cord and massage of the uterus after expulsion of the placenta

AMTSL has been demonstrated to reduce substantially the incidence and severity of PPH [49–51].

## 9.6 Random Treatment of PPH and Resuscitation in PPH

As in many medical situations, the Pareto principle (*the majority of the results is due to the contributions of a minority of factors or agents*) also applies for the reduction of PPH mortality and morbidity: a small percentage of measures and interventions will have a greater impact on the outcome and the failure to initiate these interventions in time cannot be compensated by other and more sophisticated measures. The single most important factor in preventing an adverse maternal outcome is the early recognition of an imminent or ongoing PPH [52], something that the anaesthetist cannot influence. In this case the underestimation of blood loss is a key factor in delaying therapy [13, 19, 26]. The second most important factor is the need for an early resuscitation, largely dependent on the hospital facilities, the organisation of the medical emergency teams, the activation of procedures and finally by the staff training [53].

In a single institution, PPH is a relatively rare complication that affects 1 out of 1,000 live births [54], and births are such a frequent event that they often cause a high workload. Hence, it is simply impossible for the staff to develop routine skills for treating severe PPH, especially in small delivery rooms.

Nonetheless, in European countries, PPH often occurs in contexts where virtually all the necessary resources for an initial resuscitation are available, including an expert staff (e.g. MET medical emergency team or outreach team), a laboratory for blood analyses and a transfusion centre for obtaining blood. What must be avoided is an ineffective resuscitation after hypothermia, acidosis and coagulopathy, dubbed the lethal triad [55].

Panels of international experts emphasise that it is necessary to have standard procedures and protocols for massive transfusions as well as realistic field drills, instrumental simulations that are immensely valuable if not essential [13, 30,

56–59]. After each case of severe PPH, a multidisciplinary debriefing session must be promptly organised to identify and discuss any problems that could have emerged in the local management of the PPH [60].

## 9.7 Medical and Surgical Treatment

### 9.7.1 Uterotonics and Volaemic and Haemostatic Resuscitation

#### 9.7.1.1 Uterotonic Drugs

The majority of PPH cases will be primary PPH caused by uterine atony, in which the uterus does not contract sufficiently to clamp the vascular bed of the decidua. Atony can occur in some 5 % of births but is more often found in births with complications. It usually occurs with painless vaginal bleeding that develops slowly at the beginning. A flaccid uterus can easily contain more than a litre of blood, to be added to an underestimation or a non-recognition of PPH. Table 9.2 shows which uterotonic drugs are mainly used.

It is important for all members of the team to be familiar with these important drugs and their properties. In the case of acute PPH, obstetricians can rely on anaesthetists for medical treatment while they operate on the patient. WHO recommends the preventive administration of uterotonics during the third labour stage with oxytocin (IM/IV, 10UI), and this is supported by strong evidence (type A). When oxytocin is not available, WHO recommends the use of other injectable uterotonics (ergometrine/methylergometrine or oxytocin/ergometrine) or oral misoprostol (600 micrograms) (*World Health Organisation. WHO recommendations for the prevention and treatment of postpartum haemorrhage 2012*).

The current evidence for other components of the active management of the third stage of labour (AMTSL) has prompted WHO to change its recommendations on the controlled traction of the umbilical cord (CCT). It is now considered optional when a well-trained and expert staff is present, otherwise is not recommended. NICE and the International Federation of Gynaecology and Obstetrics (FIGO) support AMTSL, albeit the individual components vary from institution to institution [61]. NICE advises early clamping and early cutting of the cord, whereas massage of the uterine fundus followed by expulsion of the placenta is recommended by FIGO. WHO recent recommendations suggest clamping the cord later (1–3 min after birth) and an intermittent assessment of the uterine tone. AMTSL also requires well-trained health practitioners for this management; the risks of an AMTSL performed by inexpert practitioners, and particularly the CCT, have not yet been studied.

At the moment, oxytocin is the preferred uterotonic for preventing and initially treating PPH caused by uterine atony [62]. However, its efficacy can be limited, and repeated doses might not produce a further effect, probably explained by the desensitisation of the uterine receptors [63].

The most important side effects of oxytocin are vasodilatation and reflex tachycardia through the calcium-dependent activation of the NO (nitric oxide) pathway.

**Table 9.2** Uterotonic drugs

| | Dosage | Cautions |
|---|---|---|
| *Oxytocin analogs* | | |
| Oxytocin | Bolus: 3–10 UIi.v./10 UI i.m.; continuous: 10 UI/h titrated | Vasodilatation, tachycardia, hypotension (especially with hypovolaemia), antidiuresis (fluid overload), caution in preeclampsia, nausea, vomiting |
| Carbetocin | 100 mcg i.v. | |
| *Ergot derivates* | | |
| Ergometrine | 0,25 mg i.m./i.v; can be repeated every 5 min Maximum 5 doses | Potent vasoconstrictor: contraindicated in hypertensive disease of pregnancy, extreme caution for use in combination with other uterotonics, myocardial ischaemia, pulmonary arterial hypertension, nausea / vomiting/dizziness |
| Methergonovine | 0.20 mg i.m; every 5 min; maximum 5 doses | |
| *Prostaglandin derivates* | | |
| Sulprostone | 8.3 mcg/min (≤500 mcg/h) Maximum 1,500 mcg/24 h, de-escalation of dosing necessary | Careful in hypertensive/ hypovolemic patients, gastrointestinal disturbance, shivering, pyrexia, hypotension with $PGF_{2\alpha}$<br>Bronchospasm (extreme caution in patients with asthma), pulmonary arterial hypertension |
| Carboprost (15-metil-$PGF_{2\alpha}$) | 0.25 mg im/intramyometrically every 15 min, maximum 2 mg | |
| Dinoprostone | 2 mg per rectum every 2 h | |
| Dinoprose | 0.5–1mg intramyometrically or 20 mg + 500 ml NaCl 0.9 % infused into uterine cavity | |
| Gemeprost | 1–2 mg intra uterus/1 mg per rectum | |
| Misoprostol ($PGE_2$) | 600–1,000 mcg per rectum/ intra uterus/sublingually | |

From B-Lynch et al. [52]

This increases the cardiac output in healthy subjects, but decreases it if the physiological cardiac response is affected as it does in the PPH situation [64]. It must also be remembered that oxytocin has a similar action to ADH and has almost the same chemical structure. Oxytocin must be used with extreme caution in the PPH patient who has not been resuscitated. The German Society of Anaesthesiology and Intensive Care strongly warns against a bolus administration of oxytocin [65]; the Confidential Enquiry into Maternal and Child Health (CEMACH) recorded a maternal death following the administration of an oxytocin bolus in a hypovolaemic patient [66]. In women with preeclampsia, the cardiovascular effects can be more intense and less predictable, so that oxytocin must be used with specific precautions in these patients [67].

Some years ago carbetocin, analogous to oxytocin, started to be used in clinical practice. Its main advantage is that its action lasts longer than that of oxytocin (plasma half-life of approximately 40 min vs. under 180 s for oxytocin) [68, 69].

The use of 100 micrograms of carbetocin is the equivalent of oxytocin for PPH prevention with less need for a uterine massage [70]. However, there is no data for the treatment of manifested PH, meaning that this new drug cannot be recommended for it, especially as from a purely mechanistic point of view it shares the ceiling-effect problems and possible haemodynamic side effects of oxytocin.

It should be recalled that this is the only drug with a specific indication for PPH in caesarean sections. If the oxytocin agonists fail as front-line treatment, alternative uterotonics should not be delayed, such as the prostaglandin derivatives now used extensively, especially PGE1 (misoprostol) that can be given in the dose of 800/1,000 mg through the vagina, rectum or sublingual route, which seems to be the most rapid, although not always practicable, route. It is usually the preferred drug in low-resource countries and has limited cardiovascular effects. But it is also extensively used in the majority of protocols in Italy, with few side effects and excellent results. When administered singularly, misoprostol is associated with a higher blood loss than oxytocin [71, 72], but when associated to oxytocin, it seems to have less side effects than other combinations, albeit there is no conclusive data as yet. It has to be remembered that this is an off-label drug, but several regions, including Tuscany, have given specific indications for its use in PPH and medical abortion. Sulprostone, prostaglandin PgE2, has long been used in PPH and can still be considered as an alternative to misoprostol, although with greater side effects and risk (one maternal death by myocardial infarction). Ergot derivatives with less efficacy and greater side effects are also used as second-line uterotonic drugs.

All these drugs can cause side effects and should not be administrated as a bolus. Their combination can cause unpredictable cardiovascular effects, especially if there is continuous bleeding. In many obstetrics departments, the combination of two uterotonic drugs, with the exception of oxytocin-misoprostol, is discouraged. Nevertheless, the fixed combination of oxytocin and ergometrine is available today.

### 9.7.2 Aetiological Diagnosis of the Haemorrhage and Management of Non-atonic PPH

The treatment of PPH is specific for every cause of bleeding, and an appropriate aetiological management must be developed. The identification of the bleeding source and its subsequent repair can control bleeding from lacerations of the genital tract. If the bleeding is so severe, the formation of the haematoma so rapid or the vaginal tissue so friable that it is impossible to repair, then conservative and mechanical surgery can be entirely justified. The manual removal of the retained placenta is the definitive treatment and should be effected after a gentle attempt on umbilical cord traction compressing the uterus upwards (a manoeuvre only to be carried out by very expert staff), at the same time administering oxytocin IM or IV, but not ergometrine and prostaglandin E2 alpha.

The Cochrane critical review of nine trials suggests that the injection of prostaglandin or plasma expander in the umbilical vein can reduce the need for a manual removal of the placenta, but further research is needed to determine better the effect on the demand for transfusion or uterotonics [73]. Abnormal placentation (placenta accreta, increta and percreta) must be suspected if the manual extraction of the retained placenta is unsuccessful. An antenatal ultrasound scan supplemented by magnetic resonance imaging will minimise maternal and neonatal mortality and morbidity, and it is particularly important for women who have had a previous caesarean delivery. There are less blood losses and minor complications in planned caesarean hysterectomies than in urgent ones, even if overall the risk of PPH is greater in caesarean section compared to the vaginal delivery. Programmed caesareans at 34–35 weeks balance out the increased risks associated with an emergency caesarean at an advanced gestational age, albeit maximising foetal maturity [74].

An optimal management of the delivery includes antenatal optimisation of the mother's haemoglobin level, an early anaesthesiologic assessment, the use of graduated compression stockings, the administration of shared prophylactic antibiotics, the execution of preoperative cystoscopy, warning the transfusion centre about a possible massive haemorrhage and the guarantee of having blood products available in the delivery room. When women strongly desire a future fertility, conservative approaches to the management of the placenta accreta must be attempted, such as ligature, suture or embolisation of the uterine artery and the use of methotrexate to accelerate the placental regression. But concrete evidence is lacking for all these methods [75–77].

The rupture of the uterus and uterine inversion are rare, albeit very serious, complications that can lead to a postpartum haemorrhage. The most common aetiology of the uterine rupture is scarring from a caesarean section or other uterine surgery [78], although it is often caused by a prolonged obstructed labour or the use of herb-based preparations to induce or accelerate delivery in low-resource countries [79]. The rupture can extend upwards towards the uterine fundus, downward towards the bladder or vagina or sideways towards the broad ligaments, thus increasing the risk of substantial haemorrhage and consequent maternal morbidity and mortality. Induced labour is also implicated in the rupture of the uterus, with greater evidence for prostaglandin than for oxytocin [80].

The American College of Obstetricians and Gynaecologists (ACOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) recognise the potential greater risk of the uterus rupturing with induction but recommend its rational use together with appropriate patient counselling. ACOG and RCOG recommend always performing a vaginal delivery after a caesarean (VBAC) in a well-equipped delivery room with a trained staff to guarantee all possible emergency care and assistance. SOGC indicates that laparotomy must be available within 30 min. Signs and symptoms of rupture include abdominal pain and abdominal guarding, vaginal or intra-abdominal bleeding, thoracic pain, foetal deoxygenation, cessation of uterine contractions and palpation of the foetus outside the uterus. But the diagnosis is mainly carried out with cardiotocography, the reason why a continuous CTG is necessary in the event of VBAC. An early detection or the simple

suspicion of rupture allows a prompt surgical assessment, foetal delivery and surgical repair of the uterus. Delays in the diagnosis and treatment can result in the death of the foetus and/or the mother.

Uterine inversion can be the result of either an overly forceful traction of the placental cord when the placenta is being expelled, especially when the uterus is not well contracted or spontaneously with a Valsalva manoeuvre [81]. Manually returning the uterus to its proper anatomic position will correct the inversion and the resulting PPH. Tocolytics, halogenated anaesthetics or nitroglycerin can be administered with the purpose of relaxing the uterus and helping it to return to its normal situation. If the inversion resists manual efforts, then surgery can be requested.

Bleeding caused by an inherited or acquired coagulopathy is an uncommon cause of PPH; nevertheless, it should be considered when there is a family history of coagulation defects or a personal history of menorrhagia [82]. More common is the development of DIC, a consumption coagulopathy, caused by a severe PPH. In DIC, the coagulation cascade is activated, and fibrin thrombi are deposited at intravascular level. This process leads to a rapid depletion of the platelets and coagulation factors, and this develops a severe bleeding caused by the body's incapacity to continue to form coagulates because factors V and VII, the platelets, the prothrombin and the fibrinogen are rapidly consumed. The haemorrhage caused by the depletion of these factors is treated by replacing them and by transfusion of blood products [83, 84].

Treatment of the obstetric population with a fibrinogen concentrate suggests a rapid and efficient treatment of hypofibrinogenaemia without serious side effects. Clinical trials on fibrinogen concentrate conducted on elective and cardiac surgery patients have demonstrated an improvement in the haemostasis and less need for other blood products, although the first randomised controlled trial specifically focussed on PPH is still underway [85–88].

### 9.7.3 Mechanical Procedures for the Treatment of PPH

The mechanical procedures used to treat PPH from atonic and non-atonic uterus include massage, uterine packing and tamponade. WHO and FIGO strongly recommend the use of uterine massage for the treatment of PPH immediately after diagnosis. WHO no longer recommends uterine packing because of the potential damage it could cause but instead recommends a tamponade with intrauterine balloon (IUB) for atonic PPH that does not respond to uterotonics or when they are not available. The use of the IUB can reduce the need for invasive procedures; however, to date there is no real evidence but only case reports [89]. Uterine balloons such as the Sengstaken tube or Bakri and Rush balloons are available in countries with high economic resources, but their cost is prohibitive (a Foley or a catheter for prostate can also be used) in lower-resource countries.

Any problems that could arise from increased infection rates following the use of the IUB are not today supported in literature but are certainly presumably less than with a vaginal tamponade. The intravaginal tamponade has been suggested for

treating vaginal lacerations, but has not yet been adequately explored. The IUB can also be used as a diagnostic instrument to indicate if a laparotomy is necessary. Finally, the use of the IUB with the B-Lynch or other compression sutures is called a "uterine sandwich"; this technique has been successful in avoiding a hysterectomy in all the cases reported with no postpartum morbidity, and it needs further investigation. Chemical agents have also been studied for the PPH tamponade [90–94].

### 9.7.4 Measures for Gaining Time and Other Procedures for PPH

The recommended measures for gaining time in intractable PPH from atonic or non-atonic uterus include:

- External aortic pressure
- Double-handed uterine compression
- NASG (non pneumatic antishock garment)

External aortic pressure significantly reduces the blood flow to the pelvic organs while the supply of oxygenated blood to the surrounding organs is preserved [95]. It is traditionally performed manually by applying pressure with a closed fist on the abdominal aorta slightly on the patient's left and immediately above the umbilicus. A recent invention is an external aortic compression device (EACD), comprising a spring compression kept in place by leather belts. The use of EACD has proved useful in significantly reducing the time for the uterine bleeding to cease, although further studies are needed to determine the efficacy of this instrument.

The NASG is a low-technology instrument for the primary resuscitation to be used to stabilise women suffering from hypovolaemic shock secondary to obstetric haemorrhage (OH) [96]. It is a light, reusable garment made of neoprene and Velcro for compressing the lower part of the body. The NASG plays a unique role in haemorrhagic shock treatment by controlling the shock and reducing blood loss, stabilising a woman until definitive care is available. The NASG increases blood pressure by decreasing the vascular volume and raising vascular resistance in the areas of the body submitted to compression, but does not exercise enough pressure to generate tissue ischaemia as in previous instruments. It can be used for obstetric haemorrhages of every aetiology, can be applied by health practitioners with minimum training and does not compete with other PPH treatments. Some experimental studies have shown a significant reduction in blood loss, a quicker recovery from shock and a lower mortality rate [97, 98]. The NASG is recommended as a measure for gaining time in PPH both by WHO and FIGO, and RCOG indicates that the NASG can be useful during transfer to more specialised units and also while waiting for procedures or surgery.

Arterial occlusion and embolisation of the uterine artery are procedures that can prevent a greater loss of blood, avoiding the need for massive blood transfusions and hysterectomy. It is recommended trying them before deciding on surgery, although these procedures can only be performed by a team of expert interventional radiologists. Occlusion is often a prophylaxis for a known placenta accrete,

performed by positioning occlusive balloons in the internal iliac and uterine arteries, balloons that are inflated in the case of PPH [99]. If the bleeding continues even after the balloons are inflated, then an embolisation can be performed through the same catheters, positioning microparticles, polyvinyl alcohol, gel foam or spirals that occlude the blood flow to the uterine arteries [100].

UAE is recommended as an alternative conservative treatment for haemorrhages with multiple aetiologies when the resources to perform it are available. It is not widely used, albeit clinical case studies show high success rates (95 %) and low complication rates (4.5 %) and the evidence, albeit preliminary, of fertility conservation [101, 102]. Some complications have been reported such as uterine necrosis, thromboembolic events or fistula, indicating that these techniques require great experience [103].

### 9.7.5 Surgical Treatment of PPH

Should the medical and mechanical treatments of PPH fail, then a surgical exploration is needed [104]. The surgical approach differs according to the method used for delivery, the suspected aetiology and the patient's clinical state [105, 106].

The surgeon has to decide rapidly if an intervention is necessary. A curettage can be useful in the case of suspected placental residues, the use of a balloon up to a laparotomy (or re-laparotomy after a caesarean section) with exploration and conservative treatments; if these fail, a hysterectomy could be necessary.

The B-Lynch suture is a compression suture, used like braces between the front and rear of the uterus with the aim of promoting its contractibility. It can be an initial attempt to stop the bleeding while trying to preserve fertility. Alternatively, the uterine and internal iliac arteries can be tied bilaterally to diminish temporally the blood flow to the uterus. Whereas the internal iliac artery legation was once more common, the uterine artery legation is now preferred because it is easier to identify and it has higher success rates (80–96 %) [107, 108]. Also to be considered, where possible, is the embolisation of the uterine arteries that can also be used as a prophylaxis, for example, in central placenta previa.

### 9.7.6 Resuscitation with Fluids and Haemostatic Interventions

There is no doubt that massive transfusion protocols can improve the outcome of patients with massive bleeding [109, 110]. Although these protocols were derived from military medicine and their adoption for PPH ignores some important differences, they are frequently performed for this specific indication and can certainly be useful in severe PPH [83, 101, 111].

A key factor in the protocols of massive transfusions is the fixed ratio of blood products administered, with the aim of avoiding delays in haemostatic resuscitation while waiting for laboratory results. Another factor is that massive transfusion protocols are constructed around local circumstances and local resources. They are

usually developed by multidisciplinary teams involving obstetricians, anaesthetists, haematologists, blood bank and transport staff available locally. However, it must be borne in mind that PPH occurs in a context where resuscitation can begin immediately after diagnosis; this is not the case for trauma victims, who could arrive in the emergency room having already lost a great amount of blood and after having had a prolonged resuscitation with crystalloids and colloids.

These events are exactly those which can and must be avoided in PPH [112], since doubts have arisen about the over triage of massive transfusion protocols [113]. It would be desirable to develop, validate, adopt and strengthen specific transfusion protocols in PPH, because they can help to avoid the most common reason for inadequate care that is an insufficient and delayed administration of blood products [114]. Vigorous, strengthened protocols for PPH emergencies could be defined, with continuous staff training, drills and a scrupulous management of quality that could save many more lives at a lower cost than any other pharmacological intervention.

The main difference between traumatic bleeding and PPH lies in the pregnant woman's haematological profile compared to that of a trauma victim. PPH occurs in an already activated coagulation system: the coagulation factors have increased in action, fibrinolysis has been activated and the antifibrinolysis damaged; in addition the cross-link between the fibrin monomers has weakened, rendering the fibrin less stable and less resistant to fibrinolysis. The resulting hypercoagulable state followed by hyperfibrinolysis has been interpreted as a chronic low degree of disseminated intravascular coagulation [115]. Other authors have used the term pelvic consumption coagulopathy [116], suggesting that this latent disorder can rapidly evolve towards a massive DIC and consequently consumption coagulopathy, a frequent early characteristic of PPH. Otherwise, the coagulopathy of trauma victims has been typically described as a dilutional coagulopathy. Early changes in the coagulative state of trauma victims and the significance of these changes have only recently been the subject of specific studies [117, 118]. It is still not clear if acute coagulopathy from trauma can be considered similar to early PPH.

### 9.7.7 Tranexamic Acid

The D-dimer and fibrinogen degradation product levels are regularly raised during pregnancy and are further increased postpartum because of placental derived PAI-2 (plasminogen activator inhibitor) as a sign of activated fibrinolysis [119, 120]. All this makes therapy with antifibrinolytics, such as tranexamic acid, attractive in PPH situations. There is also convincing clinical evidence for the use of tranexamic acid in bleeding trauma patients and in surgical patients [121, 122].

Current guidelines recommend antifibrinolytic agents for treating trauma [123]. In obstetrics, tranexamic acid is shown to reduce blood loss after a caesarean section in a Cochrane review and in two recent randomised trials [124–126]. But there is little clinical evidence for tranexamic acid as a treatment for manifest PPH [127]. An initial randomised trial on 144 women diagnosed with a blood loss of >di 800 ml

has demonstrated that a high dose of tranexamic acid (4 g) can significantly reduce this loss, albeit by only 50 ml [128]. Many other surrogate parameters, such as treatment with first-line uterotonics, were considerably improved. However, the study has not demonstrated significant differences on some major outcomes such as the hysterectomy rate or that of recovery in intensive care.

One problem in using antifibrinolytic agents is the risk of vascular occlusive events, a complication encountered by pregnant women. Aprotinin, another antifibrinolytic, has been withdrawn from sale after a large trial was prematurely halted [129]. A meta-analysis of the data available on thrombotic side effects after the prophylactic use of tranexamic acid has not shown any increase in these effects (no effect is observed in 461 patients included in the meta-analysis) [127]. Another meta-analysis, which included case reports and nonrandomised trials, identified two cases of pulmonary embolism but also established that a causal relationship was not clear [130].

Ducloy-Bouthors et al.'s study report many vascular occlusive events after the administration of 4 g of tranexamic acid compared to the control group [128] but always far from statistic significance, although the study did not have the necessary power to evaluate this parameter. In bleeding trauma patients, however, tranexamic acid was found to reduce the risk of vascular occlusive events [121]. The results of a great randomised controlled international trial which enrolled 15,000 parturients, initiated by the CRASH trial collaborative group, will be of great interest but are not available before 2015. Until then, the potential benefits must be weighed against the risk of individual continuous bleeding. Bearing in mind that parturients regularly have an increased fibrinolysis, that the effect of tranexamic acid on blood loss after delivery without PPH has been documented and that there is the strong evidence for using tranexamic acid in bleeding trauma patients and in surgical patients, then it could be appropriate to administer 1 or 2 g of this agent in severe bleeding cases that endanger life even without laboratory evidence of hyperfibrinolysis. A further administration can be decided on the basis of more specific laboratory analyses.

Many authors and WHO's current guidelines have considered the use of tranexamic acid in severe PPH [65, 131–133], although it is pointed out that there is limited evidence. This endorsement does not mean that tranexamic acid should be used as a routine prevention. In uncomplicated vaginal or caesarean deliveries, such a small blood-saving effect (around 50 ml) and the risk of adverse events encouraged by the induced hypercoagulability of pregnancy have not yet been adequately evaluated [65].

### 9.7.8 Fibrinogen

Fibrinogen levels are usually high in pregnancy at term (average 4.8 g/l vs. 1.8–4 g/l of non-pregnant women) [134, 135] and can decrease with the onset of PPH. During a massive haemorrhage, fibrinogen is one of the first factors to drop under critical values, mainly following the blood loss that depletes the coagulation factors and consumes factors associated with the activation of the coagulation [137]. Laboratory tests show that the clotting process needs an adequate presence of the substrate, i.e. fibrinogen, generally guaranteed by its higher than 1 g/L levels [136]. The

progression of PPH is associated with fibrinogenaemia values (<2 g/L) that fall within the normal range in non-pregnant women [182]. In particular, a hypofibrinogenaemia value higher than 4 g/L has a 79 % negative predictive value, while the positive predictive value of a less than 2 g/l concentration is 100 % [137] .

These findings have recently been confirmed [137] and have ignited an interesting debate about whether this decrease in plasmatic fibrinogen levels plays a pathophysiological role in the development of severe PPH or if it is instead an epiphenomenon of continuous bleeding.

The 2013 guidelines of the European Society of Anaesthesiology for severe postoperative bleeding recommend using a fibrinogen concentrate for significant haemorrhages and for hypofibrinogenaemia (assessed by conventional laboratory tests such as the Clauss test or by thromboelastometry/graphy) [181].

An indisputable advantage of the fibrinogen concentrate currently on the market is that:

- It has undergone a viral inactivation process by pasteurisation.
- It has a standard fibrinogen content.
- It can be stored at room temperature in delivery rooms as an immediately available resuscitation agent.
- Small volumes are sufficient, to be administrated as a bolus to restore fibrinogen levels.

To achieve plasmatic fibrinogen concentrations of 1.5 g/L starting with a 1.3 g/L fibrinogenaemia, 1 g of concentrated fibrinogen in a volume of 50 ml can be used, as well as around 1,250 mL of fresh frozen plasma [182]. But when the fibrinogenaemia target exceeds 1.8 g/L, the quantity of fresh frozen plasma needed grows exponentially until it is impossible to reach this target [182].

Cryoprecipitate is another potential source of fibrinogen even though the effective fibrinogen content is rather variable and other clotting factors such as VWF, FVIII and FXIII are also present [122]. However, cryoprecipitate is not available in most European countries for the well-known risk of viral transmission [122]. As in the case of tranexamic acid, we have to wait for the results of randomised trials on the use of fibrinogen in PPH. A medium-sized study on women with criteria for "mild" PPH is currently enrolling patients and should be completed in 2013 (*clinical trial.gov NCT 1359878*). Until the trial data are available, the reasonable approach to fibrinogen and cryoprecipitate would be to keep it available in life-threatening PPH cases, to bypass the logistic constraints of fresh frozen plasma, i.e. its transport and thawing and in case of hypofibrinogenaemia as demonstrated by laboratory tests [86, 114, 138, 139].

In patients with ongoing ascertained hyperfibrinolysis, it is appropriate to administer the antifibrinolysis agent before undertaking a substitute therapy with fibrinogen to avoid the early consumption of this latter. The infusion of HES solutions can also influence fibrinogen laboratory tests. If patients have been treated with HES, it is advisable to raise to 1.5–2 g/l the threshold of the fibrinogen plasmatic concentration under which to supplement with the concentrate [114].

### 9.7.9 Recombinant Activated Human Factor VII

Recombinant activated human factor VII (rhFVIIa) was originally developed for patients with classic haemophilia and haemophiliacs with inhibitor antibodies. Physiologically, factor VII is activated by tissue factor and in turn activates factors IX and X to IX activated. The link of factor VIIa to TF starts the cascade, prompting the activation of the prothrombin to form thrombin and then this latter from fibrinogen to fibrin, thus constructing the clot. In high doses, FVIIa or rhFVIIa directly activates factor X on the surface of the activated platelets, bypassing factors VIII and IX and creating what has been called a "thrombin burst", generating great quantities of fibrin at the lesion site. The potential of rhFVIIa to reduce blood loss in off-label use for controlling an otherwise uncontrollable bleeding because of its unique action mechanism has generated great expectations [140]. Nonetheless, the recent Cochrane meta-analysis on the therapeutic use of FVIIa, with 11 studies on 2,732 patients suffering continuous bleeding, has not demonstrated any effect on mortality and on control of the bleeding [141].

In the clinical condition of PPH, some case series and some reports have been encouraging [142–144]. For this type of publication, a substantial bias must always be taken into account, and moreover no controlled trial has yet been published. A randomised trial has been completed in France, but the results are not yet available (*NCT 00370877*). Many institutions have raised the problem of the increase in thromboembolic complications, but a Cochrane analysis [145] has not demonstrated any increase in these events in the therapeutic or prophylactic use of rhFVIIa. Despite this, an increase in thromboembolic complications has been observed in over 65-year-old patients. It is unclear how this safety data can apply to PPH because the procoagulant state of a parturient should lead to an increased risk of thromboembolic complications.

At the moment, the majority of specialists, including a panel of experts set up by rhFVIIa manufacturers, only recommend the use of rhFVIIa in some very specific situations [114, 138, 146–148]:

(a) rhFVIIa cannot substitute the proper medical and surgical treatment. In any case, before using it, there must be a definitive diagnosis of the causes of PPH. Practically all cases except for uterine atony without retained foetal tissue must be treated surgically, and rhFVIIa cannot be used. For PPH from uterine atony, after uterotonic agents and properly performed uterine massage, interventions such as balloon tamponade, B-Lynch suture or radiological embolisation of the uterine arteries must be considered (this latter procedure is not however suitable for massive and continuous PPH) [30] .
(b) Before considering rhFVIIa, acidosis and hypothermia must be corrected, and the plasmatic levels of calcium, fibrinogen and platelets must be recovered since not doing so would damage or prevent the effectiveness of rhFVIIa. rhFVIIa is also prone to failure in the presence of continuous arterial bleeding. If these points are addressed promptly and vigorously, the bleeding will stop in

the majority of cases before using rhFVIIa; otherwise, rhFVIIa can be used off-label in the attempt to avoid a hysterectomy.

The recommended dose is 90 mcg/kg body weight. If the bleeding continues after 10–20 min, a second dose can be administered. If the bleeding continues even after two doses of rhFVIIa and despite the fact that sufficient levels of calcium, fibrinogen and platelets have been reached, then a hysterectomy cannot be further delayed.

A second reason for using rhFVIIa is an immediate lack of blood products, although in these cases an urgent hysterectomy seems more appropriate than attempting treatment with rhFVIIa. It must be emphasised that the availability of VIIa is never a substitute for an adequate infrastructure and logistics nor should its administration delay any other life-saving intervention [149]. All cases of rhFVIIa must be recorded in a register, in those countries which possess one. Unlike tranexamic acid, rhFVIIa is extremely expensive, which makes its use problematic in low-income countries, which is also where 99 % of PPH cases occur.

It should be pointed out that in the Ministry of Health's guidelines for the prevention of maternal mortality, factor VII, currently under debate, is one of the drugs to administer in the case of PPH.

### 9.7.10 Recovery of Blood

Childbirth has traditionally been used as a counterindication for the transfusion of autologous blood collected from the operation site, especially during a caesarean section, because of problems caused by the amniotic fluid, foetal squames or embolisation of phospholipids, thus adding further problems to the quality of the coagulation process. However, these problems have been overcome by using filters that eliminate leucocytes. Recovery of blood in obstetrics has been supported by the major Obstetric Anaesthesia Societies and by the Royal College of Obstetricians and Gynaecologists of Great Britain following laboratory studies demonstrating the efficacy of the removal of amniotic fluid components and foetal cell detritus and also following numerous publications on this subject. Around a third of delivery rooms possess the technology for blood recovery, and the majority of them have added them to PPH protocols [150].

The peripartum use of technologies for recovery of blood has been the subject of a recent critical review [151]. Logistics are the main critical area for their use in PPH because in majority of cases it cannot be predicted. Only in high-risk caesarean sections and with a diagnosis of placenta percreta does its use become possible, and in some departments, the recovery of blood is available for these cases. Depending on the local facilities, blood recovery machines disposables are cost efficient after 1–2 units of frozen red globules have been saved [152]. For these cases, leucocitary depletion filters should always be available.

### 9.7.11 Monitoring the Coagulation

Marked changes to the haemostasis can be observed during pregnancy [153] (Fig. 9.2). Compared with the non-pregnant state, the procoagulant levels are generally high while the coagulation antagonists either diminish or remain unchanged. This hypercoagulant state can reduce the risk of haemorrhage during the delivery and postpartum. On the other hand, the platelets typically diminish during pregnancy, but the clinical significance of this fall is uncertain [154, 155].

Haemostasis can be further influenced by anaemia and by preeclampsia [156, 157].

Anaemia (Hb < 11–10.5 g/dl in the second trimester) affects some 20 % of pregnant women worldwide and is associated with an increased blood loss and a greater probability of transfusion during delivery. Similarly, preeclampsia, occurring in 0.4–2.8 % of births, is associated with haemostasis abnormalities, including thrombocytopenia and DIC [158].

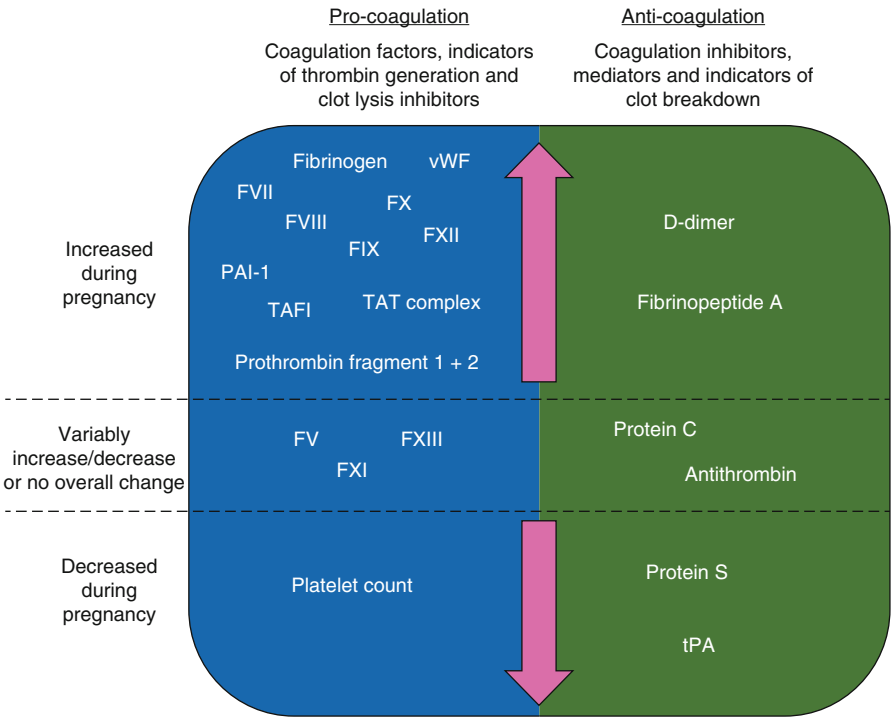


**Fig. 9.2** Changes in haemostatic variables observed during normal, healthy pregnancy. The overall increase in pro-coagulant factors results in a typically hypercoagulable state which increases throughout pregnancy. Increases and decreases are relative to non-pregnancy. Positioning of factors is not indicative of the precise level of increase or decrease. *FV* Factor V; *FVII* Factor VII; *FVIII* Factor VIII, *FIX* Factor IX, *FX* Factor X, *FXI* Factor XI, *FXII* Factor XII, *FXIII* Factor XIII, *PAI-1* plasminogen activator inhibitor 1, *TAFI* thrombin activatible fibrinolysis inhibitor, *TAT* complex thrombin–antithrombin complex, *vWF* von Willebrand factor

Monitoring coagulation in obstetric patients raises an important issue regarding the reference values that can best represent a normal haemostasis in the pregnant woman. PT and aPTT can remain in the normal range even in severe PPH, whereas thrombocytopenia is common even during normal pregnancy [155, 159]. Fibrinogen levels increase during the third trimester [160], and levels under 2 g/l could indicate the need for an intervention during genital tract bleeding. This raises again the problem of what the target level of fibrinogen is during PPH and if this level differs from other causes of massive haemorrhage [46, 134]. Current guidelines for treating PPH recommend maintaining PT and aPTT at ≤1.5 times the normal control values, the platelet count at $\geq 50 \times 10^9$/L and the plasmatic fibrinogen at ≥1 g/L, values identical to the recommendations for non-pregnant populations [161–163]. Both PT and aPTT are thus of limited value for monitoring haemostasis during PPH.

We do not yet know the clinical significance of gestational thrombocytopenia or if the drop in the number of platelets is counterbalanced by an increased platelet reactivity [155, 164]. The platelet count in patients with PPH is significantly lower than those of normal parturients, and a drop in platelets during an obstetric bleeding can be associated with a progression towards severe PPH [134, 165]. The fibrinogen concentration is linked to the incidence and severity of the bleeding. Unfortunately, despite the fact that the fibrinogen concentration and the platelet count are the aims of haemostatic therapy, their usefulness in treating PPH is thwarted by the long turnaround times (typically 30–60 min) [160, 166–168]. Such long TAT is incompatible with an efficient treatment of bleeding in PPH, particularly when the results do not reflect the current haemostasis and the delayed treatment can easily lead to an adverse outcome, including the mother's death [169]. Rapid bedside POC tests such as Roche's CoaguChek device monitor parameters that include PT and INR, but they do not evaluate the dynamics of the coagulation, and they are not widely used in the delivery room.

For all these reasons, thromboelastography (TEG) and thromboelastometry (ROTEM) are being increasingly used as a point of care for evaluating coagulation (Fig. 9.3). Compared with the classic laboratory evaluation of coagulation, TEG and ROTEM have better sensitivity for detecting some abnormalities in the coagulation process [170]. TEG/ROTEM monitoring is performed on the entire blood and assesses the process from the start of the coagulation up to the clot lysis including the strength of the coagulation and its stability. This dynamic assessment can thus give an idea of what changes in the haemostatic balance have repercussions on coagulation, enabling a more complete diagnosis of the coagulopathy and a rapid evaluation of the haemostatic intervention on the coagulation [171–176].

There is increasing attention being paid to hyperfibrinolysis and to hypofibrinogenaemia, to their prognostic value and to the interventions recommended for treating these conditions. In this context, useful and rapid parameters seem to be provided by monitoring with a point of care of coagulation, for example, with thromboelastography (TEG) or rotational thromboelastometry (ROTEM) and its related FIBTEM [165, 177–180]. A problem in monitoring methods is that they can be useful for evaluating a specific parameter, but they do not influence the therapy.

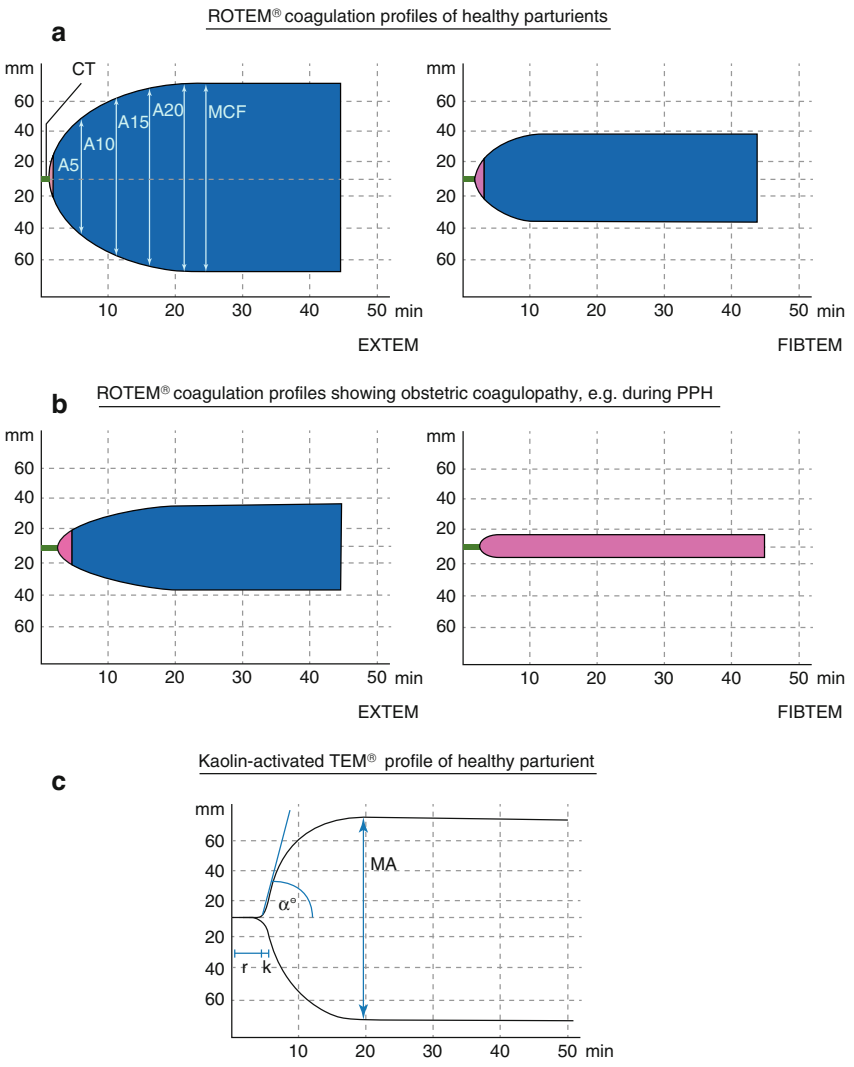


**Fig. 9.3** ROTEM®- and TEG®-based coagulation profiles in the peripartum period. Schematic representation of healthy (**a**) and coagulopathic (**b**) obstetric coagulation profiles for EXTEM and FIBTEM tests. Coagulation parameters which are typically reported for these tests are indicated in the top-left panel. The profiles reflect EXTEM and FIBTEM test results reported for healthy patients around the time of delivery, and for patients with PPH associated with poor fibrin-clot quality. Clot lysis parameters are not indicated; if (hyper)fibrinolysis is suspected, an APTEM test can be performed. APTEM profiles mirror EXTEM profiles under healthy conditions, and show enhanced coagulation vs EXTEM during fibrinolysis. Also presented (**c**) is a healthy, obstetric coagulation profile for kaolin-activated thrombelastography, with typically reported parameters indicated for this test. The profile reflects kaolin-TEG® values observed for healthy patients in the third trimester, and before elective Caesarean delivery. Owing to the lack of available evidencefor typical test results, profiles are not presented for kaolin-TEG® during PPH, or for other TEG®-based tests in obstetric patients. $\alpha^\circ$ alpha angle, *A5–A20* clot amplitude at 5–20 min after CT, *CT* clotting time, *MA* maximum amplitude, *MCF* maximum clot firmness, *PPH* postpartum haemorrhage, *r* reaction time

They can only say how good the treatment can be, and in some cases, they can even be harmful. As previously pointed out, there is still no conclusive evidence for many interventions that could be guided by the point of care monitoring of coagulation. However, without questioning the efficacy of antifibrinolytic agents and of fibrinogen, the point of care monitoring of coagulation can be a valid instrument for goal-directed haemostatic resuscitation.

Like recovery of blood, logistic constraints also exist for this monitoring process. If a delivery room is not close to a central TEG or ROTEM, it is unlikely that they will be available for its parturients. Since the platelet count is an important obstetric parameter (e.g. in the diagnosis of HELLP), many delivery rooms are equipped with a point of care for this possibility which can also be useful for massive PPH.

## Conclusions

Postpartum haemorrhage (PPH) is a major risk factor and main cause of maternal mortality and morbidity worldwide. Albeit global efforts have helped to reduce maternal mortality everywhere, the percentage of PPH in developed countries is increasing while still today 99 % of PPH cases occur in developing countries. The international scientific community must concentrate more on achieving the millennium goal, reducing maternal mortality by at least three quarters between 1990 and 2015.

Numerous factors can initiate PPH, and this makes difficult to predict its onset and severity. Risk profiles can help to identify a patient more liable to bleeding. The main risks in the antenatal stage are:

- A history of PPH
- Anomalous placental insertion
- Multiple gestations
- Thrombocytopathy and a medical history of coagulopathy
- Pre-existing anaemia

The patient with a high risk of PPH must always give birth in a specialised centre.

Specific protocols must be used and consents obtained in the case of Jehovah's Witnesses. However many, if not the majority, of PPH cases cannot be predicted, and they end up occurring outside an optimal quality and safety setting.

Again considering the importance of prevention, it is necessary to recall peri- and postpartum risk factors:

- Retained placenta or even a pathologically adherent placenta
- Small for gestational age baby
- Prolonged labour
- Rupture of the uterus and cervical lacerations
- Emergency caesarean section
- Repeated caesarean sections
- Advanced maternal age
- Multiple births

These peri- and post-delivery risk factors warn us that it is anyway safer to give birth in a hospital where the staff are experienced in tackling these problems. On the organisational side, closing birth centres with only a small volume of births is recommended, and in any case a flexible and highly efficient local network of birth protection should be created.

Although many pharmacological interventions have been proposed and have proved useful in high-resource countries, the focus must be on development, on training and on the quality control of postpartum haemorrhage in every local operative context as well as on the massive transfusion protocols that the specific local facility adopts. This rational approach can basically help to prevent and treat severe PPH.

The main reasons for a fatal outcome in massive PPH lie in the initial basic approach and include:

- Late diagnosis
- Slow activation of staff
- Insufficient and delayed resuscitation

The majority of maternal deaths caused by PPH must be considered preventable in rich countries, rather because of basic measures and organisation than the advanced medical treatment of the coagulopathy. Among the pharmacological interventions proposed, uterotonics constitute the main therapy.

The main objectives in resuscitation must be a suitable fluid therapy, appropriate and dynamically monitored, and an early administration of blood products, ideally based on a massive transfusion protocol. A major priority in anaesthesia and intensive care management is the maintenance of the basic framework necessary for the coagulation which include:

- Normocalcaemia
- Prevention or correction of acidosis (importance of monitoring lactate)
- Normothermia (monitoring of temperature and heating systems)
- Platelet count

Again these priorities indicate what type of equipment a delivery room must have to work under quality and safety norms. The technology that enables the health professional to work under safe conditions and which must be present is:

- A point of care that can provide blood gas analysis (pH, PCO2, PO2, Hb, Hct etc) and also electrolytes (Na, K, Ca, Cl) and lactate
- A point of care for coagulation monitoring (platelets and TEG or ROTEM)
- Minimally invasive multiparametric and haemodynamic monitoring
- Pumps for drug and fluid infusion
- Temperature monitoring
- Patient heating systems
- Instruments for recovery of blood and leukocyte removal filters

The use of antifibrinolytics such as tranexamic acid and the early substitution of fibrinogen at >1.5 g/L levels have been recently studied in large trials and have the potential to be widely applied.

Unfortunately rhFVIIa plays a minor role, because its off-label use is only permitted in specific situations.

The recovery of blood and point of care coagulation monitoring are highly recommended today, difficult from a logistic point of view but constantly remaining a target in terms of patient safety-oriented innovation. Whatever the future trends, the successful treatment of PPH will always be an interdisciplinary task. The creation of a multidisciplinary and multi-professional team of midwives, obstetricians-gynaecologists, anaesthetists, laboratory clinicians expert in coagulation and transfusion medicine specialists must underpin an appropriate management of postpartum haemorrhage. A team that works in a collaborative environment, centred on the patient and her mental and physical health inclusive of her family and continually aiming to improve its quality and results, must be the strategic target of a safe, effective and efficient, and because of this more economically sustainable, healthcare system.

## Bibliographic References


1. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF (2006) WHO analysis of causes of maternal death: a systematic review. Lancet 367:1066–1074
2. Lozano R, Wang H, Foreman K et al (2011) Progress toward Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet 378: 1139–1165
3. Abouzahr C (2003) Global burden of maternal death and disability. Br Med Bull 67:1–11
4. Clark SL, Belfot MA, Dildy GA, Herbst MA, Meyers JA, Hankins GD (2008) Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol 199(1):36.e1–e5 discussion 91–92.e7–e11
5. Guillermo Carroll CC, Edgardo Abalos A (2008) Metin Gulmezoglu Epidemiology of post partum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol 22:999–1012
6. Wen SW, Huang L, Liston R et al (2005) Severe maternal morbidity in Canada 1991–2001. CMAJ 173:759–764
7. Waterstone M, Bewley S, Wolfe C (2001) Incidence and predictors of severe obstetric morbidity: case control study. BMJ 322:1089–1093
8. Hogan MC, Foreman KJ, Naghavi M et al (2010) Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet 35: 1609–1623
9. Creanga AA, Berg CJ, Syverson C et al (2012) Race, ethnicity and natività differentials in pregnancy related mortality in United States: 1993–2006. Obstet Gynecol 120:261–268
10. Lutomski JE, Byrne BM, Devane D et al (2012) Increasing trends in atonic postpartum haemorrhage in Ireland: an 11 year population based cohort study. BJOG 119:306–334
11. Bateman BT, Barman MF, Riley LE, Leffert LR (2010) The epidemiology of PPH in a large nationwide sample of deliveries. Anesth Analg 110:1368–1373
12. Calvert C, Thomas SL, Ronsmans C, Wagner KS, Adler AJ, Filippi V (2012) Identifying regional variation in the prevalence of PPH: a systematic review and meta-analysis. PLoS One 7:e41114
13. Knight M, Callaghan WM, Berg C et al (2009) Trends in postpartum haemorrhage in high resource countries: a review and recommendations from the International PostPartum Hemorrhage Collaborative Group. BMC Pregnancy Childbirth 9:55

14. Joseph KS, Rouleau J, Kramer MS, Young DC, Liston RM, Baskett TF (2007) Investigation of an increase in postpartum haemorrhage in Canada. BJOG 114:751–759
15. Wu S, Kocherginsky M, Hibbard U (2005) Abnormal placentation: twenty year analysis. Am J Obstet Gynecol 192:1458–1461
16. Berg CJ, Callaghan WM, Syverson C et al (2010) Pregnancy related mortality in United States 1998 to 2005. Obstet Gynecol 116:1302–1309
17. Schutte JM, Steegers EAP, Schuitemaker NWE et al (2010) Rise in maternal mortalità in the Netherlands. BJOG 117:399–406
18. Berg CJ, Harper MA, Atkinson SM (2005) Preventability of pregnancy related death: result of a state wide review. Obstet Gynecol 106:1228–1234
19. Lewis G The confidential enquiry into maternal and child health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safe – 2003–2005. The seventh report on confidential enquiries into maternal death in the United Kingdom. Available at: http://www.publichealth.hscni.net/sites/default/files/Saving%20Mothers'%20Lives%202003-05%0.pdf
20. Thaler I, Manor D, Itskovitz J et al (1990) Changes in uterine blood flow during human pregnancy. Am J Obstet Gynecol 162:121–125
21. Sloan NL, Durocher J, Aldrich T et al (2010) What measured blood loss tell us about postpartum bleeding: a systematic review. BJOG 117:788–800
22. Andersen HF, Hopkins MP (2012) Gynecology and Obstetrics Volume 2 Chapter 80 Postpartum Hemorrhage Lippincott Williams and Wilkins
23. Schorn MN (2010) Measurement of blood loss: review of the literature. J Midwifery Womens Health 55:20–27
24. Chandraharan E, Arulkumara S (2008) Surgical aspects of postpartum haemorrhage. Best Pract Res Clin Obstet Gynecol 22:1089–1102
25. Lu MC, Fridman M, Korst LM et al (2005) Variations in the incidence of postpartum hemorrhage across hospitals in California. Matern Child Health J 9:297–306
26. Stafford I, Dildy GA, Clark SL et al (2008) Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol 519.e:1–7
27. Gares EE, Albert SN, Dodek SM (1962) Intrapartum blood loss measured with Cr 51 tagged erythrocytes. Obstet Gynecol 19:455–462
28. Carroli G, Cuesta C, Abalos E et al (2008) Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynecol 22:999–1012
29. Biguzzi E, Franchi F, Ambrogi F et al (2012) Risk factors for postpartum haemorrhage in a cohort of 6011 Italian women. Thromb Res 19:e1–e7
30. Clark SL, Hankins GDV (2012) Preventing maternal death: 10 clinical diamonds. Obstet Gynecol 119:360–364
31. Leveno KJ et al (2007) In: Snyder A, Loeb M, Boyle PJ, editors. Williams Mamual in Obstetrics: Pregnancy complications. 22nd ed. Mc Graw-Hill, New York, pp 192–194
32. Rudra A, Chatterjee S, Sengupta S et al (2010) Management of obsteric haemorrhage. Middle East J Anesthesiol 20:499–507
33. Nielson EC, Varner MW, Scott JR (1991) The outcome of pregnancies complicated by bleeding during the second trimester. Surg Gynecol Obstet 173:371–374
34. Justus Hofmeyr G, Say L, Metin Gulmezoglu A (2005) Systematic review: WHO systematic review of maternal mortalità and morbidity: the prevalence of uterine rupture. BJOG 112: 1221–1228
35. Guise JM (2004) Systematic review of the incidence and consequences of uterine rupture in women with previous caesarean section. BMJ 329:19–25
36. Farinelli CK, Hameed AB (2012) Cardiopulmonary resuscitation in pregnancy. Cardiol Clin 30:453–461
37. Mercier FJ, Van de Velde M (2008) Major obstetric haemorrhage. Anesthesiol Clin 26:53–66
38. Oyelese Y, Ananth CV (2010) Postpartum hemorrhage epidemiology, risk factors and causes. Clin Obstet Gynecol 53:17–156
39. Bauer ST, Bonanno C (2009) Abnormal placentatio. Semin Perinatol 33:88–96

40. Benedetto C, Marzio L, Tavella AM, Salton L, Grivon S, Di Giampaolo F (2010) Coagulation disorders in pregnancy: acquired and inherited thrombophilia. Ann N Y Acad Sci 1205: 106–117
41. Carle C, Alexander P, Columb M, Johal J (2013) Design and internal validation of an obstetric early warning score: secondary analysis of the Intensive Care National Audit and Research Centre Case Mix Programme database. Anaesthesia 68:354–367
42. Singh S, Mcglennan A, England A, Simons R (2012) A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia 67: 12–18
43. Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists. Prevention and management of post partum haemorrhage. RCOG Green top guideline April 2011 N° 52
44. Pacagnella RC, Souza JP, Durocher J et al (2013) A systematic review of the relationship between blood loss and clinical signs. PLoS One 3, e57594
45. Patel A, Goudar SS, Geller SE et al (2006) Drape estimation vs. visual assessment for estimating postpartum hemorrhage. Int J Gynecol Obstet 93:220–224
46. Gayat E, Resche-rigon M, Morel O et al (2011) Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. Intensive Care Med 37: 1816–1825
47. Naef RW 3rd, Chauhan SP, Chevalier SP et al (1994) Prediction of haemorrhage at cesarean delivery. Obstet Gynecol 83:923–926
48. Pata N, Hamza S, Bell S et al (2011) Inability to predict postpartum hemorrhage: insights from Egyptian intervention data. BMC Pregnancy Childbirth 11:97
49. Begley CM, Gyte GML, Devane D et al (2011) Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev 11:CD007412
50. Leduc D, Senikas V, Lalonde AB et al (2009) Active management of the third stage of labour: prevention and treatment of postpartum haemorrhage. J Obstet Gynecol Can 31:980–993
51. Rogers J, Wood J, McCandlish R et al (1998) Active versus expectant management of third stage of labour: the Hinchingbrooke randomized controlled trial. Lancet 351:693–699
52. B-Lynch C, Keith LG, Llonde AB, Karoshi M (2006) A textbook of postpartum haemorrhage: a comprehensive guide to evaluation, management and surgical intervention. Sapiens Publishing, Duncow
53. Leong BSH, Chua GSW (2011) Quality of resuscitation in hospitals. Singapore Med J 52: 616–619
54. Drife J (1997) Management of primary postpartum haemorrhage. BJOG 104:275–277
55. Sihler KC, Napolitano LM (2010) Complications of massive transfusion. Chest 137:209–220
56. Crofts JF, Ellis D, Draycott TJ et al (2007) Changes in knowledge of midwives and obstetricians following obstetric emergency training: a randomised controlled trial of local hospital, simulation centre and teamwork training. BJOG 114:1534–1541
57. Merien AER, van der Ven J, Mol BW et al (2010) Multidisciplinary team training in a simulation setting for acute obstetric emergencies: a systematic review. Obstet Gynecol 115:1021–1031
58. Rizvi F, Mackey R, Barrett T et al (2004) Successful reduction of massive postpartum haemorrhage by use of guidelines and staff education. BJOG 111:495–498
59. Siassakos D, Crofts JF, Winter C et al (2009) The active components of effective training in obstetric emergencies. BJOG 116:1028–1032
60. Su LL, Chong YS (2012) Massive obstetric haemorrhage with disseminated intravascular coagulopathy. Best Pract Res Clin Obstet Gynaecol 26:77–90
61. National Institute for Health and Clinical Excellence CG 55 Intrapartum care: care of healthy women and their babies during childbirth 2007; Lalonde A (2012) Prevention and treatment of postpartum hemorrhage in low resource settings. Int J Gynaecol Obstet 117:108–118
62. Vercauteren M, Palit S, Soetens F et al (2009) Anaesthesiological considerations on tocolytic and uterotonic therapy in obstetrics. Acta Anaesthesiol Scand 53:701–709

63. Magalhaes JKRS, Carvalho JCA, Parkes RK (2009) Oxytocin pretreatment decreases oxytocin induced myometrial contractions in pregnant rats in a concentration-dependent but not time dependent manner. Reprod Sci 16:501–508
64. Dyer RA, Butwick AJ, Carvalho B (2011) Oxytocin for labour and caesarean delivery: implications for the anaesthesiologst. Curr Opin Anaesthesiol 24:255–261
65. Gogarten W, Van Aken H, Kessler P et al (2009) Durchfuehrung von Analgesie und Anaesthesieverfahren in der Geburtshilfe 2. Uberarbeitete Empfehlungen der Deutschen Gesellschaft fur Anaesthesiologie und Intensivmedizin. Anaesth Intensivmed 50:S502–S507
66. Thomas TA, Cooper GM (2002) Maternal deaths from anaesthesia: an extract from why mothers die 1997–1999. The confidential enquiries into maternal deaths in the United Kingdom. Br J Anaesth 89:499–508
67. Langesaeter E, Rosseland LA, Stubhaug A (2011) Hemodynamic effects of oxytocin in women with severe preeclampsia. Int J Obstet Anaesth 20:26–29
68. Sweeney G, Holbrook AM, Levine M et al (1990) Pharmacokinetic of carbetocin, a long acting oxytocin analogue, in non pregnant women. Curr Therapeutic Res 47:528–540
69. Ryden G, Sjoholm I (1969) Half life of oxytocin in blood of pregnant and non pregnant women. Acta Endocrinol 61:425–431
70. Su LL, Chong YS, Samuel M (2012) Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2:CD005457
71. Gohil JT, Tripathi B (2011) A study to compare the efficacy of misoprostol, oxytocin, methyl ergometrine and ergometrine-oxytocin in reducing blood loss in active management of 3rd stage of labor. J Obstet Gynaecol India 61:408–412
72. Gibbins KJ, Albright CM, Rouse DJ (2013) Postpartum hemorrhage in the developed world: whither misoprostol ? Am J Obstet Gynecol 208:181–183
73. Nardin JM, Weeks A, Carroll G (2011) Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev (on line 5):CD001337
74. Robinson BK, Grobman WA (2010) Effectiveness of timing strategies for delivery of individuals with placenta pevia and accreta. Obstet Gynecol 116:835–842
75. Blanc J, Courbiere B, Destriere R et al (2012) Uterine sparing surgical management of postpartum haemorrhage: is it always effective ? Arch Gynecol Obstet 285:925–930
76. Provansal M, Courbiere B, Agostani A, D'Ercole C, Bouli L, Bretelle F (2010) Fertility and obstetric outcome after conservative management of placenta accreta. Int J Gynaecol Obstet 109:147–150
77. Portilla D, Hernandez-Giraldo C, Moreno B et al (2013) A local hemostatic agent for the management of postpartum hemorrhage due to placenta previa ad placenta accreta: a cross sectional study. Arch Gynecol Obstet 288:543–549
78. Fofie C, Baffoe PA (2010) A two year review of uterine rupture in a regional hospital. Ghana Med J 44:98–102
79. Holmgren CM (2012) Uterine rupture associated with VBAC. Clin Obstet Gynecol 55:978–987
80. Hill JB, Ammons A, Chauan SP (2012) Vaginal birth after cesarean delivery: comparison of ACOG practice bulletin with other national guidelines. Clin Obstet Gynecol 55:969–977
81. Hostetler DR, Bosworth MF (2000) Uterine inversion: a life-threatening obsteric emergency. J Am Board Fam Pract 13:120–122
82. Silver RM, Major H (2010) Maternal coagulation disorders and postpartum hemorrhage. Clin Obstet Gynecol 53:252–264
83. Onwuemene O, Green D, Keith L (2012) Postpartum hemorrhage management in 2012: predicting the future. Int J Gynaecol Obstet 119:3–5
84. Padmanabhan A, Schwartz J, Spitalnik SL (2009) Transfusion therapy in postpartum hemorrhage. Semin Perinatol 33:124–127
85. Thorainsdottir HR, Sigurbjornsson FT, Hreinsson K, Onundarson PT et al (2010) Effects of fibrinogen concentrate administration during severe hemorrhage. Acta Anaesthesiol Scand 54:1077–1082

86. Bell SF, Rayment R, Collis PW, Collis RE (2010) The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. Int J Obstet Anesth 19: 218–223
87. Warmuth M, Mad P, Wild C (2012) Systematic review of the efficacy and safety of fibrinogen concentrate substitution in adults. Acta Anaesthesiol Scand 56:539–548
88. Wikkelsoe AJ, Afshari A, Stensballe J et al (2012) The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomized controlled trial. Trials 13:110
89. Georgiu C (2009) Ballon tamponade in the management of postpartum haemorrhage: a review. BJOG 116:748–757
90. Tindell K, Garfinkel R, Abu-Haydar E et al (2013) Uterine balloon tamponade for the treatment of postpartum haemorrhage in resource poor settings: a systematic review. BJOG 120:5–14
91. Stefanovic V, Gronvall M, Tikkanen M, Tallberg E, Paavonen J (2013) Bakri baloon tamponade for postpartum hemorrhage. Acta Obstet Gynecol Scand 92:1119
92. Frenzel D, Condous GS, Papageorghiou AT, Mcwhinney NA (2005) The use of the tamponade test to stop massive haemorrhage in placenta accreta. BJOG 112:676–677
93. Yoong W, Ridout A, Memtsa M et al (2012) Application of uterine compression uture in association with intrauterine balloon tamponade (uterine sandwich) for postpartum hemorrhage. Acta Obstet Gynecol Scand 91:147–151
94. Lemmer R, Albrech M, Bauer G (2012) Use of FloSeal hemostatic matrix in a patient with severe postpartum hemorrhage. J Obstet Gynaecol Res 38:435–437
95. Riley DP, Burgess RW (1994) External abdominal aortic compression: a study of a resuscitation manoeuvre for postpartum haemorrhage. Anaesth Intensive Care 22:571–575
96. Miller S, Fathalla MM, Ojengbede OA et al (2010) Obstetric hemorrhage and shock management: using the low technology Non pneumatic Anti Shock Garment in Nigerian and Egyptian tertiary care facilities. BMC Pregnancy Childbirth 10:64
97. Miller S, Turan JM, Dau K et al (2007) Use of the non pneumatic anti shock garment (NASG) to reduce blood loss and time to recovery from shock for women with obstetric haemorrhage in Egypt. Glob Public Health 2:110–124
98. Miller S, El Aydi A (2012) Meta-analysis of 3,651 women with severe obstetric hemorrhage/ hypovolemic shock treated with non pneumatic anti shock garment. FIGO XX World Congress, Rome
99. Royal College of Obstetricians and Gynaecologists, Royal College of Radiologists, British Society of Interventional Radiology (2007) The role of emergency and elective interventional radiology in postpartum haemorrhage. Good Practice N°6
100. Lagrew D, Hull A Uterine artery occlusion and embolization CMCC Obstetric Hemorrhage toolkit Obstetric hemorrhage care guidelines and compendium of best practices reviewed by CADPH-MCAH 12/22/2009
101. Pacheco LD, Saade GR, Gei AF, Hankins GD (2011) Cutting edge advances in the medical management of obstetrical hemorrhage. Am J Obstet Gynecol 205:526–532
102. Ganguli S, Stecker MS, Pyne D, Baum RA, Fan CM (2011) Uterine artery embolization in the treatment of postpartum uterine hemorrhage. J Vasc Interv Radiol 22:169–176
103. Maassen MS, Lambers MD, Tutein Nolthenius RP, Van der Valk PH, Elgersma OE (2009) Complications and failure of uterine artery embolisation for intractable postpartum haemorrhage. BJOG 116:55–61
104. Acog. Practice Bulletin (2006) Clinical management guidelines for obstetricians_gynecologists 76: postpartum haemorrhage. Obstet Gynecol 108:1039–1047
105. Luo FY, Chen M, Zhang L et al (2012) A comparison of the effectiveness of five types of hemostatic surgeries for intractable postpartum haemorrhage and the factors of failed hemostasis. Zhonghua fu chan ke za zhi 47:641–645
106. Walfish M, Neuman A, Wlody D (2009) Maternal Haemorrhage. Br Anaesth 103(Suppl 1):i47–i56

107. Rath W, Hackethal A, Bohlmnn MK (2012) Second line treatment of postpartum haemorrhage (PPH). Arch Gynecol Obstet 286:549–561
108. Shain AY, Fargaly TA, Mohamed SA, Shokry M, Abd-El-Aal DE, Youssef MA (2010) Bilateral uterine artery ligation plus B-Lynch procedure for atonic postpartum hemorrhage with placenta accreta. Int J Gynaecol Obstet 108:187–190
109. Borgman MA, Spinella PC, Perkins JG et al (2007) The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 63:805–813
110. Cotton BA, Au BK, Nunez TC et al (2009) Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma Acute Care Surg 66:41–49
111. Gutierrez MC, Goodnough LT, Druzin M et al (2012) Postpartum hemorrhage treated with a massive transfusion protocol at a tertiary obstetric center: a retrospective study. Int Obstet Anaesth 21:230–235
112. Snegovskikh D, Clebone A, Norwitz E (2011) Anesthetic management of patients with placenta accreta and resuscitation strategies for associated massive hemorrhage. Curr Opin Anaesthesiol 24:274–281
113. Callum L, Rizoli S (2012) Plasma transfusion for patients with severe haemorhage: what is the evidence? Transfusion 52(suppl 1):30S–37S
114. Gogarten W (2011) Postpartum hemorrhage – an update. Anesthesiol Intensivmed Notfallmed Schmerzther 46:508–514
115. Cerneva F, Ricci G, Simeone R et al (1997) Coagulation and fibrinolysis changes in ormal pregnancy: increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis. Eur J Obstet Gynecol Reprod Biol 73:31–36
116. Macphail S, Talks K (2004) Massive postpartum haemorrhage and management of disseminated intravascular coagulation. Curr Opin Obstet Gynecol 14:123–131
117. Potzsch B, Ivaskevicius V (2011) Haemostasis management of massive bleeding. Hamostaseologie 31:15–20
118. Rugeri L, Levrat A, David JS et al (2007) Diagnosis of early coagulation abnormalities in trauma patients by rotation thromboelastography. J Thromb Haemost 5:289–295
119. Brenner B (2004) Haemostatic changes in pregnancy. Thromb Res 114:409–414
120. Epney M, Boehlen F, Boulvain M et al (2005) D-dimer levels during delivery and the postpartum. J Thromb Haemost 3:268–271
121. Shakur H, Roberts I, Bautista R et al (2010) CRASH 2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH 2): a randomized placebo controlled trial. Lancet 376:23–32
122. Ker K, Edwrds P, Perel P, Shakur H, Roberts I (2012) Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 344:e3054
123. Rossaint R, Bouillon B, Cerny V et al (2010) Management of bleeding following major trauma: an updated European guideline. Crit Care 14:R52
124. Novikova N, Hofmeyr GJ (2007) Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev CD007872
125. Gungorduk K, Yildirim G, Asicioglu O et al (2011) Efficacy of intravenous tranexamic acid in reducing blood loss after elective caesarean section: a prospective randomized, double blind, placebo controlled study. Am J Perinatol 28:233–240
126. Movafegh A, Eslamian L, Dorabadi A (2011) Effect of intravenous tranexamic acid administration on blood loss during and after caesarean delivery. BJOG 115:224–226
127. Ferrer P, Roberts I, Sydenham E et al (2009) Anti fibrinolytic agents in post partum haemorrhage: a systematic review. BMC Pregnancy Childbirth 9:29
128. Ducloy-Bouthors AS, Jude B, Duhamel A et al (2011) High dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care 15:R17

129. Fergusson DA, Hebert PC, Mazer CD et al (2008) A comparison of aprotinin and lysine analogous in high risk cardiac surgery. N Engl J Med 358:2319–2331
130. Peitsidis P, Kadir RA (2011) Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. Export Opin Pharmacother 12:503–516
131. Onwuemene O, Green D, Keith L (2012) Postartum hemorrhage management in 2012: Predicting the future. Int J Gynecol Obst 119:3–5
132. Lier H, Rath W (2011) Current interdisciplinary recommendations for the management of severe postpartum haemorrhage (PPH) Geburtshilfe und Frauenheilkunde
133. WHO guidelines for the management of postpartum haemorrhage and retained placenta (2009) WHO press, Geneva
134. Charbit B, Mandelbrot L, Samain E et al (2007) The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 5:266–273
135. Kratz A, Ferraro M, Sluss PM et al (2004) Laboratory reference values. N Engl J Med 351:1548–1564
136. Mercier FJ, Bonnet MP (2010) Use of clotting factors and other prohemostatic drugs for obstetric hemorrhage. Curr Opin Anaesthesiol 23:310–316
137. Cortet M, Deneux-Tharaux C, Dupont C et al (2012) Association between fibrinogen level and severità of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth 108:984–989
138. Ahonen J, Stefanovic V, Lassila R (2010) Management of postpartum haemorrhage. Acta Anaesthesiol Scand 54:1164–1178
139. Lier H, Rath W (2011) Current interdisciplinary recommendations for the management of severe postpartum haemorrhage (PPH). Geburtshilfe Frauenheilkd 71:577–588
140. Wood AJJ, Vannucci PM (1998) Hemostatic drugs. N Engl J Med 339:245–253
141. Lin Y, Staworth S, Brchall J et al (2011) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev 2:CD005011
142. Ahonen J, Jokela R, Korttila K (2007) An open non randomized study of recombinant factor VII in major postpartum haemorrhage. Acta Anaesthesiol Scand 51:929–936
143. Boehlen F, Morales MA, Fontana P et al (2004) Prolonged treatment of massive postpartum haemorrhage with recombinant factorVIIa: a case report and review of the literature. BJOG 111:284–287
144. Segal S, Shemesh IY, Blumental R et al (2004) The use of recombinant factor VIIa in severe postpartum hemorrhage. Acta Obstet Gynecol Scand 83:771–772
145. Lin Y, Staworth S, Brchall J et al (2011) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev. CD005011
146. McLintock C, James AH (2011) Obstetric hemorrhage. J Thromb Haemost 9:1441–1451
147. Van De Velde M (2008) Massive obstetric hemorrhage due to abnormal placentation: uterotonic drugs, cell salvage and activated recombinant factor seven. Acta Anaesthesiol Belg 59:197–200
148. Welsh A, Mclintock C, Gatt S et al (2008) Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust N Z J Obstet Gynaecol 148:12–16
149. Vincent JL, Rossaint R, Riou B et al (2006) Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding – a European perspective. Crit Care 10:R120
150. Teig M, Harkness M, Catling S et al (2007) Survey of cell salvage use in obstetrics in the UK. J Obstet Anaesth 16(suppl 1):30
151. Tevet A, Grisaru-Granovsky S, Samueloff A et al (2012) Peripartum use of cell salvage: a university practice audit and literature review. Arch Gynecol Obstet 285:281–284
152. Allam J, Cox M, Yentis SM (2008) Cell salvage in obstetrics. Int J Obstet Anesth 17:37–45
153. Franchini M (2006) Haemostasis and pregnancy. Thromb Haemost 95:401–413
154. Pitkin RM, Witte DL (1979) Platelet and leukocyte counts in pregnancy. J Am Med Ass 242:2696–2698

155. Simon L, Santi TM, Sacquin P, Hamza J (1997) Pre-anaesthetic assessment of coagulation abnormalities in obstetric patients: usefulness, timing and clinical implication. Br J Anaesth 78:678–683
156. Goonewardene M, Shehata M (2012) Anemia in pregnancy. Best Pract Res Clin Obstet Gynaecol 26:3–24
157. Kavle JA, Stoltzfus RJ, Witter F et al (2008) Association between anaemia during pregnancy and blood loss at and after delivery among women with vaginal births in Pembia Island, Zanzibar, Tanzania. J Health Popul Nutr 26:23240
158. Zhang J, Meikle S (2003) Trumble Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. Hypertens Pregnancy 22:203–212
159. de Lloyd L, Bovington R, Kaye A et al (2011) Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth 20:135–141
160. Huissoud C, Carrabin N, Benchalb M et al (2009) Coagulation assessment by rotation thromboelastometry in normal pregnancy. Thromb Haemost 101:755–761
161. Arulkumaran S, Mavrides E, Penney GC, Royal College of Obstetricians and Gynaecologists Green Top Guidelines 52. 2009 Prevention and Management of postpartum haemorrhage
162. Bolton-Maggs PH, Perry DJ, Chalmers EA et al (2004) The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organization. Haemophilia 10:593–628
163. Lee CA, Chi C, Parvod SR et al (2006) The obstetric and gynaecological management of women with inherited bleeding disorders- review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. Haemophilia 12:301–336
164. Zeeman GS (2006) Obstetric critical care: a blueprint for improved outcome. Crit Care Med 34:S208–S214
165. Huissoud C, Carrabin N, Audibert F et al (2009) Bedside assessment of fibrinogen level in postpartum haemorrhage by thromboelastometry. BJOG 116:1097–1102
166. Kozek-Langenecker SA (2010) Perioperative coagulation monitoring. Best Pract Res Clin Anaesthesiol 24:27–40
167. Haas T, Spielmann N, Mauch J et al (2012) Comparison of thromboelastometry (ROTEM) with standard plasmatic coagulation testing in paediatric surgery. Br J Anaesth 108:36–41
168. Kashuk JL, Moore EE, Sawyer M et al (2010) Postinjury coagulopathy management goal directed resuscitation via POC thromboelastography. Ann Surg 251:604–614
169. Bouvier-Colle MH, Ould EL, Joud D, Varnoux N et al (2001) Evaluation of the quality of care for severe obstetrical haemorrhage in three french regions. BJOG 108:898–903
170. Zuckeman L, Cohen E, Vagher JP, Woodward E, Caprini JA (1981) Comparisn of thromboelastography with common coagulation tests. Thromb Haemost 46:752–756
171. Gorlinger K, Dirkmann D, Hanke AA et al (2011) First line therapy with coagulation factor concentrates combined with point of care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single center cohort study. Anesthesiology 115:1179–1191
172. Ogawa S, Szlam F, Chen EP et al (2011) A cmparative evaluation of rotation thromboelastometry and standard coagulation tests in haemodilution induced coagulation changes after cardiac surgery. Transfusion 52:14–22
173. Schochl H, Cotton B, Inaba K (2011) FIBTEM provides early prediction of massive transfusion in trauma. Crit Care 15:R265
174. Schochl H, Nienaber U, Maegele M (2011) Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate based therapy versus standard fresh frozen plasma based therapy. Crit Care 15:R83
175. Coakley M, Reddy K, Macie I, Mallett S (2006) Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyze, the thromboelastogram and conventional coagulation tests. J Cardiothorac Vasc Anesth 20:548–553

176. Larsen OH, Fenger-Eriksen C, Cristiansen K, Ingerslev J, Sorensen D (2011) Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. Anesthesiology 115:294–302
177. Solomon C, Collis RE, Collins PW (2012) Haemostatic monitoring during postpartum haemorrhage and implication for management. Br J Anaesth 109:851–863
178. Solomon C, Collis RE, Collin PW (2013) Erythrocytes, Haemostasis and coagulation monitoring in postpartum haemorrhage (PPH). Br J Anaesth 110:1054–1055
179. Solomon C, Sorensen B, Hochleitner G et al (2012) Comparison of whole blood fibrin based clot tests in thromboelastography and thromboelastometry. Anesth Analg 114:721–730
180. Venema LF, Post WJ, Endriks HG et al (2010) An assessment of clinical interchangeability of TEG and ROTEM thromboelastographic variables in cardiac surgical patients. Anesth Analg 111:339–344
181. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, Fries D, Görlinger K, Haas T, Imberger G, Jacob M, Lancé M, Llau J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelsø AJ, Wouters P, Wyffels P (2013) Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 30(6):270–382. doi:10.1097/EJA.0b013e32835f4d5b, Review. Erratum in: Eur J Anaesthesiol. 2014 Apr;31(4):247
182. Collins PW, Solomon C, Sutor K, Crispin D, Hochleitner G, Rizoli S, Schöchl H, Schreiber M, Ranucci M (2014) Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. Br J Anaesth 113(4):585–595

# Noninvasive Ventilation Outside the Critical Care Unit

10

Cesare Gregoretti, Alessio Mattei, and Annalisa Carlucci

## 10.1 Introduction

Noninvasive ventilation (NIV) refers to the noninvasive delivery of mechanical ventilation or continuous positive airway pressure (CPAP) through the patient's mouth, nose, or both via different external interfaces. Differently from conventional invasive mechanical ventilation (IMV) delivered via endotracheal tube or tracheostomy, NIV does not impair patient's native upper airway, and overall it does not impair glottis function. As a matter of fact, it is able to reduce work of breathing and improve gas exchange while preserving the ability to cough, swallow, and speak. Furthermore, NIV averts iatrogenic complications associated with endotracheal intubation and reduces the risk of ventilator-associated pneumonia (VAP) [1, 2]. NIV includes both noninvasive positive pressure ventilation (NPPV) and CPAP. During CPAP the pressure applied to the respiratory system is generated exclusively by the patient's respiratory muscles. Consequently, the indications of this technique are limited to patients who, despite an alteration of the ventilation-perfusion (VA/Q), still have a muscular activity sufficient to maintain a spontaneous breath (absence of signs of severe fatigue of the respiratory muscles and ability to develop muscle strength in the face

C. Gregoretti (✉)
Department of Anesthesia Emergency, Citta' della Salute e della Scienza,
C.so Bramante 88, Torino 10126, Italy
e-mail: c.gregoretti@gmail.com

A. Mattei
Cardiothoracic Department, Citta' della Salute e della Scienza,
C.so Bramante 88, Torino 10126, Italy
e-mail: mattei.alessio@virgilio.it

A. Carlucci
Respiratory Intensive Care Unit, Fondazione S. Maugeri, IRCCS,
Via Salvatore Maugeri, 4, Pavia 27100, Italy
e-mail: annalisa.carlucci@fsm.it



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of an increased impedance of the respiratory system). Clinical indications to CPAP are therefore hypoxemia with alterations of the ratio VA/Q without hypercapnia and signs of respiratory distress. Unlike CPAP, during NPPV the inspiratory flow generated in the respiratory system is variably generated by the respiratory muscles and the pressure applied by the ventilator (partial support) or completely generated by the ventilator (total support). Consequently, the possible indications for this technique are patients who have hypoxemia and/or signs of fatigue of the respiratory muscles, paradoxical breathing, or simply insufficient muscular activity to maintain a correct spontaneous breathing and alveolar ventilation.

Noninvasive ventilation (NIV) has found a wide application both in home care and in the hospital setting. However, most of the studies on the acute application of NIV were carried out in the intensive care unit (ICU), emergency room, or in step-down units. These locations represent an "ideal" environment for the safe treatment of patients with moderate to severe acute respiratory failure (potentially with need of airway intubation) for the expertise of the staff and careful monitoring [1].

## 10.2 NIV Outside the Critical Area: Myth or Reality

Landoni et al. [1] in a recent monograph reported that over the last 15 years, there has been a steady increase in the number of publications on the use of NIV in departments that do not belong to the critical care area. Plant et al. [3] at the beginning of the present century demonstrated the efficacy of NIV in noncritical area during exacerbations of chronic obstructive pulmonary disease (COPD). In a study [4] where all the doctors could order the NIV for patients with acute respiratory failure, the authors reported that 41 % of cases were treated in noncritical departments without having a worse outcome. Surveys in Canada have shown that NIV was applied in departments outside of the critical area [5].

In the United States in a survey [6] conducted in 82 hospitals, 18 % of NIV treatments were initiated in noncritical departments. In a subsequent survey, which involved physicians and respiratory therapists of 63 hospitals, Bierer and Soo Hoo [7] reported that 40 % of respondents claimed the use of NIV in the departments. Interestingly 42 % of them reported of any restriction on the place of use.

Schettino et al. [8], in a single-center prospective observational study, reported that among 449 treated patients, NIV was introduced in noncritical departments in 33 % of cases. In addition, 35 % of the NIV treatments (some of which started in the critical area) were then run in noncritical units. The outcome of these patients led to a rate of intubation of 27.3 %; out of them 14.9 % died.

The effectiveness and feasibility of positive results have also been reported in other countries [9–14]. Carlucci et al. [9] reported that with the acquisition of a greater confidence to the use of NIV, there was a greater tendency to treat more severe acute exacerbation of COPD patients in a noncritical area. Cabrini et al. [10] reported, in a survey carried out in Italy and specifically related to the use of NIV outside the ICU, that 65 % of respondents claimed that NIV was applied in general wards and 28 % has allowed the use of NIV in every ward.

An observational study in a single center on 129 consecutive patients treated with the medical emergency team (MET) [1, 15–18] service in the medical and surgical wards has shown a high success rate, with only a few minor complications. However, the workload related to the NIV for a medical emergency team demonstrated to be intense with a high commitment in terms of time [17].

Recently, there have been published reports of centers with a medical emergency team similar to that managed by nonmedical health personnel (CCOT) [18].

In a randomized controlled trial, an NIV service managed by a medical emergency team in a hematology department was associated with a reduced risk of death [19].

## 10.3 Rational Use of NIV Outside the Critical Care Area

The intensive care unit is considered to be the safest environment to deliver NIV in a hypoxemic patient especially if suffering from "de novo acute respiratory failure" [20].

The failure of NIV in such patients seems linked to increased mortality rate. The critical area provides monitoring, experienced staff, and a high nurse-patients ratio [21], in the face of high costs. However, if the use of NIV is only allowed in the ICU, you run the risk of its underuse [1, 22].

The use of NIV outside the critical area as in general wards may allow certain categories of patients (e.g., COPD and neuromuscular patients) to be treated at an early stage. This is less cost-effective, and patients present a lower risk of problems as "posttraumatic distress disorders" [23]. NIV in general wards has been used in "not to intubate" patients. Interestingly, approximately 50 % of patients survive acute events [21, 24].

In patients with terminal disease, NIV may be indicated to relieve the symptom of dyspnea that can be compared to pain or as a therapeutic option to allow you to save time and allow the patient to consent to diagnostic or therapeutic procedures [25].

There is also a general consensus that the effectiveness of NIV is greatest when treatment is started at the beginning of deterioration of pulmonary function to avoid the need for endotracheal intubation [1, 19, 21, 26–31]. This is particularly true in acute hypoxemic patients [20]. Paus-Jenssen et al. [4], in a prospective study in which NIV was introduced in all hospital wards without a formal protocol and with no prior training in response to financial constraints and limitations of beds, concluded that "patients in whom NIV was introduced outside the ICU did not seem to have worse outcomes" compared to similar patients treated in intensive care.

There is no doubt that the use of NIV outside the critical area should theoretically lead to greater cost-effectiveness as demonstrated in two studies [3, 9]. Plant et al. [3], in a prospective randomized study of 118 patients (NIV vs standard therapy) performed in "general ward," showed that the introduction of an NIV service for the treatment of mild exacerbations of COPD has saved about 70,000 euro. In addition the mortality rate in the group treated with NIV was halved.

Carlucci et al. [9] observed a daily reduction of 90 € for each NIV treatment (comparing patients treated in critical vs noncritical area) over a period of 8 years.

The savings according to the authors was due to a greater percentage of patients treated in noncritical area. So, provided that the safety of the patient and the effectiveness of the technique are retained, the use of NIV outside the critical area could also reduce the costs [1].

As mentioned earlier the use of NIV outside of departments of critical care [3, 4, 9] allows to anticipate the medical act and to improve the cost-effectiveness. It must be stressed, however, that the concept of intubation delay remains valid especially in the hypoxemic patient. In COPD patients, it has been shown that delaying intubation did not increase mortality in patients who failed NIV [32].

Squadrone and Coll [33] have shown that the early use of CPAP in "general ward" may decrease the incidence of tracheal intubation and other complications in patients who develop respiratory failure after major abdominal surgery. The same author [19] demonstrated that in hematologic patients undergoing helmet CPAP in the hematologic department, the setup of NIV by a dedicated service team had a lower need for ICU admission (4 vs 16 patients, $P = 0.0002$). The CPAP reduced the relative risk of intubation 0.46 (95 % confidence interval 0.27–0.78). This study suggests that the early use of a "simple" CPAP in a noncritical area in this patient population can reduce the rate of intubation.

## 10.4 NIV Relationship Between Training and Results

The training and experience of the staff are considered the most important factors that determine the effectiveness of the NIV [25] beyond the choice of a proper setting on where to start it. Although many centers have applied the NIV outside the ICU, without any education program [1, 4, 10], "noncritical" health-care personnel may not have specific experiences on acute respiratory failure and NIV [1].

Training on NIV should be considered mandatory before introducing this technique in medical wards [1, 6, 34, 35] to achieve maximum effectiveness while maintaining patient safety. Although the NIV can be easily applied, its success is highly dependent on many factors. Patient's intolerance to the treatment is a common reason for the NIV failure [36]. In particular, the ward staff should be able to recognize promptly the failure of the technique without delaying tracheal intubation especially in hypoxemic patients [20].

It is clear that if the department staff cannot reach the required level of knowledge and experience in optimizing the effectiveness of NIV, a lower efficacy can be expected compared to the treatment of the patient in the critical care area. In addition, a periodic retraining of personnel should be carried out in particular, if one considers the often high staff turnover [1, 5, 31].

The requirements of basic training should include [1, 25, 34, 35]:

- The basis of mechanical ventilation
- Assembly of the NIV setup
- Understanding of the functioning of the ventilator or CPAP systems

- The choice of the interface
- The decision to start treatment
- General and specific indications and contraindications to NIV
- Prevention and treatment of its complications
- Patient selection and safety

The training should also take into account the local organization of the service of NIV (i.e., if the NIV is prescribed by a medical emergency team, a respiratory therapist, or by an attending physician of the department) [1]. The decision to start treatment is particularly critical, since it must be based on an overall assessment of the patient's condition, the human and technical resources, and the possible alternatives, in order to balance risks and benefits [1]. As a result, operators prescribing the NIV should be fully trained and experienced on its use, on local resources, and their reliability.

Finally, whenever possible and if the patient's condition permits, training on the use of NIV should be offered to him and his family, in order to increase patient compliance and to allow careful monitoring even by relatives. This concept is also very important when dealing with children. This would also result in an economization of human resources.

The resolution of the problems and the solution of serious matters (sudden desaturation, patient intolerance, coma, respiratory failure during NIV) should be addressed in simulated scenarios [1]. The need for tracheal intubation in a mixed population undergoing NIV outside the critical area ranges from 19 to 27 % [8, 17].

When the NIV is applied at an early stage of the disease, the failure rate seems significantly lesser [3, 19, 29]. However, in all studies, a significant percentage of patients had to be transferred to intensive care, while another subgroup, considered "do not intubate," died in the ward [1]. According to an Italian survey [10], the perception of physicians and respiratory therapists on the success rate of NIV (reported as low as about 50 %) confirms this data. However, these results were always found in hospitals with extensive experience regarding the use of NIV, and the worst results could be expected in other centers. Only two prospective studies from the same center reported data on complications during the application of NIV in the ward departments [17, 29].

Of a total of 214 patients, the only major complication was an episode of arterial hypotension which resolved immediately after discontinuation of NIV; minor complications (about 10 %) were skin lesions and patient discomfort. The most common problems, without consequences for patients, were about technical or organizational issues, such as the nonideal positioning of the mask, excessive air leakage, ventilator malfunctioning, and the omission of prescribed ventilation cycles. However, two subsequent investigations of the same hospital showed a different picture. Ninety ward nurses have reported a high incidence of potentially serious complications such as desaturation and sudden ventilator malfunctioning. The identification of the problem or medical intervention has an average delay of more than 5 min in one-third of cases [31]. However, although nurses reported a

very low incidence of errors in the management of NIV by the staff, only 23 % reported that the NIV prescribed cycles have always been administered, while 18 % said that the NIV was quite often interrupted with some delay, and 6 % reported that NIV was stopped too soon.

In a study carried out by interviewing 45 patients after successful treatment of the NIV, all patients reported at least one complication (with a worsening of breathing during NIV in 18 % of cases). In addition 28 patients reported to have suffered a medical emergency, and four have detected expectations of help from the staff, for more than 3 min [37].

It should be also noted that there is any agreement on patient selection and choice of monitoring. Hypoxemic patients, as mentioned above, are particularly at risk [1, 20] given that the deterioration can be very rapid. NIV failure may increase the risk of death [20]. As stressed in a recent monograph [1], patients who present the following conditions should not be considered suitable for a general ward [1, 21, 36]:

- Have known risk factors for failure of NIV as acute respiratory distress syndrome (ARDS)
- Have multiple or severe morbidity factors
- Have low tolerance or no improvement after first 1–2 h of treatment
- Are unable to maintain spontaneous breathing for at least 15–60 min without the aid of NIV

In conclusion, waiting for more data [1], all noncritical departments, with the possible exception of the departments of pulmonary rehabilitation, are commonly inadequate to safely monitor patients treated with NIV [38, 39].

Finally, it has been correctly stated [1] that the workload required by the NIV could adversely affect the safety (and quality of care) of the other patients in the wards.

## 10.5 How to make safe and effective NIV outside the Critical Area

The first and most important requirement is the presence of a multidisciplinary motivated group [1, 34], within the hospital or within the department where the NIV is implemented.

Two main organization models have been reported [1, 3, 4] although there are no studies comparing their pros and cons [1–11]:

1. NIV can be prescribed by an attending physician of the department and fully managed by the staff of the department.
2. Alternatively, it can be prescribed by a qualified health-care personnel outside the department which is better trained in the use of NIV (pulmonologist, respiratory therapist, medical emergency team, etc.). Once started, the treatment is then managed in collaboration with the staff of the ward [1, 17].

With the exception of respiratory departments, Landoni et al. [1] suggest that given the complexity of the use of NIV and especially the need for an expert assessment of the risk/benefit ratio, the decision to prescribe the NIV should be carried out by well-trained and experienced external departments of general medicine that are always present in hospitals.

It is also mandatory [1] that an emergency service able to assist the patient in case of clinical deterioration and capable of performing tracheal intubation be immediately available within the hospital.

Simple global guidelines [1] should include indications, contraindications, complications, mode of start and end of the NIV, and solutions to common problems. The real problem is to know when to start, how to proceed, and when to stop [1]. The main factors to be taken into account when starting NIV include:

- The risks of failure (the cause and severity of acute respiratory failure, comorbidities, patient safety, the nurse-patient monitoring adequate experience and training of staff, state of consciousness, and autonomy of the patient without NIV)
- Possible alternatives (is the patient considered unsuitable for intensive care?) [1, 17, 34, 35, 40]
- Adequate ventilators and interfaces [41, 42]

Although turbine-driven ventilators have outperformed compressed air-driven ICU ventilators, few of them have the possibility to administer a constant oxygen inspiratory fraction ($FiO_2$) [43, 44]. During the treatment of mild to moderate acute hypoxemic respiratory failure, physicians need to compute the $PaO_2/FiO_2$ ratio in order to follow up their patients [45]. To deliver CPAP, cheaper devices as "high continuous flow" may be used.

A wide range of interfaces with different sizes and models [21] (helmets, face masks, nasal masks, etc.) should also be available. If humidification is requested, active heated humidifiers are recommended. The monitoring should be dictated by the severity of the patient's illness and the resources available.

At the very least, pulse oximetry and continuous electrocardiogram (preferably telemetry) must be available for every patient [25] although, in selected cases, regular assessment of vital signs may be sufficient [1].

**Conclusions**

There are insufficient data to date to indicate an indiscriminate use of NIV outside the critical area. Until now, we know very little about the outcome of patients treated with NIV in ordinary wards; in a national survey, some form of data collection was carried out only by 18 % of hospitals with NIV outside of the intensive care unit [10]. Since departments and the organization for the administration of NIV are heterogeneous, only the analysis of local data can be informative for individual centers.

Multicenter studies are needed to explore the limits and possibilities of NIV outside the ICU.

## References


1. Landoni G, Zangrillo A, Cabrini L (2012) Non-invasive ventilation outside the ICU. In: Annual update of intensive care and emergency medicine. Vincent, Jean Louis (ed.) Springer-Verlag, Berlin Heidelberg, pp. 207–218
2. Boldrini R, Fasano L, Nava S et al (2012) Non invasive mechanical, ventilation. Curr Opin Crit Care 18:48–53
3. Plant PK, Owen JL, Elliot MW (2000) Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multiple centre randomized controlled trial. Lancet 355:1931–1935
4. Paus-Jenssen EX, Reid JK, Cockroft DW, Laframboise K, Ward HA (2004) The use of non-invasive ventilation in acute respiratory failure at a tertiary care center. Chest 126: 165–172
5. Burns KEA, Sinuff T, Adhikari NKJ et al (2005) Bilevel positive pressure ventilation for acute respiratory failure: survey of Ontario practice. Crit Care Med 33:1477–1483
6. Maheshwari V, Paioli D, Rothaar R, Hill NS (2006) Utilization of noninvasive ventilation in acute care hospitals. Chest 129:1226–1233
7. Bierer GB, Soo Hoo GW (2009) Noninvasive ventilation for acute respiratory failure: a national survey of Veterans Affair Hospitals. Respir Care 54:1313–1320
8. Schettino G, Altobelli N, Kacmarek RM (2008) Noninvasive positive-pressure ventilation in acute respiratory failure outside clinical trials: experience at Massachusetts General Hospital. Crit Care Med 36:441–447
9. Carlucci A, Delmastro M, Rubini F, Fracchia C, Nava S (2003) Changes in the practice of noninvasive ventilation in treating COPD patients over eight years. Intensive Care Med 29: 419–425
10. Cabrini L, Antonelli M, Savoia G, Landriscina M (2011) Noninvasive ventilation outside the intensive care unit: an Italian survey. Minerva Anestesiol 77:313–322
11. Gonzalez Barcala FJ, Zamarron Sanz C, Salguiero Rodriguez M, Rodriguez Suarez JR (2004) Non invasive ventilation in chronic obstructive pulmonary disease patients with acute respiratory hypercapnic failure in a conventional hospital ward. An Med Interna 21:373–377
12. Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease (2005) Early use of non invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicentre randomized controlled trial. Chin Med J 118:2034–2040
13. Dikensoy O, Ikidag B, Filiz A, Bayram N (2002) Comparison of noninvasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomized controlled study at a tertiary health centre in SE Turkey. Int J Clin Pract 56:85–88
14. Al-Mutairi SS, Al-Deen JS (2004) Non invasive positive pressure ventilation in acute respiratory failure. An alternative modality to invasive ventilation at a general hospital. Saudi Med J 25:190–194
15. De Vita MA, Bellomo R, Hillman K et al (2006) Findings of the first consensus conference on medical emergency teams. Crit Care Med 34:2463–2478
16. Badiger R, Green M, Hackwood H, Palin C, Shee CD (2004) Noninvasive ventilation in surgical patients in a district general hospital. Anaesthesia 59:967–970
17. Cabrini L, Idone C, Colombo S et al (2009) Medical emergency team and non-invasive ventilation outside ICU for acute respiratory failure. Intensive Care Med 35:333–343
18. Sumner K, Yadegafar G (2011) The utility and futility of noninvasive ventilation in non-designed areas: can critical care outreach nurses influence practice? Intensive Crit Care Nurs 27:211–217
19. Squadrone V, Massaia M, Bruno B et al (2010) Early CPAP prevents evolution in acute lung injury in patients with hematologic malignancy. Intensive Care Med 36:1666–1674
20. Demoule A, Girou E, Richard JC, Taillé S (2006) Brochard Increased use of noninvasive ventilation in French intensive care units. Intensive Care Med 32:1747–1755
21. Nava S, Hill NH (2009) Non-invasive ventilation in acute respiratory failure. Lancet 374: 250–259

22. British Thoracic Society Standards of Care Committee (2002) Non invasive ventilation in acute respiratory failure. Thorax 57:192–211
23. Samuelson KA (2011) Unpleasant and pleasant memories of intensive care in adult mechanically ventilated patients-findings from 250 interviews. Intensive Crit Care Nurs 27:76–84
24. Azoulay E, Demoule A, Jaber S et al (2011) Palliative noninvasive ventilation in patients with respiratory failure. Intensive Care Med 37:1250–1257
25. Elliott MW, Confalonieri M, Nava S (2002) Where to perform non invasive ventilation? Eur Respir J 19:1159–1166
26. Liesching T, Kwok H, Hill NS (2003) Acute applications of non invasive positive pressure ventilation. Chest 124:699–713
27. Cabrini L, Monti G, Landoni G, Colombo S, Savia I, Zangrillo A (2011) Non-invasive ventilation, ordinary wards and medical emergency team: maximizing effectiveness while preserving safety. Resuscitation 82:1464
28. Jabber S, Chanques G, Jung B (2010) Postoperative noninvasive ventilation. Anesthesiology 112:453–461
29. Olper L, Cabrini L, Landoni G et al (2002) Non invasive ventilation after cardiac surgery outside the intensive care unit. Minerva Anestesiol 77:40–45
30. Chiumello D, Chevallard G, Gregoretti C (2011) Noninvasive ventilation in postoperative patients: a systematic review. Intensive Care Med 37:928–929
31. Cabrini L, Monti G, Villa M et al (2009) Non invasive ventilation outside the intensive care unit for acute respiratory failure: the perspective of the general ward nurses. Minerva Anestesiol 75:427–433
32. Squadrone E, Frigerio P, Fogliati C, Gregoretti C, Conti G, Antonelli M, Costa R, Baiardi P, Navalesi P (2004) Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. Intensive Care Med 30(7):1303–1310
33. Squadrone V, Coha M, Cerutti E, Schellino MM, Biolino P, Occella P, Belloni G, Vilianis G, Fiore G, Cavallo F, Ranieri VM, Piedmont Intensive Care Units Network (PICUN) (2005) Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. JAMA 293:589–595
34. Hess DR (2009) How to initiate a noninvasive ventilation program: bringing the evidence to the bedside. Respir Care 54:232–245
35. Davis JD, Gentile MA (2009) What does it take to have a successful noninvasive ventilation program? Respir Care 54:53–61
36. Hess DR (2011) Patient ventilator interaction during noninvasive ventilation. Respir Care 56:153–165
37. Cabrini L, Moizo E, Nicelli E et al (2012) Noninvasive ventilation outside the intensive care unit from the patient point of view: a pilot study. Respir Care 57:704–709
38. Chiumello D, Conti G, Foti G, Giacomini M, Braschi A, Iapichino G (2009) Non invasive ventilation outside the intensive care unit for acute respiratory failure. Minerva Anestesiol 75:459–466
39. Ambrosino N, Vagheggini G (2008) Noninvasive positive pressure ventilation in the acute care setting: where are we? Eur Respir J 31:874–886
40. Cabrini L, Silvani P, Landoni G, Monti G, Colombo S, Zangrillo A (2010) Monitoring non invasive ventilation outside the intensive care unit. Minerva Anestesiol 76:71
41. Schonhofer B, Sortor-Leger S (2002) Equipment needs for noninvasive mechanical ventilation. Eur Respir J 20:1029–1036
42. Chatburn RL (2009) Which ventilators and modes can be used to deliver noninvasive ventilation? Respir Care 54:85–101
43. Gregoretti C, Navalesi P, Ghannadian S, Carlucci A, Pelosi P (2013) Choosing a ventilator for home mechanical ventilation. Breathe 10:395–408
44. Scala R, Naldi M (2008) Ventilators for noninvasive ventilation to treat acute respiratory failure. Respir Care 53:1054–1080
45. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A et al (2012) The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 38:1573–1582

# Interventional Cardiology: The Role of the Anesthesiologist

# 11

Franco Cavaliere

Recent years have seen a significant increase in the activity of interventional cardiology. Primary angioplasty has become the standard of management of acute myocardial infarction, and new techniques have been developed to treat cardiac diseases as mitral regurgitation, aortic stenosis, and atrial septal defects [1].

Advances in interventional cardiology have led to an increasing involvement of the anesthesiologist. In the activity of the cardiac catheterization lab, many procedures, as mitral clip and TAVI, require general anesthesia or deep sedation. Besides, there is the evermore frequent recourse to diagnostic coronary angiography and primary angioplasty in patients with cardiogenic shock. In this case, the anesthesiologist intervenes at an early stage in assisting in the emergency room and then transporting to the cath lab. Periprocedural management includes sedation and analgesia, monitoring and pharmacological support of circulation, and the handling of respiratory failure from pulmonary edema, while the operator focuses on the procedure. In the electrophysiology lab, sedation or general anesthesia is often necessary to carry out long-lasting procedures in poorly cooperative patients. Finally, the anesthesiologist is called to handle the complications that cause circulatory or respiratory failure or require surgery.

From the point of view of the anesthesiologist, however, the cath lab is still a working environment less familiar than the operatory theater. In fact, he/she intervenes only in a limited part of the activity performed by the interventional cardiologist. Many procedures are managed directly by the cardiologist, using local anesthesia by infiltration and mild forms of sedation, in order to avoid the risk of respiratory depression. When the presence of an anesthesiologist is needed, it is still a matter of debate if he/she should preferably be a cardiac anesthesiologist. Favorable ones argue that cardiac anesthesiologists are more familiar with the

F. Cavaliere
Department of Cardiovascular Science, Catholic University of the Sacred Heart,
Largo Francesco Vito, 1, Rome 00168, Italy
e-mail: f.cavaliere@rm.unicatt.it



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techniques to be applied in case of complications, such as the use of the intra-aortic balloon pump (IABP) or ventricular assistance, and the management of sternotomy and extracorporeal circulation and are usually able to perform transesophageal echocardiography [2, 3]. In practice, however, the choice between sedation managed by a cardiologist and an anesthesiologist (cardiac or not) is strongly influenced by the availability of the latter [4].

A further aspect is the significant differences between the cath lab and the operatory theater. In some facilities, there is a hybrid operating room, designed to perform the functions of both a cath lab and an operating room, which allows to work in a comfortable environment, characterized by areas of adequate size and amenities similar to those of an operating room. More frequently, however, the activity is performed in smaller rooms, where the space available for the anesthesia machine and anesthesiological material is limited, as it is that for the surgical team and its equipment, in the event of a complication that requires surgery. The relative difficulty of movement and access to the patient during the procedures affects the preparatory phase. Quality and stability of vascular accesses, airway control, and availability of adhesive plaques for electrical defibrillation or external pacing are particularly important. Moreover, the absence of the anesthesiologist in most of the activities performed in the room can lead to a lower confidence of nurses with anesthesiological techniques and airway management. Finally, it is necessary that the anesthesiologist periodically checks the equipment functionality and the availability of drugs and materials, maintains an elevated degree of attention during procedures that see him/her involved, and puts in place all possible measures to guarantee a safety standard as high as that present in the operating theater.

## 11.1 Percutaneous Mitral Valve Repair (MitraClip®)

Mitral regurgitation is a relatively frequent pathology, which can cause a progressive dysfunction of the left ventricle, up to congestive heart failure. In the past, the most common etiology was acute articular rheumatism; now it is the myxomatous degeneration of the valve, which determines the prolapse. Other possible causes are ischemic dysfunction of the papillary muscles and connective tissue diseases, such as Marfan and Ehlers-Danlos syndromes. Finally, functional insufficiency may result from the increase in size of the left atrium and ventricle. The indication for surgery (plastic repair or replacement) arises in moderate-to-severe (3 +) or severe (4 +) regurgitation, when this is associated with symptoms indicative of a significant ventricle dysfunction [5].

One of the surgical techniques used in plastic repair of the valve is the “edge-to-edge” method, proposed by Alfieri et al. in 1998. It involves the central suture of the two valve leaflets with the formation of a double orifice [6]. A similar result has been obtained with a percutaneous approach by joining anterior and posterior leaflets with a clip [7], that is, a structure of chrome-cobalt, about 4 mm wide, which is placed by a specific catheter. The catheter is introduced from the femoral vein and pushed into the right atrium and then into the left atrium through transseptal access. The tip of the catheter is advanced into the ventricle until the clip is positioned so

that, by closing it, it grasps the central part of the two mitral valve leaflets and approximates them. This maneuver is carried out under a fluoroscopic and echocardiographic control, with the placement of a transesophageal probe.

The effectiveness of the percutaneous placement of a mitral clip has been investigated by numerous studies. Among them, the first EVEREST study (Endovascular Valve Edge-to-Edge Repair Study), conducted on 27 patients, showed a reduction in the degree of valvular insufficiency of one or two functional classes 6 months after the procedure [8]. The second EVEREST study, carried out on 279 patients, compared the results of mitral clip positioning with surgical intervention, 1 year after the procedure [9]. The primary objective of that study was to evaluate the percentage of patients who were still alive, had not been operated or reoperated for valve replacement, and presented a degree of insufficiency lower than moderate-to-severe (3 +). The percentage was significantly higher in surgical patients (73 %) than in patients who were treated with the percutaneous approach (55 %). Even so, the former presented more complications, mainly the need for blood transfusion and for invasive mechanical ventilation lasting more than 48 h. Four years after the procedure, the primary endpoint was still reached by more patients in the surgical group (53 %) than in the mitral clip group (40 %), but the difference was not statistically significant, and mortality was similar. However, the percentage of patients undergoing cardiac surgery for the presence of residual regurgitation was significantly lower after surgery (2 % vs 20 %) [10]. Those findings support the currently accepted indications for MitraClip® procedure, i.e., the presence of severe degenerative or functional mitral insufficiency, which meets the criteria for surgical correction, but presents a surgical risk deemed unacceptable.

### 11.1.1 The Role of the Anesthesiologist

A mitral clip is usually positioned under general anesthesia. The main reason is that the patient has to bear the transesophageal ultrasound probe all over the procedure, a condition that is generally poorly tolerated. Supine position and the need to maintain a relative immobility accentuate this difficulty, particularly in subjects with severe cardiac dysfunction. The procedure is indeed quite long; its average duration is about 3 h, but it is very variable. The length is influenced by patient anatomy, the possible need to place a second clip, and finally the ability of the operator. In this respect, the learning curve is quick enough, and there is often a significant shortening of the average duration of the procedure with increasing experience.

Preoperative evaluation by an anesthesiologist is an important part in the initial multidisciplinary assessment of surgical risk. Once the indication to MitraClip® percutaneous mitral valve repair is put, the informed consent is gathered, and blood unit availability is obtained (in our center, two units are requested). A light premedication with benzodiazepines may facilitate patient management. The technique can be either intravenous or inhalation anesthesia. Monitoring includes two-lead ECG, invasive blood pressure, pulse oximetry, and capnometry. It is good to have one, preferably two, venous access of a good caliber; a central venous catheter is useful, while a pulmonary artery catheter is seldom necessary. After anesthesia induction, a muscle

relaxant is given, and a tracheal tube is positioned to control airways. Heparin is administered at the beginning of the procedure to maintain the activated clotting time around 250 s. Most patients are awakened in the cath lab at the end of the procedure.

In special cases, it is possible to avoid general anesthesia and endotracheal intubation. Recently, a few case reports have been published, in which the procedure was performed under sedation without airway control. Ussia performed the mitral clip procedure under sedation with remifentanil, 0.08 mcg/kg/min, in a patient who had a contraindication to the use of muscle relaxants for the presence of a neuromuscular disease [11]. The performance was facilitated by highly experienced operators who performed the whole process very quickly (time interval between the atrial septal puncture and the retraction of the probe in the right atrium of about 35 min). A series of five cases was performed in the USA with a light sedation, based on an initial bolus of midazolam, 2 mg iv, followed by boluses of propofol, 20 mg, as needed [12].

The complications that may arise during and after the procedure are numerous, and often their management involves the anesthesiologist. First, it may be not successful so that surgical correction in election is required. Furthermore, the clip can come loose from the valve leaflets during the procedure or in the following days, and this causes the reappearance of a regurgitation equal to or worse than the initial one; fortunately, no case of embolization has been reported in literature. Mechanical damages of the mitral valve and its apparatus include fissured valve leaflet and the rupture of a tendon rope or, more rarely, of a papillary muscle (one case with a fatal outcome has been reported in a patient suffering from recent myocardial infarction) and often aggravate valvular insufficiency. No case of the appearance of significant mitral stenosis has been reported. Mechanical complications often need surgical elective or emergency intervention. Aortic counterpulsation and left ventricular assistance can provide a temporary support in case of cardiogenic shock. Bleeding from the entry point of the catheter is relatively frequent and may result in the loss of significant amounts of blood. In some series, the incidence of blood transfusions related to the procedure of MitraClip® reaches 8 % [13]. In the EVEREST II study, 13 % of patients received blood transfusion in the first 30 postoperative days.

## 11.2 Transcatheter Aortic Valve Implantation (TAVI)

Aortic stenosis is the most common valvular heart disease in the elderly. The natural history of the disease is characterized by a progressive reduction of the valve area and an increase in the transvalvular gradient. Consequent left ventricular hypertrophy and chronic myocardial ischemia finally result in both systolic and diastolic dysfunctions. Symptoms include syncope, angina attacks, and exertional dyspnea. When signs of congestive heart failure appear, life expectancy is just few years. Surgical replacement of the valve is indicated in the presence of severe stenosis (valve area <1 $cm^2$, transvalvular gradient >40 mmHg, or aortic jet velocity >4 m/s), associated with clinically manifest left ventricular systolic dysfunction.

About 15 years ago, a technique was developed to implant an aortic valve prosthesis without opening the aorta or performing extracorporeal circulation. As for

MitraClip®, transcatheter aortic valve implantation (TAVI) is taken into account when the operative risk is too high. The procedure includes a valvuloplasty which is performed by inflating a balloon inside the aortic valve in order to eliminate the stenosis. Afterwards, a stent containing the bioprosthetic valve is positioned in the aorta by inflating a second balloon. During aortic occlusion, left ventricle contraction is impaired by rapid ventricular pacing at about 200 BPM, induced by a catheter electrode in the right ventricle. The delivery system can be positioned by different approaches. In most cases, a femoral artery is cannulated by transcutaneous puncture or surgical preparation. If this is impossible, usually because of severe arterial stenosis, trans-apical or subclavian/axillary approaches are utilized. In the former, the device is introduced through the apex of the heart after an anterolateral minithoracotomy and pericardiotomy. In the latter, it is introduced through the left subclavian or axillary artery, which is punctured after surgical preparation. TAVI is often performed under local analgesia and conscious sedation if transfemoral access is utilized. Otherwise, it is usually performed under general anesthesia.

TAVI has proven to be an effective alternative to conventional therapy. Compared with medical treatment, it is associated with an improvement in quality of life, a resolution of symptoms, and a decrease in mortality of about 20 % after 1 year [14]. Compared to surgery, symptoms improve faster, but results are similar in 1 year; TAVI is associated to a higher incidence of vascular complications, surgery to more serious bleeding and more frequent episodes of atrial fibrillation. Stroke incidence is equal after TAVI or surgery [15].

### 11.2.1 The Role of the Anesthesiologist

Anesthesiologists collaborate with cardiologists and cardiac surgeons to assess the risk associated with surgery and to plan the approach for TAVI. Risk evaluation includes the calculation of indices such as EuroSCORE or the Predicted Risk of Mortality according to the Society of Thoracic Surgeons (STSPROM). The indication for TAVI arises when the operative risk is unacceptable; limit values are usually a EuroSCORE higher than 15 % or an STSPROM equal to or greater than 10. With regard to the approach, percutaneous femoral artery catheterization is the preferred route of entry, although valve positioning can be more difficult with this approach and the risk of significant bleeding from the entry point of the catheter is high. The presence of severe arterial disease can make this route impractical. Access through the apex of the heart facilitates valve positioning, but requires a minithoracotomy; consequently, pain is greater and postoperative bleeding is more difficult to control. Access through the subclavian or axillary artery is placed in an intermediate position because it requires surgical preparation of the vessel, but is less invasive than minithoracotomy. Inadequate size of the artery is a contraindication because of the risk of upper limb ischemia. Preoperative anesthetic visit includes a careful assessment of comorbidity, airway and drug treatment, the collection of informed consent, and the demand for blood units (in our center, two units).

The conduct of anesthesia has as main objective to preserve adequate hemodynamics in patients with severe symptomatic aortic stenosis, who are subjected to

pacing at a frequency of 200 BPM for a few seconds [16]. Excessive bradycardia and tachycardia should be avoided all over the procedure because both impair myocardial perfusion and ventricular filling (most patients have significant diastolic dysfunction). A proper preload should also be maintained because hypovolemia hinders ventricular filling and volume overload can result in pulmonary hypertension and congestion. Vasoconstrictors are often useful to prevent vasodilation in the presence of cardiac output limitations due to aortic stenosis. Inotropic agents are sometimes necessary to support myocardial contractility, in the case of severe left ventricular systolic dysfunction. Adequate monitoring is essential for hemodynamic optimization. An arterial cannula is positioned to monitor blood pressure. A central venous catheter is important for preload evaluation and vasoactive drug infusion; it is also particularly valuable in case emergency surgery becomes necessary. In few cases, the indication to place a catheter in the pulmonary artery may be evaluated to monitor pulmonary capillary wedge pressure and cardiac output. Echocardiography provides information on heart volumes and general and segmental contractility.

TAVI is performed under local or general anesthesia. The femoral approach with or without the use of transthoracic echocardiography is well suited to the use of anesthesia by infiltration associated with sedation. The techniques used for sedation include the infusion of propofol and/or remifentanil. The use of target-controlled anesthesia (TCA) facilitates the task of the anesthesiologist in maintaining effective concentrations of drugs without reaching dangerous levels. The introduction of a large cannula in the femoral artery is very painful and is easier under analgesia with opioids. General anesthesia, which is associated with a longer duration of procedures and a greater hemodynamic instability [17], is commonly considered necessary for both trans-apical and subclavian/axillary approaches. In the literature, however, the former has been successfully managed with epidural anesthesia and the latter by local anesthesia associated with deep sedation.

The success rate of TAVI is high, reaching percentages close to 90 %. The most important complications are cardiac tamponade caused by hemopericardium and heart failure [18]. Perioperative bleeding is more frequent when the transfemoral approach is utilized and may require blood transfusions, surgical hemostasis, and vascular stenting. Other possible complications are the rupture of the aortic ring, aortic dissection, and embolization. Many of these complications require surgical intervention and often the transition from percutaneous to surgical valve replacement. The potential occurrence of such complications must be kept in mind. Placement of a central venous catheter and venous cannulas of a large caliber and immediate availability of homologous blood allow to treat hemorrhagic and cardiogenic shock promptly.

## Conclusions

Recent successes of interventional cardiology have required a greater involvement of the anesthesiologist, whose role is not limited to the administration of sedative and analgesic drugs, but includes preoperative evaluation and management of complications.

## References


1. Haas S, Richter HP, Kubitz JC (2009) Anesthesia during cardiologic procedures. Curr Opin Anaesthesiol 22:519–523
2. Mahajan A, Chua J (2011) Pro: a cardiovascular anesthesiologist should provide services in the catheterization and electrophysiology laboratory. J Cardiothorac Vasc Anesth 25:553–556
3. Elkassabany NM, Mandel JE (2011) Con: a general anesthesiologist with a certain skill set is qualified to provide services in the interventional cardiology and electrophysiology laboratory. J Cardiothorac Vasc Anesth 25:557–558
4. Gaitan BD, Trentman TL, Fassett SL et al (2011) Sedation and analgesia in the cardiac electrophysiology laboratory: a national survey of electrophysiologists investigating the who, how, and why? J Cardiothorac Vasc Anesth 25:647–659
5. Bonow RO, Carabello BA, Chatterjee K et al (2008) Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 52:e1–e142
6. Alfieri O, Maisano F, De Bonis M et al (2001) The double-orifice technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg 122:674–681
7. Fann JI, St Goar FG, Komtebedde J et al (2004) Beating heart catheter-based edge-to edge mitral valve procedure in a porcine model: efficacy and healing response. Circulation 110:988–993
8. Feldman T, Wasserman HS, Herrmann HC et al (2005) Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol 46:2134–2140
9. Feldman T, Foster E, Glower DD et al; EVEREST II Investigators (2011) Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 364:1395–1406
10. Mauri L, Foster E, Glower DD et al; EVEREST II Investigators (2013) 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol 62:317–328
11. Ussia GP, Barbanti M, Tamburino C (2010) Feasibility of percutaneous transcatheter mitral valve repair with the MitraClip system using conscious sedation. Catheter Cardiovasc Interv 75:1137–1140
12. Teufel T, Steinberg DH, Wunderlich N et al (2012) Percutaneous mitral valve repair with the MitraClip® system under deep sedation and local anaesthesia. EuroIntervention 8:587–590
13. Armoiry X, Brochet E, Lefevre T et al (2013) Initial French experience of percutaneous mitral valve repair with the MitraClip: a multicentre national registry. Arch Cardiovasc Dis 106:287–294
14. Leon MB, Smith CR, Mack M et al; PARTNER Trial Investigators (2010) Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 363:1597–1607
15. Smith CR, Leon MB, Mack MJ et al; PARTNER Trial Investigators (2011) Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 364:2187–2198
16. Covello RD, Landoni G, Zangrillo A (2011) Anesthetic management of transcatheter aortic valve implantation. Curr Opin Anaesthesiol 24:417–425
17. Dehédin B, Guinot PG, Ibrahim H et al (2011) Anesthesia and perioperative management of patients who undergo transfemoral transcatheter aortic valve implantation: an observational study of general versus local/regional anesthesia in 125 consecutive patients. J Cardiothorac Vasc Anesth 25:1036–1043
18. Guinot PG, Depoix JP, Etchegoyen L et al (2010) Anesthesia and perioperative management of patients undergoing transcatheter aortic valve implantation: analysis of 90 consecutive patients with focus on perioperative complications. J Cardiothorac Vasc Anesth 24:752–761

# All You Need to Know About the Meaning of Plasmatic Lactate Level

12

L. di Girolamo, R. Iorio, G. Spinelli, and M. Dei Poli

Every time we make simplifications in critical care, there is a risk of building monomodal connections (i.e., low values of hemoglobin – need of blood transfusion, oliguria – loop diuretic infusion, and so on).

Even when dealing with blood lactates, the risk of unreasoned conclusions and precipitous therapy exists, mainly if the physician lacks sufficient knowledge about the normal and pathological biochemistry of lactate.

During most of the past century, there has been much negativity around lactate: as a waste product of glycolysis in an anaerobic environment, when the muscle effort causes an oxygen debt, lactate is involved in the acidotic tissue damage.

Since the 1970s, discoveries like the "lactate shuttle" generated a true revolution in looking at this molecule.

Nowadays, most part of scientific evidences shows that lactate is an important intermediate of various metabolic processes, is a substrate of the aerobic energetic pathway, and probably is an intermediate of the redox reactions between intracellular and extracellular compartments.

In order to make this overview useful for clinical scenarios, we will start from a biochemical perspective.

## 12.1 Glycolysis

When speaking about energetic metabolism, the main catabolic pathway is represented by glycolysis (the Embden–Meyerhof–Parnas pathway, from the Greek words glykis, meaning sweet, and *lysis*, meaning breakdown).

In a non-strict anaerobic context, one glucose molecule is broken down into two pyruvate molecules, in order to generate two molecules of adenosine triphosphate

L. di Girolamo (✉) • R. Iorio • G. Spinelli • M.D. Poli
Intensive Care Unit, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
e-mail: luca.digirolamo@unimi.it



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(ATP) and two molecules of nicotinamide adenine dinucleotide (reduced NADH or reduced NAD); these by-products have a higher energetic content.

The free energy released by the conversion of glucose to pyruvate is therefore used to build high-energy compounds, like ATP and NADH [1].

In nature, glycolysis is the most common and most used way to produce energy, even if it is not the most efficient one, mainly due to its anaerobicity; even prokaryotic cells (dated probably 3.5 billion years) carried out this pathway, which therefore gave a decisive input to the primordial phases of the evolution.

Why does glucose bear a very essential role in the energetic metabolism?

The answer is that glucose is the most widely present carbohydrate in the living world, and, inside the cell cytosol, it shows a very modest attitude to glycosylate the proteins, either spontaneously or enzymatically. Indeed glucose is essentially a closed-configuration molecule.

The strategy of glycolysis is aimed to trap the glucose molecule inside the cell and to form some phosphorylated tricarbonic units from an esacarbonic molecule.

The entire process constitutes nine steps, with each chemical reaction being catalyzed by a specific enzyme.

It can be further divided into three phases.

The first three reactions need energy (2 ATPs are expended): the glucose enters the cell through specific transport proteins and it is phosphorylated by ATP. Its phosphorylated form (glucose 6-phosphate) is no longer able to cross the plasma membrane, since it isn't recognized by transporters anymore. Furthermore, it is unstable.

The second phase – which together with the first one is called the "investment phase," as it requires an energy intake – consists of the split of the 6-carbon molecule (fructose 1,6-diphosphate) into two different fragments comprising 3 atoms of carbon each: glyceraldehyde 3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP). Those are interconvertible isomers; at equilibrium, 96 % is represented by DHAP.

The third stage is the "pay-off phase." It comprises three reactions (from 6th to 9th). These pick up a part of the energy contained in the GAP, thereby transforming it into ATP molecules.

Furthermore, the two molecules of GAP are converted into two molecules of pyruvate. It follows a production of 4 ATP molecules and 2 NADH molecules (by reduction of NAD+). Consequently, a net energy production (2 molecules of ATP are expended while 4 are produced) and a regeneration of the reducing molecules pool (reduced NAD, NADH) occur.

When the 9th reaction (production of pyruvate) comes to an end, the whole glycolytic pathway returns a net energy gain (Fig. 12.1).

## 12.2 Pyruvic Acid

Pyruvic acid ($CH_3COCOOH$) is an organic acid, the simplest of alpha-keto acids (obtained by pyrolysis of tartaric acid). The anionic form of pyruvic acid is pyruvate ($CH_3$ CO CO $O^-$): it represents the intermediate key factor in a lot of metabolic paths, particularly related to energetic metabolism (Fig. 12.2).

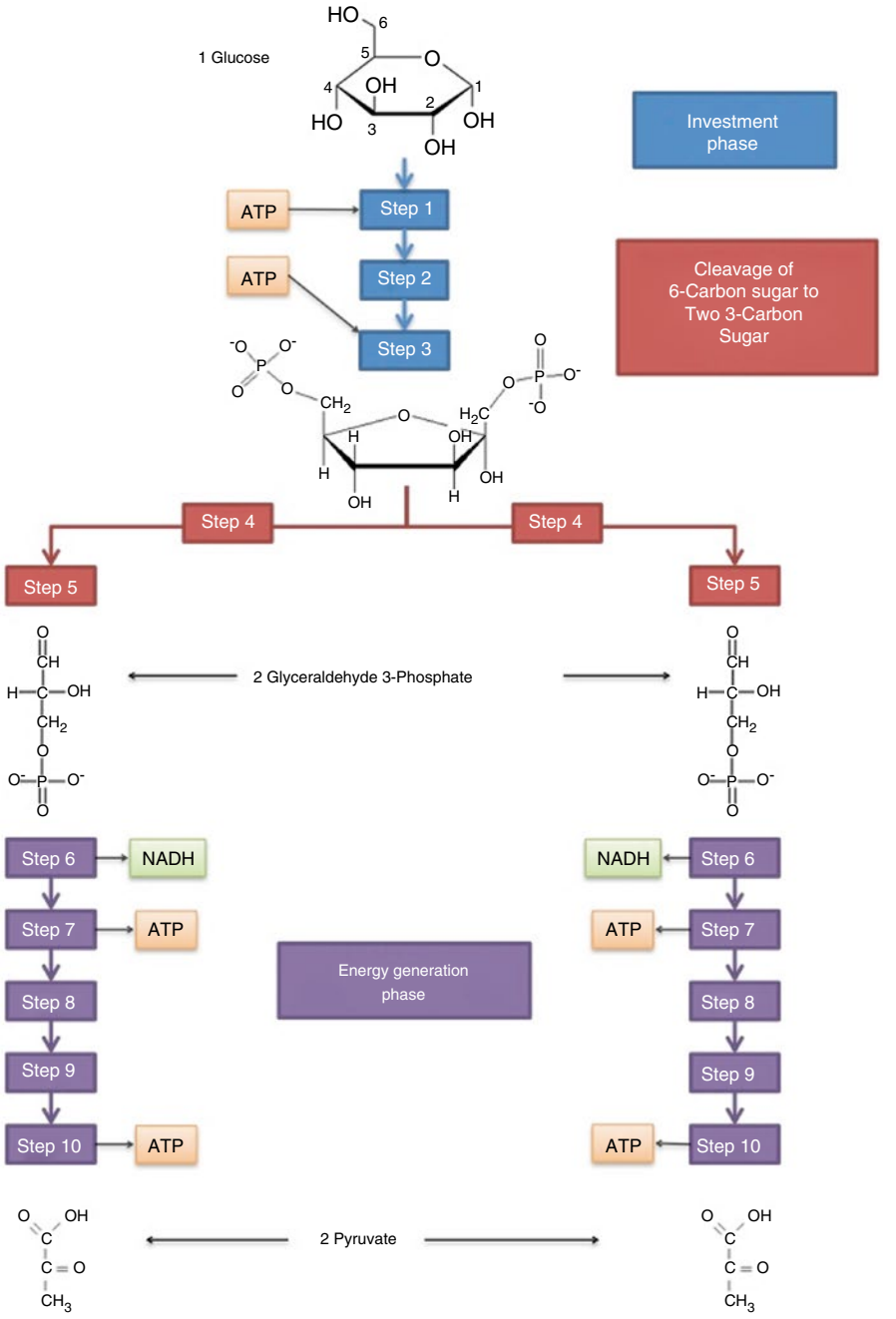


**Fig. 12.1** The glycolysis pathway

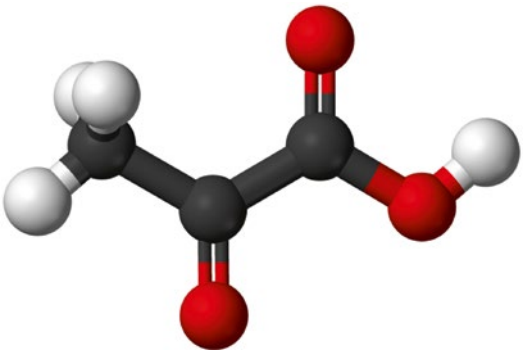

**Fig. 12.2** The pyruvic acid molecule; *black circles* represent carbon atoms, *red circles* represent oxygen atoms, and *white circles* represent hydrogen atoms

Generated through glycolysis from glucose, pyruvate may:

1. Be reconverted to carbohydrate through "gluconeogenesis"
2. Be reconverted to fatty acids through acetyl-CoA
3. Be used to synthesize the amino-acid alanine
4. Be fermented to ethanol or lactate

Particularly, as an energy compound:

1. It can enter the Krebs cycle (thereby entering the oxidative phosphorylation in aerobiosis conditions).
2. It can undergo alcoholic (particularly in vegetables) or lactic fermentation.

## 12.3 From Pyruvate to Lactate

As glycolysis comes to an end, one molecule of glucose is split into two molecules of pyruvate (from a 6-carbon molecule to two molecules composed of 3 carbons each).

During this process, a small proportion of the whole available energy contained in one molecule of glucose is released. Indeed, since pyruvates are still relatively reduced, they already contain most of the energy.

Further energy can be released by pyruvate through two main paths.

In aerobic conditions, the pyruvate-dehydrogenase complex, a multienzymatic compound composed of three proteins located in both the mitochondria of eukaryotic cells and the cytosol of prokaryotic cells, oxidizes pyruvic acid to acetyl-CoA and $CO_2$ [2].

The overall resultant reaction (actually three subunits catalyze three different reactions) is represented by an oxidative decarboxylation which also sets out the intervention of several coenzymes and prosthetic groups (namely, coenzyme A, lipoic acid, FAD, NAD).

The resulting acetyl-CoA enters the mitochondrial next phase of aerobic metabolism, which is alternatively named tricarboxylic acid cycle, or Krebs cycle.

As the cycle starts, acetyl-CoA is condensated with oxaloacetate to generate citrate.

From this point on, oxaloacetate will be cyclically regenerated (and here again condensated with acetyl-CoA). Each cycle will produce one molecule of ATP and, most importantly, NADH and FADH.

Those are reduced cofactors whose entrance into the electron transport chain – known as "oxidative phosphorylation" – catalyzes energy production of 36 molecules of ATP.

On the other hand, under conditions of low oxygen availability, pyruvate undertakes the path of lactic fermentation. This will produce L-lactate and oxidized NAD [3].

It is noteworthy that a true anaerobic state didn't represent the unique circumstance characterized by the activation of lactic fermentation since it also takes place under different conditions like intense muscular activity, where insufficient local content of $O_2$ is present.

## 12.4 What Is Lactate?

Lactic acid (whose IUPAC classification name is hydroxypropanoic acid) is a chemical compound that plays a significant role in many biochemical processes.

It is a large carboxylic acid characterized by the chemical formula $C_3H_6O_3$. Its deprotonation (loss of a $H^+$) gives rise to the lactate ion (Fig. 12.3) [4].

Actually, the commonly called "lactate ion" is represented by just the L-lactate stereoisomer. D-lactate is in fact only present in patients affected by short bowel syndrome and requires special measures to be determined.

Given a pH of 7.4, the lactate/lactic acid ratio is in the order of 3,548:1.

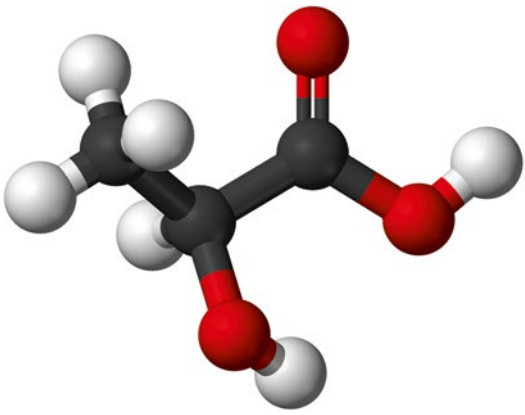

**Fig. 12.3** The lactic acid molecule; *black circles* represent carbon atoms, *red circles* represent oxygen atoms, and *white circles* represent hydrogen atoms

Lactic acid is therefore a strong acid (at least in a biological context), which strongly dissociates into lactate ions and hydrogens when it is solved in a solution (pKa = 3.9 to 7.4). Lactate is therefore a strong ion as well.

It is noteworthy that, in clinical settings, one commonly speaks about lactate instead of lactic acid.

## 12.5 What Is Lactate Unit of Measurement? What Are Its Normal Values?

Lactate should be measured in mmol/L (millimoles per liter).

An easy method for converting mg/dl to mmol/L with regard to lactate is to divide the former by 9.01.

When lactate concentration is expressed in mmol/L, one can directly use it for the "anion gap" computation.

The normal plasmatic concentration of lactate in health individuals is traditionally considered to be 1 ± 0.5 mmol/L. In critically ill patients, values up to 2 mmol/L are considered normal.

Since the 1970s, clinicians made a distinction between "hyperlactacidemic states," conditions characterized by lactate values ranging from 2 to 5 mmol/L, and "lactic acidosis," more alarming circumstance characterized by higher-than-5 mmol/L values and usually associated with decrements of pH [5].

Both venous and arterial blood samples are accepted for clinical purposes. In almost every ICU worldwide, lactate is measured through complex instrumentations, the same used for the determination of blood gases, hemoglobin (Hb), and electrolytes.

Specifically, lactate concentration is measured within an amperometric cell. Here, after the enzymatic scission of lactate into hydrogen peroxide, an electric current, whose intensity is proportional to the peroxide concentration, is quantified.

The normal arterial and/or venous lactate value strictly represents the balance between lactate production and lactate disposal, for consumption or removal (clearance).

Notably, although this concentration is less than 2 mmol/L, the daily production of lactate is around 1,500 mmol/day (0.8 mmol/kg/$h^{-1}$).

## 12.6 Which Tissues Are Responsible for Lactate Production?

In physiological conditions, lactate is produced by:

1. Muscular cells (25 %)
2. Skin (25 %)
3. Brain (20 %)
4. Erythrocyte (20 %)
5. Intestinal cells (10 %)

and, actually, by all the cells whose main energetic source is glycolysis, especially in its low efficient form, characterized by the shift of pyruvate to lactic fermentation [4].

We must notice that erythrocytes, that can be considered as a 2,500 g "organ", are forced to anaerobic metabolism since they don't have mitochondria: their cellular respiration thereby relies exclusively on their lactate production. Lactate is then converted into fatty acids by the liver.

## 12.7 Which Tissues Can Use Lactate as an Energy Source?

The energy demand of the heart is high and continuous at the same time. The maintenance of an energetic homeostasis relies on a continuous supply of ADP, inorganic phosphate, oxygen, and reducing equivalents (NADH). Unlike the brain, the heart may utilize different energy substrates depending on different conditions (e.g., rest or exercise). Traditionally, only glucose and long-chain fatty acid were thought to play a pivotal role. Lactate, thus, seems to be crucial as well.

The uptake of lactate by the heart depends, in vivo, on its concentration in serum.

Significant interactions occur between lactate and glucose and between lactate and fatty-acid beta-oxidation, giving lactate the role of a potential energy substrate.

The human brain contains 1,000 billions of cells, 90 % of them being represented by glial cells serving multiple functions (trophic, energetic, and immune functions; regulation of ionic concentration; and nervous impulse conduction support). The remaining 10 % is represented by neurons. The brain has an elevated energy consumption: it accounts for only 2 % of body weight but consumes 50 and 10 % of blood oxygen and glucose, respectively. It exclusively employs glucose as energy substrate. Energy is consumed mainly by neurons, mostly for the Na/K active antiport (50 % of energy) necessary for their activity (i.e., to generate electrical signals). Glucose is therefore stored in the form of glycogen into glial cells (namely, astrocytes). Astrocytes can recognize neurons' activity identifying the presence of neurotransmitters into the extracellular spaces.

The brain contains an average amount of 115 mg of glycogen per 100 g of tissue; its needs are instead approximately 120 g/day and are all provided by blood circulation.

Glucose is absorbed by the astrocytes, whose "feet" overlay cerebral capillaries surface. The absorbed glucose is turned into astrocytes and converted to lactate. This represents the actual main substrate used by neurons. Astrocytes are sensitive to glutamate, the main neurotransmitter of the human brain. Being an indicator of neuronal activity, it can induce an increased glucose uptake in astrocytes. The more neurons are active, the more glucose is absorbed.

Glutamate is removed from extracellular spaces by entering into astrocytes and being turned into glutamine. It will then be provided to neurons, where it will be transformed back to glutamate. Glutamine is carried into the astrocyte by a symport system together with Na, while the Na/K pump will proceed to the extrusion of the latter. This causes an energy consumption supported by the 2 ATPs obtained through

the anaerobic glycolysis. Glucose thereby begins its metabolic pathway in astrocytes (anaerobic glycolysis = 2 ATPs), and it is carried as lactate into neurons and then turned again into pyruvate and consequently into acetyl-CoA, which enters the tricarboxylic acid cycle, thus producing 34 molecules of ATP.

## 12.8 What's the Relationship Between Pyruvate and Lactate?

The LDH-mediated reaction that turns pyruvate into lactate, with NADH transformed into $NAD^+$, tends largely towards the lactate side, with a lactate/pyruvate ratio = 10. Thus, when the pyruvate follows the way of lactic fermentation, the conversion of pyruvate into lactate is really favorable.

In any time that pyruvate tends to accumulate in cells, it undergoes this easy and immediate metabolic path.

## 12.9 What Makes It Easier for Pyruvate to Accumulate?

The pyruvate accumulates every time that its production, especially through glycolysis, exceeds its usage by the mitochondria.

Therefore, a quantitative increase in glycolysis production and an obstacle in entering the oxidative phosphorylation through the Krebs cycle (the aerobic way) are either cause of pyruvate overload: at this point, pyruvate is necessarily converted into lactate through fermentation.

## 12.10 What Is Lactate Metabolic Destiny?

Although lactate is an electrically charged molecule, it can easily cross the membranes through a transmembrane transport system (monocarboxylate transporter). This couples lactate to $H^+$ during the transfer.

This active transport outward the cell is vital because it avoids an undesired alteration of intracellular pH.

After its production, lactate can:

1. Be transformed into oxaloacetic acid after reconversion to pyruvate (carboxylation)
2. Be converted into alanine after reconversion to pyruvate (transamination)
3. Be used untransformed directly by the periportal hepatocytes, in order to produce glucose (gluconeogenesis) or glycogen (glycogenesis).

The liver manages 60 % of the total lactate and most of the aforementioned metabolic pathways.

Kidneys are the second most important organs involved in lactate metabolism: their cortex can produce glucose through the gluconeogenic pathway.

Kidneys don't excrete lactate unless their plasmatic levels reach a warning threshold. This is due to its important role as an energy substrate.

When hyperlactatemia occurs, we are unavoidably facing an increased production of lactate or a reduced clearance or both.

In case of a severe systemic hypoperfusion (shock), the regional blood flows are the main determinant of each organ's relative contribution to lactate production and extraction.

In experimental hemorrhagic models, with moderate hypoperfusion, low splanchnic flow is not associated with low hepatic flow, whose perfusion is essentially preserved. In case of worsening of hemorrhage and hypoperfusion, the liver itself becomes a lactate producer.

## 12.11 What Is "Cori Cycle"?

*Cori cycle is named after the spouses Gerty and Carl Cori, who won the Nobel Prize in 1947 for this discovery.*

In an anaerobiotic environment, a muscle in activity would inevitably develop lactic acidosis and local decrease of pH, if a prompt transfer of lactate to the liver through the circulation didn't take place.

The hepatocytes move lactate to gluconeogenesis (which consist in a reverse fermentation and glycolysis: from lactate to pyruvate and from pyruvate to glucose): the glucose produced is addressed again to the working muscle by the systemic circulation.

The cost of each molecule of lactate transformed into glucose through the Cori cycle is 6 ATP molecules, instead of the 2 molecules normally produced in the glycolytic cycle. It follows that, given its high energy cost, the cycle cannot be indefinitely sustained.

Indeed, this is the reason why a prolonged effort has to be performed through the much cheaper aerobic pathway.

When muscular effort ceases, the regenerated glucose follows the path of glycogen regeneration (glycogenosynthesis) in order to compensate for the amount of glycogen used in the first phases of muscular work.

## 12.12 NADH and NAD

To fully understand the energetic metabolism and the role played by lactate within it, one needs to understand the role of NAD and its corresponding reduced form NADH.

NAD is an acronym for redox coenzyme "nicotinamide adenine dinucleotide."

It is a biomolecule whose biological role is to transfer electrons, thus realizing oxidation–reduction reactions, and move hydrogen atoms.

The term "NAD" stands for the oxidized form of the molecule, while "NADH" indicates its reduced form (sometimes referred to as $NADH_2$).

Since it takes part in a redox (reduction–oxidation) reaction, the reduction of the coenzyme (NAD to NADH) promotes the oxidation of a substrate.

It has already been reported that glycolysis of one glucose molecule consumes 2 NAD, thereby generating 2 NADH molecules. On the other hand, lactic fermentation reoxidizes NADH to NAD.

The physiological mechanism of glycolysis towards aerobic energy production and oxidative phosphorylation requires a balance between the levels of NAD and NADH: a correct NADH/NAD ratio ensures a correct pyruvate usage which, as we have seen before, is a paramount turning point for energy metabolism.

The rate of conversion from pyruvate to lactate is in fact controlled by the NADH availability: NADH excess facilitates the lactic fermentation that produces NAD.

Actually, when an excess of NADH (and therefore lack of NAD) occurs, alternative mechanisms (shuttles) are activated in order to force the conversion of NADH to NAD at a mitochondrial level (namely, malate–aspartate shuttle and glycerol-3-phosphate shuttle).

## 12.13 When Does Lactate Exceed Normal Values?

The most important use of high plasmatic lactate levels is to integrate an accurate clinical examination in order to uncover and monitor a global or local hypoperfusion state. Undoubtedly, it also represents a useful prognostic indicator [6, 7].

There is no way that plasmatic lactate could be a sensitive indicator for mild or moderate hypovolemia since its value is not increased by those conditions [8].

As a matter of fact, an increased lactate concentration stands for a severe rather than moderate hypoperfusive state.

Hyperlactatemia is neither specific to hypoperfusion at all. Many different situations could lead to an increase in lactate concentration (Table 12.1). We must consider that, as already mentioned, values > 5 mmol/L can occur in hypoperfusive states or following strenuous muscle exercise and seizures [9].

The Cohen–Woods classification categorizes hyperlactatemia (and lactic acidosis) as follows:

1. In type A, hyperlactatemia is caused by a decrease of tissue perfusion and oxygenation. In this case, lactate production is faster than its disposal.
2. In type B, hyperlactatemia is caused (with different mechanisms) by:

   - Underlying disease (e.g., pheochromocytoma)
   - Drugs and toxins (phenformin, cyanides, alcohol)
   - Inborn errors of metabolism (e.g., pyruvate carboxylase deficiency), given that a manifest tissue hypoxia wasn't the real cause

The long list of possible hyperlactatemia causes can be usefully structured in several other ways.

**Table 12.1** Causes of lactic acidosis

| Cause | Presumed mechanism or mechanisms | Comments |
|---|---|---|
| Cardiogenic or hypovolemic shock, advanced heart failure, or severe trauma | Decreased $O_2$ delivery to tissues; epinephrine-induced β2-adrenoceptor stimulation can be a contributory factor | With sepsis, these causes account for the majority of cases of lactic acidosis |
| Sepsis | Epinephrine-induced β2-adrenoceptor stimulation with or without decreased $O_2$ delivery to tissues; reduced clearance of lactate even in hemodynamically stable patients | Evidence of decreased $O_2$ delivery can be subtle; even in the absence of macrocirculatory impairment, dysfunction of microcirculation can be present |
| Severe hypoxemia | Decreased $O_2$ delivery to tissues | Requires $PaO_2 < 30$ mmHg |
| Carbon monoxide poisoning | Decreased $O_2$ delivery to tissues, interference with oxidative phosphorylation | Hyperbaric $O_2$ therapy is recommended if pH <7.1 |
| Severe anemia | Decreased $O_2$ delivery to tissues | Requires hemoglobin level <5 g/dl |
| Vigorous exercise, seizures, or shivering | Increased $O_2$ requirements | The decrease in pH and hyperlactatemia are transient; lactic acidosis can impair exercise performance |
| Diabetes mellitus | Mechanism unclear | The risk of death in patients with ketoacidosis can be increased by coexisting lactic acidosis |
| Cancer | Increased glycolytic activity of tumor (Warburg effect), tumor tissue hypoxia, decreased clearance of lactate with severe liver metastases | Lactic acidosis can be seen in association with lymphomas, leukemias, and solid tumors; $HCO_3$ – administration may increase lactic acid production; acidic microenvironment is critical for tumorigenesis, angiogenesis, and metastasis |
| Liver disease | Lactate clearance decreased | Fulminant liver disease can cause substantial hyperlactatemia; hyperlactatemia is usually mild with chronic liver disease alone; lactate clearance can also be decreased when liver function is normal, in association with sepsis |
| Pheochromocytoma | Decreased $O_2$ delivery to tissues and epinephrine-induced β2-adrenoceptor stimulation | In rare cases, lactic acidosis is a presenting feature of pheochromocytoma |

(continued)

**Table 12.1** (continued)

| Cause | Presumed mechanism or mechanisms | Comments |
|---|---|---|
| Metformin | Interference with oxidative phosphorylation, suppression of hepatic gluconeogenesis | This is usually seen in association with high plasma metformin levels; treatment with dialysis is beneficial |
| Nucleoside reverse-transcriptase inhibitors | Interference with oxidative phosphorylation | Marked hyperlactatemia is uncommon in the absence of other predisposing factors |
| Cocaine | Decreased $O_2$ delivery to tissues and epinephrine-induced β2-adrenoceptor stimulation | Marked hyperlactatemia is seen in some patients having seizures or being restrained |
| Toxic alcohols, methanol, ethylene glycol, diethylene glycol | Interference with oxidative phosphorylation | The increase in lactate is small; a small increase in the osmolal gap (usually <20 mOsm/kg $H_2O$) can be seen in some cases of lactic acidosis without toxic alcohols |
| Propylene glycol | d-Lactate and l-lactate are normal products of metabolism | Lactic acidosis can occur in the absence of impaired oxidative phosphorylation |
| Salicylates | Interference with oxidative phosphorylation | Hyperlactatemia is usually minimal |
| Cyanide | Interference with oxidative phosphorylation | Lactic acidosis is an important manifestation of poisoning |
| β2-Agonists | Stimulation of aerobic glycolysis | This is most common with treatment of acute asthma; hypokalemia can result from enhanced cellular uptake of potassium |
| Propofol | Interference with oxidative phosphorylation | Lactic acidosis can be seen with prolonged high-dose infusion |
| Thiamine deficiency | Impairment of pyruvate-dehydrogenase activity | This is most common in children or adults receiving parenteral nutrition or those with fulminant beriberi |

Data from Indelfinger [18]
*PaO2* denotes partial pressure of arterial oxygen

Among the most schematic classifications we report the one which distinguishes:

1. Increased lactate production
2. Decreased lactate clearance (liver)

## 12.14 What Is the Influence of Hyperlactatemia on Acid–Base Balance?

A quantitative increase of lactic acid in plasma leads to a metabolic acidosis characterized by an increased anion gap (normal values, 12±2). In such a condition, while bicarbonatemia decreases, base excess (BE) becomes progressively negative [10].

According to the traditional approach to acid–base balance, both the increase of acidemia and the decrease of pH are explained by the elevation of fixed acids (non-volatile, such as $CO_2$).

However, if acid–base balance is interpreted according to the Stewart approach, things will get a little more complicated. From this point of view, lactate production modifies one of the three independent variables that determine the pH of a solution, namely, the strong ion difference (SID), which is understandably reduced.

In order to compensate for the addition of a strong anion, the mass equation

$$CO_2 + H_2O \langle - \rangle H_2CO_3 \langle - \rangle HCO_3^- + H^+$$

shifts to the left, with the effect of dissolving $CO_2$.

Notably, a decrease of pH still represents an adaptive mechanism: indeed, pH regulates the oxygen–hemoglobin (Hb) dissociation curve, the phosphofructokinase activity (therefore regulating the glucose input of glycolysis), and the lactate uptake in the hypoxic muscle.

## 12.15 What Happens During Tissue Hypoxia?

Hypoxia blocks mitochondrial oxidative phosphorylation and therefore the production of ATP from ADP and the reoxidation of NADH to NAD.

1. The ATP/ADP ratio decreases.
2. The NADH/NAD ratio increases.

Additionally, an increase of pyruvate is observed at a cytosolic level. This is due to:

1. The inhibition of pyruvate carboxylase and therefore inhibition of the conversion to oxaloacetate
2. The inhibition of pyruvate dehydrogenase and therefore inhibition of the conversion to acetyl-CoA
3. The inhibition of gluconeogenesis

The excess of pyruvate is converted to lactate. This allows to supply the anaerobic glycolysis of NAD, albeit in a barely economic way.

The lactate/pyruvate ratio increases as well as the glucose consumption, while the cellular energy production decreases.

Given the uncertainty of pyruvate measurement, which is highly unstable for the substance's degradability, the lactate/pyruvate ratio is poorly feasible for clinical purposes.

## 12.16 Biochemical Meaning

Lactate production is a protective response of the organism, which allows the continuation of cellular energy production when tissue $O_2$ availability is inadequate for aerobic metabolism. We pointed out how glycolysis produces much less energy (on a molar basis) than aerobic metabolism.

Even if metabolically unfavorable, glycolysis can proceed much faster than aerobic energy production.

Thanks to pyruvate conversion to lactate, the cell can manage every excess of pyruvate and restore NAD, allowing the continuation of anaerobic energy production.

The lactic fermentation doesn't produce hydrogen ions ($H^+$), while glycolysis does: at the end of glycolysis, in the presence of an adequate concentration of oxygen, $H^+$ ions enter the mitochondria and combine with oxygen during the oxidative phosphorylation to produce water molecules: in hypoxic conditions, instead, oxidative phosphorylation doesn't occur, and $H^+$ can accumulate in the cytosol, inducing both intracellular acidosis and extracellular acidosis.

Lactic fermentation counteracts the $H^+$ excess, so impeding the development of acidosis: lactate protects cells from acidosis.

We can look at the lactate production, occurring in the presence of tissue $O_2$ deficit, as a protective response that allows the continuation of energy production and the protection of tissues from acidosis.

## 12.17 $VO_2$ and $DO_2$: The Relationship with Lactate

Humans, unlike other species, aren't "oxygen conformers": that means they can't drastically decrease the oxygen-dependent energy expenditure in low availability conditions (species that can conform to hypoxia block the energy wasting due to the transmembrane ion traffic, managed by ion pumps).

Humans are compelled to an energy expenditure not related to oxygen availability: the imbalance between demand and availability causes cellular death in conditions of prolonged hypoxia. In addition, humans have an adaptive capacity too, even if moderate, to hypoxia [11].

In this way, the so-called $DO_2/VO_2$ dependency must be clarified. Facing a decreasing oxygen availability ($DO_2$), the oxygen expenditure ($VO_2$) remains constant until a critical point (identified at approximately 600 ml/min of $DO_2$). From

this point on, a further decrease of $O_2$ availability causes a decrease in oxygen expenditure too.

This phenomenon was always considered as a metabolic "limit" of the human beings, but we could overturn our point of view considering the "$DO_2/VO_2$ dependency phase" as an adaptive phenomenon which places humans close to "oxygen conformer" species: it is the metabolism itself that adapts to "hypoxia" by consuming less energy, instead of decreasing the amount of energy produced.

The amount of plasma lactate peaks at the beginning of $DO_2/VO_2$ dependency. Therefore, hyperlactatemia must be interpreted as an escape from a condition that is potentially lethal: hypoxemia. Indeed, we know that – in addition to be a marker of "energy failure" and an important critical prognostic factor – the reconfiguration of energy metabolism towards lactate production is a fundamental protective mechanism for life: proofs are represented by aerobic glycolysis facilitation, hepatic gluconeogenesis, insulin resistance increase, and addressing of glucose/lactate metabolism towards those cells more efficient in using lactate.

## 12.18 Lactate and Systemic Shock

The association between a decreased tissue perfusion, tissue hypoxia, and hyperlactatemia represents the mainstay of all the conditions characterized by low flow states (e.g., cardiogenic shock) and maximally increased lactate/pyruvate ratios. Similar observations characterize hemorrhagic shocks.

Septic shock has to be considered from different points of view. The early resuscitation phase, brought on when a complete volume repletion hasn't been already obtained, and the catecholamine-resistant cardiovascular failure fit well with the aforementioned conditions. The lactate/pyruvate ratio is therefore augmented in these conditions, since these are characterized by low blood flows.

Furthermore, the classic presentation of septic shock, characterized by high blood flows, low systemic resistance, mitochondrial dysoxia, high muscular $PO_2$, and normal ATP levels, almost certainly doesn't fit in the hypoperfusion model [12].

The so-called *accelerated aerobic glycolysis associated with sepsis* typically implies a boost in glucose membrane transporter 1 ($GLUT_1$) synthesis, an increase in catecholaminergic-induced glycolysis, and an inflammatory state: all these elements lead to an elevated pyruvate production. Usually, the rate of carbohydrate metabolism (hypermetabolic septic state) outruns the mitochondrial oxidative capacity: the increased uptake of glucose and the overstimulated protein catabolism enlarge the amount of pyruvate which is produced [13].

Furthermore, sepsis is responsible for a dysfunction of the multienzymatic complex called pyruvate dehydrogenase which leads to a further pyruvate overload.

It's interesting to observe that besides glycolysis directed to the oxidative pathway (Krebs cycle and beyond), a second pathway that associates glycolysis directly to the Na/K/ATPase pump is hidden. The ATP produced through the latter sustains the energetic needs of ionic pumps.

Muscle tissue is the preferential site of this glycolysis (muscle cells are 40 % of total body cells). Its activity relies on the stimulation of adrenergic receptors, which actually induce glycolysis, glycogenolysis, and Na/K/ATPase activation.

The hyperlactatemia seen during septic states is therefore the result of a hyperstimulation of the aerobic pathway, linked to the increased activity of the ionic pumps.

## 12.19 What Does This Interpretation of Facts Tell Us in the Context of a Septic Shock?

The high muscular production of lactate which occurs during septic shocks is addressed to the dispendious Cori cycle since mitochondrial activity is impeded, not for the lack of $O_2$ but because the mitochondria, at their peak activity, aren't further available.

The potential benefit of this pathway is amplified by the liver faculty of using the ATP generated by the fatty-acid beta-oxidation to produce glucose from lactate.

Fatty acids release great amount of energy they contain to produce limited amounts of glucose from lactate. This "shuttle of lactate" enhances its central role in the aerobic energy metabolism.

The aerobic lactate production – during a septic shock – may constitute an adaptive mechanism of protection. In some tissues, where oxygen is available – i.e., in aerobiosis conditions – lactate can be oxidized in place of glucose, preserving the same glucose for the anaerobic glycolysis carried out where oxygenation is precarious [14].

An example of this opportunity is seen in stressed brain and heart, which are able to use lactate as preferential energy source. A demonstration of its utility is given by the reduction in myocardial performance when the hemorrhagic shock reduces the myocardial availability of lactate.

## 12.20 Lactatemia, Prognosis, and Therapeutic Strategies

Though an elevated serum lactate doesn't necessarily imply inadequate tissue perfusion, it seems reasonable to assume that during the early phase of shock, there is a correlation between lactate elevation and $DO_2$ decrease and that an efficient therapy should result in lactatemia normalization.

Persistent high levels of lactate in critical patients, even after the reestablishment of an adequate tissue oxygenation, are a negative prognostic factor.

The last 40 years of scientific literature has shown a correlation between lactate plasmatic levels and patient outcomes [15]. Lactatemia has therefore been used to stratify critical patients into severity classes, high values identifying the beginning of a $VO_2/DO_2$ dependency phase, a type B lactic acidosis, which are probably non reversible conditions.

As previously discussed, the initial treatment for a patient with hyperlactatemia should target for an improvement in tissue oxygenation.

In addition, $DO_2$ depends on three factors: hemoglobin levels and its capacity of releasing oxygen to the tissues, arterial oxygen saturation of hemoglobin, and blood flow, which in turn depends on stroke volume, regional perfusion, and microcirculation.

Thus, available therapeutic options can have an effect on:

1. *Tissue $O_2$ need* (the local $VO_2$): control of pain, anxiety, tachypnea, fever, and delirium and evaluation of the opportunity of respiratory assistance
2. *Hemoglobin level* : number of blood units needed
3. *Level of arterial blood oxygen saturation*: increase in $FiO_2$, PEEP, recruitment maneuver
4. *Blood flow*: stroke volume optimization (adequate preload), inotropic drugs, regional perfusion improvement, and the use of vasodilators

A consistent and convincing decrease in lactate levels should be a therapeutic target; furthermore, the extent of this reduction is not easy to be quantified. Some data suggest that an increased survival is associated with a 10 % decrease of lactate in the first 6 h of treatment, while other studies alternatively proposed the normalization of central venous $SO_2$ ($Sv_cO_2$) to the lactate reduction [16].

Others suggest to consider a 20 % lactate decrease for two consecutive hours in the duration of the treatment.

Nonresponsive patients should get a treatment adjustment.

## 12.21 Other Situations, Beyond Hypoperfusion, in Which We Have to Clarify the High Lactate Values

### 12.21.1 Septic States

As previously stated, while in the early phase of septic shocks, a high lactate value can represent the mirror of hypoperfusion (and for this reason, resuscitation protocols focus on fluids and catecholamines), in the subsequent stabilized phase, the interpretation of hyperlactatemia may be more difficult.

Macrophages and monocytes contribute to lactate hyperproduction in response to endotoxins and tissue trauma. Hepatocytes otherwise reduce their metabolic activity towards lactate, with a net effect on its clearance decrease. At the same time, aerobic lactate production (of which a wide description is provided above) takes part in the modulation of carbohydrate metabolism during stress, and catecholamines (both those endogenous overexpressed in the acute phase and those exogenous used sometimes in maximal doses during therapeutic attempts) induce an acceleration of glycolysis, particularly in the previously illustrated way, which involves Na/K ATPase-dependent pumps.

### 12.21.2 Chronic Liver Diseases

The reduced functionality of a chronically ill liver (cirrhosis) and, indeed, its reduced ability to handle and clear lactates are amplified both when the peripheral production of lactate abruptly increases and when the hepatic illness worsens [17].

### 12.21.3 Intestinal Infarction

This is one of the commonly seen clinical pictures in the intensive care where lactates play a striking role.

Splanchnic hypoxia, and particularly that of the gut (both small intestine and large intestine), induces anaerobic metabolism: the liver receives a huge amount of lactate by portal circulation, which is oxidized or converted into glucose by periportal hepatocytes. The collapse of splanchnic circulation is promoted by bacterial translocation and by the increase of capillary permeability, which causes the loss of fluids in the interstitial spaces. At first, the fall of splanchnic $DO_2$ is offset by the action of endogenous catecholamines, which moreover leads to a net increase in lactate by inducing an increase in glycolysis. The progress of shock inevitably leads to hepatic hypoperfusion, and the intracellular acidosis of hepatocytes inhibits gluconeogenesis from lactate. The liver itself handles more lactate than it can dispose of.

Intestinal bacteria continue to produce lactate through the metabolism of glucose and other carbohydrates.

This process is cyclic and quickly worsening.

## 12.22 Metformin Overdose

Lactic metabolic acidosis is one of metformin's – and biguanides', in general – most dangerous side effects. It is a potentially lethal condition, which can appear either at therapeutic dosage or in case of overdose. The mechanism remains mostly unclear (perhaps it implies an interference with oxidative phosphorylation), but it is certain that metformin induces a block in hepatic gluconeogenesis. The accumulation of substrates, e.g., alanine and pyruvate, leads therefore to lactate interconversion.

This condition is of particular concern in diabetic patients on oral therapy with biguanides and affected by alterations in renal function. Fortunately, severe events are rare, with an incidence in the USA of three cases for every 100,000 patients treated with metformin.

**Conclusions**

A better comprehension of lactate and its biochemistry allows us to understand how – from the point of view of metabolic pathways – lactate represents not only a "warning sign" but also an opportunity for the organism.

It looks necessary for intensivists to fully understand how lactate is produced, transformed, modified, and metabolized always targeting the generation of energy at the lowest price and highest priority.

It is clear that the main clinical use of lactate values is referred to hypoperfusive states (e.g., cardiogenic, hemorrhagic, or hypovolemic shock, etc.) and that these data could help clinicians in making diagnosis, formulating prognosis, and planning the therapy.

We hope to have shown enough reasons not to doubt about the appropriateness of a fluid or aminic treatment strongly oriented to correct lactatemia, since other mechanisms may be – at least in part – involved.

The parallel – and apparently difficult – biochemical and clinical interpretation of lactate values can really contribute to a better clinical method in the fields of critical care medicine, anesthesia, and intensive care.

## References

1. Baynes JW, Dominiczak MH (2006) Biochimica per le discipline biomediche. Ambrosiana, Casa Editrice. ISBN 88-408-1353-5
2. Van Hall G (2010) Lactate kinetics in human tissues at rest and during exercise. Acta Physiol (Oxf) 199:499–508
3. Phypers B, Pierce TJM (2006) Lactate physiology in health and disease. Contin Educ Anesth Crit Care Pain 6(3):128–132
4. Toffaletti JG (1991) Blood lactate: biochemistry, laboratory methods, and clinical interpretation. Crit Rev Clin Lab Sci 28:253–268
5. Bakker J, Jansen T (2012) Blood lactate levels: a manual for bedside use da: annals update in intensive care and emergency medicine 2012. Berlin, Heidelberg: Springer; p 383–390
6. Bakker J, Nijsten MW, Jansen TC (2013) Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care 3:12
7. Kruse O, Grunnet N, Barfod C (2011) Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review. Scand J Trauma Resusc Emerg Med 19:74
8. Gladden LB (2004) Lactate metabolism: a new paradigm for the third millennium. J Physiol 558(1):5–30
9. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW (2013) Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc 88:1127–1140
10. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP (1990) Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. Crit Care Med 18:275–277
11. Valenza F et al (2005) Lactate as a marker of energy failure in critically ill patient: hypothesis. Crit Care 9(6):588–593
12. Levraut J, Ciebiera JP, Chave S et al (1998) Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 157:1021–1026
13. Levy B, Desebbe O, Montemont C, Gibot S (2008) Increased aerobic glycolysis through beta2 stimulation is a common mechanism involved in lactate formation during shock states. Shock 30:417–421
14. Chatam JC (2002) Lactate. The forgotten fuel. J Physiol 542(2):333
15. Gunnerson KJ, Saul M, He S, Kellum JA (2006) Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care 10:R22–R32
16. Jones AE (2011) Point: should lactate clearance be substituted for central venous oxygen saturation as goals of early severe sepsis and septic shock therapy? Yes. Chest 140:1406–1408
17. Jeppesen JB, Mortensen C, Bendtsen F, Møller S (2013) Lactate metabolism in chronic liver disease. Scand J Clin Lab Invest. 2013 Mar 20. [Epub ahead of print]
18. Indelfinger JR (2014) Lactic acidosis. N Engl J Med 371:2309–2319

# Clinical Use of Indocyanine Green (ICG) Kinetics in Liver Anaesthesia and ICU

13

Andrea De Gasperi and Ernestina Mazza

## 13.1 Notes on Liver Anatomy and Physiology

The liver is the largest visceral organ, weighing, in healthy adults, between 1,500 and 1,600 g: it has two anatomical lobes (left and right) separated by a reflected surface of peritoneum (falciform ligament) [1]. Instead, from the surgical point of view, the porta hepatis, point of division of the hepatic artery and portal vein into right and left branches, is the reference point for the division. Based on the branches of portal and hepatic veins, the two lobes are divided into eight segments, allowing the definition of the various types of hepatic resection (Couinaud) [1, 2] (Fig. 13.1).

The *hepatic lobule* is the anatomical and functional unit of the liver. It has the shape of a polygonal (hexagonal) pyramid with an apex trunk of 1 mm in diameter and a height of about 1.5–2 mm, delimited by a layer of connective tissue (reticular connective). Each lobule is formed by numerous cellular laminae consisting of hepatocytes; the plates are perforated and anastomosed with each other and define a system of irregular vascular spaces: the *hepatic sinusoids*. The cellular edges and capillaries show a radial arrangement converging from the periphery toward the centre of the lobule. The axis of the lobule is occupied by the centrilobular vein, tributary of the hepatic vein, within which the sinusoids open up. The area where three or more adjacent lobules are in contact with each other is called a *portal space* ('portal triad', containing a bile duct, a terminal branch of the hepatic artery and the portal vein). Metabolic zones form the hepatic acinus [2]. *Zone 1* is the periportal zone, is centred around the portal triad and, being close to the hepatic artery, is oxygen rich. It is more resilient to hemodynamic stressors, least susceptible to necrosis and first to regenerate. These zones are involved in gluconeogenesis/

A. De Gasperi, MD (✉) • E. Mazza, MD
2° Servizio Anestesia e Rianimazione, Ospedale Niguarda Ca' Granda,
Piazza Ospedale Maggiore 3, Milan 20162, Italy
e-mail: andrea.degasperi@ospedaleniguarda.it; c.ernestina.mazza@ospedaleniguarda.it



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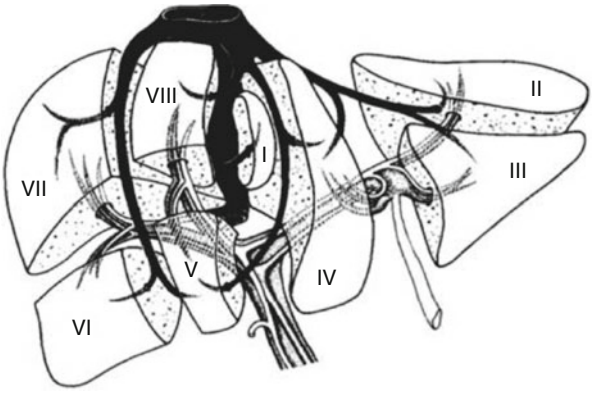


**Fig. 13.1** Liver segmental anatomy (From Mulaikal and Edmond [2])

glycogenolysis. *Zone 3* is the pericentral or perivenous zone, very close to the central vein: it has the lowest oxygen tension. This zone is highly susceptible to stressors, hypoxia and is the last to regenerate. Zone 3 is the site of drug detoxification and phase 1 and 2 metabolism [2].

The liver has a dual blood supply, which includes an arterial system (hepatic artery, HA) and a venous system (portal vein, PV). The total liver blood flow is approximately 1,500 ml/min (100 ml/min/100 g). The hepatic artery flow is approximately 300 ml/min (30 % of total hepatic flow, 45–50 % of total oxygen intake), while portal vein is usually estimated between 1,000 and 1,200 ml/min (70 % of total blood flow, 50–55 % of oxygen supply). The $O_2$ hepatic extraction, normally less than 40 % (4–6 ml/100 g/min), is increased in case of increased demand [2].

Both the terminal portal venules and the terminal hepatic arterioles end in the hepatic sinusoids, through which the entire afferent hepatic blood flows before reaching the efferent vascularisation (terminal hepatic venules). Hepatic blood drainage is via the hepatic veins (right, left, middle) which drain into the inferior vena cava.

The portal system is a low-pressure (5–12 mmHg)/low-resistance system: the gradient between portal vein and hepatic vein (HVPG) ranges between 1 and 5 mmHg: portal hypertension is defined as a pressure of >12 mmHg or for a portal vein–inferior vena cava (IVC) gradient >5 mmHg. The arterial system has a high level of resistance and a high flow. Hepatic blood flow and distribution are dependent on hepatic arterial resistance, intrahepatic portal resistance and portal flow. Intrinsic and extrinsic mechanisms regulate the hepatic blood flow. Among the extrinsic factors, sympathetic innervation plays an important role in controlling vascular tone (adjusting the capacitance of the uptake capacity of circulating blood). Within the hepatic arterial bed, both alpha (alpha 1 and 2) and beta (beta 2) receptors are represented, while only alpha receptors are present in the portal vein. Dopaminergic receptors are present in both vessels. Vasopressin, able to increase the hepatic artery resistances, reduces the PV resistances, thus playing a relevant role in the treatment of portal hypertension. Maintaining a constant hepatic inflow is crucial to optimise drug metabolism and synthetic functions. Self-regulating mechanisms, present in the hepatic artery, are not demonstrated in the portal vein.

Among the intrinsic factors (working independently of humoral neuroregulation) are self-regulating mechanisms for flow/pressure: in case of critical drop in blood pressure, arterial hepatic blood flow is maintained until systolic arterial pressure falls below 75–80 mmHg, via reduction of resistance mechanism. In case of reduced portal flow, hepatic artery flow increases, buffering the changes in portal flow (*hepatic artery buffer response*, HABR). In a situation of critical drop in portal flow (flow reduction of 20–30 %), there is an increased vicarious flow in the hepatic artery (increase up to 100 %) in order to maintain the hepatic blood supply. The mechanism is supported by the reduction of adenosine washout (present with normal portal flow, but missed in the presence of low flow) followed by hepatic artery vasodilatation. A portal flow counterbalance in the presence of hepatic artery occlusion does not seem to exist. Instead, there is an increased hepatic arterial resistance with flow reduction in case of elevated hepatic venous pressure [1, 2].

The liver performs many functions such as protein synthesis; uptake, storage and metabolism (biotransformation and degradation) of endogenous and exogenous substances (among them carbohydrates, lipids, proteins, hormones, drugs); bile production; and immune defence with different mechanisms, mainly operated by the Kupffer cells (KC, so-called fixed hepatic macrophages, 80–90 % of the reticular endothelial system, 10 % of the entire liver cell mass), responsible of phagocytosis (bacteria, fungi, viruses, immune complexes, antigens), clearance of endotoxin and secretion of mediators capable of adjusting microcirculatory hepatic protein catabolism. Due to the indeed wide variety of processes the liver is involved, no single parameter or test able to measure all components simultaneously has been available so far [1–4].

## 13.2 Static and Dynamic Liver Function Tests [1–5]

To assess liver function, static (also called conventional tests) and dynamic tests are available [3–5]. The static tests track the different functions separately, and, in the event of injury, they might describe its size: these tests are, since long, part of scoring systems, able to track chronic (Child–Pugh; MELD) or acute (SOFA) functional impairment of the liver. However, static tests are not able to predict the quality and the extent of the functional recovery of the liver (or of a newly grafted liver), as they essentially show a 'frozen' (*static*) representation of the integrity (or not) of hepatocytes and of metabolic and synthetic pathways (Fig. 13.3). Metabolic function includes enzymes of the cytochromes (*phase 1*) and the phase of glucuronide conjugation (*phase 2*). Bilirubin, derived from haemoglobin catabolism, expresses the capacity of uptake, conjugation and excretion in the bile of haeme (breakdown product of haemoglobin; 1 g Hb leading to 36 mg bilirubin). After uptake by the liver cell, the haeme is exposed to glucuroconjugation (metabolic phase 2) for solubilisation, aimed at excretion in the bile: the process can be relatively insensitive to ischaemic insult, at least in the early stages. In general, hyperbilirubinaemia depends on haemolysis (pre-hepatic disease), cell damage or reduced intrahepatic bile excretion (cholestasis). Albumin, vitamin K-dependent

coagulation proteins (factors II, VII, IX, X; protein C; protein S; and protein Z), factor V, fibrinogen, antithrombin, alpha 2 plasmin inhibitor, and plasminogen represent the (elevated) share of synthetic activity of the liver. The short half-life of FV (4 h) and FVII (4–6 h) might quantify the liver damage in acute liver failure and is used in the Clichy criteria, together with the presence of hepatic encephalopathy, to indicate LTx for FHF [6].

## 13.3 Liver Enzymes, Liver Function and Liver Injury [4, 5]

AST (*aspartate aminotransferase*) and ALT (*alanine aminotransferase*), present in various organs, have an important role for the metabolism of amino acids. AST is less specific, being present at cardiac and muscular level. ALT is more liver specific, is highly represented in the cytoplasm and is, for the most part, in the periphery of the liver lobule: moderate increase is reported in case of centrilobular hypoxia. In the presence of acute hepatic injury (acute hepatitis), the serum concentration of ALT, mainly represented in the periportal areas of the liver, increases significantly, as a consequence of increased permeability of the cell membrane or necrosis. Increased AST/ALT is associated with ischaemic injury and its size (liver injury), but does not provide information on functional hepatic impairment and therefore is considered inferior to dynamic tests when assessing hepatic functional reserve [3–5]. *Alkaline phosphatase* (ALK) and *gamma-glutamyl transferase* (GGT) are mainly used to quantify cholestasis. *Lactate dehydrogenase* (LDH, mainly fraction 5) is a rather nonspecific index of ischaemic liver (but not only!).

Dynamic tests [3, 7] are related to the ability of the liver to metabolise or eliminate substances. Unlike conventional tests, dynamic tests are able to assess liver function within a relatively short time span, are repeatable in relatively short time and may confidently provide a reliable and more global prognostic assessment (Fig. 13.2). Among them are ICG clearance, caffeine test, BSF clearance, amino acid clearance, galactose elimination capacity, formation of *monoethylglycinexylidide* from lignocaine (MEGX test) and aminopyridine test.

- The aminopyrine breath test measures the microsomal metabolical capacity of the liver cell. The test is based on demethylation and subsequent metabolism of $^{14}$C-aminopyrine marked by the microsomal enzyme cytochrome P450 dependent. The extent of demethylation is measured indirectly by the exhaled $CO_2$.
- Galactose elimination capacity (depending on cytosolic mitochondrial function) studies the function of the liver cell. Metabolisation occurs through phosphorylation by the galactokinase. The test is complex in clinical practice since it requires samples over 20–50 min and presents false positives in relation to fasting and liver regeneration.
- Monoethylglycinexylidide (MEGX) is a derivative of lidocaine metabolism and is related to the activity of cytochrome P450. It has been used in the past (and still by some) in liver surgery (value >25 ng/ml predicts safe liver resection) and as a prognostic indicator in patients candidate for liver transplantation. The results

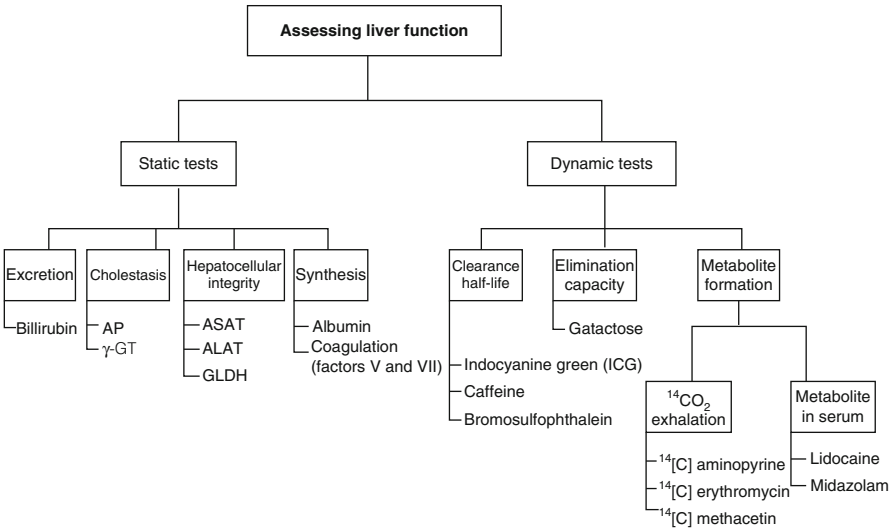


**Fig. 13.2** Static and dynamic assessment of liver function (From Sakka [3])

can be altered by interaction with other drugs that affect the cytochrome P450. The test, performed in the laboratory and whose results are not obtained in real time, has not been used in the field of anaesthesia and ICU.

## 13.4 The Clearance Principle: Liver Function and Hepatic Perfusion [8]

Most quantitative liver function tests rely on the clearance principle: the hepatic clearance (Cl) is the product of flow ($Q$) and hepatic extraction (Ex).

$$\mathrm{Cl} = Q \times \mathrm{Ex} \tag{13.1}$$

According to this principle [8], substances are classified at high or low hepatic extraction rate. In case of drugs at *high extraction rate*, liver blood flow becomes the limiting factor, and clearance will approach liver blood flow. Instead, *low extractable compounds* are flow independent: in this case, the hepatic clearance is the measure of the metabolism and/or elimination process, or more precisely, it represents the intrinsic ability of the liver to remove substances without flow limitation, i.e. the intrinsic hepatic clearance. Equation 13.1 can be rewritten as

$$\mathrm{Cl} = \left(Q \times \mathrm{Clint}\right) / \left(Q + \mathrm{Clint}\right) \tag{13.2}$$

Then, according to Imamura et al. [8], the measure of clearance of compounds with high extraction rate is an indicator of *liver blood flow*, while the clearance of low extractable substances represents *intrinsic clearance* (*Clint*). In healthy subjects, with very high extraction, indocyanine green (ICG) clearance is considered a

surrogate of hepatic blood flow; on the contrary, in cirrhotic patients, due to the reduced hepatic extraction secondary to the disease, ICG clearance represents the intrinsic clearance, characterised by a reduced uptake: steady-state hemodynamic conditions are mandatory to adequately assess liver function.

## 13.5 Indocyanine Green Clearance: The Tests

Among the dynamic tests, *indocyanine green* (ICG) clearance remains the most relevant, widely used in clinical practice today both in the surgical and medical critically ill patient [9–12]. ICG is a fluorescent, water-soluble, inert, tricarbocyanine with a very high hepatic extraction (70–80 %) and a very low toxicity (the side effects described are very rare, about 1/40,000): the only known contraindications are allergy (non-immunological histamine release), iodine allergy or thyrotoxicosis, the latter due to the presence of iodine in the molecule. Since 1960, its elimination rate has been largely used to measure liver function and hepatic blood flow [13–15]: in the late 1990s, Lau had shown the superiority of ICG clearance ($ICG_{Cl}$) compared to the aminopyrine breath test and the clearance of amino acids as a predictor of mortality in patients undergoing liver resection [15]. Important applications are now available in liver resection surgery, in liver transplantation and in intensive care [3, 9–11]. The conventional measurement of $ICG_{Cl}$ requires serial blood sampling after ICG injection. Ex vivo photometric analysis of consecutive arterial blood samples after intravenous bolus injection is the gold standard; however, being a time-consuming and complex procedure, it has now been abandoned in favour of the more recently developed monitors that allow transcutaneous noninvasive pulse dye densitometry (PDD) tests at the bedside (LiMON, Pulsion, Germany; DDG-2001 Nihon Kohden, Japan) [9–11]. Available monitors express ICG elimination in terms of the ICG plasma disappearance rate ($ICG_{PDR}$) or retention rate at 15 min ($ICG_{R15}$), since only relative ICG concentration changes have to be assessed (Fig. 13.3).

The results of ICG elimination measured by the PDD method have been shown to correlate with those obtained by the invasive method used in critically ill patients (whether or not haemodynamically stable) and in patients after liver surgery. Both devices calculate the rate constant ($k$) of the ICG indicator–dilution curve using backward dynamic extrapolation of the elimination phase [9]. Appropriate calculations using $K$ value allow the determinations of functional parameters able to quantify liver function. The ICG kinetics have been studied since 1960 in animals and humans to measure blood flow, cardiac output and circulating blood volume and, later, to assess liver function [9–11]. Due to high hepatic extraction (70–80 %), ICG clearance has been used as an index (measure) of liver blood flow. The usual ICG dose of 0.5 mg/kg generates in the average subject an initial plasma concentration of 100 mg/ml: according to Sakka, however, reliable results are also available using 0.25 mg/kg [3]. Once injected, ICG shows a very high protein binding (95 % to albumin, alpha1 lipoproteins and beta lipoproteins) and a very short half-life (3–5 min) [9–11]. It distributes uniformly and rapidly (2–3 min) in the blood, with a volume of distribution approximately equal to that of plasma. ICG is almost entirely

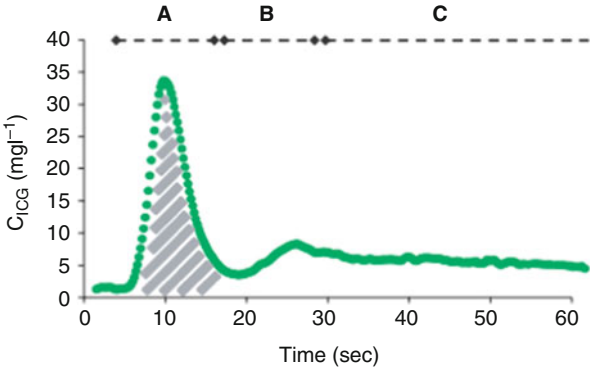


**Fig. 13.3** ICG indicator dilution curve. *ICG* indocyanine green, *C ICG*, ICG blood concentration. *A* Primary peak, *B* secondary peak (recirculation phase), *C* (hepatic) elimination phase (From Vos et al. [9])

extracted by the liver (uptake across the sinusoidal plasma membrane) and transported within the liver cells by transporting polypeptides (1 B3 and Na-taurocholate cotransporting polypeptides). It is excreted unchanged almost exclusively into the bile in nonconjugated form with neither metabolism nor enterohepatic recirculation, carried by the ATP-dependent export pump multidrug resistance-associated protein 2 (MDRP2) and multidrug resistance P-glycoprotein (MDR3), reflecting hepatic excretory function and hepatic energy status [9–11]. Then two processes are involved in hepatic ICG clearance: sinusoidal uptake and canalicular excretion, the former playing the most important role in humans. Due to the very high hepatic extraction, ICG clearance is, in normal conditions, hepatic blood flow limited. After the intravenous bolus administration, the ICG dilution curve shows (i) a primary peak (used to calculate cardiac output); (ii) a second elimination peak (recirculation phase), sometimes followed by smaller peaks, used to estimate circulating blood volume; and (iii) an (hepatic) elimination phase, lasting 10–20 min [9].

In the dye dilution time curve, two components are recognised [8]: (a) the *distribution* phase, representing ICG removal from the plasma, due to the uptake by the liver cells; and (b) the *elimination* phase in the bile (97 % of the entire elimination process) (Fig. 13.4).

The decay is bi-exponential, with linear kinetics up to a dose of 1 mg/kg. The ICG hepatic clearance therefore depends on hepatic blood flow and transporter capacity: signs of liver dysfunction as indicated by impaired clearance of ICG (see below) may depend on reduction of blood flow, on impaired cellular function, or on both (blood flow clearance and transporter capacity). ICG half-life is substantially prolonged in the case of liver disease. Different from the usual two-compartment model, ICG is excreted from the peripheral compartment (the liver) and not from the central compartment (plasma). According to this model, the initial rapid fall in concentration, called the *distribution phase*, represents the uptake of ICG from the plasma by the liver; the subsequent relatively slow fall, called the *elimination phase*, represents the elimination of ICG from the liver into the bile. The transition from the distribution phase to the elimination phase of ICG occurs approximately 20–30 min after the administration. $ICG_K$ (min$^{-1}$) is usually determined from the first 15-min component of the ICG disappearance curve.

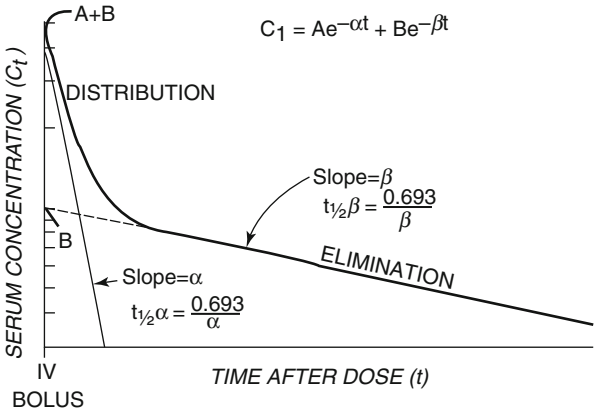


**Fig. 13.4** Graphic representation of ICG kinetics (From Imamura et al. [8])

The ICG transport capacity may be reduced either because of the downregulation of organic anion-transporting polypeptides [4] or by competitive inhibition due to hyperbilirubinaemia [16]. With respect to the former, cytokines such as tumour necrosis factor-α (TNF-α) and interleukin 6 (IL6), released by Kupffer cells in patients with steatosis and/or hepatic injury (hepatitis), are able to affect the expression of organic anion-transporting polypeptide isoforms and sodium taurocholate cotransporting polypeptide, thereby affecting ICG uptake by the liver. Bilirubin and ICG share the same enzyme transport system (ATP export pump MDRP2), making high the chance of altered results (false pathological values) in the presence of hyperbilirubinaemia (vide infra) [9, 16, 17]. Consequently, the ICG test may be of limited value in patients with a condition of global hepatocellular dysfunction and in the case of hyperbilirubinaemia (generation of false poor results) [9, 10]. At the opposite site are high flow states, able to mask an altered excretory function and providing false-reassuring results (better than expected liver function), due to the generation of false 'normal or near-normal' results [10]. It has been documented that $ICG_{Cl}$ is not adequate to measure hepatic blood flow in specific clinical settings: for example, the fraction of hepatic extraction (70–80 % in healthy subjects) is greatly reduced in cirrhotic patients (20–30 %), making $ICG_{Cl}$ a representation of Cint (uptake clearance; *see above*) [18]. Studying ICG kinetics in patients with cirrhosis, Kawasaki et al. [19] reported significant alterations of uptake and release constants (k) (but the release constant is questioned by other authors). Instead, the constant of elimination of ICG in the bile seems to be normal. In the same study, measuring hepatic blood flow with the galactose clearance test, it was shown that in cirrhotic patients, the reduction of $ICG_{Cl}$, expressed as $ICG_{R15}$ (the circulatory retention of ICG 15 min after bolus injection, vide infra), does not (only) depend on hepatic blood flow reduction but also on a reduced extraction of the liver cells. In cirrhotic patients, this phenomenon seems to be related to the extent of the sinusoidal capillarisation and to the presence of intrahepatic shunts [9, 19, 20]. In normal conditions, substances (including proteins) diffuse freely between the sinusoids and hepatocytes. As sinusoid capillarisation develops, diffusion of these substances

becomes impaired and barrier limited, as is in the capillaries of other districts. Due to its high protein binding, ICG is very sensitive to the sinusoidal capillarisation. Figure 13.6 shows the disappearance of ICG from plasma in normal subjects (full signs) and cirrhotic subjects (empty signs). According to Imamura, in cirrhotic patients, $ICG_K$ and $ICG_{R15}$ might reflect the degree of sinusoidal capillarisation, intrahepatic shunts and, in part, reduced liver blood flow [19].

The logarithmic transformation of the curve in the distribution phase allows the measurement of different parameters that quantitatively assess the removal of ICG by the liver cells [9, 10].

1. *Constant K* ($ICG_K$) – disappearance rate constant or elimination rate constant
2. *Clearance* of green indocyanine ($ICG_{Cl}$)
3. *Plasma disappearance rate* ($ICG_{PDR}$)
4. *Retention rate at 15 min* ($ICG_{R15}$)

In clinical practice, $ICG_{PDR}$ and $ICG_{R15}$ are the ICG kinetic parameters most frequently used to dynamically assess liver function [9, 10] (Fig. 13.5):

1. *$ICG_{PDR}$ – plasma disappearance rate*
   (a) Reduction of ICG blood concentration expressed as the percentage change over time, starting (time 0) from a concentration of 100 % (normal values >18 %/min). The method, having satisfactory correlation ($r^2 = 0.77$) with $ICG_{Cl}$, is validated as a surrogate for clearance in the critically ill)
   (i) $PDR(\%/\text{min}) = \ln 2/t½ \times 100$ $ICG_{PDR}$ might represent, at variance of $ICG_{R15}$, ICG uptake by hepatocytes, its excretion into the bile, blood flow-dependent liver metabolism and energy status [21]
2. *$ICG_{R15}$ – retention ratio after 15 min*
   (a) The relationship between the concentration of ICG at 15 min and initial concentration (normal <10 %)
   (i) $R15\ (\%) = C_{ICG15}/C_{ICG\ T0} \times 100$
   Assuming an initial plasma concentration of 100 mg/ml (0.5 mg/kg ICG in a subject with a plasma volume of 50 ml/kg BW), $ICG_{R15}$ can be determined by transforming the ICG concentration curve to a 'point

Frequently used variables for quantification of hepatic indocyanine green (ICG) extraction.

| Variable | Description | Unit | Calculation | Normal value |
|---|---|---|---|---|
| $PDR_{ICG}$ | ICG plasma disappearance rate | % $min^{-1}$ | Backward extrapolation of k, curve fitted as: $C_{ICG}(t) = C_0 * e^{-kxt}$ | > 18 |
| $Cl_{ICG}$ | ICG clearance | $ml.min^{-1} \cdot kg^{-1}$ | $k * V_D$ | 6–12 |
| ICGR15 | ICG retention ratio after 15 min | % | $(C_{ICG\ (15)}/C_{ICG\ (0)}) * 100$ | < 10 |
| $ICG_{t\ 1/2}$ | ICG half-life | min | $(\ln 2 * V_D)Cl_{ICG}$ | 3–5 |

e = Euler's number (approximately 2.718); k = fractional ICG concentration change per minute; t = time (min); $V_D$ = ICG volume of distribution; $C_{ICG\ (t)}$ = ICG concentration at time point t (min); $Cl_{ICG}$ = ICG clearance ($ml.min^{-1}.kg^{-1}$).

**Fig. 13.5** Variables to quantificate ICG kinetics (From Vos et al. [9])

zero' (100 %) and then describing the decay (at min 15) as percentage change per time (%/min) in a logarithmic graph, seen as a negative slope. According to Imamura, as the assumption of the initial concentration of ICG is correct, $ICG_{R15}$ is pharmacologically equivalent to ICG K, and it has been widely used as an alternative to $ICG_K$ for its convenience [8]. It might represent the hepatic blood flow.

3. *ICG plasma clearance* 500–700 ml/min/$m^2$
   (i) It depends on hepatic blood flow, liver function and bile flow. It describes the volume of blood completely purified by ICG in the time unit.

$ICG_{PDR}$ and $ICG_{R15}$ are the two sides of the same phenomenon: $ICG_{PDR}$ reads the disappearance of ICG from plasma (% per min) and $ICG_{R15}$ the amount of ICG remaining in circulation 15 min after the administration. However, these tests are used in the literature in a different (and potentially confounding) manner. $ICG_{R15}$ is mainly used in the evaluation of the functional reserve of the liver in case of hepatic resection in cirrhotic patients [8, 11], $ICG_{PDR}$ and $ICG_{R15}$ in the assessment of liver graft function [22] and PDR and clearance in critically ill patients [3, 21].

As mentioned above, *plasma disappearance rate* ($ICG_{PDR}$) and *retention rate at 15 min* ($ICG_{R15}$) are calculated using either the conventional invasive method or, more recently and more simply, a noninvasive method (pulse dye densitometry (PDD) and spectrophotometry) [9–11]. The conventional invasive method involves the construction of the dilution curve by measuring the concentration of ICG in plasma by spectrophotometry of various arterial blood samples taken at defined times: it has been used in many studies dealing with functional assessment of the liver even in recent times [19]. However, this method is expensive and difficult to implement in clinical practice. In the 1990s, it was possible to measure PDR through a fibre-optic catheter placed in the femoral artery and connected to a computer (COLD System, Pulsion) which allowed, together with the measurement of PDR, the study of volumetric haemodynamics [23]. As already mentioned, the noninvasive method relies, instead, on the measurement of ICG concentrations using PDD and spectrophotometry via an optical transcutaneous pulse spectrophotometric sensor (DDG-2001 Nihon Kohden; LiMON, Pulsion) [11, 24–26]. Pulse dye densitometry measures the concentration of ICG in blood based on the principle of the difference in absorption of the light wave with two different frequencies: 805 nm (absorption frequency of the peak of ICG) and 905 nm (frequency at which ICG has no absorption); the principle is analogous to the mechanism of absorption of the difference between oxyhaemoglobin and reduced haemoglobin. There is no influence of haemoglobin, whether oxidised or reduced, absorption being very low at the frequency wave used for ICG. The same is true for bilirubin (absorption peak at 470 nm) [9, 10]. This method has been validated both in conditions of haemodynamic stability in critically ill patients as well as in unstable conditions, such as in liver transplantation [22–25]. Both systems have algorithms which calculate the constant K ('rate constant') using an equation which deals with the elimination phase ('backward dynamic extrapolation') [9]. The ICG kinetic parameters are determined by monoexponential transformation of the original ICG concentration

curve, backward extrapolation to the time point 'zero' (100 %), and describing the decay as percentage change per time [9]. The algorithm was validated by Purcell et al. determining $ICG_{R15}$ with LiMON and direct measurement of blood samples [26]. The most recent revisions on this item insist on the need for haemodynamic stability in order to obtain reliable data on liver function [9, 11]. In fact, as already underlined, hepatic blood flow and cellular uptake are variables able to impact on ICG elimination (increasing or decreasing the elimination). The hepatic blood flow can be altered by systemic factors (reduced cardiac output able to impact on the hepatosplanchnic perfusion) or by local factors (thrombosis of the hepatic artery or abdominal hypertension); both tend to reduce ICG elimination. On the contrary, the possibility exists that a splanchnic hyperperfusion results in a rise in the extraction of ICG and therefore in a (false) increased PDR.

True pathological $ICG_{PDR}$ or $ICG_{R15}$ is present in the case of end-stage liver failure (cirrhosis) or of severe rejection after liver transplantation, both conditions able to reduce ICG liver extracting abilities [9, 10]. Elevated $ICG_{R15}$ in cirrhotic patients may be due to:

1. Decreased ICG transport from the systemic circulation to the liver
2. Decreased uptake from the sinusoids into hepatocytes

Altered $ICG_{PDR}$ and $ICG_{R15}$ are present also in case of cholestasis: as mentioned above, ICG and bilirubin, competing for the same carrier in the transport process in hepatocytes (sodium taurocholate cotransporting peptide), can alter ICG elimination parameters (by competition and not by functional defect). This condition, not uncommon in the early postoperative period of liver transplantation, can be associated with falsely pathological results, leading to misinterpretation of the tests. Generally speaking, the pathological results may be wrongly attributed to a condition of liver dys/malfunction (falsely reduced function) which might not be the real condition: falsely altered $ICG_{R15}$ or $ICG_{PDR}$ is present when serum bilirubin level is >3 mg/dl [9, 10]. Thus, extreme caution must be used interpreting ICG tests in the presence of hyperbilirubinaemia. In the literature, bilirubin level above 3 mg/dl is reported as the cut-off value: in AA's personal experience in a series of liver-transplanted patients, the cut-off should be at 6 mg/dl [27].

$ICG_{PDR}$ and $ICG_{R15}$ can be used as a starting point for preoperative screening and evaluation of the functional reserve in the case of liver resection, as proposed by Makuuchi's group [8]; with sequential assessments during liver transplantation or during the early postoperative period of liver transplant (OLT) (functional recovery of the transplanted liver); after hepatic resection (functional assessment of the remnant liver after hepatic resection, also in case of living-related donation). In both cases, mandatory is caution in interpreting the results in the presence of hyperbilirubinaemia, frequent in post-liver transplantation and able to give false/altered information on ICG results (high R15/low PDR) [27]. Finally, too short intervals between sequential ICG administrations (<30 min) might significantly alter ICG clearance parameters: this phenomenon is correlated with a baseline drift associated with residual circulating ICG, possibly leading to an (incorrectly) increased $ICG_{PDR}$ [9].

Clinical indications for ICG elimination in perioperative liver medicine and ICU are the following [3, 9–11]:

1. Assessment of hepatic functional reserve and prediction of mortality and morbidity in hepatic resection in cirrhotic patients
2. Evaluation of liver function in cadaveric and living donors (not included in this review)
3. Quality assessment of functional recovery of the liver graft in liver transplant (OLT) recipient
4. Prognostic index in critically ill patients with septic shock in the ICU

## 13.6 ICG Clearance in the Preoperative Assessment of Liver Resection in Cirrhotic Patients

Liver resection and liver transplantation are the surgical procedures able to treat or even cure hepatocellular carcinoma in patients with cirrhosis. Liver resection is reserved to patients with compensated liver function as assessed by static or dynamic tests, scores and imaging [28]. Despite the improvements in surgical techniques and perioperative management, postoperative liver failure still remains an extremely feared complication in cirrhotic patients undergoing liver resection: it ranges, according to the literature, between 5 and 8 % and is associated with a high mortality rate [9, 30–32]. As a matter of fact, while Imamura et al. reported in 2003 0 % mortality out of 1,056 hepatectomies [29], other series still report mortality rate ranging from 2 to 5 % [11, 25–29]. Inadequate functional hepatic reserve, the extent of resection, blood loss/transfusion needs and severe sepsis/septic shock are among the major causes of postoperative liver failure, more frequent in cirrhotic patients [32–38]. Preoperative evaluation of the extent of liver resection is usually based on clinical conditions (the presence or absence of ascites and hepatic encephalopathy), routine liver function tests (AST/ALT, bilirubin, ALK), dedicated MRI/CT volumetric imaging for the estimation/prediction of the volume of the remnant liver and scoring systems [11, 35–38]. For a global assessment, Child–Pugh (CTP) and MELD scores are the most widely used classification systems in clinical practice [32–37]. CTP score was introduced in 1964 by Child and Turcotte and then modified in 1973 by Pugh (CTP) [39, 40] to predict the operative risk in cirrhotic patients undergoing shunt surgery for portal hypertension (Fig. 13.8). Using common biochemical (albumin, bilirubin, prothrombin time) and clinical parameters (the presence of ascites and encephalopathy, classified according to increasing severity), the Child–Pugh classification identifies in chronic liver diseased patients three classes of severity (A, B, C). Different scores for different values of the biochemical and clinical parameters identified subgroups of patients at increasing severity within the three classes (A 5–6, B 7–9; C 10–15) [11]. The classes and the score are able to predict mortality after general surgery in the different classes (CTP A-10 %; CTP B up to 30 %; CTP-C >50 %) [9]. Major flaws of CTP score are global (instead of regional) evaluation of liver function and no indication of the amount of liver parenchyma safely resectable [9, 10] (Fig. 13.6).

| Parameters | Child–Pugh scores | | |
|---|---|---|---|
| | 1 point | 2 points | 3 points |
| Albumin (mg/dl) | >3.5 | 3.5–2.8 | <2.8 |
| Bilirubin (mg/dl) | <2 | 2–3 | >3 |
| PT-INR | <1.7 | 1.7–2.3 | >2.3 |
| PT (%) | >70 | 40–70 | <40 |
| Ascites | None | Small or controlled | Tense |
| Encephalopathy | Absent | State I or II | State III or IV |

Class A: 5–6 total points, class B: 7–9 total points, class C: 10–15 total points

**Fig. 13.6** Child–Pugh classification (From Mizuguchi et al. [11])

MELD =9.57 × loge(creatinine, mg/dl) + 3.78 × loge (total bilirubin, mg/dl + 11.2 × loge (INR) + 6.43
MELDNa =MELD + 1.59 × x (135 – serum sodium)
iMELD = MELD score + (age × 0.3) – (0.7 × serum sodium) + 100
MESO index = [MELD/Na (mEq/l)] × 100
UKELD = 5 × [1.5 × loge (INR) + 0.3 × loge(creatinine, μmol/l) + 0.6 × loge (bilirubin, μmol/l) – 13 × loge(serum sodium, mmol/l + 70]
Re-weighted MELD = 1.266 loge (1 + creatinine, mg/dl) + 0.939 loge (1 + bilirubin, mg/dl) + 1.658 loge (1 + INR)

*MELDNa* model for end-stage liver disease with the incorporation of serum, *iMELD* integrated model for end liver disease, *MESO* model for end-stage liver disease to sodium, *UKELD* United Kingdom end-stage liver disease. *INR* international ratio

**Fig. 13.7** MELD and derived scores (From Mizuguchi et al. [11])

In spite of that, in the Western world, the liver function is still evaluated primarily using CTP [39, 40] and the degree of portal hypertension: hepatic resection in cirrhotic patients is usually reserved for Class A patients and, with limitations, for class B patients (vide infra). In this specific setting, the definition of the extent of the resection is crucial to avoid postoperative hepatic dysfunction [8, 29–32].

The use of MELD score and its derivates (Fig. 13.7, MELD, NaMELD and iMELD) is instead controversial in this specific setting. The MELD score is based on prothrombin time (PT) as INR, bilirubin and creatinine. MELD was first introduced to evaluate the outcome in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS): now MELD score is widely used to assess the severity of chronic liver diseases and its prognosis, as a prognostic indicator of survival in patients awaiting liver transplantation and to prioritise the transplant procedure [41–43]. Its predictive value for mortality in liver resection is debated, due to the narrow range of values in which it is used. In a retrospective study, Cucchetti et al. observed a high frequency of postoperative liver failure in patients with MELD >10 [44]. While uniform agreement exists to exclude for hepatic resection patients in CTP class C or with MELD score >14, subjects in CTP class B or with MELD score ranging from 9 to 14 should undergo a thorough evaluation to determine if and to what extent a liver resection might be feasible [44–46].

On the contrary, the Eastern surgical schools (Japanese, Chinese and Korean) have used, since the 1980s, the quantitative tests, particularly ICG clearance (usually as $ICG_{R15}$) [8, 34–36] to assess the maximum extent of major hepatic resection associated with good function of the remnant liver. Recently, $ICG_{R15}$ was added to a score of liver functional evaluation derived from the CTP classification (Liver Damage Grading System) (Fig. 13.8) and recommended by the Liver Cancer Study Group of Japan: according to the proponents, it might become a more accurate tool to assess functional hepatic reserve if compared to the original CTP score [11].

| Parameters | Liver damage grades | | |
|---|---|---|---|
| | A grade | B grade | C grade |
| Albumin (mg/dl) | >3.5 | 3.5–3.0 | <3.0 |
| Bilirubin (mg/dl) | <2 | 2–3 | >3 |
| PT (%) | >80 | 50–80 | <50 |
| Ascites | None | Small or controlled | Tense |
| $ICGR_{15}$ (%) | <15 | 15–40 | >40 |

If the liver damage final grade meets more than one grade, then the worst grade should be adopted.

*PT* prothrombin green time, *INR* international ratio, $ICGR_{15}$ indocyanine green retention rate at 15 min

**Fig. 13.8** Liver damage grading system (From Mizuguchi et al. [11])

At the beginning of the 1990s, Hemming et al. studied liver function with both conventional and ICG kinetic tests in a group of 22 cirrhotic patients undergoing major liver surgery [46]. While conventional liver function tests were not able to predict mortality, the AAs found ICGcl ≤5.2 ml/kg/min strongly associated with mortality. Lau et al. [15], during the period 1989–1993, preoperatively studied 127 candidates for liver resection with aminopyrine breath test, clearance of amino acids and ICGcl measured as $ICG_{R15}$ (normal value 0–8 %, range 3.5–10.6). Unlike the other tests, $ICG_{R15}$ was able to predict in-hospital mortality and specifically to define the $ICG_{R15}$ values above which the test correctly predicted mortality in major (>14 %) and minor (>23 %) liver resections. According to the literature, resection of three or more Couinaud segments is defined as 'major' resection, 'minor' being considered the resection of up to two contiguous or isolated segments (see Fig. 13.1) [9–11]. Of the utmost importance was in authors' view the thorough preoperative liver function assessment and the meticulous and careful surgical technique. In more recent series, which included younger patients with adequate remnant liver volume [35, 47], $ICG_{R15}$ values associated with mortality after major liver resection were slightly higher (17 % vs. 14 %), thus allowing an extension of the indication of major resections to more compromised patients. In addition to their predictive value, ICG clearance tests may allow a reliable assessment of the extent of the resectable liver parenchyma, keeping in mind in particular that the higher the R15, the smaller the amount of resectable parenchyma should be. In the years 1985–1995, Nonami reported in 318 cirrhotic patients undergoing liver resection a reduction in mortality from 11 to 7 %. The extension of liver resection was mainly guided by an $ICG_K$ algorithm: $ICG_K$ and the amount of blood loss were predictive of mortality [36]. Major liver resections are usually performed with $ICG_{R15}$ <15 %; however, in one series, right hepatectomies were performed in patients with $ICG_{R15}$ >10 % and left hepatectomies with $ICG_{R15}$ between 10 and 19 % [9–11, 48–50]. In other experiences, in the presence of an estimated 'sufficient' remnant liver volume, major hepatic resections were successfully performed with a slightly higher $ICG_{R15}$ (15–20 %) [47]. $ICG_{R15}$ became a reference standard after the publication of the results of Makuuchi's group [8]. The authors reported zero mortality in 1,056 hepatectomies performed in the period 1994–2002; particular attention was given to the following three variables: (i) the presence of ascites, (ii) serum bilirubin values and (iii) ranges of $ICG_{R15}$ [8, 29].

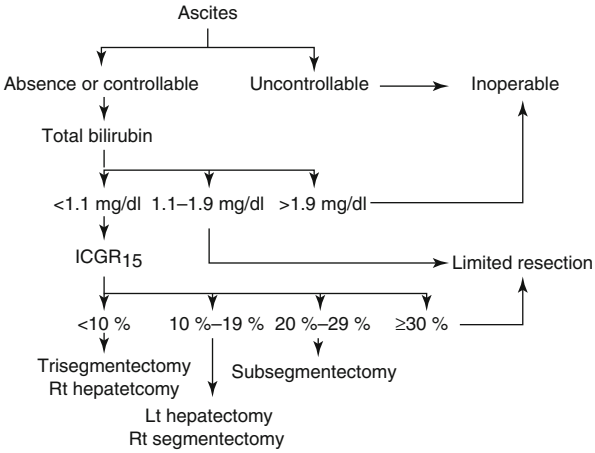


**Fig. 13.9** Makuuchi decision tree to select operative procedure in patients with impaired liver function reserve (From Mizuguchi et al. [11])

Main points of the algorithm are:

1. Absolute contraindication to hepatic resection in case of uncontrolled ascites and serum bilirubin >1.9 mg/dl
2. Limited (minor) resections possible in case of bilirubin >1 mg <1.9 mg/dl, depending on serum bilirubin
3. With no ascites and serum bilirubin <1.1 mg/dl, different types of liver resection possible according to the interval of ICG $_{R15}$ (see original algorithm in [8] and Fig. 13.9)

Very interesting, even if to be definitively implemented so far, is the use of the test in case of liver resection with $ICG_{R15}$ 15–20 % and remnant liver volume deemed 'not sufficient'. In these cases, preoperative selective portal vein embolisation (PVE) is performed to increase the future 'remnant' liver volume by inducing hyperplasia of liver lobules perfused by the contralateral portal vein [9, 10]. The $ICG_{R15}$ values correlate with volumetric changes of the liver following PVE. $ICG_{R15}$ after embolisation and immediate before surgery correlates with both volumetric and functional reserve changes [9, 51]. The relationship relies upon the preservation of total hepatic blood flow and the induced hepatic hyperplasia (see original algorithm proposed by Poon and Fan) [35]. In 2009, the Japanese guidelines for the treatment of hepatocellular carcinoma recommended $ICG_{R15}$ as test for preoperative liver function evaluation (level of evidence B) [48].

Interesting is the use of ICG kinetic tests (R15 or PDR) during or immediately after surgical resection. Recent studies confirm the ability of the ICG tests to predict postoperative morbidity (mainly hepatic dysfunction), but not mortality, due to the absence of a significant number of deaths [49]. Similar results were found at our centre in a series of 100 consecutive cirrhotic patients undergoing liver resection: ICG $_{R15}$ >40 % was predictive of morbidity but not of mortality [52]. In another smaller study, using intraoperative $ICG_{PDR}$ (normal value >18 %/min), a value of

<9 %/min predicted (sensitivity 88 %, specificity 82 %) postoperative liver failure [49]. In another experience, $ICG_{PDR}$ <7 %/min on the first postoperative day was associated, 2–5 days ahead, with the onset of liver failure [50].

As mentioned above, in case of biliary obstruction, a prolonged preoperative $ICG_{R15}$ value may falsely suggest impaired liver function. Should it be the case, the test must be interpreted with caution and should not be used, as it is, to withhold the intended surgical strategy: in this specific setting, further and multimodal investigations are mandatory [9]. ICG $_{R15}$ remains a valuable tool to assess functional hepatic reserve together with the liver volume evaluation using tomography or magnetic resonance. In the case of hyperbilirubinaemia, as reported by Ge et al., the Korean and Japanese schools suggest Tc-galactosyl serum albumin scintigraphy (Tc GSAS), to study liver function. GSA is the ideal agent to predict hepatocyte mass and function due to the ability to monitor functional status and distribution of asialoglycoprotein receptor [21].

## 13.7 Indocyanine Green Kinetics and Liver Transplantation

The conventional static tests of liver function may sometimes leave doubts or uncertainties about the functional recovery of the newly grafted liver, both from cadaveric and living donors [9]. The clearance of ICG expressed as plasma disappearance rate ($ICG_{PDR}$) or *K* constant of elimination (the use of ICG $_{R15}$, is, in fact, much less frequent in liver-transplanted patients) has been used to assess liver function in the cadaveric donor before harvesting and in the liver transplant recipient during and after transplantation, to predict early complications and survival of both the graft and the recipient after the transplant procedure [9].

Organ shortage is one of the major problems in the field of organ transplantation. Marginal or so-called extended criteria donors are now increasingly considered for organ harvesting to expand the donor pool. In this setting, $ICG_{PDR}$ was used in few small single centre studies to assess the quality of the potential graft and to assist the decision about using marginal or extended criteria donors. Unfortunately, the role of $ICG_{PDR}$ to assist in the assessment of graft suitability is weak at best: a value < 15 % $min^{-1}$ before organ harvesting was associated with primary graft non-function [9]. A combination of ICG kinetics and MELD score (ICG-MELD score) was recently considered to refine the accuracy of survival prediction in candidates awaiting liver transplantation: the ICG-MELD score improved prediction performance in patients with MELD score ranging from 10 to 30 points (intermediate to severely compromised patients) [53].

In liver-transplanted patients, the most feared complications early after the surgical procedure are primary graft non-function (PGNF) and hepatic artery thrombosis (HAT). Both conditions deserve very aggressive treatment: in large part of the cases, urgent/emergent retransplantation is the only solution able to avoid fatality. The studies of Jalan et al. [54], Plevris et al. [55] and Tsubono et al. [56] at the end of the 1990s confirmed the great interest in the use of ICGcl in assessing early liver function and in predicting graft function, graft and patient survival and the final

outcome. Essentially, in the early post-transplant period, a 'low' $ICG_{PDR}$ (an ill-defined value ranging from 5 to 12 % $min^{-1}$) was associated with graft malfunction/failure: the major problem in this specific setting is to define a reliable and reproducible cut-off value, not affected by parameters or conditions able to generate falsely altered results (hyperbilirubinaemia, as mentioned above, not uncommon reported early after OLT), which make data unreliable at best and extremely difficult to be interpreted. Jalan et al. [54], invasively studying ICG clearance, observed that ICGcl values greater than 200 ml/min were associated with immediate recovery of liver function and a normal function after 3 months; on the contrary values, <200 ml/min predicted PGNF, retransplantation, long-term care and death. 200 ml/min was found to be the $ICG_{cl}$ value able to predict outcome (100 % sensitivity and 95 % specificity) [55]. Faybik studied the ICGcl in liver-transplanted patients using both invasive (COLD system, Pulsion, Germany) and noninvasive techniques (LiMON, Pulsion, Germany) as $ICG_{PDR}$ [57]. $ICG_{PDR}$ <10 % min was predictive of postoperative complications. In 30 patients who underwent living donor liver transplantation, Hori et al. [58] monitored liver function using ICG test, expressed as $ICG_K$ (DDG-2001 Nihon Kohden) for 14 consecutive postoperative days and then at postoperative days (PODs) 21 and 28. According to the outcome, patients were subsequently allocated to two groups. The six patients with unfavourable outcome (increased morbidity and mortality) had $ICG_K$ <0.180 24 h after transplantation; this value was able to predict poor outcome at 28 days.

More recently, Levesque et al. identified two main objectives: (a) to determine if the value of $ICG_{PDR}$ measured by noninvasive technique (LiMON, Pulsion) might predict early postoperative complications and (b) to hypothesise the cause of early graft dysfunction [59, 60]. The test was performed daily from POD 1 to POD 5. $ICG_{PDR}$ of 24.4 ± 6.8 % was recorded in the group of patients with good functional recovery of the graft, regular postoperative course and favourable outcome [59]. Patients who suffered early complications were retrospectively divided into two groups: the first included patients with early postoperative complications (PGNF, HAT, septic shock or haemorrhagic shock) and the second, patients with late complications (mainly rejection). $ICG_{PDR}$ in the first group was low during the first 5 days (8.8 ± 4.5 %); in the second group, on the contrary, the $ICG_{PDR}$, initially normal, decreased significantly within 3–5 days (10.3 ± 2.5 %). Levesque et al. proposed an $ICG_{PDR}$ <12.85 % $min^{-1}$ in the very early postoperative days as a marker of almost immediate postoperative complications, mainly associated with hepatocellular dysfunction (PGNF) or perfusion deficit secondary to hepatic artery thrombosis (HAT); late (3–5 days after OLT)-onset low $ICG_{PDR}$ (<12.85 % $min^{-1}$) was instead associated with acute rejection [60], underlining the importance, in authors' view, of both time course and absolute values of the ICG kinetics. Recently, Olmedilla et al. [61] reported similar results using ICG elimination at the end of surgery (neohepatic phase) or on POD 1. $ICG_{PDR}$ in patients with severe hepatic dysfunction was <10.8 % min and was associated with increased mortality; on the contrary, $ICG_{PDR}$ >10.8 % min was associated with a good outcome and showed high (99 %) negative predictive value [52]. Very recently, Escorsell et al. [62] were not able to confirm the ability of $ICG_{PDR}$ performed on POD 1 to predict liver

dysfunction and survival. In fact, the group of patients with $ICG_{PDR}$ <8.8 % $min^{-1}$ (group A) did not show an outcome worse than the group with value >.8 (group B): in group A, however, bilirubinaemia was significantly higher, likely determining a false reading of the low $ICG_{PDR}$ value (therefore, a falsely malfunctioning graft). Very similar results were found by our group in a series of 76 consecutive patients who underwent OLT. Mazza et al. were unable to confirm $ICG_{PDR}$ <10 % $min^{-1}$ as reliable predictor of both early graft dysfunction and poor outcome; in this experience, $ICG_{PDR}$ <8 % $min^{-1}$ was associated with the presence of serum bilirubin >6 mg/dl (the same was for $ICG_{R15}$), making the results, as above underlined, unreliable [27]. Essentially, the presence of hyperbilirubinaemia altered the test results, falsely showing an initial hepatic dysfunction that was not confirmed by the subsequent clinical course and outcome of both the graft and the patients. In this study, lactate clearance was strongly correlated with the functional recovery of the grafted livers, showing a high positive predictive value, thus confirming a previous study performed by our group [63]. It has to be underlined that other factors/conditions (different values of total protein or haematocrit) might induce similar interferences with ICG kinetics [64].

The need for caution in the interpretation of low values of $ICG_{PDR}$ in order to indicate malfunction of the graft is having further confirmations in studies using LiMAx test (maximal enzymatic liver function), a test used since 2010 to identify patients at risk for hepatic failure, both after liver surgery or liver transplantation [65, 66, 68]. Intravenously administered $^{13}$C-methacetin is metabolised to paracetamol and $^{13}CO_2$. Continuous and noninvasive breath analysis of $^{13}CO_2$ production is measured as a surrogate of maximal liver metabolic capacity. Lock et al. reported a better predictive ability of LiMAx than $ICG_{PDR}$. Patients suffering from initial graft dysfunction (defined as technical complications or primary non-function ($n=8$)) had significantly decreased LiMAx results, making the test potentially effective to identify very early life-threatening complications after OLT. These observations emphasise once again the importance of the interference of various parameters on PDR/R15 results and the caution needed in the interpretation of these values [9, 10]. In the most recent experience with LiMAx in 167 chronic ESLD patients evaluated for liver transplantation, taking as primary end point 6 months liver-related death, median LiMAx values were significantly lower in patients who died, at variance of $ICG_{PDR}$, not different in survivors or non-survivors. LiMAx, if compared to $ICG_{PDR}$ and MELD, showed a slightly higher negative predictive value in predicting risk of death within 6 months [66]. The use of ICG kinetics in acute liver failure as prognostic indicator has been reported in small or preliminary series with interesting results [10, 67]: however, it must be underlined that high bilirubin values (present by definition in patients suffering for acute subacute or hyperacute liver failure) might critically influence the results, likely making unreliable or doubtful the tests in this setting. LiMAx has very recently been considered in patients with acute liver failure. The LiMAx was significantly lower in patients who did not recover, whereas neither biochemical parameters nor MELD score showed difference. According to these data, LiMAx test might be effective in predicting the individual prognosis and the need for OLT in ALF [68].

## 13.8 ICG Kinetics as a Prognostic Score in Intensive Care

ICG kinetics have been long used even within the ICU, to determine the severity of the disease and/or to predict mortality [1, 3, 9, 10, 68–71]. In this setting, it might be interesting to differentiate, having achieved an acceptable haemodynamic stability, the different contributions given to the ICG elimination by parenchymal liver function and hepatic blood flow [1, 68]. In critically ill patients, very common is the use of scores based on clinical and biochemical variables (APACHE II, SAPS II, SOFA), designed to quantify the severity of the disease or to predict mortality. In a retrospective study of 336 critically ill patients, $ICG_{PDR}$ was able to predict mortality in ICU patients similar to SAPS II and APACHE II [70]. Non-survivors had significantly lower values compared with survivors (6.4 %/min vs. 16.5 %/min). In patients with septic shock, ICG kinetics parameters evaluating liver function and perfusion might be able to give a reliable prognostic evaluation. $ICG_{PDR}$ values <8 %/min predicted mortality in patients with septic shock: again sensitivity and specificity were similar to those determined by APACHE II score [70]. Kimura et al. were able to document a favourable outcome associated with an improvement in $ICG_{PDR}$, while extremely low levels were predictive of poor outcome [71]. It might be hypothesised that in critically ill septic patients in which splanchnic perfusion is appropriately supported by inotropes/pressors, $ICG_{PDR}$ could be considered an indicator of hepatocellular dysfunction if haemodynamic improvement is not associated with a favourable trend in ICG kinetics. Since long, ICG kinetics have been demonstrated of interest to document, in trauma patients, hepatic dysfunction (ICG clearance results preceding the increase in serum bilirubin)[72]. Pollack et al. were able to demonstrate the superiority of ICG clearance compared to the value of bilirubin in predicting survival in patients with trauma or shock [68]. As already reported, the cytokine increase associated with shock might constitute a factor able to interfere with the ICG transport within the liver cell, making not completely reliable the results [9]. Abdominal hypertension (defined as an intraabdominal pressure exceeding 12 mmHg, with values above 20 mmHg associated with abdominal compartment syndrome) [72] might impact on ICG kinetics. Low values of $ICG_{PDR}$ (unfortunately an univocal cut-off is not available, so far) are associated with reduced splanchnic perfusion, and extremely low values of $ICG_{PDR}$ correlate with mortality [9, 10, 72–77]. According to preliminary reports, it might be speculated that low $ICG_{PDR}$, even if in the presence of normal or near-normal intraabdominal pressure (<15 mmHg) might unveil a suboptimal splanchnic blood flow, thus making $ICG_{PDR}$ a possible early marker of inadequate splanchnic perfusion [76].

**Conclusions**

Used since the 1960s for research purposes, the ICG kinetics have received a major boost in clinical use in the recent years, with the introduction of reliable and simple noninvasive monitoring methods (LiMON, Nihon Kohden). The applications in the field of major liver surgery (resection in cirrhotic patients) underscore the relevant implications in predicting both the resectability of liver cancer in cirrhotic patients and the potentials for postoperative liver failure:

relevant in this setting are the studies coming from Japan, China and Korea. The ability to predict mortality, however, is still under debate. Despite initial enthusiasms, post-OLT ICG kinetics for the prediction of mortality and morbidity still raise some concerns. This refers, in particular, to the presence of mixed results and 'false positives' in the presence of hyperbilirubinaemia (liver grafts falsely classified, according to $ICG_{PDR}$, as severely dysfunctioning or at unfavourable outcome). Problems are still encountered with the PDR/R15 cut-off values below which they reliably assess poor graft function. While negative predictive values are indeed relevant in predicting good graft outcome (no complications in the presence of 'normal' PDR or R15 values), caution is still needed in case of 'low' or pathological values. As appropriately commented by Vos et al., 'further prospective, randomised controlled trials of the ability of ICG elimination measurement to impact positively on outcome are required before the green light can be given for routine clinical use' [9].

## Bibliography

1. Hawker F (1993) The liver, chap 1. Saunders Co., London, UK, pp 1–43
2. Mulaikal TA, Edmond JC (2012) Physiology and anatomy of the liver: chap 1. In: Wagener G (ed) Liver anesthesiology and critical care medicine. Springer, New York, pp 3–20
3. Sakka SG (2007) Assessing liver function. Curr Opin Crit Care 13:207–214
4. Hoekstra LT, De Graaf W, Niboug G, Heger M, Bennick JR, Stieger B, Van Gulik TM (2013) Physiological and biochemical basis of clinical liver function tests. Ann Surg 257:1–27
5. Dufour DR, Qazi N (2012) Evaluation of liver disease: chap 4. In: Wagener G (ed) Liver anesthesiology and critical care medicine. Springer, New York, pp 51–58
6. Slack A, Ladher N, Wendon J (2012) Acute hepatic failure: chap 2. In: Wagener G (ed) Liver anesthesiology and critical care medicine. Springer, New York, pp 21–41
7. Wagener G (2013) Assessment of hepatic function, operative candidacy, and medical management after liver resection in the patient with underlying liver disease. Semin Liver Dis 33: 204–212
8. Imamura H, Sano K, Sugawara S, Kukudo N, Makuuchi M et al (2005) Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg 12:16–22
9. Vos JJ, Wietasch JKG, Absalom AR, Hendriks HGD, Scheeren TWL (2014) Green light for liver function monitoring using indocyanine green? An overview of current clinical application. Anesthesia. doi:10.1111/anae.12755
10. Halle BM, Poulsen TD, Pedersen HP (2014) Indocyanine green plasma disappearance rate as dynamic liver function test in critically ill patients. Acta Anesthesiol Scand 58:1214–1219
11. Mizuguchi T, Kawamoto M, Meguro M, Hui TT, Hirata K (2014) Preoperative liver function assessments to estimate the prognosis and safety of liver resections. Surg Today 44:1–10
12. Leevy CM, Mendenhall CL, Lesko W, Howard MM (1962) Estimation of hepatic blood flow with indocyanine green. J Clin Invest 41:1169–1180
13. Pessayre D, Lebrec D, Descantoire V et al (1978) Mechanism for reduced drug clearance in patients with cirrhosis. Gastroenterology 74:566–571
14. Paumgartner G, Probst P, Kraines R, Leevy CM (1970) Kinetics of indocyanine green removal from the blood. N Y Acad Sci 170:134–147
15. Lau H, Man K, Fan ST et al (1997) Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg 84:1255–1259

16. Shinohara H, Tanaka A, Kital T et al (1996) Direct measurement of hepatic indocyanine green clearance with near-infrared spectroscopy: separate evaluation of uptake and removal. Hepatology 23:137–144
17. Cui Y, Konig J, Leier J et al (2001) Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. J Biol Chem 276:9626–9636
18. Keiding S (1987) Hepatic clearance and liver blood flow. J Hepatol 4:393–398
19. Kawasaki S, Sugiyama Y, Yga T et al (1985) Pharmacokinetic study on the hepatic uptake of indocyanine green in cirrhotic patients. Am J Gastroenterol 80:801–806
20. Huet PM, Goresky CA, Villeneuve JP et al (1982) Assessment of liver microcirculation in cirrhosis. J Clin Invest 70:1234–1244
21. Ge PL, Du SD, Mao YL (2014) Advances in preoperative assessment of liver function. Hepatobiliary Pancreat Dis Int 13:361–370
22. Faybik P, Krenn C-G, Baker A, Lahner D, Berlakovich G, Steltzer H, Hetz H (2004) Comparison of invasive and noninvasive measurement of plasma disappearance rate of indocyanine green in patients undergoing liver transplantation: a prospective investigator-blinded study. Liver Transpl 10:1060–1064
23. Kisch H, Leucht S, Lichtwarck-Aschoff M et al (1995) Accuracy and reproducibility of the measurement of actively circulating blood volume with an integrated fiberoptic monitoring system. Crit Care Med 23:885–893
24. Aoyagi T, Fuse M et al (1994) Pulse dye-densitometry. Jpn J Clin Monit 5:371
25. Sakka SG, Reinhart K, Meier Hellmann A (2000) Comparison of invasive and non invasive measurements of indocyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable hemodynamics. Intensive Care Med 26:1553–1556
26. Purcell R, Kruger P, Jones M (2006) Indocyanine green elimination: a comparison of the Limon and serial blood sampling methods. ANZ J Surg 76:75–77
27. Mazza E, Prosperi M, DeGasperi A et al (2008) Plasma disappearance rate of indocyanine green after liver transplantation: always a reliable tool to predict graft function and out come? Liver Transpl 14:S201
28. Manizate F, Hiotis SP, Labow D et al (2010) Liver functional reserve estimation: state of the art and relevance for local treatments. J Hepatobiliary Pancreat Sci 17:385–388
29. Imamura H, Makuuchi M et al (2003) One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 138:1198–1206
30. Bellavanca EC, Lumpkins KM et al (2008) Surgical management of early – stage hepatocellular carcinoma: resection or transplantation ? J Gastrointest Surg 12:1699–1708
31. Jarnagin W, Gonen M, Fong Y et al (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutives cases over the past decade. Ann Surg 236: 397–407
32. Fan ST (2010) Liver functional estimation: state of art and relevance for local treatments: the eastern perspective. J Hepatobiliary Pancreat Sci 17:380–384
33. Bruix J, Castells A, Bossch J et al (1996) Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 111: 1018–1022
34. Lee S, Shin Hwang (2005) How I do it: assessment of hepatic functional reserve for indication of hepatic resection. J Hepatobiliary Pancreat Surg 12:38–43
35. Poon RT, Fan ST (2005) Assessment of hepatic reserve for indication of hepatic resection: how I do it. J Hepatobiliary Pancreat Surg 12:31–37
36. Nonami T, Nakao A et al (1999) Blood loss and ICG clearance as best prognostic markers of post-hepatectomy liver failure. Hepatogastroenterology 46:1669–1672
37. Janssen MW, Druckerey-Fiskaaen KY et al (2010) Indocyanine green R 15 ratio depends directly on liver perfusion flow rate. J Hepatobiliary Pancreat Sci 17:180–185
38. Capussotti L, Viganò L et al (2009) Liver dysfunction and sepsis determine operative mortality after liver resection. Br J Surg 96:88–94
39. TurcotteJ G, Child GG (1964) Surgery and portal hypertension. Major Probl Clin Surg 1: 1–85

40. Pugh RWH, Murray –Lyon IM et al (1983) Transection of the esophagus for bleeding esophageal varices. Br J Surg 60:646–649
41. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC (2000) A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 31:864–871
42. Dutkowski P, Oberkofler CE, Béchir M, Müllhaupt B, Geier A, Raptis DA et al (2011) The model for end-stage liver disease allocation system for liver transplantation saves lives, but increases morbidity and cost: a prospective outcome analysis. Liver Transpl 17:674–684
43. Cholongitas E, Marelli L, Shusang V et al (2006) A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl 12:1049–1061
44. Cucchetti A, Ercolani G, Vivarelli M et al (2006) Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on liver cirrhosis. Liver Transpl 12(6):966–971
45. Teh SH, Christein J et al (2005) Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. J Gastrointest Surg 9:1207–1215
46. Hemming AW, Scudamore CH, Shackleton CR, Pudek M, Erb SR (1992) Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. Am J Surg 163: 515–518
47. Lam CM, Fan S, lo CM, Wong J (1999) Major hepatectomy for hepatocellular carcinoma in patients with an unsatisfactory indocyanine green clearance test. Br J Surg 86:1012–1017
48. Kokudo N, Makuuchi M (2009) Evidence–based clinical practice guidelines for hepatocellular carcinoma in Japan: the Japan _HCC guidelines. J Gastroenterol 44:119–121
49. Ohwada S, Kawate S, Hamada K et al (2006) Perioperative real time monitoring of indocyanine green clearance by pulse spectrophotometry predicts remnant liver functional reserve in resection of hepatocellular carcinoma. Br J Surg 93:339–346
50. Greco E, Nanji S, Bromberg IL, Shah S, Wei AC, Moulton C-A, Greig PD, Gallinger S, Cleary SP (2011) Predictors of periopertative morbidity and liver dysfunction after hepatic resection in patients with chronic liver disease. HPB (Oxford) 13:559–565
51. Shindoh JD, Tzeng CW, Vauthey JN (2012) Portal vein embolization for hepatocellular carcinoma. Liver Cancer 1:159–167
52. Mazza E, Kroeller D, Prosperi M et al (2013) Does ICG clearance (ICGR15) predict morbidity and mortality after hepatic resection for hepatocellular carcinoma in cirrhotic patients? Intensive Care Med Abs. Transpl Inter (Suppl 2) 185–329, S609
53. Zipprich A, Kuss O, Rogowski S et al (2010) Incorporating indocyanine green clearance into the model for end stage liver disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. Gut 59:963–968
54. Jalan R, Plevris JN, Jalan AR, Bzeizi KI, Dollinger MM, Lee A, Garden OJ, Hayes PC (1994) A pilot study of indocyanine green clearance as an early predictor of graft function. Transplantation 58:196–200
55. Plevris JN, Jalan R et al (1999) Indocyanine green clearance reflects reperfusion injury following liver transplantation and is an early predictor of graft function. J Hepatol 30:142–148
56. Tsubono T, Todo S, Jabbour N, Mizoe A, Warty V, Demetris AJ, Starzl TE et al (1996) Indocyanine green elimination test in orthotopic liver recipients. Hepatology 24(5): 1165–1171
57. Faybik G, Hetz H (2006) Plasma disappearance rate of indocyanine green in liver dysfunction. Transplant Proc 38:801–802
58. Hori T, Lida T et al (2006) Kicg value, a reliable real–time estimator of graft function, accurately predicts outcomes in adult living-donor liver transplantation. Liver Transpl 12: 605–613
59. Levesque E, Saliba F, Benhamida S et al (2009) Plasma disappearance rate of indocyanine green: a tool to evaluate early graft outcome after liver transplantation. Liver Transpl 15: 1358–1364

60. Levesque E, Hoti E, Azoulay D, Saliba F et al (2011) Non-invasive ICG-clearance: a useful tool for the management of hepatic artery thrombosis following liver transplantation. Clin Transpl 25:297–301
61. Olmedilla L, Perez-Pena JM et al (2009) Early noninvasive measurement of the indocyanine green plasma disappearance rate accurately predicts early graft dysfunction and mortality after deceased donor liver transplantation. Liver Transpl 15:1247–1253
62. Escorsell A, Mas A et al (2012) Limitations of use of the noninvasive clearance of indocyanine green as a prognostic indicator of graft function in liver transplantation. Transplant Proc 44: 1539–1541
63. De Gasperi A, Mazza E, Corti A et al (1997) Lactate blood levels in the perioperative period of orthotopic liver transplantation. Int J Clin Lab Res 27:123–128
64. Kim GA, Bae KS, Noh GJ et al (2009) Estimation of indocyanine green elimination rate constant k and retention rate at 15 min using patient age, weight, bilirubin and albumin. J Hepatobiliary Pancreat Surg 16:521
65. Lock JF, Schwabauer E, Martus P et al (2010) Early diagnosis of primary nonfunction and indication for reoperation after liver transplantation. Liver Transpl 16:172–180
66. Jara M, Malinowski M, Lüttgert K, Schott E, Neuhaus P, Stockmann M (2015) Prognostic value of enzymatic liver function for the estimation of short-term survival of liver transplant candidates: a prospective study with the LiMAx test. Transpl Int 28:52–58
67. Merle U, Sieg O, Stremmel W, Encke J, Eisenbach C (2009) Sensitivity and specificity of plasma disappearance rate of indocyanine green as a prognostic indicator in acute liver failure. BMC Gastroenterol 9:91
68. Lock JF, Kotobi AN, Malinowski M, Schulz A, Jara M, Neuhaus P, Stockmann M (2013) Predicting the prognosis in acute liver failure: results from a retrospective pilot study using the LiMAx test. Ann Hepatol 12:556–562
69. Pollack DS, Sufian S, Matsumoto T (1979) Indocyanine green clearance in critically ill patients. Surg Gynecol Obstet 149:852
70. Inal MT, Memis D, Kargi M, Sut N (2009) Prognostic value of indocyanine green elimination assessed with LiMON in septic patients. J Crit Care 24:329–334
71. Sakka SG, Reinhart K, Meier-Hellmann A (2002) Prognostic value of the indocyanine green plasma disappearance rate in critically ill patients. Chest 122:1715–1720
72. Kimura S, Yoshioka T et al (2001) Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival. Crit Care Med 29(6): 1159–1163
73. An G, West MA (2008) Abdominal compartment syndrome: a concise clinical review. Crit Care Med 36:1304–1310
74. Gottlieb ME, Stratton HH, Newell JC et al (1984) Indocyanine green. Its use as an early indicator of hepatic dysfunction following injury in man. Arch Surg 119:264
75. Sakka SG (2007) Indocyanine green plasma disappearance rate as an indicator of hepatosplanchnic ischemia during abdominal compartment syndrome. Anesth Anal 104:1003–1004. 109
76. Thumer O, Huttemann E, Sakka SG (2007) Indocyanine green plasma disappearance rate. Marker of partial hepatosplanchnic ischemia. Anaesthesist 56:339–344
77. Seibel A, Muller A, Sakka SG (2011) Indocyanine green plasma disappearance rate for monitoring hepatosplanchnic blood flow. Intensive Care Med 37:357–359