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Annual Update in Intensive Care and Emergency Medicine 2021

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Abbreviations

AKI	Acute kidney injury
APACHE	Acute Physiology And Chronic Health Evaluation
ARDS	Acute respiratory distress syndrome
COVID	Coronavirus disease
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CSF	Cerebrospinal fluid
DO_2	Oxygen delivery
ECMO	Extracorporeal membrane oxygenation
GCS	Glasgow Coma Scale
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
LV	Left ventricular
MAP	Mean arterial pressure
NO	Nitric oxide
NOS	Nitric oxide synthase
PEEP	Positive end-expiratory pressure
RBC	Red blood cell
RCT	Randomized controlled trial
RRT	Renal replacement therapy
RV	Right ventricular
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOFA	Sequential organ failure assessment
TBI	Traumatic brain injury
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia

Part I

Sepsis

Effect of Sex and Gender in Sepsis and Septic Shock: A Narrative Review

1

A. Lopez, I. Lakbar, and M. Leone

1.1 Introduction

Most diseases are expressed differently in men and women. While nearly 80% of cases of autoimmune disease occur in women, cancer is more frequent in men. This sexual dimorphism effect is also present in infectious diseases [1], which are one of the leading causes of mortality in the world.

In the intensive care unit (ICU), sepsis and septic shock are frequent and still have high mortality rates, reaching 45% for patients with septic shock [2]. Patient outcomes seem to rely on different phenotypes [3]. Sexual dimorphism could be approached as a first step in the personalized management of septic patients.

In this narrative review, we describe sex differences in infectious diseases in patients admitted to the ICU.

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1.2 Epidemiology

Men are more likely to develop infectious disease than women, with a mean annual relative risk (RR) of 1.28 (95% confidence interval [CI] 1.24–1.32) [4]. Over the last decade, large-scale studies have reported a higher incidence of sepsis in men than in women [4]. To understand the extent of this challenge, one should know that the number of men admitted to the ICU for sepsis and septic shock is higher than the number of men admitted to the ICU for other medical reasons [5]. Despite this finding, a multicenter study did not find any differences in patient sex on the decision to admit to the ICU [6].

1.2.1 Source of Infection

Epidemiological studies suggest different susceptibility to infectious diseases according to sex (Fig. 1.1). Men are more likely to have lower respiratory tract infections than women [7], whereas sinusitis and tonsillitis occur more frequently in women than in men because of differences in respiratory tract anatomy [8]. Men are overrepresented among patients with severe bloodstream infections, with a relative risk of 1.3 (95% CI 1.1–1.6, $P < 0.05$) [9], and among patients

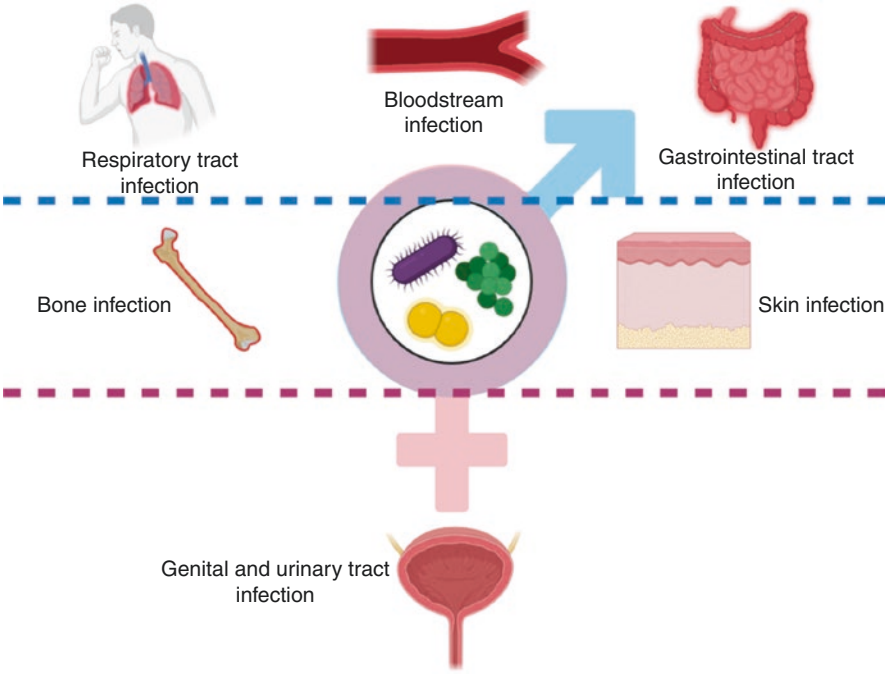

Fig. 1.1 Differences in source of infection according to sex

Table 1.1 Differences in sex distribution according to source of infection

Source of infection	Common causative bacteria	More frequent in
Respiratory tract	*Streptococcus pneumonia*	Men
	Chlamydophila pneumoniae	
	Legionella spp.	
	Mycoplasma pneumoniae	
	Mycobacterium tuberculosis	
	Pseudomonas aeruginosa	
	Acinetobacter baumanii	
Bloodstream	*Escherichia coli*	Men
	Staphylococcus aureus	
	Coagulase-negative staphylococci	
	Streptococcus pneumonia	
	Klebsiella spp	
Gastrointestinal tract	*Salmonella typhi*	Men
	Helicobacter pylori	
	Yersina enterocolitica	
	Escherichia coli	
	Enterobacteria	
	Enterococcus faecalis, Enterococcus faecium	
Urinary tract	*Escherichia coli*	Women
	Enterococcus spp.	
	Staphylococcus saprophyticus	
	Klebsiella pneumonia	

with digestive infections [10], probably in relation to differences in dietary and hygiene behavior between men and women. However, an animal study showed that the female intestinal mucosa was more resistant to hypoxia and acidosis than that of males and that the production of pro-inflammatory markers was increased in males. This production was decreased after administration of flutamide, a testosterone antagonist [11].

In contrast, women are more likely to develop urinary and genital tract infections than men. Differences in anatomy, physiology, and cell biology of the lower urinary tract may explain this finding. Moreover, the urinary microbiome and hormonal regulation may amplify the rate of urinary and genital tract infections in the female population [12]. Table 1.1 summarizes this sexual dimorphism in source of infection.

1.2.2 Sepsis and Septic Shock

Population-based cohort studies have identified an increase in the incidence of sepsis over time, probably due to an improvement in clinical diagnosis after the new Sepsis 3 definitions, but also to an increasing proportion of frail patients in the population [13]. In a recent review [14] of large multicenter studies, 54–61% of patients admitted to the ICU for sepsis or septic shock were men. Offner et al. identified male sex as an independent risk-factor for severe infections after trauma (odds ratio [OR] 1.58 [95% CI 1.01–2.48], $P = 0.04$) [15].

As the production of sex hormones evolves with aging, age interferes with the relationship between sex hormones and infectious diseases. In children, most studies show that sepsis distribution is similar in boys and girls. In adults, the widest difference in sepsis incidence between the sexes occurs between 25 and 30 years of age [16]. However, a small difference between male and female patients is still observed at extreme ages [16]. In elderly patients, sepsis tends to affect women at older ages than men [4].

1.2.3 Sepsis and Shock Septic Outcomes

Sepsis and septic shock are a worldwide public health problem. Sepsis involves life-threatening organ dysfunction, and has a global incidence of almost 50 million cases per year worldwide, with a mortality rate of nearly 20% [16]. In a meta-analysis, the frequency of septic shock was estimated at 10.4% for patients diagnosed at ICU admission and 8.4% for patients diagnosed at any time during an ICU stay [17]. In general, women seem to have better clinical outcomes than men, who have longer ICU and in-hospital lengths of stay [18]. A retrospective analysis of a large clinical database reported that male patients with sepsis were more likely to require mechanical ventilation ($P = 0.012$) and vasoactive agents (dopamine [$P = 0.113$], norepinephrine [$P = 0.016$], and epinephrine [$P = 0.093$]) during an ICU stay than women [18]. Men are also more likely to develop acute kidney injury than women [19].

All-cause ICU mortality and in-hospital mortality rates for septic shock are 37% and 39%, respectively [17]. In terms of differences according to sex, contrasting evidence is reported. Most epidemiological studies do not show sex differences in terms of sepsis-related deaths [20]. In a retrospective analysis of patients admitted to a polyvalent ICU, a higher mortality rate was found in older women with sepsis than in men [21]. However, age confounds the relationship between sex and mortality. In European countries, the median age at death in men in 2015 was 78 years, compared with 83 years in women [22]. Men are at higher risk of dying from major trauma, cancer, and cardiovascular diseases than women [1]. This can affect the findings associated with sepsis mortality.

1.2.4 Coronavirus Disease 2019 (COVID-19)

Another sexual dimorphism has recently been illustrated in ICUs around the world, with men developing more severe forms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than women. Men have been reported to be almost three times more likely to be admitted to the ICU with SARS-CoV-2 infection than women (OR = 2.84; 95% CI 2.06–3.92) [23], although this study was unable to adjust the data for sex differences in comorbidities. In a cohort of 1522 ICU patients, Moiseev et al. reported higher mortality rates in men over 50 years of

age than in women of the same age, although women had a higher occurrence of chronic diseases and comorbidities [24]. Therefore, sex disparities in disease severity may be explained by immune, hormonal, and chromosomal differences rather than by differences in comorbidities. Women exhibit higher CD4 T-cell counts and higher type I interferon (IFN-I) serum concentrations than men during viral disease [25]. IFN-I is believed to play a critical role in the immune response to SARS-CoV-2 infection [26]. On the other hand, estradiol reportedly stimulates humoral-mediated immune responses and increases the production of antibodies [26]. With respect to chromosome-bias differences, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE-2), a protein encoded by X chromosome genes. Since ACE-2 is expressed differently in men and women, this may partly explain the lack of protection against SARS-CoV-2 in men [27].

1.3 Mechanisms Underlying Sex Differences

1.3.1 Animal Models

The effect of sexual dimorphism on infection has been determined by comparing males and females before and after castration. Males are less resistant to the development of endotoxic shock than females. The castration of males prevents this sexual dimorphism, but ovariectomy has no effect. The survival rate of females is higher than that of males and ovariectomized females in cecal ligation and puncture models [28]. In murine models, pro-inflammatory cytokines are higher in male than in female mice. In a murine model of intra-abdominal sepsis caused by injection of endotoxin, exogenous estradiol prevented organ oxidative damage [29].

Hence, sexual dimorphism reported in epidemiological studies is confirmed in experimental models of infection. A similar pattern has been found for most intracellular bacteria. Leone et al. showed that male and ovariectomized mice infected by *Coxiella burnetii* exhibited higher rates of tissue infection than female mice [30]. The susceptibility of male and ovariectomized female mice to *Mycobacterium avium-intracellulare* infection and resultant mortality were higher than those of females [31].

1.3.2 Sex Hormones

Merkel et al. showed excess mortality after induction of sepsis in ovariectomized female rats, which was corrected by the administration of estradiol; treatment with estradiol reduced mortality from 80% to 50% [32]. Female sex hormones seem to have a protective role and androgens an immunosuppressive action [1]. In animal models of infection, an immunosuppressive effect of androgens has been observed, resulting in worse outcomes in males [1].

Unfortunately, the picture at the bedside is more complex, with dual effects of sex hormones according to their concentrations. In the ICU, a high serum estradiol concentration is associated with increased mortality [33]. In elderly patients with infections, mortality is associated with elevated estradiol concentrations in both sexes [34]. At variance with previous studies, elevated testosterone concentrations were found in women who did not survive [34].

1.3.3 Chromosomes

The X chromosome supports not only many genes that affect sex hormone levels but also genes involved in the immune response. The X chromosome, X-linked genes, and X chromosome inactivation mechanisms contribute to male susceptibility to infectious diseases [35]. This observation arises from studies in autoimmune diseases. For example, an autoimmune female predisposition is found in systemic lupus erythematosus; indeed, the interleukin receptor-associated kinase 1 enzyme (IRAK-1), encoded by the X chromosome, is a risk factor for the occurrence of the disease [36]. In genetic chromosomal pathologies, there is a decrease in circulating T and B lymphocytes in Turner syndrome (45, X), but the opposite is noted in Klinefelter syndrome (47, XXY). Men with lowered serum testosterone concentrations exhibit immunoglobin levels close to those of healthy women [37]. In an experimental study on *Drosophila melanogaster*, X chromosome genes involved in the immune response were found to have a role in regulating bacterial load [38]. This can be a selective advantage for the female sex in the immune response to infection. The inactivation of the X chromosome during embryonic development in women is not complete, because 10% of the genes are not inactivated. Thus, this genetic dimorphism may give women a natural advantage over men in fighting infections.

1.3.4 Immune Response

Immune functions are affected by a specific sex response. Male and female lymphocyte cells possess sexual hormone receptors on their surface, which work as nuclear transcription factors [39]. Estrogens directly stimulate B-lymphocyte cells and antibody production. This explains the greater humoral immune response with higher levels of immunoglobins in women than in men [40]. Androgen receptors have also been described on the surface of immune cells. Testosterone reduces natural killer (NK)-lymphocyte cell activity and the production of pro-inflammatory cytokines by inhibiting the nuclear factor-kappa B (NF-κB) pathway. Testosterone has a negative control on Th1 differentiation, decreasing the production of IFNγ and tumor necrosis factor (TNF)-α, and increasing susceptibility to bacterial infection. Animal studies have observed a negative effect of testosterone also on the development of B-lymphocyte cells and thus on the development of antibody production [41].

1.3.5 Behavioral Factors and Gender Dimorphism

Exposure to pathogens and different social behaviors may interfere with the effect of sex in explaining differences between men and women. For a long time, smoking was more prevalent in men than in women [42] and was associated with an increased risk of respiratory diseases and infection [43]. Observational data may not discriminate between male groups and smoker groups among patients at high risk of infection; thus, the increased rate of infected men may be due to a higher prevalence of smokers among men than in women. This underlines the need for experimental investigations looking at the role of sex hormones in the process of infectious diseases.

Lifestyle is also influenced by gender. In a population of 761 adolescents, young girls did less physical exercise and had lower physical and psychological well-being but higher vegetable consumption and greater satisfaction from an educational context [44]. Such stereotypes may influence behavior and affect susceptibility to infection.

Gender inequalities also exist regarding access to healthcare. The prevalence of perceived unmet health care is significantly higher in women than in men. In 2019, the #LancetWomen movement was created to promote sex equality worldwide and highlight the inequalities in science, medicine, and global health between men and women [45].

In summary, the term 'sex' concerns biological features, chromosomes and hormone expression, whereas 'gender' refers more to social roles and human behavior (Fig. 1.2); both can influence the susceptibility and response to sepsis.

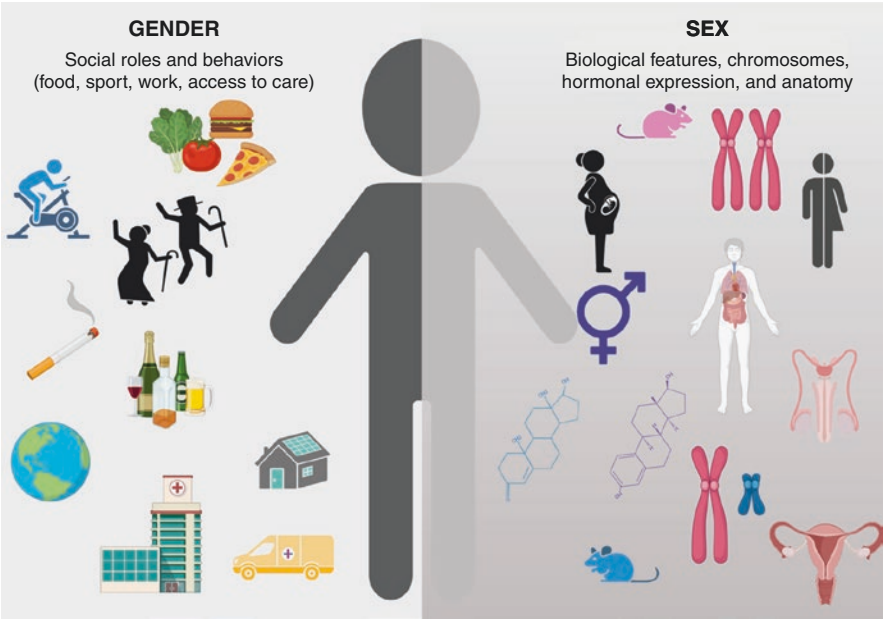

Fig. 1.2 Differences between gender and sex

1.4 Therapeutic Strategies and Sex Inequalities

Physicians should consider sex differences as the first step toward personalized management patient in sepsis. In an observational study on tuberculosis, women had a significantly longer delay before diagnosis and introduction of specific treatment [46]. In contrast, men had worse outcomes because of lower sputum culture conversion and higher mortality rates despite specific treatment [47]. These findings reflect a sexual dimorphism in patient management. In patients with septic shock, intravenous antimicrobials should be introduced as soon as possible after diagnosis [2]. However, the DISPARITY-II study found a delay of 31 min before antimicrobial onset in septic women compared with men after recognition of infectious sources [48]. This finding is in line with a nationwide cohort study, in which swifter diagnosis and shorter time to antibiotics were noted for men, without a significant difference in ICU nursing workload [49]. These findings justify the implementation of preventive protocols to reduce sex inequalities in health and wellbeing from an early age [45]. Finally, pharmacokinetics differs in men and women. In healthy volunteers, the median elimination half-life of Ringer's acetate was shorter in women than in men [50]. In animal studies, cardiac dysfunction during sepsis has been described in both sexes, but was more marked in male mice. Mathieu et al. compared the performance of landiolol, a short-acting beta-blocker, to prevent deleterious cardiac damage in male and female septic mice [51]. There were significant differences, with a dual effect being highlighted in males and females: whereas cardiac performance was improved in the male rats treated with landiolol, the treatment was deleterious in females. A sexual dimorphism of beta-receptors was described on tissue analysis [52]. This was related to sex hormones, because ovariectomy corrected this deleterious effect (personal data).

Regarding the effect of adjunctive corticosteroids during septic shock, hydrocortisone decreased the ICU length of stay and duration of mechanical ventilation in men compared to women, but no significant differences were found for outcomes, support therapy, or health-related quality of life [53]. It is still too early to direct therapy based on these findings; further multicenter studies are necessary.

1.5 Conclusion

Male sex predisposes to developing sepsis and septic shock. This difference between men and women seems to get worse until the onset of menopause in females, supporting a strong role for sex hormones. By contrast, the mortality of patients with sepsis is not affected by sex, probably because age confounds this outcome. Knowledge of sexual dimorphism mechanisms may offer an opportunity to personalize the management of patients with sepsis according to their age and sex.

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Complex Immune Dysregulation in COVID-19 and Implications for Treatment

2

M. Mouktaroudi and E. J. Giamarellos-Bourboulis

2.1 Introduction

The rise of the pandemic by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generated a state of urgency within the medical community. This urgency was further aggravated by the accumulating number of critically ill patients admitted with acute respiratory distress syndrome (ARDS) and the considerable mortality. Early publications suggesting that the ARDS was associated with a storm of cytokines led to the administration of various anti-cytokine drugs for treatment. After several months of pandemic, data now suggest that complex immune phenomena exist in the host and they mandate a personalized approach for management. The purpose of this review is to focus on the change in the function of monocytes in severe coronavirus disease 2019 (COVID-19) and to propose therapeutic interventions for restoration of the immune function.

2.2 What Does Cytokine Storm Signify in COVID-19?

The dawn of the SARS-CoV-2 pandemic was followed by several publications describing increased concentrations of pro-inflammatory cytokines in the circulation of patients [1, 2], giving birth to the idea that hospitalized patients with severe or critical illness were suffering from cytokine storm syndrome. The real question is whether excess cytokine production is a unique feature for all patients with COVID-19 or whether the cytokine patterns in COVID-19 resemble what is seen in bacterial sepsis. Existing publications comparing the kinetics of cytokines in sepsis

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with those in COVID-19 are limited. In one, the distribution of pro-inflammatory cytokines, namely interleukin (IL)-1β, IL-6, IL-8, IL-18 and tumor necrosis factor-alpha (TNF-α) was compared in nine patients with severe COVID-19, 12 patients with ARDS due to SARS-CoV-2, and 16 patients with bacterial sepsis; no differences were found [3]. In another publication, IL-1β, IL-6 and IL-10 were measured in the plasma of critically ill patients; 20 patients had pneumonia due to SARS-CoV-2 and 20 patients had bacterial community-acquired pneumonia (CAP). Concentrations of IL-1β and IL-6 were greater in patients with critical COVID-19 than in those with bacterial CAP, whereas patients with bacterial CAP had significantly greater concentrations of IL-10. These findings suggest that one main feature of severe COVID-19 is a shift in the pro-inflammatory/anti-inflammatory balance of the host towards the pro-inflammatory spectrum [4].

It seems that, contrary to ARDS due to other causes, ARDS of COVID-19 origin is dominated by two main clusters of cytokines. The first is the cluster of C-X-C motif chemokine ligand 10 (CXCL10), granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-10 which drives progression to ARDS; the second is the cluster of IL-6, IL-1 receptor antagonist (IL-1ra), chemokine (C-C motif) ligand 20/macrophage inflammatory protein-3a (CCL20/MIP-3a), C-X3-C motif chemokine ligand 1 (CX3CL1) and IL-15, which drives organ dysfunction [5]. Cytokine concentrations increase when the disease is worsening but their comparative distribution in different patients is linear and is statistically better expressed in box plots showing individualized patterns. The increase in circulating cytokines follows the increase in circulating viral load and is accompanied by a decrease in monocytes and lymphocytes [6]. These findings suggest that COVID-19 is dominated by complex immune dysregulations that do not follow a unique pattern and in which individualization may play a major role. This individualization may arise from the different pattern of stimulation of monocytes that starts the inflammatory response of the host to an infectious trigger.

2.3 The Role of Monocytes

Circulating monocytes and tissue macrophages are the first line of host defence against the offending pathogens. The traditional paradigm from bacterial sepsis is that the interaction of pathogen-associated molecular patterns (PAMPs) of bacteria with pattern recognition receptors (PRRs) of monocytes and macrophages leads to the over-production of pro-inflammatory cytokines and to subsequent organ dysfunction. The detection of increased circulating levels of pro-inflammatory cytokines, namely of IL-6, at the start of the COVID-19 pandemic led to the assumption that these cytokines resulted from the excess stimulation of monocytes and macrophages by PAMPs of SARS-CoV-2. The described increase in the monocyte distribution width further corroborated this hypothesis [7].

Surprisingly, the addition of the spike S glycoprotein or of the entire viral particle of SARS-CoV-2 to the growth medium of monocytes does not stimulate high cytokine production. When cells are primed with one PRR ligand, the production of

IL-1β becomes marked. This is also accompanied by increased formation of caspase-1 [6], which is greater among patients who are receiving mechanical ventilation than among patients not on mechanical ventilation and which is also positively associated with the circulating levels of C-reactive protein (CRP) and IL-6. These findings suggest that early during the course of COVID-19 pneumonia, SARS-CoV-2 is able to act as a ligand for the NLRP3 inflammasome and this leads to over-production of caspase-1 and to the subsequent cleavage of pro-IL-1β to IL-1β [8]. The exaggerated production of IL-1β is also indirectly evidenced by the increased serum concentrations of ferritin in patients. High ferritin concentration is characteristic of the macrophage activation syndrome present in critically ill patients with sepsis [9] and is produced following the excess production of IL-1β by liver Kupffer cells. The hyperferritinemia of patients with COVID-19 led us to hypothesize that the macrophage activation syndrome may be a major element in the pathogenesis of the ARDS of COVID-19 caused by excess production of IL-1β.

Early during the course of the pandemic, we hypothesized that the progression of a patient with pneumonia from SARS-CoV-2 to ARDS was driven by two pathways: macrophage activation syndrome and complex immune dysregulation [10]. To classify patients, we used serum ferritin measured by an enzyme immunoassay and the expression of HLA-DR on circulating CD14-monocytes measured by flow cytometry. Macrophage activation syndrome was defined as serum ferritin >4420 ng/ml, as suggested in the past for sepsis [9]. Complex immune dysregulation was defined as an absolute number of HLA-DR molecules on CD14-monocytes of <5000 when ferritin was ≤4420 ng/ml. We compared patients with ARDS due to COVID-19 to patients with ARDS developing after bacterial CAP and found that contrary to bacterial CAP where most of the patients remain unclassified, all patients with COVID-19 ARDS could be classified into either macrophage activation syndrome or complex immune dysregulation. Macrophage activation syndrome was found in 25% of cases with COVID-19 ARDS and these patients also had increased hemophagocytosis scores (HScores). When monocytes with low HLA-DR expression in patients with complex immune dysregulation were stimulated for cytokine production, they retained their capacity to produce TNF-α and IL-6. The decrease in HLA-DR with maintenance of cytokine production is a unique immunological pattern that is different from the pattern of sepsis-induced immunosuppression in which monocytes defective for HLA-DR expression are unable to produce cytokines. This led us to name this new immune pattern, complex immune dysregulation. The decreased HLA-DR expression of complex immune dysregulation also drives the CD4-lymphopenia, CD8-lymphopenia, B-lymphopenia and hypoglobulinemia of ARDS COVID-19 [10].

Our findings have been corroborated by recent publications by other groups that described increased monocytes and decreased lymphocytes in the circulation of severe patients [11], increased monocytes in the alveolar space [12] and decreased CD4-lymphocytes in the alveoli [13]. These investigators described compartmentalized pro-inflammatory responses that were much more pronounced in the alveolar space than in the circulation. Inflammation in the alveoli is propagated over the time course of the disease as alveolar macrophages are replaced by monocytes migrating

from the circulation [12]. Using single-cell RNA sequencing, distinct clusters of monocyte activation were found in eight patients with mild COVID-19 and in 10 patients with severe COVID-19. Monocytes from patients with mild disease had aberrant expression of HLA-DR and remained potent for the production of antiviral cytokines. Monocytes from patients with severe disease had low HLA-DR expression and abnormal expression of alarmins [14].

2.4 From Pathogenesis to Treatment: Suggestion for an Individualized Approach

The dispersion within the ICU community of the idea that the pathogenesis of COVID-19 ARDS was driven by a storm of cytokines led to the clinical use of anakinra and tocilizumab for management. Anakinra is the recombinant human receptor antagonist of IL-1 and it blocks the action of both IL-1α and IL-1β. Tocilizumab blocks the receptor of IL-6. Mimicking the approach that was followed almost 30 years ago with sepsis, both agents were studied for *all* patients with critical COVID-19 without any selective approach.

A search in the PubMed database as of 15 February 2021, using the key-words "tocilizumab" and "COVID-19" and "clinical trials", retrieved 15 studies. We selected six of these studies because they reported clinical efficacy of tocilizumab in patients with severe or critical COVID-19 compared to controls. The six studies were either double-blind randomized clinical trials (RCTs), open-label RCTs or cohorts of patients using matched comparators [15–20]. Clinical benefit was reported in three of the studies. A summary of these studies is provided in Table 2.1. At the time this chapter was written, the results of the RECOVERY arm for patients receiving tocilizumab had not been published. According to the pre-print publication of the RECOVERY results [21], 2022 patients with COVID-19 receiving mechanical ventilation received one or two doses of tocilizumab and standard-of-care treatment, which included glucocorticoids; 2094 patients received standard-of-care treatment alone. The 28-day mortality rates were 29% and 33%, respectively (P = 0.007), showing a survival benefit from the addition of tocilizumab to glucocorticoids.

A search in the PubMed database as of 15 February 2021, using the key-words "anakinra" and "COVID-19", retrieved 150 studies. Six studies were selected because they reported on the clinical efficacy of anakinra using comparators [22–27]. Only one of these studies was an open-label RCT and the remaining were cohort studies with matched comparators. Clinical benefit was reported in five of the studies. A synopsis of these studies is provided in Table 2.2.

We believe that the selection of anakinra or tocilizumab as immunomodulatory treatment should be guided by biomarkers reflecting the mechanism of pathophysiology and the degree of severity. We have recently treated seven patients with ARDS COVID-19 and macrophage activation syndrome with intravenous

Table 2.1 Summary of the six published clinical trials of patients with COVID-19 treated with tocilizumab using parallel comparators

Reference	Design	Severity	Groups (n)	Primary endpoint	Efficacy (treatment vs. control)	Serious adverse events
[15]	RCT, open-label	Severe or critical	Standard-of-care (64) Standard-of-care + TCZ (65)	Death by day 15	3% vs. 17%	Study prematurely stopped for safety
[16]	RCT, double-blind	Hospitalized, without MV	Placebo (128) TCZ (249)	MV or death by day 28	19.4% vs. 12.0% (P = 0.04)	7.1% vs. 5.2%
[17]	RCT, double-blind	Hospitalized in need of oxygen	Standard-of-care (82) Standard-of-care + TCZ (161)	MV or death in time analysis	• Day 14: 10.0% vs. 9.9% • Day 28: 12.5% vs. 10.6%	• Neutropenia: 1.2% vs. 13.7% (P = 0.002) • Infections: 17.3% vs. 8.1% (P = 0.03)
[18]	RCT, open-label	Hospitalized, without MV	Usual care (67) Usual care + TCZ (63)	• Death, MV, NIV or HFO by day 14 • Death by day 28	• 35.8% vs. 23.8% (HR: 0.58; 95% CI: 0.30–1.11) • 25.3% vs. 26.9%	All reported: 43% vs. 32% (P = 0.210)
[19]	RCT, open-label	Hospitalized, without MV	Standard-of-care (66) Standard-of-care + TCZ (60)	Worsening into death or need for invasive ventilation	27.0% vs. 28.3%; prematurely stopped for futility	• All reported: 11.1% vs. 23.3% • Infections: 6.3% vs. 1.7%
[20]	Cohort using matched comparators	Patients with ≥2 of CRP >100 mg/l; ferritin >900 µg/l; D-dimer >1500 µg/l	Controls (86) Methylprednisolone for 5 days + TCZ if no response (86)	• Clinical improvement in WHO score by at least 2 points • Hospital mortality	• 51.2% vs. 74.4% (P = 0.0025) • 48.5% vs. 16.8% (P = 0.0004)	Bacterial infection: 8% vs. 9% (P = 0.787)

CRP C-reactive protein; *HFO* high-flow oxygen; *NIV* non-invasive ventilation; *MV* mechanical ventilation; *n* number of patients; *RCT* randomized clinical trial; *TCZ* tocilizumab; *vs.* versus; *WHO* World Health Organization

Table 2.2 Summary of the six published cohorts of patients with COVID-19 treated with anakinra using parallel comparators

Reference	Design	Severity	Groups (n)	Primary endpoint	Efficacy (treatment vs. controls)	Serious adverse events
[22]	Retrospective cohort with matching	Severe + CRP >100 mg/l or ferritin >900 ng/ml	Controls (56) ANA (56)	28-day survival	48.2% vs. 75.0% ($P = 0.007$)	Infections: 16.1% vs. 26.8% ($P = 0.260$)
[23]	RCT, open-label	Moderate or severe with no need for ICU	Usual care (57) ANA (59)	• Death or need of MV/NIV by day 4 • Survival without MV/NIV by day 14	• 38% vs. 36% • 54.5% vs. 51%	38% vs. 46% ($P = 0.450$)
[24]	Prospective, cohort	Severe + CRP >100 mg/l or ferritin >1000 ng/ml	Controls (55) Glucocorticoid + ANA (65)	28-day mortality	23% vs. 13.9% ($P = 0.004$)	Bloodstream infections: 7.3% vs. 13.8% ($P = 0.230$)
[25]	Retrospective cohort	Severe	Controls (24) ANA (45)	• Need for MV • In-hospital death	• 75% vs. 31% ($P < 0.0001$) • 46% vs. 29% ($P = 0.159$)	Bloodstream infections: 18% vs. 11% ($P = 0.461$)
[26]	Open-label, single arm with historical comparators	Severe	Controls (44) ANA (52)	MV and/or death	73% vs. 25% ($P < 0.0001$)	Increase of liver aminotransferases: 9% vs. 13%
[27]	Retrospective	Severe + CRP >100 mg/l or ferritin >900 ng/ml	Controls 16) ANA (29)	21-day mortality	44% vs. 10% ($P = 0.009$)	Bacteremia: 13% vs. 14%

ANA anakinra; *CRP* C-reactive protein; *ICU* intensive care unit; *NIV* non-invasive ventilation; *MV* mechanical ventilation; *n* number of patients; *RCT* randomized clinical trial; *vs.* versus

anakinra for 7 days; five patients improved by the end of treatment as demonstrated by increased baseline respiratory ratio and resolution of lung radiological opacities [28]. In the ESCAPE (Efficiency in management of organ dysfunction associated with infection by the novel SARS-Cov-2 virus through A PErsonalized immunotherapy approach) open-label trial, critically ill patients with COVID-19 received intravenous treatment with either anakinra or tocilizumab, based on their immune classification into macrophage activation syndrome or complex immune dysregulation. More precisely, 60 patients with macrophage activation syndrome or complex immune dysregulation and increased liver enzymes were treated with anakinra and 42 patients with complex immune dysregulation and normal liver enzymes were treated with tocilizumab. The primary study endpoint was either at least a 25% decrease in the baseline sequential organ failure assessment (SOFA) score or at least a 50% increase in the respiratory ratio by day 8. This endpoint was achieved in 58.3% of the patients treated with anakinra and 33.3% of the patients treated with tocilizumab ($P = 0.016$) [29].

The recent findings of monocytes highly expressing alarmins in severe COVID-19 [14] corroborates our hypothesis that progression into ARDS is a process of serial monocyte cell stimulation by alarmins produced by the bronchial tree upon invasion by SARS-CoV-2. These alarmins may be necessary for the priming of pro-IL-1β in monocytes and the subsequent cleavage to excess IL-1β through the SARS-CoV-2-stimulated NLRP3 inflammasome. We believe that concentrations of the biomarker soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/ml may indicate early which patients are likely to develop ARDS through exposure to alarmins. As a consequence, early treatment with anakinra driven by suPAR may block alarmins and prevent deterioration of these patients. We called this strategy SAVE (Suparguided Anakinra treatment for Validation of the risk and Early management of severe respiratory failure by COVID-19) and conducted a single-arm, open-label trial to demonstrate the safety and efficacy of anakinra administered as 100 mg once daily subcutaneously for 10 days to prevent progression into ARDS and need for mechanical ventilation (ClinicalTrials.gov Identifier: NCT04357366). As our comparators, we used parallel patients managed using standard-of-care in other departments of academic hospitals in whom the inclusion and exclusion criteria of the SAVE trial applied and who were propensity-score matched for age, comorbidities, admission severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] II, SOFA, pneumonia severity index, WHO scale) and for treatment with azithromycin, hydroxychloroquine and dexamethasone. The incidence of ARDS after 14 days was 22.3% (95% confidence intervals [CI] 16.0–30.2%) among anakinra-treated patients and 59.2% (95% CI 50.6–67.3%) in the control group [30]. Following advice from the Emergency Task Force for COVID-19 of the European Medicine Agency, the pivotal, confirmatory phase III RCT with the acronym SAVE-MORE has been designed which is currently ongoing in 40 study sites; 32 sites in Greece and 8 sites in Italy (ClinicalTrials.gov Identifier: NCT04680949).

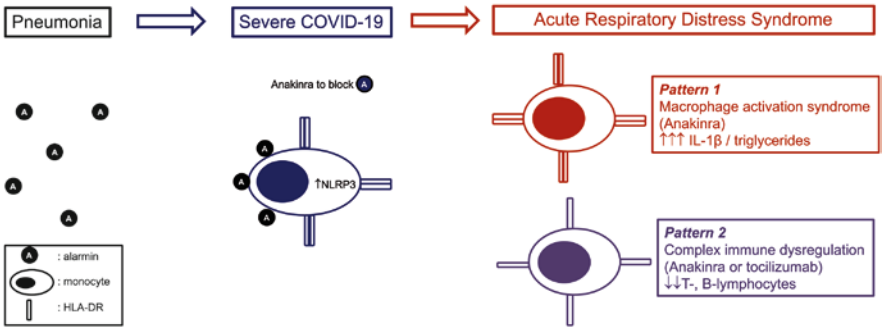

Fig. 2.1 Proposed mechanism of individualized pathogenesis in COVID-19
Pneumonia by SARS-CoV-2 stimulates the release of body alarmins. When severe disease emerges, alarmins stimulate monocytes and this is associated with activation of the NLRP3 inflammasome. The continuous alarmin stimulation leads to acute respiratory distress syndrome (ARDS) with the immune features either of macrophage activation syndrome or of complex immune dysregulation. Complex immune dysregulation is dominated by decreased expression of human leukocyte antigen (HLA)-DR on monocytes. Suggested immunomodulatory treatment directed on each target is given. *IL* interleukin

2.5 Conclusion

The above discussion suggests that there is heterogeneity in the pathogenesis of COVID-19 regarding the functional state of monocytes and their implications for the host. Different patterns seem to predominate upon transition from severe illness to ARDS and with different patterns of ARDS. The distinction of these different states of immune activation can only be done with the use of biomarkers and may help guide personalized immunotherapy (Fig. 2.1).

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3 Measuring Vitamin C in Critically Ill Patients: Clinical Importance and Practical Difficulties—Is It Time for a Surrogate Marker?

S. Rozemeijer, F. A. L. van der Horst, and A. M. E. de Man

3.1 Introduction

Interest in intravenous vitamin C administration has rapidly increased in the field of critical care medicine over recent years. The first studies investigating the effect of intravenous vitamin C in septic (shock) patients showed a decrease in organ dysfunction, vasopressor dependency, and even a reduction in mortality [1–3]. Within a short period of time, multiple trials in septic patients were conducted to confirm these promising findings, but results were not uniform [4–12]. The inconsistencies in effects on outcome may partially be explained by differences in study design [8], in particular the dosing regimens (timing, duration and dose) and choice of co-medication. For example, vitamin C administration has been investigated alone, or in combination with thiamine and/or hydrocortisone, sometimes with uncontrolled use of hydrocortisone in the control group. There is also considerable variety among septic patients as sepsis is a heterogeneous syndrome. Therefore, some subgroups of patients might benefit more than others from intravenous vitamin C therapy. A recently published meta-analysis on mortality performed subgroup analyses and found a beneficial effect of vitamin C on short-term mortality (<30 days). Additionally, survival was improved by a treatment duration of 3-4 days [13]. The results of vitamin C alone versus combination therapy were not different. A particular subgroup of interest is patients with vitamin C deficiency. None of the studies performed

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subgroup analyses on vitamin C deficient patients. This is unfortunate, but understandable, since the measurement of plasma vitamin C concentration is difficult.

In this chapter, we discuss the practical problems and pitfalls of measuring vitamin C and describe a novel potential surrogate marker that can estimate vitamin C status.

3.2 Rationale of Vitamin C Administration

Vitamin C has pleiotropic functions in the human body, including anti-oxidative, anti-inflammatory and immune-supporting effects. It serves as a cofactor in the biosynthesis of norepinephrine and vasopressin, increases catecholamine sensitivity, protects the microcirculation, and improves wound healing [14]. Therefore, low plasma concentrations may have untoward effects in the ICU population.

Decreased plasma vitamin C concentrations are common in critically ill patients with sepsis, trauma, hemorrhage, post-cardiac arrest and burns [15–20]. In septic shock patients, hypovitaminosis C (<23 μmol/l) and vitamin C deficiency (<11 μmol/l) rates are as high as 88% and 38%, respectively [15]. Causes of deficiency are decreased intake and absorption, and, most importantly, increased metabolic consumption and reduced recycling due to overwhelming oxidative stress [14]. This increase in oxidative stress plays a key role in the pathophysiology of systemic inflammation and ischemia/reperfusion injury [17–20]. Vitamin C protects against oxidative injury to lipids, proteins and DNA by donating its electrons. When the amount of oxidative stress is overwhelming, vitamin C is readily consumed, recycling becomes insufficient and deficiency develops. As a result, the body's protection against oxidative injury becomes inadequate.

This effect creates a strong rationale for vitamin C supplementation in vitamin C deficient patients with overwhelming oxidative stress [21]. Available literature has already addressed the importance of selecting vitamin C deficient patients by measuring baseline plasma vitamin C concentrations to create a clear difference in tissue and plasma vitamin C concentrations between control and treatment groups after supplementation [22]. In addition, measuring achieved plasma vitamin C concentrations could help to estimate optimal plasma concentrations. The direct radical scavenging effect of vitamin C increases with higher, supraphysiological concentrations [23]. Therefore, measuring vitamin C will provide more insight into the dose-concentration–clinical outcome relationship [22].

3.3 Plasma Vitamin C Measurement

The determination of plasma vitamin C, or ascorbic acid, necessitiates considerable logistical and analytical effort.

3.3.1 Drawing Blood

To assess the *in vivo* vitamin C status, it is crucial to avoid *ex vivo* artefacts, i.e., the oxidation of vitamin C (ascorbic acid) to dehydroascorbic acid (DHA) and

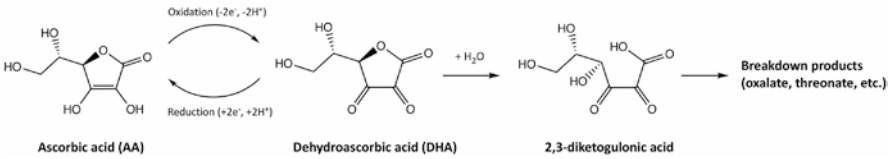

Fig. 3.1 Degradation of vitamin C (ascorbic acid). By donating two electrons, dehydroascorbic acid (DHA) is formed. After hydrolysis, DHA is irreversibly degraded to 2,3-diketogulonic acid, leading to further breakdown products of vitamin C. The half-life of DHA is only minutes due to hydrolytic ring rupture. DHA can be reversibly reduced (recycling) by glutathione or enzyme-dependent mechanisms

subsequent irreversible hydrolysis of DHA to 2,3-diketogulonic acid (Fig. 3.1). For this reason, samples have to be handled quickly after drawing blood to obtain a reliable vitamin C result. Several environmental factors have been shown to increase the rate of oxidation of vitamin C into DHA, of which the type of tube anticoagulant and surrounding temperature are the most prominent.

Vitamin C remains most stable in heparin during the first few hours [24, 25]. Ethylenediaminetetraacetic acid (EDTA) and serum whole blood are unstable at room temperature, with losses up to 15% and 20% within 2 h, respectively [24, 25]. In EDTA plasma, approximately 50% of vitamin C was lost at room temperature by 2 h, whereas in ice a significant decrease was observed from 4 h [25]. EDTA chelates of iron and copper are still redox active at physiological pH, and can still facilitate oxidation of ascorbate, particularly at room temperature. Therefore, samples should be handled quickly and kept cold during the whole period of handling and processing to reduce the loss of vitamin C after blood draw [25]. However, the use of ice water to reduce the temperature during transportation is difficult to manage. Nevertheless, although room temperature is a convenient logistical condition to transport samples, complying with the time constraints to process samples within less than 1 h to maintain sample integrity at room temperature is a considerable challenge for many hospitals.

3.3.2 Sample Treatment

The stability of vitamin C and DHA in plasma is significantly improved by acidification of the sample with, for example, metaphosphoric acid, trichloroacetic acid or perchloric acid, which also results in concomitant precipitation of the plasma proteins (deproteinizing). Acidification is commonly done after removal of the erythrocyte mass through centrifugation to ensure an efficient precipitation process of the remaining proteins. Deproteinization and stabilization can also be achieved by adding an organic modifier such as methanol, but these agents are less commonly used in the routine setting of hospital laboratories. The metal chelator EDTA or diethylene-triaminepentaacetic acid (DTPA) can be added at this point to further prevent *ex vivo* oxidation of vitamin C [25–27]. After acidification of the sample, this should be stored at low temperature, preferably at -80 °C. Stability has been demonstrated for both vitamin C and DHA at -80 °C for at least 5 years [28].

There is ongoing controversy in the literature about the generation of DHA in clinical samples [25]. Physiologically, the amount of DHA in plasma *in vivo* is <2% of that of total vitamin C (ascorbic acid + DHA) [22]. Higher amounts of DHA can be expected in critically ill patients because of overwhelming oxidative stress with reduced recycling of DHA [14, 29], and in patients receiving vitamin C at pharmacological doses [22]. However, one study showed that the amount of DHA was low to negligible in clinical samples. Only samples that contained hemolysis had appreciable amounts of DHA, which was explained by the *ex vivo* release of iron from hemoglobin during the acidification step in the sample pretreatment [25]. An *in vitro* study showed that an increase in DHA due to ferric ions only occurred in plasma acidified with trichloroacetic acid or perchloric acid, not with metaphosphoric acid. Nevertheless, plasma hemoglobin catalyzed the oxidation of vitamin C in all acidic solutions [30]. Therefore, hemolysis should be avoided. Metaphosphoric acid is the best stabilizing agent of choice, as ferric ions, which are more easily released from transferrin in acidic solutions, did not accelerate the oxidation of vitamin C into DHA when using metaphosphoric acid [30]. One study showed a higher proportion of total vitamin C as DHA in metaphosphoric acid-acidified clinical samples compared to controls [31], implying that *in vivo* generation of DHA may also occur.

In a pharmacokinetic study we performed in critically ill patients, 10 patients received 2 g vitamin C and 10 patients received 10 g vitamin C intravenously, as a twice daily bolus or continuously over 48 h [32]. In the entire population, the median total vitamin C concentration at baseline was 22.7 [interquartile range (IQR) 14.7–39.5] μmol/l, and the median plasma DHA was 2.5 [0.9–5.1] μmol/l which was 10% [95% confidence interval (CI) 6.1–14.0%] of the total vitamin C (unpublished data). Patients receiving a bolus dosing regimen achieved peak plasma concentrations 1 and 2 h after infusion compared to the continuous dosing regimen in which peak plasma concentrations were achieved 24 and 48 h after infusion. In Table 3.1, total vitamin C (ascorbic acid + DHA), DHA, and DHA as

Table 3.1 Total vitamin C and DHA in plasma samples of critically ill patients receiving vitamin C therapy. Data from [32]

Bolus dosing regimen	T = 1		T = 2	
	2 g (n = 5)	10 g (n = 5)	2 g (n = 5)	10 g (n = 5)
Total vitamin C, μmol/l	174 [163.8–254.8]	1101 [1067.5–1287.6]	136.1 [97.2–203.3]	733.1 [703.2–879.6]
DHA, μmol/l	12.7 [7.5–25.6]	100.3 [61.9–113.2]	8.7 [3.3–24.8]	63.6 [31.2–69.5]
DHA, % of Tot (95% CI)	**7.7 (2.8–12.7)**	**7.7 (4.1–11.2)**	**8.8 (0.8–16.8)**	**6.8 (3.6–10.0)**
Continuous dosing regimen	T = 24		T = 48	
	2 g (n = 5)	10 g (n = 5)	2 g (n = 5)	10 g (n = 5)
Total vitamin C, μmol/l	101.4 [15.8–134.9]	428.3 [352.8–612]	108.2 [42.0–174.1]	453.5 [318.9–1230.8]
DHA, μmol/l	11.7 [1.5–18.3]	31.9 [15.2–48.7]	8.4 [4.2–18.9]	18.6 [9.1–50.3]
DHA, % of Tot (95% CI)	**13.7 (5.3–22.0)**	**6.5 (3.1–9.9)**	**10.2 (2.5–17.9)**	**4.2 (0.1–8.3)**

Data are presented as median [IQR]

a percentage of total vitamin C are shown at these peak moments. The absolute amount of DHA increased in patients receiving intravenous vitamin C therapy, but the percentage DHA of the total vitamin C remained comparable to baseline. Thus, DHA amounts greater than 2% may be caused by increased oxidative stress with reduced recycling due to critical illness, by supraphysiological plasma concentrations, and by the *ex vivo* oxidation of vitamin C despite adequate sample handling and processing [32].

3.3.3 Analysis

There are two distinct approaches to quantitative determination of vitamin C in plasma samples: enzymatic and chromatographic.

3.3.3.1 Enzymatic Vitamin C Assays

There are several commercially available kits based on enzymatic conversion of vitamin C resulting in a signal that can be detected photospectrometrically. Normally, the enzyme ascorbate oxidase is used in this type of assay. The common method for these assays is the enzyme-linked immunosorbent assay (ELISA), which is well suited for batchwise processing of samples, but less convenient for immediate determination of values in a few samples.

There have been several attempts to adapt these enzyme-based assays to automated analyzers, but based on the methods reported in a European External Quality Assessment Scheme (Instand EQAS) enzyme-based assays are not routinely used within hospitals. If the clinical demand for immediate vitamin C determination increases, these enzyme-based assays could be used in point-of-care or centralized platforms because of their straightforward technical nature [33].

3.3.3.2 Chromatographic Vitamin C Assays

Quantitative ascorbic acid and DHA measurements are currently performed by high-performance liquid chromatography (HPLC) methods. HPLC methods are superior if multiple compounds with similar properties have to be analyzed or if there are many substances that might interfere with the quantification of a compound of interest.

After injection of the acidified sample into the HPLC instrument, the compounds are separated by passing through a column that differentially retains compounds based on their physical properties. As a result, at the end of the separation column, ascorbic acid and DHA can be detected selectively without interference of other compounds. Currently, there are two methods to detect ascorbic acid and DHA after passing through the column [34]. First, electrochemical detection, which uses the redox-properties of ascorbic acid and DHA, and second, ultraviolet (UV) detection, which is based on the UV absorption of these compounds. Despite the fact that both detection methods give identical results, UV detection is more widely used in the routine setting because of its relative technical simplicity [34]. Other detection techniques have been used, such as fluorescence detection after pre-column chemical

modification of ascorbic acid and DHA into a fluorescent compound, but are less common. Colorimetric/fluorometric methods may generate higher DHA concentrations due to the lack of specificity of the method [25].

3.3.3.3 Chromatographical Assessment of Ascorbic Acid, DHA and Total Vitamin C

To assess the total vitamin C status, both ascorbic acid and DHA have to be determined. Although in principle these compounds can be quantified simultaneously in a single HPLC run, this approach is not often used because there is no traditional need for the separate quantification of DHA to assess vitamin C deficiency in patients. Another reason is that it is technically much easier to determine only ascorbic acid instead of both ascorbic acid and DHA simultaneously. Therefore, medical laboratories have optimized their HPLC assays to optimally detect ascorbic acid and not the combination of ascorbic acid and DHA. A convenient way to solve this is to convert DHA into ascorbic acid in the sample prior to HPLC analysis. Any generated DHA that has not yet been hydrolyzed to the irreversible 2,3-diketogulonic acid can be reduced to ascorbic acid by adding a reducing agent, such as tris(2-carboxyethyl)phosphine hydrochloride (TCEP) or dithiothreitol (DTT). It is even possible to use pre-modified heparinized tubes with added DTT to immediately reduce any formed DHA [35]. In this manner, the total vitamin C concentration (ascorbic acid + DHA) in the sample can be measured. It has been shown that compared to its instability at room temperature, DHA is stable for several hours at 4 °C, for at least a year when stored non-acidified at -80 °C [25], and for at least 5 years when stored acidified at -80 °C [28]. Thus, if samples are appropriately handled and processed, it should be possible to recover any oxidized ascorbic acid with agents such as TCEP and DTT.

With respect to clinical utilization of the total vitamin C determination, response times have to be considered. If sample pre-treatment is limited to centrifugation and deproteination prior to analysis, this will take approximately 45 min, whereas the analytical procedure itself, including calculations and verification, will take an additional 30 min. So, under optimized and dedicated conditions, it will take over 1 h to obtain quantitative results.

Because of the analytical complexity, many clinical chemistry laboratories outsource the analysis of vitamin C to reference laboratories, making vitamin C determination unavailable for routine care. If they do supply this diagnostic service themselves, it is unlikely this it is available for immediate determinations. Moreover, the sample pre-treatment to safeguard correct determination of vitamin C is rather cumbersome and not easily accommodated into routine hospital logistics, especially not in intensive care and emergency departments. A point-of-care vitamin C measurement could therefore be useful, but such a measure is not available yet. A potential surrogate marker is the static oxidation-reduction potential (sORP), which can be measured quickly at the bedside.

3.4 Static Oxidation-Reduction Potential

The sORP is a marker that reflects the overall amount of oxidative stress in the blood, as measured by the RedoxSYS Diagnostic System (Aytu Bioscience, Englewood, CO, USA) [36]. It consists of a portable RedoxSYS analyzer and a disposable sensor strip (Fig. 3.2). This point-of-care device quickly measures the net balance between the total amount of known and unknown oxidants and reductants in a biological sample, e.g., whole blood, plasma, serum or urine. The sORP results are shown on a small display screen within 4 min after applying approximately 30 µl of the sample to the sensor. The total time between obtaining blood and getting a sORP test result is less than 20 min. More detailed technical information about the test is available elsewhere [36, 37]. One of the advantages of measuring sORP is that it does not rely on a single biomarker of oxidative stress, such as lipid peroxidation. It provides a complete picture of the total amount of oxidative stress in the sample.

sORP was strongly inversely associated with plasma vitamin C concentration in healthy volunteers and critically ill patients (Fig. 3.3) [17]. While sORP increased, plasma vitamin C concentration and total plasma antioxidant capacity decreased during the ICU stay. In patients who received vitamin C therapy, sORP decreased significantly. Furthermore, in previous *in vitro* studies, sORP also decreased after adding vitamin C [36–39]. This strong relationship is expected, because vitamin C is an excellent reducing agent [40]. Vitamin C is able to rapidly scavenge free radicals, and can be recycled afterwards. As a result, the total amount of oxidative stress will have a significant impact on the total amount of vitamin C and *vice versa*.

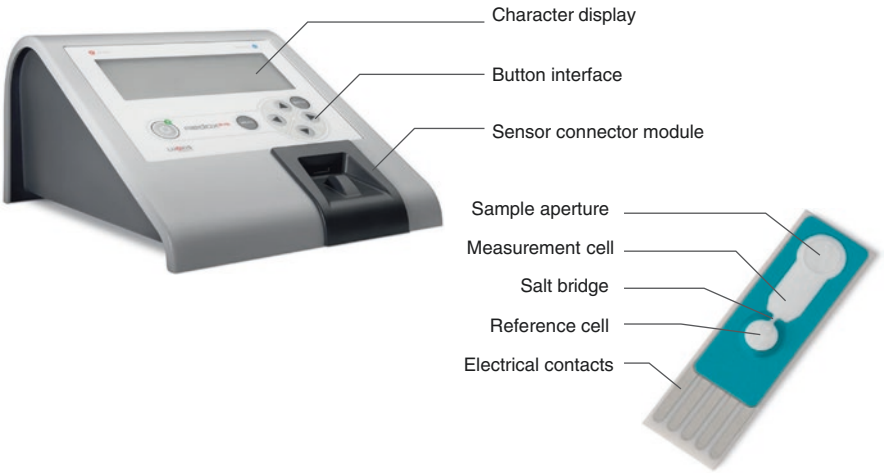

Fig. 3.2 Image of the portable RedoxSYS analyzer and disposable strip. From [36] with permission

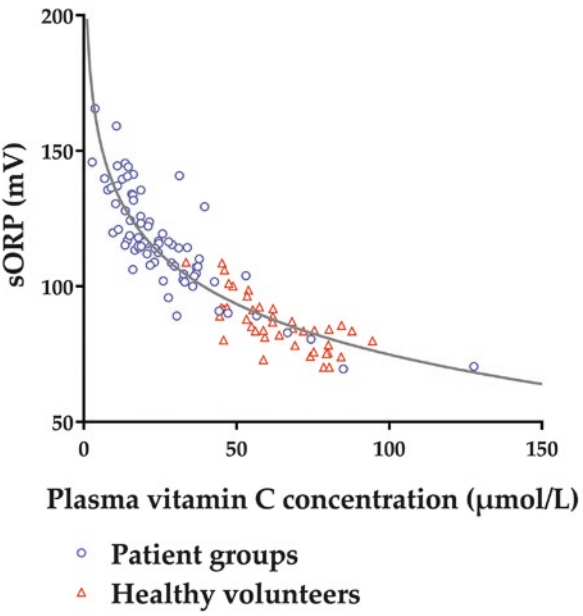

Fig. 3.3 Scatter plot showing the association between the static oxidation-reduction potential (sORP) and plasma vitamin C concentration. From [17] with permission

These results show that sORP has the potential for use to estimate plasma vitamin C concentrations and to screen for low vitamin C status. Preliminary data from our diagnostic accuracy study show that sORP estimates low plasma vitamin C concentrations accurately, whereas it is less precise at higher ranges. In contrast to the laborious handling, processing and analysis of samples to measure vitamin C, sORP is measured in non-acidified, non-reduced plasma within 20 min, directly after centrifugation and even after storage at -80 °C for many years [17]. When used at the bedside, it is recommended that the sORP measurement is performed as soon as possible after drawing blood and centrifugation to minimize the *ex vivo* oxidation of vitamin C. Notwithstanding the short handling time, the sORP measurement can become very useful in intensive care and emergency medicine.

3.5 Conclusion

This chapter underlines the potential clinical relevance of measuring plasma vitamin C concentrations in critically ill patients and the practical difficulties that go along with the currently available measurement. Multiple clinical studies have investigated the effects of intravenous vitamin C in critically ill patients, but results are not uniform. A possible explanation is the heterogeneity in study designs and included patients. Patients with vitamin C deficiency might benefit more from vitamin C therapy compared to non-deficient patients. Rapid plasma vitamin C measurement could identify this subgroup, but the ready oxidation of vitamin C *ex vivo* leads to several practical difficulties. Vitamin C measurement is therefore cumbersome, time consuming and not available for routine care. Proper blood handling,

processing and analysis to estimate plasma vitamin C concentrations are crucial to obtain reliable results. It is recommended to use heparin-anticoagulated tubes, to process the samples within less than 1 hour at low temperature, and to stabilize the sample through acidification and deproteinization with metaphosphoric acid. Oxidized vitamin C (DHA) can be recovered using a reducing agent such as DTT. The sORP can estimate vitamin C status at the bedside within 20 minutes using fresh unprocessed plasma samples. As this measurement is much more practical, especially for emergency medicine, sORP can serve as a surrogate marker for vitamin C allowing evaluation of the effectiveness of vitamin C therapy in the subgroup of patients with low vitamin C status.

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Controversies on Non-renal Extracorporeal Therapies in Critically Ill COVID-19 Patients

4

S. Romagnoli, Z. Ricci, and C. Ronco

4.1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes coronavirus disease 2019 (COVID-19). In adults and children, the clinical spectrum of the syndrome ranges from a completely asymptomatic response or mild upper respiratory tract infection to severe respiratory and multiorgan failure requiring intensive care support [1, 2]. The clinical course of COVID-19 has been conveniently divided into three main phases: (1) early infection phase; (2) pulmonary phase; (3) hyperinflammation phase [1] (Fig. 4.1). Phases 2 and 3 may overlap considerably and represent the period when multiorgan failure develops and progresses. Kidney involvement in patients with COVID-19 has been shown to be highly variable. Pathophysiological mechanisms involved in COVID-19 acute kidney injury (AKI) include cytokine and inflammatory mediated injury, organ crosstalk (lung-kidney and heart-kidney) and systemic effects [3]. In patients with COVID-19 respiratory failure, AKI affects over 20% of hospitalized patients and

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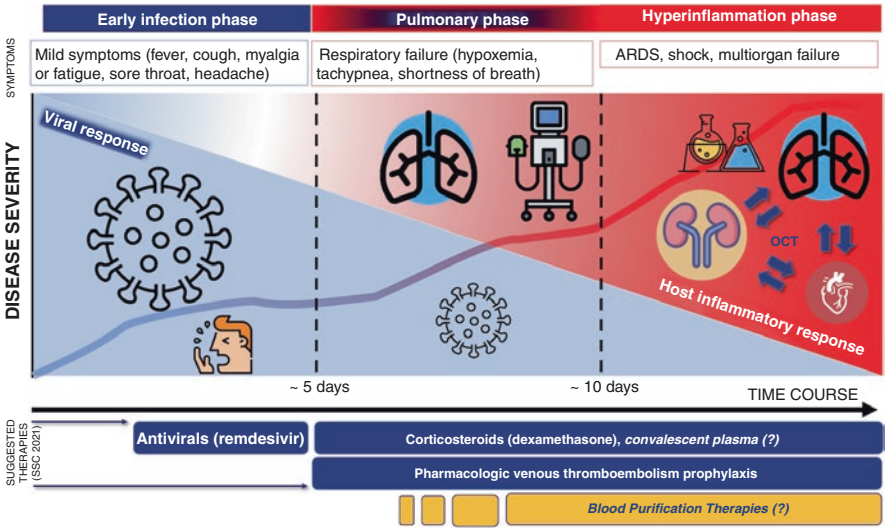

Fig. 4.1 COVID-19: The three different phases, symptoms and suggested therapies according to the 2021 Surviving Sepsis Campaign (SSC) Guidelines [13]. *OCT* organ crosstalk; *ARDS* acute respiratory distress syndrome

over 50% of patients in the intensive care unit (ICU) [4]. Renal replacement therapy (RRT) is frequently required to treat ICU patients with severe AKI. In particular, careful management of fluid balance and electrolyte disorders has been found to be beneficial in patients with severe AKI requiring RRT [5]. However, the unexpected catastrophic surge in ICU-bed occupation during the pandemic meant that some centers have complained about resource shortages, including lack of adequate numbers of RRT machines.

In this context, we tackle the controversial issue of using non-renal extracorporeal blood purification to influence the immune system (immunomodulation) in patients with COVID-19, focusing on the two sides of the debate: enthusiasts and opponents.

4.2 The Enthusiast

During the pulmonary/hyperinflammation phases of convalescence, hospitalized patients with COVID-19 can develop a syndrome characterized by systemic immune overactivation, described as “cytokine storm”, “hyperinflammatory syndrome” or “cytokine release syndrome”, which eventually develops into acute respiratory distress syndrome (ARDS) and can lead to multisystem organ failure [6–8]. Hypercytokinemia has been documented in many patients with COVID-19 since the first cases were reported [9]. Similar to sepsis and septic shock [10], COVID-19 patients with cytokine storm syndrome eventually develop organ dysfunction as a

result of inflammation, increased vascular permeability, capillary spillover, volume depletion, cardiomyopathy, endothelial injury, tissue edema, pleural effusions, intra-abdominal hypertension, arterial hypotension, hypovolemia, hypoperfusion, and multiple mechanisms of organ crosstalk (e.g., cardiorenal syndrome type 1, gut congestion, and polymicrobial translocation) [3, 10]. Therapeutic approaches to mitigate severe acute lung injury and multiorgan failure associated with SARS-CoV-2 infection have found their way into clinical practice although initially based on anecdotal observations and few clinical studies. Therapies aimed at suppressing hypercytokinemia with anti-inflammatory treatments directed at reducing interleukin-6 (IL-6) (e.g., tocilizumab, sarulimab, siltuximab), IL-1 (e.g., anakinra, canakinumab, rilonacept), or even tumor necrosis factor-α (TNF-α) (e.g., adalimumab) have been tested with variable but sometimes promising results [1, 7]. The theoretical basis of single cytokine inhibition has been expanded, with the hypothesis that potential benefits might be gained from other immunomodulators that could prove more efficacious by targeting different types of cytokines [6].

Corticosteroids, such as hydrocortisone and dexamethasone, have immunomodulatory and anti-inflammatory effects [11]. Corticosteroid administration in patients with ARDS and septic shock has been tested with unclear results [12]. However, in severe or critical COVID-19, both the recently updated Surviving Sepsis Campaign Guidelines [13] and the World Health Organization [14] strongly recommend using systemic corticosteroids.

As previously applied in sepsis, extracorporeal blood purification has also been proposed as an adjuvant therapy in hyperinflamed COVID-19 patients [15] based on the principles of removal of cytokines and other inflammatory mediators and prevention of organ damage [3]. Different approaches can be used for cytokine removal and immunomodulation, including therapeutic plasma exchange, hemoperfusion using sorbents, plasma adsorption on a resin after plasma separation from whole blood, continuous RRT (CRRT) with hollow fiber filters with adsorptive properties, and high-dose CRRT with medium cut-off or high cut-off membranes [5]. Use of extracorporeal blood purification for patients with severe COVID-19 and AKI has several aims: (1) removal of solutes such as creatinine and urea nitrogen; clearance of inflammatory mediators by convection, absorption, or therapeutic plasma exchange; reshaping of immune homeostasis; (2) regulation of body water and reduction of fluid overload; (3) correction of electrolyte and acid-base balance disorders; (4) physical reduction of hyperthermia [3].

CRRT is considered the predominant method for extracorporeal blood purification and is commonly used in COVID-19 patients with severe AKI, who are also septic and show signs of ARDS, with the aim of reducing inflammation through blood perfusion/plasma absorption. Recently, Villa and collaborators presented preliminary results on the clinical application of CRRT in critically ill patients with COVID-19 using a hemodiafilter characterized by enhanced cytokine adsorption properties (oXiris® membrane; Baxter, IL, USA). The authors observed a significant reduction in IL-6 concentrations during the treatment, correlated with a decreased Sequential Organ Failure Assessment (SOFA) score and improvement in organ function [8] (Fig. 4.2). These findings are consistent with observations from a recent

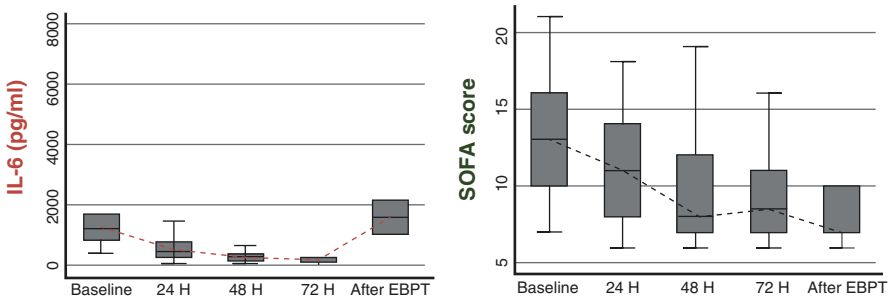

Fig. 4.2 Data on interleukin 6 (IL-6) and Sequential Organ Failure Assessment (SOFA) score over 72 h of extracorporeal blood purification treatment (EBPT) with the oXiris membrane [8]. The last time point indicates parameters after EBPT discontinuation

paper showing that IL-6 blood level concentrations decrease when extracorporeal blood purification with oXiris® was prescribed compared to extracorporeal blood purification with a polysulfone membrane [16]. Morath and collaborators reported five severely ill COVID-19 patients with elevated IL-6 levels, ARDS, severe AKI, and multiorgan failure treated with therapeutic plasma exchange [17]. During the treatment, the authors observed a striking reduction in the inflammatory markers C-reactive protein (CRP) (-47%) and IL-6 (-74%), as well as a significant reduction in ferritin (-49%), lactate dehydrogenase (LDH) (-41%), and D-dimer (-47%). A reduction in vasopressor infusion during the treatment was also reported and general clinical improvement was observed in three out of five patients. In a recent retrospective analysis of 280 COVID-19 patients with cytokine release syndrome, 71 subjects treated with therapeutic plasma exchange had more rapid cytokine release syndrome resolution and higher survival rates than 209 controls [18].

In summary, adoption of a rational extracorporeal blood purification program for patients with COVID-19 may imply the following progressive multi-step approach: first, assessment of whether patients with severe COVID-19 require blood purification (renal and non-renal indications, contraindications, cytokine levels, hyperinflammation, AKI severity, timing); second, prescription of extracorporeal blood purification therapy (CRRT with standard membrane and convective modality for cytokine clearance, CRRT with special membranes such as high cut-off membranes or those with adoptive surfaces, therapeutic plasma exchange); third, monitoring of the effects and adjustment of treatment parameters during blood purification (hemodynamic monitoring, respiratory parameters, cytokine levels over time, organ function).

4.3 The Opponent

According to the recently published consensus statement of the Acute Dialysis Quality Initiative (ADQI) group on the use of extracorporeal blood purification in patients with COVID-19 [4], “the potential biological rationale for using

(non-renal) extracorporeal blood purification in critically ill patients with COVID-19" is: (1) inflammatory cytokines, damage associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), including endotoxins and SARS-CoV-2 particles, potentially contribute to the development of multiple organ failure and mortality in critically ill patients with COVID-19; (2) as remarked earlier, extracorporeal blood purification has been shown to be effective in the removal of cytokines, DAMPs and PAMPs, including endotoxins and circulating viral particles. However, the following important issues should be considered. A recent rapid review [19] comparing cytokine elevations in different inflammatory syndromes provides some interesting information. The cytokine storm, i.e., a burst of inflammatory cytokines circulating in the bloodstream of COVID-19 critically ill patients, is profoundly lower than that reported in patients with ARDS unrelated to COVID-19, sepsis, and chimeric antigen receptor (CAR)-T cell-induced cytokine release syndrome. This difference is significant in terms of IL-6 elevations and ranges from 10 to 100-fold. This finding raises the possibility that alternative pathways of inflammation with respect to the traditional paradigm that is currently explored, may be at the basis of COVID-19-related organ dysfunction (e.g., vasculitis, direct viral injury and lymphodepletion, or viral-induced immunosuppression). It is currently unknown whether such alternative pathways are typical of specific COVID-19 phenotypes and whether they might still benefit from extracorporeal blood purification. Furthermore, no high-quality controlled trials in any cytokine release syndrome (i.e., sepsis, septic shock) have so far been able to show any efficacy in terms of cytokine clearance [20, 21] or clinical outcomes [22]. Typically, studies that report some beneficial results are uncontrolled reports or case series, which generally include highly selected patients and present preliminary results [23]. Consequently, even if a cytokine storm was an actual fundamental aspect of the pathophysiology of COVID-19 multiorgan failure, extracorporeal blood purification does not appear to have consistent clinical efficacy and might be difficult to recommend, especially in a period of resource constraint [24].

A further issue that is frequently addressed in the debate over treatment of sepsis-like syndromes concerns timing and monitoring of treatment. Some clinical conditions can be rationally treated with extracorporeal blood purification because the timing of disease onset is clear, namely when bloodstream mediators peak and blood purification is immediately required. To cite some examples, rhabdomyolysis [25], thrombocytopenia-associated multiorgan failure [26], multiple myeloma [27], and acute rejection after solid organ transplantation [28] all have in common the fundamental principles for extracorporeal blood purification. After the symptoms start, it is possible to detect a clear biomarker of the disease (e.g., myoglobin, von Willebrand factor and ADAMTS-13, light chains, donor specific antibodies) that is also strictly related to disease pathophysiology. The same biomarker can be repeatedly dosed, and the efficacy of treatment followed up not only through clinical observations (e.g., initial symptom relief) but also through objective laboratory evaluation. Under these circumstances, extracorporeal blood purification is goal-directed and timing for initiation and end of treatment is evident and clear. Generally speaking, patients with conditions such as those mentioned above do not present

with a cascade of targets or multiple mediators that need to be modulated by extracorporeal blood purification but follow a single pathway. Nobody would ever treat diabetic ketoacidosis with insulin just by assessing a patient's symptoms and without monitoring glycemia.

A final aspect that needs to be addressed involves treatment indication according to severity of disease. Similarly to critically ill patients with refractory multiorgan failure, patients with COVID-19 may occasionally present with very severe clinical conditions for which, paradoxically, extreme therapeutic measures may appear acceptable to give patients a chance of survival. While ethical issues are beyond the scope of this review, it is nonetheless important to note that in times of COVID-19, economical, organizational and staff safety issues may significantly limit indications for aggressive and invasive treatments in patients who are very unlikely to recover. It appears that extracorporeal blood purification may be indicated in the early phases of COVID-19 critical illness, before multiple organ failure is established. In such phases, the risk/benefit ratio of applying invasive treatments with uncertain efficacy remains open to debate.

4.4 The ADQI Workgroup: Recommendations from the COVID-19-Associated Acute Kidney Injury Consensus Report

According to experts, a better understanding of the role of systemic inflammation and immune dysfunction in the development of COVID-19-associated AKI and of the role of innate and adaptive immune dysfunction in patients with AKI should represent research priorities. As a general criterion for the treatment of patients with COVID-19-associated AKI, standards of care should follow the Kidney Disease Improving Global Outcomes 2012 guidelines [29]. Nevertheless, a potential biological rationale for using (non-renal) extracorporeal blood purification in critically ill patients with COVID-19 does exist. Extracorporeal blood purification can be considered as an adjuvant therapy for critically ill patients with COVID-19. However, cytokine activation in COVID-19 may not be as robust as in other viral pandemics (e.g., severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) or comparable to that described in CAR-T therapy or bacterial sepsis [19]. Thus, careful patient selection is required if extracorporeal blood purification is to be used and the benefits and adverse effects in patients with COVID-19 have not been formally studied.

Different extracorporeal blood purification techniques are currently available to clinicians. Hemoperfusion techniques can remove potential inflammatory target molecules, DAMPs, and PAMPs, including SARS-CoV-2 particles; therapeutic plasma exchange can remove inflammatory mediators and proteins associated with hypercoagulability; CRRT with surface-modified AN69 or polymethylmethacrylate (PMMA) membranes can remove target molecules by adsorption, whereas CRRT with medium cut-off or high cut-off membranes can remove target molecules by

diffusion or convection [4]. However, indications, timing, and recommendations on the use of each methodology cannot be currently provided.

4.5 Conclusion

As a general rule, extracorporeal blood purification techniques may be beneficial for some patients with COVID-19 and have no effect or even be injurious to others. Cytokine removal strategies should be reserved for COVID-19 patients with evidence of high circulating cytokines, high SOFA scores, clinical symptoms of hemodynamic instability requiring vasopressors, and multiorgan dysfunction. While waiting for the vaccines to generate immunity and definitively eradicate the pandemic, it seems rational to adopt immunomodulatory strategies, including extracorporeal blood purification therapies, to help critically ill patients with COVID-19, for whom there are currently limited treatment options. Discussions on a case-by-case basis should be held at the bedside by skilled healthcare providers and extracorporeal blood purification treatments never administered as part of routine care.

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Secondary Infections in Critically Ill Patients with COVID-19

5

G. Grasselli, E. Cattaneo, and G. Florio

5.1 Introduction

Since December 2019, when the first case of human transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan (China), more than a hundred million confirmed cases of coronavirus disease 2019 (COVID-19) have been described worldwide, and the pandemic declared on March 11, 2020 by the World Health Organization is still ongoing.

The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic disease to severe disease requiring hospitalization and admission to the intensive care unit (ICU) [1]. Recent multicenter studies showed that 5–32% of hospitalized patients with COVID-19 needed ICU admission [2–5], mainly for acute respiratory distress syndrome (ARDS) requiring endotracheal intubation and invasive mechanical ventilation [2–4, 6, 7]. According to the available published data, the mortality of critically ill patients with COVID-19 ranges from 16 to 78% [3, 6–8].

For a number of reasons, patients with COVID-19 admitted to the ICU are at high risk of developing infectious complications during their ICU stay. First, they frequently develop multiple organ failure with need for vasopressors, renal replacement therapy (RRT) and, in some cases, extracorporeal membrane oxygenation support. The duration of mechanical ventilation and the ICU lengths of stay of these patients are therefore usually prolonged (up to 19 days for mechanical ventilation and up to 49 days for ICU length of stay [5, 9]). Second, COVID-19 *per se* is associated with significant dysfunction of the patient's immune system. Multiple studies have shown the involvement of both innate and acquired immunity as a response to

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SARS-CoV-2 infection. Preliminary Chinese studies detected a reduction in both CD4+ T and CD8+ T lymphocyte counts, an increase in neutrophils and a reduction in interferon gamma (IFN-γ) serum concentrations [10, 11]. Further studies confirmed these findings and showed a cytokine pattern characterized by excess pro-inflammatory molecules (cytokine storm [12]), inhibition of natural killer cells (NK and NKT) and cytotoxic lymphocytes, and morphological and phenotypical alterations of monocytes [13–15]. Third, after the publication of the results of the RECOVERY trial [16], treatment with systemic corticosteroids has become standard of care in all patients requiring supplemental oxygen. In addition, a number of drugs aimed at blunting the immune system response to the viral infection (for example cytokine inhibitors [tocilizumab, anakinra, sarilumab] or complement inhibitors [eculizumab]) are frequently administered to these patients and several trials are ongoing to assess their efficacy. Finally, secondary bacterial and fungal infections as a complication of viral respiratory diseases have been described during previous pandemics (2002 severe acute respiratory syndrome [SARS] [17], 2009 swine influenza pandemic [18], and 2012 Middle East respiratory syndrome [MERS] [19]) and some studies have highlighted their role in increasing the severity of the viral pneumonia [18]

A recent review of the literature showed that the incidence of co-infections (i.e., infections detected at admission) in patients with COVID-19 is less than in previous pandemics [20]. Data on secondary infections (i.e., infections acquired during the course of ICU stay) are scarce. The aim of the present chapter is to summarize the available evidence on the epidemiology, risk factors, impact on outcome and principles of treatment of secondary infections in critically ill patients with COVID-19.

5.2 Epidemiology and Risk Factors

5.2.1 Bacterial Infections

In patients with H1N1 influenza, the incidence of bacterial infections complicating the course of the viral pneumonia is 25–50% and they are associated with increased duration of mechanical ventilation, prolonged ICU stay and increased mortality [21]. For these reasons, early diagnosis and adequate management are mandatory in critically ill patients. As mentioned above, limited data are available on secondary bacterial infections in patients hospitalized for SARS-CoV-2 infection. A recent review reports a low incidence of bacterial or fungal infections in hospitalized COVID-19 patients, ranging from 6% to 15%, but most of the cited studies were conducted in China and included patients admitted mainly to ordinary wards and not to the ICU; hence, these data cannot be extrapolated to the population of critically ill patients admitted to the ICU in western countries.

The most common bacterial complication of COVID-19 is ventilator-associated lower respiratory tract infection (VA-LRTI), which includes ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis. The mechanism underlying bacterial co-infection in viral pneumonia is

damage to the ciliated cells, which leads to impaired mucociliary clearance and increased adhesion of bacteria to mucins, resulting in enhanced bacterial colonization of the airways [22]. In addition to these mechanisms, other risk factors for bacterial secondary infections typical of ICU patients are the presence of ARDS and the prolonged duration of mechanical ventilation [23]. A recent multicenter European study described the cumulative incidence of VA-LRTI in patients with COVID-19 admitted to the ICU compared to patients with other viral and non-viral pneumonias. The overall incidence of VA-LRTI was 50%, significantly higher than in the other two groups, despite the fact that patients with SARS-CoV-2 pneumonia had lower severity scores (Simplified Acute Physiology Score [SAPS II] and Sequential Organ Failure Assessment [SOFA] score) at ICU admission and fewer comorbidities [24]. This finding has been confirmed by two other studies. The first evaluated the incidence of VAP in critically ill COVID-19 patients in the UK and showed that COVID-19 patients were significantly more likely to develop VAP than patients without COVID-19 [25]. The second study was a multicenter, observational trial conducted in several European countries and described the clinical characteristics of 4244 critically ill COVID-19 patients; the incidence of VAP in intubated patients was 58% [9]. As previously mentioned, prolonged duration of mechanical ventilation and a high incidence of ARDS, both typical of COVID-19, together with the administration of drugs affecting immune system function (in the multicenter European study 37.3% of the patients were treated with steroids) certainly contribute to this increased risk of secondary respiratory infections.

The most common bacteria involved in VA-LRTI in COVID-19 patients are Gram-negative bacilli, mainly *Pseudomonas aeruginosa*, *Enterobacter* spp. and *Escherichia coli*, followed by Gram-positive cocci, mainly *Staphylococcus aureus* [24]. Notably, some smaller reports describe different microorganism prevalence. For example, Sharifipour et al. [26] reported that among 19 ICU patients, secondary respiratory infections were caused by *Acinetobacter baumannii* in 90% of the cases and *S. aureus* in the remaining 10%. However, the findings of these small, single-center case series are clearly influenced by the local epidemiology and are not representative of the general population of COVID-19 ICU patients.

The second most common secondary infections in critically ill COVID-19 patients are bloodstream infections (BSI). An Italian report estimated a cumulative risk of developing an episode of BSI of nearly 25% after 15 days of ICU stay and higher than 50% after 30 days. In multivariable analysis, anti-inflammatory treatment with tocilizumab or with methylprednisolone was independently associated with the development of BSI [27]. Buetti et al. [28] conducted a case control study comparing BSIs in 235 COVID-19 and 235 non-COVID-19 patients admitted to the ICU in France and described incidences of 14.9% and 3.4%, respectively. In patients infected with SARS-CoV-2, BSIs occurred a median of 12 days after ICU admission. The most common microorganisms responsible for BSIs were coagulase-negative staphylococci (36%). The authors also observed a significant increase in the risk of BSIs in COVID-19 patients treated with tocilizumab or anakinra [28] (Table 5.1).

Table 5.1 Characteristics and main findings of the studies describing secondary infections in patients with COVID-19

Study [ref]	Sample size	Setting	Incidence of secondary infections, %	Type and site of infection (%)	Microorganisms isolated (%)
Giacobbe et al. [27]	78	ICU	40	BSI (100)	Coag- neg staphylococci (24) *E. faecalis* (18) *S. aureus* (13)
He et al. [46]	918	Hospital	7	Pneumonia (32) BSI (25) UTI (22)	Coag- staphylococci (28) *A. baumannii* (21) *P. aeruginosa* (14)
Sharifipour et al. [26]	19	ICU	100[a]	VAP (100)	*A. baumannii* (90) *S. aureus* (10)
Fu et al. [47]	36	ICU	14	VAP (100)	*S. mantophilia* (40)
Li et al. [48]	1495	Hospital	7	Pneumonia (86) BSI (34) UTI (8)	*A. baumannii* (36) *K. pneumoniae* (31) *S. mantophilia* (6)
Rouzé et al. [24]	568	ICU	51	VAP (71) VAT (29)	*P. aeruginosa* (22) *Enterobacter* spp. (18) *S. aureus* (12)
Buetti et al. [28]	321	ICU	15	BSI	Coag-staphylococci (36) *Enterobacterales* (13) *P. aeruginosa* (13)
Dudoignon et al. [49]	54	ICU	37	VAP (75)	*P. aeruginosa* (33) *Enterobacteriaceae* (33) *S. aureus* (20)
Ripa et al. [50]	731	Hospital	9	BSI (85) LRTI (32)	Coag-staphylococci 70% of BSI *A. baumannii* 30% of LRTI

BSI bloodstream infection, *UTI* urinary tract infection, *VAP* ventilator associated pneumonia, *VAT* ventilator associated tracheobronchitis, *LRTI* lower respiratory tract infection
[a]Only patients who developed secondary infections were included in this study

5.2.2 Fungal Infections

It is well known that viral pneumonia caused by influenza virus can facilitate the development of invasive pulmonary aspergillosis, especially in patients presenting with ARDS, with a marked impact on the duration of hospitalization and mortality [29]. The limited data available in critically ill patients with COVID-19 seem to confirm the association between SARS-CoV-2 infection and development of invasive aspergillosis and some authors have suggested the existence of a clinical entity called COVID-19-associated pulmonary aspergillosis [30]. Risk factors for invasive pulmonary aspergillosis in COVID-19 patients are the direct lung damage due to the

viral infection, use of corticosteroids, ARDS at presentation, treatment with broad-spectrum antibiotics, and comorbidities [30]. The initial reports from China were very heterogeneous, describing an incidence of infection with *Aspergillus* ranging from 3% up to 23% among critically ill patients with COVID-19 [31, 32]. This variability could be due to the lack of precise definition criteria and of a standardized diagnostic algorithm for invasive pulmonary aspergillosis, possibly resulting in the underestimation of the real incidence of invasive pulmonary aspergillosis in some studies, while in others the misinterpretation of colonization may have led to an overestimation of the risk. European studies report a high rate (from 20% to 35%) of invasive pulmonary aspergillosis among critical patients with ARDS due to COVID-19, with a high mortality rate, ranging from 45% to 67% [33, 34]. The most common *Aspergillus* spp. responsible for invasive pulmonary aspergillosis in these patients seems to be *Aspergillus fumigatus* (isolated in 90% of the cultures), followed by *Aspergillus flavus* [30].

5.3 Diagnosis of Secondary Infections

5.3.1 Bacterial Infections

As previously mentioned, the most common secondary infections in critically ill patients with COVID-19 are VAP and BSIs. The diagnosis is made when the patient shows clinical symptoms and signs of infection and a new pathogen is detected in a biological specimen.

VAP is defined as the association of persistent pulmonary infiltrates on radiological imaging and positive microbiological cultures from a lower respiratory tract specimen with clinical suspicion of new onset pneumonia in a patient that has received at least 48 h of invasive mechanical ventilation [35–37]. Scores, such as the Clinical Pulmonary Infection Score (CPIS) [38] (based on six variables: temperature, blood leukocytes, aspect of tracheal secretions, oxygenation, radiographic infiltrates, and Gram stain on tracheal aspirates), have been developed to help clinicians diagnose VAP, but the most recent guidelines [36, 39] highlight the role of clinical signs of infection (i.e., new onset of fever, purulent secretion from the airway, leukocytosis or leukopenia, worsening of blood oxygenation, increased need for inotropic and vasoactive agents) rather than the use of a score. Imaging techniques, such as chest X-ray [37], chest computed tomography, and, more recently, lung ultrasound [40, 41], tailored to detect new pulmonary infiltrates, and markers of inflammation (e.g., C-reactive protein, procalcitonin) can support the clinical diagnosis.

Adequate and specific antibiotic therapy, however, requires a microbiological diagnosis based on culture examinations and tests (e.g., Gram stain, biomarkers, rapid diagnostic assay, polymerase chain reaction [PCR]) to enable identification of the involved bacteria. Samples can be obtained from the distal airway in a more invasive way using bronchoscopy (i.e., bronchoalveolar lavage [BAL], protected specimen brush [PSB]), in a ‘less-invasive’ way (i.e., blind mini-BAL, blind PSB)

or from the proximal airway (endotracheal aspirate); a recent meta-analysis [42] comparing cultures from proximal and distal airways showed no differences in patient outcome, but it should be remembered that sampling from the distal airway may be associated with an increased risk for the patient (i.e., hypoxemia, bleeding). Furthermore, invasive procedures are associated with potential exposure to aerosolized viral particles, which represents a risk for healthcare personnel.

BSI in critically ill patients is defined as the onset of signs and symptoms of infection within 24 h of a positive blood culture. Blood cultures and identification of specific bacteria represent the gold standard for the diagnosis, but a single positive culture is not suggestive of infection when a typical human skin contaminant is involved; in this case, the diagnosis requires at least two positive blood cultures for the microorganism within 48 h.

5.3.2 Fungal Infections

COVID-19-associated pulmonary aspergillosis should be suspected in all patients with COVID-19 who present with refractory fever lasting more than 3 days after an initial 48-h period of defervescence (following appropriate antibiotic therapy), worsening of gas exchange, onset of hemoptysis, or new pleural rubs [29]. A complete and accurate algorithm for diagnosing COVID-19-associated pulmonary aspergillosis is still lacking but it would be useful to search for *Aspergillus* spp. in respiratory samples (e.g., bronchoalveolar lavage, tracheal aspirate) and to use serologic biomarkers such as galactomannan on respiratory samples and serum. Other tests that may help in diagnosing COVID-19-associated pulmonary aspergillosis are aspergillus PCR and serum (1→3)-β-D-glucan.

5.4 Principles of Treatment

5.4.1 Bacterial Infections

The initial Surviving Sepsis Campaign guidelines for the management of critically ill patients with COVID-19 suggested an empiric antibacterial agent in all mechanically ventilated patients [43]. However, subsequent data have shown that, at ICU admission, patients infected with SARS-CoV-2 seldom have concomitant bacterial infection. For this reason, and because of the high incidence of infectious complications caused by multidrug-resistant (MDR) germs, most experts agree that prophylactic administration of an empiric antibiotic therapy in the absence of clear signs of a co-infection or of a secondary infection should be discouraged. Indeed, it has been demonstrated that inappropriate initial antimicrobial treatment is associated with increased mortality in VAP and with increased bacterial resistance [44]. In addition, in critically ill patients, different doses from those usually recommended may be used, either because normal doses may not achieve effective drug concentrations at the target site or because they can be associated with adverse reactions due to toxic

concentrations. For these reasons, therapeutic drug monitoring of plasma trough levels is recommended.

Available guidelines [35, 36] recommend that empirical therapy should be started as soon as VAP is clinically suspected. The empirical therapy should be modified based on the results of the culture tests. The choice of the empirical treatment is based mainly on the patient's risk factors for MDR pathogens, and on the local pattern of antimicrobial susceptibility. Among the risk factors for MDR is ARDS prior to VAP and hospital stay >5 days, both very likely to be present in COVID-19 patients. In this case, the empirical treatment of choice should be a broad-spectrum anti-pseudomonas β-lactam plus a non-β-lactam antipseudomonal agent (e.g., piperacillin-tazobactam plus amikacin). When choosing the antibiotic, it is important to consider the local pattern of susceptibility, and the results of microbiological surveillance for patient colonization. Empiric coverage of methicillin-resistant *S. aureus* (MRSA) should be considered in units where the incidence of VAP is higher than 20% [35]. Once culture and susceptibility results are obtained, the main goal should be to remove unnecessary antibiotics (especially anti-MRSA and carbapenems) and use a narrow spectrum agent if possible.

5.4.2 Fungal Infections

Patients with invasive aspergillosis often have many comorbidities that, together with the underlying disease, can affect the pharmacokinetics of antifungal medications. As reported earlier for antibacterial agents, even for antimycotics the risk of not reaching the target concentration at the infection site or of toxicity exists, especially in critically ill patients, thus therapeutic drug monitoring is recommended. Given the high mortality rate of patients with critical COVID-19 and concomitant invasive pulmonary aspergillosis, treatment should be started as soon as the diagnosis of invasive pulmonary aspergillosis is made.

Voriconazole is recommended as first line treatment in invasive pulmonary aspergillosis, with a target plasma trough concentration of 2–6 mg/l. Repeated monitoring is indicated until steady-state level is confirmed or if there is a change in the patient's clinical condition or suspected toxicity. In patients with liver dysfunction or when voriconazole cannot be administered, liposomal amphotericin B is appropriate. In patients who do not respond or do not tolerate initial therapy an echinocandin alone or in combination with voriconazole is indicated [45].

5.5 Conclusion

Secondary infections, frequently caused by MDR germs, are common in critically ill patients with COVID-19 admitted to the ICU, as a result of a number of favoring conditions. Early and accurate diagnosis and institution of adequate antimicrobial treatment are essential to improve patient outcome. Preliminary published data indicate that secondary infections are associated with increased duration of mechanical

ventilation and of ICU stay, and that they may have an impact on patient survival. However, data from large, well-designed studies are needed to confirm these findings and to improve our knowledge of the epidemiology and treatment of infections complicating the clinical course of COVID-19.

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Part II

Shock

Heart Dysfunction in Septic Patients: From Physiology to Echocardiographic Patterns

6

A. Messina, F. Villa, and M. Cecconi

6.1 Introduction

Septic shock represents the vast majority of cases of shock in intensive care unit (ICU) patients and is a life-threatening condition needing prompt recognition and treatment to provide adequate oxygen utilization to the cells [1, 2]. Initial characterization of sepsis-associated cardiovascular dysfunction was based on clinical patterns identified in patients with septic shock by physical examination [3]. From the very first clinical description of "warm" and "cold" shock, to the introduction of the pulmonary artery catheter and ability to measure cardiac output at the bedside, and, finally, to the use of less invasive tools and echocardiography, the histories of septic shock and cardiac dysfunction have been closely linked together.

Septic shock progression is associated with mitochondrial dysfunction and dysregulated cell-signaling pathways, which lead to multiple organ damage and failure and, eventually, to untreatable hemodynamic instability and death [4]. The heart is one of the organs most frequently failing in sepsis; however, depending on the definition used, the prevalence of sepsis-induced cardiac dysfunction may vary between 10% and 70% [5]. The sepsis-induced dysregulated inflammatory response has been directly linked to cardiomyocyte dysfunction, leading to a broad spectrum of cardiomyopathies, including ventricular impairment during systole or diastole, and inadequate cardiac output, oxygen delivery, or primary myocardial cellular injury.

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Hence, in patients with septic shock, echocardiography can play a pivotal role, identifying most of the clinical cardiac patterns related to acute systolic dysfunction and chamber dilation using basic level 2D and M-mode echocardiography (Table 6.1). A more comprehensive diagnosis can be achieved with advanced levels

Table 6.1 Main echocardiographic features in critically ill patients with septic shock

Assessment	Measurements and clinical implications	Echocardiographic findings
LV systolic dysfunction • *LVEF*	Reduced LVEF, a measure commonly used to assess LV systolic function, is a common and often early feature of septic cardiomyopathy and is dependent on the timing of assessment in relation to the septic insult. LVEF is a dependent variable based on the complex physiological interaction between preload and afterload conditions. The prognostic value of LVEF in septic patients has been investigated by several recent meta-analyses showing no association with mortality [6–9].	• LVEF normal or even increased, no LV enlargement • Normal mitral inflow (no increased LV filling pressure) • LVEF depression associated with LV enlargement • LVEF changes are often transient • Stroke volume normal or low
LV systolic dysfunction • *TDI*	TDI assessment of LV systolic function with s′ wave is performed at the mitral annulus and is considered a useful index of longitudinal LV systolic function, potentially offering advantages over LVEF since it may be less affected by loading conditions [10]. A recent meta-analysis regarding the use of s′ wave velocity in 13 ICU studies enrolling septic patients found no significant difference between survivors and non-survivors.	• TDI assessment of LV systolic function via s′ measurement (reference values in adult non-ICU patients 8-10 cm/sec, according to the sampling region, being slower at septal level) [11]
LV systolic dysfunction • *Other*	STE is based on a semi-automated algorithm that tracks the displacement of acoustic "speckles" in the myocardium, the change in length of myocardial segments is measured. Compared to LVEF, STE is affected to a much lesser degree by changes in ventricular loading conditions, myocardial compliance, and afterload properties because it measures myocardial deformation directly. Global longitudinal strain (GLS) is obtained, averaging the longitudinal strain for all 17 myocardial segments. This technique requires significant expertise and is challenging during ICU conditions; however, a study reported the overall feasibility of performing STE analysis in patients with severe sepsis and septic shock ranging between 63% and 98% [12].	• Impaired GLS in systole (- values) and/or diastole (+ values) • LV GLS >-13% associated with mortality, independent of LVEF changes [13] • Subclinical LV systolic dysfunction, defined using the cutoff value of GLS ≥-15%, was detected in 50 patients with septic shock (55.6%) and in 6 patients in the control group (16.2%) ($P < 0.05$) [14]

Table 6.1 (continued)

Assessment	Measurements and clinical implications	Echocardiographic findings
LV diastolic dysfunction	Unmasked by volume expansion and related to fluid management in sepsis, LV diastolic dysfunction may exist without concurrent systolic dysfunction. A recent meta-analysis reported an incidence ranging from 20 to 57.1%, with three included studies reporting an incidence of 50% or higher [7]. The association between LV diastolic dysfunction and mortality has been confirmed by two meta-analyses [7, 15].	• Clinical signs of congestion • e′ (TDI) <8–10 cm/s, E/e′ >12 • (increase LV filling pressure in case of fluid overload)
RV dysfunction	RV dysfunction in sepsis is multifactorial and can be related to direct myocardial depression or preload change or increase in RV afterload due to hypoxemia, hypercapnia, and mechanical ventilation for associated acute respiratory failure. A recent meta-analysis of 10 studies, including 1373 patients, reported RV dysfunction in 477 (34.7%). RV dysfunction was associated with higher short- and long-term mortality [16].	• Elevated central venous pressure • Decreased cardiac output • RV dilatation, TAPSE • RV myocardial peak systolic velocities (Sm, cm/s) and myocardial performance index
Cardiovascular clusters	Using a more extensive and multivariable approach—"clustering" approach, characterization of cardiovascular septic phenotypes without any prior cardiac dysfunction criteria—including echocardiographic and clinical features.	The first study identified five different clusters [17]: • Well-resuscitated patients (16.9%) • LV systolic dysfunction (17.7%) • Hyperkinetic profile (23.3%) • RV failure (22.5%) • Sustained hypovolemia (19.4%)

ICU intensive care unit, *LVEF* left ventricular ejection fraction, *TDI* tissue Doppler imaging, *STE* speckle tracking echocardiography, *GLS* global longitudinal strain, *TAPSE* tricuspid annular plane systolic excursion, *s′* peak systolic velocity measured at the mitral annulus, *e′* maximal velocity of the mitral annulus at the early phase of diastole, *E/e′* ratio of the maximal velocities during the early stage of diastole of mitral inflow and mitral annulus, *Sm* maximal velocity of the tricuspid annulus movement during systole

of competency. Simultaneously, hemodynamic evaluation and monitoring are possible with advanced levels of competency, including the use of color Doppler, spectral Doppler, tissue Doppler imaging, and, eventually, 3D or speckled tracking. Specific pathways can now achieve all these steps of competence for skills certification, developed by intensive care medicine societies [3, 18].

A variety of cardiac changes can be associated with septic shock, although a normal study is not unusual [19]. Abnormalities in left ventricular ejection fraction (LVEF) (i.e., contractile impairment that may be associated with either global dysfunction or exhibited as specific patterns with apical akinesis and ballooning accompanied by good basal LV contraction and almost always reversible over days), LV

diastolic dysfunction, and right ventricular (RV) dysfunction have all been described [20–22]. Since resuscitation in septic shock is mainly focused on aggressive and rapid fluid resuscitation associated with administration of systemic vasopressors to optimize cardiac preload, output, and peripheral perfusion [1, 23], the assessment of basal cardiac function is critical and should be routinely performed at the bedside.

6.2 Septic Heart Pathophysiology: Myocardial Cellular Injury

The pathophysiology of myocardial dysfunction in sepsis has been intensely studied during the last two decades, starting from an initial hypothesis of global myocardial ischemia. This assumption, however, was challenged and later dismissed due to the growing evidence from both animal and humans showing the absence of significant myocardial cell death and the reversible nature of myocardial dysfunction. Therefore, observations focused on functional rather than anatomical abnormalities and on the potential role of circulating myocardial "depressant factors" [24].

In this context, several alterations in intracellular signaling pathway mechanisms have been proposed to explain the pathophysiology of septic cardiomyopathy, affecting cytosolic calcium (Ca^{2+}), myofilament function, and cardiac contractile force, finally leading to the broad spectrum of cardiac abnormalities called septic cardiomyopathy [5, 24, 25].

Septic cardiomyopathy (as other sepsis-associated organ dysfunctions) is due to the excessive host response to an infection. The host recognizes the presence of a pathogen using recognition receptors, such as Toll-like receptors (TLRs). TLRs interact with different pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), inducing nuclear factor-kB (NF-κB) and pro-inflammatory cytokine activation. In LPS animal models of sepsis, interfering with the TLR4 activation caused by LPS improved cardiovascular outcome and decreased mortality [26]. However, in another animal study, the genetic deletion of TLR4, NLRP3, and caspase-1 did not improve cardiac function in a severe model of sepsis, despite a reduction in the levels of pro-inflammatory cytokines; this finding may be explained by the fact that other cell wall components of microorganisms, such as lipoproteins, are recognized by pattern recognition receptors, resulting in cardiomyocyte inflammation and dysfunction [27]. At the cytokine level, tumor necrosis factor-α (TNF-α) plays a key role in the cardiovascular changes (including myocardial dysfunction) associated with septic shock, probably because of its effect on nitric oxide (NO) and Ca^{2+} metabolism and on the downregulation of the beta-adrenergic receptors [24].

6.2.1 Danger-/Damage-associated Molecular Patterns

Endogenous ligands/mediators (danger-/damage-associated molecular patterns (DAMPs) have been described as causative agents of tissue injury and cell damage.

In contrast with PAMPs, the origin of DAMPs lies within the host. In particular, high-mobility group protein B1 (HMGB1) is a DAMP released by cardiomyocytes in the presence of LPS; HMGB1 mediates calcium release from the sarcoplasmic reticulum, which leads to a decrease in calcium content [5, 24, 25].

6.2.2 Nitric Oxide

NO is produced by all cardiac cells and plays different roles in the cardiovascular system of healthy individuals and critically ill patients. Sepsis-induced NO effects include vasodilation, depression of mitochondrial respiration, and further release of pro-inflammatory cytokines.

About 10 years ago, in an experimental setting, Bougaki et al. [28] showed that NO synthase (NOS) activation might decrease inflammatory cytokine synthesis and prevent myocardial dysfunction. However, current evidence suggests that early myocardial dysfunction in sepsis may occur through the overproduction of NO and resultant cyclic guanosine monophosphate (cGMP) through NOS activation in cardiac cells. NOS activation affects the downregulation of beta-adrenergic receptors, a reduction in Ca^{2+} response of myofilaments, and, finally, enhanced NO formation seems to play a role in mitochondrial dysfunction [5, 24, 25].

6.2.3 Intracellular Ca^{2+} Metabolism

Septic cardiomyopathy develops as the final result of myocardial Ca^{2+} dysregulation. The amount of Ca^{2+} stored and ready for cytosolic release is regulated in the heart by the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2). The inhibition of SERCA2 impairs diastolic relaxation, which is secondary to the blocked reuptake of Ca^{2+} into the sarcoplasmic reticulum [24]. SERCA2 inhibition after endotoxemia has also been described in a murine model of polymicrobial sepsis and was associated with a decline in ejection fraction and cardiac dysfunction [27]. Calcium signaling and metabolism are linked to mitochondrial function, which is also altered in sepsis.

6.2.4 Mitochondrial Dysfunction

Mitochondrial function is significantly impacted in sepsis, and the extent of mitochondrial dysfunction has also been correlated with clinical outcomes [29]. Different mitochondrial dysfunction features have been described in septic cardiomyopathy, including structural changes in mitochondrial architecture (swelling, internal vesicle formation, and abnormalities in cristae), mitochondrial DNA damage, elevation in mitochondrial permeability transition, and inhibition of cytochrome C oxidase activity.

The final result of mitochondrial injury is altered ATP production, and the persistence of this metabolic state may activate intracellular pathways, leading to cell

apoptosis. However, since cardiomyocyte death does not seem to be the main feature of septic cardiomyopathy, cells may adapt their metabolism by reducing overall metabolic activity and entering a sort of 'hibernation' to prevent death [25, 30].

6.3 Septic Heart Dysfunction: Role of Echocardiography on Clinical Assessment and Prognosis

6.3.1 Left Ventricular Systolic Septic Dysfunction and Prognosis

6.3.1.1 Left Ventricular Ejection Fraction

A reduced LVEF, a measure commonly used to assess LV systolic function, is a common feature of septic cardiomyopathy. However, although LVEF is frequently used to estimate LV systolic dysfunction in the ICU and in the cardiology setting, it is based on significant geometric assumptions and, more importantly, it is also highly dependent on systemic cardiovascular variables. LVEF is a dependent variable based on the complex physiological interaction between preload (i.e., volume status associated with fluid resuscitation and vasoactive drug infusion, the degree of endothelial insult and the presence of vascular leakage) and afterload (i.e., ventriculo-arterial coupling associated with vasoplegia and vasoconstrictor administration) conditions. Accordingly, LVEF changes do not accurately reflect true variations in intrinsic myocardial contractility [31], and its estimation often does not fit with clinical outcomes in septic patients. A higher LVEF may be associated with a more pronounced reduction in afterload secondary to vasoplegia, and a recent study showed higher mortality in septic patients with hyperdynamic LVEF (<70%) compared to those with normal LVEF (55–70%) [32]. By contrast, initial evidence showing paradoxically lower LVEF in survivors of septic shock [33] was not confirmed in subsequent studies [34, 35]. The prognostic value of LVEF in septic patients was investigated in several recent meta-analyses, which showed no association with mortality [6–9].

6.3.1.2 Left Ventricular Systolic Function and Tissue Doppler Imaging

Tissue Doppler imaging (TDI), a method based on high-amplitude, low-frequency, pulsed-wave Doppler, may be an easier method to estimate LV systolic function and an alternative to 'conventional' LVEF. TDI seems to be influenced to a lesser extent by loading conditions [10], thus potentially being more appropriate for the study of LV systolic dysfunction in septic patients. The TDI assessment of LV systolic function with the s′ wave is performed at the mitral annulus and is considered a useful index of longitudinal LV systolic function, potentially offering advantages over the use of LVEF, as previously demonstrated in patients with cardiac disease [36]. The TDI evaluation of the s′ wave is directly measured without integration with other parameters or algorithms (as for LV diastolic function), not relying on geometric assumptions (as for LVEF), and is feasible even when the echocardiography window is suboptimal (does not need full visualization of the LV chamber). The TDI

assessment of LV systolic function via peak systolic velocity measured at the mitral annulus (s′) has reference values in adult non-critically ill patients of 8–10 cm/s, according to the sampling region, being slower at the septal level [11].

However, despite its promising use in the ICU, a recent meta-analysis regarding the use of s′ wave velocity in 13 studies in ICU patients with sepsis found no significant difference between survivors and non-survivors (standardized mean difference [SMD] 0.20, 95% CI -0.18, 0.59; prediction interval -1.15, 1.56) with high overall heterogeneity (I^2 = 80%) [9]. This finding reinforces the message that systolic dysfunction does not seem to play a primary role in the prognosis in septic patients, as in previous reports regarding the role of LVEF [6–9].

6.3.1.3 Left Ventricular Systolic Function and Speckle-tracking Echocardiography

An alternative echocardiographic modality, speckle-tracking echocardiography, first described in 2004 as a method of non-Doppler-based and angle-independent measurement of LV function, is emerging as a better marker of intrinsic LV function [37]. Based on a semi-automated algorithm that tracks the displacement of acoustic 'speckles' in the myocardium, the change in myocardial segment length is measured. Compared to LVEF, speckle-tracking echocardiography is affected to a much lesser degree by changes in ventricular loading conditions, myocardial compliance, and afterload properties because it measures myocardial deformation directly [37]. The most common unit of measurement in speckle-tracking echocardiography is strain, defined as the change in the length of myocardial fiber at end-systole compared to its original length at end-diastole, expressed as a percentage. Strain can be measured in longitudinal, radial, and circumferential directions. Global longitudinal strain, averaging the longitudinal strain for all 17 myocardial segments, has been validated as the most consistently reproducible measurement [38, 39]. However, better image definition is required for speckle-tracking echocardiography than for TDI [40].

Global longitudinal strain is emerging as a new tool for assessing patients with septic shock; however, few data are available. Five years ago, a systemic review reported only ten studies performed in ICU patients, and even fewer in those admitted for septic shock [12]. Interestingly the authors reported that the overall feasibility of performing speckle-tracking echocardiography analysis in patients with severe sepsis and septic shock ranged between 63% and 98% [12]. Among these studies, Ng et al. recruited 33 patients with septic shock and 29 matched patients with sepsis but no septic shock. The first group had greater global longitudinal strain (-14.5% vs. -18.3%, $P < 0.001$), and the myocardial strain differed on diagnosis and recovery (-14.5% vs. -16.0%, $P = 0.010$), whereas conventional echocardiographic assessment did not differ between the groups [41]. Similarly, Shahul et al. showed that global longitudinal strain worsened over 24 h in septic shock, but LVEF did not change significantly [42]. A similar, more recent investigation conducted on 90 patients with septic shock and matched with 37 patients with sepsis but no septic shock, found that global longitudinal strain was significantly reduced in patients with septic shock compared with control patients (-14.6 ± 3.3 vs. -17.1 ± 3.3;

$P < 0.001$). Moreover, subclinical LV systolic dysfunction, defined using the cutoff value of global longitudinal strain ≥-15%, was detected in 50 patients with septic shock (55.6%) and in 6 patients in the control group (16.2%) ($P < 0.05$) [14].

6.3.2 Left Ventricular Diastolic Dysfunction

In critically ill patients, TDI has been predominantly used in the assessment of LV diastolic function with the use of the e′ wave and the ratio of the E/e′ ratio [15]. These two parameters are considered as pivotal in the diagnosis and grading of LV diastolic dysfunction according to recent recommendations [43]. The early diastolic velocity of the mitral annulus (e′) reflects myocardial relaxation, and there is evidence of a significant association between mortality of septic patients and TDI parameters reflecting worse LV diastolic function [15].

About 20% of patients with sepsis demonstrate LV diastolic dysfunction, which may also be related to concurrent vasopressor and volume therapy [13]. In this setting, after the publication of a few studies enrolling a relatively small number of patients (ranging between 21 and 54), the first large observational study, including 262 ICU patients, showed that in patients with severe sepsis and septic shock diastolic dysfunction was the strongest independent predictor of early mortality, even after adjusting for severity scores, low urine output, low LV stroke volume index, and lowest arterial oxygen saturation. Moreover, although there is a known association between diastolic dysfunction, age, hypertension, diabetes mellitus, and ischemic heart disease, diastolic dysfunction was a stronger independent predictor of mortality than age and the other co-morbidities [44].

Two meta-analyses have confirmed the association between LV diastolic dysfunction and mortality [7, 15]. Sanfilippo et al. retrieved data from 16 studies in severe sepsis and/or septic shock, enrolling a total of 1507 patients. There was a significant association between mortality and both lower e′ (SMD 0.33; 95% CI 0.05, 0.62; $P = 0.02$) and higher E/e′ (SMD -0.33; 95% CI -0.57, -0.10; $P = 0.006$) [15]. The same group, in a previous meta-analysis, reported that 48% of 305 patients included had some degree of diastolic dysfunction (the reported incidence ranging from 20% to 57.1%, and three studies reporting an incidence of 50% or higher), and also showed that mortality at the longest follow up was significantly higher in patients with diastolic dysfunction versus patients with normal diastolic function (relative risk [RR] 1.82, 95% CI 1.12–2.97, $P = 0.02$) [7].

6.3.3 Right Ventricular Systolic Septic Dysfunction and Prognosis

Most of the studies about the pathophysiology of septic cardiomyopathy have focused primarily on systolic and diastolic dysfunction of the left ventricle, with RV dysfunction receiving less attention [21, 31, 45]. The right ventricle is more challenging to image, and there is a lack of consensus regarding which echo parameters

should be used to define RV dysfunction. Moreover, the right and left ventricles are anatomically and functionally connected in series and via a common septum, leading to ventricular interdependence [45]. Finally, RV dysfunction in sepsis is multifactorial and can be related to direct myocardial depression or preload change or increase in RV afterload due to hypoxemia, hypercapnia, and mechanical ventilation for associated acute respiratory failure [21, 31]. However, increasing attention to the right side of the heart has shown that the right ventricle may also play an important and independent role in myocardial dysfunction in sepsis. After early studies of RV dysfunction in sepsis using invasive tools, TDI assessment of RV function has gained in popularity.

In 2013, Harmankaya et al. first reported the recording of RV-TDI parameters (the RV myocardial peak systolic velocities [Sm, cm/s] and myocardial performance index [MPI]) in 55 ICU patients, in addition to the standard echocardiographic evaluation. The RV-Sm value was significantly lower in the most severely ill sepsis or septic shock patients and non-surviving patients, and the RV-MPI was higher in non-survivors [46].

In 2017, a large study by Vallabhajosyula et al. applied the multimodal American Society of Echocardiography (ASE) criteria for RV dysfunction and found a high prevalence of isolated RV dysfunction associated with long-term (1-year) mortality. RV dysfunction was present in 214 (55%) of 388 included patients. Isolated RV dysfunction was seen in 100 (47%) patients and combined RV and LV dysfunction in 114 (53%). Isolated RV dysfunction was independently associated with reduced 1-year survival (hazard ratio [HR] 1.6 [95% CI 1.2–2.1, $P = 0.002$) in patients with sepsis and septic shock [47]. More recently, Lanspa et al. reported RV dysfunction in 48% of 393 patients, and that this condition was associated with increased mortality (OR 3.4, 95% CI 1.7–6.8, $P = 0.001$), but LV systolic dysfunction was not (OR 0.63, 95% CI 0.3–1.2, $P = 0.32$) [48].

Vallabhajosyula et al., in 2020, performed a meta-analysis of 10 studies, including a total of 1373 patients, and reported RV dysfunction in 477 (34.7%). RV dysfunction was associated with higher short-term (pooled OR 2.42 [95% CI 1.52–3.85], $P = 0.0002$); moderate heterogeneity) and long-term (pooled OR 2.26 [95% CI 1.29–3.95], $P = 0.004$); low heterogeneity) mortality [16].

6.4 Beyond Echocardiography: Cardiovascular Clusters in Septic Shock Combining Clinical and Echocardiographic Parameters

Recent advances in the understanding of the septic heart and the extensive use of echocardiographic assessment have shown the intrinsic limitations of the approaches used in the past, which focused too much on specific predefined ‘time-points’ (i.e., early phase, late phase) or isolated cardiovascular elements (e.g., right ventricle, left ventricle, peripheral resistance). It is well known that sepsis-related cardiovascular dysfunction is variable and changeable within the same patient. That characterization of cardiovascular septic phenotypes should be managed using a more extensive

and multivariable approach, such as the newly proposed "clustering" approach, without any *a priori* criteria of cardiac dysfunction [17]. In this study by Geri et al., the authors combined echocardiographic and clinical hemodynamic measurements obtained from 310 patients. They obtained five distinct cardiovascular phenotypes, the hemodynamic profiles of which corresponded to "well-resuscitated" patients (16.9%, cluster 1), patients with LV systolic dysfunction (17.7%, cluster 2), hyperkinetic profile (23.3%, cluster 3), RV failure (22.5%, cluster 4), and sustained hypovolemia (19.4%, cluster 5). This new approach may help customize therapy at the bedside and enable targeted/personalized medicine for hemodynamic support (i.e., need for fluids or inotropic support) [17].

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Non-adrenergic Vasopressors in Septic Shock: Overview and Update

7

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7.1 Introduction

Sepsis and septic shock are leading causes of intensive care unit (ICU) admission worldwide, with significant impact on resource utilization and adverse outcomes. A recent systematic review and meta-analysis of the literature showed that the hospital mortality rate was 39% in patients with septic shock, regardless of the time-point of assessment [1]. Septic shock is a medical emergency and vasoactive medications must be promptly used to achieve hemodynamic stabilization if fluid therapy is not sufficient to achieve this goal. Current guidelines recommend norepinephrine as the first-choice vasopressor in this context [2]; however, some conditions, such as refractory septic shock, may require high doses of norepinephrine, which may be associated with various adverse effects and increased mortality rates [3]. Accordingly, administration of non-adrenergic vasopressors has been proposed as a possible therapeutic option in patients with septic shock requiring high norepinephrine doses [4–7]. These non-adrenergic vasopressors include arginine vasopressin (AVP) and its derivatives (terlipressin and selepressin), as well as angiotensin II. However, few studies have investigated the role of these agents, leaving no conclusive evidence about their possible beneficial effects on outcome.

In this concise review, we discuss the pathophysiological aspects related to septic shock in patients requiring high doses of norepinephrine, the clinical rationale

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for the use of non-adrenergic vasopressors, and the current evidence about the use of these agents.

7.2 Hyporesponsiveness to Catecholamines in Septic Shock

Septic shock is characterized by a hyperdynamic circulation, mainly due to reduced vascular resistance and increased cardiac output. Vascular hyporesponsiveness, a condition defined as a decreased pressure response to vasopressor agents, often occurs in septic patients and usually requires progressive administration of increasing doses of norepinephrine to achieve hemodynamic stabilization. The pathophysiology underlying this disorder is linked to an imbalance between vasoconstrictor and vasodilator mediators. On the one hand, the vascular response to catecholamines, AVP and angiotensin II may be decreased [8]. In particular, catecholamine 'desensitization' is a well-known phenomenon resulting from α1-adrenergic receptor downregulation or uncoupling between receptors and their intracellular messengers [8]. Septic states are also associated with decreased plasma AVP levels [9] and downregulated AVP receptor type-1 (V1R) expression [9]. On the other hand, various vasodilator factors (e.g., nitric oxide [NO], tumor necrosis factor alpha [TNF-α], kinins, and prostaglandins) are released during sepsis [10]. Other possible mechanisms involved in the increased vasodilator effects include the sepsis-associated increased production of endogenous peroxynitrite, superoxide anion, and prostacyclin; activation of ATP-sensitive potassium channels (K-ATP); and corticosteroid insufficiency [10]. Moreover, in advanced stages of sepsis, vascular hyporesponsiveness has been linked to rho-kinase inhibition of myosin light chain phosphatase (MLCP) opposing vascular smooth muscle contraction [11].

7.3 Rationale for the Use of Non-adrenergic Vasopressors

High doses of norepinephrine were reported to be independently associated with the risk of death in the ICU, probably due to the possible adverse effects of norepinephrine therapy. Indeed, high doses of norepinephrine may induce peripheral and splanchnic ischemia, acute myocardial infarction, increased oxygen consumption and hyperglycemia [3]. Norepinephrine has also been suggested to be related to ICU-acquired weakness [12] and immunodepression in critically ill patients [13]. Although the reported adverse effects of norepinephrine therapy may have been confounded by the severity of illness in patients requiring higher doses in earlier observational studies [3, 12, 13], a randomized control trial (RCT) by Asfar and coworkers [14] showed that the incidence of arrhythmias was higher in patients with septic shock who received high doses of norepinephrine to achieve a mean arterial pressure (MAP) of 80–85 mmHg than in patients in a lower target group (MAP 65–70 mmHg). This suggests that the deleterious effects of high doses of norepinephrine may not be related, *per se,* to the severity of illness.

The use of epinephrine as an alternative vasopressor has also been assessed in several studies [15, 16]. In a RCT in 280 patients with septic shock, epinephrine was as effective as norepinephrine in achieving MAP targets, despite the development of potential drug-related adverse effects with epinephrine [15]. A systemic review and meta-analysis of 32 studies showed no survival benefit of using epinephrine compared to norepinephrine [16].

The combination of two catecholamines in refractory septic shock could also be counter-productive, stressing the same receptors (for example β-receptors) and increasing oxygen consumption. A RCT compared the administration of epinephrine to norepinephrine plus dobutamine in 330 patients with septic shock [17]. Patients in the epinephrine group had lower survival rates at 28 days than those in the norepinephrine + dobutamine group. Moreover, in the first days after randomization, pH levels were lower and lactate levels higher in the epinephrine group than in the control group.

Taken together, the possible deleterious effects of high doses of norepinephrine or a combination of catecholamines may provide a plausible rationale for the use of non-adrenergic vasopressors. Figure 7.1 shows the mechanisms of action of non-adrenergic vasopressors on vascular smooth muscle cells. A recent meta-analysis of 23 studies (4380 patients) showed that addition of norepinephrine to a non-adrenergic vasopressor was associated with a marginally significant reduction in

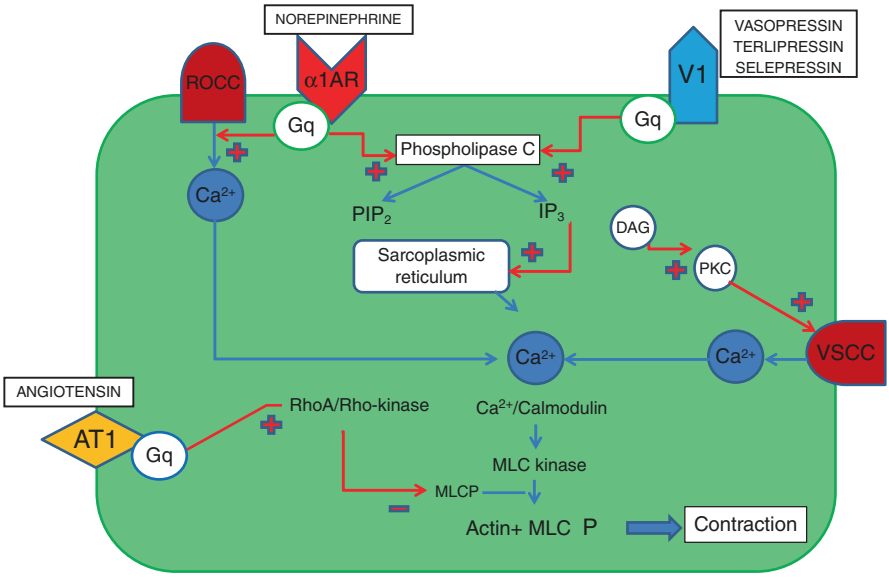

Fig. 7.1 Mechanisms of action of non-adrenergic vasopressors on the vascular smooth muscle cell. *ROCC* receptor-operated Ca^{2+} channels, *VSCC* voltage-sensitive calcium channels, *α1AR* alpha-1 adrenergic receptor, *V1* vasopressin V-1 receptor, *AT1* angiotensin II receptor type 1, *Gq* guanine nucleotide-binding proteins, Ca^{++} ionized calcium, PIP_2 phosphatidylinositol 4,5-bisphosphate, IP_3 inositol 1,4,5-triphosphate, *DAG* diacylglycerol, *PKC* protein kinase C, *MLC* myosin light chain, *MLCP* myosin light chain phosphatase

28-day mortality [18]. Moreover, administration of a non-adrenergic vasopressor showed some advantages, such as an increased 6-h shock reversal success rate, reduced length of mechanical ventilation, and improved renal function [18]. Nonetheless, because of insufficient RCT evidence (Table 7.1), only a weak recommendation for adding AVP (up to 0.03 U/min) or epinephrine to norepinephrine to achieve a target MAP of 65 mmHg, or adding AVP (up to 0.03 U/min) to decrease norepinephrine dosage is suggested in the current guidelines [2]. Further RCTs are needed to provide more insight on these potentially useful vasoactive agents.

7.4 Available Non-adrenergic Vasopressors

7.4.1 Vasopressin and Vasopressin Derivatives

7.4.1.1 Vasopressin

AVP (also called "antidiuretic hormone") is a nonapeptide produced by the hypothalamic supraoptic nuclei and paraventricular nuclei, and released by the posterior pituitary gland in response to changes in blood osmolality, blood pressure and volemia [19]. AVP exert its actions by binding to specific receptors, such as V1a, V1b and V2. V1a-R stimulation induces significant vasoconstriction on the smooth muscle of the vasculature [20]; at the same time, V1a-R activation can induce vasodilatation in the pulmonary and coronary vessels, probably mediated by NO release from the endothelium [20]. Activation of V1b-R leads to release of adrenocorticotropic hormone (ACTH) from the pituitary gland, and stimulation of V2-R involves water homeostasis mechanisms (anti-diuretic effects), induces vasodilation through NO, and releases clotting factors acting at the hepatic level [20]. AVP concentrations are usually lower in septic shock than in other types of circulatory failure [21]. Because of this relative AVP deficiency, AVP administration may increase blood pressure during septic shock. Furthermore, AVP hypersensitivity may occur in sepsis, probably due to decreased numbers and/or affinity of V1a-R and increased hypothalamic-pituitary axis activity [19]. AVP administration significantly reduces norepinephrine requirements and also heart rate [22]. Conversely, AVP infusion may also alter splanchnic perfusion more than norepinephrine, reducing flow in the celiac trunk and portal vein [22].

A large multicenter, randomized, double-blind trial compared the use of low dose AVP plus open label norepinephrine versus norepinephrine alone in 779 patients with septic shock (the VASST trial) [4]. AVP infusion was started at a dose of 0.01 U/min and titrated to a maximum of 0.03 U/min, while norepinephrine infusion was started at 5 μg/min and titrated to a maximum of 15 μg/min. The initial target MAP was 65–75 mmHg; open-label vasopressors were increased only if the target MAP was not reached on maximal study-drug infusion. Despite the rapid decrease in the total norepinephrine dose allowed by AVP infusion, the authors found no significant differences in terms of mortality rate at 28 days or serious adverse effects between the groups. There was a significantly lower mortality in patients treated with AVP with less severe septic shock (defined as norepinephrine

Table 7.1 Summary of randomized control studies, investigating the possible impact of non-adrenergic vasopressors on outcome in patients with septic shock

Authors [ref]	Agent	Dose	Type of study	Number of patients	Outcomes	Findings
Russell et al. [4]	AVP	0.01–0.03 U/min	Multicenter, double-blind RCT	778	• 28-day mortality • 90-day mortality • Organ dysfunction-free days • Days free of vasopressor use, MV, RRT	• No differences in 28-day or 90-day mortality. • No difference in serious adverse effects (myocardial infarction; digital or mesenteric ischemia; cardiac arrest)
Gordon et al. [23]	AVP	0.01–0.06 U/min	Multicenter, double-blind RCT	408	• Kidney failure-free days • RRT rates and duration • Mortality • Serious adverse effects	• No differences in kidney failure free-days • Less use of RRT in AVP group than in NE group • No difference in mortality rates or incidence of serious adverse effects
Morelli et al. [26]	Terlipressin	1.3 μg/kg/h	RCT	45	• Effects of TP and AVP infusion on open-label NE • Effects on systemic and regional hemodynamics and organ function	• Low dose of TP reverses sepsis-induced hypotension and reduce NE requirements
Liu et al. [5]	Terlipressin	20–160 μg/h	Multicenter, double-blind RCT	526	• 28-day mortality • Changes in SOFA score on day 7 after randomization • Days alive and free of vasopressor during 28 days after randomization	• No differences in 28-day mortality • TP reverses sepsis-induced arterial hypotension • TP improves serum creatine and SOFA score
Russell et al. [28]	Selepressin	• 1.25 ng/kg/min • 2.5 ng/kg/min • 3.75 ng/kg/min	Multicenter, double-blind RCT	52	• Stabilization of MAP >60 mmHg without NE at 12, 24, 48, 96 h and day 7 • NE infusion rates and cumulative dose • Proportion of patients maintaining MAP >60 mmHg at 12, 24, 48, 96 h and day 7	• Infusion rate of 2.5 ng/kg/min reduced NE doses, maintained MAP, improved fluid balance and shortened time of MV

(continued)

Table 7.1 (continued)

Authors [ref]	Agent	Dose	Type of study	Number of patients	Outcomes	Findings
Laterre et al. [6]	Selepressin	• 1.7 ng/kg/min • 2.5 ng/kg/min • 3.5 ng/kg/min	Multicenter, double-blind RCT	828	• Ventilator- and vasopressor-free days up to day-30 • 90-day all-cause mortality • 30-day RRT-free days • 30-day ICU-free days • Adverse effects	• No differences in ventilator- and vasopressor-free days • No differences in 90-day mortality, RRT free days; ICU free days; cardiac arrhythmias; myocardial infarction; mesenteric ischemia
Chawla et al. [30]	Ang II	5–40 ng/kg/min	RCT	20	• Effect of Ang II on the dose of NE required to maintain a MAP of 65 mmHg • 30-day mortality	• Significant reduction in NE requirements • No differences in 30-day mortality
Khanna et al. [7]	Ang II	20–200 ng/kg/min	RCT	344	• Response to MAP at 3 h • Changes in cardiovascular and total SOFA score	• Significant increase in MAP • Significant decrease in NE and AVP doses • No differences in adverse events • Improvement in cardiovascular SOFA in Ang II group at 48 h

Ang II Angiotensin II, *AVP* vasopressin, *MAP* mean arterial pressure, *MV* mechanical ventilation, *NE* norepinephrine, *RCT* randomized clinical trial, *RRT* renal replacement therapy, *SOFA* Sequential Organ Failure Assessment

dose <15 μg/min). Subsequently, the Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial [23] investigated whether the early use of AVP could improve kidney outcomes in 409 patients with septic shock compared to norepinephrine. AVP was titrated at double the dose used in VASST (up to 0.06 U/min) and norepinephrine was titrated up to 12 μg/min, in order to maintain a target MAP of 65–75 mmHg. Patients were randomized into four groups: AVP + hydrocortisone; AVP + placebo; norepinephrine + hydrocortisone; norepinephrine + placebo. The early use of AVP compared with norepinephrine did not improve the number of kidney failure-free days. However, AVP spared the total dose of norepinephrine required to maintain the blood pressure. Serum creatinine levels were lower and urine output slightly higher over the first 7 days in the AVP group than in the norepinephrine group. Furthermore, there was no significant difference in the mortality rate between groups. These observations [4, 23] suggest that, although the impact of the use of AVP on mortality has not yet been confirmed in patients with septic shock, it may be a safe adjunct to reduce norepinephrine requirements. Nevertheless, the current evidence does not support the routine use of this agent in patients with septic shock.

7.4.1.2 Terlipressin

Terlipressin is a synthetic tri-glycyl vasopressin, with a longer duration of action (4–6 h) and a greater selectivity for vascular V1a receptors than AVP [24]. It is administrated as a pro-drug, slowly degraded by the liver and kidney to lysine vasopressin [24]. Due to its long effective half-life, terlipressin is commonly administered as a high-dose bolus infusion (about 1 mg every 4–6 h). However, there is no consensus about the best mode of terlipressin administration (bolus vs. continuous infusion) in septic shock patients. In an experimental model of endotoxemia [24], continuous infusion of terlipressin improved surrogate measures of myocardial, hepatic and renal perfusion. Few trials have compared the administration of terlipressin with that of other vasopressors in humans. In 20 patients with septic shock, Albanese and coworkers showed that norepinephrine and terlipressin both increased MAP [25]. In addition, terlipressin reduced oxygen consumption more effectively than norepinephrine. In a RCT of 45 patients with septic shock, Morelli et al. compared the effects of terlipressin with those of AVP on open-label norepinephrine requirements. Patients in the terlipressin group received a continuous infusion of terlipressin of 1.3 μg/kg/h; patients in the AVP group were treated with a continuous infusion of AVP of 0.03 U/min [26]. A control group received a fixed dose of norepinephrine (15 μg/min). Compared with the infusion of norepinephrine or AVP, the relatively low dose of terlipressin was effective at reversing sepsis-induced hypotension and reducing norepinephrine requirements. More recently, a multicenter randomized double-blinded trial enrolled 526 patients with septic shock: 260 were randomized to a terlipressin group and 266 to a norepinephrine group [5]. Terlipressin infusion was started at 20 μg/h and titrated to a maximum of 160 μg/h, and norepinephrine infusion was started at 4 μg/min and titrated to a maximum of 30 μg/min; in both groups the initial target MAP was 65–75 mmHg. There was no significant difference in the 28-day mortality rate between the terlipressin (40%) and the

norepinephrine (38%) groups. There was also no significant difference between the groups in the number of days alive and free of vasopressors. Conversely, serious adverse events were more common in the terlipressin group than in the norepinephrine group (30% vs. 12; $P < 0.001$). In conclusion, terlipressin may be considered as an alternative vasopressor agent to reduce norepinephrine requirements in patients with refractory septic shock when AVP is not available. However, the current evidence does not support the routine use of terlipressin in patients with septic shock.

7.4.1.3 Selepressin

AVP stimulates vasoconstrictor receptors (V1a) and vasodilatory receptors (V1b and V2). In this respect, the use of selepressin, a selective V1a-R agonist could be more useful to optimize hemodynamics in septic shock. In an ovine model of sepsis, early administration of selepressin ameliorated hemodynamic variables when compared to AVP and norepinephrine [27]. A first human phase 2a trial showed that selepressin at a dose of 2.5 ng/kg/min enabled rapid discontinuation of norepinephrine while maintaining adequate MAP [28]. Selepressin may also improve fluid balance and shorten the duration of mechanical ventilation. More recently, the Selepressin Evaluation Programme for Sepsis-Induced Shock-Adaptive Clinical (SEPSIS-ACT)Trial [6] tested the hypothesis that selepressin may improve patient outcomes, defined as an increase in the number of days alive and free of both ventilation and vasopressor use, compared to placebo. SEPSIS-ACT was a multicenter, blinded, randomized, placebo-controlled trial, designed to determine the efficacy of multiple dosing regimens of selepressin in the treatment of septic shock. Patients were randomly assignment to 1 of 3 selepressin dosing regimens (1.7, 2.5, 3.5 ng/kg/min; $n = 585$) or to placebo ($n = 283$). After enrollment of 817 patients, the trial was stopped for futility. Among patients receiving only norepinephrine, administration of selepressin, compared with placebo, did not result in a reduction in ventilator- and vasopressor-free days or key secondary end-point (90-day mortality, renal replacement therapy [RRT], rates of adverse effects). The current evidence does not therefore support the use of selepressin in these patients.

7.4.2 Angiotensin II

Angiotensin II is a principal product of the renin-angiotensin-aldosterone system (RAAS) which governs essential homeostatic mechanisms that counteract hypotension and hypovolemia [29]. During septic shock, the administration of angiotensin II could ameliorate hemodynamic status, enabling norepinephrine doses to be reduced [29]. The intravenous Angiotensin II for the Treatment of severe hypotension in High Output Shock (ATHOS) study [30], a phase II RCT, analyzed the role of angiotensin II in the treatment of distributive shock and sought the optimal angiotensin II doses in this setting. Twenty patients with septic shock were randomized to receive either angiotensin II or placebo. Angiotensin II was given at an

initial dose of 20 ng/kg/min plus standard-of-care therapy for distributive shock (norepinephrine plus AVP or epinephrine). Angiotensin II was administered for 6 h with hourly adjustments of doses (minimum 5 ng/kg/min; maximum 40 ng/kg/min) to achieve an MAP of 65 mmHg. Compared with the placebo group, angiotensin II administration was associated with a significant reduction in norepinephrine requirements. The 30-day mortality was similar for the two groups. In 2017, an international RCT (ATHOS-3) [7] showed that angiotensin II could induce a significant increase in MAP compared to placebo. Moreover, during the first 48 h after randomization, doses of the vasopressors norepinephrine and AVP were significantly reduced in the angiotensin II group but not in the placebo group. Interestingly, there was no difference in adverse effects between the groups. More recently, the use of angiotensin II was explored in patients requiring extracorporeal membrane oxygenation (ECMO) [31] and RRT [32] with some beneficial results (reduced requirement of vasopressors, discontinuation of RRT). However, the safety profile of angiotensin II has never been tested in patients with vasodilatory shock and concurrent myocardial dysfunction. Indeed, angiotensin II may reduce cardiac output as a result of increased afterload secondary to its preferential vasoconstrictive action. Large RCTs are needed to investigate the possible impact of angiotensin II in patients with refractory septic shock and identify patients who may or may not benefit from this therapy.

7.5 Future Perspectives

Although non-adrenergic vasopressors have not been shown to influence outcome in patients with septic shock, future research should be directed to identify possible subgroups of patients who may benefit from these agents. In particular, therapeutic targets should not only consider global hemodynamic parameters, such as MAP and cardiac output, but also indices of microvascular perfusion. Indeed, the so called "hemodynamic incoherence" or the failure of macrohemodynamic parameters to reflect microvascular perfusion may be an important determinant of therapeutic success in patients with septic shock [33].

7.6 Conclusion

Refractory septic shock may require high doses of norepinephrine, which may be associated with various adverse effects and increased mortality rates. The use of non-adrenergic vasopressors may be a possible therapeutic option in these patients. Few studies have investigated the role of these agents, leaving no conclusive evidence about their possible beneficial effects on outcome. The current evidence does not support the routine use of these agents; however, AVP may be a safe adjunct to reduce norepinephrine requirements in patients with septic shock.

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8 Pathophysiology and Clinical Implications of the Veno-arterial PCO_2 Gap

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8.1 Introduction

The persisting high mortality of circulatory shock highlights the need to search for sensitive early biomarkers to assess tissue perfusion and cellular oxygenation, which could provide important prognostic information and help guide resuscitation efforts. Although blood lactate and venous oxygen saturation (SvO_2) are commonly used in this perspective, their usefulness remains hampered by several limitations. The veno-arterial difference in the partial pressure of carbon dioxide (Pv-aCO_2 gap) has been increasingly recognized as a reliable tool to evaluate tissue perfusion and as a marker of poor outcome during circulatory shock, and it should therefore be part of an integrated clinical evaluation. In this chapter, we present the physiological and pathophysiological determinants of the Pv-aCO_2 gap and review its implications in the clinical assessment of circulatory shock.

8.2 Physiological Aspects of CO_2 Production and Transport

Under aerobic conditions, CO_2 is produced at the mitochondrial level as a by-product of substrate oxidation (pyruvate and citric acid cycle intermediates) (Fig. 8.1). The relationship between the amount of oxygen consumed (VO_2) and

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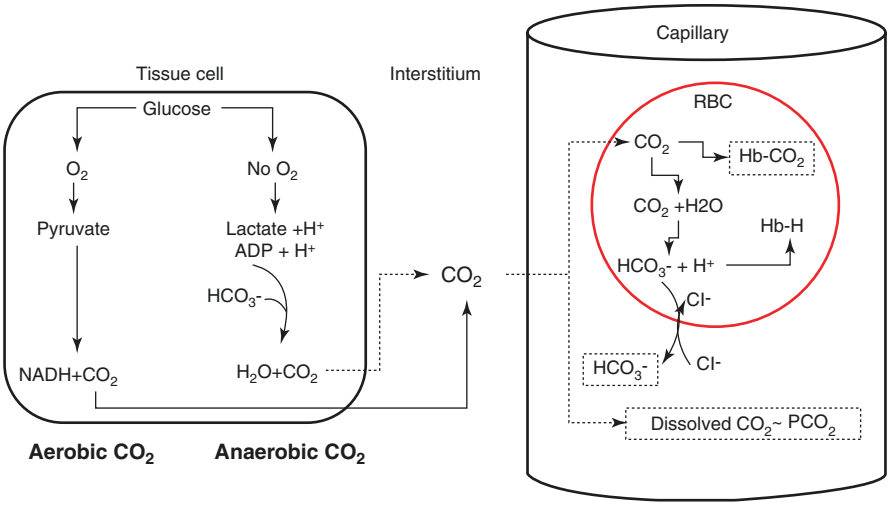

Fig. 8.1 Physiology of CO_2 production and transport. In cells, CO_2 is produced (in mitochondria) as a byproduct of substrate oxidation. Under anaerobic conditions, CO_2 is generated in small amounts, as the results of HCO_3^- buffering of protons released by lactic acid and the hydrolysis of ATP. CO_2 diffuses into the interstitial tissues and then into capillaries, where it is transported as dissolved CO_2 in plasma (in equilibrium with the PCO_2), bound to hemoglobin as carbamino-hemoglobin ($HbCO_2$) in red blood cells (RBC), and as HCO_3^-, following the reaction of CO_2 with H_2O within RBC, a reaction catalyzed by carbonic anhydrase to form HCO_3^- and H^+. HCO_3^- exits the RBC in exchange with chloride anions (Cl^-), whereas protons are buffered by hemoglobin, forming HbH

CO_2 produced (VCO_2) during aerobic metabolism is termed the respiratory quotient ($RQ = VCO_2/VO_2$), and differs according to the main type of oxidized substrate (glucose, RQ = 1; proteins, RQ = 0.8; lipids, RQ = 0.7). Under anaerobic conditions, protons (H^+) resulting from lactic acid production and ATP hydrolysis may generate CO_2 following buffering by bicarbonates (HCO_3^-), leading to the formation of so-called "anaerobic CO_2" [1]. Once formed, CO_2 diffuses within the surrounding environment and capillary blood, to be transported to the lungs for elimination. In blood, CO_2 transport is partitioned into three distinct fractions [2]:

1. Dissolved CO_2 fraction, which is in equilibrium with the partial pressure of CO_2 (PCO_2), according to Henry's law of gas solubility: $V_{gas} = S_{gas} \times (P_{gas}/P_{atm})$, where V_{gas} is the volume of dissolved gas (in ml/ml), S_{gas} is the Henry's constant of gas solubility (0.52 ml/ml for CO_2 at 37 °C), and P_{atm} the atmospheric pressure. Thus, in arterial blood with a $PaCO_2$ of 40 mmHg (at sea level, 37 °C), dissolved $CO_2 = [0.52 \times (40/760)] = 27$ ml/l, which is about 5% of the total CO_2 (note that, in mmol/l, Henry's constant for CO_2 = 0.03 mmol/l/mmHg; also note that the conversion factor from mmol to ml CO_2 is ~22.3).
2. Bicarbonate (HCO_3^-). CO_2 in blood readily diffuses within red blood cells (RBCs), where it combines with H_2O to form carbonic acid (H_2CO_3), a reaction

catalyzed by the enzyme carbonic anhydrase. In turn, H_2CO_3 dissociates to form HCO_3^- and H^+. While H^+ is buffered by hemoglobin (formation of HbH), HCO_3^- exits the RBC in exchange for a chloride anion (Cl^-) via a HCO_3^--Cl^- transporter (erythrocyte chloride shift or Hamburger effect). Thus, the HCO_3^- concentration increases in venous blood whereas the Cl^- concentration diminishes. CO_2 transport as HCO_3^- (RBC and plasma fraction) represents about 90% of the total CO_2 content in arterial blood (this proportion is lower in venous blood due to the Haldane effect). Taking into account a normal hematocrit of 0.45, the CO_2 content under the form of HCO_3^- (in whole blood) is ~435 ml/l.

3. Formation of carbamino compounds within hemoglobin: part of the CO_2 within the RBC combines with free amino (R-NH_2) groups within hemoglobin to form carbamino-hemoglobin (R-NH_2-CO_2). This reaction is enhanced when hemoglobin carries less oxygen, implying that more CO_2 is transported as (R-NH_2-CO_2) when the PO_2 decreases, which is the basis of the Haldane effect described below. CO_2 transport under the form of (R-NH_2-CO_2) represents about 5% of the total CO_2 content in arterial blood (~1.1 mmol/L ≈ 25 ml/l).

In summary, the total CO_2 content of blood under physiological conditions equals:

$$\left[\text{Dissolved } CO_2\right]+\left[HCO_3^-\right]+\left[R-NH_2-CO_2\right]$$

which is ≈490 ml/l in arterial blood and ≈535 ml/l in mixed venous blood, hence a veno-arterial difference of approximately 45 ml/l. A more precise calculation of the CO_2 content of blood can obtained by the Douglas equation, but this is too complex to be calculated at the bedside [3].

8.2.1 The CO_2 Dissociation Curve (PCO_2-CCO_2 Relationship)

As is the case for oxygen, a relationship exists between the PCO_2 and the CO_2 content (CCO_2) of blood (Fig. 8.2). However, in contrast to the sigmoid shape of the O_2 dissociation curve, the CO_2 dissociation curve is slightly curvilinear, indicating a proportional increase in CCO_2 over a wide range of PCO_2. In the physiological range, the relationship between CCO_2 and PCO_2 can therefore be resolved by the equation:

$$PCO_2 = k \times CCO_2 \tag{8.1}$$

Important information provided by the PCO_2-CCO_2 relationship is the shift produced at different values of oxygen saturation of hemoglobin (HbO_2). Indeed, as hemoglobin gets saturated with O_2, it can carry less CO_2 as carbaminoHb, and inversely. This behavior is known as the Haldane effect, which implies that for a same PCO_2, CCO_2 is higher at lower HbO_2 saturation. In other words, this means that as the k constant in the relationship above decreases, the PCO_2-CCO_2 curve is shifted to the left. The consequence of this effect is that, in tissues, more CO_2 is loaded by Hb as it releases O_2, allowing PCO_2 to increase only moderately (from 40

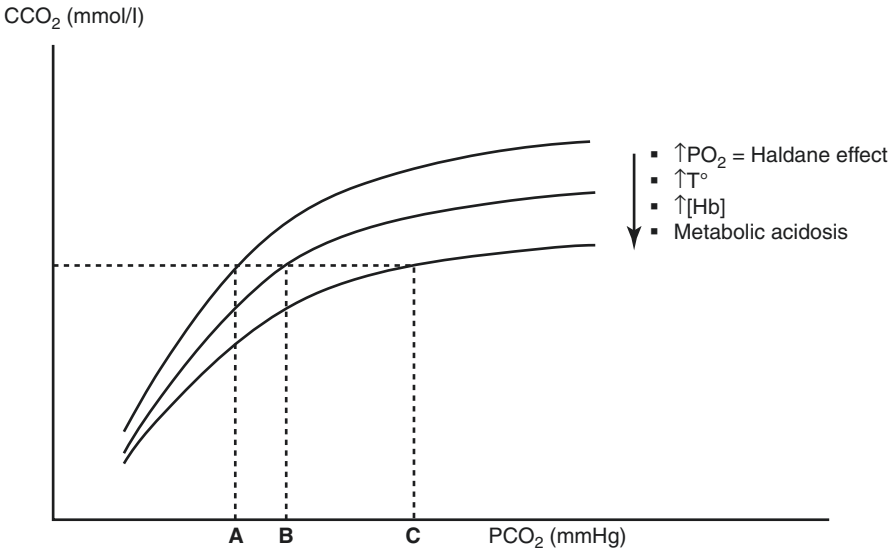

Fig. 8.2 The CO_2 dissociation curve. A curvilinear relationship exists between CO_2 partial pressure (PCO_2) and CO_2 content (CCO_2), so that $PCO_2 = k \times CCO_2$. At low values of PCO_2, the slope of the relationship is steeper, implying a smaller increase of PCO_2 at any CCO_2 than at high values of PCO_2, where the slope of the relationship flattens. The position of the relationship is modified by various factors. A rightward and downward shift of the curve, corresponding to an increase of the k coefficient is produced by high PaO_2 (Haldane effect), elevated temperatures, high hemoglobin concentrations and metabolic acidosis. A rightward shift of the curves implies that, for a same CCO_2, the PCO_2 increases, as indicated by the points A, B and C

to 46 mmHg), in spite of a marked increase in CCO_2 due to the tissue production of CO_2. Without the Haldane effect, the venous PCO_2 would increase significantly more for a similar increase in CO_2 content.

The curvilinearity of the CO_2 dissociation curve indicates that CCO_2 increases more steeply at low values of PCO_2 and is more flat at high PCO_2 values. It is also noticeable that the curve can be displaced by a certain number of factors: In conditions of metabolic acidosis, the reduction in HCO_3^- due to H^+ buffering reduces the formation of carbamino ($R\text{-}NH_2\text{-}CO_2$) compounds inside hemoglobin [4]. As a result, for a given CCO_2, the PCO_2 must increase, which means an increase in the *k* constant, and a rightward shit of the relationship. The opposite occurs under conditions of metabolic alkalosis. Other factors influencing the curve are the hematocrit and temperature. At increasing hematocrit, there is a decrease in plasma space with a reduction of HCO_3^- and a decrease in CO_2 content at any value of PCO_2, with a shift to the right of the curve. At increasing temperatures, the reduced CO_2 solubility also shifts the relationship to the right [4]. These considerations imply, therefore, that $PvCO_2$ may vary at constant total venous CCO_2 according to the particular conditions (HbO_2 saturation [i.e., the Haldane effect], arterial pH, temperature and hematocrit).

8.3 The Pv-aCO_2 Gap: Pathophysiology and Clinical Implications

A discussed earlier, the CCO_2 in the venous side of the circulation is determined by the aerobic production of CO_2 in tissues, influenced by the metabolic rate and the respiratory quotient, and may also increase via non-aerobic production of CO_2. The generation of CO_2 *de facto* increases the CCO_2 on the venous side of the circulation, implying an obligatory difference between arterial and venous CCO_2, termed the veno-arterial difference in CCO_2, or veno-arterial CCO_2 gap: va-CCO_2 gap = (venous - arterial) CCO_2 [1].

The tissue VCO_2 does not accumulate under normal conditions, being washed out by the blood flowing across the tissue and eliminated by the lungs. Accordingly, any reduction in tissue blood flow (stagnant condition) will result in an accumulation of tissue CO_2, implying an increase in the va-CCO_2 gap, in accordance with Fick's principle:

$$VCO_{2tissue} = \left[\left(\text{Blood flow}_{tissue} \times \left(va - CCO_2\ gap_{tissue}\right)\right)\right]$$

At the systemic level, the relationship is:

$$VCO_2 = \left[\left(\text{Cardiac output} \times \left(va - CCO_2\ gap\right)\right)\right]$$

According to the equation ($PCO_2 = k \times CCO_2$), the Fick equation for CO_2 can be rewritten as:

$$k \times VCO_2 = \left[\text{Cardiac output} \times \left(Pv - PaCO_2\right)\right]$$

and

$$\left(Pv - PaCO_2\right) = \left[\left(k \times VCO_2\right) / \text{Cardiac output}\right]$$

Therefore, the Pv-aCO_2 gap represents a very good surrogate indicator of the adequacy of cardiac output and tissue perfusion under a given condition of CO_2 production. The normal Pv-aCO_2 gap is comprised between 2 and 6 mmHg [5], and many studies assessing Pv-aCO_2 gap in clinical conditions used a cut-off value of 6 mmHg above which the gap is considered abnormally elevated. Although the venous PCO_2 should ideally be obtained in a mixed venous blood sampling, good agreement between central and mixed venous PCO_2 values has been reported [6]. Therefore, both central and mixed venous PCO_2 can be used for the calculation of the va-CO_2 gap, as long as the variables are not interchanged during treatment in a given patient.

8.3.1 The Inverse Relationship Between Cardiac Output and the Pv-aCO_2 gap

The inverse relationship between cardiac output and the Pv-aCO_2 gap (Fig. 8.3) has been repeatedly demonstrated in both experimental [7] and clinical [8] settings. It is

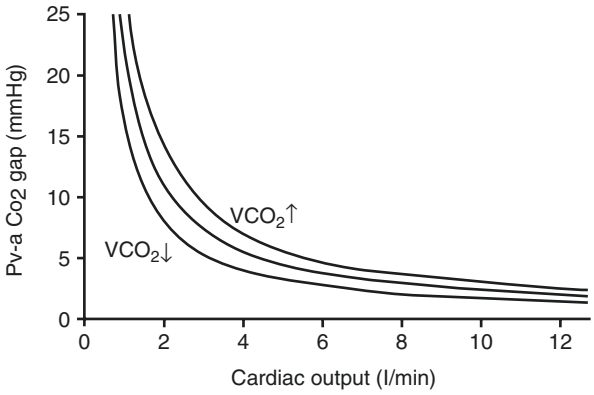

Fig. 8.3 The inverse relationship between cardiac output and the Pva-CO_2 gap. A reduction in cardiac output is associated with a progressive increase in the Pva-CO_2 gap, which becomes exponential at very low cardiac output values, because of the flat slope of the CO_2 dissociation curve in conditions of tissue hypercarbia. The relationship is displaced to the right at higher CO_2 production (VCO_2)

noteworthy that this relationship is not linear, but curvilinear (Fig. 8.3). At very low cardiac output, the (Pv-aCO_2 gap) indeed increases more rapidly. This large increase in Pv-aCO_2 gap is primarily due to the flattened relation between CCO_2 and PCO_2 at high values of CCO_2 in conditions of tissue hypercarbia [5], and this is further magnified if tissue metabolic acidosis develops, due to the rightward shift of the PCO_2-CCO_2 relationship in acidic conditions (increased *k* coefficient, see above). Also, venous accumulation of CO_2 will increase as a consequence of low pulmonary perfusion and CO_2 elimination, further widening the gap [9]. In contrast, the increase in Pv-aCO_2 in very low flow states with conditions of VO_2-oxygen delivery (DO_2) dependence will be attenuated by the mandatory reduction in aerobic VCO_2. Such a decrease in VCO_2 results in a leftward shift of the cardiac output/Pv-aCO_2 gap relationship, as shown in Fig. 8.3 [5].

8.3.2 Pv-aCO_2 Gap and Tissue Dysoxia

In addition to tracking changes in cardiac output and tissue perfusion, the Pv-aCO_2 gap can increase through an augmentation of VCO_2 [8]. Under *aerobic* conditions, that is in the absence of any clinical sign of shock or increased blood lactate, such an increase reflects an increased metabolic demand or an increase in RQ (glucidic diet), or both. Physiologically, an increased metabolic rate is generally coupled with an increase in cardiac output, but such adaptation may not occur in critically ill patients with inadequate cardiovascular reserves, which may result in an increased Pv-aCO_2 gap. Interventions should here be targeted first to reduce the metabolic demand. Persistence of an increased Pv-aCO_2 gap should not necessarily

prompt therapies to increase cardiac output, given the risk associated with deliberate increase in cardiac output in the absence of tissue dysoxia [10]. However, it is noteworthy that an increased Pv-aCO_2 gap immediately after surgery in high risk patients, independent of their hemodynamic condition, SvO_2 and lactate, has been associated with significantly more complications [11]. This suggests that a high Pv-aCO_2 gap could track insufficient resuscitation and might represent a goal for hemodynamic optimization in such patients, but this issue is controversial and remains to be proven [9].

Under *anaerobic* conditions, the question as to whether the Pv-aCO_2 gap can be used as a marker of tissue dysoxia, by detecting increased anaerobic VCO_2 from H^+ buffering, has attracted much attention. An advantage of Pv-aCO_2 gap in this sense would be its ability to rapidly track changes in CO_2 formation, hence providing sensitive, rapid and continuous detection of ongoing anaerobiosis. This would contrast from usual markers of tissue dysoxia, such as SvO_2 or lactate. Indeed, SvO_2 can be unreliable in conditions of reduced oxygen extraction and hyperdynamic circulation (sepsis) [12]. The disadvantage of lactate is its lack of specificity as a marker of dysoxia (type A vs type B hyperlactatemia), and its relatively slow clearance kinetics dependent on liver perfusion and function [13], which limits its utility to rapidly track changes in tissue oxygenation [9].

8.3.2.1 The Pv-aCO_2 Gap in Stagnant Dysoxia

In essence, tissue dysoxia is classically attributed to stagnant, hypoxic, anemic and cytopathic mechanisms. As a sensitive marker of reduced cardiac output, an increased Pv-aCO_2 gap is a reliable indicator of stagnant dysoxia. Importantly, the major gap noted under very low flow conditions (see earlier) has been associated with a global reduction in VCO_2 (VO_2-DO_2 dependence), implying that any increase in anaerobic VCO_2 could not offset the depressed aerobic VCO_2 [7]. Therefore, the increased Pv-aCO_2 gap depends entirely on the stagnant accumulation of tissue CO_2, but not on increased anaerobic VCO_2 in low flow conditions [1, 14].

8.3.2.2 The Pv-aCO_2 Gap in Hypoxic or Anemic Dysoxia

To address the role of the Pv-aCO_2 gap to detect hypoxic dysoxia, Vallet et al. reduced DO_2 below the critical threshold in an isolated dog hindlimb model, by reducing blood flow or by decreasing PO_2 [15]. Both conditions similarly reduced VO_2 and O_2 extraction, but the Pv-aCO_2 gap increased exclusively in the ischemic, but not hypoxic condition, implying that stagnant, but not hypoxic dysoxia was the responsible mechanism [15]. Comparable results were obtained by Nevière et al. in the intestinal mucosa of pigs, following the systemic reduction in DO_2 to similar levels either by reduction of cardiac output or arterial PO_2 [16]. With respect to anemic dysoxia, similar conclusions were obtained in sheep hemorrhage models, in which no increase in Pv-aCO_2 gap was detected under conditions of VO_2/DO_2 dependency due to reduced hemoglobin concentration [17], unless there was a concomitant reduction in cardiac output [18]. Hence, significant hypoxic or anemic dysoxia occurs in the absence of any Pv-aCO_2 gap increase.

8.3.2.3 The Pv-aCO_2 Gap in Cytopathic dysoxia

An acquired intrinsic abnormality of tissue O_2 extraction and cellular O_2 utilization, primarily related to mitochondrial impairment, defines the concept of cytopathic hypoxia, and the resulting cellular bioenergetic failure could represent an important mechanism of organ dysfunction in sepsis [19]. Mitochondrial defects have been demonstrated in several tissues obtained from animals in various models of sepsis, and limited data also exist on altered mitochondrial metabolism in human biopsy samples or circulating blood cells [20]. The detection of cytopathic hypoxia, however, is still not feasible at the bedside, although new techniques such as the measurement of mitochondrial O_2 tension using protoporphyrin IX-Triplet State Lifetime Technique (PpIX-TSLT) are currently being developed [21]. Furthermore, impaired O_2 extraction in sepsis does not necessary imply cytopathic hypoxia, as it may be related to impaired microcirculation.

Theoretically, the increased anaerobic CO_2 generation in conditions of cytopathic hypoxia could result in increased anaerobic VCO_2 leading to an increased Pv-aCO_2 gap. This assumption has been evaluated in a porcine model of high dose metformin intoxication, which induces mitochondrial defects comparable to cyanide poisoning [22]. As expected, treated pigs exhibited reduced VO_2 and marked lactic acidosis, in spite of preserved systemic DO_2. However, although VCO_2 decreased less than VO_2, suggesting some anaerobic VCO_2, no significant increase in Pv-aCO_2 gap was noted. In a human case report of massive metformin intoxication, Waldauf et al. also reported no elevation in Pv-aCO_2 gap despite major lactic acidosis and reduced aerobic VO_2, as detected by increased SvO_2 [23]. Therefore, although data are very limited, cytopathic dysoxia related to impaired mitochondrial respiration appears not to widen the Pv-aCO_2 gap.

8.3.3 The Pv-aCO_2 Gap in Sepsis

Ongoing tissue dysoxia with persistent lactic acidosis is a hallmark of sepsis, and associated with a poor prognosis. Although a hyperdynamic circulation is characteristic of sepsis, many septic patients may have a cardiac output that is insufficient to meet metabolic demands, because of persistent hypovolemia or concomitant myocardial dysfunction. An increased Pv-aCO_2 gap has been reported in patients with lower cardiac output in sepsis, consistent with the ability of the Pv-aCO_2 gap to detect stagnant dysoxia, also in the context of sepsis [24]. In such conditions, an increase in cardiac output correlates with a parallel decrease in Pv-aCO_2 gap [25]. Importantly, as reported by Vallee et al. [26], the Pv-aCO_2 gap is able to detect persistently low cardiac output even in patients with a normal SvO_2. Such a high Pv-aCO_2 gap during the early resuscitation of septic shock has been correlated with more organ dysfunction and worse outcomes [27].

Many septic patients display persistent lactic acidosis in spite of an elevated cardiac output and normal or even increased SvO_2. This implies that mechanisms

unrelated to macrohemodynamics sustain tissue dysoxia in this setting, i.e., a loss of so-called hemodynamic coherence, with significant negative impact on outcome [28]. Impaired microcirculatory perfusion is indeed a prototypical perturbation in experimental [29] and human sepsis [30], which may impair tissue oxygenation. Such microcirculatory derangements result in tissue CO_2 accumulation, which can be tracked, for example, by sublingual capnometry, as shown by Creteur et al. [31]. Accordingly, in a prospective observational study including 75 patients with septic shock, Ospina-Tascon et al. found a significant correlation between Pv-aCO_2 gap and microcirculatory alterations. These were independent of systemic hemodynamic status and persisted even after correction for the Haldane effect [32], indicating that the Pv-aCO_2 gap may be a useful tool to assess impaired microcirculation in sepsis [33]. Furthermore, Creteur et al. reported that increasing cardiac output with dobutamine in patients with impaired microcirculation resulted in a decreased regional PCO_2 gap (sublingual and gastric mucosal) that was associated with a significant increase in well-perfused capillaries [31].

In summary, an elevated (>6 mmHg) Pv-aCO_2 gap in sepsis detects stagnant dysoxia, whether related to a low cardiac output or a derangement in microcirculatory blood flow, and this holds true even in the presence of a normal or elevated SvO_2. As such, a high Pv-aCO_2 gap might prompt a trial to improve tissue blood flow by increasing cardiac output [34].

Finally, many septic patients with an elevated cardiac output exhibit a normal Pv-aCO_2 gap, resulting from elevated CO_2 washout by increased tissue blood flow. Many of these patients still display signs of ongoing dysoxia with lactic acidosis and organ dysfunction. Whether this pattern reflects cytopathic dysoxia or regional microcirculatory alterations not tracked by Pv-aCO_2 gap elevation remains to be established.

8.4 Use of the Pv-aCO_2 Gap as a Prognostic Tool

In sepsis, evidence exists that a Pv-aCO_2 gap >6 mmHg, even after normalization of blood lactate, is predictive of poor outcomes [35–37], which has been highlighted in a recent systematic review of 12 observational studies [38]. Whether this holds true for a broader population of critically ill patients with circulatory shock has been questioned in a recent meta-analysis of 21 studies with a total of 2155 patients from medical, surgical and cardiovascular ICUs [37]. Overall, a high Pv-aCO_2 gap was associated with higher lactate levels, lower cardiac output and central venous oxygen saturation ($ScvO_2$), and was significantly correlated with mortality. The latter was however restricted to medical and surgical patients, with no association found for cardiac surgery patients. Since the meta-analysis included only two studies in cardiac surgery, this negative result should be interpreted with caution. Three recent retrospective studies not included in the meta-analysis [39–41] indeed reported a negative impact of high postoperative Pv-aCO_2 gap on major complications and mortality after cardiac surgery, although with limited diagnostic performance [41].

Future studies are needed to refine the value of the Pv-aCO_2 gap as a prognostic biomarker in cardiac surgery patients, taking into account the low mortality (3.4%) in this population [42].

8.5 Pitfalls in the Interpretation of the Pv-aCO_2 Gap

As already mentioned, several factors may influence the position of the PCO_2-CCO_2 relationship by influencing the *k* factor of proportionality between both variables (see Fig. 8.2), which must be taken into account for a proper interpretation of the Pv-aCO_2 gap. These include the oxygen saturation of hemoglobin (Haldane effect), metabolic shifts of pH, temperature and hemoglobin concentration. In addition, it is essential to consider possible sources of errors in the measurement of PCO_2, including contamination of the samples with fluid or air bubbles, and insufficient precision of the gas analyzer. When comparing successive determinations of Pv-aCO_2 gap, it is therefore recommended to consider only variations of at least ± 2 mmHg as real changes [43].

Two additional confounders in the interpretation of the Pv-aCO_2 gap require some discussion. The first is hyperoxia. It has been observed that, in patients with circulatory shock, ventilation at 100% inspired oxygen fraction (FiO_2) for 5 minutes increased venous PCO_2, and hence the Pv-aCO_2 gap, independent of changes in the hemodynamic status [44]. While this observation may be explained by a lower CO_2 affinity of hemoglobin due to elevated venous PO_2 (Haldane effect) [44], it may also reflect some impairment in microcirculatory blood flow, owing to the vasoconstrictive effects of hyperoxia [45]. The second confounder is acute hyperventilation with respiratory alkalosis. For example, as shown by Mallat et al. in 18 stable septic shock patients [46], an acute decrease in arterial PCO_2 from 44 to 34 mmHg produced by transient hyperventilation (30 min) induced a significant increase in PCO_2 gap (absolute 2.2 mmHg, relative +48.5%). Possible mechanisms include, first, increased aerobic production of CO_2 due to stimulated aerobic glycolysis under conditions of cellular alkalosis, and second, a reduction in microcirculatory blood flow due to the acute drop of CO_2. Thus, both acute hyperoxia and hypocapnia may be important confounders in the interpretation of an increased Pv-aCO_2 gap, which must be taken into account by the clinician.

8.6 Conclusion

The Pv-aCO_2 gap is a reliable indicator of impaired tissue perfusion, whether the result of a global reduction in cardiac output or to microcirculatory abnormalities, but it does not track tissue dysoxia, unless related to a stagnant mechanism. Being easily accessible and readily available, the Pva-CO_2 gap should be included in the integrated evaluation of the patient in circulatory shock. Several diagnostic algorithms incorporating Pva-CO_2 gradients have been proposed, such as those presented in Figs. 8.4 and 8.5. It remains to be established whether the Pva-CO_2 gap should be part of a resuscitation bundle protocol, and whether therapies aimed at normalizing an increased Pva-CO_2 gap could improve the dismal prognosis of circulatory shock.

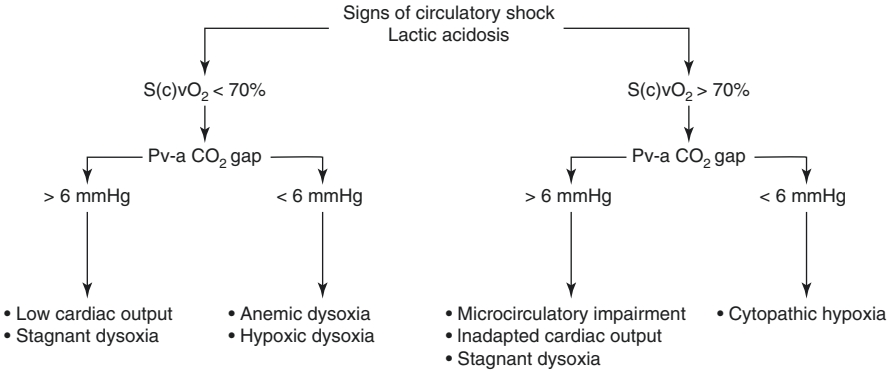

Fig. 8.4 Usefulness of the Pva-CO_2 gradient under conditions of circulatory shock. Proposed diagnostic algorithm integrating lactate, mixed (central) venous oxygen saturation ($S(c)vO_2$) and the Pva-CO_2 gap in patients with circulatory shock

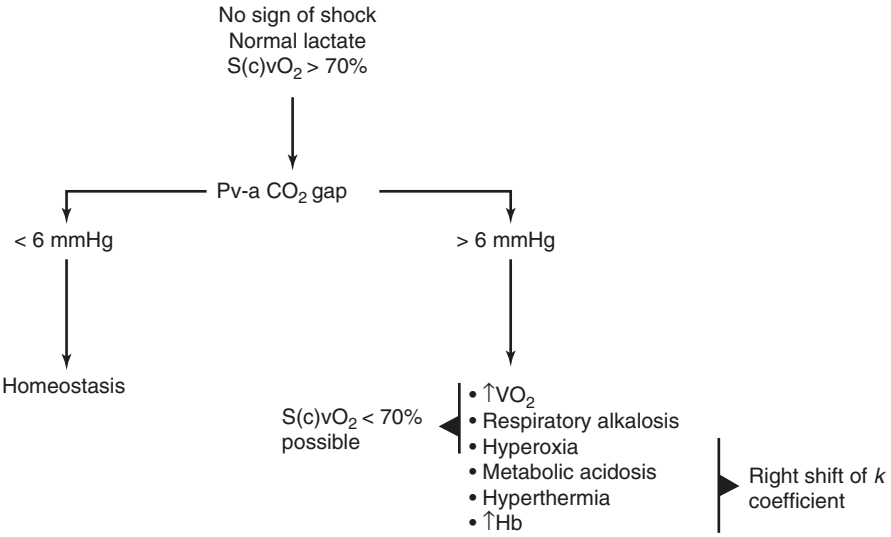

Fig. 8.5 The Pva-CO_2 gradient in the absence of circulatory shock. Proposed diagnostic algorithm to interpret an elevation in the Pva-CO_2 gap in the absence of circulatory shock and with normal blood lactate. *S(c)vO₂* mixed (central) venous oxygen saturation

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9 Still a Place for Aortic Counterpulsation in Cardiac Surgery and Patients with Cardiogenic Shock?

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9.1 Introduction

Since its introduction into clinical practice in 1967 [1], the intra-aortic balloon pump (IABP) has played a prominent and steadily increasing role in cardiovascular medicine as the most frequently used mechanical circulatory support device. However, since the publication of a neutral Shock II trial on the effects of aortic counterpulsation in patients with myocardial infarction complicated by cardiogenic shock [2], use of this technology has decreased tremendously in many countries. It is of note that this decline has been observed not only in the field of cardiology—a finding that may easily be explained by guideline recommendations more or less prohibiting the use of an IABP in cardiogenic shock [3]—but also in cardiac surgery. In many European cardiac surgery centers, the IABP has been more or less completely substituted by other mechanical circulatory support modalities like the Impella® or—more frequently—by veno-arterial extracorporeal life support (ECLS) systems. Unfortunately, the clinical results with both technologies are more than disappointing and show an unacceptably high mortality rate [4–6]. This finding is in clear contrast to several meta-analyses [7, 8] highlighting the beneficial effects on clinical outcomes of preemptive use of an IABP in cardiac surgery and an increasing number of publications showing beneficial hemodynamic and outcome effects of the IABP in cardiogenic shock [9–11].

The present chapter gives an overview of the effects of aortic counterpulsation in patients with cardiogenic shock and in patients with reduced myocardial function undergoing cardiac surgical procedures.

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9.2 Technological Aspects and (Patho-)physiological Effects

The technological basis of aortic counterpulsation has been detailed recently [12]. Briefly, an IABP-system consists of a driving console and a helium-filled balloon that is usually inserted via the femoral route, and positioned into the descending aorta with the tip of the catheter just below the left subclavian artery. Triggered either by the electrocardiogram (EKG) or the arterial pressure curve derived from an integrated pressure line, the balloon is inflated during the diastolic part of the cardiac circle immediately after aortic valve closure and deflated just before the aortic valve opens again during ventricular systole, leading to an increase in diastolic pressure (and thereby coronary perfusion), and a reduction in left ventricular (LV) afterload [12]. Alternative insertion modalities may be used in which the balloon is directed in an antegrade fashion via the ascending aorta (typically in a patient with severe peripheral artery disease needing IABP-support for weaning from cardiopulmonary bypass [CPB]) or via the left axillary artery for prolonged support in patients with end-stage heart disease awaiting transplantation or implantation of a LV assist device (LVAD).

In patients with reduced LV ejection fraction (LVEF), intraaortic counterpulsation had a pronounced effect on cardiovascular dynamics as determined from a leftward shift of the pressure-volume curve associated with an increase in stroke volume and a reduction in LV end-diastolic pressure [12]. It is of note that the increase in stroke volume depends on the balloon volume used [13] and the compliance of the arterial system [14]. Consequently, increasing balloon size from the usual size of 30 or 40–50 ml leads to an increase in stroke volume and a more pronounced decrease in LV filling pressure [13]. In contrast, higher arterial compliance will render diastolic augmentation and afterload reduction during LV ejection less effective [14].

Unfortunately, since the diameter of the descending aorta is a natural limit, balloons with higher volumes are slightly longer than low volume balloons and may thus—even if the tip of the catheter is correctly positioned 1 cm below the orifice of the left subclavian artery—extend beyond the celiac trunk or even the renal arteries and thereby—at least if inflated—occlude these visceral arteries. Consequently, adequate sizing of the balloon is crucial to avoid decreased intestinal perfusion. To appropriately size the balloon, an equation based on age, height, sex, and the distance between the jugular notch and the symphysis has been suggested, by which the distance between the left subclavian artery and the celiac axis (LSA-CA) can be calculated and the optimal balloon size may be chosen [15]. Recently a specifically designed ‘short’ balloon has been developed that may overcome this problem [16]. Unfortunately, this balloon has not been tested in larger patient series.

9.3 Intraaortic Counterpulsation in Cardiogenic Shock

After introduction into clinical practice [1], observational trials in the pre-percutaneous coronary intervention (PCI) era revealed beneficial effects of intraaortic counterpulsation on hemodynamics, metabolism, kidney function, and

mortality in patients with cardiogenic shock [17, 18]. Based on these observations, the 2008 version of the European Society of Cardiology (ESC) guideline on the management of cardiogenic shock gave a class 1 level C recommendation to use the IABP in the management of this condition [19].

As noted earlier, this perspective has completely changed following the IABP-Shock II trial [2], and the current ESC-guideline on the management of acute heart failure now states that the IABP is not routinely recommended in cardiogenic shock due to myocardial infarction (class III, level B) [3]. Moreover, the guideline authors state that there are also sparse data to support the use of aortic counterpulsation in other clinical settings. Thus it is far from astonishing that the use of IABPs has decreased tremendously in cardiology practice [20, 21].

Interestingly, a recent analysis of a German register for health outcomes showed that some centers continued to treat cardiogenic shock patients with an IABP and that these patients had a higher survival rate than patients managed conservatively or with other mechanical support systems (Fig. 9.1) [20]. Unfortunately, these data were not adjusted for disease severity and etiology of shock and may thus be subject to confounding. Interestingly, data from Israel, prospectively sampled in the Acute Coronary Syndrome Israeli Survey (ACSIS), point in the same direction and show that cardiogenic shock patients were frequently treated with an IABP from 2002 to 2012 (the year the IABP-Shock II data led to a downgrading of the IABP in the ESC guidelines) and had a significantly lower mortality than did conventionally treated

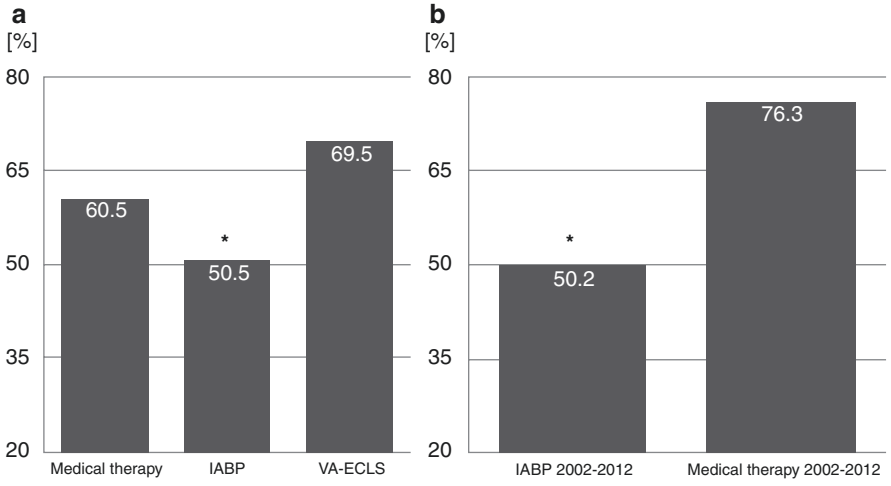

Fig. 9.1 The effects of different treatment strategies on hospital mortality in patients with cardiogenic shock. (**a**) Hospital mortality from cardiogenic shock (based on ICD-10 code R57.0 as a main or secondary diagnosis) derived from the German Research Data Center of the Federal Bureau of Statistics (DESTATIS). Data are based on 333,459 patients treated medically, 36,805 patients treated with an intra-aortic balloon pump (IABP), and 9774 patients treated with veno-arterial extracorporeal life support (VA-ECLS) from Ref. 20. (**b**) Hospital mortality from cardiogenic shock derived from the "Acute Coronary Syndrome Israeli Survey" (ACSIS) in 428 patients with cardiogenic shock treated with an IABP (n = 217) or medically (n = 211) from Ref. 21. *Significant difference between medical and IABP treatment

patients (Fig. 9.1) [21]. Taking a detailed look at the IABP Shock II trial [2] and recent data analyzing the hemodynamic effects of the IABP in cardiogenic shock—with and without myocardial infarction—[9], these observations sound rather plausible.

Multiple criticisms of the study design and performance were raised after the publication of the IABP-Shock II trial [2]. However, to the best of our knowledge, the limitation of inadequate statistical power has not been discussed. Nevertheless, the power analysis of this trial was based on a mortality rate more than twice as high as that observed in the IABP-Shock trial [22], a sort of pilot trial for the IABP—Shock II study [2]. Consequently, at least based on the results of the *per protocol* analysis (showing a mortality rate of 36.5% in the IABP and 41.4% in the control group), the IABP-Shock II study would have shown a significant mortality benefit of the IABP if the trial had been powered according to the pilot trial that revealed a mortality of only 28.6% in the control group [22] instead of the 56% that was used to calculate the necessary sample-size for IABP-Shock II [2].

The recent literature on intraaortic counterpulsation reveals that there has been renewed interest in this technology and that the IABP seems far from outdated. Very recently, Malick and coworkers retrospectively analyzed the hemodynamic effects of intra-aortic counterpulsation in cardiogenic shock patients with acute myocardial infarction and acute decompensated heart failure and observed that the heart failure patients showed a significantly more pronounced increase in cardiac output in comparison with the myocardial infarction patients; the majority of patients with acute decompensated heart failure increased cardiac output, some even up to 3 l/min. Filling pressures decreased comparably in both patient groups [9]. The pathophysiological basis for this difference in efficacy remains speculative, but may be related to the vasodilatation often observed in patients with cardiogenic shock from acute myocardial infarction [23].

By contrast, several recent observational studies support the notion that aortic counterpulsation is beneficial not only in patients with acute decompensated heart failure and severely reduced myocardial function but also in cardiogenic shock and acute myocardial infarction. Gul and coworkers reported on a series of patients with cardiogenic shock (70% with acute coronary syndrome; 30% with other causes) with an overall mortality rate of 36.3% [10]. However, if an IABP was implanted within 1 h after admission, mortality was only 24% in comparison with 49% if the pump was inserted later. These findings are in line with another recent observational trial in 57 patients with reduced ejection fraction admitted with a systolic blood pressure <100 mmHg. Patients treated early with an IABP had significantly lower 30-day mortality than patients who received the IABP later or were not treated with counterpulsation [24].

Den Uil et al. performed a small single center study comparing the effects of IABP-treatment (with a 50 ml balloon) compared to inotropes (enoximone or dobutamine) on mixed venous oxygen saturation (SvO_2) in patients with decompensated heart failure and low cardiac output and showed that SvO_2 normalized within 3 h in patients treated with an IABP but not in patients treated with inotropes. Ninety-day

mortality in the inotropic group was twice as high as in the IABP group, but this failed to reach statistical significance due to the small sample size [11].

A propensity-matched comparison study analyzed the effects of IABP versus a micro-axial LVAD (Impella®) in patients with acute myocardial infarction and cardiogenic shock and observed that the mortality was almost significantly higher with the Impella® than with the IABP (45% vs. 34%) and that bleeding complications were twice as high with the Impella® [6].

The observational data presented so far show, that—despite appropriate and early use of an IABP—a certain number of patients cannot be adequately stabilized with this technology and may need to be resuscitated using extracorporeal veno-arterial perfusion [9, 10]. This, however, is associated with an increase in afterload of the failing left ventricle and may not only lead to an increased myocardial work and oxygen consumption but also sometimes to disastrous complications, such as intraventricular thrombosis. There is ongoing debate on the optimal mode to unload the left ventricle during ECLS. However, some recent data show that the concomitant use of an IABP during veno-arterial ECLS is an effective way to unload the left ventricle and has comparable efficacy to that of the Impella® system [25].

Taken together, the observational data suggest that patients with acute decompensated heart failure and cardiogenic shock may benefit from aortic counterpulsation. Moreover, several trials contradict the neutral results of the IABP-Shock II trial [2] and show that the early use of an IABP may improve outcomes from cardiogenic shock complicating acute myocardial infarction. However, based on the observations of Malick and coworkers [9] this benefit may be restricted to patients presenting with increased systemic vascular resistance and supports the need to found the decision to start aortic counterpulsation on robust hemodynamic data. If an ‘upgrade’ to veno-arterial ECLS becomes inevitable, the IABP may still be used to ‘unload’ the left ventricle [25].

9.4 Intraaortic Counterpulsation in Cardiac Surgery

For many years, aortic counterpulsation was the modality of choice for mechanical support in cardiac surgery patients. Since the publication of the IABP-Shock II trial [2], the use of IABPs has also decreased in cardiac surgery, and many institutions now mostly rely on veno-arterial ECLS to support patients who cannot be weaned from CPB or only when using excessive doses of inotropes and vasopressors. There are no convincing prospective data available to support the use of ECLS in cardiac surgery patients. Moreover, meta-analyses suggest that the use of ECLS in cardiac surgery, even in experienced centers, is associated with an unacceptably high hospital mortality rate that is rarely below 60% [4].

By contrast, multiple meta-analyses support the notion that the preemptive, preoperative implantation of an IABP in high-risk patients reduces mortality [7, 8]. Based on this, a German S3-guideline on the use of the IABP in cardiac surgery recommends that hemodynamically stable, high-risk cardiac surgery patients should

be treated with intra-aortic counterpulsation, and that insertion should be performed preoperatively and before induction of anesthesia (grade of recommendation B, level of evidence 1b) [26].

There has been some criticism of these guidelines, because the studies included in the meta-analyses were small and monocenter, and several were performed by only one group of investigators. Additionally, two more recent trials [27, 28] failed to show a difference in the primary endpoint when comparing treated patients with a control group not supported by intra-aortic counterpulsation. However, in these studies, the methods clearly state that the IABP was switched off during CPB and therefore patients in the intervention group were devoid of an important effect of intra-aortic counterpulsation in cardiac surgery: the induction of pulsatility during CPB.

Several medium sized but elegantly performed studies have shown that induction of pulsatility by an IABP improves visceral and renal perfusion and thereby ameliorates the deleterious effects of non-pulsatile flow during CPB (overview in: [26]). Serraino and coworkers studied 501 patients in two groups—one supported by IABP during CPB and a control group with standard perfusion—and showed that IABP-pulsatile flow stabilized creatine clearance perioperatively and significantly reduced the incidence of grade 3 acute kidney injury from 20.4% to 7.8% [29]. Based on these findings, the German S3-guideline recommends that "upon preoperative insertion of an IABP this should be used to induce pulsatile blood flow during cardiopulmonary bypass" (grade of recommendation: A, level of evidence: 1b) [26].

In contrast to preoperative use, the intra- or postoperative use of an IABP—despite sometimes helpful to avoid an escalation to more invasive forms of mechanical support—has been associated with increased mortality [30]. Thus it is important to note that the German S3-guideline—based on the available literature—recommends a preemptive, prophylactic approach in a patient that typically has a normal or elevated systemic vascular tone. In line with the data of Malick et al. [9], this may help to avoid the insertion of an IABP when systemic vascular resistance is reduced (as is typically the case at the end of a long CPB run).

9.5 Conclusion

Taken together, there seems to still be a place for intra-aortic counterpulsation in cardiogenic shock and cardiac surgery. Unfortunately, large scale trials supporting this technology are still missing. This may be explained by the fact that public funding organizations (and their reviewers) categorize the technology as outdated and useless (mostly based on the findings of the IABP-Shock II trial [2]); however—and especially in countries like Germany in which invasive technologies like ECLS are largely reimbursed [31]—clinical and industrial interests are now focusing on more invasive mechanical and life support technologies. Nonetheless, as recently proposed in an editorial, "the tide seems to be turning" and "there is some sun on the horizon regarding the use of the IABP" [32].

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Part III

The Microcirculation

The Clinical Relevance of High-Altitude Microcirculation Studies: The Example of COVID-19

10

G. Capaldo, C. Ince, and M. P. Hilty

10.1 Introduction

Critical illness is often associated with impaired tissue oxygenation. As a consequence, the determinants of oxygen delivery are widely used treatment targets in the intensive care unit (ICU). The optimal treatment targets for the hemoglobin concentration and the hemoglobin oxygen saturation depend heavily on individualized aspects and global targets are of limited value. In the quest to better understand the underlying physiological mechanisms and help to guide individualized treatment decisions, it has been hypothesized that high-altitude research may provide a model for processes in critical illness associated with inadequate delivery of oxygen to the tissues and to help understand the underlying mechanisms and physiological adaptation to hypoxemia [1]. The impact of adaptation to high altitude exposure on several important regulation mechanisms has been uncovered, such as the finding that cerebral autoregulation is impaired in high-altitude Himalayan residents [2]. Adaptation processes have also been shown to be protective, with pulmonary vascular remodeling protecting from high-altitude pulmonary edema but increasing right ventricular afterload, precipitating the risk for subacute right heart failure known as subacute mountain sickness [3], or through the induction of hypoxic tolerance in parenchymatous organ cells in animal models [4].

However, despite these compelling links, a direct connection between high-altitude research and clinical relevance in critically ill patients has never been shown. It was not clear whether critical illness modifies the response to hypoxemia

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or whether the adaptation processes may be available to critically ill patients [5]. These questions have been very acutely brought to the spotlight during the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic with its high incidence of acute respiratory distress syndrome (ARDS) associated with the coronavirus disease 2019 (COVID-19), often accompanied by severe hypoxemia during a long treatment course.

10.2 Microcirculatory Function Regulates Oxygen Delivery to the Tissue

The most basic mechanisms underlying the response to hypoxemia are those related to the delivery of oxygen to the organs. Even though the global oxygen delivery capacity of the circulatory system may be quantified with the straightforward measurements of cardiac output, hemoglobin concentration and arterial hemoglobin oxygen saturation, it has become clear that in critical illness the ability of the microcirculation to distribute red blood cells (RBCs) in the tissues determines the outcome [6, 7]. Oxygen transport to the tissues through the microcirculation is accomplished by the RBCs through convection and diffusion [8, 9]. Mathematical models show how tissue oxygenation is affected by changes in capillary blood flow and hematocrit, with the latter having the greater effect on tissue oxygenation [10, 11]. Consistently, a microcirculatory reduction in RBC availability with capillary derecruitment and resulting tissue hypoxia is seen in postoperative anemia [12] as well as after fluid expansion in experimental [13] and clinical settings [14]. This effect may be counteracted with RBC transfusion [12]. It thus follows that the main method to increase oxygen delivery to the tissues is by increased RBC availability, a parameter we have referred to as tissue RBC perfusion [15]. It must be remembered that this RBC availability and anemia tolerance are highly dependent on the organ type, with each organ having its own characteristic functional capillary density dependent on its metabolic needs [16].

10.3 Measuring Oxygen Delivery to the Tissue

In the microcirculation, the direct visualization of the distribution and movement of RBCs in the tissue can serve to assess these effects [9]. The ability to independently quantify the determinants of oxygen delivery through the microcirculation forms the basis for the assessment of the adequacy of oxygen supply to the tissues and the effects of hypoxic exposure. However, the quantification of microcirculatory delivery of oxygen has remained challenging. Many advances on visualizing RBC movement through the tissues have been made over the last few decades, leading to the development of handheld vital microscopy, and the improvement in microscopy techniques from orthogonal polarization spectral, to sidestream dark field [17] and incident dark field [18] imaging. The latter technique enables the accurate *in vivo*

visualization of the microcirculation on the surface of organs in two spatial dimension and a time axis, and through its implementation in a truly portable device, has brought the measurement of the sublingual microcirculation to the bedside and to high altitude research. Recent improvements in advanced computer vision algorithms have enabled the use of handheld vital microscopy image sequences to estimate functional capillary density and capillary hematocrit as measures of microcirculatory diffusion capacity, and quantitative RBC velocity as a measure of microcirculatory convection capacity [19]. These advances form the basis to better understand the effect of changes in oxygen availability in mountaineers as well as in critically ill patients.

10.4 Recruitment of Non-perfused Sublingual Capillaries as a Mechanism to Increase Microcirculatory Oxygen Extraction Capacity at High Altitude

These techniques enabled the physiologic adaptation mechanisms to high altitude to be studied in a large expedition to the Himalayan mountains. During the ascent to 7126 m, changes in microcirculatory function were studied in 41 healthy mountaineers [20]. By hypoxia-induced capillary recruitment, the diffusion distance could be decreased and thus the microcirculatory oxygen extraction capacity increased. A concurrent decrease in cardiac output and unchanged blood pressure showed that these mechanisms were an intrinsic function of the sublingual microcirculation, independent of macrocirculatory function. Similar findings were made comparing the microcirculation of Sherpas and lowlanders while ascending to high altitude [21]. At high altitude, Sherpas showed an increase in both microcirculatory blood flow and capillary density as compared to baseline. The difference between Sherpas and lowlanders was the extent of the adaptation process. Sherpas were found to increase small vessel density and flow to a greater extent than the lowlanders. Moreover, the former study showed that the mountaineers who did not eventually reach the summit, had a lower functional capillary density at baseline, suggesting that different states of microcirculatory baseline function may correspond to differences in physiological reserve. As opposed to the changes in microcirculatory function induced by hypoxic exposure, in response to a supra-physiologic increase in oxygen supply, the sublingual microcirculation shows a dose-dependent decrease in the indexes of capillary perfusion and an increase in the heterogeneity of perfusion in healthy volunteers [22, 23]. Some of the observed alterations even persisted in the measurements taken after the return to normoxia [23]. Taken together, these observations at high altitude demonstrate that the mechanism to increase microcirculatory delivery of oxygen at high altitude is to increase RBC availability. This agrees with the theoretical considerations that prioritize RBC availability over plasma expansion and the increase in convection capacity at the cost of capillary hematocrit [10, 11], as discussed above.

10.5 The Microcirculation in Critically Ill Patients with COVID-19

The outbreak of the COVID-19 pandemic provided both the need to treat an unprecedented number of severely hypoxemic patients in ICUs around the world, and a renewed incentive to understand the interaction between the physiological adaptations to hypoxemia and critical illness. Once COVID-19 has progressed to critical illness, the disease is characterized by hypoxic respiratory failure, inflammatory and coagulation activation, and approximately 24% of cases progress to multi-organ failure and death [24]. The microcirculation was soon identified as a target to help understand this novel disease [25]. A multicenter study of the sublingual microcirculation in mechanically ventilated COVID-19 patients, aimed to identify whether the COVID-19-associated inflammatory reaction would lead to microcirculatory dysfunction similar to sepsis, and if characteristic changes could be identified in the systemic microcirculation [26]. Rather unexpectedly, in this study, similar mechanisms of microcirculatory adaptation were found in COVID-19 patients as previously found in healthy mountaineers at high altitude [20], demonstrating intact adaptation mechanisms within the microcirculation to the hypoxemia caused by the severe pulmonary dysfunction. Microcirculatory measurements in COVID-19 patients showed that an intact microcirculation is able to increase the oxygen extraction capacity by decreasing diffusion distances between capillaries (by increased functional capillary density, increased capillary hematocrit and capillary-to-systemic hematocrit ratio) and by increasing convection of RBCs (Fig. 10.1a, b, c, d) [26]. The feature that most clearly differentiated the microcirculatory function in COVID-19 patients as compared to healthy volunteers was the capillary-to-systemic hematocrit ratio (Fig. 10.1e). COVID-19 patients were also found to have raised leukocyte and RBC microaggregate counts in their microcirculation as was expected in response to the inflammation and coagulopathy seen in these patients. Nevertheless, the adaptation mechanisms of the microcirculation were largely unaffected as long as the sequential organ failure assessment (SOFA) score was below a threshold of 10.

10.6 Clinical Implications Relating to the Treatment of Critically Ill and Perioperative Patients

Demonstration of the ability of the microcirculation to adapt to hypoxemia in the same way in mechanically ventilated COVID-19 patients as in healthy mountaineers ascending to high altitude, provides a clear link between high altitude research and critical care medicine. This mechanism pertains to the basic physiological principle of RBC availability in the tissues as the main determinant of oxygen delivery. This connection may help to guide the design of studies in hemodynamic management, and, by emphasizing the importance of adaptation to hypoxemia in critically ill patients, may provide the rationale to promote its beneficial effects not only by avoidance of treatment-induced hyperoxia, but by choice of optimal oxygenation

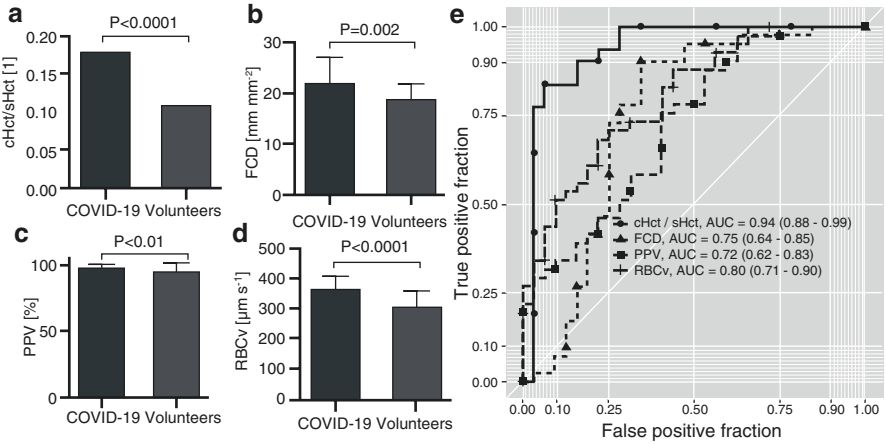

Fig. 10.1 Compared with healthy volunteers, patients with COVID-19 were found to have a higher capillary-to-systemic hematocrit (cHct/sHct) ratio (**a**), functional capillary density (FCD) (**b**) and red blood cell velocity (RBCv) (**d**). There was no evidence of plugged vessels in the COVID-19 patients as evidenced by a proportion of perfused vessels (PPV) > 94% in both groups (**c**). Receiver operating characteristic curve analysis of the different microcirculatory hemodynamic parameters identified cHct/sHct and RBCv as the most sensitive parameters for distinguishing the microcirculatory function of COVID-19 patients compared to healthy volunteers (**e**). *AUC* area under the curve. Reproduced with permission from [26]

targets. The former has been clearly shown in non-critically ill as well as in critically ill patients [27]. Recent randomized trials have further explored the latter hypothesis. It has been shown that lower oxygenation targets are safe [28–30], potentially triggering protective adaptive processes and avoiding episodes of hyperoxemia. The lowest safe dose of oxygen still remains to be defined. Similar to interventions to optimize tissue RBC perfusion, different oxygen strategies might be appropriate for different patient groups as part of an individualized treatment strategy. A post hoc analysis of the ICU-ROX trial (Intensive Care Unit Randomized trial comparing two approaches to OXygen therapy) raised the possibility of harm when using conservative oxygen therapy in patients with sepsis [31]. Interestingly, the physiologic microcirculatory increase in oxygen extraction capacity to hypoxemia in COVID-19 patients is lost with higher SOFA scores [26], strongly suggesting that it is the loss of the physiological ability to adapt to hypoxemia that promotes organ failure. This important conclusion can be expected to have significant consequences for the choice of therapeutic strategies.

These clinical findings underscore the physiological importance of RBC availability in the tissue. Increasing RBC availability by increasing the hematocrit through blood transfusion seems therefore a reasonable response. However, clinical trials evaluating RBC transfusion thresholds failed to show a benefit of a liberal over a restrictive transfusion threshold [32]. When examining the effect of different transfusion thresholds on the microcirculation, it has been found that transfusion thresholds do not reflect the microcirculatory perfusion of patients, as an impaired

microcirculation could be found independent of their hemoglobin level [33]. Positive and negative effects on the microcirculation have been observed with both liberal and conservative transfusion thresholds. Tissue RBC perfusion has recently been suggested as a quantitative parameter that can be automatically measured using handheld vital microscopy imaging, to enable individualized targeting of RBC availability in the tissue [15]. Taking into account all its determinants, including functional capillary density, capillary hematocrit and RBC velocity, it may be best suited to individually determine RBC transfusion thresholds within safety boundaries that are to be established.

10.7 Conclusion

Physiologic adaptive mechanisms observed in the systemic microcirculation in healthy volunteers at high altitude have also been detected in critically ill COVID-19 patients. This is proof for the clinical relevance of high-altitude research and underscores its utility as a model for hypoxemia in the critically ill patient. Facilitated by newly developed parameters, such as tissue RBC perfusion as automatically measured via handheld vital microscopy in the sublingual microcirculation, future studies may determine the optimal targets for tissue RBC perfusion and oxygenation and provide a promising approach to improve morbidity and mortality in critically ill patients.

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11 Observation of Leukocyte Kinetics Using Handheld Vital Microscopes During Surgery and Critical Illness

Z. Uz, C. Ince, and M. S. Arbous

11.1 Introduction

Systemic inflammation occurs in a wide range of disease states [1–3], including sepsis [4] and ischemia/reperfusion injury such as can occur following cardiac surgery [5]. Leukocyte recruitment and adhesion to the endothelial cell wall followed by extravasation are hallmarks of the systemic inflammation that occurs during these diseases.

The interaction between leukocytes and the endothelium can be best observed in the postcapillary venules of the microvascular system [6]. Many studies have underlined the relevance of the observation of microvascular alterations in red blood cell (RBC) kinetics as an early recognition of the clinical severity and response to therapy, in advance, and independent of, changes in systemic hemodynamic parameters [7–11]. Consequently, expanding such microvascular alterations by identification of the interaction between leukocytes and the endothelium may provide additional information regarding the severity of inflammation in relation to the pathophysiological condition of patients. The ability to assess the behavior of microvascular leukocytes can potentially provide a relevant diagnostic tool for assessment of the severity of inflammation at the bedside [12].

Intravital microscopy in combination with fluorescent dyes attached to leukocytes is considered as the golden standard for quantification and identification of leukocyte kinetics in the postcapillary venules of the microvascular system [6]. Studies using this technique, which can be only applied in animal experiments, have provided basic knowledge regarding the cascade of events involved in the recruitment of leukocytes

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to sites of inflammation in the microvascular system. Clinical studies observing leukocytes have mainly been limited to the human skin and eye [13–15]. A limitation associated with the need to use a dye to visualize leukocyte kinetics is the potential deleterious effects of such dyes. Another limitation is the need for surgical interventions to access the site of interest, which in itself can induce a cascade of events leading to leukocyte activation due to induced surgical trauma [6, 16].

In the last few years, new methodologies have been introduced to assess leukocyte kinetics in patients using non-invasive handheld vital microscopy devices. Hand-held vital microscopy imaging allows direct observation of the microcirculation at the bedside of the patient.

In this chapter, we present an overview of methodologies applied to hand-held vital microscopy images to assess leukocyte kinetics in surgical (cardiac surgery, liver resection surgery) and critically ill (sepsis, coronavirus disease 2019 [COVID-19] pneumonia) patients.

11.2 Microcirculation and Hand-held Vital Microscopes

The microcirculation consists of the smallest blood vessels, with diameters less than 100 μm. In the microcirculation, oxygen rich blood flows from the arterioles into the capillaries, and exits the capillary system through the venules into the systemic venous system. Although the morphological properties of the microcirculation vary in the different organ systems, the three microcirculatory vessel types (arteriole, capillary, venule) can be readily distinguished from each other [17].

In the microcirculation, oxygen is released by the RBCs in the capillaries to the tissue and this function is essential for delivering the adequate tissue oxygenation needed to support organ function. The microcirculation also has a central role in the action of the immune system, providing an interface between the circulation and tissue cells [17]. Monitoring such important functions of the microcirculation at the bedside during disease had previously not been available. However, with the introduction of hand-held vital microscopy devices, many clinical microcirculation studies have been carried out [18].

Adaptation and implementation of hand-held vital microscopy to assess the microcirculation started in the 1990s with the introduction of orthogonal polarization spectral (OPS) imaging [19]. This technique was improved upon by the introduction of a second-generation device based on sidestream dark field (SDF) imaging [20]. More recently, incident dark field (IDF) imaging was introduced with better and greater capillary visualization when compared to the previous versions of hand-held vital microscopy [21]. As a result of these technological developments in hand-held vital microscopy, an expanding number of studies in many different clinical scenarios have been carried out showing the potential importance of microcirculatory imaging at the bedside. The microcirculation is now considered as an essential hemodynamic compartment in addition to systemic variables in the clinical setting [12, 18, 22].

The sublingual microcirculation, located in the sublingual cave of the mouth, has been the best studied location of the microcirculation using hand-held vital microscopy [7, 18, 22]. The sublingual microcirculation is easily accessible, which allows rapid acquisition of microcirculatory images of sufficient quality for analysis. Additionally, the non-invasive character of sublingual microcirculatory measurements makes it ideal for use at the bedside [18].

In the last few decades, many sublingual microcirculatory studies have been performed in emergency departments, intensive care units (ICUs) and operating rooms. These measurements have shown that the sublingual microcirculation is commonly affected in critically ill patients [18]. These studies have also shown that such microcirculatory alterations can occur independent of changes in the systemic circulation, a condition referred to as a loss of hemodynamic coherence between the micro- and macrocirculation, emphasizing the importance of monitoring the microcirculation in parallel to the systemic circulation. The nature of shock and resuscitation as it affects tissue perfusion therefore cannot be readily understood without assessment of the microcirculation [7, 18]. In the clinical setting of the ICU, cardiovascular failure manifests first in the microcirculation. Furthermore, upon resuscitation of the cardiovascular system, the microcirculation is the last to improve. In critically ill patients, several studies have shown that adverse outcome is associated with a persistently altered microcirculation despite the presence of a normalized systemic circulation [7, 23].

Besides monitoring alterations in RBC kinetics in the microcirculation, there is also a need to assess the inflammatory status of the microcirculation, which can be accomplished by observation of the kinetics of microcirculatory leukocytes. The possibility of accomplishing this, opens the door to a new way of monitoring inflammation at the bed side.

11.3 Microcirculation and Inflammation

The microcirculation plays a central role in the response to inflammation, with all the important compartments of the microcirculation participating in the inflammatory response.

These microvascular compartments show specific phenotypic alterations during inflammation aimed at facilitating the transport of inflammatory cells, chemokines and cytokines to the site of inflammation following injury or infection, to dilute the injurious trigger or agents, to isolate the healthy site and the systemic circulation from the ongoing inflammatory response, and to prepare the physiological phase for regeneration and tissue repair in order to heal the affected area [1].

These compartments include: arterioles can be subjected to oxidative stress, which can lead to impaired vasomotor function and enhanced thrombosis; capillaries can show reduced perfusion (decreased RBC flow) due to capillary plugging by leukocytes, which can obstruct the capillary flow; and the venules, which can be subjected to oxidative stress, show increased leukocyte rolling, leukocyte adhesion

and leukocyte transmigration, increased vascular permeability due to the chemical mediators (chemokines/cytokines), platelet recruitment and increased thrombosis/coagulation.

Being able to visualize such microvascular changes can provide important clinical information at the bedside and contribute to individualized medicine regarding the presence of inflammatory pathology. Such information could guide clinical decision making of the surgical and critically ill patient in real time. In recent years, several methodologies have been introduced to assess microcirculatory leukocytes at the bedside using hand-held vital microscopy methodologies [12, 24–26].

11.4 Observation of Leukocyte Kinetics Using Handheld Vital Microscopy

The latest generation of hand-held vital microscopy techniques is the IDF imaging technique [21]. IDF imaging uses green light with a wavelength of 548 nm, emanating from circumferential light-emitting diodes placed at the tip of a light guide that illuminates the tissue surface of interest. A magnifying lens is situated in the middle of these circumferential light-emitting diodes. The green light is absorbed by deoxyhemoglobin and oxyhemoglobin present in the RBCs of the microcirculation enabling visualization of RBCs as dark globules flowing through the microcirculation giving a sharp contour visualization of the microvasculature. The unabsorbed light is scattered into the surrounding tissue providing a white background. The direction and amount of microvascular flow as well as vessel diameters are important measures used to distinguish between an arteriole, capillary and a venule. The venules are the largest vessels; the capillaries are the smallest vessels with single file movement of the RBCs one at a time. The arterioles are characterized by fast flow making it difficult to see the RBCs individually. In contrast, RBCs can be individually visualized in the capillary moving at a much slower velocity. Hand-held vital microscopy imaging records images at a frame rate of 25 frames/s. The hand-held vital microscopy device is a digital computer-controlled camera attached to a hand-held microscope. The field of view of the image area is 1.55 mm × 1.16 mm. The image-clips obtained by hand-held vital microscopy imaging are computer stored, and analyzed off line. Hand-held vital microscopy imaging is non-invasive and thereby an ideal device for use at the bedside.

The assessment of the microcirculation by hand-held vital microscopy imaging provides quantitative measurement of functional microvascular parameters. Two main functional parameters are present, related to convection and diffusion. Convection is quantified by flow parameters, such as microvascular flow index and RBC velocity [18]. The diffusion capacity of the microcirculation is quantified by functional density parameters, such as the total vessel density, perfused vessel density and the functional capillary density. Density is characterized by the sum of the vessel length corrected for the presence of flow [18].

Methods to assess leukocyte kinetics in the microcirculation using hand-held vital microscopy have been recently introduced. The challenge in visualizing

leukocytes is that they are invisible for hand-held vital microscopy imaging as they do not contain hemoglobin. Instead these have to be detected by their specific kinetics since leukocytes are large and show characteristic motion when activated by pro-inflammatory chemokines and endothelial structures (sticking, rolling, adhesion, and transmigration). Furthermore, they move slower than RBCs due to their size and composition. Three methods have been developed: conventional manual counting [12], frame averaging [26, 27] and the space time diagram [24, 25].

11.4.1 The Conventional Manual Counting Method

The first observations of human leukocytes obtained by hand-held vital microscopy were described by Bauer et al. [12]. In their study, rolling leukocytes were quantified using the manual counting method with OPS imaging. OPS imaging of the sublingual microcirculation was applied in 47 patients during coronary artery bypass surgery on cardiopulmonary bypass (CPB). In all the patients, the microcirculatory flow and density parameters were assessed by OPS. In a subpopulation of eight patients, rolling leukocytes were counted and their CD18 measured. The measurements showed a threefold increase in leukocyte count 1 h after termination of CPB, and a significant increase in the CD18 in the late phase of CPB. In parallel, the systemic leukocyte count also increased significantly at the late phase of CPB and 1 h after termination of CPB.

This methodology for measuring leukocytes from the sublingual microcirculation video images obtained by OPS, consists of dividing the image into nine quadrants. In each quadrant, the post-capillary venules and the rolling leukocytes are counted manually by eye. The average of rolling leukocytes per post-capillary venule over 20 s is reported. A major difficulty with this method is the inability to distinguish between plasma gaps and leukocytes, both of which appear as colorless on hand-held vital microscopy, whereas the RBCs appear as dark structures. Nevertheless, this was the first report identifying rolling leukocytes in the microcirculation, measured non-invasively using hand-held vital microscopy at the bedside during cardiac surgery.

11.4.2 The Frame Averaging Method

Recently another manual counting method was introduced using a frame averaging method [26]. This method was aimed at overcoming the inability to distinguish between leukocytes and plasma gaps. To count the microcirculatory rolling and adhered leukocytes, the obtained video-clips were first frame averaged and stabilized using a Gaussian filter method [26, 27]. This filter slows down the frame rate, which results in a blurred column of RBCs, plasma and non-rolling leukocytes. With this technique, the adhering and rolling leukocytes are not blurred, however, enabling their detection. With the application of this frame averaging method, the researchers could quantify not only the rolling, but also the adhered leukocytes.

The methodology was first applied to SDF images of the sublingual microcirculation by Fabian-Jessing et al. [26]. In their study, septic shock patients were compared to non-infected patients in the emergency department. A higher number of rolling and adhered leukocytes was found in septic shock patients when compared to the non-infected patients. The authors also found an increased number of adhered leukocytes in the non-surviving patients. In their study, the activated leukocytes (adhered/rolling leukocytes) were presented per unit vessel length of the total sum of vessels in the entire field of view. The systemic leukocyte count was not reported in these patients so that no comparison was possible between the systemic and microcirculatory leukocyte count.

We also applied this frame averaging method intraoperatively in 10 on-pump coronary artery bypass graft (CABG) patients [27], using images obtained from the IDF technique. To count the leukocytes after frame averaging, the observer identified at least one capillary-postcapillary venule unit in each image clip of the sublingual microcirculation (venule distal) over 4 s of time duration. Our study showed a significant increase in microcirculatory rolling and systemic leukocytes measured at the end of surgery. A drawback of our study was the inability to identify non-rolling leukocytes.

11.4.3 The Space-Time Diagram Method

The first objective quantification and identification of human microcirculatory leukocyte kinetics in the sublingual microcirculation, validated by our group, was made possible by the use of the space-time diagram [24]. A space-time diagram, introduced by Ellis and co-workers [28], is obtained by analysis of a single blood vessel whereby the y-axis represents the length of the vessel and the x-axis the time of blood cells entering the blood vessel. Such a diagram generates slated dark lines, each of which represents a RBC moving across the blood vessel, the slope of which measures its velocity. Plasma gaps and leukocytes are shown as white slated lines. The space-time diagram analysis allows the identification and kinetics of leukocytes in the human sublingual microcirculation. This methodology was validated by choosing specific anatomical units of a capillary connected to a venule. Analysis of such a unit allows precise identification of rolling and non-rolling leukocytes. In addition to the identification of rolling and non-rolling leukocytes, it was also possible to measure the velocity of the leukocytes and the RBCs by measurement of their slopes in the space-time diagram [24].

The space-time diagram uses the rheological characteristics of the leukocytes and RBCs in the microcirculation, taking into account the specific leukocyte-RBC interaction. The passage of RBCs and of leukocytes from arterioles to the capillary, and further into the venules, show different kinetics. RBCs are pliable, small and fast whereas leukocytes are large, stiff, heavy and slow. Thus, when they become activated, resulting in sticking, adhering and rolling, leukocyte velocity decreases and they can even stop moving, prior to their transmigration through the endothelial layer. Due to their slower movement through the capillaries, RBCs accumulate

behind the leukocytes forming a thicker dark diameter column, a formation referred to as the train formation [24]. By eye, these physiological characteristics of the leukocytes and RBCs are difficult to visualize by direct observation, but can be revealed using space-time diagram analysis.

A space-time diagram can be generated by specialized microcirculatory analysis software, such as Automated Vascular Analysis (AVA) [11] and the recently introduced MicroTools software [29]. The space-time diagram, as described above, provides dark and white slanted lines with each black line being generated by an RBC and each white line by a plasma gap or leukocyte. Due to the physiological nature of the train formation, a large white line coupled to a thick black line identifies the presence of a leukocyte.

By choosing capillary-postcapillary anatomical units without branches, it is possible to precisely identify the behavior of the leukocytes as they enter the postcapillary venule. The activated leukocytes show a significant change in velocity as they hit the venule and start sticking to the endothelium, and the large white band with the train formation of RBCs previously seen in the capillary is no longer linear, but rather shows a parabolic shape due to the change in velocity thus allowing identification of rolling-leukocytes. In this methodological study, the velocity of the rolling leukocyte was slower than that of the non-rolling leukocytes. RBC velocity was higher when compared to the rolling and non-rolling leukocyte velocities [24].

In a study performed by our group, this space-time diagram method was applied to the analysis of sublingual and intestinal microcirculation in the perioperative phase of patients having major liver resection [30]. IDF imaging revealed a higher number of rolling leukocytes at the end of major liver resection, parallel in the sublingual and intestinal microcirculation. Also, a diminished microvascular flow was found 24 h after surgery, with persistently higher rolling leukocytes when compared to the baseline sublingual microcirculation, suggesting a relationship between the blood flow obstruction and the presence of activated leukocytes. In parallel to the rolling leukocytes in the microcirculation of the sublingual and intestinal microcirculation, systemic leukocytes and syndecan-1 levels were also significantly increased at the end of surgery. A moderate correlation was found between rolling leukocyte numbers and syndecan-1 levels in the blood, indicating the association of endothelial glycocalyx shedding and the activation of leukocytes.

11.5 Clinical Perspective and Future Expectations

Various diseases (sepsis, shock, stroke, cancer) are accompanied by an immune response that activates leukocytes, resulting in leukocyte sticking, rolling and adhesion to the endothelium [31]. The upregulation of endothelial adhesion molecules facilitates leukocyte sticking and rolling, eventually leading to para- and transcellular diapedesis. The endothelial glycocalyx is a protective layer, and its degradation precedes the expression of endothelial adhesion molecules making the leukocyte-endothelium interaction possible. In this manner, the direct visualization

of leukocyte adhesion to the endothelium is also a direct indication of a compromised glycocalyx [32]. This leukocyte-endothelium interaction is an important clinical measure of vascular pathology [33].

Few non-invasive techniques are available at the bedside that allow demonstration of the presence of leukocyte-endothelium interactions at a cellular level other than the use of biomarkers or dyes attached to leukocytes. The ability to visualize and identify the kinetics of leukocyte-endothelium interactions at the bedside may have significant clinical applications and may even offer a therapeutic goal.

However, for such an application to be realized, automated, fast and easy to use, clinically applicable software applications are needed to overcome the time-consuming character of the existing methodologies described in this chapter. Recently, a complete, automated software called MicroTools was clinically validated to quantitatively and automatically measure hand-held vital microscopy-generated functional microcirculatory parameters [29]. Addition of the observation and assessment of leukocyte kinetics to MicroTools is expected to be an important innovation to this software in the future.

A further required development is that currently each method (manual, frame averaging and space-time diagram) has different units for describing leukocyte presence: rolling leukocytes/post-capillary venule/20 s, number of leukocytes/mm, rolling leukocytes/capillary-postcapillary venule/4 s, non-rolling leukocytes/capillary-postcapillary venule/4 s. Nevertheless, all the studies in surgery and critical illness have shown a significant increase in microcirculatory leukocytes over a time period, irrespective of the different units used. To compare the results from different studies measuring microcirculatory leukocytes, it will be important to have a consensus regarding a uniform unit for the leukocyte kinetics obtained by hand-held vital microscopy imaging.

Recently we carried out a multicenter international microcirculation study in which we focused on three alterations excepted to occur during COVID-19: alterations in microcirculatory hemodynamics, the presence of microaggregates in the microcirculation, and an enhanced presence of microcirculatory leukocytes [25]. The response of the micro-hemodynamics to COVID-19 was interesting in that, in contrast to the conventional microcirculatory response to sepsis consistent with distributive shock, in COVID-19 we saw an adaptive response to hypoxemia similar to that found at high altitude. This response was characterized by an increase in functional capillary density and capillary hematocrit at the expense of systemic hematocrit, which was lower than that found in health. We also noted the presence of microaggregates, a rare occurrence in the sublingual microcirculation, which we had only previously found in a case study in a cardiac surgery patient receiving protamine at the end of surgery [34]. The most striking feature of the COVID-19 microcirculation was the expected large numbers of leukocytes, which were also present in the microcirculation of the COVID-19 patients (Fig. 11.1). These we were able to quantify by identifying them in capillary venule microcirculatory units using the space-time diagram methodology described above.

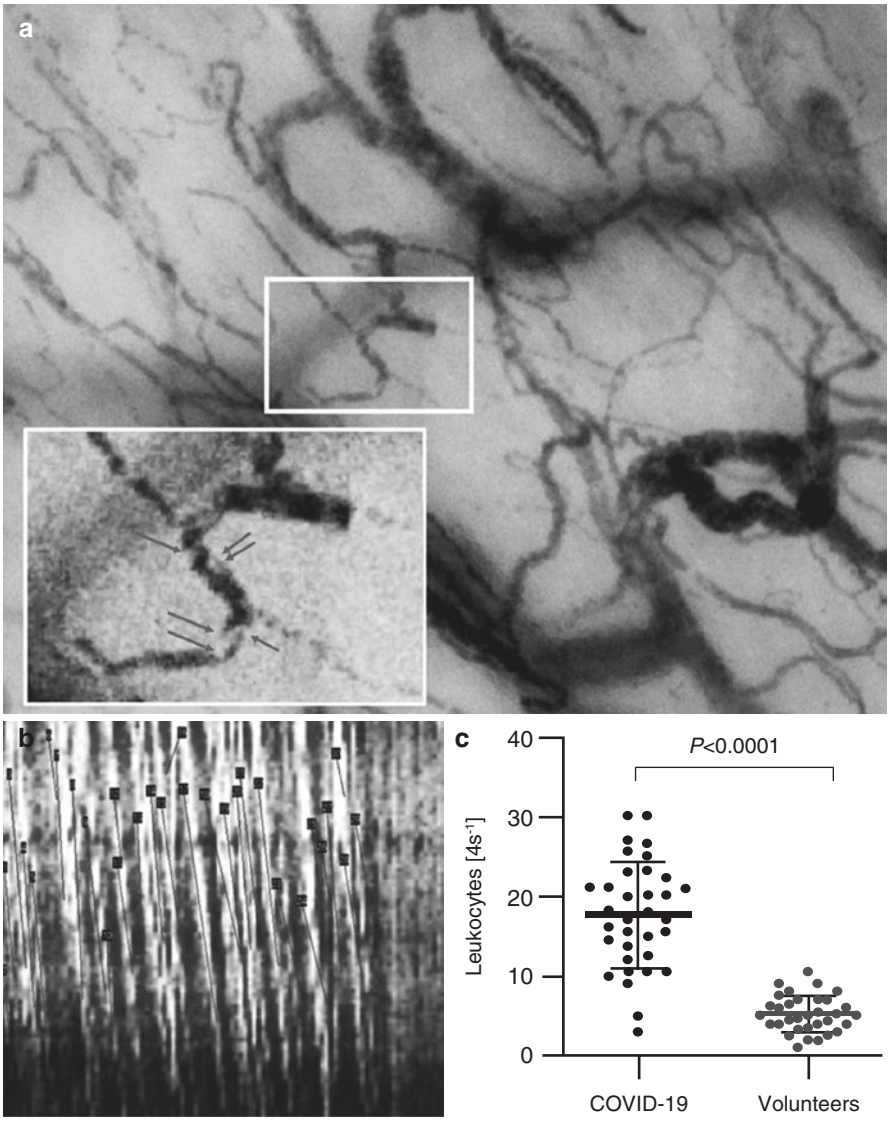

Fig. 11.1 Microcirculatory leukocyte quantification in coronavirus disease 2019 (COVID-19) patients using the space-time diagram method. (**a**) A screenshot of the sublingual microcirculation with the presence of leukocytes is shown. The black globules present the red blood cells, the white/grey globules are leukocytes. In the left corner of the image, a capillary-postcapillary venule is superimposed, the gray arrows indicate the presence of leukocytes. (**b**) An example of a space-time diagram with the presence of leukocytes as slanted white lines. The leukocytes travel down the length of a capillary (y-axis) over 4 s (x-axis). The number of such white lines in the space-time diagram is used to calculate the leukocyte per 4-s clip (leukocytes/4 s). The black slanted lines are the red blood cells, the slopes of these lines are used to measure the red blood cell velocity. (**c**) The total count of sublingual microcirculatory leukocytes measured in the capillary-postcapillary venule units of COVID-19 patients is significantly higher than that of healthy volunteers
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11.6 Conclusion

The advent of automated quantitative microcirculatory analysis platforms, such as MicroTools, and integrating leukocyte detection into these software platforms will provide a unique diagnostic tool for point-of-care combined evaluation of hemodynamic and inflammatory alterations in critically ill patients, as shown in our COVID 19 study. It is expected that in the future microcirculatory analysis will be able to be included in triage procedures to support clinical decision making at the bedside.

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Part IV

Airway and Non-invasive Ventilation

Tracheostomy for COVID-19: Evolving Best Practice

12

T. Williams and B. A. McGrath

12.1 Introduction

The global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a dramatic impact upon all areas of healthcare, and this is no more evident than in critical care. Management of the critically ill evolved over time, with variability in admission criteria and the use of invasive ventilation reported from around the world and within individual countries [1]. However, the majority of patients admitted to intensive care units (ICUs) required advanced respiratory support [1], often for longer periods than expected when compared with historical viral pneumonias [2]. Tracheostomy is an entrenched element of modern critical care, with the dominant indication established as facilitating long-term ventilation and 'weaning' from respiratory support. Additional indications include actual or threatened upper airway obstruction, facilitating pulmonary clearance and to offer a degree of 'protection' against pulmonary aspiration. Prior to this pandemic, tracheostomy could be anticipated in 8–13% of patients receiving advanced respiratory support in modern ICUs [3]; usually temporary, but often *in situ* for several weeks (a median of 28 days in one recent UK-wide study) [4]. Reported

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rates of tracheostomies utilized during the coronavirus pandemic vary significantly from 16% to 61% [5, 6], but are certainly significantly higher than pre-pandemic rates.

As with many aspects of management, our understanding of how best to employ tracheostomy during the pandemic has evolved. There are many potential benefits of tracheostomy for the patient and for stressed healthcare systems, which have led some institutions to employ tracheostomy relatively early in the patient's ICU stay, but detailed outcome data from large case series are not available. Tracheostomy insertion and subsequent management also requires trained, equipped and supported staff to minimize the potential for complications and patient safety incidents [7]. It is essential that we understand which patients with coronavirus disease 2019 (COVID-19) may benefit from tracheostomy, along with when and how it should be employed. Importantly, in non-COVID-19 patients, only around 20% of tracheostomy patients survive beyond ICU discharge to 1 year [8], repeatedly raising questions about patient selection, which are relevant as hospitals around the world struggle to manage large volumes of critically ill patients. These problems are compounded in the pandemic with patients frequently managed in makeshift or unfamiliar settings, often by non-ICU trained medical, nursing and allied healthcare professional staff.

In this state-of-the-art review, we consider these important issues affecting around one-fifth of critically ill patients presenting to our ICUs with severe respiratory failure resulting from COVID-19.

12.2 Why Perform a Tracheostomy?

Tracheostomy can benefit patients who require prolonged ventilation: enabling sedation to be reduced or stopped; enabling the removal of the trans-laryngeal tube to facilitate laryngeal rehabilitation; and offering an interface for variable invasive ventilatory support without having to resort to re-sedation and tracheal re-intubation [9]. Considering that patients with COVID-19 typically have longer periods of ventilation than patients with other viral pneumonias [2], it is not surprising that studies have demonstrated that tracheostomy for COVID-19 may confer a survival benefit [5], aid weaning from ventilatory support [6], and may ease the burden upon critical care resources [10]. Recent UK data highlighted that non-COVID-19 tracheostomy patients typically spend a median of 50 days in hospital, 28 days with a tracheostomy *in situ*, and 23 days within the ICU [4]. It is easy to appreciate how critical care resources may become overwhelmed following a surge in demand. When resources become stretched, decisions regarding resource allocation become more challenging, and difficult judgments balancing tracheostomy, prolonged ventilation, rehabilitation and the potential of providing a real benefit for long-term quality of life need to be made.

What makes a patient with COVID-19 different when considering tracheostomy? With the high transmissibility and risk of serious illness, the potential risks to healthcare staff need to be considered in addition to the potential benefits to the patient. One argument surrounds the challenges of primary extubation, with higher rates of re-intubation reported in patients with COVID-19 [11]. Prolonged periods of tracheal intubation associated with the use of neuromuscular blocking agents [2] and the routine use of systemic corticosteroids [12] contribute to respiratory muscle

deconditioning [13], which can make going straight from an endotracheal tube to self-supported breathing challenging. Urgent re-intubation of a critically hypoxic patient has clear risks for the patient, but it is also important to consider the risks to attending staff. Non-invasive ventilation, face-mask continuous positive airway pressure, or high-flow nasal oxygen pose potential risks to healthcare staff through infectious aerosol generation [14], compounded by the risks associated with re-intubation [15].

SARS-CoV-2 itself may contribute to the increased rates of laryngeal edema and pathology reported in patients with COVID-19 [16, 17]. It is difficult to distinguish whether laryngeal pathology is a consequence of coronavirus infection, a sequel to the associated prolonged tracheal intubation, ventilation, prone positioning, and re-intubation, or more likely a combination of these direct and indirect factors [16–18].

An elective tracheostomy can provide a closed respiratory circuit to facilitate weaning (when used with an inflated tube cuff), allowing for a more controlled wean than an attempt at primary extubation considered at high risk of failure. However, tracheostomy care still requires airway interventions that may be considered aerosol-generating and tracheostomy is not recommended in patients who are likely to require management in the prone position [19].

In addition to benefits for patients and staff, tracheostomy may also provide additional logistical and resource benefits for the hospital [20]. Patients with a tracheostomy typically require reduced or no sedation, reducing resource pressures on drugs, equipment and monitoring [21] and allowing for less intensive nursing care, as the patient may be able to assist in their own movement and self-care and be less dependent on multiple staff for re-positioning. During the pandemic, with increased demand for critical care beds compounded by staff absence through illness or shielding, there has been a reliance on non-critical care nurses and other healthcare professionals to assist within the ICU. Tracheostomy patients may be easier to care for than fully sedated patients, but adequate training must be undertaken to ensure these healthcare professionals are able to manage tracheostomies and identify any potential complications [22] and a role for nursing specialties already experienced with tracheostomies (head and neck surgery for example) may be beneficial.

It remains essential that the potential benefits of a tracheostomy are weighed against the potential burden for patients and risks to staff and local critical care resources. Tracheostomy should only be considered in patients recovering from critical illness who have a good chance of making a meaningful recovery.

12.3 When to Perform a Tracheostomy?

Tracheostomies can pose a risk for the patient and the staff both in terms of insertion and subsequent management and, thus, the first priority when considering optimal timing for tracheostomy is whether the procedure will benefit the patient. Exposing the patient and staff to procedural risks when the patent is unlikely to survive does not benefit anybody. However, predicting which patients might benefit is difficult, both within and outside of the pandemic period. Considering that tracheostomy is indicated in those patients who have difficulty breathing and coughing

independently, it is no surprise that mortality rates are high during critical illness and following ICU or hospital discharge [8]. Tracheostomies should only be undertaken in patients who are clinically improving. Patients requiring (or likely to require) prone positioning for respiratory failure should not be considered for tracheostomy due to the increased risk of tube displacement, occlusion, or impaired ability to identify tracheostomy-related complications in the prone position [23]. As with all complex decisions, a multidisciplinary approach is recommended [22].

Optimal timing for tracheostomy remains controversial in non-COVID-19 patients [24] and becomes more complicated in patients with COVID-19 due to the perceived risk of aerosol generation. Virological evidence suggests that the viral load falls from a peak associated with the onset of symptoms, although the window of detection is prolonged in critical illness [19] (Fig. 12.1). Considering

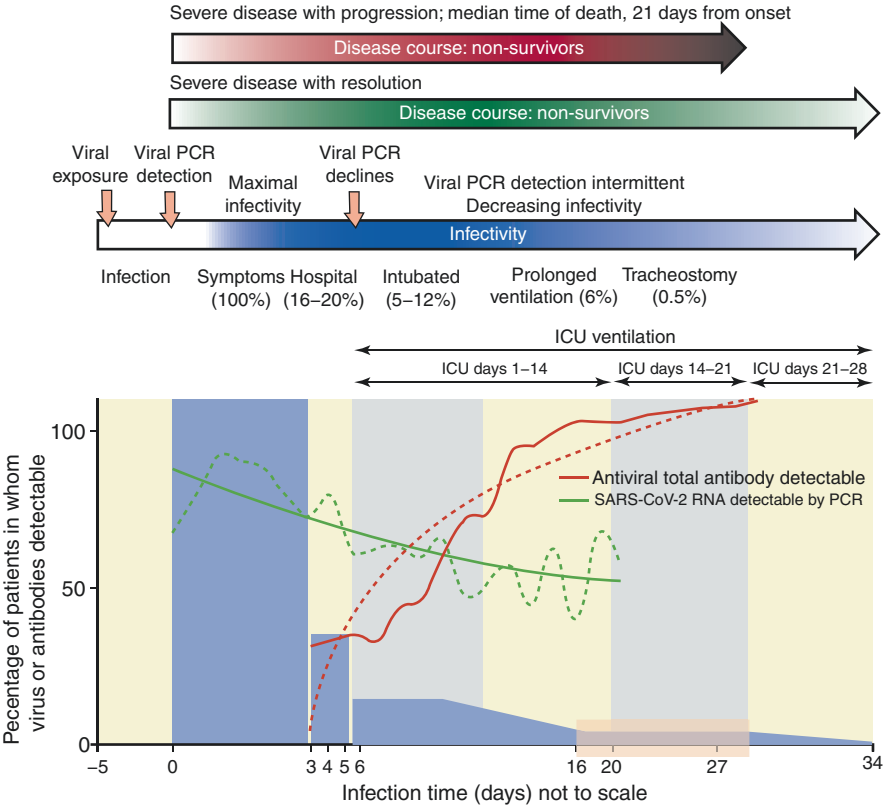

Fig. 12.1 Typical clinical course, viral polymerase chain reaction (PCR), and antiviral antibody detection and infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The transparent red box shows the suggested window for tracheostomy, on ICU days 10–21, which corresponds with 16–30 days from symptom onset. The solid bars and curves represent the proportion of all cases. Time zero is symptom onset (the *x*-axis is not to scale). Adapted from [19] with permission

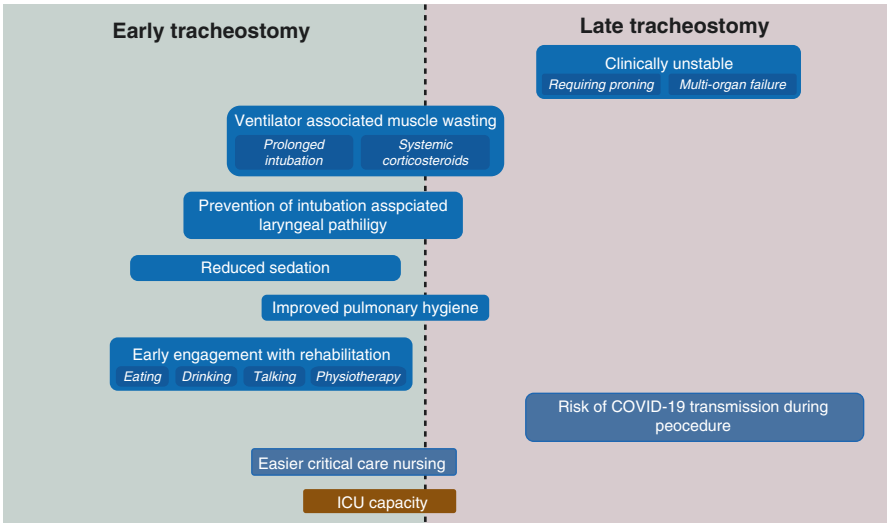

Fig. 12.2 Factors favoring early or late tracheostomy in patients with COVID-19. Patient factors (blue), staff factors (paler blue) and critical care resource factors (brown). Adapted from [19] (with permission)

that the insertion procedure is aerosol-generating, therefore posing risks to operators and attending staff, delaying tracheostomy is likely to benefit staff by reducing the risk of transmission [25, 26]. This must be balanced against the potential benefits to the patient of early tracheostomy, such as reducing laryngeal injury and laryngeal dysfunction associated with prolonged tracheal intubation, reducing the cumulative burden of sedative agents, and promoting pulmonary hygiene through better secretion clearance [27–29]. Earlier tracheostomy also allows for outcomes that patients find particularly important, such as an earlier return to eating, drinking, talking, and engaging in proactive rehabilitation [30–32]. The factors favoring early or late tracheostomy in patients suffering from COVID-19 are summarized in Fig. 12.2.

Early in the evolution of the pandemic, healthcare workers were rightly concerned about the risks of transmission during the tracheostomy insertion procedure, which has the potential to generate infectious aerosols. While many organizations in different countries advocated a cautious and therefore delayed approach to tracheostomy, a review of 26 international protocols demonstrated that timing for tracheostomy in COVID-19 varied from 3 to >21 days [33]. The majority of protocols considered the implied infectivity of the critically ill patient, and as the predicted viral load and antibody response became more precisely characterized as the pandemic unfolded, most recommended a minimum of 14 days of mechanical ventilation prior to tracheostomy, balancing the risks of patient benefit with risks to staff (Fig. 12.3). As staff became more confident with personal protective equipment (PPE) and in managing patients with severe COVID-19, reports emerged indicating a role for early tracheostomy in some

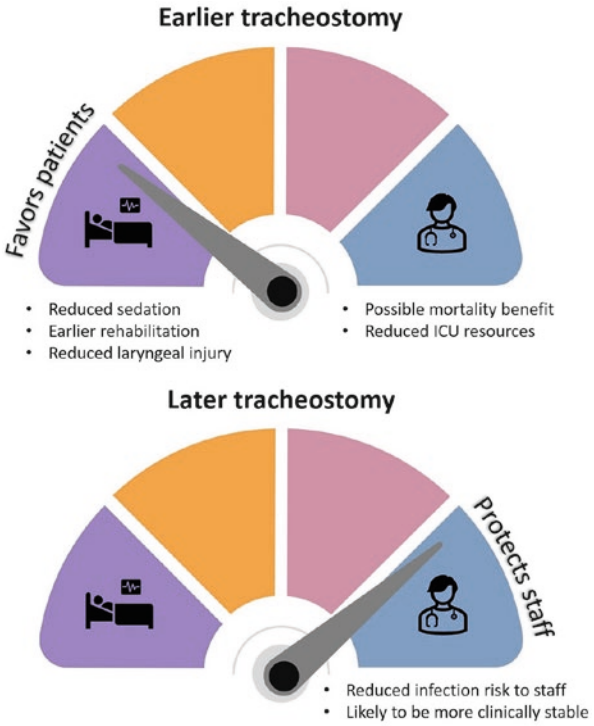

Fig. 12.3 Balancing the benefit to the patient versus the risk to the staff

patients, with potential mortality benefits [5]. Although case selection for early tracheostomy will remain an evolving challenge, what is clear is that the timing of tracheostomy in the management of severe COVID-19-associated respiratory failure is returning to 'business as usual' [23].

The question of whether the patient is physiologically stable enough to tolerate the tracheostomy insertion is very relevant, as the time to discover that the patient will desaturate rapidly when ventilation is suspended is not when the neck has just been opened. Physiological deterioration can be anticipated to some degree in all tracheostomy procedures due to inadequate ventilation, transient suspension of ventilation and the lung de-recruitment associated with exchanging the trans-laryngeal tube for a new tracheostomy. However, the deranged respiratory physiology associated with severe COVID-19 may cause an exaggerated deterioration if the patient has not recovered sufficient physiological reserve to tolerate the procedure. An international expert panel suggested a pre-procedural 'apnea test' which attempts to simulate the procedural conditions and thus predict physiological readiness. Pre-oxygenation, followed by a trial of apnea in the ICU, with a FiO_2 of 1. 0 and positive

end-expiratory pressure (PEEP) of 5 cmH_2O in the supine patient is suggested [19]. Rapid desaturation predicts a similar response during tracheostomy, indicating risk to the patient (and also to staff who may be required to undertake unplanned or additional airway interventions). Tracheostomy should be deferred in these circumstances. Importantly, the ability to conduct or tolerate an apnea trial should not replace multidisciplinary clinical judgement regarding the risks and benefits of undertaking tracheostomy in a given patient at a particular time [34].

12.4 What is the Best Technique for Inserting a Tracheostomy?

The first consideration is location. Performing the procedure in the ICU minimizes patient movement, avoids the logistical considerations of assembling an operating room team, but brings technical obstacles such as the large ICU bed and deficiencies in trained assistance, the environment, and with equipment (Table 12.1). Ideally, aerosol-generating procedures in potentially infectious patients should occur in negative pressure isolation rooms. These are not universally available, but conditions are probably most closely replicated in the operating room suite [35].

Second, the choice of insertion technique is essentially between an open surgical or a percutaneous approach. Hybrid approaches have been described and there are variations in all techniques described in the literature and facilitated by a wide range of equipment. An open technique was favored during the earlier severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and Avian influenza A (H5N1) viral pandemics based on low reported rates of transmission to operators [36, 37]. However, percutaneous techniques have progressed substantially in the last 20 years and many single centers have reported successful percutaneous approaches during the current pandemic, with apparently low rates of infectivity among attending staff [38–40].

Table 12.1 Advantages and disadvantages of performing a tracheostomy in the intensive care unit or operating room

Intensive care unit		Operating room	
Advantages	Disadvantages	Advantages	Disadvantages
No transfer required Timely (not dependent on operating rooms) Convenient for ICU team	Positioning can be difficult Less equipment available for complications Fewer resources in the event of a complication Suboptimal lighting Potential for distractions	Support available Controlled (aerosol) environment Typically performed by surgeons (may save ICU resources) Good lighting	Requires patient transfer (exposure risks to patient, staff and others) Requires a surgeon to be available Takes an operating slot

The relative risks and benefits of percutaneous or surgical approaches have been debated in the literature for many years. Perceived benefits to the percutaneous technique are: familiarity to critical care staff; reduced air leak from the smaller stoma; fewer wound infections; and reduced bleeding complications. However, percutaneous approaches involve: more airway manipulation than a surgical procedure; withdrawal of the tracheal tube risking extubation and aerosol generation; and, when combined with endoscopic visualization, may result in inadequate ventilation, significant upper airway gas leak and aerosol generation during the procedure. Perceived advantages to an open surgical technique relevant to COVID-19 are that it allows for a more controlled procedure, performed under direct vision. When combined with an expert anesthesiologist manipulating the tracheal tube in an ideal operating room environment, a surgical procedure may be safer.

Third, there may be situations where the patient's condition favors a particular approach. Difficult neck anatomy, obesity or overlying thyroid gland or vessels are established indications for a surgical approach. What is less clear is how to manage patients who are receiving anticoagulants, receiving antiplatelet medication, or who are at an increased risk of bleeding—all of which are common dilemmas during the coronavirus pandemic. A percutaneous approach involves less dissection, a smaller stoma and thus a tamponading effect from the newly inserted tube, which may reduce post-procedural bleeding. A surgical approach offers more direct access to control specific bleeding sources, although the use of diathermy may be implicated in aerosolizing viral particles and diathermy should be kept to a minimum [19].

Fourth, modifications and considerations have been proposed to help reduce the risk of aerosol generation during tracheostomy insertion. Most advocate suspending ventilation at key steps in the insertion process: manipulation of the tracheal tube within the upper airway; opening the trachea; any dilatation of the stoma; and during insertion of the new tracheostomy tube [41]. This period of apnea, however brief, risks significant de-recruitment and hypoxia, and a period of pre-oxygenation can help mitigate this. During a surgical insertion, the tracheal tube with the balloon inflated may be advanced distally within the trachea beyond the tracheotomy, thus keeping the breathing circuit 'closed' [42]. Clear communication between all team members is essential. Communication may be impeded by PPE and planning, rehearsal, and simulated practice are recommended [19]. It is also recommended that the patient should be paralyzed, thus preventing coughing and unwanted movement and reducing peak airway pressures [19, 41].

Finally, the logistics of managing multiple critically ill patients in our hospitals may influence the choice of technique simply through the availability of trained staff to undertake the procedure, with many centers reporting a significant rise in the number of surgical procedures undertaken during the pandemic [23, 39–42]. Because of the aerosol-generating nature of this procedure, it is imperative that appropriate PPE is always worn by whoever undertakes the tracheostomy insertion, and only essential staff are present in the immediate environment [36]. What

is clear is that more research is needed to understand the optimal technique for a particular set of circumstances and while we await clearer answers, practitioners are advised to do what works best in their institution, with their local resources, practice and expertise used optimally following multidisciplinary discussion between all stakeholders.

12.5 Subsequent Management of a Patient with a Tracheostomy

For patients with COVID-19 who have a tracheostomy, the aims of care are to minimize airway interventions and potential aerosol generation, whilst maintaining standards of safe care and ensuring that patients are proactively rehabilitated. All interventions should involve thorough planning to reduce risks to both patients and staff, and care should be performed by staff experienced with tracheostomy care [22]. Strategies to minimize aerosol production have been proposed, which include reducing 'routine' suction and inner cannula care to a minimum [43], using 'closed suction' systems, and using heat and moisture exchange (HME) filters in ventilator circuits instead of heated water-based 'active' humidification systems [44]. All of these strategies require regular review for each patient. If, for example, secretions become thicker, additional therapies such as mucolytic drugs, nebulizers, or switching to active humidification may be required [19].

It is recognized that tracheostomy weaning in a patient with COVID-19 provides a unique challenge. In non-COVID-19 patients, the process of weaning would involve gradually decreasing the ventilatory support alongside periods of cuff deflation, strategies which clearly promote aerosol generation [43, 45]. A 'cuff-up' strategy is initially suggested for patients with COVID-19, and only when the patient is deemed at lower risk of infectivity should the cuff be deflated [18]. Others have argued that this cautious approach disadvantages patients and may slow their recovery and laryngeal rehabilitation, instead advocating for adequate staff PPE in dedicated clinical areas alongside face and tracheostomy shields to reduce aerosol risks [19]. The optimal strategy is yet to be determined, but will be heavily influenced by local infrastructure, the environment and the experience and confidence of attending staff.

The deep psychological impact of an ICU stay on patient wellbeing during and beyond the ICU is well documented [46]. However, COVID-19 has posed new challenges by limiting the interactions that patients can have with family and staff. Speech for patients with a tracheostomy usually requires cuff deflation, risking aerosolization if positive pressure ventilation or ventilatory support is still required. Innovative communication methods include communication boards, 'speaking' tracheostomy tubes, above-cuff vocalization strategies, the use of an electrolarynx and other alternative communication devices [47]. Oral feeding, following a rigorous swallow assessment may also provide psychological benefit [32]. Such patient-focused outcomes are highlighted in Fig. 12.4.

Fig. 12.4 Patient-focused outcomes in tracheostomy care (the patient provided permission to publish the photo)

Safe decannulation should occur as soon as clinically possible [19]. Some have argued that decannulation should occur only following negative COVID-19 test results [48], but this may not be feasible if intensive care beds are limited, especially as complete viral clearance may take a significant period of time [49], thus delaying necessary patient care.

12.6 Conclusion

Tracheostomy is an important therapeutic intervention in the critically ill. The coronavirus pandemic has seen a significant increase both in the proportion of critically ill patients who become tracheostomy candidates and the absolute numbers of patients undergoing tracheostomy. Decisions surrounding candidacy, optimal timing, optimal technique and the optimal multidisciplinary aftercare of tracheostomies in the critically ill can be complex outside of the pandemic—a situation made yet more complex by the potential to transmit disease by infectious aerosols from those with COVID-19. After a steep learning curve, our multidisciplinary community is well placed to protect healthcare staff while ensuring that the best possible, proactive care is delivered to the many patients who will benefit from tracheostomy as part of their critical illness management. Many questions remain, and continued tracheostomy research, global collaboration and quality improvement is imperative [50] to ensure the boundaries of quality tracheostomy care continue to be pushed for the benefit of our patients.

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Modernizing Tracheostomy Practice to Improve Resource Utilization and Survivorship Outcomes

13

G. Hernandez, M. Brenner, and B. A. McGrath

13.1 Introduction

Tracheostomy has attracted increasing attention in recent years, owing to progress in team-based care and demonstrable advances in weaning and decannulation. A cardinal objective of the intensive care unit (ICU) is to stabilize critically ill patients, but it is increasingly recognized that the quality of life that patients and their families experience after an ICU stay is also important. Many patients who require invasive mechanical ventilation will manifest long-lasting physical, cognitive and/or mental health impairments. While many factors that affect survivorship after an ICU stay are poorly understood, tracheostomy plays an important role in alleviating this burden through reducing cumulative sedation dose, expediting physical therapy and rehabilitation, and potentially allowing patient-focused benefits such as earlier eating, drinking, talking and mobilization. Such observations highlight the importance of modernizing tracheostomy practice using evidence-based approaches.

Tracheostomy is associated with significant healthcare expenditure as well as high personal and social costs secondary to reduced quality of live and dependency. Improved practices around tracheotomy care, weaning, and decannulation reduce ICU

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and hospital lengths of stay. The coronavirus disease 2019 (COVID-19) pandemic, which has seen a surge in patients requiring tracheostomy for prolonged mechanical ventilation, has underscored the importance of effective tracheostomy practice in efficient resource allocation and optimizing survivorship outcomes following ICU stay.

13.2 What is the Pre-COVID-19 Evidence for Early Tracheostomy?

Conflicting results regarding timing of tracheostomy were reported in meta-analyses published in 2015 [1–4], and repeated in 2018 [5, 6], with no major trials published between them. Most recently, a meta-analysis of 17 randomized trials and 3145 participants found that early tracheotomy in adults receiving invasive mechanical ventilation was associated with a decrease in the occurrence of ventilator-associated pneumonia (VAP), more ventilator-free days, and fewer ICU days [7]. However, the evidence suggests limited, if any, benefit on survival rates with early compared to later tracheostomy.

Despite the marked heterogeneity across trials, there are populations who benefit from early tracheostomy (e.g., selected patients with burns, trauma, or stroke), and there are also populations who are well-served by attempts at extubation without increasing length of ICU stay or duration of mechanical ventilation. Several mechanisms may account for this benefit from early tracheostomy. Tracheostomy reduces the cumulative sedation dose administered [8] and allows for earlier rehabilitation and physical therapy, thereby reducing the likelihood of venous thromboembolism and risk for critical illness myopathy. Early tracheostomy also allows for earlier walking, talking and eating [9]. Earlier extubation also reduces the risk of numerous airway complications that may arise from prolonged translaryngeal intubation, including laryngeal diastasis, scarring, tracheomalacia, and tracheal stenosis.

Nonetheless, an important caveat remains the heterogeneity found among trials. Studies vary in the patients recruited, definition of ‘early’ tracheostomy, and outcomes studied. Tracheostomy is performed for a variety of indications, and patients differ widely in their underlying disorders and morbidities. Furthermore, studies span multiple ICU settings: findings for stroke patients in the neuro-ICU may not generalize to patients with respiratory failure within the medical ICU. Randomized controlled trials conducted over several years may have confounders relating to evolving practices and protocols. The literature also reflects a wide range of disease severity. Finally, a critical knowledge gap remains on how to predict whether a patient will require prolonged mechanical ventilation.

13.3 What Does ‘Early’ Tracheostomy Really Mean?

Definitions of early tracheostomy range from <4 to 15 days [10, 11], and criteria are invariably time-delimited, rather than linked to physiological parameters or phase of illness. This observation reflects our limited mechanistic understanding of the

factors that determine weaning and course of illness. Studies that have found benefit with early tracheostomy have often reported reduced before-tracheostomy time or reduced weaning time only, not necessarily modifying the period spanning from onset of invasive mechanical ventilation to initiation of weaning [12, 13], thus making results difficult to compare depending on case-mix. To our knowledge, no trial has defined 'early' based on this more physiological concept, which is notable as weaning time may account for nearly 40% of total time on ventilator.

Some aspects of COVID-19 can substantially modify time on ventilator: first, time to tracheostomy may be delayed due to perceived risk for infection transmission to healthcare workers; second, the need for prone position during the early stage of the disease may delay tracheostomy; third, the surge conditions in overwhelmed units may modify bedside decisions over the course of successive pandemic waves; fourth, COVID-19 has a high prevalence of late complications (e.g., delirium, ICU-associated weakness, secondary nosocomial infections, etc.) prolonging the weaning time and posing difficulties in establishing when weaning attempts were initiated. Therefore, it has proven challenging to define the optimal early-timing for tracheostomy in the pre-COVID-19 era and even harder during the COVID-19 surges.

13.4 What Respiratory Parameters or Criteria Ensure It Is Safe to Perform a Tracheostomy?

Ensuring adequate pulmonary reserve was a key prerequisite for early tracheostomy prior to the COVID-19 era. A large randomized trial comparing early (after 6–8 days of endotracheal intubation) versus late (after 13–15 days of endotracheal intubation) tracheostomy, in which 46% of patients had primary respiratory failure, excluded patients from having a tracheostomy if they had recovered lung function up to a PaO_2 >60 mmHg with a FiO_2 <50% and a positive end-expiratory pressure (PEEP) <8 cmH_2O [11]. The reason for this exclusion was to reduce the number of unnecessary tracheostomies. Using these criteria, 28.3% of enrolled patients did not receive a tracheostomy because they were close to fulfilling weaning criteria before day 15 (21.3% before day 11). Abe et al. [14] reported a 12.9% rate of tracheostomy after a median time of 14 days in a large population of patients with acute respiratory distress syndrome (ARDS), with a median PaO_2/FiO_2 ratio of 156 with a median PEEP of 8 cmH_2O at ARDS onset. Moreover, in a randomized clinical trial comparing early (within 4 days) versus late (after 10 days) tracheostomy, Young et al. [10] included patients for tracheostomy if they had been receiving mechanical ventilation for less than 4 days and were expected by the attending physician to need mechanical ventilation for at least 7 more days, with no pre-specified ventilator setting limitation. This led to the exclusion from statistical analysis after randomization of 53.7% of the patients in the late tracheostomy group because they did not meet the attending physician criteria.

After the COVID-19 pandemic started in 2020, respiratory safety criteria for performing a tracheostomy changed, mainly because the overriding concern was to

reduce unnecessary tracheostomies but to protect healthcare workers and unstable patients. Bier-Laning et al. [15] found, in their state-of-the-art review, 14 different protocols listing unstable respiratory status criteria contraindicating tracheostomy. Late tracheostomy is not usually limited by unstable respiratory conditions, but safety protocols for early tracheostomy demonstrate a wide range of criteria, from an apnea test [16] to definitions of very high ventilatory requirements (e.g., FiO_2 >60–70% and/or PEEP >12 cmH_2O) [17, 18].

There are several reasons for these pre- and post-COVID-19 differences. First, pre-COVID-19 randomized trials on this topic recruited patients in whom the tracheostomy was performed for indications other than primary respiratory failure. Such studies had a low percentage of patients with ARDS, limiting comparisons with COVID-19 evidence for early tracheostomy [10, 11]. Second, prioritization of healthcare worker safety resulted in modifications to procedural recommendations (e.g., disconnecting patients from mechanical ventilation before opening the trachea or delaying reconnection though tracheal cannula after cuff is inflated). These modifications result in a longer apnea period, often with total depressurization of the tracheal tree, thus putting patients at risk for respiratory deterioration. Third, some expert panels recommended the open technique, probably resulting in longer procedure times. In light of these observations, it seems that very high ventilatory requirements did not limit early tracheostomies, and severe deterioration was not reported after early tracheostomies in many experienced centers [13, 19].

13.5 What Does Predicting Prolonged Mechanical Ventilation Really Mean?

Traditional models for predicting prolonged mechanical ventilation aim to estimate at the earliest time point on mechanical ventilation the likely duration the patient will remain on the ventilator, ranging from 1 day to 21 days [20]. In addition, only one study has prospectively validated a model capable of predicting patients needing mechanical ventilation for more than 14 days [21]. This model loses close to 20% of the patients when optimizing specificity at 100%.

As already mentioned, a large UK trial aimed at elucidating a possible benefit for early tracheostomy, assessed the attending physicians' ability 4 days after intubation to predict 7 additional days on the ventilator [10]. Others have randomized patients 3 days after endotracheal intubation, including those with persistent respiratory failure fulfilling gasometric criteria of moderate ARDS (PO_2/FiO_2 ratio <120 with a FiO_2 ≥50% and PEEP ≥8 cmH_2O) [11]. Importantly, this trial excluded patients with a respiratory infection mainly because of the increased difficulty in accurate prediction in these cases. Under these conditions, those trials lost 48.4% [10] and 18.6% [11] of the randomized patients because of clinical improvement.

In the case of COVID-19 patients, guidelines recommend performing a tracheostomy when the expected total duration of mechanical ventilation is greater than 10 days [16]. The median duration of mechanical ventilation in COVID-19 patients has been reported according to the severity of ARDS at onset, ranging from 12 (6–18)

days in mild ARDS to 14 (10–19) days in severe cases, with tracheostomy rates ranging from 10% to 7% respectively [22]. Anticipating the clinical course of patients remains challenging, although innovations continue to emerge, including those arising from machine learning in tracheostomy [23] and more broadly in critical care [24].

13.6 Why Has Prone Position Been Considered a Limitation For Early Tracheostomy?

Prone positioning has traditionally been considered a relative contraindication for tracheostomy because of an increased risk for cannula displacement or accidental decannulation [25]. Prone ventilation has been extensively used in ARDS patients with COVID-19 with up to 80% of patients receiving at least one session in severe cases [22]. Most guidelines have recommended 12–16 h per day sessions and the median number of sessions reported in many large cohort studies is 3–4 (2–6) [22, 26], similar to that described previously in non-COVID-19 patients [27]. This observation means that around 25% of patients are definitively turned supine by day 3 after intubation and around 75% of patients who need prone positioning finish this therapy before the first week on mechanical ventilation. Some studies on tracheostomy in COVID-19 patients have reported pronation rates up to 80% within the first 14 days [13]. Although some COVID-19 patients require prolonged prone position therapy, it seems that most can safely receive a trachesotomy within the first 14 days after intubation without the need to modify postural therapies.

13.7 What Is the Real Risk for Healthcare Workers Performing Tracheostomies During the COVID-19 Pandemic?

Tran et al. [28] performed a systematic review of the risk of transmission of acute respiratory infections to healthcare workers during aerosol-generating procedures during the 2003 severe acute respiratory syndrome (SARS) pandemic, reporting an increased risk for tracheostomy (odds ratio 4.2 [1.5–11.5]). Notably, only one case-control study was included [29]. Moreover, tracheostomy was not independently related to the risk of infection transmission when the multivariable analysis included a logistic regression. Comparable data have not been published for COVID-19. The observational studies on tracheostomy during the COVID-19 pandemic have shown no infection or rates of infection no higher than the base rate for individuals involved in non-aerosol generating procedures. Most tracheostomies have been performed in a scheduled fashion, with minimal emergent techniques. The data on rates of healthcare worker infections associated with tracheostomies have largely demonstrated limited or absent viral transmission; however, many reports are anecdotal case series. Another limitation is that in cohorts with tracheostomy performed by proceduralists, viral transmission in the broader team was not reported.

Even when infection occurs in healthcare professionals involved in performing tracheostomy, the source of infection is often unclear, as evident in the study by Rosano and colleagues, who collected data on severe acute respiratory coronavirus 2 (SARS-CoV-2) infection in ICU nurses and physicians involved in 121 percutaneous tracheostomies and compared it to the prevalence of SARS-CoV-2 infection in ICU healthcare professionals not participating in tracheostomies. The 7.7% prevalence of infection in doctors and nurses performing tracheostomies was not significantly different from the 11.5% prevalence of infection in healthcare worker not involved in any tracheostomy procedure [30].

13.8 Post-tracheostomy Care

Most recent advances to accelerate weaning and decannulation in patients with a tracheostomy tube include aerosol-generating protocol modifications (e.g., disconnection from mechanical ventilation, increasing effective airway diameter including cuff deflation, use of tracheal high flow therapy) [31–33]. During the COVID-19 pandemic, perceived risk for healthcare workers took precedence, and guidelines on COVID-19 management have recommended against cuff deflation during the pandemic to protect healthcare workers [16–18]. We can interpret this information in two different ways: on the one hand, the risk for healthcare workers remains a challenge, and on the other hand, it can be assumed that the risk for infection transmission has declined by the time patients with a tracheostomy tube can be considered for disconnection from mechanical ventilation. Performing a tracheostomy in a COVID-19 patient has been delayed to a median time of about 19–20 days since symptom onset [16], and the first weaning attempts are delayed to about 28–30 days [13], thus likely increasing safety for healthcare workers.

Another important aspect of post-tracheostomy care is related to the expected probability of meaningful recovery. Many healthcare systems manage these patients in step-down units or long-term care centers, aiming to improve the quality of life of the patients with little hope of a full recovery [31]. However, recent advances in centers managing patients with a tracheostomy tube in high-dependency units report higher expectations for final decannulation when more aggressive protocols are applied [33].

Jubran et al. [31] reported several important results: first, close to 30% of patients with a tracheostomy tube were transferred to a chronic center without previous clear effort to advance in the disconnection process; second, in was not possible to wean 22.5% of a general population of tracheostomized patients under these conditions; third, patients with a limited pulmonary reserve detected by delayed failure after first disconnection were more prone to respond to aerosol-generating protocols. Hernandez et al. [33] found that reducing the effective airway diameter not only during weaning but also during the decannulation period reduced successful progression to final decannulation, as a prolonged capping trial seems to impose a

limitation for secretion management, even increasing the probability of delayed weaning failure.

These recent advances in the management of patients with a tracheostomy tube include some aspects that must be taken into account [32]. A more proactive approach to early detection and treatment of the limiting factors for decannulation involves pre-emptive diagnostic testing. Both airway patency problems and risk of aspiration should be detected not after weaning but at its beginning, as clinically significant stenosis (secondary to inflammation due to the prolonged presence of the artificial airway or directly because the tracheal cannula reduces the effective airway diameter) calls for specific treatment or a down-sized tracheal cannula and severe risk for aspiration precludes some measures facilitating the weaning process (e.g., deflating the tracheal cuff).

Diagnostic testing for impaired swallowing can be performed using a clinical test (e.g., deglutition test or FEES [fibreoptic endoscopic evaluation of swallow]), allowing for detection of severe cases of swallowing dysfunction. Mild and moderate swallowing dysfunction limit progression to oral intake, but do not delay progression to weaning and decannulation. Endoscopic procedures can confirm and specifically diagnose anatomical injuries needing direct attention by Head and Neck surgical teams. In addition, deflating the cuff has been associated with an improved recovery of swallowing function [32]. Although this result is hypothesis-generating and must be confirmed, reduced vertical movement of the trachea while swallowing with the cuff inflated could explain, at least in part, the frequent swallowing dysfunction observed in patients with a tracheostomy tube. Early restoration of translaryngeal airflow promotes laryngeal rehabilitation, coughing, swallowing and of course vocalization—all of which can have a positive physical and psychological benefit in those recovering from prolonged critical illness.

Conditioning the gases inhaled directly through the trachea helps accelerate both weaning and decannulation [32, 33] by improving secretion management and reducing the respiratory infection rate. Surprisingly, deflating the cuff significantly reduced the respiratory infection rate during weaning when combined with tracheal high flow. Although explanations for these results remain speculative, high flow seems to facilitate avoiding micro-aspirations around the cannula. This result was confirmed in a second study during the decannulation process [33].

These modifications taken together can increase the weaning and decannulation success rate by up to 93% and 95%, respectively [32, 33]. The subgroup of patients with a tracheostomy tube in which these aggressive protocols are limited are those with low level of consciousness, mainly because of a high risk of aspiration. Although level of consciousness is frequently recovered later in the course of the ICU or hospital admission, these patients are usually analyzed in specific studies and excluded from general trials because the time for recovery is difficult to predict and the time sensitive analysis of the trials could report spurious results depending on the case-mix. However, after these patients recover a good level of consciousness, the protocols could be applied without modification.

13.9 What Are the Implications of Tracheostomy for COVID-19 Survivorship?

Advances in critical care medicine are to be credited for the many survivors of severe COVID-19 (Table 13.1). Among such advances are the benefits of use of small tidal volumes, prone ventilation, conservative fluid management, lung protective ventilation, and other principles of the Surviving Sepsis Campaign guidelines for management of critically ill patients with COVID-19 [34]. However, despite this success, approximately 80% of patients surviving critical illness after mechanical ventilation in the ICU will experience physical, cognitive and/or mental health impairments, which are recognized as the post-intensive care syndrome (PICS).

Timely tracheostomy, when indicated, may shorten the duration of ICU stay and thereby potentially reduce the impairments associated with PICS [35]. For some aspects of survivorship after critical illness, a longer duration of critical illness is associated with greater impairment. Patients' survivorship experience reflects the complex interplay of critical illness and the iatrogenic effects of aggressive treatment. For example, the cumulative effects of sedation and restraints on the neuromuscular system, cognition, and overall rehabilitation are sometimes underrecognized. These are summarized in Figure 1. Temporary or permanent effects of translaryngeal intubation on dyphonia, dysphagia, and airway patency may not be recognized until long after the acute phase of illness and are increasingly documented in patients with COVID-19 [36]. Other physical impairments after critical illness may include joint contractures and critical illness-associated neuropathy or myopathy.

Table 13.1 Core principles for modernizing tracheostomy care

Principle	Practical implementation
Overarching drivers for improved tracheostomy care	• Multidisciplinary care and rounds • Engagement of patient and family members • Standardized protocols • Broad-based staff education • Data collection and analysis (e.g., globaltrach.org)
Critical care best practices	Instituting evidence-based use of prone ventilation, conservative fluid management, lung protective ventilation, pre-tracheostomy oxygenation
Assessing readiness for tracheostomy (COVID-19 era)	Initial assessment by day 10 of invasive ventilation. Patient should demonstrate clinical improvement; apnea test can verify pulmonary reserve
Best practices for technique and postoperative care	Appropriate personal protective equipment (PPE) and coordinated postoperative care including multidisciplinary collaboration with defined protocols, education, and data tracking
Enhanced decannulation protocols	High-flow oxygen with suctioning to accelerate tracheostomy decannulation
Early rehabilitation and transition from ICU	Interprofessional collaboration for comprehensive rehabilitation across specialties to help survivors of COVID-19 attain full and meaningful lives

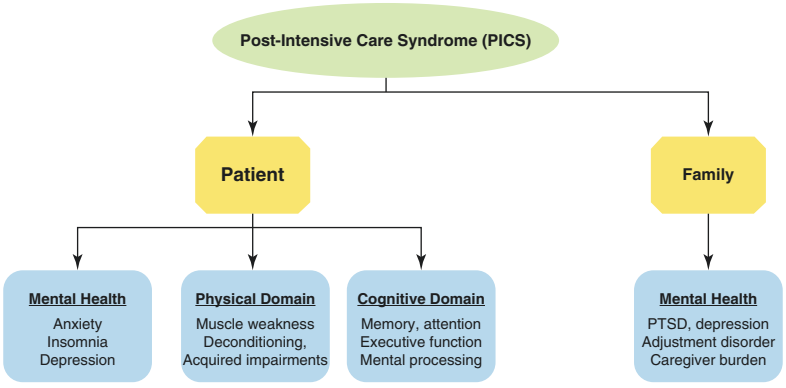

Fig. 13.1 Post-intensive care syndrome (PICS) affects patients and family members, affecting mental health, physical, and cognitive domains. From [35] with permission

Modernizing tracheostomy care can serve as a catalyst for improving efficiencies in resource utilization and enhancing survivorship outcomes. Evidence-based, multidisciplinary critical care plays a critical role in improving patients' long-term quality of life. Awareness of these survivorship considerations is important for all members of the healthcare team, including clinicians as well as patients and families, to maximize the likelihood of restoring fulfilling and meaningful lives (Figs. 13.1 and 13.2). Lack of coordination of care is a major factor in prolonged ICU stay and delayed decannulation. Patients may suffer persistent sleep impairment, pain, fatigue, and overall degraded health-related quality of life. Patients' loved ones have significant rates of mental health impairment.

13.10 Lessons from COVID-19

The COVID-19 pandemic has overwhelmed ICUs around the world, affecting not only healthcare workers, but also ICU capacity including ICU beds and ventilators. What mainly defines an ICU bed is the attending staff and the supplies and equipment required to manage a patient with endotracheal intubation, so the limiting factor for ICU equipment capacity in this context is availability of ventilators. Unfortunately, few measures can help optimize this capacity, including considering transport ventilators, operating room equipment, military supplies, long-term ventilators, veterinary ventilators, magnetic resonance imaging compatible ventilators, non-invasive ventilators, or even prolonged manual ventilation [37, 38]. These recommendations are based on best practice statements, except the recommendation against using one ventilator for multiple patients (strong recommendation with low quality evidence), that was based on animal or mechanical models [38].

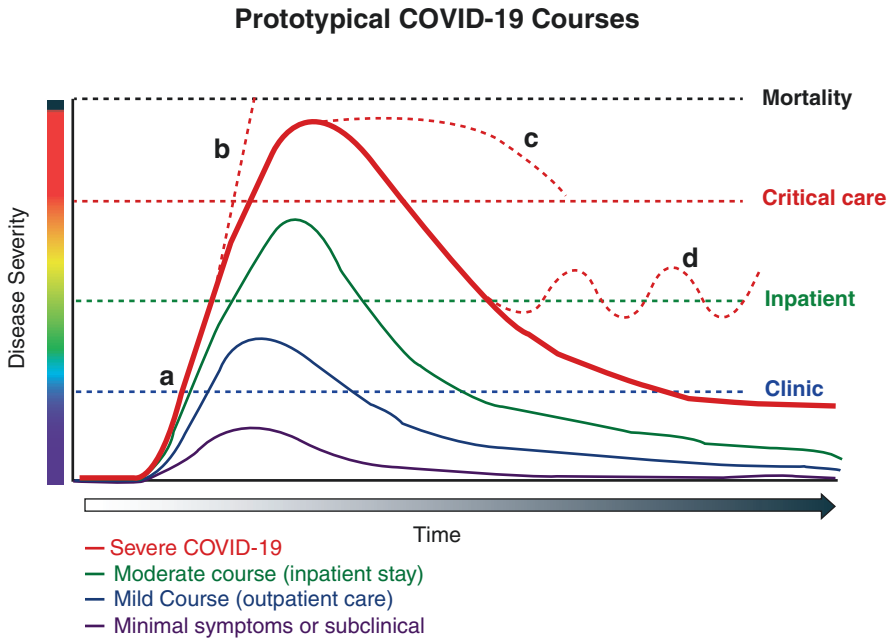

Fig. 13.2 Clinical courses of patients with COVID-19. **a**. Prototypical course of severe COVID-19, **b**. Progressive multiorgan failure; **c**. Protracted critical illness requiring extracorporeal membrane oxygenation (ECMO), **d**. Relapsing course requiring readmission. Other survivorship streams also depicted. Reproduced from [35] with permission

There is limited evidence for early timing of tracheostomy before the COVID-19 pandemic. There are many explanations for this paucity of evidence: first, the difficulty for physicians to predict prolonged mechanical ventilation and limited internal validity of randomized trials; second the great variability in definition of early tracheostomy, increasing the heterogeneity in meta-analyses, and the heterogeneous outcomes analyzed, with different results for duration of mechanical ventilation and ventilator-free days [2]. The reason for this disparity in results depending on the outcome analyzed could be the high mortality of patients needing prolonged mechanical ventilation, modifying the results when a failure-free days composite end-point is used instead of the duration of mechanical ventilation. A meta-analysis published in 2015 showed a significant increase in ventilator-free days with early tracheostomy (mean difference for ventilator-free days 2.12, 95% CI 0.94 to 3.30) [2], and others confirmed a reduced duration of mechanical ventilation with a trial-sequential analysis (mean difference -0.91, 95% CI -1.45 to -0.38) [5] in 2019. These results have been confirmed in a recent meta-analysis by Chorath et al. [7].

Specific data regarding COVID-19 patients is scarce, as performing a randomized trial is difficult under surge conditions. Some studies suggest a benefit for early trachoestomy in COVID-19 patients. Aviles-Jurado et al. [13] reported the

possibility of decreased use of ICU beds during the pandemic when tracheostomy is properly indicated early in the course of the disease. Possible reasons for this include the following: first, it is easier to predict prolonged mechanical ventilation in this population, second the high volume of patients with low heterogeneity facilitate the statistical analysis.

Recommended ventilator settings for safely performing an early tracheostomy during the COVID-19 pandemic are the following: PEEP <12 cmH_2O, FiO_2 <60%, respiratory rate <30 bpm, $PaCO_2$ <60 mmHg, and able to tolerate a period of apnea, but more relaxed approaches have shown good results. In their single center study, Aviles-Jurado et al. [13] performed tracheostomies within the first 8 days in patients with PEEP of 10 cmH_2O and PaO_2/FiO_2 about 200.

13.11 Conclusion

Despite important recent advances in tracheostomy and post-tracheostomy care, we have a long way to go before we can confidently answer important questions about the insertion and subsequent management of tracheostomy for the maximum benefit of our patients and for our healthcare systems. We have detected a slowing down in progression, but the window for improvement remains open. The COVID-19 pandemic has increased our understanding of many aspects of tracheostomy care, but our learning must go on.

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Helmet Non-invasive Ventilation in Acute Hypoxemic Respiratory Failure Due to COVID-19

14

S. Aldekhyl, H. Tlayjeh, and Y. Arabi

14.1 Introduction

Data from randomized controlled trials have demonstrated the benefit of non-invasive ventilation (NIV), typically delivered through a face mask in reducing the need for invasive mechanical ventilation and reducing mortality in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), and possibly in patients with acute decompensated heart failure and immunocompromised patients [1, 2]. However, the role of NIV in acute hypoxemic respiratory failure has been less clear [3, 4]. With the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, NIV has been used with the premise of preventing intubation, using a mask or helmet interface. Continuous positive airway pressure (CPAP) delivered through a helmet interface has been used commonly during the coronavirus disease 2019 (COVID-19) pandemic in Italy to increase the critical care bed capacity outside the intensive care unit (ICU) [5].

It has been recognized that the choice of interface to deliver NIV is critical for treatment success. Mask NIV provides the best compromise between comfort and leak prevention [6]. However, many patients do not tolerate mask NIV due to pressure point discomfort, pain, and claustrophobia. Additionally, most mask NIV protocols include frequent interruptions of positive pressure for pressure ulcer prevention and nursing care, which may contribute to treatment failure possibly due to alveolar recruitment. The helmet interface, if appropriately used, may have better

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tolerability and be superior to mask NIV in delivering positive airway pressure, and possibly reducing the need for invasive mechanical ventilation and mortality [7–9].

The objective of this chapter is to review the current evidence on helmet NIV, including the pathophysiological rationale and clinical data from patients with acute hypoxemic respiratory failure in general and COVID-19 in particular.

14.2 Helmet Description

The helmet comprises a transparent hood that surrounds the patient's head and a collar base that seals around the neck (Fig. 14.1). The helmet has inspiratory and expiratory tube connectors. Certain models feature special access ports on the base to allow suctioning, medication administration and feeding. Two underarm straps are used to secure the helmet over the patient's shoulder. Others have a side anti-suffocation valve that entrains external air when the helmet airflow drops below a certain level.

This configuration confers several advantages. First, it enhances tolerability and duration of use due to the lack of contact with the face, capacity for oral intake, and

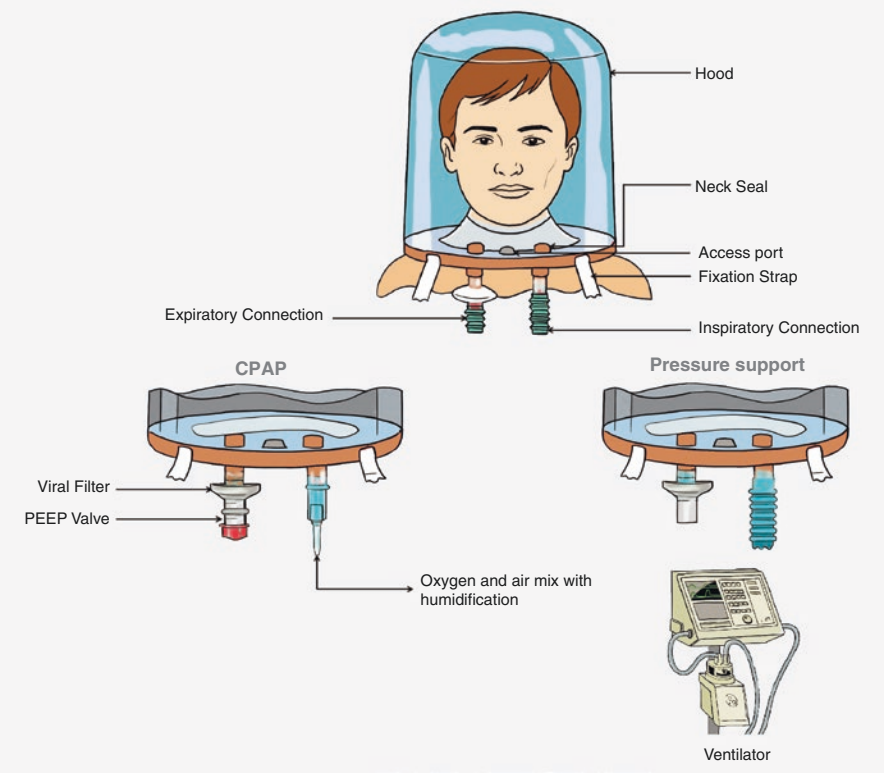

Fig. 14.1 Helmet non-invasive ventilation. *PEEP* positive end-expiratory pressure, *CPAP* continuous positive airway pressure

better visibility of the surrounding. Second, it reduces the risk for eye irritation, facial skin necrosis, and gastric distention [10]. Third, it reduces air leaks and decreases the risk of aerosolization compared to face masks [11]. Of note, several models, textures, and sizes are commercially available and may have different mechanical properties in response to ventilatory settings.

14.3 Physiologic Considerations of Helmet NIV

Helmet NIV has a unique set of physiological and therapeutic effects on the respiratory system. Ongoing research is evaluating these effects under different modes of ventilation and between different interfaces (ClinicalTrials.gov Identifier NCT04241861). In the following section, we will explore some of the physiological underpinnings that justify the settings generally used for helmet NIV.

14.3.1 Oxygenation and Work of Breathing

Applying positive end-expiratory pressure (PEEP) to patients with acute hypoxemic respiratory failure is associated with improved oxygenation likely through alveolar recruitment [12]. In addition, PEEP delivered through helmet NIV may serve to decrease lung injury by reducing inspiratory effort, tidal volume, and transpulmonary pressures [13]. Physiological studies have demonstrated that delivering helmet NIV was comparable to mask NIV in increasing end-expiratory volume and minimizing airway pressure fluctuations [14]. Helmet NIV allows the use of higher pressures without compromising patient comfort or air seal, thus facilitating better patient synchrony and decreased work of breathing [15–17]. On the other hand, the helmet's high compliance and large volume function as a pressure damper between the patient and ventilator, interfering with pressurization and ventilator settings [18, 19]. A prospective crossover study showed that delivering helmet NIV with identical parameters to mask NIV resulted in less respiratory muscle unloading as indicated by the trans-diaphragmatic pressure measurement. Adjusting the PEEP and pressure support to higher levels resulted in similar unloading as mask NIV [17]. In a randomized controlled trial (RCT) of helmet NIV versus mask NIV, patients in the helmet NIV group received higher PEEP but less pressure support compared to those receiving mask NIV [9]. The two studies demonstrated that higher PEEP was achieved with helmet NIV compared to mask NIV. On the other hand, both demonstrated variations in lung mechanics, which may be related to the different patient populations or helmet mechanical properties. Lower pressure support used in helmet NIV compared to mask NIV [9] may be related to improvement in lung recruitment; and higher pressure support compared to mask NIV-in the other study [17]- may reflect the dissipated pressure in the helmet. This is an area that requires further investigation.

The pressure applied during NIV is generated against the interface and the respiratory system in series. During helmet NIV, triggering and cycling-off of ventilatory

support should be synchronized with the patient's inspiratory efforts. Due to the high compliance and large volume of the helmet, there may be a delay between the patient's inspiratory effort and the initiation of the positive pressure support. This can lead to patient-ventilator asynchrony. A ventilator setting characterized by fast inspiratory rise time and prolonged cycling-off percentage can significantly decrease patient-ventilator asynchrony and unload respiratory muscles [17, 19]. Pressurization time or inspiratory rise time is the time needed to reach the targeted pressure in pressure support ventilation [20]. Lower pressurization rates were associated with increased respiratory rate and work of breathing and reduced tidal volume. However, the relationship between pressurization rate and work of breathing is not straightforward and individual titration of the pressurization time is recommended to optimize the patient's comfort [21].

14.3.2 Ventilation: Carbon Dioxide (CO_2) Exchange

CO_2 rebreathing could be a concern with helmet NIV due to its large internal volume. However, physiological studies showed that the effective dead space of an interface does not correlate with the total gas volume contained; therefore, reducing the helmet size does not mitigate CO_2 rebreathing [22]. A more important determinant of CO_2 rebreathing is the rate of CO_2 accumulation in the helmet. Breathing within a helmet can be thought of as breathing within a closed room in which the CO_2 level depends on the rate of accumulation. CO_2 accumulation in a leak-proof chamber is the function of the rate of production and flush-out with fresh air [23].

When a helmet is used to deliver CPAP through a ventilator or with a continuous low-flow rate, the risk of CO_2 rebreathing increases as the flow provided is not sufficient to flush out the accumulated CO_2. Therefore, helmet CPAP should only be used with a high gas flow (40 l/min or higher) to minimize the risk of CO_2 rebreathing [14]. In addition, high gas flow ensures that the patient's peak flow rate is exceeded, which maintains positive airway pressure throughout the respiratory cycle. This reduces pressure swings that increase patient fatigue and lung injury [19, 24]. During pressure support NIV, higher flow rates can be achieved by maximizing the pressurization time [25]. The level of pressure support does not affect the proportion of CO_2 rebreathing [15].

14.3.3 Aerosol Generation

Mask NIV is considered an aerosol-generating procedure that has been associated with the nosocomial transmission of respiratory pathogens [26]. Measurement of air dispersion during helmet NIV with a ventilator showed that the risk of spread is significantly lower than with mask NIV. Leakage can be further minimized by ensuring a good seal at the neck and by using double-limb circuits with viral filters

(Fig. 14.1) [11]. The risk of aerosolization with helmet CPAP (without ventilator) is not clear. However, the enhanced patient tolerability compared to mask NIV minimizes the need for frequent mask adjustments and treatment interruption by healthcare workers and possibly decreases the risk of exposure to respiratory droplets. Data on the risk of transmission of COVID-19 with helmet NIV compared to mask NIV are sparse [27].

14.3.4 Hemodynamic Effects

Excessive PEEP, confounded with sedation, during invasive ventilation, has been shown to be detrimental to cardiac output especially in patients with abnormal cardiac function. However, an important hemodynamic effect has not been observed with helmet NIV compared to NIV via face mask or oxygen therapy [9, 28].

14.4 Clinical Evidence for Helmet NIV in Non-Covid-19 Acute Hypoxemic Respiratory Failure

Helmet NIV has been shown to significantly improve oxygenation compared to standard oxygen therapy in patients with acute hypoxemic respiratory failure. In a small RCT, Consentini et al. showed rapid improvement in oxygenation in patients with moderate acute hypoxemic respiratory failure (PaO_2/FiO_2 [P/F] 210–285) with helmet NIV compared to oxygen therapy via face mask [28]. In this trial, 95% of patients on helmet NIV achieved a P/F ratio of 315 in 1.5 h compared to 35% of patients on oxygen therapy who achieved a P/F ratio of 315 after 48 h [28]. In a multicenter RCT (81 patients), helmet CPAP decreased the need for endotracheal intubation compared to Venturi mask from 63% to 15% ($p < 0.001$) in patients with severe acute hypoxemic respiratory failure [29].

Patel et al. [9] compared helmet NIV to mask NIV in 83 patients with moderate to severe acute hypoxemic respiratory failure due to acute respiratory distress syndrome (ARDS). The study was stopped early for efficacy. Helmet NIV reduced intubation rates compared to face mask NIV from 61.5% to 18.5%. Hospital and 90-day mortality were also significantly lower in the helmet group than in the face mask group. The unadjusted hazard ratio for death at 90 days with helmet NIV compared to mask NIV was 0.47 (95% CI, 0.24 to 0.91 days; $P = 0.03$) [9]. In a recent systematic review and network meta-analysis, helmet NIV was associated with a significant decrease in mortality compared with high-flow nasal oxygen (RR 0.46 [95% CI, 0.26–0.80], low certainty) and mask NIV (RR 0.48 [95% CI, 0.29–0.76], low certainty) in patients with acute hypoxemic respiratory failure [30].

In another meta-analysis that included both RCTs and observational studies, pooled results showed that helmet NIV was associated with lower hospital mortality (OR 0.43, 95% CI 0.26 to 0.69, $P = 0.0005$) [7].

14.5 Helmet NIV in COVID-19

Data on the clinical efficacy of helmet NIV in patients with COVID-19 pneumonia are limited. In a multicenter cohort study, Aliberti et al. showed that helmet CPAP prevented intubation in 56% of patients with moderate to severe acute hypoxemic respiratory failure due to COVID-19 pneumonia [31]. Multiple ongoing RCTs are testing the efficacy of helmet NIV in COVID-19 pneumonia (Table 14.1).

14.6 Application

There is considerable variability in institutional guidelines for helmet NIV. Below are some of the general principles for setting up helmet NIV.

14.6.1 Mode of Ventilation

There are two modes of ventilation that can be used with the helmet interface (Fig. 14.1). Helmet NIV can be provided using a ventilator, typically with pressure support mode. Helmet CPAP is provided without a ventilator using a high-flow oxygen-air mix [13]. At present, there is insufficient evidence regarding the indications and advantages of one mode over the other. Detailed and updated step-by-step guides for setting up helmet NIV are available online [32–34].

Table 14.1 Ongoing randomized controlled trials (RCTs) on helmet non-invasive ventilation (NIV) in COVID-19 registered on ClinicalTrials.gov

Trial	Registration number	Intervention	Design	Country
Helmet Non-Invasive Ventilation for COVID-19 Patients (Helmet-COVID)	NCT04477668	Helmet vs. standard of care	Multicenter	Saudi Arabia
Comparison of High Flow Nasal Cannula (HFNC), Face-mask Non-Invasive Ventilation (NIV) & Helmet NIV in COVID-19 ARDS Patients (NIV COVID19)	NCT04715243	HFNC vs. helmet NIV vs. mask NIV	Multicenter	Oman
Helmet CPAP Versus HFNC in COVID-19 (COVID HELMET)	NCT04395807	HFNC vs. helmet CPAP	Single center	Sweden
COVIDNOCHE Trial (HFNO Versus CPAP Helmet) in COVID-19 Pneumonia (COVIDNOCHE)	NCT04381923	HFNC vs. helmet CPAP	Single center	USA
Early CPAP in COVID-19 Patients with Respiratory Failure (EC-COVID-RCT)	NCT04326075	Early helmet CPAP vs. current clinical practice	Single center	Italy

CPAP continuous positive airway pressure

14.6.2 Humidification

Humidification of inspired gas during helmet NIV is essential to maintain the integrity of the respiratory mucosa. The recommended absolute humidity to achieve this is 10 mg H_2O/l. Delivering helmet CPAP with a high flow of medical air reduces the desired humidity level significantly. Using heated humidifiers set to 26–28 °C allows the delivery of adequately humidified air (~15 mg H_2O/l) regardless of the flow rate, FiO_2 or system used [35]. Some of the most frequently used humidifiers have a higher minimum temperature setup, and when used they lead to water condensation inside the helmet. Non-heated humidification, for example using a bubble humidifier with water at room temperature, can be an alternative [36].

14.6.3 Noise Management

Helmet NIV (particularly helmet CPAP) causes air turbulence resulting in noise that may exceed tolerated levels. One study showed that using a heat and moisture exchange (HME) filter at the inspiratory junction reduced the noise level significantly and was associated with increased patient comfort and better communication [37]. Earplugs can mitigate the effects of noise and help improve sleep but can render communication difficult.

14.6.4 Nursing Care

Compared to mask NIV, helmet NIV enhances patient comfort by providing better visibility of the surroundings through the transparent hood and facilitates better communication. In addition, it allows the patient to apply glasses, use headphones, read, cough, speak and drink.

Nurses play a critical role in further optimizing the patient experience and, hence, treatment success. Lucchini et al. suggested the use of a nursing "helmet bundle" including proper helmet anchorage, noise reduction, and humidification [18]. Nutrition can be provided through the patient access opening in the helmet and is usually given through a straw. Other aspects of nursing care during helmet NIV include maintaining central vascular access and nasogastric tubes, which can be threaded between the collar and the patient's neck.

14.7 Limitations

In addition to the classical limitations and contraindications for NIV, the following limitations of helmet NIV should be noted:

14.7.1 Claustrophobia

Although a majority of patients tolerate helmet NIV, many do not. Severe claustrophobia and agitation are considered one of the relative contraindications for helmet NIV. Intermittent or continuous light sedation, typically with dexmedetomidine [38], can improve a patient's tolerability of helmet NIV. However, data are currently limited about the optimal sedation use with helmet NIV.

14.7.2 Team Experience

Helmet NIV is a relatively new ventilation modality with limited evidence-based guidelines on its application, management, titration, and weaning. The limited familiarity of the treating team with helmet NIV may result in poor helmet performance and possibly adverse patient outcomes [39]. Adequate training is needed for all involved medical, nursing, and respiratory therapy staff.

14.7.3 Limited Ability for Tidal Volume Measurement

Spontaneous breathing during mechanical ventilation can induce self-inflicted lung injury. The patient respiratory effort, in addition to the pressure support provided by the ventilator, can result in high tidal volume and transpulmonary pressure swings. This is of particular concern in patients with a high respiratory drive, such as in acute hypoxemic respiratory failure, where accurate measurement of tidal volume is crucial for proper management [16]. During helmet NIV, measurements of tidal volume as displayed on the ventilator are unreliable, as large measured tidal volume reflects not only patient tidal volume but also the hood tidal volume. A more accurate estimate of patient tidal volume can be calculated using a special setup that is not routinely available [40, 41]. The inability to accurately measure tidal volume makes it a challenge for the provision of a lung-protective strategy.

14.7.4 Neck and Axillary Pain and Ulceration

Although the helmet interface is associated with a reduced risk of facial ulceration, neck, and axillary ulceration can develop at the contact points with the collar and underarm shoulder straps, respectively. Applying a barrier dressing over the neck before the application of the apparatus and using a counterweight anchoring system to fix the straps can help alleviate the pain and reduce the risk of ulceration [42].

14.7.5 Barotrauma

Barotrauma can complicate NIV in general, but the risk is lower than that associated with invasive ventilation [43]. Barotrauma has been reported in patients with COVID-19 pneumonia treated with mask NIV [44], but the incidence and risk factors of barotrauma with helmet NIV are unclear at this point.

14.7.6 Delayed Intubation

Similar to mask NIV**,** failure of helmet NIV should be recognized promptly, as delayed intubation after failed NIV has been associated with worse outcomes [45]. Prominent respiratory effort, persistent tachypnea, inability to maintain a P/F ratio > 150, and persistent requirement of FiO_2 > 80% for more than 1 h of helmet NIV are suggested criteria to consider invasive ventilation [46].

14.8 Conclusion and Future Directions

Helmet NIV appears to be a promising modality for managing patients with acute hypoxemic respiratory failure in general, and COVID-19 in particular. More research is required to uncover its potential and its limitations. There is a need to better define the efficacy compared to other respiratory support approaches, to identify the optimal approach to improve tolerability, to define early helmet failure, and to improve monitoring in order to provide lung-protective ventilation. Further research is required to facilitate a more optimal approach and an evidence-based utilization of this ventilation mode.

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Part V

Acute Respiratory Distress Syndrome

Mechanisms of Hypoxemia in the Acute Respiratory Distress Syndrome

15

I. Marongiu, B. Pavlovsky, and T. Mauri

15.1 Introduction

The acute respiratory distress syndrome (ARDS) is defined by arterial hypoxemia despite a positive airway pressure, associated with non-cardiogenic bilateral pulmonary edema [1]. Pathophysiological mechanisms leading to hypoxemia in ARDS are heterogeneous, with different responses to treatments. Precise understanding of such mechanisms may contribute to the identification of specific ARDS phenotypes [2].

In the present chapter, we discuss the main pathophysiological mechanisms leading to hypoxemia. Bedside recognition of the prevalent mechanisms in each ARDS patient might support physiologic reasoning and guide personalized interventions.

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15.2 Mechanisms of Hypoxemia in ARDS

15.2.1 Loss of Alveolar Inflation

ARDS is characterized by reduced size of the normally-aerated lung, i.e., by the "baby lung" [3]. Loss of aeration increases the fraction of non-ventilated perfused pulmonary units (shunt), thus being a major determinant of arterial hypoxemia. Figure 15.1a shows computed tomography (CT)-scan imaging of lungs affected by ARDS with dorsal collapsed regions (upper panel) and corresponding reduced ventilation in the same areas detected by electrical impedance tomography (EIT) (bottom panel).

Three main pathophysiological mechanisms contribute to loss of aeration. First, ARDS is characterized by pulmonary epithelial dysfunction due to local or systemic inflammatory processes [4]. Epithelial failure determines death of type I and proliferation of type II alveolar cells [4, 5], recruitment of inflammatory cells (e.g., non-constitutive neutrophils) and excessive production of proteins (e.g., fibrin, cytokines) in the alveolar space [5], altering the physiologic clearance of alveolar fluid [8]. This further impairs function of alveolar type I and II cells which amplifies the injury. The final result of this process is diffuse alveolar damage (DAD), which is the histological hallmark of ARDS: endothelial and alveolar lining cell injury

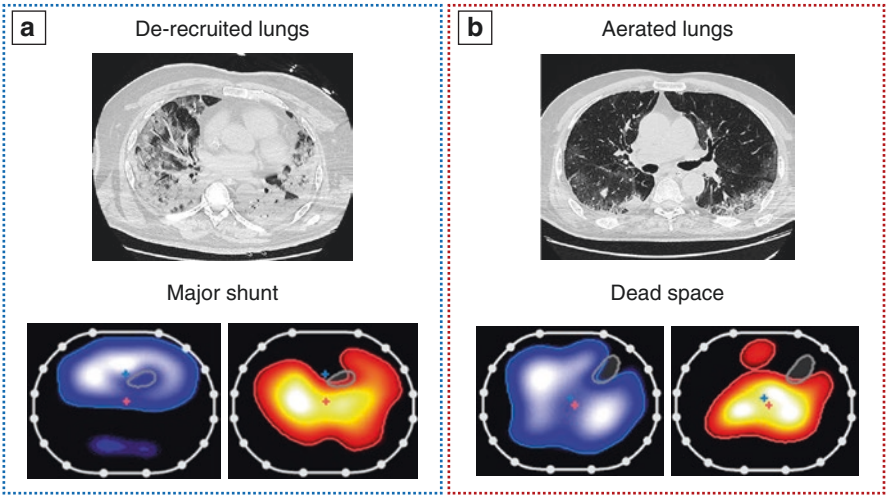

Fig. 15.1 Lung imaging to assess ventilation/perfusion mismatch. (**a**) Upper panel shows computed tomography (CT)-scan of lungs affected by acute respiratory distress syndrome (ARDS), characterized by large collapsed dorsal regions. Bottom panels show representative electrical impedance tomography (EIT) imaging of ventilation (left) and perfusion (right) distribution in the same lungs, with non-ventilated but still perfused dorsal regions generating shunt. (**b**) Upper panel shows CT-scan imaging of normally aerated lungs. Bottom panels show representative imaging of ventilation and perfusion distribution in the same lungs, with non-perfused but ventilated units generating dead space

leading to fluid exudation filling up the alveoli [4]. Second, epithelial dysfunction during ARDS depletes surfactant, as a result of type II cell failure and surfactant inactivation by inflammatory mediators. In this context, low tidal volume ventilation with relative alveolar hypoventilation causes an increase in surface tension contributing to alveolar collapse [6]. In mechanically ventilated patients, application of positive intrathoracic pressure may enable the re-opening, in part, of these collapsed alveoli. Alveolar recruitment is one of the cornerstones of ARDS management, but it is also a double-edged sword. Structural lung inhomogeneities between collapsed regions and the "baby lung" triggers ventilator-induced lung injury (VILI). The shear forces occurring in the frontier zone (namely, lung strain) during the tidal cycle generates volutrauma [7], and cyclic alveolar opening and closing induces atelectrauma [8, 9]. VILI aggravates lung inflammation [10], further contributing to the inflammatory vicious circle leading to loss of aeration, shunt and hypoxemia.

15.2.2 Increased Dead Space

Although the hallmark pathologic finding of ARDS is DAD, lung injury is always associated with endothelial injury too [11, 12]. Interest in this 'vascular' side of ARDS pathophysiology recently increased because of the outbreak of the severe acute respiratory coronavirus 2 (SARS-CoV-2) pandemic. From early reports, coronavirus disease 2019 (COVID-19) ARDS showed 'atypical' features, with marked hypoxemia in the presence of limited alveolar collapse, advocating alternative mechanisms for gas exchange impairment [13, 14]. At autopsy, lungs from patients with COVID-19 showed peculiar vascular alterations with endothelial injury, diffuse microthrombosis and microangiopathy [15]. Perfusion defects have previously also been detected by bedside angiography in ARDS of other etiologies, likely representing a consistent characteristic in a subgroup of ARDS patients [16]. Diffuse vascular pulmonary occlusion is associated with a reduction in blood flow to ventilated regions, generating an increase in the physiological dead space ('wasted ventilation'), which is an independent predictor of mortality [17]. Figure 15.1b shows CT-scan imaging of almost normally-aerated ARDS lungs (upper panel), with EIT allowing detection of the mismatch between ventilation and perfusion due to high dead space (bottom panel). Experimental and clinical studies have shown that dead space may aggravate hypoxemia as a consequence of the redistribution of ventilation and perfusion with increased ventilation/perfusion (V/Q) inequality across the lung. Levy and Simmons conducted a study on anesthetized ventilated dogs and demonstrated redistribution of ventilation away from the non-perfused regions following pulmonary embolism [18]. Assessment of V/Q distribution by the inert gas method in patients with pulmonary embolism showed that blood flow redistribution with overperfusion of low V/Q areas induced hypoxemia [19]. Moreover, 'wasted ventilation' generates alveolar hypocapnia which, in turn, triggers diffuse regional bronchoconstriction and loss of alveolar compliance. Worsening mechanics in hypo-perfused lung regions cause a non-selective reduction in ventilation increasing the proportion of low V/Q units [18–21]. More recently, Busana et al. elaborated a computational model of pulmonary V/Q inequality

in patients with COVID-19 ARDS confirming redistribution of blood flow to very low V/Q units associated with high dead space [22]. Finally, preliminary experimental data have shown that wasted ventilation may act as a multiplicator of VILI through local hypocapnic injury and redistribution of tidal volume inducing volutrauma in perfused regions [23].

In summary, increased dead space may worsen hypoxemia by redistribution of blood flow to low V/Q areas, by non-selective reduction of ventilation in normally perfused regions near hypo-perfused ones, and by specific amplification of VILI, aggravating alveolar edema and collapse [18, 20, 22, 24].

15.2.3 Loss of Hypoxic Pulmonary Vasoconstriction

Hypoxic pulmonary vasoconstriction is a physiological mechanism that reduces shunt through regional increase in pulmonary vascular resistance, diverting blood flow from poorly or non-ventilated (i.e., hypoxic) units to ventilated ones [25]. Sensors of alveolar hypoxia reside on the mitochondria of epithelial cells, where pulmonary vasoconstriction is triggered by a redox signal that inhibits potassium channels and activates voltage-gated calcium channels causing an influx of Ca^{++} into the cell, finally determining arteriolar vasoconstriction [26].

Evidence exists that hypoxic pulmonary vasoconstriction may be impaired in patients with ARDS. Indeed, findings of abnormally dilated vessels in poorly or not-ventilated units (low V/Q areas) suggest that hyperperfusion of non-oxygenated regions might be a major contributor to hypoxemia in COVID-19 ARDS [27, 28]. Autopsy studies also showed that the mediators released during ARDS may impair hypoxic pulmonary vasoconstriction, promoting vessel dilation in hypo-ventilated regions, increasing regional blood flow and shunt [29]. At the molecular level, hypoxic pulmonary vasoconstriction is determined by the imbalance between endothelium-derived vasoconstrictors (e.g., endothelin and thromboxane) vs. vasodilators (e.g., nitric oxide [NO] and prostacyclin) resulting in increased vascular resistance [26]. Experimental studies in different ARDS models (experimental pneumococcal pneumonia [30], acute ethchlorvynol lung injury [31], acute oleic acid lung injury [32]) confirmed that excessive production of prostanoids, via the cyclooxygenase-mediated arachidonic acid pathway, contribute to attenuation of hypoxic pulmonary vasoconstriction in injured lung regions, which increases intrapulmonary shunt. Other vasodilatory mediators, in addition to prostaglandins, also influence hypoxic pulmonary vasoconstriction. Experimental acute lung injury induced by burn and smoke inhalation was associated with an upregulation of interleukin-1 and increased levels of endotoxin in the circulation, both causing induction of NO synthase (iNOS) in the alveolar epithelial cells and production of NO, a potent vasodilator [33]. Similarly, experimental studies in sepsis (the most common etiology of ARDS) induced by infusion of *Pseudomonas aeruginosa* in sheep demonstrated loss of hypoxic pulmonary vasoconstriction with preserved blood flow in the lung ventilated with 100% nitrogen; hypoxic pulmonary vasoconstriction was partially restored with administration of an iNOS inhibitor [34].

15.2.4 Low Mixed Venous Oxygen Saturation

Oxygen delivery (DO_2) is the product of the arterial content of oxygen (CaO_2) and cardiac output. In the presence of reduced DO_2 and/or increased systemic O_2 consumption (VO_2) (both common conditions in patients with ARDS), the difference between arterial and venous oxygen content increases, leading to lower mixed venous oxygen saturation (SvO_2). However, a physiological study in patients with ARDS suggested that the relationship between VO_2 and DO_2 might become linear only at low DO_2 values [35] and that SvO_2 could be low even in the presence of preserved hemodynamics and low VO_2. Whatever the cause for a larger artero-venous oxygenation gap, there exists an inverse correlation between the CaO_2–CvO_2 gradient and PaO_2, according to the Berggren equation of shunt [36]. In other words, a decrease in SvO_2 (which linearly reflects the decreases in venous oxygen within the physiologic oxygenation range) induces hypoxemia in the presence of shunt [36]. This mechanism has been confirmed in patients, by artificially decreasing mixed venous oxygen tension (PvO_2) at constant inspired oxygen fraction (FiO_2) [37]. The larger the shunt, the more the mixed venous saturation will impact the arterial saturation: shunted pulmonary blood flow will reach the systemic circulation with unchanged SvO_2 and the resulting arterial saturation will be a weighted average between this and the one reached by the oxygenated pulmonary blood flow. Indeed, increased pulmonary blood flow reaching shunted regions is one of the main features explaining worsening of hypoxemia in ARDS patients who subsequently have a pulmonary embolism [38]. However, clinicians need to remember that, in patients with hemodynamic impairment, the redistribution of pulmonary blood flow generates a reduction in shunt, thus limiting the effects of decreased SvO_2 on arterial hypoxemia [39].

15.2.5 Intracardiac and Intrapulmonary Anatomical Shunts

Patent foramen ovale is a defect in the cardiac intra-auricular septum, potentially allowing a right-to-left shunt which misses the pulmonary circulation. This foramen usually closes spontaneously in the first months of life, but remains patent in around 25% of subjects in the general population, usually without causing any symptoms [40]. In ARDS, the increase in intrathoracic pressure due to mechanical ventilation, and the rise in pulmonary vascular resistance as a result of lung injury and microthrombosis lead to an increase in right ventricular diastolic pressure, and thus in right atrial pressure, which may exceed the left atrial pressure and re-open this right-to-left intracardiac anatomical shunt [41]. Clinical studies have shown that the prevalence of a significant patent foramen ovale in ARDS is around 15–20% and it seems to be independent from right heart dysfunction [40, 41]. Diagnosis of patent foramen ovale is performed at the bedside by transthoracic echocardiography (Fig. 15.2), with an agitated saline (or gelatin) bolus test, enabling detection of a right-to-left passage of bubbles [42, 43].

Of note, other conditions may increase intrapulmonary anatomical shunt and worsen hypoxemia. The hepatopulmonary syndrome leads to pulmonary vessel

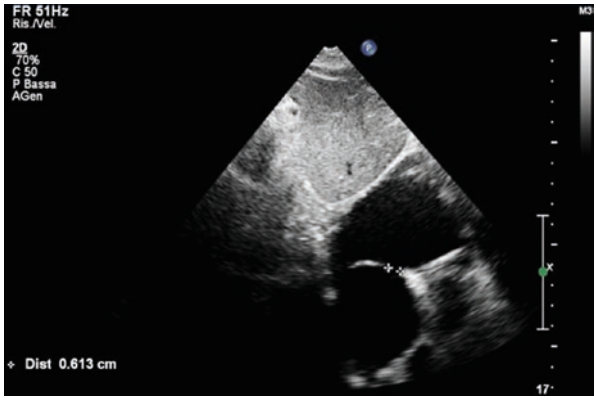

Fig. 15.2 Echocardiographic view of patent foramen ovale (subcostal window). The patent foramen ovale appears like an interruption in the interatrial septum

dilation, potentially increasing the pulmonary blood flow fraction reaching shunted regions in advanced cirrhosis [43]. Inflammation and vasodilation with decreased blood flow velocity may trigger exaggerated neo-angiogenesis (intussusceptive angiogenesis) redirecting blood to non-ventilated areas. Angiocentric inflammation with diffuse microthrombi, and compensatory vasodilation may both cause opening of an anatomical intrapulmonary shunt in COVID-19 ARDS [15, 44, 45].

15.3 Recognizing ARDS Phenotypes Based on the Prevalent Mechanisms of Hypoxemia

Although all the previously described mechanisms usually coexist in the same ARDS patient, recognition of the predominant phenotype may lead to different physiologic reasoning and to personalized therapies (Fig. 15.3).

The most 'classical' phenotype of ARDS should be characterized by loss of aeration with low lung compliance due to alveolar collapse and de-recruitment. In this context, hypoxemia will mainly depend on intrapulmonary shunt and re-opening of the recruitable lung tissue by positive end-expiratory pressure (PEEP) may improve oxygenation and protect the lungs [11]. An alternative strategy to recruit collapsed lung tissue is prone positioning, which reduces the transpulmonary pressure needed to re-open dorsal regions. However, the clinical benefits of prone position are not correlated with improved oxygenation, potentially indicating specific protective effects of this maneuver for patients with ARDS [46].

In the case of increased dead space, impaired hypoxic pulmonary vasoconstriction, and/or overperfusion of poorly ventilated regions as leading mechanisms of hypoxemia, the ARDS patient may be severely hypoxemic but with preserved respiratory mechanics. In these patients, the calculated shunt (i.e., 'functional shunt') will be larger than the expected one based on loss of aeration. Attempting aggressive recruitment using high PEEP will therefore carry more risks than benefits (e.g., overdistension, barotrauma and negative hemodynamic effects [47]). Instead, specific interventions could be evaluated, such as anticoagulation in the case of diffuse microthrombosis [48]. A simple bedside maneuver to detect the dissociation

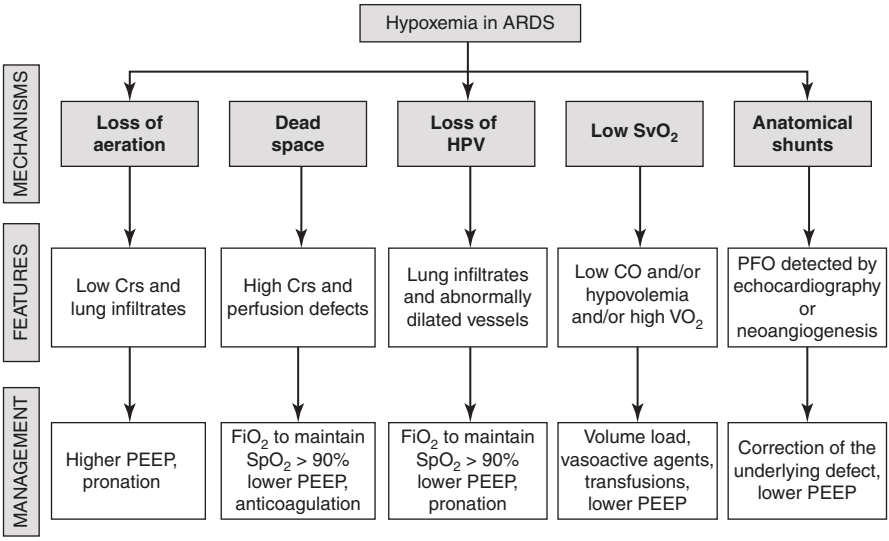

Fig. 15.3 Flow chart of mechanisms, main features, and management of hypoxemia in acute respiratory distress syndrome (ARDS). *HPV* hypoxic pulmonary vasoconstriction, *Crs* respiratory system compliance, *CO* cardiac output, FiO_2 fraction of inspired oxygen, *PFO* patent foramen ovale, *PEEP* positive end-expiratory pressure, SpO_2 pulse oximetry oxygen saturation, SvO_2 mixed venous oxygen saturation, VO_2 oxygen consumption

between the functional shunt and the loss of aeration is to increase the FiO_2 to 100%: if arterial oxygenation improves, 'non-classical' causes of V/Q mismatch may be the main determinants of hypoxemia [49].

Finally, when low SvO_2 is suspected in a hypoxemic ARDS patient, target etiologic therapies could be implemented. If the patient has cardiovascular shock, fluid resuscitation therapy, vasopressors and inotropic agents represent first line interventions, whereas application of PEEP requires caution, because it may reduce venous return and further impair hemodynamics [47]. In such conditions, interventions to be considered include deep sedation and paralysis to decrease VO_2 and correction of anemia to optimize DO_2.

15.4 Conclusion

Hypoxemia in ARDS derives from different pathophysiological mechanisms, including loss of aeration, increased dead space, loss of hypoxic pulmonary vasoconstriction, low SvO_2 and intracardiac and intrapulmonary anatomical shunts. Early recognition of the predominant mechanisms of hypoxemia at the individual patient level may be key to providing safe and effective personalized interventions. Bedside methods to assess lung recruitability, V/Q mismatch, and central hemodynamics are becoming easier and more widely available as is cardiac imaging. Thus, in the near future, intensivists could aim at more accurate mechanism-based bedside assessment of ARDS pathophysiology.

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To Prone or Not to Prone ARDS Patients on ECMO

16

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16.1 Introduction

The prone position is recommended as a supportive therapy in patients with moderate-to-severe acute respiratory distress syndrome (ARDS). It is usually associated with improved oxygenation and pulmonary mechanics as the result of a more homogeneous distribution of mechanical forces and better ventilation/perfusion (V/Q) matching. These effects lead to a lower risk of aggravating preexisting lung injury and, ultimately, a decrease in mortality. Despite widespread use of the prone position in patients with ARDS, even in awake non-intubated spontaneously breathing patients, its use dramatically decreases once the patient has been placed on extracorporeal membrane oxygenation (ECMO). In this chapter, we discuss the available evidence regarding use of the prone position in ARDS patients treated with ECMO.

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16.2 Physiological Effects of Prone Position in Patients with ARDS

The physiological effects of the prone position have been well described [1]. However, individual responses to the prone position may vary from one patient to another or even in the same patient at two different time points of his/her course in the ICU.

16.2.1 Effects on Respiratory Mechanics and Ventilation-Perfusion Ratio

Normally, the prone position decreases chest wall compliance [2] as a result of the limitation of abdominal expansion from contact with the bed and the fact that the posterior chest wall is less compliant. By contrast, the prone position generates a more homogeneous distribution of stress and strain in the lung parenchyma [3]; therefore, it may lead to more homogeneous inflation of the lung, decreasing the risk of tidal hyperinflation of non-dependent lung regions while simultaneously decreasing the cyclic opening and closing of alveolar units of the dependent lung. Hence, the prone position generates opposite effects on the chest wall and lung compliance. It should also be noted that the prone position may increase lung recruitment, defined as the total number of opened alveolar units. This effect is because the dorsal mass of the lung is greater than the ventral and not because there is any change in the average density of the lung, which remains unchanged regardless of the patient's position. Finally, we should also remember that these changes in regional ventilation associated with prone position lead to a more homogeneous V/Q distribution [4] as perfusion remains mainly in the dorsal regions of the lungs when the patient is prone.

16.2.2 Effects on Gas Exchange

The prone position may improve oxygenation as a result of the mechanisms mentioned earlier (more alveolar units open, better V/Q matching, and lower chest wall compliance of the anterior wall). However, the prone position may also have effects on the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) levels. Indeed, patients who responded to decreased $PaCO_2$ while maintaining the same minute ventilation presented better outcomes [5]. These changes have been associated with increased lung recruitment [6].

16.2.3 Hemodynamic Effects of Prone Position

Prone position has also been associated with right ventricular unloading, which leads to an increase in the cardiac index and a decrease in heart rate [7]. This is easily explained if we consider that hypoxemia, hypercapnia, and high driving and

plateau pressures have been described as risk factors for acute cor pulmonale in ARDS patients [8] and could be reduced by the use of the prone position. Importantly, it may also partially explain the survival improvement described with the prone position in patients with ARDS [9], as no association between oxygenation improvement and survival has been observed [10].

16.2.4 Effects on Hospital-Acquired Respiratory Infections

Another potentially significant effect of prone positioning is that, for anatomical reasons and the effect of gravity, when the patient is in the prone position, the dorsal part of the lung remains higher than the mouth, which favors the drainage of respiratory secretions. However, in an ancillary study of the PROSEVA (Proning Severe ARDS Patients) trial, prone positioning was not associated with a reduced incidence of ventilator-associated pneumonia (VAP) [11].

16.3 Indications and Contraindications

16.3.1 Indications

According to the inclusion criteria used in the PROSEVA study, one may accept that the prone position is indicated in ARDS patients with a ratio of arterial oxygenation to fraction of inspired oxygen (PaO_2/FiO_2) <150 mmHg [9]. However, despite the observed mortality benefits, the results of a large multicenter observational study published 5 years after the PROSEVA trial to determine the prevalence of use of the prone position in ARDS, showed that the prone position was only used in 33% of patients with severe ARDS [12]. Thus, there is a critical gap between the evidence of mortality improvement and actual use of this management strategy. This gap is mainly due to the increase in workload, the absence of trained staff to perform the maneuver, and the possibility that it is still considered as a rescue maneuver that should be applied only to patients who present with refractory hypoxemia. However, the prone position may decrease mortality in patients with mild-to-moderate ARDS [13]. During the coronavirus pandemic, the results of some studies showed that the prone position was more widely used regardless of the severity of ARDS [14] and it was also used in non-intubated patients [15]. In fact, the prone position has been shown to decrease inspiratory effort and lung stress and to improve gas exchange while attenuating systemic inflammation in patients with ARDS [16]; the same effects might apply in awake patients.

16.3.2 Contraindications

The absolute contraindication to using the prone position is the presence of unstable spinal fractures. All other contraindications are relative; therefore, decisions

to use the prone position should be individualized. These relative contraindications include hemodynamic instability, unstable large bone or pelvic fracture, open abdominal wounds, increased intracranial pressure, or a risk of intracranial hypertension without adequate intracranial pressure monitoring. Although extracorporeal membrane oxygenation (ECMO) has not traditionally been considered a contraindication for prone positioning, proning is only used in 15% of patients who need to be placed on ECMO [17]. Several reasons may explain why the prone position is not continued when ECMO is started. First, there is a risk of ECMO-related complications when the patient is in the prone position. Second, is the fact that these patients were categorized as non-responders in the prone position in terms of oxygenation (this is the main reason for ECMO initiation). However, it is worth noting that the prone position has several essential benefits beyond oxygenation improvement, which may explain the survival benefit observed in prone patients; therefore, the absence of an oxygenation improvement after proning may not be sufficient to decide to discontinue the technique. Third, the fact that the patients were not proned before ECMO may partially explain why it is not used in these patients.

16.4 How to Perform Prone Positioning in ECMO Patients

The prone position maneuver in patients treated with ECMO should not differ from that performed on non-ECMO patients. However, more staff members should participate in the maneuver [18]. Between four and eight persons will be needed depending on the experience of the team and the body mass index of the patient. One person should be dedicated to managing the head of the patient and the artificial airway. In the case of an ECMO jugular cannula, this person will also control this cannula during the procedure. This person coordinates the entire prone position procedure. Another person must assess the correct functioning of ECMO and take care of the femoral ECMO lines. Finally, between one and three staff members on each side of the bed should perform the turning. During the proning maneuver, special attention needs to be paid to the ECMO flow and the integrity and potential displacement of the ECMO lines. Indeed, as the turning could be done with two persons on each side of the bed, another person could be in charge of fixing the cannulas at the insertion site in case of femoral insertion (jugular cannula will be controlled by the person allocated to the head of the patient).

Another critical issue is the direction of the turning. It has been proposed that turning should prioritize the reinjection line of VV-ECMO or the central venous lines, leaving them on the top during the turning, especially in patients with femorojugular access. It is essential to check the appropriate length of all the lines (ECMO, central venous, arterial, and ventilator circuits) before starting the maneuver. It should also be noted that the use of pillows is necessary to avoid compression of the femoral cannulas and to facilitate correct assessment of the insertion site to detect any bleeding.

16.5 Clinical Evidence of Benefit from the Prone Position in Patients Treated with ECMO

Evidence regarding use of the prone position in patients treated with ECMO is continuously growing. Several studies have reported improvements in oxygenation [18–24] and respiratory system compliance (Crs) [18, 24, 25] after proning (Table 16.1). Improvement in respiratory mechanics, when it was specifically defined as an increase in Crs >3 ml/cmH_2O (which represents a tidal volume increase of approximately 40 ml), was associated with a higher body mass index, more frequent viral pneumonia, shorter ECMO duration, and lower dorsal tidal volume distribution [25]. Interestingly, this higher increase in Crs observed in mechanical responders persisted for up to 6 h after returning to the supine position. These patients also presented a concomitant decrease in $PaCO_2$ with no changes in the ventilator settings of sweep gas flow [25].

Other important conclusions can be drawn from studies that used electrical impedance tomography (EIT) to monitor ECMO patients during proning. First, the optimal positive end-expiratory pressure (PEEP) levels in the prone position, determined by EIT and defined as the minimum sum of collapse and overdistension in a decremental PEEP maneuver, were significantly lower than in the supine position [25]. Moreover, as the prone position increases lung homogeneity, the same PEEP levels are less likely to generate tidal hyperinflation. Finally, it could also be observed that the lower levels of PEEP needed during proning and the associated changes in regional ventilation distribution were independent of the mechanical response. Thus, mechanical changes after proning are not good surrogates for proning-induced ventilation distribution changes. Indeed, changes in regional ventilation were also observed, even in patients who presented with lower Crs after proning.

Two studies have used the prone position as rescue therapy [18, 21]. The first study included patients who had failed to wean from ECMO after 7 days or those who had a PaO_2/FiO_2 <85 mmHg despite an FiO_2 of 1 on both ventilator and ECMO, combined or not with plateau pressure >25 cmH_2O [18]. The second study included patients who met at least one of the following three conditions: PaO_2/FiO_2 < 70 mmHg despite maximal oxygenation, plateau pressure >32 cmH_2O, or failure to wean from ECMO after 10 days of support [21]. In both studies, improvements in oxygenation were observed. It should be noted that, in the study by Kimmoun et al. [18], prolonged prone position sessions of 24 h were used, and the results showed improvement in both oxygenation and respiratory mechanics at the end of the prone session. Similarly, the results of a more recent study showed that improvements associated with the prone position continued to evolve during the 16-h sessions in the prone position, emphasizing the need for longer durations of prone sessions to achieve the maximal benefit [25].

Three studies have analyzed the effect of proning ARDS patients receiving ECMO [23, 24, 26]. The first was a single center retrospective study that compared 14 patients with ARDS on ECMO who were proned with 11 who were not proned [23]. Patients who were proned were less likely to be weaned from ECMO and had

Table 16.1 Summary of key studies on prone positioning in patients with acute respiratory distress syndrome (ARDS) treated with extracorporeal membrane oxygenation (ECMO)

Reference	Type of study	Patients included	Prone position characteristics	Main results	Adverse events
Kipping et al. [19]	Retrospective cohort	12	Duration of prone sessions: 8 h Number of prone sessions: median of 6 (IQR 4–8) Total number of prone sessions: 74	58% reported an improvement in the PaO_2/FiO_2 ratio > 20% No change in MAP, HR, but mPAP significantly increased during proning and decreased after proning Dose of norepinephrine could also be decreased	One lost NGT Bleeding from ECMO cannulation sites (11/74) or tracheal tube (10/74) or central venous lines (8/74) or chest tubes (10/74) One endotracheal tube obstruction One pulmonary embolism Drop in SpO_2 > 2% (10/74) One temporary reduced blood flow of ECMO Hemodynamic instability (7/74) Temporary bradycardia (3/74)
Masuda et al. [20]	Cohort	5	Duration of prone sessions: mean 15.3 ± 0.5 h Number of prone sessions: mean 1.8 ± 0.8	Oxygenation improvement: PaO_2/FiO_2 ratio in supine 143 ± 38 mmHg vs. prone 263 ± 99 mmHg	None
Guervilly et al. [21]	Prospective cohort	15	Initiation after a median of 9 (IQR 5–10) days on ECMO Duration of prone sessions: 12 h Number of prone sessions: 1.4 per patient Total number of prone sessions: 21	Oxygenation improvement: PaO_2/FiO_2 ratio increased from 103 (78–135) vs. 160 (96–215); $P = 0.007$ The oxygenation improvement persisted after returning the patients to the supine position No changes in $PaCO_2$ and Crs were observed	No major adverse events Variations in ECMO flow were small (1.6 ± 4% compared to baseline) Two patients required crystalloid infusions of 500 ml for MAP < 65 mmHg during proning One pneumothorax occurring during proning was diagnosed and drained only after returning to supine position.

Kimmoun et al. [18]	Retrospective cohort	17	Initiation after a median of 6 (4–12) days on ECMO Duration of prone sessions: 24 h Total number of prone sessions: 27	Oxygenation improvement: PaO_2/FiO_2 ratio in supine 111 (IQR 84–128) mmHg vs. at the end of prone session 173 (120–203) mmHg Oxygenation improvement occurred more frequently in patients who were proned after 7 days of ECMO therapy Improvement in Crs: From 18 (12–36) to 32 (15–36) ml/cmH_2O 24 h after the return to supine position, tidal volume was increased from 3.0 (2.2–4.0) to 3.7(2.8–5.0) ml/kg No correlation was observed between the oxygenation improvement and the amount of non-aerated lung tissue in the CT scan	One membrane thrombosis, one drop in ECMO blood flow
Lucchini et al. [22]	Retrospective cohort	14	Duration of prone sessions: median 8 h (IQR 6–10) Number of prone sessions: (median 1 – IQR 1–1.5) Total number of prone sessions: 45	Oxygenation improvement: PaO_2/FiO_2 ratio in supine 123 (IQR 82–135) mmHg and at the end of prone session 149 (90–186) mmHg This improvement was not maintained when the patient was turned to supine 113 (74–182) No significant hemodynamic variations (HR, SAP, PAPm, CO, PWP, SvO_2)	None
Rilinger et al. [26]	Retrospective cohort propensity score matched	38	Initiation after a median of 1.7 (0.5–5.0) days on ECMO Duration of prone sessions: median 19.5 (IQR 16.8–20.8) hours Number of prone sessions: 2 (1–3)	No difference in hospital survival (36.8% vs. 36.8%, $P = 1.0$) No difference in ECMO weaning rate (47.4% vs. 44.7%, $P = 0.82$) Hospital survival was superior in the subgroup of patients treated with early proning (<17 h) as compared to late or no proning (81.8% vs. 33.3%, $P = 0.02$) 60-day mortality was 18% for the early proning and 65% for the late and no proning group, respectively ($P = 0.027$) Survival rate of early proning was higher compared to late proning or no prone (81.8% vs. 18.5% and 36.7%, $P < 0.001$ and $P = 0.003$, respectively)	No relevant complications

(continued)

Table 16.1 (continued)

Reference	Type of study	Patients included	Prone position characteristics	Main results	Adverse events
Franchineau et al. [25]	Prospective cohort	21	Duration of prone sessions: 16 h	Static Crs during proning increased from 23 (17–29) to 27 (20–37) ml/cmH_2O ($P < 0.01$) 13 (62%) patients increased their static Crs by 3 ml/cmH_2O after proning on ECMO (mechanical responders) EELI was redistributed from ventral to dorsal regions during proning Optimal PEEP determined by EIT was lower in prone position (14 (12–16) vs. 10 (8–14) cmH_2O	None
Garcia et al. [23]	Retrospective cohort	14 (SARS-CoV-2)	Duration of prone sessions: median 16 h (IQR 15–17) Total number of prone sessions: 24	Oxygenation improvement: PaO_2/FiO_2 ratio in supine 84 (IQR 73–108) vs 112 (83–157) after proning The median PaO_2/FiO_2 ratio improvement after proning was 28% [2–36]. 62.5% high responders (increase PaO_2/FiO_2 ratio > 20%), 16.7% moderate-responders (increase PaO_2/FiO_2 < 20%), and 20.8% non-responders (decrease PaO_2/FiO_2) Patients in the prone ECMO group were less likely to be weaned from ECMO, and 28-day mortality rate was significantly higher.	Three minor hemorrhages at site of cannula insertion Three moderate flow drops of VV-ECMO that required fluid resuscitation
Giani et al. [24]	Multicenter retrospective cohort propensity score matched	240 patients (66 matched pairs)	Initiation after a median of 4 (IQR 2–7) days on ECMO Duration of proning: mean 15 (12–18) h Total number of prone sessions: 326	Improvement in oxygenation, intrapulmonary shunt fraction and static Crs that persisted after supination Minor differences in hemodynamics (mPAPm and PWP were slightly higher during proning and HR was lower) Lower hospital mortality in proned patients (OR = 0.50, 95%CI: 0.29–0.87) PS matched cohort: • proned patients had a lower mortality (30% vs. 53%, $P = 0.0241$) • proned patients had a longer duration of ECMO (16 vs10 days, $P = 0.0344$)	No major complication 6% minor complications Six procedures aborted due to respiratory or hemodynamic instability during prone positioning

IQR interquartile range, *PaO_2/FiO_2* ratio of arterial oxygenation to fraction of inspired oxygen, *MAP* mean arterial pressure, *HR* heart rate, *mPAP* mean pulmonary arterial pressure, *NGT* nasogastric tube, *$PaCO_2$* partial pressure of carbon dioxide in the arterial blood, *Crs* respiratory system compliance, *SAP* systolic arterial pressure, *CO* cardiac output, *EELI* end-expiratory lung impedance, *PEEP* positive end-expiratory pressure, *EIT* electrical impedance tomography

a higher 28-day mortality rate. However, there was an important selection bias as the prone position was initiated if the PaO_2/FiO_2 ratio was <80 mmHg despite an FiO_2 of 1 both on the ventilator and the ECMO circuit and in the case of consolidation of more than 50% of the lung volume. The second study analyzed 38 matched pairs of patients with ARDS [26]: no differences in ECMO weaning rates or hospital survival were observed. However, by contrast to the results of the study by Kimmoun et al. [18], which reported that oxygenation improvements (increase >20% in the PaO_2/FiO_2 ratio) were more frequently observed in patients who had been treated for 7 days or more with ECMO therapy, patients who were proned within the first 17 h of ECMO therapy had lower in-hospital and 60-day mortality rates compared to those who were proned later or those who were not proned at all [26]. Finally, in a multicenter retrospective study of 240 patients with ARDS receiving ECMO [24], multivariate analysis showed that the prone position was associated with lower hospital mortality. Moreover, in 66 matched pairs of patients in this cohort, proned patients had lower mortality and longer duration of ECMO.

16.6 Complications during Prone Positioning in ECMO Patients

One of the main reasons for not proning patients who are receiving ECMO is the risk of ECMO-related complications, which could be fatal. The most dangerous complications are ECMO cannula dislodgment or a sudden decrease in blood flow. From the analyzed studies, four reported no relevant complications [20, 22, 25, 26]. Others reported minor complications [21, 23, 24], such as minor bleeding at the cannula insertion site and a temporary decrease in ECMO blood flow, which responded to fluid administration. Occasionally, endotracheal tube occlusion or ECMO membrane thrombosis has been reported. In the largest study analyzed, six prone position maneuvers needed to be aborted because of the appearance of respiratory or hemodynamic instability during the procedure [24].

One recent review that included 49 patients from seven different studies demonstrated that the development of complications during the proning of ECMO patients was very limited [27]. More importantly, all adverse events were rapidly and successfully reversed. In fact, they reported no cases of ECMO cannula dislodgment or chest tube or airway dislodgment.

16.7 Which ECMO Patients Should Be Proned?

There are three possible answers to this question. The first is that ECMO patients should not be proned. Possible arguments to support this are the fact that they were proned prior to ECMO but no oxygenation improvement was observed, and the potential increased risk of complications during proning. Nevertheless, it should be noted that the benefits of the prone position beyond oxygenation improvements are well described and widely accepted. Moreover, when the maneuver is performed

adequately, the incidence of complications during the treatment of ECMO patients has not been demonstrated to be higher than that in non-ECMO patients.

The second possible answer is that only a select group of patients should be proned. However, this implies that we need to define which ECMO patients would benefit the most from proning. In this sense, some authors decided to prone patients with dorsal infiltrates on computed tomography (CT) [20] as one may expect that they have a more heterogeneous ventilation distribution in the supine position and, therefore, would benefit most from proning. In fact, a greater improvement in compliance has been described in patients with a lower dorsal tidal volume/global tidal volume ratio [25]. Therefore, this approach emphasizes the change in the paradigm of prone position indication in patients with ARDS, moving from gas exchange criteria to lung mechanics criteria. In contrast, other studies that demonstrated the presence of approximately 50% of non-aerated or poorly aerated lung parenchyma on the CT scan of ECMO patients who were proned [18] found no correlation between CT scan findings and Crs and oxygenation after proning [18].

Finally, one could argue that all patients with ARDS who are receiving ECMO should be proned. This idea could be supported by the fact that the prone position has been shown to increase the survival of non-ECMO patients with ARDS [9]. Second, it is worth noting that most of these patients had a preferred distribution of tidal ventilation to the ventral zones in the supine position; therefore, they could benefit from homogenizing lung inflation (Fig. 16.1). Moreover, as this increase in lung homogeneity was also present in patients with lower Crs and was independent of the mechanical response generated, it has been suggested that all ARDS patients who are receiving ECMO should benefit from proning [25].

Although it has been recently shown that the prone position may reduce inspiratory effort during spontaneous breathing in non-ECMO ARDS patients [16], the prone position is usually associated with the use of neuromuscular blockade and deeper sedation, avoiding spontaneous breathing. Conversely, the European Life Support Organization guidelines recommend an early reduction in sedation levels and a switch to spontaneous breathing after 24–48 h of ECMO initiation [28]. It is important to highlight that when this strategy is implemented one should be aware that monitoring respiratory drive and inspiratory effort [29] is strongly recommended to minimize the risk of patient self-inflicted lung injury. Indeed, it has been shown that around 50% of ARDS patients on ECMO present injurious inspiratory effort despite increasing sweep gas flows [30].

16.8 Research Priorities

Several questions remain unanswered, so there is a lot of room for improvement in this field. The evidence is mainly based on physiological or observational studies that included a small number of patients and studies in ARDS patients not receiving ECMO. Large randomized controlled trials (RCTs) are therefore needed to establish the role of the prone position in ARDS patients treated with ECMO. One of the most important unanswered questions is which ECMO patients would benefit from proning. It is also important to know about the relevance of

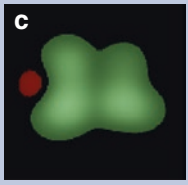
	Baseline	Prone 30 minutes	Prone 180 minutes
Vt (ml)	257	334	388
Vt (ml/kg of PBW)	3.2	4.2	4.9
Pplateau (cmH_2O)	26	26	26
PEEP (cmH_2O)	16	16	16
Compliance (ml / cmH_2O)	25.7	33.4	38.8
Regional ventilation distribution			
Anterior (%)	62	53	50
Posterior (%)	38	47	50
EIT ventilation image			
Compliance gain map			
			

Fig. 16.1 Example of the changes in pulmonary mechanics and regional ventilation distribution observed in one patient with acute respiratory distress syndrome (ARDS) treated with extracorporeal membrane oxygenation (ECMO) and ventilated with pressure-control ventilation. (**a**) represents the change in compliance observed between supine position and 30 minutes after prone position; (**b**) represents the variation in compliance between 30 and 180 min after prone position, and (**c**) represents the change in compliance between supine and 180 min after proning. *Green area* represents compliance gain and *red region* represents compliance loss. *Vt* tidal volume, *PBW* predicted body weight, *Pplateau* plateau pressure, *PEEP* positive end-expiratory pressure, *EIT* electrical impedance tomography

timing of proning, as controversial results exist regarding the effectiveness of early and late proning [18, 26]. Finally, the duration of proning sessions is also important, as some data suggest that the benefits of the prone position may continuously increase beyond 16 h [18, 25].

Currently, two large RCTs have been designed to analyze the effect of the prone position on ARDS patients treated with ECMO. The first study (ClinicalTrials.gov Identifier NCT04139733) is designed to address the effect of early proning on the duration of ECMO. The second study (ClinicalTrials.gov Identifier NCT04607551) aims to analyze the effects of proning on weaning from ECMO.

16.9 Conclusion

Use of the prone position has been shown to improve the survival of patients with moderate-to-severe ARDS. The results of observational studies have demonstrated that the prone position in ARDS patients treated with ECMO can be safely performed and has many physiological benefits that may potentially lead to a decrease in mortality. However, several questions remain unanswered and large RCTs that address the effectiveness of proning ECMO patients are still needed.

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Mesenchymal Stromal Cell Therapy in Typical ARDS and Severe COVID-19

17

F. F. Cruz, P. R. M. Rocco, and P. Pelosi

17.1 Introduction

Minimum criteria have been established by the Mesenchymal and Tissue Stem Cell Committee of the International Society of Cell Therapy to define human mesenchymal stromal (or stem) cells (MSCs): (1) they must be plastic-adherent, when kept in standard culture conditions; (2) they must be positive for the surface markers CD105, CD73, and CD90, and negative for the hematopoietic markers CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR; and (3) they must differentiate into adipocytes, chondroblasts and osteoblasts *in vitro*, under specific culture conditions [1]. MSCs have been widely investigated over the past decades, for their therapeutic properties in acute lung diseases and critical illness, such as acute respiratory distress syndrome (ARDS), and recently in coronavirus disease 2019 (COVID-19) [2].

ARDS has been known for more than 50 years as a multifactorial syndrome characterized by severe acute respiratory failure. Its hallmarks are the acute onset of severe and refractory hypoxemia, increased elastance, diffuse alveolar damage on histology, and noncardiogenic bilateral pulmonary infiltrates [3]. ARDS is a devastating and life-threatening critical condition associated with high mortality rates, ranging from 34.9% to 46.1% [4]. Its pathophysiology includes a hyperinflammatory response that leads to epithelial dysfunction and apoptosis, endothelial activation, increased alveolar-capillary permeability, alveolar and interstitial edema, fibrin

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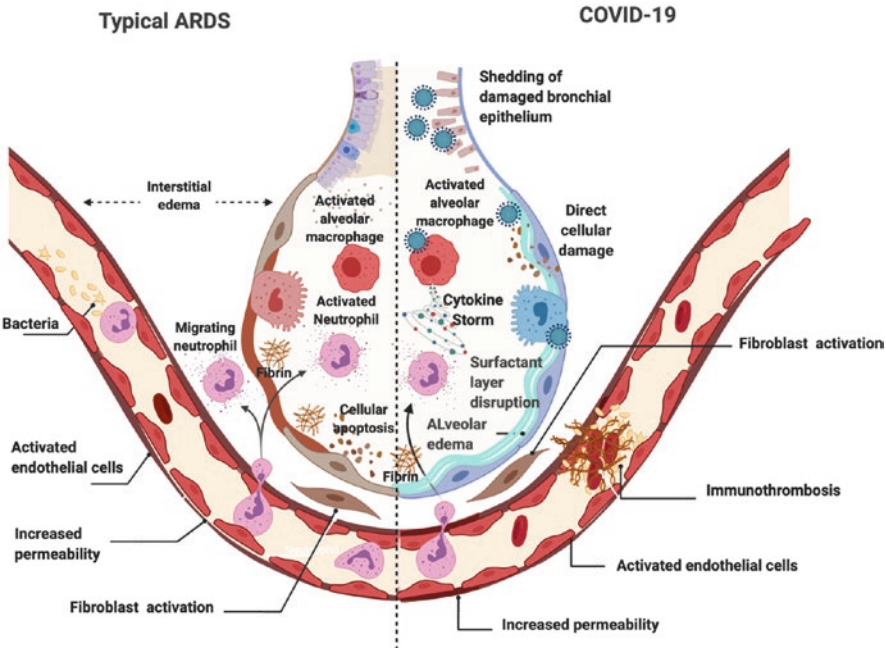

Fig. 17.1 Pathophysiology of typical acute respiratory distress syndrome (ARDS) and coronavirus disease 2019 (COVID-19). ARDS is characterized by a pro-inflammatory response (activation and recruitment), increased permeability of the alveolar–capillary membrane, interstitial edema, fibrin net deposition, epithelial and endothelial apoptosis, and fibroblast activation. COVID-19 is characterized by direct viral injury, endothelial dysfunction, thromboinflammation, dysregulation and exacerbation of the immune response (cytokine storm), and further tissue fibrosis. Created with BioRender.com

deposition, further fibroblast production, and deposition of collagen fibers in lung parenchyma (Fig. 17.1) [3, 4].

The COVID-19 pandemic has focused global efforts on finding novel therapies. The majority of patients develop a mild or moderate flu-like disease, but a substantial portion of those infected develop pneumonia, and can progress to respiratory failure. COVID-19 patients can develop moderate-to-severe ARDS, with very high mortality rates (up to 70%) [5]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can induce direct lesions on epithelial cells, activate alveolar macrophages that secrete several cytokines, and recruit leukocytes to the alveolar space. A local and widespread dysregulation and exacerbation of the immune response, known as a cytokine storm, can occur, amplifying cell damage and inducing an intense systemic inflammatory response. This promotes endothelial hyperactivation, immune thrombosis, increased endothelial permeability, alveolar fluid effusion, and fibrin deposition (Fig. 17.1) [5].

Typical ARDS and severe COVID-19 share an unclear physiopathology, high mortality rate, and unmet need for effective therapeutics; thus, therapy with MSCs has emerged as a promising potential therapy for both [2]. In this chapter we will

discuss the rationale for using MSCs, preclinical and clinical evidence, and limitations of cell therapy with MSCs in ARDS and COVID-19.

17.2 Mechanisms of Action of MSCs

MSCs can be isolated from several tissues, including bone marrow, adipose tissue, lungs, umbilical cord, placenta, and menstrual blood [6]. Initially, scientific interest in MSCs was due to their plasticity; MSCs are able to differentiate *in vitro* into the three classic lineages (adipocytes, chondroblasts, and osteocytes), but also into other cell types, including epithelial and endothelial cells, after exposure to specific molecular signaling [7]. *In vivo* differentiation is still a controversial question and has become less important over the years [6].

The ability of MSCs to interact with target cells and modulate their function has gained attention in the regenerative medicine field. MSCs interact with target cells through cell-to-cell contact, or even in the absence of cell engraftment, through paracrine/endocrine effects, by secreting soluble mediators, extracellular vesicles, or by transferring organelles, such as mitochondria (Fig. 17.2).

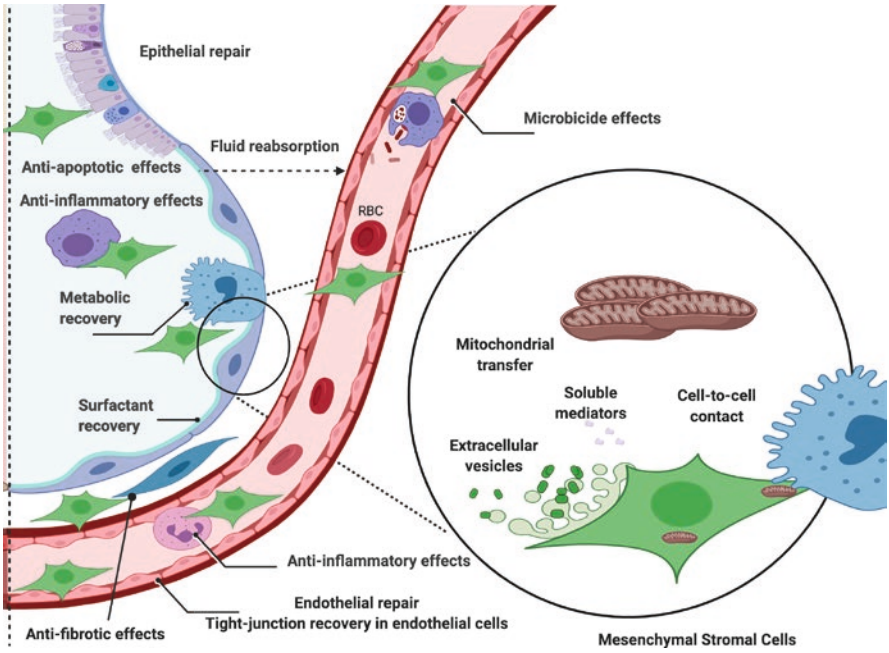

Fig. 17.2 Mechanisms of action of mesenchymal stromal (or stem) cell (MSC) therapy. MSCs act through cell-to-cell contact or through the secretion of soluble mediators, extracellular vesicles, or mitochondrial transfer. MSCs have anti-inflammatory, anti-fibrotic, anti-apoptotic, and microbicidal effects. MSCs can also improve metabolic dysfunction and reduce edema through rearrangement of endothelial tight junctions and increased alveolar fluid clearance. No antiviral activity has been described to date. Created with BioRender.com

Different groups have shown in several experimental models of lung disease and critical illness, including ARDS, that systemic administration of MSC-conditioned media instead of MSCs *per se* promoted protective effects [8]. It has been suggested that some specific mediators, including soluble and membrane proteins, mRNAs, microRNAs, long non-coding RNAs, and other molecules, play an important role in these effects; nevertheless, they seem to be produced differentially according to MSC source and to be differently relevant for each disease model [8]. Although some single mediators have been shown to be important, none alone is sufficient to induce all the regenerative properties of MSCs. Some soluble mediators implicated in different ARDS model systems include angiopoietin-1, interleukin (IL)-1 receptor antagonist (IL-1ra), IL-10, hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), lipoxin (LX)A-4, tumor necrosis factor-inducible gene protein (TSG)-6, tumor growth factor (TGF)-β, and antimicrobial peptides [9].

In parallel, several researchers have investigated the effects of administration of isolated extracellular vesicles derived from MSCs [10]. Extracellular vesicles are membrane vesicles that contain several substances that can mediate intercellular communication and can also modulate functional activities in target cells [11]. Extracellular vesicles were historically classified according to their origin and size into exosomes (30–100 nm, originating from multivesicular bodies in an endosome) and microvesicles (100–1000 nm, formed by shedding off the cell membrane). The International Society of Extracellular Vesicles recently urged researchers to consider use of terms that classify extracellular vesicles in reference to their (a) physical characteristics, such as size (small extracellular vesicles when <100 nm or < 200 nm, medium/large extracellular vesicles when >200 nm); (b) biochemical composition (surface markers); or (c) descriptions of conditions or cell of origin (MSC-extracellular vesicles, for instance), replacing the classic terms 'exosome' and 'microvesicle', which were hampered by contradictory definitions and by inaccurate expectations of unique biogenesis [11].

Several manuscripts have shown beneficial effects after administration of MSC-derived extracellular vesicles in ARDS models, including viral-induced ARDS [12–15]. Finally, the beneficial effects of MSCs have recently been associated to their capacity to transfer mitochondria to target cells, such as leukocytes (monocytes, macrophages, lymphocytes) and structural cells (including endothelial, epithelial, and smooth-muscle cells). Mitochondrial transfer can occur through tunneling nanotubes, gap junctions, or extracellular vesicles [16]. In a model of ARDS induced by *Escherichia coli*, mitochondrial transfer from bone marrow-derived MSCs to alveolar epithelium increased alveolar ATP levels, improving metabolic capacity [17]. Furthermore, *in vitro* and *in vivo* mitochondrial transfer from MSCs to macrophages can exert MSC immunomodulatory properties, improving the phagocytic capacity and antimicrobial effects of macrophages and suppressing pro-inflammatory cytokine release in an *E. coli* induced ARDS environment [13, 18].

17.3 Effects of MSCs in Models of ARDS

As a result of their immunomodulatory and regenerative properties, MSCs have been used therapeutically in acute systemic and pulmonary inflammatory conditions. Experimental studies have been run in several models of pulmonary and extrapulmonary ARDS (lipopolysaccharide [LPS], *E. coli, Pseudomonas aeruginosa,* influenza virus, cecal ligation and puncture, pancreatitis, etc.), at different stages of the disease (prophylactic, early, and late) and in many species (mice, rats, rabbits, sheep, pigs, and human explants). Groups have also tested different sources of MSCs (bone marrow, adipose tissue, placenta, umbilical cord, etc.), types of transplant (autologous, allogeneic, syngeneic, and xenogeneic), routes of administration (intravenous, intratracheal, intraperitoneal), numbers of doses, number of cells in each dose, and protocols for cell extraction, culture, and preservation [6]. In the experimental setting, MSCs were able to reduce ARDS mortality, improve lung function and gas exchange, and promote alveolar–capillary membrane repair and fluid clearance through anti-inflammatory, bactericidal, anti-apoptotic, anti-fibrotic, and anti-edema effects.

In models of ARDS, plasma and bronchoalveolar levels of several inflammatory mediators–such as IL-1β, IL-6, IL-8, interferon (IFN)-γ, macrophage inflammatory protein (MIP)-1α, and tumor necrosis factor (TNF)-α [19–21]–are reduced after MSC therapy. MSCs are able to:

1. inhibit LPS-mediated apoptosis of alveolar macrophages [22]; increase macrophage phagocytosis [13, 18]; induce macrophage polarization toward anti-inflammatory M2 phenotype, which is beneficial for tissue repair and may prevent release of other pro-inflammatory cytokines [13, 18, 20]; increase macrophage secretion of anti-inflammatory cytokines (such as IL-10, which suppresses T-cell proliferation [20, 23]) and chemokine ligand (CCL)-18, which recruits regulatory T (Treg) cells [24];
2. impair neutrophil migration, activation and myeloperoxidase production [25];
3. induce a shift in $CD8^+$ cytotoxic lymphocytes, considered to be pathogenic in the early phases of ARDS, towards a suppressive phenotype with regulatory functions [26], via TGF-β, HGF and indoleamine 2,3-dioxygenase (IDO); inhibit Th-17 lymphocytes, which are associated with neutrophil chemotaxis [27]; and induce Treg cells, thus reducing the Th17/Treg ratio towards an anti-inflammatory phenotype [28].

In ARDS, MSC-mediated beneficial effects not only reduce inflammation but also reduce the bacterial load by direct and indirect effects. MSCs are known to recognize the molecular microenvironment, and the microenvironment in turn can interfere with MSC phenotype and secretome. Endotoxin can activate MSCs through Toll-like receptors (TLR), particularly TLR3, and increases the antibacterial effects of MSCs, both directly (through secretion of microbicide mediators such

as β-defensin, regenerating islet-derived protein 3 gamma (RegIIIγ), cathelicidin, lipocalin, and the peptide LL-37) and indirectly (through secretion of mediators that can increase neutrophil extracellular traps [NET] and boost macrophage and neutrophil phagocytosis, increasing bacterial clearance) [29].

As mentioned before, MSCs can rescue epithelial cells with metabolic dysfunction by mitochondrial transfer, recovering endotoxin-depleted ATP stores and restoring surfactant secretion by pneumocytes [13, 17, 18]. By decoupling oxidative phosphorylation, MSCs reduce concentrations of reactive oxygen species (ROS) and shift the metabolism to sugar metabolism, thereby promoting cell survival and reducing cell death [30]. Endothelial cells and type II alveolar epithelial (AT-II) cells can be induced to regenerate by MSC-secreted HGF, KGF, and vascular endothelial growth factor (VEGF) [6].

Simultaneously, Na+-K+-ATPase is upregulated in lung AT-II cells, inhibiting fibrosis [30]. In animal models of ARDS, MSCs regulate tissue remodeling processes and attenuate lung fibrosis by increasing metalloproteinase (MMP)-8 and decreasing levels of tissue inhibitor of metalloproteinase (TIMP)-1, IL-1β, and TGF-β1 [31, 32]

Finally, MSCs promote alveolar fluid clearance, which is impaired by inflammation and edema in ARDS, by increasing levels of fibroblast growth factor 7 (FGF7) and angiopoietin-1 (Ang-1), which can restore epithelial and endothelial permeability [30, 33]; furthermore, MSC-secreted KGF induces type II epithelial cells to increase expression of ion channels and Na + -K + -ATPases [22, 34].

17.4 MSCs in Typical ARDS: Clinical Trials

Some clinical trials have been conducted to investigate the effects of MSCs in ARDS (Table 17.1). The main goal of these studies was to address safety as the primary outcome; secondary outcomes included inflammatory markers and cardiovascular, respiratory, and systemic parameters. These studies were very heterogeneous regarding MSC numbers, dosing schemes, sources and routes of administration, and patient selection criteria. Conclusions were limited primarily by small sample sizes.

Intravenous infusion of allogeneic human adipose tissue-derived MSCs was tested in ARDS patients in China during a phase I, randomized, double-blind, placebo-controlled trial with 1:1 allocation [35]. A single intravenous dose of MSCs (1×10^6 cells/kg) appeared to be safe for the treatment of ARDS, and induced a reduction in surfactant protein (SP)-D serum levels and a trend to reduced IL-6 ($p = 0.06$) five days after MSC therapy. Patients showed no improvement in ventilator-free days, ICU-free days, or length of hospital stay, although short-term improvements in oxygenation occurred after MSC administration [35]. The main limitations of this study were the small number of enrolled patients ($n = 12$), short follow-up period (28 days), and administration of only one dose at only one time point, thus precluding collection of time– and dose–response data.

Table 17.1 Published clinical trials of mesenchymal stromal (or stem) cell (MSC) therapy in typical acute respiratory distress syndrome (ARDS) and coronavirus disease 2019 (COVID-19)

Authors [ref]	Study design	Cell therapy	Patients	Results
Zheng et al. [35]	Phase I – Double-blind, randomized, placebo-controlled	1 i.v. dose of AD-MSCs (1×10^6 cells/kg)	Moderate-to-severe ARDS diagnosed within 48 h	12 patients enrolled (6 MSC, 6 placebo). Safe; reduction in SP-D serum levels; no improvement in PaO_2/FiO_2 ratio, hospital indices (length of hospital stay, ventilator-free days and ICU-free days at day 28) or serum levels of IL-6 and IL-8
Simonson et al. [36]	Open-label, non-randomized, uncontrolled, compassionate use	6 i.v. doses of BM-MSCs (2×10^6 cells/kg total)	Severe ARDS patients on ECMO (2 days, 23 days)	2 patients enrolled (2 MSC). Safe; resolution of respiratory, hemodynamic, and multiorgan failure. Decrease in multiple pulmonary and systemic markers of inflammation, including epithelial apoptosis, alveolar-capillary fluid leakage, and pro-inflammatory cytokines, microRNAs, and chemokines
Wilson et al. [37]	Phase I, open-label, non-randomized, dose escalation	1 i.v. dose of BM-MSC (1, 5, 10×10^6 cells/kg)	Moderate-to-severe ARDS diagnosed within 96 h	9 patients enrolled (3:3:3). Safe. Mortality rate in this cohort was 22%, lower than in the general population with this severity
Matthay et al. [38]	Phase II, double-blind, randomized, placebo-controlled	1 i.v. dose of BM-MSC (10×10^6 cells/kg)	Moderate-to-severe ARDS diagnosed within 96 hours	60 patients enrolled (40 MSC, 20 placebo). Safe. Numerically (but not statistically) higher mortality (28 and 60 days) and fewer ventilator-free and ICU-free days in MSC group compared to placebo. Higher baseline severity (not significant) in MSC group.
Leng et al. [46]	Phase I, open label, non-randomized, not-controlled	1 i.v. dose of BM-MSC (10^6 cells/kg)	Severe COVID-19 pneumonia	7 patients (MSC). Safe. Improved clinical outcomes, anti-inflammatory effects
Shu et al. [47]	Phase I, open label, randomized, conventional-treatment controlled	1 i.v. dose of UC-MSC (2×10^6 cells/kg)	Severe COVID-19 pneumonia	41 patients (12 MSC: 29 standard treatment). Safe. Reduction in mortality, clinical symptoms, clinical and radiological progression; anti-inflammatory effects
Sengupta et al. [48]	Phase I, open label, non-randomized, not-controlled	1 i.v. dose of exosomes (ExoFlo™) from BM-MSC	Different stages of COVID-19 (mild, moderate, severe)	24 patients (1 mild, 20 moderate, 3 severe; all received ExoFlo™). Safe. Improvement in clinical status, oxygenation, lymphocyte cell counts. Reduction in neutrophil count, CRP, D-dimer and ferritin

i.v. intravenous, *AD* adipose tissue-derived, *BM* bone marrow-derived, *CRP* C-reactive protein, *ECMO* extracorporeal oxygenation, *ICU*, intensive care unit, *IL* interleukin, PaO_2 arterial partial pressure of oxygen, *UC* umbilical cord

In Sweden, a single dose of allogeneic bone marrow-derived MSCs (2×10^6 cells/kg) was administered systemically to two patients with severe refractory ARDS who had failed to improve after all standard life support measures, on a compassionate-use basis [36]. The authors performed a detailed analysis of the immunomodulatory and proteomics characteristics. Both patients showed resolution of respiratory, cardiovascular, and multiorgan failure, as well as a decrease in several lung and systemic markers of pathology, including epithelial apoptosis, alveolar–capillary fluid leakage, and pro-inflammatory cytokines, microRNAs, and chemokines [36]. This was not a randomized clinical trial, but whether the beneficial effects observed in this study, conflicting with the absence of clinical improvements seen in previous study, was due to differences in cell origin (adipose tissue versus bone marrow) or to the number of administered cells remains unclear.

A phase I, open-label, non-randomized dose escalation trial (1, 5, 10×10^6 cells/kg), the STemcells for ARDS Treatment (START), was conducted in the United States with nine patients with moderate to severe ARDS [37]. All nine patients tolerated a single intravenous administration of MSCs, which were thawed immediately before administration. No evidence of immediate clinical instability, pre-specified infusion-related adverse events, or dose-limiting toxicity at any of the doses tested was observed. Favorable changes were observed in lung injury score and systemic outcomes, including improved daily sequential organ failure assessment (SOFA) score with the high dose of MSCs (10 million cells/kg) compared to lower doses. This is consistent with the hypothesis that higher doses of MSCs might provide greater clinical benefit. However, none of these differences were statistically significant, and given the sample size and lack of a control group, one cannot conclude that these differences reflect a true dose response [37].

Based on these promising results, the same group conducted the phase II START trial [38]. This was a multicenter, double-blind, randomized trial designed to assess treatment with one intravenous dose of allogeneic bone marrow-derived MSCs (10^7 cells/kg) compared with placebo (2:1 ratio). The authors recruited ventilated patients with moderate to severe ARDS within the first 7 days after diagnosis (exudative phase) in five university medical centers in the USA. The primary outcome was safety, and all analyses were intention-to-treat. Secondary outcomes included respiratory, systemic, and serum biomarkers.

Sixty patients were enrolled in this study. No patients had any of the prespecified adverse hemodynamic or respiratory safety events during product infusion or up to 6 h after injection. Despite numerical differences in clinical outcomes, there were no statistical differences between groups. No improvement was observed in the major efficacy outcomes: 28-day mortality (15% placebo versus 30% MSC, 95%CI 0.5 to 15.1), 60-day mortality (25% placebo versus 38% MSC, 95%CI 0.5 to 7.6), ventilator-free days adjusted to day 28 (17 placebo versus 2 MSC, 95%CI -12 to 0), number of ICU free days adjusted to day 28 (14 placebo versus 2 MSC group, 95%CI 11 to 0). The authors reported numerical (but not statistical) differences in disease severity scores at baseline, in which the placebo group presented better clinical scores than the experimental group: Acute Physiology and Chronic Health Evaluation III (APACHE III) score (89 ± 33 placebo versus 104 ± 31 MSC), minute

ventilation (9.6 ± 2.4 l/min placebo versus 11.1 ± 3.2 l/min MSC), and PEEP (10.8 ± 2.6 cmH_2O placebo versus 12.4 ± 3.7 cmH_2O MSC). Additionally, the mortality rate in the placebo group was lower than expected based on disease severity. After adjustment for APACHE III score, the hazard ratio for mortality at 28 days changed from 2.4 (95%CI 0.5 to 15.1, $P = 0.34$) to 1.43 (95%CI 0.4 to 5.1, $P = 0.58$). On the other hand, evaluation of biomarkers revealed a decrease in circulating angiopoietin 2 concentrations in MSC recipients [38]. The authors reported an unexpectedly wide range of MSC viability at the time of administration (36% to 85%). Finally, there was a strong indirect correlation between viability and levels of angiopoietin 2, and between viability and improvement in oxygenation index. This wide range of viability might have a role in the lack of efficacy observed, but MSC biology is still not fully understood. Some authors have found that MSC death correlates with ineffective therapy [39]. On the other hand, it has been suggested that MSC apoptosis is protective, and even mandatory, for promotion of their immunoregulatory effects. In graft-versus-host disease, individual cytotoxic ability to induce MSC cell death is directly correlated to the success of cell therapy [40]. Thus, the real impact of cell viability at the time of administration requires further investigation in different clinical contexts.

Other researchers have wondered why the MSC-treated group exhibited increased 28-day mortality (although not significantly so) in the START trial. MSC treatment might be beneficial or detrimental depending on each patient's specific pulmonary microenvironment, particularly regarding levels of IL-6, fibronectin, and total antioxidant capacity. MSC therapy was protective in a mouse model with reduced concentrations of IL-6 and fibronectin and increased levels of total antioxidant capacity, whereas MSCs worsened injury in the opposite conditions. This finding provides an important rationale for a precision-medicine approach to guide MSC treatment in future [41].

Other clinical trials are registered or underway (Table 17.2). In conclusion, the clinical studies published to date have reported that MSC administration is safe, with few infusion reactions or late adverse effects. Further investigations with larger sample sizes, powered to detect safety and even efficacy differences, such as mortality, clinical status, and respiratory mechanics, are necessary.

17.5 MSCs in Severe COVID-19

There is a large body of literature demonstrating that MSC therapy reduces mortality in bacterial-induced acute lung injury models [6], but only a small number of experimental studies on respiratory viral diseases, mainly focusing on influenza-induced pneumonia, and none on coronavirus infection. Results are also conflicting.

Murine bone marrow-derived MSCs or xenogeneic human bone marrow-derived MSCs were ineffective in lung injury induced by mouse-adapted influenza H1N1 or swine-origin pandemic influenza H1N1, regardless of the timing of administration after disease induction [42]. Similarly, intravenous and intratracheal administration of human and mouse bone marrow-derived MSCs administered in two doses, earlier

Table 17.2 Clinical trials of mesenchymal stromal (or stem) cell (MSC) therapy in typical acute respiratory distress syndrome (ARDS) and coronavirus disease 2019 (COVID-19) registered on ClinicalTrials.gov

MSC source	Typical ARDS	COVID-19
Bone marrow	**Phase I** (NCT02112500, NCT02215811)	**Phase I** (NCT04397796, NCT04467047, NCT04400032), **Phase I/II** (NCT04345601, NCT04346368, NCT04445454), **Phase II** (NCT04377334, NCT04361942, NCT04444271)
Adipose tissue		**Phase I** (NCT04352803, NCT04611256), **Phase I/II** (NCT04341610), **Phase II** (NCT04348461, NCT04728698)
Umbilical cord/ Wharton's jelly	**Phase I** (NCT02444455, NCT03608592, NCT04347967)	**Phase I** (NCT04313322, NCT04456361, NCT04457609, NCT04490486), **Phase I/II** (NCT04273646, NCT04333368, NCT04339660, NCT04355728, NCT04390152, NCT04398303, NCT04399889, NCT04390139, NCT04461925, NCT04494386), **Phase II** (NCT03042143, NCT04269525, NCT04288102, NCT04416139, NCT04429763, NCT04437823, NCT04625738)
Cord blood		**Phase I** (NCT04565665)
Olfactory mucosa	**Phase I/II** (NCT04382547)	
Menstrual blood	**Phase I** (NCT02095444)	
Placenta		**Phase I/II** (NCT04461925), **Phase II** (NCT04389450, NCT04614025)
Investigational MSC products	**Phase I/II** (Multistem® NCT 02611609)	**Phase I** (KI-MSC-PL-205 NCT04447833, Remestemcel-L NCT04366830, NCT04371393, NCT04456439, DW-MSC NCT04535856), **Phase I/II** (BX001 NCT04452097, CYP001 NCT04537351), **Phase III** (Remestemcel-L NCT04371393)
Exosomes		**Phase I/II** (NCT04491240), **Phase II** (NCT04602442)
Not mentioned		**Phase I** (NCT04252118, NCT04525378, NCT04615429), **Phase I/II** (NCT04392778), **Phase II** (NCT04366063, NCT04466098, NCT04615429)

or later in the post-infection period, failed to improve lung injury in a mouse-adapted influenza H1N1-induced lung injury model [43].

On the other hand, other recent studies have shown that intravenous administration of bone marrow-derived MSCs in rodent and pig models of influenza (H5N1 and H7N9 influenza viruses) improved alveolar fluid clearance ability, reduced alveolar–capillary membrane permeability to proteins, and reduced virus-induced mortality and body-weight loss without influencing virus titers. The authors noted that beneficial effects appeared to depend on the age of the animals (the older, the better) [34]. Efficacy was also observed with murine bone marrow-derived MSCs in avian influenza virus (H9N2) infection [44] and umbilical cord-derived MSCs in a murine model of influenza A (H5N1) infection [45]. Finally, extracellular vesicles

from bone-marrow derived MSCs have also been tested in a pig model of mixed swine (H3N2, H1N1) and avian (H9N5, H7N2) influenza-induced lung injury, with promising results [15].

Based on the positive results obtained in preclinical studies with viral-induced lung injury, and taking into consideration the ability of MSCs to immunomodulate, repair endothelial and epithelial cells, and promote endothelial-epithelial barrier integrity, cell therapy with MSCs or even their subproducts might be an option for COVID-19, especially during the cytokine storm phase. A few manuscripts have been published (Table 17.1), and 25 clinical studies have been registered in ClinicalTrials.gov (Table 17.2), testing MSCs or their derivatives (extracellular vesicles or conditioned media), either intravenously or intranasally administered, in patients with SARS-CoV-2-ARDS.

In an open-label, non-randomized, conventional treatment-controlled clinical trial, enrolling seven patients with severe COVID-19 in China, therapy with MSCs (10^6 cells/kg) was safe and improved clinical outcomes of all patients 14 days after MSC injection. Two days after cell therapy, patients had better respiratory function and reduced symptoms. After MSC administration, increased levels of circulating lymphocytes, circulating CD14+CD11c+CD11b_{mid} regulatory DC cells, and IL-10 levels were observed. Levels of C-reactive protein (CRP) and TNF-α, as well as pro-inflammatory cells such as CXCR3+ cells (either CD4+ T, CD8+ T, or NK cells), were reduced [46]

A single-center, open-label, randomized, conventional treatment-controlled trial conducted in China tested the impact of umbilical cord MSCs (2×10^6 cells/kg) in severe COVID-19. The authors showed that cell therapy reduced mortality and clinical symptoms, improved clinical and radiological progression, and reduced inflammatory mediators such as CRP and IL-6. They concluded that intravenous transplantation of human umbilical cord-derived MSCs is safe and effective, and can be considered an alternative for severe COVID-19 [47].

In a non-randomized, open-label, uncontrolled study, exosomes from allogeneic bone marrow-derived MSCs (ExoFlo™) were administered intravenously to COVID-19 patients with different degrees of disease severity (mild, moderate and severe). No adverse events were observed within 72 h of ExoFlo administration. After one administration, clinical status and oxygenation improved; laboratory findings showed reduction in neutrophil count, and increase in $CD3^+$, $CD4^+$, and $CD8^+$ lymphocyte counts. Furthermore, concentrations of acute phase mediators, such as CRP, D-dimer, and ferritin were reduced. In conclusion, owing to its safety profile, capacity to restore oxygenation, downregulate cytokine storm, and reconstitute immunity, ExoFlo is a promising therapeutic candidate for severe COVID-19 [48].

Intravenous administration of MSCs and exosomes proved safe and effective for treatment of patients with COVID-19 pneumonia, especially those in critical condition. Future randomized placebo-controlled trials with larger sample sizes are needed to determine the protective effects of MSC and their derivatives, the optimal timing of administration, and which patients would benefit from cell therapy [2, 32].

17.6 Conclusion

ARDS and severe COVID-19 carry high mortality rates and lack effective therapeutic options. Although MSCs or their derivatives seem to be promising and clinical trials have shown that cell therapy is safe, they have also shown only modest improvement in clinically important outcomes. Several challenges have yet to be overcome and further clinical studies, particularly randomized clinical trials enrolling larger numbers of patients and adequately powered to identify changes in clinically relevant outcomes, are needed.

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Part VI

Renal Issues

Acute Kidney Injury in ECMO Patients

18

M. Ostermann and N. Lumlertgul

18.1 Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-saving therapy for patients with severe respiratory and/or cardiovascular failure. There are two main configurations: (1) veno-arterial ECMO (VA-ECMO) in patients with refractory cardiogenic shock or combined cardiorespiratory failure, and (2) veno-venous ECMO (VV-ECMO) in patients with potentially reversible causes of respiratory failure. Over the past decade, use of ECMO has increased substantially in critical care units, emergency departments, interhospital transfers, operating rooms, and during cardiopulmonary resuscitation (CPR) [1].

The in-hospital mortality ranges from 21 to 37% in patients receiving VV-ECMO compared to 40–60% in patients treated with VA-ECMO [2–4]. Despite improving survival in recent years, adverse effects are common including acute kidney injury (AKI), infection, thrombosis, and bleeding [5]. AKI is a frequent complication among patients treated with ECMO, resulting in increased morbidity and mortality [6]. Understanding the impact of AKI and its contributing factors, and of renal replacement therapy (RRT) is essential to inform clinical practice and design future studies for prevention and management of this high-risk group.

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18.2 Incidence of AKI in ECMO

The reported incidence of AKI in patients treated with ECMO varies from 26 to 85% due to differences in patient characteristics, AKI definition, and clinical settings. The pooled estimated incidence of severe AKI requiring RRT is 45% [6]. AKI is more common in VA-ECMO than in VV-ECMO (61% vs. 46%) and is most often present on the day of ECMO cannulation [6, 7]. The Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) and Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trials demonstrated a lower incidence of AKI and use of RRT in patients receiving VV-ECMO compared with standard treatment [2].

18.3 Pathophysiology of AKI in ECMO

The underlying mechanisms of AKI in patients treated with ECMO are complex and multifactorial (Table 18.1).

Table 18.1 Risk factors for acute kidney injury (AKI) during extracorporeal membrane oxygenation (ECMO)

Factors	Pathophysiological mechanisms
Patient-related variables	Hypoperfusion Loss of autoregulation Hypoxia Hypercapnia Nephrotoxins Systemic inflammation Cardiorenal syndrome Increased intrathoracic pressure Increased intra-abdominal pressure Neuro-hormonal effects
IMV-related factors	Biotrauma PEEP
ECMO-related factors	
• Hemodynamic variables	Continuous flow (VA-ECMO) Ischemia-reperfusion injury
• Hormonal variables	RAAS dysregulation ANP downregulation
• Circuit-related factors	Blood shear stress Rhabdomyolysis Hemolysis and oxidative stress Embolism Aortic dissection
• Systemic inflammation	Systemic inflammation Renal macro/microcirculatory dysfunction Bioincompatibility Blood/air/surface interaction Hypercoagulable state

IMV invasive mechanical ventilation, *PEEP* positive end-expiratory pressure, *VA* veno-arterial, *RAAS* renin-angiotensin-aldosterone system, *ANP* atrial natriuretic peptide

18.3.1 Patient Factors and Critical Illness

Prior to ECMO initiation, hemodynamic instability, low cardiac output, high intrathoracic pressure, exposure to nephrotoxic agents, severe hypoxemia, hypercapnia, systemic inflammation/immune-mediated effects, and neurohormonal dysregulation can contribute to AKI [8]. In patients with heart failure, cardiac dysfunction, increased intra-abdominal pressure (IAP), and renal congestion contribute to impaired renal blood flow and cardiorenal syndrome [9]. AKI might also occur in the context of other critical illness-related complications including bleeding, limb ischemia, infection, and coagulopathy [8].

18.3.2 Impact of Mechanical Ventilation

Invasive mechanical ventilation is associated with altered hemodynamics and release of pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6 and IL-8) [10]. Plasma cytokine concentrations are predictive of AKI development and renal non-recovery [11]. The application of positive end-expiratory pressure (PEEP) has several beneficial effects for lung recruitment and decrease in left ventricular (LV) pre- and afterload. However, increasing PEEP and/or tidal volumes may elevate intrathoracic pressure, reduce venous return, decrease cardiac output, and increase right ventricular (RV) afterload, resulting in elevated systemic venous pressure, venous congestion, and reduction of renal perfusion. In addition, fluid retention may develop as a result of activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS), and suppression of atrial natriuretic peptide (ANP) release [9]. Lung-protective ventilation limits lung injury and has potential to reduce the risk of AKI [12]. However, permissive hypoxia and hypercapnia might ensue and decrease renal blood flow [9].

18.3.3 ECMO-Related Factors

Following ECMO cannulation, an improvement in oxygenation helps restore the microcirculation in previously hypoxic and hypoperfused organs and tissues, often in association with a degree of ischemia-reperfusion injury and production of reactive oxygen species (ROS) [13]. Continuous flow during VA-ECMO reduces pulsatility, which may compromise renal cortical blood flow and upregulate the RAAS inducing systemic vasoconstriction [14]. Circuit-related factors contributing to the development of AKI include hemolysis, rhabdomyolysis from local ischemia, hemorrhage, renal microthrombosis, and cannula-related complications (e.g., malposition of the cannula leading to venous obstruction, cholesterol embolism following cannulation, aortic dissection) [15, 16]. Hemolysis may occur due to a combination of shear stress from blood travelling through the blood pump, negative intra-circuit pressures, and contact with the non-biological and non-endothelialized surface of ECMO membranes [15]. This leads to elevated plasma free hemoglobin, release of

free iron, oxidative stress, and filtered heme pigments causing tubular obstruction [17]. Blood exposure to artificial surfaces also induces the release of inflammatory cytokines, complement and leukocyte activation, and hypercoagulability. Finally, although VA-ECMO improves oxygenation and peripheral circulation, limited LV off-loading combined with low ejection fraction can result in LV overdistension and worsening pulmonary edema.

18.4 Risk Factors for AKI

Reported risk factors for AKI during ECMO are older age, pre-existing comorbidities (e.g., cirrhosis), post cardiotomy shock as indication for ECMO, late implantation of ECMO, reduced LV ejection fraction (LVEF), intraoperative transfusion, high lactate, high plasma free hemoglobin, increased bilirubin, and high neutrophil-to-lymphocyte ratio [18]. Red blood cell distribution width >14.1%, a marker of inflammation and anemia, has also been found to be associated with an increased risk of severe AKI [19]. During ECMO, high inotropic equivalents, ECMO pump speed, and ECMO duration are linked to AKI development [20]. Higher pump speeds are associated with hemolysis, leukocyte and platelet destruction, and complement activation [21]. To prevent heme pigment-associated AKI, pump revolutions/min (RPM) should be limited to safe levels to avoid excessive negative pressures. AKI patients who required RRT whilst receiving ECMO were more likely to be treated with VA-ECMO, had more organ dysfunction at the time of ECMO insertion, and required more transfusions [22].

18.5 RRT and ECMO

18.5.1 Indications

Fluid overload is highly prevalent and associated with higher mortality and prolonged ECMO duration [23]. According to a recent survey, fluid overload management (43%) or prevention (16%) are the predominant triggers for RRT initiation during ECMO, followed by AKI (35%), and electrolyte disturbances (4%) [24].

18.5.2 Timing

Theoretically, early initiation of RRT may help resolve fluid overload faster and achieve better sodium removal per unit volume than diuretics in ECMO patients. In general ICU patients, recent randomized controlled trials (RCTs) not only failed to demonstrate the survival benefits of early over standard initiation strategy, but also showed increased harm in the early-initiation group including an increased risk of dialysis dependence at 90 days and adverse events [25–27]. A post-hoc sub-analysis of The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial in acute respiratory distress syndrome (ARDS) also demonstrated similar outcomes between early and

standard initiation strategies [28]. Another study using propensity-score matching compared early versus late initiation of CRRT after ECMO (median time from ECMO to CRRT initiation 1 vs. 15 days) and found no difference in survival [29].

In light of the fact that serum creatinine, AKI stage and urine output are poor markers to guide initiation of RRT, the demand-capacity concept has been proposed as a method to guide the decision-making process. Accordingly, RRT should be considered if the degree of fluid overload and AKI-related metabolic derangements are likely to overwhelm the kidneys' capacity to compensate, and pharmacological measures (diuretic therapy, sodium bicarbonate) are unlikely to be effective [30]. The expert committee of the 21st Acute Dialysis Quality Initiative (ADQI) meeting concluded that there was no evidence of benefit for pre-emptive use of RRT in patients treated with ECMO [9]. Therefore, the decision to initiate RRT in patients receiving ECMO should be based on usual absolute and relative indications for critically ill patients.

18.5.3 Modality

RRT options include continuous RRT (CRRT), prolonged intermittent renal replacement therapy (PIRRT), intermittent hemodialysis (IHD), and peritoneal dialysis. Each modality has advantages and disadvantages (Table 18.2). CRRT and

Table 18.2 Advantages and disadvantages of each renal replacement modality during extracorporeal membrane oxygenation (ECMO)

Modality	Advantages	Disadvantages
IHD	• Integration in ECMO circuit possible • Reduced filter downtime • Lower costs than CRRT	• Need for more rapid fluid removal • Risk of hemodynamic instability • Disequilibrium syndrome
PIRRT	• Integration in ECMO circuit possible • Reduced filter downtime • Lower costs than CRRT • Slower volume and solute removal than IHD	• Risk of hemodynamic instability in high-risk patients
CRRT	• Integration in ECMO circuit possible • Continuous fluid and solute removal • Allows more precise control of fluid balance • Better hemodynamic stability	• Patient immobilization • Increased risk of hypothermia • High costs
PD	• Better hemodynamic stability • Technically simple • Lower cost • No addition of anticoagulation	• Less experience in adult patients • Requires specific intraperitoneal catheters • Risk of peritonitis • Risk of hyperglycemia • May interfere with diaphragmatic movements

IHD intermittent hemodialysis, *PIRRT* prolonged intermittent hemodialysis, *CRRT* continuous renal replacement therapy, *PD* peritoneal dialysis

peritoneal dialysis are suitable for patients with hemodynamic instability although CRRT enables more precise fluid and electrolyte management. Meanwhile, PIRRT and IHD allow planned circuit downtime. It is possible to provide CRRT, PIRRT and IHD via integration into the ECMO circuit or separately. When choosing CRRT, any mode of clearance can be delivered, namely slow continuous ultrafiltration (SCUF), continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF).

18.5.4 Techniques

There are three ways to provide RRT with ECMO: using an in-line hemofilter, connecting a RRT device to the ECMO circuit (integrated system), or using a separate RRT access from the ECMO circuit (parallel system) [31, 32] (Table 18.3). In the absence of evidence-based data, practice is based on expert opinion, availability of machines, local expertise, and staff organization. A 2013 survey of 65 ECMO centers showed that 50.8% of centers used independent CRRT circuits while 21.5% used in-line hemofilter [24]. The results of a recent survey of ECMO centers in France and Switzerland are awaited.

18.5.4.1 In-Line Hemofilter

It is possible to provide RRT by incorporating a hemofilter into the ECMO circuit [9, 15, 31] (Fig. 18.1a). The hemofilter is placed after the pump pre-oxygenator so that the oxygenator can trap air and clots. The positive pressure from the ECMO circuit will forward the blood flow through the hemofilter. Then, blood is returned from the filter to the ECMO circuit before the pump. The blood flow rate in the hemofilter is the difference between the total ECMO blood flow rate and the actual flow delivered to the patient, which is measured by placing an ultrasonic probe on the arterial return line from the ECMO circuit. This technique is mainly used for ultrafiltration via the SCUF mode. CVVH or CVVHD can be delivered by adding replacement fluid (CVVH) or dialysis fluid (CVVHD) through standard infusion pumps. Ultrafiltration rate is regulated by connecting a standard infusion device to the effluent port of the hemofilter. However, the amount of removed fluid is less accurate and prone to error up to 800 ml/day [34]. A more precise method is to weigh the actual volume of ultrafiltration using a scale or a volumetric measuring device but this method is labor-intensive. Since hemofilters are not designed for use with high pressure systems and the maximal volume of the infusion pump is limited at 1 l/h, convective and diffusive clearance are less effective than with CRRT using conventional membranes. The hemofilter blood flow rate can be adjusted via a stopcock or a flow-restrictor. Nevertheless, the generated turbulent flow might cause hemolysis and trigger thrombus formation. Most importantly, there is no pressure

Table 18.3 Advantages and disadvantages of renal replacement therapy (RRT) techniques during extracorporeal membrane oxygenation (ECMO) [31, 33]

Techniques	Advantages	Disadvantages
In-line hemofilter	• Low cost • Generates large volumes of UF • No need for separate anticoagulation • Small priming volume	• No pressure monitoring • Requires external infusion device to control UF and deliver replacement fluid • Less precise UF • Limited solute clearance • Flow turbulence and risk of hemolysis
Independent RRT access (parallel system)	• Allows fine-tune adjustment of solute and fluid removal • Able to provide RRT independent of ECMO • Allows use of regional anticoagulation • Simplified circuit changing without need for perfusionist • Mode of solute clearance not restricted	• Need for separate vascular access • Risk of mechanical and infectious complications • Higher extracorporeal blood volume • Technically more complex to manage two separate circuits
RRT connected to ECMO circuit (integrated system)	• Allows fine-tune adjustment of solute and fluid removal • Mode of solute clearance not restricted • No need for separate vascular access • Avoids complications related to line insertion	• Pressure alarms (low pressure alarms if connected pre-pump and high pressure alarms when connected post-pump) • Requires a RRT machine capable of adjusting alarm settings • Risk of air entrapment if access line is connected before centrifugal pump • Flow turbulence with risk of hemolysis and thrombus formation • Generation of shunt within ECMO circuit • Recirculation

RRT renal replacement therapy, *UF* ultrafiltration

monitoring with this technique, which may lead to delayed detection of hemolysis, filter rupture or clot formation.

18.5.4.2 Parallel System (Independent RRT Access)

Setting up an independent RRT device is simple as it does not require ECMO circuit manipulation (Fig. 18.1b). Dose and modality can be adjusted, and fluid balance can be controlled in a precise manner as per usual protocol. Regional anticoagulation can also be added and optimised to prolong filter longevity. However, the need to insert a separate vascular access whilst systemically anticoagulated poses a risk for line-related mechanical and infectious complications. This technique also requires an additional extracorporeal blood volume, which might interfere with ECMO performance [9, 15, 31].

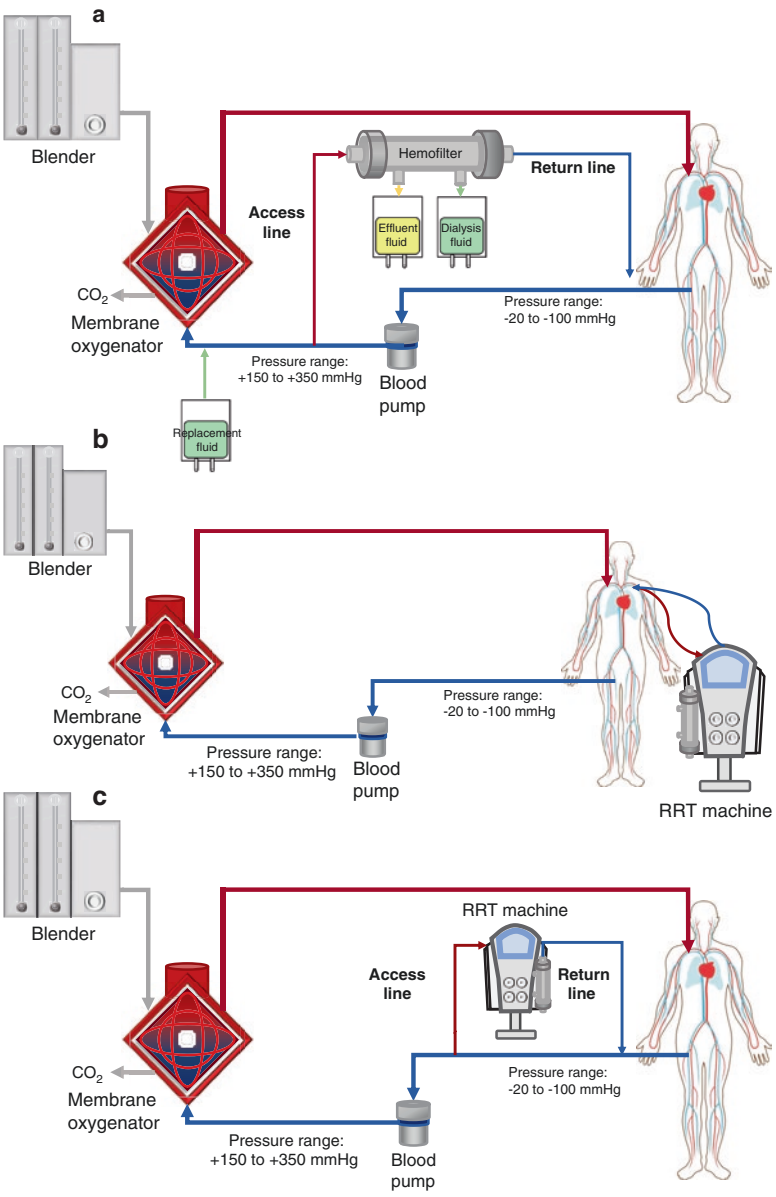

Fig. 18.1 Options for combining extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) circuits. (**a**) An in-line hemofilter is integrated into the ECMO circuit. Replacement fluid is directly administered into the ECMO circuit. Alternatively, dialysis fluid can be supplied in a counter-current position. Replacement/dialysis fluid rates and ultrafiltration rates can be controlled via infusion pumps. (**b**) The CRRT device is connected to the patient through a separate catheter independent of the ECMO circuit. (**c**) The access (inlet) and the return (outlet) lines of the CRRT device are connected before the centrifugal blood pump (low-pressure part) of the ECMO circuit. (**d**) Both the access and the return lines of the CRRT device are connected after the blood pump. (**e**) The access line of the CRRT device is connected after the blood pump (high-pressure), while the CRRT return line is connected before the centrifugal blood pump. (**f**) The access line of the CRRT device is connected directly after the membrane oxygenator, while the return line is connected directly before the oxygenator

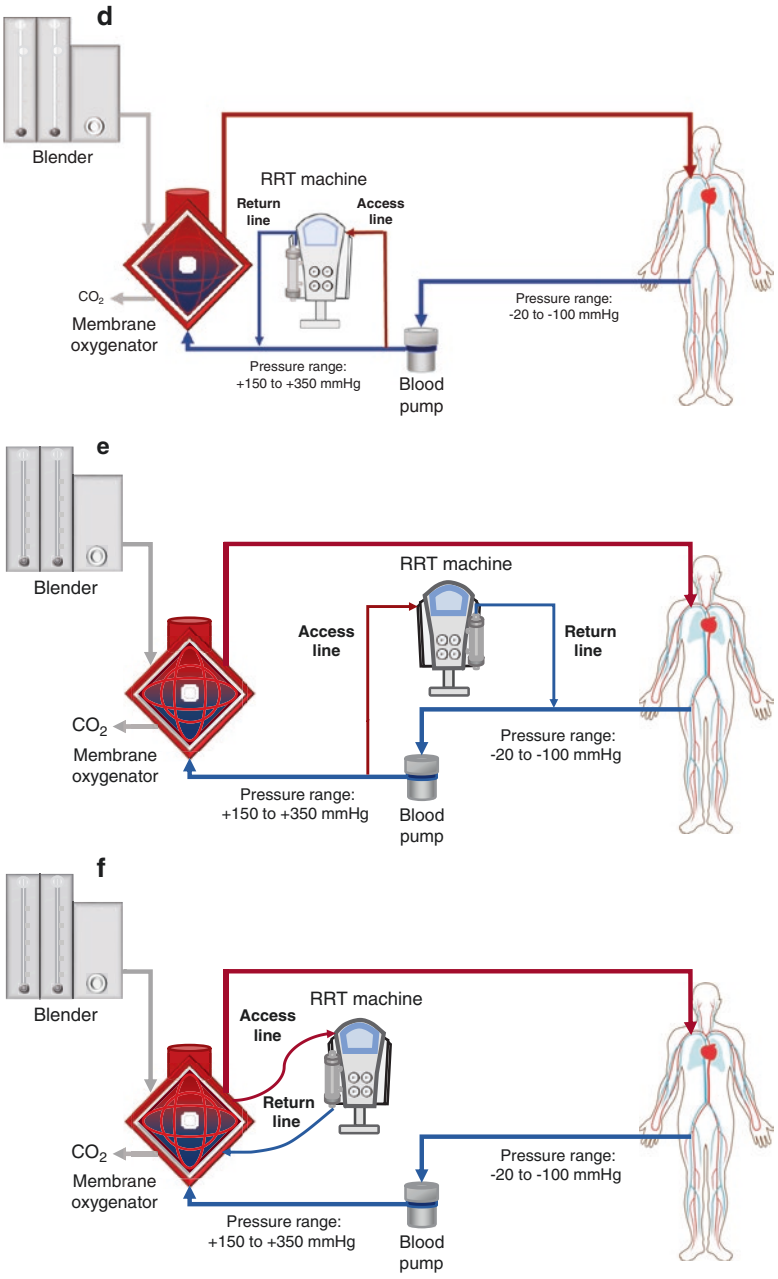

Fig. 18.1 (continued)

18.5.4.3 Integrated System (Combining RRT Machine into the ECMO Circuit)

There are several ways to incorporate a RRT device into the ECMO circuit using two high-flow Luer lock three-way taps as connectors to the RRT access (inlet) line and return (outlet) line [9, 31, 33, 35] (Fig. 18.1c–f). The pressure before the ECMO pump is negative (range: -20 to -100 mmHg) and post-pump is positive (range: +150 to +350 mmHg), which might interfere with the RRT circuit. If a centrifugal pump is used, the RRT access line should be placed post-pump (either before or after the oxygenator) to avoid air entrapment (Fig. 18.1d, e). The RRT return line should be connected before the oxygenator (either pre- or post-pump) to avoid air embolism, clot formation and venous admixture. Careful attention should be paid to the inherently set pressure limits of the ECMO circuit and RRT devices from different manufacturers. The default access pressure of the RRT machine is typically negative. High post-pump pressure may trigger pressure alarms at the entry point of the RRT machine although current RRT machines can tolerate higher pressures or allow adjustment of alarm settings up to +350 to +500 mmHg. To overcome the alarm limits of the RRT machine, a long monitoring extension line attached to the RRT access tubing or reducing the blood flow rates can help to lower the pressure from the ECMO circuit [8]. Another option is to use clamps on the connectors or flow restrictors placed outside the tubing to adjust the RRT circuit pressure on the access or, alternatively, on the return line to avoid extreme pressures [36]. However, this may cause turbulence in blood flow and trigger hemolysis or thrombosis. When withdrawing blood post-oxygenator and returning blood before pump, re-circulation in the RRT circuit (shunt within a shunt) and RRT underdosing may occur. Alternatively, the access and return lines may be safely connected through Luer locks immediately before and after the oxygenator to avoid pressure alarms (Fig. 18.1f).

Combining RRT into the ECMO circuit has several benefits. No additional vascular access is needed and complications related to line insertion are avoided. This method is more effective than using an in-line hemofilter and provides more precise ultrafiltration control and solute clearance by any modality of choice. Use of the heater on the CRRT device is optional. There is also no need for routine additional anticoagulation. However, every connection and disconnection requires support from an ECMO specialist/perfusionist and might pose a risk of air embolism/clot to both devices.

18.5.4.4 Comparison of Different Techniques

There are few studies comparing the efficacy between the different techniques. Compared with an in-line hemofilter technique, integrating a RRT machine into the ECMO circuit was shown to provide more accurate fluid management [37]. A recent study concluded that independent RRT access was associated with fewer effective sessions and shorter filter lives in comparison with the integrated system [38]. However, the average prescribed RRT dose was 40 ml/kg/h, which is higher than currently recommended. In addition, the CVVH modality was used with 33% of replacement fluid given pre-filter, which might result in a relatively high

filtration fraction. Regional citrate anticoagulation was not used [39]. Another study also reported longer filter life for the integrated system compared with the parallel technique [35]. With regards to clearance, a recent study demonstrated similar efficacy for solute clearance and ultrafiltration between the parallel and the integrated methods [40].

18.5.5 Technical Aspects

18.5.5.1 Mediator Removal

Although raised cytokine concentrations have been demonstrated in patients with AKI receiving ECMO and might be implicated in multiorgan dysfunction [41], there is insufficient evidence to recommend blood purification therapy outside the setting of AKI for patients receiving ECMO. Therefore, the use of RRT and/or hemoadsorption with the sole intention of clearing pro- or anti-inflammatory mediators during ECMO is not recommended [9].

18.5.5.2 Anticoagulation

Systemic infusion of unfractionated heparin is the standard anticoagulation in patients receiving RRT and ECMO unless contraindicated. However, significant clotting or excessive bleeding precluding the use of systemic heparin may require the addition of regional citrate anticoagulation to ensure effective RRT delivery [42]. Nevertheless, significant citrate dilution might occur. If the RRT access line is connected from the post-oxygenator limb and the return line is connected to the pre-oxygenator limb, infused citrate will be partially delivered and mixed with pre-oxygenator blood. This may reduce clotting in the oxygenator. Calcium should be infused via a separate central venous access to reduce clotting in the system.

18.5.5.3 Drug Dosing

ECMO and RRT can significantly alter the pharmacokinetics of medications such as antibiotics and sedatives, yet little is known about the optimal regimen for patients treated with both RRT and ECMO. Generally, ECMO increases the volume of distribution and reduces drug clearance. The ECMO circuit might act as a reservoir and redistribute the sequestered drug back into the patient leading to prolonged effects, especially of lipophilic medications with a large volume of distribution (e.g., voriconazole, propofol, fentanyl, midazolam) [8]. In contrast, the ECMO membrane and tubing may adsorb some drugs and reduce plasma concentrations. The presence of RRT increases the risk of both under- and over-dosing further. A preliminary analysis showed that standard dosing of meropenem (1 g 8-hourly) is likely to maintain sufficient trough concentrations (>2 mg/l) to treat highly susceptible Gram-negative pathogens but might be inadequate for higher trough targets [43]. Individualizing drug regimens in patients receiving concomitant ECMO and RRT using therapeutic drug monitoring is suggested where possible until more pharmacokinetic data become available.

18.6 Short-Term Outcomes

AKI and RRT have been shown to be independently associated with mortality but it is uncertain whether they directly increase the risk of dying or merely represent the acuity and severity of the illness [19]. The pooled estimated hospital and/or 90-day mortality rates of patients with AKI and severe AKI requiring RRT while on ECMO were 62.0% and 68.4%, respectively [6]. The likelihood of dying in hospital of ECMO patients receiving RRT is three times that of those without RRT [6]. Importantly, mortality has decreased by >20% since 2016 compared with data from before 2015, possibly due to better patient selection, timing, and clinical application [44].

AKI requiring RRT is associated with other complications, including sepsis, need for fasciotomy/amputation, respiratory failure, intra-aortic balloon pump (IABP) usage, massive blood transfusion, and failure to wean from ECMO [45]. Acute respiratory failure can also be worsened following AKI due to fluid overload, pulmonary edema, increased inflammatory mediators and increased risk of intercurrent sepsis. Other risk factors for mortality include age, oliguria, AKI stage 3, RRT duration hypercapnia, high sequential organ failure assessment (SOFA) score, blood loss, transfusion requirement, hemodynamic instability, liver failure, low Glasgow coma score, and fluid overload [7, 46, 47].

18.7 Renal Recovery and Long-Term Outcomes

The long-term renal prognosis in ECMO survivors is uncertain. Previous studies showed high rates of liberation from dialysis at hospital discharge [4, 48]. However, only 42% of AKI stage 3 survivors had complete renal recovery [7]. In a cohort of 347 post-cardiotomy patients with cardiogenic shock receiving VA-ECMO, all but 2 patients recovered from AKI stage 3 at 6 months [18]. However, it should be noted that creatinine at discharge might be falsely low due to loss of muscle mass and malnutrition following prolonged hospitalization. Therefore, low serum creatinine levels may lead to erroneous glomerular filtration rate (GFR) results and mislead clinicians, resulting in inappropriate drug dosing and inadequate follow-up.

It is established that AKI survivors are at increased risk for long-term mortality, end-stage kidney disease, chronic kidney disease (CKD), and poorer quality of life. However, only a few studies have explored the long-term outcomes of ECMO patients with AKI. In children, two large ECMO studies independently reported a 20-year experience and showed no incidence of end-stage kidney disease in the absence of primary renal disease [38, 48]. In contrast, analysis of a VA-ECMO cohort of adult population showed an 85% incidence of major adverse kidney events, comprised death, end-stage kidney disease, and reduced GFR at 1 year [49]. Risk factors for 1-year major adverse kidney events included lower GFR at baseline, higher AKI stage at ECMO cannulation, and number of red blood cell transfusions. Moreover, the median GFR decline was 20 ml/min/1.73 m^2, and half of AKI survivors had a GFR decline of more than 30%. Decline of GFR by >30% is associated with >5 times increased risk of end-stage kidney disease [50]. Therefore, the

risk of serious long-term renal outcomes should not be underestimated in ECMO patients with AKI. Analysis of a national Taiwan database including 3200 adult patients receiving ECMO with up to 10-year follow-up data revealed higher rates of all-cause mortality, end-stage kidney disease and CKD in patients with RRT-requiring AKI compared with non-dialysis-requiring AKI patients [45]. Prolonged CRRT use (>7 days vs. ≤6 days) was associated with an increased risk of end-stage kidney disease, ventilator dependence, and readmission rate but not survival after discharge [51].

18.8 Conclusion

AKI is extremely common and associated with worse short-term and long-term outcomes in patients receiving ECMO, especially when RRT is required. The most common indication for RRT initiation in these patients is fluid control. RRT should be initiated when the anticipated demand from fluid overload and metabolic derangements exceeds the capacity of the kidneys to compensate. The modality and techniques of providing RRT in patients receiving ECMO depend on local practice and expertise. Provision of RRT as an armamentarium of multiorgan support therapy requires a multidisciplinary team engagement (such as intensivists, nephrologists, cardiologists, cardiac, thoracic and vascular surgeons, perfusionists, dedicated nurses, pharmacists, dietitians, and others) from admission, through ECMO cannulation and RRT initiation, until after discharge. Further research should determine the optimal technique to combine ECMO and RRT, optimal drug dosing and long-term renal prognosis.

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Management of Acute Metabolic Acidosis in the ICU: Sodium Bicarbonate and Renal Replacement Therapy

19

K. Yagi and T. Fujii

19.1 Introduction

Metabolic acidosis is a process caused by an increase in weak acids or a decrease in strong ion difference (SID) [1]. Serum proteins, albumin, and inorganic phosphate are considered as weak acids. Strong ions, such as Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^-, exist at a fully ionized status in body fluids. SID is the presence of an excess of strong cations over strong anions, and the normal value in plasma is 42 mEq/l. The method to quantify metabolic acidosis using SID and weak acids was introduced by Stewart in the 1980s and still creates debate in its clinical application [2]. Plasma base excess is widely used to identify a metabolic component of acidosis in clinical practice. The base excess approach was shown to be equivalent to Stewart's SID approach in quantifying acid-base status in critically ill patients [3].

Metabolic acidosis is classified into acute and chronic. Although it is not clearly defined, acute metabolic acidosis occurs within a few days. Chronic acidosis is a condition that lasts for weeks or even years [4]. In this chapter, we focus on acute metabolic acidosis in intensive care unit (ICU) patients and provide an update from recently published clinical studies.

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19.2 Epidemiology of Metabolic Acidosis in the ICU

Acute metabolic acidosis is well-recognized in the ICU. However, epidemiological data are scarce, which has limited our understanding of the approach to metabolic acidosis until recently.

A retrospective observational study using a large bi-national ICU database in Australia and New Zealand examined the incidence, characteristics, and outcomes of patients with various definitions of metabolic acidosis [5]. Severe metabolic acidosis was defined as a pH ≤ 7.20, $PaCO_2$ ≤ 45 mmHg, HCO_3^- ≤ 20 mmol/l, and total sequential organ failure assessment (SOFA) score ≥ 4 or lactate ≥ 2 mmol/l [6] and occurred in 1.5% of the patients in the ICU. The ICU and hospital mortality rates of these patients were 43.5% and 48.3%, respectively. Moderate or severe metabolic acidosis was defined as pH < 7.30, base excess < -4 mmol/l and $PaCO_2$ ≤ 45 mmHg, and occurred in 8.4% of ICU patients. The ICU and hospital mortality rates were 17.3% and 21.5%, respectively [5]. The mortality of patients with moderate or severe metabolic acidosis was higher than that of patients with sepsis observed in the same database [7], suggesting the clinical relevance of improving care for patients with metabolic acidosis.

A French multicenter prospective study described the incidence of severe acidemia in five ICUs [8]. Severe acidemia was defined as pH < 7.2, including respiratory acidosis, metabolic acidosis, and mixed acidosis. This severe acidosis occurred in 8% (200/2550) of the patients within 24 h of ICU admission. After excluding patients with diabetic ketoacidosis (DKA), which is adjudicated to be an entity with a low risk of death, and patients with respiratory acidosis, ICU mortality of patients with metabolic or mixed severe acidosis was as high as 57% (89/155) [8].

A recently published international observational study conducted in 18 ICUs in Australia, Japan, and Taiwan reported that 14% (1292/9437) of critically ill patients had moderate or severe metabolic acidosis [9]. The median incidence of metabolic acidosis at a study ICU was 172.5 patients/year, suggesting that the management of metabolic acidosis is a relevant issue in patient care in the ICU.

19.3 Common Types of Metabolic Acidosis in the ICU

The causes of acute metabolic acidosis are diverse in critically ill patients. DKA, lactic acidosis, and hyperchloremic acidosis are responsible for most cases of severe metabolic acidosis cases due to a decreased SID [10].

DKA is a medical emergency in patients with diabetes mellitus as a result of insulin deficiency. The hepatic metabolism of fatty acids produces beta-hydroxybutyrate and acetoacetate, strong anions in the human body. As hyperglycemia induces osmotic diuresis, patients with DKA have a markedly reduced extracellular fluid volume. The available evidence was summarized in a review that revealed the paucity of sufficient data on clinical impact [11]. To date, a comprehensive epidemiological study on DKA investigating its epidemiology and clinical outcomes is still lacking.

Table 19.1 Electrolytes and strong ion difference (SID) of fluid products commonly used in the intensive care unit (ICU)

	Concentration (mEq/l)						
Ion	Plasma	0.9% NaCl	Ringer's lactate	Ringer's acetate	5% albumin	Plasma-Lyte 148	8.4% $NaHCO_3$
Na^+	140	154	131	130	148	140	1000
K^+	5	0	5	4	0	5	0
Cl^-	100	154	111	109	131	98	0
Ca^{2+}	2.2	0	2	3	0	0	0
Mg^{2+}	1	0	1	0	0	1.5	0
HCO_3^-	24	0	0	0	0	0	1000
$Lactate^-$	1	0	29	0	0	0	0
$Acetate^-$	0	0	0	28	0	27	0
Gluconate	0	0	0	0	0	23	0
SID	47.2	0	28	28	17	48.5	1000

Ions in bold font contribute to SID

Lactate is a strong anion in the human body as more than 99% of lactate is ionized. Lactic acidosis is observed in cardiogenic or hypovolemic shock, severe heart failure, severe trauma, and sepsis [8], with high mortality rates, ranging from 30% to 88% depending on the definition used [12, 13]. The mortality of patients with lactic acidosis was reportedly the highest (56%) amongst patients with metabolic acidosis defined by a SBE (standard base excess) < -2 mEq/l [14].

Recently, hyperchloremic acidosis caused by intravenous fluid products has become widely known and is reported in 19% to 45% of patients in the ICU [14, 15]. Table 19.1 shows the electrolytes and SIDs of intravenous fluid products commonly used in the ICU. Theoretically, acidosis occurs when intravenous fluid products with a SID lower than that of the patient's plasma are administered. Balanced crystalloids, i.e., Ringer's acetate, Ringer's lactate, and Plasmalyte, contain acetate, lactate, or gluconate to replace chloride. Those strong anions do not contribute to SID as they are metabolized by the liver faster than renal chloride excretion.

19.4 Why Metabolic Acidosis Matters

Metabolic acidosis can have various adverse effects, but the most critical consequence is its effect on the cardiovascular system. Recognition of this effect dates back to the 1960s when a study reported reduced cardiac contractility at pH < 7.1 when lactic acid was administered to dogs [16]. Animal experiments were also performed on dogs given lactic acid and hydrochloric acid to produce lactic acidosis and hyperchloremic acidosis. The dogs were given epinephrine, norepinephrine, and dobutamine to counteract the shock status. The cardiac index decreased when epinephrine or norepinephrine was administered; however, dobutamine administration increased the cardiac index. This result suggested that acidosis decreased the catecholamine reactivity to norepinephrine or epinephrine [17]. Pedoto et al. reported that when hydrochloric acid was administered to rats to mimic hyperchloremic acidosis, nitric

oxide (NO) production increased, provoking vasodilation, and resulting in reduced systemic blood pressure [18]. Fatal arrhythmias induced by acidosis have also been reported in an experimental model [19]. However, clinical studies in humans have not yet demonstrated a causal relationship between metabolic acidosis and cardiovascular dysfunction [20–22].

19.5 How We Manage Metabolic Acidosis in the ICU

Metabolic acidosis in critically ill patients is not a single disease but a syndrome driven by various underlying conditions. As such, the basic principle is to treat the underlying cause of metabolic acidosis. Sodium bicarbonate may be administered if there is a concern for the suppressed cardiac function that metabolic acidosis may cause. The rationale for using sodium bicarbonate for metabolic acidosis is that the intravenous administration of a high SID solution would increase the pH, resulting in improved cardiac function.

The evidence on the biochemical effects of intravenous sodium bicarbonate in acute metabolic acidosis has been systematically reviewed [23]. The summary of 12 relevant studies showed that pH, serum bicarbonate, base excess, serum sodium, and $PaCO_2$ increased during and after the intravenous administration of sodium bicarbonate [23]. By contrast, serum anion gap and potassium decreased. Some concern was raised about intracellular acidosis due to the back-diffusion of CO_2 and decreased ionized calcium that might impair cardiac contraction. However, there was no consistent evidence from the literature review that sodium bicarbonate administration was associated with decreased ionized calcium or decreased cardiac output [20, 24].

The effects of sodium bicarbonate on clinically relevant outcomes should be investigated in RCTs. The systematic review [23] identified only two RCTs that have been conducted [5, 25]. Hoste et al. compared the effect of sodium bicarbonate and tris(hydroxymethyl)aminomethane, THAM, in 18 patients with mild metabolic acidosis [25]. The trial, published in 2005, did not report clinically important outcomes, perhaps because the trial was conducted as a pilot trial. THAM has not been explored for its effects since this trial and is rarely used in current clinical practice.

An important RCT investigating the effects of sodium bicarbonate for severe metabolic acidosis was published in 2018 [5]. The BICAR-ICU trial was conducted in 26 French ICUs and enrolled 389 patients with severe acidemia ($pH \leq 7.20$, $PaCO_2 \leq 45$ mmHg, $HCO_3^- \leq 20$ mmol/l, and total SOFA score ≥ 4 or lactate $\geq$2 mmol/l). The trial excluded patients with DKA or chronic kidney disease (CKD). Patients were allocated to an intervention group receiving 4.2% sodium bicarbonate to maintain $pH > 7.3$ throughout the ICU stay or a control group with usual care. There was no difference in the primary outcome, which was a composite of death by day 28 and at least one organ failure at day 7, between the groups. However, treatment with sodium bicarbonate was associated with a reduced need for renal replacement therapy (RRT) in the ICU. Furthermore, in the pre-specified subgroup

of patients with acute kidney injury (AKI) (AKIN score 2 or 3), sodium bicarbonate was associated with improved survival and reduced need for RRT [5].

In a retrospective, observational study using the Medical Information Mart for Intensive Care (MIMIC)-III database, sodium bicarbonate administration was not associated with improved survival in patients with metabolic acidosis (pH < 7.3, HCO_3^- < 20 mmol/l and $PaCO_2$ < 50 mmHg) but was associated with improved survival in septic patients with stage 2 or 3 AKI and severe acidemia (pH < 7.2) [26].

A recent international observational study revealed that 18% of patients with moderate or severe metabolic acidosis receive sodium bicarbonate in current clinical practice [9]. However, the total amount of sodium bicarbonate given during the first 24 h of metabolic acidosis was 110 mmol, which was not adjusted for body weight or base excess. The study also reported that sodium bicarbonate administration was possibly associated with lower ICU mortality in acidotic patients with vasopressor dependency, albeit with a lack of statistical significance. Given that the rationale to use sodium bicarbonate would be to support cardiovascular function, this finding provides a sound basis for further investigation on the effect of sodium bicarbonate in patients with metabolic acidosis and on vasopressors.

19.6 Sodium Bicarbonate for Subtypes of Metabolic Acidosis

Administration of sodium bicarbonate has been considered for DKA not only because sodium bicarbonate reverses the acidotic status but because acidosis possibly contributes to insulin resistance [27]. However, a retrospective single center study from the USA reported that sodium bicarbonate administration in the emergency department was not associated with time to resolution of acidosis in patients with DKA with a pH < 7.0 [28]. There was also no difference in hospital length of stay [28]. A systematic review in 2011 found that sodium bicarbonate did not shorten the duration of acidosis, ketosis, or glycemic levels [11]. Furthermore, there was a high incidence of hypokalemia that required correction in patients who received sodium bicarbonate [11]. These findings imply that the beneficial effects of sodium bicarbonate administration for DKA might be limited. However, the systematic review by Chua et al. revealed a lack of rigorous randomized clinical trials that assessed patient-centered outcomes in these patients [11].

Sodium bicarbonate for lactic acidosis has been compared with saline in two small-scale randomized, crossover, single center trials [20, 21]. Cooper et al. reported that sodium bicarbonate administration increased pH and PCO_2 with no change in blood pressure or cardiac output [20]. Similarly, Mathieu et al. found an increase in pH but no change in hemodynamic parameters, including cardiac index [21].

For cardiac arrest, several observational studies have reported an increase in the rate of return of spontaneous circulation in patients receiving sodium bicarbonate [29–32]. However, one study found that this treatment was associated with a worse survival rate and neurological outcomes to hospital discharge [33]. A pilot RCT

showed no improvement in patient mortality [34], return of spontaneous circulation rate, or neurologically favorable status in treated patients [35]. At present, routine use of sodium bicarbonate is not recommended for cardiopulmonary resuscitation [36].

19.7 Renal Replacement Therapy for Metabolic Acidosis

There has been no clear consensus of clinical indications for RRT; however, severe acidosis is a commonly accepted indication. In RCTs on the timing of RRT that have been published over the past 5 years, i.e., the AKIKI trial, the IDEAL-ICU trial, and the STARRT-AKI trial, metabolic acidosis with severe acidemia was used as one of the absolute indications [37–39].

The AKIKI trial was a multicenter RCT in France, enrolling patients with stage 3 AKI, in which 67% of the patients had septic shock [37]. The trial compared early initiation of RRT in stage 3 AKI and delayed initiation with absolute indications. The absolute indications for RRT included severe acidemia with pH < 7.15, either metabolic acidosis or mixed acidosis. Of note, 21% of the trial participants in the control group received RRT for metabolic acidosis [37].

The IDEAL-ICU trial was another multicenter RCT conducted in France, enrolling patients with septic shock and stage 3 AKI [38]. The absolute indications for RRT included metabolic acidosis with pH < 7.15 and base deficit >5 mEq/l or HCO_3^- < 18 mEq/l. Among the patients who received RRT for the absolute indication, 13.4% met the metabolic acidosis criteria [38].

The STARRT-AKI trial was the largest international RCT, including 3019 patients from 15 countries [39]. The main aim of the trial was to assess whether an accelerated strategy to start RRT at stage 2 or 3 AKI would improve patient-centered outcomes compared with a delayed initiation with absolute indications. The absolute indications for RRT included severe acidemia and metabolic acidosis, defined as pH ≤ 7.2 or HCO_3^- < 12 mmol/l. Of the patients treated with RRT, 16.6% met the criteria for severe metabolic acidosis [39].

From the STARRT-AKI trial and the BICAR-ICU trial, patients with stage 2 or 3 AKI should avoid immediate intervention with RRT and may benefit from sodium bicarbonate if severe metabolic acidosis is present despite appropriate treatment for underlying conditions.

19.8 Agenda for Future Research

Recent clinical research, including large RCTs, has provided new evidence and advanced our understanding of the management of metabolic acidosis. However, high-quality data from rigorous clinical research to guide standard practice are still lacking. Research priorities include the following:

- The benefits and harms of sodium bicarbonate on cardiovascular function
- Sodium bicarbonate not only for severe metabolic acidosis but for moderate metabolic acidosis
- Sodium bicarbonate for severe metabolic acidosis with stage 2 or 3 AKI (BICARICU-2, ClincialTrials.gov identifier NCT04010630, in progress).

19.9 Conclusion

We have reviewed the recent clinical data on epidemiology and management of metabolic acidosis. Metabolic acidosis is common in the ICU, and even moderate metabolic acidosis carries higher mortality than severe sepsis. Sodium bicarbonate or RRT is used occasionally to normalize acid-base imbalance due to metabolic acidosis in the ICU; however, high-quality evidence is still limited. Patients with severe metabolic acidosis and stage 2 or 3 AKI might be a possible target population for sodium bicarbonate administration. Further clinical trials are required to provide more robust information in a clinically relevant patient population.

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Critically Ill Patients with Acute Kidney Injury: Focus on Nutrition

20

L. Foti, G. Villa, and S. Romagnoli

20.1 Introduction

Acute kidney injury (AKI) is a frequent condition in critically ill patients. The incidence of AKI may be greater than 50% in certain clinical settings [1]. In the intensive care unit (ICU), the incidence of AKI has been rising constantly due to population ageing, increasing numbers of surgical procedures, broader indications for surgery, and more effective resuscitation practices. AKI commonly develops in the clinical context of sepsis, multiorgan failure, major surgical procedures (particularly cardiac surgery), and polytrauma, and is associated with an increased risk for development of chronic kidney disease (CKD) and for death, in relation to disease severity (AKI stage 1, 2 and 3 according to the KDIGO—Kidney Disease: Improving Global Outcomes–guidelines, 2012 [2]).

Current standard of care mainly relies on [3]:

(a) Prevention. Identification of high-risk patients and careful consideration before administering potentially nephrotoxic agents (non-steroidal anti-inflammatory drugs, antibiotics, contrast media).
(b) Early diagnosis. It is widely accepted that variations in serum creatinine and/or urine output as markers of impaired renal function often fail to identify AKI in its earlier stage. Nonetheless, the KDIGO definition and staging of AKI are still currently based on the creatinine and urine output criteria. Although not widely used in routine clinical practice, novel AKI biomarkers have been recently discovered that can detect the presence of subclinical forms of AKI and improve early detection. Among them neutrophil gelatinase-associated

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lipocalin (NGAL) and the combination of urinary insulin-like growth factor-binding protein (IGFBP) 7 and tissue inhibitor of metalloproteinases (TIMP) 2 currently seems to be most promising [4]. These biomarkers seem to be sensitive and specific enough to be used in conjunction with serum creatinine and urinary output for a better stratification of renal injury.

Identification of high-risk patients and AKI subphenotypes and selection of specific biomarkers hold the key to further improvement in the treatment of AKI, although further research is required [5].

(c) Treatment and management. Treatment of the underlying pathology (e.g., sepsis, pancreatitis, abdominal compartment syndrome); correction of hypovolemia and hemodynamic optimization; renal replacement therapy (RRT).

(d) Follow-up. AKI patients have a higher risk of developing complications in the short- (e.g., pulmonary edema, bacterial translocation, hydroelecrolitic imbalance) and long-term, including development of CKD with or without dialysis, cardiovascular complications, and early mortality. Nevertheless, nephrology follow-up after ICU discharge is rare and there is limited research on this topic [6].

The issue of nutrition in AKI patients with and without RRT has seldom been investigated and further studies are needed to address the potential impact of RRT on clearance of molecules necessary for cellular function.

Patients with AKI should be considered at high risk for malnutrition, defined by the World Health Organization as "deficiency, excess or imbalance in a person's intake of energy and/or nutrients". Malnutrition in ICU patients is associated with increased mortality [7]. In a prospective study involving 300 patients with AKI, 42% of them had severe malnutrition at hospital admission [8]. According to clinical guidelines [9, 10], pre-existing poor nutritional status, chronic comorbidities, nutritional deficiencies, uremia, metabolic alterations typical of critical illness—including AKI—and loss of nutrients across the hemofilter during RRT are among the main causes of malnutrition.

20.2 Metabolic Alterations in AKI

AKI is associated with fluid, electrolyte and acid-base disturbances and, similar to other critical conditions, can induce specific alterations in protein, carbohydrate, and lipid metabolism. These alterations had already been described in the mid-80s [11].

Protein hypercatabolism causes excessive release of amino acids from skeletal muscle, with negative nitrogen balance and acceleration of hepatic gluconeogenesis, which, along with insulin resistance, leads to hyperglycemia. In addition, impaired lipolysis is observed, with increased secretion of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) and reduction in cholesterol, especially high density lipoprotein (HDL).

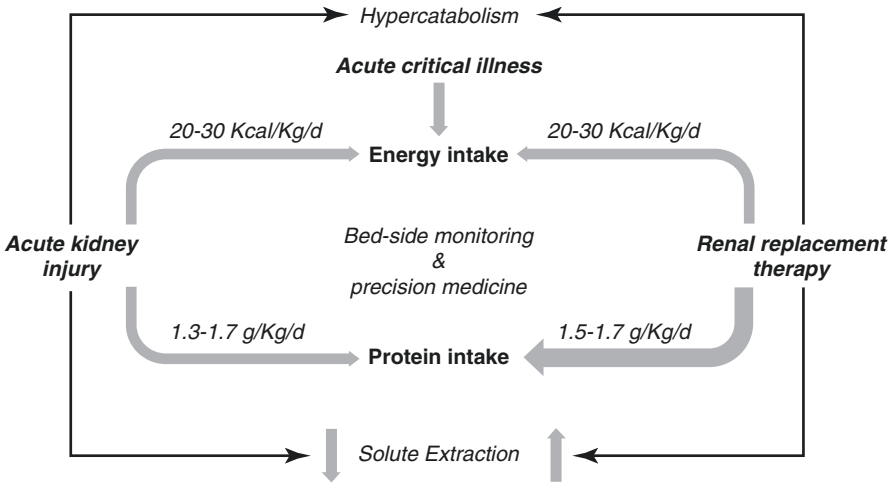

Fig. 20.1 Energy and protein intake in critically ill patients with acute kidney injury (AKI) and those receiving renal replacement therapy (RRT)

However, as stated above, AKI rarely occurs in isolation. Metabolic changes in AKI patients will be primarily caused by the underlying disease and exacerbated by nutrient losses during RRT (Fig. 20.1).

20.3 Nutritional Support

20.3.1 Strategies for Artificial Nutrition

Several studies [2, 9, 12, 13] suggest that oral diet should be regarded as the first choice in critically ill patients with AKI. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [13] also recommend that patients with insufficient calorie and protein intake receive early enteral nutrition using continuous infusion rather than bolus administration. Patients with AKI can present with reduced gastrointestinal motility and reduced adsorption of nutrients due to intestinal edema. Furthermore, several factors, including drugs (e.g., opioids, catecholamines), comorbidities (diabetes mellitus), and positive pressure ventilation negatively affect gastrointestinal function in critically ill patients. Nonetheless, enteral feeding via the intestinal lumen is preferable since it has undisputed benefits associated with improved survival [14]. Moreover, AKI is an important risk factor for gastrointestinal bleeding and enteral nutrition may have a protective effect [15].

In cases where enteral nutrition is contraindicated (ileum >5 days, severe malabsorption, incoercible vomiting or intolerance to enteral nutrition despite adequate pharmacological and non-pharmacological strategies), parenteral nutrition should be started within 3–7 days.

20.3.2 Calories in AKI

Energy expenditure and calorie intake in patients with AKI are similar to those reported in critically ill patients. Although critically ill patients have higher energy expenditure compared to healthy people, several studies [16–18] have demonstrated that both underfeeding and overfeeding are associated with prolonged length of stay in the ICU and increased mortality. The ESPEN guidelines [13] recommend early nutritional support within 24–48 h after admission, once the patient is stabilized, with gradual increase in caloric intake. After initial administration of hypocaloric nutrition below 70% of energy expenditure, optimal caloric intake should be achieved within the next 3–7 days, covering between 70 and 100% of the estimated energy expenditure.

There is currently no screening tool to evaluate nutritional requirements specifically in patients with AKI [19]. Indirect calorimetry is increasingly used in clinical practice and may become, in the near future, the reference method for measuring energy expenditure in critically ill patients. Although not yet validated in patients with AKI, equations for estimating energy requirements are currently used in cases of severe AKI. The most recent guidelines recommend using similar caloric targets (Table 20.1).

According to the same guidelines, there is no evidence that patients receiving RRT should achieve different caloric targets. However, in patients undergoing continuous RRT (CRRT) with regional citrate anticoagulation, citrate load contributes to caloric delivery (593 cal/mmol) [20].

There is still limited evidence concerning the relationship between caloric intake and clinical outcome in critically ill patients, and no research has been done recently on this topic. The impact of CRRT on energy expenditure is still a controversial issue [21, 22]. CRRT may favor a reduction in energy expenditure through development of hypothermia or lead to an increase in energy expenditure due to the amount

Table 20.1 Nutritional recommendations in patients with acute kidney injury (AKI)

Nutritional parameter	Recommendations in patients with AKI	Level of evidence
Calories	20–30 kcal/kg/day [2, 12] 25–30 kcal/kg/day [9]	Expert consensus
Protein	• without RRT: Gradual increase to 1.3 g/kg/day [13] Up to 1.7 g/kg/day [2, 12]	Expert consensus
	• with intermittent RRT: 1.0–1.5 g/kg/day [2]	Expert consensus
	• with CRRT: Up to 1.7 g/kg/day [2, 12] Up to 2.5 g/kg/day [9]	Expert consensus
Vitamins and trace elements	Supplementation of micronutrient losses during RRT [12]	Expert consensus

RRT renal replacement therapy, *CRRT* continuous renal replacement therapy

of energy expended to maintain an adequate body temperature during extracorporeal blood circulation and loss of nutrients across the filter.

20.3.3 Proteins in AKI

Protein metabolism in patients with AKI is characterized by hypercatabolism with marked muscle breakdown. This condition is associated with renal failure, which inevitably leads to increased azotemia. No data are currently available regarding optimal protein targets in patients with AKI and the evidence is poor. Both the KDIGO and the American Society for Parenteral and Enteral Nutrition (ASPEN) [9] guidelines suggest that protein restrictions to postpone the need for RRT should be avoided. Instead, nutritional support should be aimed at preventing malnutrition, which considerably increases mortality. On the other hand, there is limited evidence that excess protein intake can mitigate catabolic activity.

Observational studies [17, 18] of critically ill patients have shown that high protein intake is associated with lower mortality and suggest protein targets should be gradually achieved within 3–5 days.

Official guidelines differ in their recommendations (Table 20.1). The most recent ESPEN guidelines recommend administering 1.3 g/kg protein equivalents per day gradually [13]. As demonstrated by certain randomized controlled trials (RCTs) [16, 23], early provision of supplemental glutamine via the parenteral route may potentially be harmful in critically ill patients and should thus be avoided.

Patients receiving RRT should receive higher protein targets as it is well established that a significant amount of amino acid (up to 10–15 g/day [24]) is lost across the filter (Table 20.1 and Fig. 20.1).

The basic principle behind the use of RRT in patients with AKI is replacement of non-endocrine kidney function and removal of metabolic waste products, toxins, and, in particular, excess body water. This is achieved by movement of blood across a semipermeable membrane with or without adsorption properties. Indiscriminate removal of solutes including also "good" substances, such as medications, antibiotics, and nutrients, is amongst the potential side effects of RRT [3]. Multiple modalities of renal support may be used in the management of critically ill patients with kidney failure. These differ primarily with regard to duration of treatment and, consequently, rapidity of net ultrafiltration (Q_{UF}^{NET}) and solute clearance. The three common modalities of RRT are intermittent hemodialysis (IHD), continuous hemofiltration, and hybrid forms, which combine characteristics of both. Until recently, CRRT was the most widely adopted modality for treating critically ill patients but nowadays intermittent and, especially, hybrid forms are increasingly being used in case of hemodynamic stability. The available RRT modalities use either convection, diffusion, or a combination of both to allow water and solute transport across the filter. In a recent observational prospective study by Oh et al. [25], the authors found that total amino acid loss varied according to RRT modality, with the greatest losses for continuous hemofiltration, followed by hybrid RRT and then IHD. More specifically, about 14–22 g per session were lost during 12–24 h of continuous

veno-venous hemofiltration (CVVH), about 7–10 g during 6–8 h slow low efficiency dialysis (SLED), and about 3–6 g during 4 h of IHD. After adjustment for the delivered dose of RRT and baseline plasma amino acid concentration, the difference between modalities still remained. These data also suggest that loss of amino acids is greater in convection-based RRT than in diffusion-based treatment.

According to the ESPEN guidelines [13], both physical activity and physiotherapy are recommended whenever possible, as they may improve and enhance the beneficial effects of higher protein intake.

The issues of nutrient and protein intake during CRRT and their effects on mortality remain controversial. In a post-hoc analysis of the results of the RENAL study, originally conducted to evaluate the effect of delivered dose on mortality in critically ill patients undergoing continuous veno-venous hemodiafiltration (CVVHDF), Bellomo et al. [26] reported no significant differences in daily protein intake between survivors and non-survivors. Only 1 in 10 patients received a mean protein intake of >1 g/kg/day and even in this group protein intake was not associated with decreased mortality.

20.3.4 Micronutrients in AKI: Vitamins and Oligoelements

The term 'micronutrients' is used to describe substances required in daily amounts of generally less than 1 g/day. These compounds are not directly used by the organism to produce energy, which is mainly derived from other substances, defined as macronutrients (carbohydrates, lipids, and proteins).

Micronutrients include oligoelements or trace elements (including zinc, copper, selenium, and iron) and vitamins, which can be divided into water-soluble (including thiamine [B1], pyridoxine [B6], folic acid [B9], and ascorbic acid [C]) and fat-soluble (vitamins A, D, E, and K). These molecules support regulatory, immune, and antioxidant functions by acting as enzyme cofactors or essential components during metabolism. Critically ill patients with or without AKI typically show lower than normal serum concentrations of micronutrients. This condition may reflect deficiency, malabsorption, increased energy requirements, decreased levels of plasma transport proteins to which micronutrients are bonded, or increased rates of micronutrient loss due to RRT. The exact degree of micronutrient loss during RRT is unknown. Most data stem from small studies involving relatively short periods of treatment (24 h or less). In a prospective controlled study, Story and colleagues [27] found that eight patients treated with CRRT had significantly lower blood concentrations of selenium, zinc, vitamin C, and vitamin E compared to healthy volunteers. In the study by Berger and colleagues [28], the authors measured significant effluent concentrations of copper, selenium, zinc, and vitamin B1 in 11 patients after 8 h of CRRT. In a study by Kamel and colleagues [29], 80% of patients on CRRT had below-normal levels of at least one micronutrient among thiamine, pyridoxine, ascorbic acid, folic acid, zinc, and copper.

According to other studies, critical illness has a greater impact on micronutrient deficiency compared with CRRT alone. For example, Story and colleagues [27]

measured serum concentrations of vitamin C, vitamin E, zinc, and copper in critically patients with and without CRRT and in healthy controls but found no differences between the two cohorts of critically ill patients.

A recent study by Ostermann and colleagues [30] showed that CRRT did not significantly contribute to loss of micronutrients in patients with AKI. The authors measured serum concentrations of micronutrients in 55 patients with kidney injury, 31 with CRRT and 24 without CRRT, during a 6-day follow-up. In both the CRRT and non-CRRT groups, plasma levels of micronutrients were below normal reference range but differences between these two cohorts of patients were not statistically significant.

It should be underlined that loss of micronutrients also depends on RRT modality and its ability to remove solutes of different molecular weight. However, thiamine (337 Da), pyridoxine (3500 Da), ascorbic acid (176 Da), folic acid (441 Da), zinc (65 Da), and copper (10,000 Da) are easily removed through diffusion because of their small size (medium in the case of copper) [28]. Other factors need to be taken into account, including fat solubility (in the case of vitamins), which is thought to influence adsorption across the filter, and protein bond. In the study by Oh et al. [25], concentrations of plasma zinc—extensively bound to serum proteins—in the effluent were higher during CVVH than during SLED and IHD.

While numerous studies have investigated the impact of ascorbic acid and thiamine administration in septic patients [31], the role of these substances and other micronutrients in predicting outcomes of patients with AKI has not been fully explored. It is well known that selenium, zinc, iron, and vitamin C homeostasis is altered in critical illness with redistribution from the central circulation to tissues and organs. Vitamin D concentrations are also frequently low in critically ill patients, although the metabolism of vitamin D and other fat-soluble vitamins in AKI is not completely understood. Druml and colleagues [32] measured plasma concentrations of vitamin A, E, D and K in patients with AKI treated with hemodialysis and found profound deficiencies with the exception of vitamin K. There is a need for further research regarding the role of micronutrient supplementation in patients with AKI. In this regard, the European and American guidelines do not suggest using a different approach in AKI patients with or without CRRT compared with the general ICU population. By contrast, the Austrian and German Societies for Intensive Care [12] recommend to supplement micronutrient losses during CRRT but provide no specific information regarding dose or target (Table 20.1).

20.4 Conclusion

Nutrition in patients with AKI is not a well-developed field of research and more studies are needed. As with all medications and treatments, RRT is a life-saving procedure with a number of beneficial effects but also has undesired consequences that should always be taken into account, including the crucial issue of indiscriminate solute removal. This aspect is currently one of the main reasons why not all patients are routinely prescribed high-flow dialysis therapies. Substances that can be

removed by RRT include macro- and micronutrients whose extent of loss varies depending on delivered dose and RRT modality. This implies that nutritional requirements and, consequently, risk for malnutrition also vary among patients. While augmented protein intake during RRT is largely recommended, the role of micronutrient supplementation remains unknown. In critically ill AKI patients with and without RRT, personalized clinical nutrition should be applied as early as possible to enhance life support and optimize prognosis.

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Part VII

Acute Brain Injury

Carbon Dioxide Management in TBI: From Theory to Practice

21

E. Rossi, L. Malgeri, and G. Citerio

21.1 Introduction

Hyperventilation is a double-edged sword strategy for controlling intracranial volumes and therefore reducing intracranial pressure (ICP) after acute brain damage. The effect of hyperventilation is due to perivascular alkalosis, producing vasoconstriction and, therefore, reduced cerebral blood flow (CBF). Although this effect is short-lasting, hyperventilation carries a potential risk of cerebral ischemia. Although all patients with severe traumatic brain injury (TBI) are treated with mechanical ventilation, the target of the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) remains poorly defined and there is insufficient evidence to support any recommendation. Even the latest guidelines and consensus documents state that in patients with severe TBI, normocapnia should be maintained ($PaCO_2$ 35–45 mmHg) and that, with a low level of evidence, prolonged prophylactic profound hyperventilation is not recommended. A target $PaCO_2$ of ≈36–40 mmHg has been reported by clinicians and, in the presence of raised ICP, this is usually lowered to ≈30–35 mmHg. In this chapter, starting from physiological concepts, the evidence around $PaCO_2$ management in TBI will be reviewed and some data on current practice of use of hyperventilation in TBI will be presented.

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21.2 Cerebral Blood Flow and Cerebrovascular CO_2 Reactivity

Brain oxygen consumption is very high, i.e., about 3.5 ml per 100 g/min, which is equivalent to 20% of the oxygen consumption of the whole human body. This high metabolic energetic demand requires a fine-tuned CBF to avoid ischemic conditions, i.e., situations in which the metabolic demand is not fulfilled. Under normal conditions, the CBF is maintained at a constant flow rate of 50–60 ml per 100 g/min in young adults, and 50 ml of oxygen is drawn from 700 to 800 ml of blood per minute. The extraction rate of oxygen by the brain is very high: the arteriovenous blood difference of the brain is 6.3 ml per 100 ml of blood. Considering the high metabolic demand of the brain and the limited storage of substrates, it is necessary to maintain CBF levels within the normal range. Under physiological conditions, this is achieved through a variety of mechanisms, commonly referred to as autoregulation.

The CBF depends on the diameter of the cerebral arterioles (resistance vessels), increasing with vasodilation and decreasing with vasoconstriction. To maintain CBF constant, these vessels physiologically respond to changes in systemic blood pressure, blood viscosity, and metabolic requirements. CBF is functionally linked to regional brain metabolism as expressed in the Fick equation:

$$\mathrm{CMRO_2} = \mathrm{CBF} \times \mathrm{avDO_2}$$

where $CMRO_2$ is the cerebral metabolic rate of oxygen and $avDO_2$ is the cerebral arterio-venous oxygen difference. Metabolic activity generates CO_2 and the CO_2 reactivity relates to the response of the cerebral vessels, and consequently CBF, to local changes in CO_2.

$PaCO_2$ can be manipulated with ventilation. Changes in $PaCO_2$ will elicit movement of CO_2 across the blood-brain barrier, and consequent vascular changes. An increase in $PaCO_2$ will produce acidosis and consequently vasodilation. A reduction in $PaCO_2$ will produce alkalosis and vasoconstriction. This effect is short-lasting due to subsequent re-equilibration of the following reaction, catalyzed by carbonic anhydrase:

$$\mathrm{CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+}$$

The data obtained from *in vitro* and *in vivo* studies suggest that the endothelium and smooth muscles, as well as perivascular nerve cells, neurons, and glia, may be involved in the CO_2 reactivity and this complex mechanism seems to be correlated to changes in perivascular pH. The effect of pH variation on smooth muscle tone can be direct, modifying intracellular calcium concentration, or mediated by a second messenger system, such as nitric oxide (NO), potassium and calcium, prostaglandins, and cyclic nucleotides. Prostaglandins are effective vasodilators that can activate adenylate cyclase and increase cyclic adenosine monophosphate (cAMP). NO produced by the NO synthase (NOS) family in cerebral vascular endothelial cells, perivascular nerves, neurons, and glial cells will increase the intracellular concentration of cyclic guanosine monophosphate, thereby causing vasodilation [1]. Cyclic nucleotides reduce the entry of calcium into vascular smooth muscle and cause vasodilation directly or in a permissible manner, thereby allowing hypercapnia to

exert its vasodilation effect. The opening of potassium channels decreases the influx of extracellular calcium into cells in an indirect way, thereby reducing the tension of the vascular smooth muscle. In a clinical setting, every mmHg change in $PaCO_2$ from 20 to 60 mmHg in patients with TBI produces a CBF change of ≈3% [2] Hypoventilation leading to hypercarbia causes vasodilation and an increase in CBF, while hyperventilation causes vasoconstriction and a decrease in CBF.

21.3 Effects of Hyperventilation on Intracranial Pressure and CBF

The changes in $PaCO_2$ modify the intracranial blood volume, and therefore the pressure of the intracranial compartment (ICP). The relationship between $PaCO_2$ and ICP is not linear. In experimental studies over wide ranges of $PaCO_2$, an S-shaped relationship has been described between ICP and $PaCO_2$ [3]. Stocchetti et al. [4] calculated that for each millimeter of mercury of change in $PaCO_2$ the blood volume changed by 0.72 ± 0.42 ml. Similarly, Yoshihara et al. [5] demonstrated that, in patients with severe TBI, a change in blood volume of 0.5 ml could produce an ICP change of 1 mmHg. However, it is still unclear if the effect of hyperventilation on ICP remains during prolonged hyperventilation. After 24 h, as the pH of the perivascular spaces normalizes, the vasoconstrictive effect is reduced.

One of the main concerns in hyperventilating patients with TBI to reduce raised ICP is the risk of ischemia-induced by CBF reduction. One of the first descriptions of the therapeutic use of hyperventilation to treat elevated ICP was published by Lundberg et al. [6] in 1959. These authors stated that hyperventilation did not cause ischemia thanks to compensatory mechanisms that act to maintain tissue oxygenation. In fact, in normal conditions, cerebral oxygen delivery exceeds the brain's oxygen consumption, and this mechanism leaves an important reserve that allows the brain to tolerate CBF reduction, as occurs in hyperventilation. One year later, in 1960, Meyer et al. [7] confirmed this hypothesis, demonstrating that in healthy volunteers, hyperventilation produced no change in the $CMRO_2$. In 2002, Coles et al. [8] demonstrated that moderate hypocapnia could significantly reduce global CBF and result in significant increases in the volume of critically hypoperfused tissue in the injured brain even when improved cerebral perfusion pressure (CPP) and ICP values were recorded. These authors used positron emission tomography (PET) to quantify regional CBF and metabolism in response to CO_2 changes in 33 patients with TBI. This effect was not limited to the first 24 h after brain injury and the authors suggested that even brief periods of hyperventilation may cause a harmful reduction in CBF when $PaCO_2$ is reduced below 33 mmHg. The immediate effect on CBF of hyperventilation is clear, but the consequences of it, and the link with ischemia, is somehow controversial. Diringer et al. [9], using PET during hyperventilation in 13 patients with severe TBI in the first 8–14 h after TBI, found that CBF decreased, oxygen extraction fraction increased, and $CMRO_2$ was unchanged, suggesting that low CBF can be explained in the setting of patients with severe TBI treated with sedatives, with a primary reduction in $CMRO_2$ and a secondary passive fall in CBF.

Similarly, Letarte et al. [10], using a microdialysis probe placed adjacent to injured brain in 8 patients with severe TBI, concluded that hyperventilation that lowered $PaCO_2$ by 10 mmHg for 30 min (baseline $PaCO_2$ 35 ± 2 mmHg) reduced local CBF by 20%, while the lactate/pyruvate ratio did not change.

Ischemia is defined as a mismatch between metabolic requirements and CBF. Hyperventilation causes a reduction in CBF, but it does not always seem to be associated with a reduction in oxygen and metabolic supply. Finally, in 2006, Marion [11] explained that these discrepancies in findings concerning low $PaCO_2$ levels could be due to a loss of integrity of local CO_2 autoregulation, which may be impaired after TBI, and suggested that in patients with raised ICP responding to short-term hyperventilation, it can be considered safe.

21.4 Current Recommendations

Only one randomized controlled trial (RCT) is available about hyperventilation in TBI. In this trial, Muizelaar et al. [12] randomized 113 patients into three groups: normal ventilation, defined as $PaCO_2$ 35 ± 2 mmHg; prophylactic hyperventilation, defined as $PaCO_2$ 25 ± 2 mmHg; and prophylactic hyperventilation + THAM (tris(hydroxymethyl)aminomethane), which was added to compensate for the loss of HCO_3^- buffer from cerebrospinal fluid (CSF) that is responsible for the short-lived effect of hyperventilation on cerebral vasoconstriction. Patients were stratified based on the motor component of the Glasgow Coma Scale (GCS; 1–3 and 4–5). The outcome was assessed using the Glasgow Outcome Scale (GOS) at 3, 6, and 12 months. For patients with the higher motor GCS (motor score 4–5), the 3 and 6 month GOS scores were lower in the hyperventilated patients than in the control or THAM group but the effect was not confirmed at 12 months. This discrepancy between 3–6- and 12-month outcome may be due to a too small sample size; a direct correlation between hyperventilation and worse outcome has not been demonstrated. Moreover, CBF was lower in the hyperventilation + THAM group than in the control and hyperventilation groups, indicating a prolongation of the hyperventilation effect. There was no evidence of cerebral ischemia in any of the three groups, using CBF or $avDO_2$ data. In addition, in this trial, hyperventilation was used as a prophylactic maneuver and not as a treatment strategy and the course of ICP was most stable in the hyperventilation + THAM group.

Putting all these elements together, the fourth edition of the Brain Trauma Foundation guidelines [13] states that, in patients with TBI, there is insufficient evidence to support a strong recommendation in $PaCO_2$ management. Prolonged prophylactic hyperventilation with $PaCO_2$ of 25 mmHg or less is not recommended, but the optimal $PaCO_2$ range in these patients is still uncertain.

The recent Seattle International Severe Traumatic Brain Injury Consensus Conference [14] recommended mild hyperventilation, i.e., a $PaCO_2$ 32–35 mmHg, as a tier-two treatment if ICP remains resistant to first-line treatments, such as analgesia and sedation, osmotherapy, CPP maintenance and CSF removal. The Seattle

Consensus did not support lower $PaCO_2$ levels and recommended against routine hyperventilation to below 30 mmHg. In the same direction, a recent consensus on ventilation [15] in acute brain damage suggests that hypercapnia should be avoided in patients with acute brain injury, aiming for a physiologic range of $PaCO_2$ of between 35 and 45 mmHg. Short term hyperventilation in patients with acute brain injury and brain herniation can be considered as a therapeutic option. No consensus was reached regarding hyperventilation as a therapeutic option in patients with ICP elevation.

21.5 From Guidelines to Clinical Practice

In 2008, Neumann et al. [16] published data obtained from BrainIT (The brain monitoring with information technology) dataset analyzing 7703 blood gas analyses from 151 patients with TBI across 17 centers in Europe. The mean $PaCO_2$ was 35.8 ± 5.6 mmHg and the $PaCO_2$ was distributed in the range of normoventilation ($PaCO_2$ 36–45 mmHg) and moderate hyperventilation ($PaCO_2$ 35–31 mmHg). Early prophylactic hyperventilation as well as the use of additional cerebral oxygenation monitoring during hyperventilation, suggested by the Brain Trauma Foundation guidelines at that time, were not followed by most of the centers.

In 2018, Huijben et al. [17] performed a survey on treatment strategies before starting the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) trial. The most frequently reported $PaCO_2$ target was 36–40 mmHg in case of controlled ICP < 20 mmHg (69%), and 30–35 mmHg in case of raised ICP (62%), underlining that, in clinical practice, hyperventilation is used as a therapeutic option in patients with intracranial hypertension.

Some information on current CO_2 management was obtained by the CENTER-TBI study, a longitudinal prospective collection of data from patients with TBI across 65 centers in Europe. The study was conducted between December 19, 2014, and December 17, 2017, and aimed to better describe the incidence, management, and outcomes of patients with TBI in Europe [18]. For each patient enrolled in CENTER-TBI, along with much other information, the daily highest and lowest $PaCO_2$ values were registered for the first 7 days of admission. In 1100 mechanically ventilated patients with TBI admitted to the ICU for whom more than 2 values were available, the mean daily lowest $PaCO_2$ was 35.22 mmHg (SD = 5.27), very similar to the BrainIT data. However, there was huge variability in the mean value of the lowest $PaCO_2$ across centers (ranging from 32.3 to 38.6 mmHg) (Fig. 21.1), highlighting important differences in the way that CO_2 is managed. In patients with ICP monitoring, the observed mean values were lower compared with patients without ICP monitoring, i.e., 34.7 vs. 36.8 mmHg. A total of 397 patients had at least one episode of $PaCO_2$ <30 mmHg. These data suggest that, with considerable inter-center variability, hyperventilation is still largely used in TBI patients. At this stage, we are still exploring the effects of these management differences.

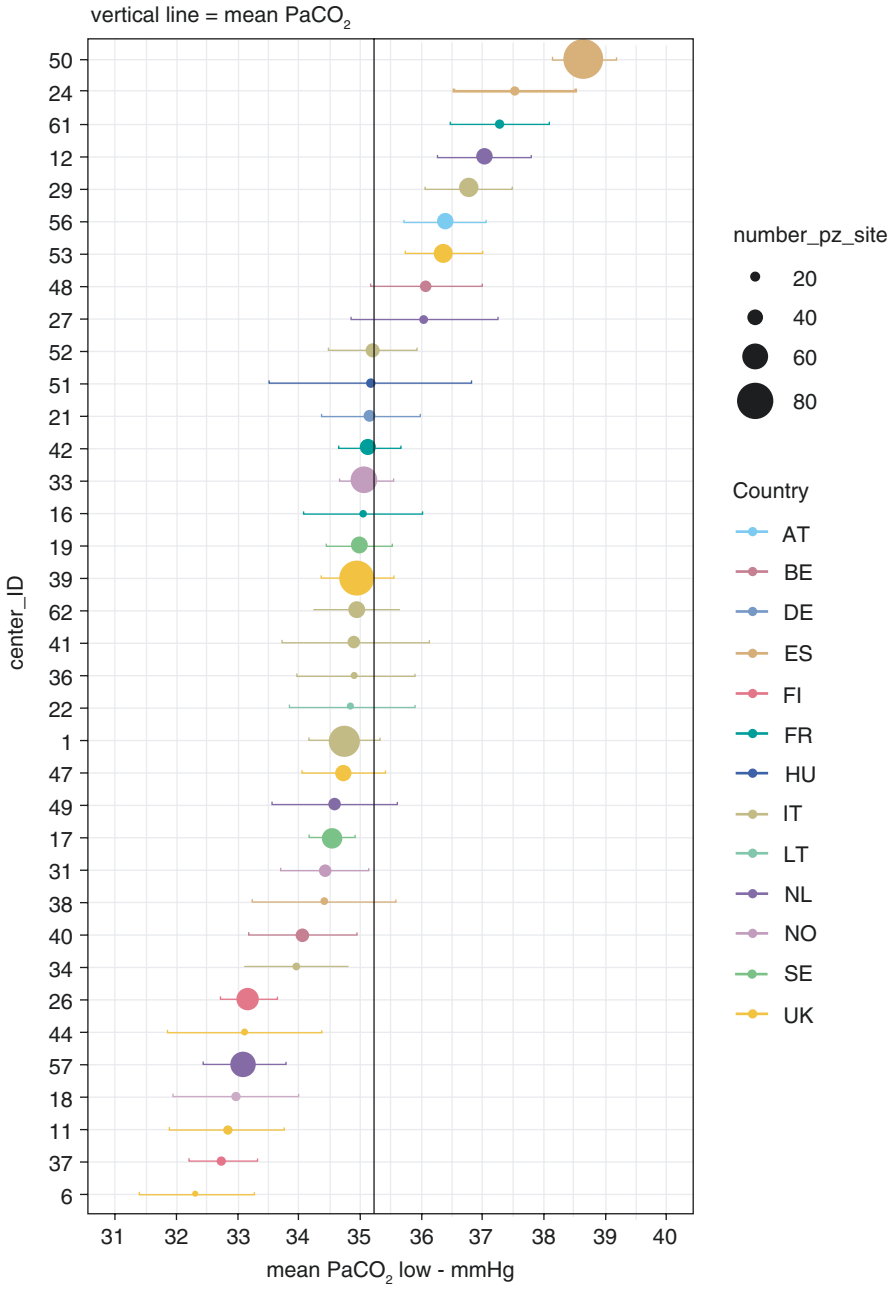

Fig. 21.1 Lowest mean $PaCO_2$ value in the CENTER-TBI trial [18]. Data from 1100 patients enrolled in 36 European centers participating in Center-TBI. For each center, the mean values of the lowest $PaCO_2$ values recorded daily in the first week are represented by a dot, with their respective confidence interval. The solid line is drawn in correspondence with the lowest mean $PaCO_2$. The mean daily lowest $PaCO_2$ from different centers ranged from 32.3 to 38.6 mmHg. This result seems to be linked more to the different management strategies of the individual centers, rather than being related to different national $PaCO_2$ management strategies

21.6 Conclusion

The relationship between CBF and $PaCO_2$ is well known. For 60 years, authors have discussed the risk of ischemia related to a reduction in CBF induced by hyperventilation but no strong evidence exists. Although hyperventilation induces a CBF reduction, it has not yet been demonstrated that this reduction always corresponds to an insufficient metabolic supply and therefore to ischemia.

In clinical practice, because of the lack of strong recommendation, the management of $PaCO_2$ is variable among centers, and hyperventilation is still commonly used, especially in patients with raised ICP. The correlation between $PaCO_2$ levels and outcome is still under exploration and further studies are required to better characterize ventilator strategies in patients with TBI and their effect on outcomes.

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22 Monitoring and Modifying Brain Oxygenation in Patients at Risk of Hypoxic Ischemic Brain Injury After Cardiac Arrest

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22.1 Introduction

The majority of adverse clinical outcomes following successful resuscitation from cardiac arrest, are attributable to hypoxic ischemic brain injury [1]. The cornerstone of hypoxic ischemic brain injury management has traditionally focused on preventing secondary ischemic injury, following the return of spontaneous circulation (ROSC) [2]. Among the various mechanisms implicated in the pathophysiology of secondary injury, post-resuscitation cerebral ischemia is linked to central physiologic variables that may be modifiable [3]. Observational data demonstrate associations between perturbations in physiologic variables known to reduce cerebral blood flow (CBF)—such as arterial hypotension [4] and hypocapnia [5]—and adverse clinical outcome. This adds credence to the importance of optimizing cerebral

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oxygen delivery, to mitigate secondary ischemic injury. Recently, sentinel randomized controlled trials (RCTs) aimed at augmenting mean arterial pressure (MAP)—a key physiologic determinant of cerebral oxygen delivery—have yielded important insights into the importance of mitigating secondary cerebral ischemia [6, 7]. Although it did not establish a definitive link to improved neurological outcome, the COMACARE study demonstrated reduced levels of neurofilament light, a biomarker of brain injury, in patients undergoing an augmented MAP strategy following ROSC [8]. Patients may continue to experience episodes of brain hypoxia following cardiac arrest, despite goal-directed therapy and augmented MAP, with considerable heterogeneity in the underlying cerebrovascular hemodynamics in individual patients [9]. Thus, a targeted approach to the individualized management of hypoxic ischemic brain injury in the post-resuscitation phase requires the longitudinal monitoring of brain oxygenation—providing clinicians with real time physiologic data points to optimize cerebral oxygen delivery, similar to that applied in patients with traumatic brain injury (TBI) [10]. Near infrared spectroscopy (NIRS) provides an easily implemented and virtually complication-free way to monitor regional cerebral oxygen saturation (rSO_2) in critically ill patients. The insertion of oxygen sensing catheters provides a real time assessment of the partial pressure of oxygen in brain tissue ($PbtO_2$). This approach has gained widespread use following neurotrauma.

In this narrative review, we discuss the available means for monitoring the occurrence of brain ischemia in patients at risk of hypoxic ischemic brain injury. Specifically, we decided to review the evidence for non-invasive monitoring, using NIRS and invasive monitoring via the insertion of tissue oxygen monitors and jugular bulb catheters. These two approaches to monitoring brain oxygenation have different advantages and limitations (Fig. 22.1). We also discuss ways to modify cerebral oxygenation, with a special focus on MAP and blood carbon dioxide and oxygen levels.

22.2 Cerebral Oxygenation Monitoring Using NIRS

The level of oxygen in brain tissue is determined by the ratio between oxygen delivery and oxygen consumption, along with factors that influence the transfer of oxygen from the intravascular to the cellular compartment. The extent of hypoxic ischemic brain injury following cardiac arrest may be variably related to the degree and timing of aberrations in any or all of these variables. Importantly, the brain is able to maintain a relatively constant delivery of oxygen by maintaining CBF across a range of arterial blood pressure. This is referred to as cerebrovascular autoregulation [11]. In commercially available NIRS monitors, near infrared light is emitted from one diode—using at least two different wavelengths to assess oxyhemoglobin (HbO_2) and total hemoglobin (Hb)—and received by another two diodes at separate distances. The latter feature enables the separation of light that has traversed the superficial (extracranial) versus deeper (intracranial, at a depth of 2–3 cm) tissues [12]. The NIRS sensors are commonly placed high on the temple in front of

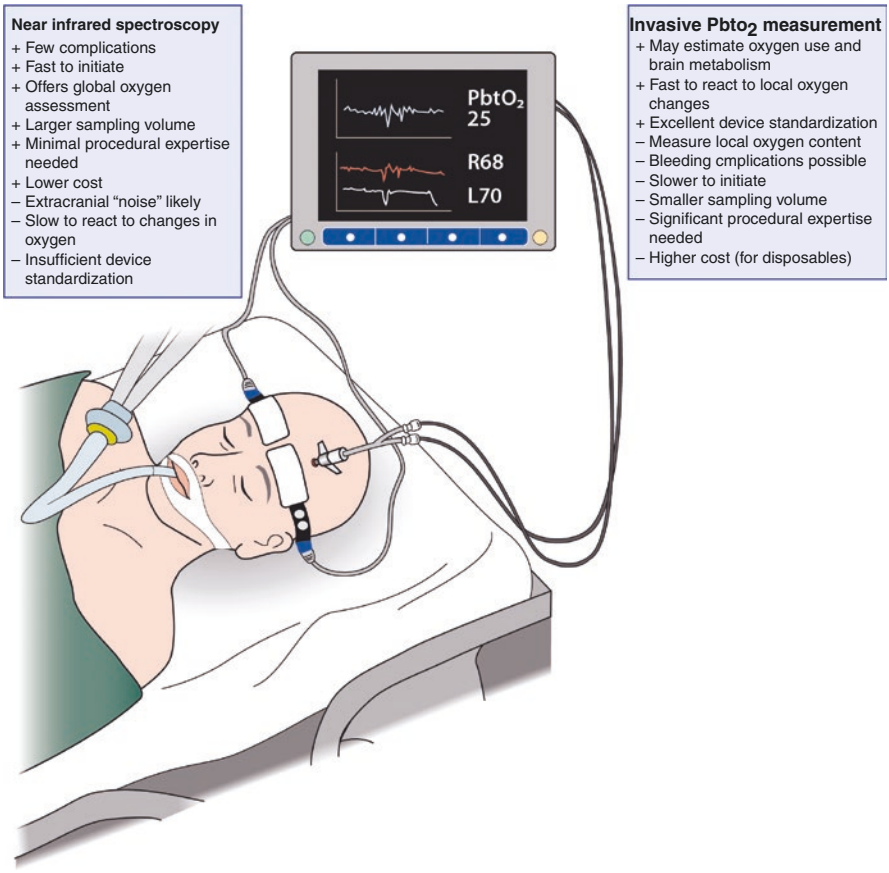

Fig. 22.1 An overview of the advantages and disadvantages of one non-invasive and one invasive method used to monitor cerebral oxygenation in cardiac arrest patients

the hairline, thus illuminating the watershed area between the anterior and middle cerebral artery vascular territories. The rSO_2 signal represents a ratio of HbO_2/Hb. It is based on an assumption of fixed arterial and venous compartments, with the latter representing 70–75%, and is derived using proprietary algorithms that make it difficult to compare results obtained by different monitors. The inherent non-pulsatile nature of rSO_2 means that it is, at best, a surrogate variable for CBF. The rSO_2 is not just affected by anatomical confounders, such as the variable thickness of the extracranial tissues, the skull and the cerebrospinal fluid (CSF) area. It is also affected by dynamic factors, including anemia; by the patient's acid-base status; by changes to the arteriovenous partitioning of blood; by tissue edema; and by progression of hypoxic ischemic brain injury to areas of non-metabolizing brain tissue. Generic to most clinical monitoring, rSO_2 trends are more informative than absolute values. Yet it is unclear whether mean values, highest/lowest values or changes in values should be used as measures, and whether trends should be used

to identify impending serious adverse events, to maintain a safety zone, or to trigger interventions. Concurrent changes in several variables—rather than in a single variable—may better reflect any underlying pathology; a growing number of reports of cerebrovascular autoregulation based on NIRS attests to an increasing interest in this approach. The physiological construct of using NIRS-derived rSO_2 to monitor and potentially guide interventions against hypoxic ischemic brain injury entails the components of the rSO_2 signal (e.g., blood transfusion, supplemental oxygen); the relation to oxygen delivery (e.g., supporting cardiac output and MAP, targeting optimal cerebrovascular autoregulation range); and the relation to oxygen consumption (e.g., targeted temperature management [TTM], analgosedation, seizure prophylaxis).

22.3 Regional Tissue Oxygenation in Hypoxic Brain Injury

While the use of rSO_2, to inform on the quality of cardiopulmonary resuscitation (CPR) or to predict ROSC [13], supports the feasibility of NIRS in cardiac arrest and its potential to guide acute resuscitation, the main focus of this text is on post-resuscitation care. Multiple studies have been conducted, giving variable results regarding the possible differences in rSO_2 values between patients with a good versus a poor functional outcome (Table 22.1). It appears biologically plausible that rSO_2 values indicating that brain oxygen homeostasis has been maintained would be associated with survival and favorable neurological outcome. In an observational study of 28 cardiac arrest patients, rSO_2 was lower following the initiation of hypothermia in non-survivors (n = 10) compared to survivors (n = 28) censored at hospital discharge [14]. Similar results were reported in 60 cardiac arrest patients, in which rSO_2 during the first 40 h of intensive care unit (ICU) monitoring, including hypothermia and rewarming, was higher in patients with good outcomes (cerebral performance category [CPC] 1–2) compared to poor outcomes (CPC 3–5), both at ICU discharge and at 6 months, albeit with a large overlap in rSO_2 values [15]. A larger prospective study (n = 107) of rSO_2 during the first 48 h of ICU admission, including hypothermia and rewarming, and its association with outcome at 3 months reported statistically higher rSO_2 in patients with good outcomes (CPC 1–2) compared to those with poor outcomes (CPC 3–5). Yet the study authors noted that the numerical differences were small and not conducive to a clinically useful discrimination of outcomes [16]. Based on data from the Japanese J-POP registry, an rSO_2 >40%—measured immediately upon arrival in the emergency department following cardiac arrest—was associated with favorable neurologic outcome at day 90 [17, 18]. A review of 22 observational studies, encompassing 2436 patients, corroborated the associations between increasing and higher rSO_2 in the post-cardiac arrest period and favorable outcomes [19]. Meanwhile, several studies since the review—including 258 out-of-hospital cardiac arrest patients—have failed to demonstrate either a correlation or sufficient discriminative power for rSO_2 and good versus poor

Table 22.1 A selection of studies evaluating associations between near infrared spectroscopy (NIRS) measured and derived variables with outcome, in intensive care unit (ICU)-treated out-of-hospital cardiac arrest

First author [ref]	Year	Design	Number of patients	Type of cardiac arrest	Outcome	Principal finding
Meex [14]	2013	Observational study	28	CA patients treated with TTM	Functional outcome by CPC at hospital discharge	Decrease in rSO_2 during induction of TTM. Lower rSO_2 levels in patients with poor outcome.
Storm [15]	2014	Observational study	60	OHCA and IHCA	Functional outcome at discharge by CPC	Higher NIRS values in patients with good outcome. An rSO_2 below 50% appeared associated with poor outcome.
Ameloot [33]	2015	Observational study	51	All types of CA	Functional outcome at 180 days by CPC	Disturbed autoregulation more common in patients with chronic hypertension. Time below an autoregulation-derived optimal MAP was negatively associated with outcome.
Pham [24]	2015	Observational study	23	OHCA	Functional outcome at 90 days by CPC	No difference in rSO_2 in patients, by outcome. Suggestion of disturbed autoregulation in poor outcome patients.
Bougle [20]	2016	Observational study	43	OHCA treated with TTM	Functional outcome by CPC on hospital discharge	Mean rSO_2 was not different, when indexed by outcome, but the lowest measured was lower in poor outcome patients.
Genbrugge [16]	2016	Observational study	107	OHCA	Functional outcome at 180 days by CPC	Slightly higher rSO_2 in patients with good outcome. No reliable threshold value was identified.
Saritas [21]	2018	Observational study	25	OHCA patients	Functional outcome by CPC on hospital discharge	No difference in rSO_2, in patients with good and poor outcome.

(continued)

Table 22.1 (continued)

First author [ref]	Year	Design	Number of patients	Type of cardiac arrest	Outcome	Principal finding
Jakkula [23]	2019	*Post hoc* analysis of interventional data	120	VF arrests with a cardiac cause	Six-month functional outcome by CPC and brain injury assessed with NSE	No association between the mean, median, lowest or highest NIRS value during the first 36 h of ICU care with outcome or the level of NSE at 48 h.

CA cardiac arrest, *CPC* cerebral performance category, *IHCA* in-hospital cardiac arrest, *MAP* mean arterial pressure, *NSE* neuron specific enolase, *OHCA* out-of-hospital cardiac arrest, *rSO_2* regional cerebral oxygen saturation, *TTM* targeted temperature management, *VF* ventricular fibrillation

outcomes [20–24], or have found it only in a specific range of initial rSO_2 (between 41% and 60%) during TTM [25]. A recent review concluded that the clinical utility of monitoring rSO_2 to prognosticate a favorable neurological outcome remains unclear [26]. Further clinical research is needed to establish the role of static versus dynamic rSO_2 values; the cut-off values for correlations to patient-centered outcomes, including during different interventions for hypoxic ischemic brain injury, notably TTM; and the minimal duration of monitoring. It is also important to address the variability in reported rSO_2 signals across different NIRS monitors [27] and overall cerebral tissue oxygenation [28].

22.4 Cerebral Oxygenation Index in Hypoxic Brain Injury

Monitoring of rSO_2 has been extended into the assessment of cerebrovascular autoregulation, by investigating the simultaneous correlation with MAP (time domain analysis) based on the premise that short-term fluctuations in rSO_2 are predominantly determined by changes in CBF. The correlation index—the cerebral oximetry index (CO_x)—may be used to assess cerebrovascular autoregulation, limits of autoregulation, and optimal MAP to support CBF [29–32]. In a prospective, observational study of 51 cardiac arrest patients monitored for the first 24 h of ICU admission during TTM at 33 °C, 35% demonstrated impaired and shifted autoregulation. A higher MAP (100 mmHg) was identified as supporting CBF, compared to patients with intact cerebrovascular autoregulation (85 mmHg). Mortality at 3 months was higher than for patients with preserved cerebrovascular autoregulation and the time spent below the optimal MAP was negatively correlated with survival [33]. In another prospective, observational study of 23 cardiac arrest patients undergoing TTM at 36 °C during the first 24 h and with active avoidance of pyrexia thereafter, intermittent monitoring during the first 3 days post-cardiac arrest demonstrated higher CO_x values. This was consistent with impaired cerebrovascular

autoregulation in non-survivors, on each day and as an overall average, compared to survivors (all with CPC 1–2 at 3 months follow up) [24]. The optimal MAP was higher in non-survivors (107 mmHg), compared to survivors (66 mmHg). In a proof-of-concept study, continuous monitoring for a median of 30 h in 20 post-cardiac arrest patients managed with TTM 33–36 °C for the first 24 h was able to generate cerebrovascular autoregulation data in all patients. Of these, 15% demonstrated impaired autoregulation with the actual MAP ±5 mmHg outside the identified optimal MAP in 50% of the monitored time. Increasing temperature was associated with an increased COx, suggesting impaired cerebrovascular autoregulation—particularly above 38 °C [34]. A prospective study in three Canadian teaching hospital ICUs demonstrated the feasibility of capturing COx and deriving optimal MAP in a median of 97% and 71%, respectively, of data collected during a median monitoring time of 47.5 h [35].

A variable correlation between COx and the pressure reactivity index—a cerebrovascular autoregulation reference standard of intracranial pressure (ICP) versus MAP—has been reported [36]. This may not seem surprising, given the limitations of rSO_2 that remain intrinsic to COx. Furthermore, cerebrovascular autoregulation is far more complex than just a linear relation between CBF and MAP. It also includes other non-linear correlations, in particular with O_2 and CO_2, as well as significant heterogeneity across the cerebral vasculature and anatomical regions of the brain. Data from the COMACARE cohort are currently undergoing further investigation, focusing on COx with the important aspect of encompassing protocolized ranges of MAP, O_2 and CO_2 [37].

22.5 Invasive Monitoring of Cerebral Oxygenation

ICP monitoring and invasive oxygen, blood flow and microdialysis catheters have mainly been used for research purposes in the management of patients after cardiac arrest, and are not recommended for routine care [38]. The risk of complications, such as brain hemorrhage, is the main reason for this; these complications may be markedly increased in cardiac arrest patients, given the use of anticoagulants, antiplatelet agents and TTM. In addition, cardiac arrest patients may be less commonly cared for in units with neurosurgical expertise. The availability and incorporation of multimodal invasive neuromonitoring is thus limited in post-cardiac arrest management. Recently, the research group of Sekhon and colleagues completed a prospective observational study using invasive $PbtO_2$ monitoring in hypoxic ischemic brain injury following cardiac arrest [9]. They established feasibility and, interestingly, demonstrated a significant burden (~40% of the monitoring duration) of brain hypoxia ($PbtO_2 < 20$ mmHg) despite goal-oriented management to optimize $PbtO_2$ [9]. They also established key relationships between the physiologic determinants of cerebral oxygen delivery and $PbtO_2$. Specifically, significant linear relationships between $PbtO_2$ with MAP and the cerebral perfusion pressure (CPP) were observed, across the cohort [9]. These data were subsequently followed up with a matched cohort study investigating clinical outcomes in patients with hypoxic ischemic brain

injury managed using goal-directed care guided by invasive neuromonitoring, compared with the standard of care that did not include invasive neuromonitoring (Sekhon, personal communication, 2021). Although the clinical outcomes were significantly better in the invasive neuromonitoring group, significant limitations—including inherent biases, small sample size and study design—are important considerations when interpreting the findings. In the studies of invasive neuromonitoring to date, serious adverse events pertaining to the placement of invasive neuromonitoring have not been noted. However, the inherent risks associated with placement—namely, precipitating intracranial bleeding—are key considerations in invasive neuromonitoring. The reported rate of intracranial bleeding with invasive neuromonitoring is approximately 0.5–1% and the necessity for therapeutic hypothermia in post-cardiac arrest patients may increase this further. While noting the inherent limitations, these two studies provide feasibility and a path to studying the use of invasive neuromonitoring in select hypoxic ischemic brain injury cases, as a prospective method.

Jugular venous bulb oximetry is an alternative method of cerebral oxygen delivery and utilization monitoring. In this method, an intravascular catheter is placed retrograde into the dominant jugular vein and positioned at the level of the jugular bulb, to measure the oxygen saturation of Hb ($SjvO_2$) as it exits the cerebral vasculature. Historically, hypoxic ischemic brain injury-related studies incorporating jugular venous bulb oximetry have focused on linking the absolute value of Hb saturation with clinical outcomes. Previous authors have shown that an increased $SjvO_2$ or decreased oxygen extraction fraction, seen at the jugular bulb, is associated with worse outcomes and mortality [39]. Monitoring the metrics of brain oxygenation seems like an attractive therapeutic target to optimize. Yet the physiologic data garnered by both brain tissue oxygen and jugular venous bulb oximetry monitoring can provide insights into the underlying pathophysiologic phenotype that may be exhibited by individual patients with hypoxic ischemic brain injury. The approach of uniform cerebral oxygen delivery augmentation assumes that—once oxygen is delivered to the cerebral capillary bed—there is intact diffusion across the blood brain barrier and normal cellular oxygen utilization, culminating in neuronal aerobic metabolism. In other words, the necessary steps in the oxygen cascade encompass a coupling between cerebral oxygen delivery and diffusion, along with cellular utilization. It was recently shown that patients with hypoxic ischemic brain injury exhibit pathophysiologic phenotypes that are characterized by an uncoupling of these components of the oxygen cascade [40]. In a *post hoc* analysis of invasive neuromonitoring in hypoxic ischemic brain injury, we characterized one subset of patients exhibiting diffusion limitation, wherein there was an uncoupling between cerebral oxygen delivery and diffusion into the brain parenchyma [41]. Conversely, the other phenotype was characterized by intact coupling between cerebral oxygen delivery and parenchymal diffusion [41].

To numerically quantify these phenotypes, the difference between the dissolved partial pressure of oxygen in the cerebral venous vasculature (PvO_2) and the observed $PbtO_2$ yields the PvO_2-$PbtO_2$ gradient. This represents the efficiency of oxygen diffusion into the parenchyma at the neurovascular unit [40].

When the patient is in a state of normal health, a reduction in cerebral oxygen delivery leads to increased oxygen extraction in the microvasculature and, hence, to a reduced PvO_2-$PbtO_2$ gradient. The inability to do so confirms a diffusion limitation; its detection is made possible by combining data points from simultaneous $PbtO_2$ and jugular venous bulb oximetry (yielding the PvO_2) monitoring [40]. Key future research must aim not just to incorporate monitoring of brain oxygenation in hypoxic ischemic brain injury, but also to use the characteristics of the cerebrovascular physiology in individual patients, to reconcile the underlying pathophysiologic processes at play and identify therapeutic targets.

22.6 Interventions Available for Modifying Cerebral Oxygenation

Studies conducted in patients with TBI have shown that, by increasing the fraction of inspired oxygen used, the amount of oxygen measured in brain tissue is greatly increased [42]. In the COMACARE trial, the use of moderate hyperoxia significantly increased cerebral oxygenation—even in the setting of normal MAP—without any major increase in markers of brain injury [8, 43]. A recent meta-analysis of RCTs, on the other hand, suggested an association between worse patient outcomes in patients routinely treated with higher oxygen fractions after cardiac arrest [44]. Importantly, no study to date has included oxygen within a multimodal strategy for the alleviation of brain tissue hypoxia.

Mild hypercapnia appeared to increase cerebral oxygenation in two conducted pilot studies, but with a variable effect on the markers of brain injury [8, 45]. The TAME (Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest) trial is currently underway, with more than 1300 patients randomized to date [46]. Conversely, hypocapnia decreased CBF and cerebral oxygenation, as measured with NIRS and jugular bulb monitoring in patients undergoing TTM at 33 °C [47]. Overall, the ultimate effect of cerebral oxygenation caused by the modification of CO_2 concentrations is likely to depend, to a large degree, on whether or not the patient has increased ICP and cerebral edema. There are limited data, thus far, on whether this is a common clinical problem in cardiac arrest patients—especially those undergoing TTM.

It is currently unclear whether targeting higher MAP, as a routine measure, will also result in increased cerebral oxygenation in cardiac arrest. The COMACARE trial included patients resuscitated from out-of-hospital cardiac arrest with ventricular fibrillation (VF) as the initial rhythm and did not demonstrate any change in rSO_2 with the higher MAP target. On the other hand, the Neuroprotect trial—which, in addition to increasing MAP, included the optimization of cardiac output with an inotrope and the use of packed red blood cell transfusions—showed increased rSO_2 in the patients randomized to the higher MAP target. Interestingly, in a pooled analysis of a subset of patients with myocardial infarction and shock, the use of a higher MAP target alleviated myocardial injury [48].

Thus far, there is limited evidence on other means to improve brain oxygenation. Hb values of less than 10 g/dl have been associated with poor outcome in patients after cardiac arrest [49]. On the other hand, in the only RCT conducted in cardiac arrest patients that included maintaining Hb greater than 10 g/dl as an intervention, the need for a transfusion of packed red blood cells was uncommon [6]. The evidence on other means used to optimize cerebral oxygenation—using, for example, osmotherapy for increased ICP—lacks evidence in cardiac arrest patients [38].

22.7 Conclusions and Need for Future Studies

There is no doubt that measuring cerebral oxygenation, either non-invasively or invasively, is necessary to detect cases of occult and potentially modifiable ischemia. The utility of NIRS to monitor cerebral oxygenation following hypoxic ischemic brain injury is exceedingly attractive—given its non-invasive ease of operation, which provides a continuous, real-time signal. Ongoing and future research will ultimately need to show whether this technology is 'making important what we can measure' or, instead, measuring what is important. The use of invasive catheters provides more detailed data, including local brain blood flow and oxygen, as well as metabolism. It may well be that invasive catheters are superior at identifying the more occult, albeit local, instances of brain hypoxia.

With regard to available interventions, there is no doubt that—by modifying MAP, blood oxygen and carbon dioxide levels—brain oxygenation can be manipulated. Whether this results in improved oxygen utilization is less clear. The approach taken in TBI care with a multimodal approach to alleviate ischemia appears very interesting [50], but will no doubt be challenging to put into practice in the general cardiac arrest population. Until more evidence is available, we should aim to treat patients according to current guidelines that include targeting a MAP greater than 65 mmHg, normocapnia with a $PaCO_2$ of 4.5–6.0 kPa, and a PaO_2 of 10–13 kPa.

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ICU Delirium in the Era of the COVID-19 Pandemic

23

K. Kotfis, J. E. Wilson, and E. W. Ely

23.1 Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a global public health threat in December 2019 and was termed a pandemic in March 2020 [1]. The novel coronavirus can cause a wide range of symptoms from mild to severe, mainly respiratory in nature (bilateral pneumonia, respiratory failure), that frequently necessitate admission to the intensive care unit (ICU) and engagement of life-sustaining interventions, especially in elderly patients with multiple co-morbidities [2]. Evidence has shown that SARS-CoV-2 causes neurological system involvement and complications,

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including delirium, which is not surprising given the pathobiology of the virus and the common presence of typical deliriogenic factors [3]. Moreover, in patients with COVID-19, delirium may be the first presenting symptom of the disease [4, 5]. Central nervous system (CNS) involvement has been identified by the World Health Organization (WHO) as one of the key features of SARS-CoV-2 infection [6].

Identification, prevention and management of delirium is challenging in the ICU. During the pandemic, unprecedented environmental factors have become apparent and exaggerated the deliriogenic load, including extreme isolation, social distancing, inability to freely ambulate, and limited family support. We have previously referred to this phenomenon as a "delirium factory" [3, 7]. The excessive workload and exhausted personnel during the COVID-19 pandemic may lead to suboptimal ICU care (avoidance of using scales for pain or delirium assessment, downscaling non-critical interventions, limiting patient care, psychological burnout). This and future pandemics can be regarded as a quality and empathy trial for healthcare professionals, especially in the acute care setting. Thus, the requirement to maximize respect and preserve human dignity during ICU care is even higher. In this chapter, we discusses the epidemiology, risk factors and approach towards COVID-19-related delirium, to provide ICU professionals with a guide as to what can be done to limit the burden of delirium despite the organizational and medical challenges posed by the pandemic.

23.2 Epidemiology and Risk Factors

The first reports from Wuhan, China, reported that only 7.5% of patients had any charted documentation of "impaired consciousness" [8]. This has changed with time as reports of studies with correct methodology for delirium assessment have been published. The rates of delirium differ substantially depending on the setting and the study population, with prevalence highest in patients admitted to the ICU. ICU delirium occurrence rates, duration and severity have been reported in five large studies that used validated tools for delirium assessment [9–13]. Delirium prevalence ranged from 45% to 84% (Table 23.1).

Table 23.1 Prevalence of delirium in intensive care unit (ICU) patients with COVID-19

Authors [ref]	Setting/country	Study period	Validated delirium assessment tool	Number of patients	Delirium prevalence
Khan et al. [9]	2 ICUs/USA	March–June 2020	CAM-ICU	144	73.6% (106/144)
Helms et al. [10]	ICU/France	March–April 2020	CAM-ICU	58	65% (26/40)
Helms et al. [11]	2 ICUs/France	March–May 2020	CAM-ICU	140	84.3% (118/140)
Jäckel et al. [12]	ICU/Germany	Until May 2020	NuDesc	44	45.4% (20/44)
Pun et al. [13]	69 ICUs/International	Jan–April 2020	CAM-ICU	2088	54.9% (1147/2080)

CAM-ICU Cognitive Assessment Method for ICU

Khan et al. retrospectively extracted data between March and June 2020 from ICUs in two large academic centers in the USA [9]. Delirium outcomes were evaluated until day 14 in the ICU. The authors included 268 consecutive patients in the analysis and concluded that nearly 30% of patients were diagnosed with delirium without coma. Delirium lasted for a median of 5 days and its severity was rated as high. In this study, after adjusting for sedatives, mechanical ventilation was significantly associated with the odds of delirium occurrence.

Pun et al. performed a multicenter cohort study between January 2020 and April 2020, including 2088 patients from 69 adult ICUs in 14 countries [13]. Data from electronic health records were collected for a 21-day follow-up period. The primary outcome in this study was to determine the prevalence of delirium and coma and to define risk factors associated with the development of delirium. In this study, 55% of patients had delirium for a median of 3 days (from 2 to 6 days). The median age of the patients was 64 years, with a median Simplified Acute Physiology Score (SAPS) II equal to 40. In this study 67% of patients were receiving mechanical ventilation on the day of admission to the ICU and 88% at some point during the hospitalization. The majority of patients were deeply sedated during mechanical ventilation, with a median Richmond Agitation–Sedation Scale (RASS) score of -4 (from -5 to -3). In this group, 64% of patients were given benzodiazepines for a median of 7 days (from 4 to 12 days) and 71% were given propofol for a median of 7 days (from 4 to 11 days). As many as 82% patients were comatose for a median of 10 days (from 6 to 15) and 55% had delirium for a median of 3 days (from 2 to 6 days) [13]. Pun et al. showed that mechanical ventilation, the use of physical restraints and certain medications (i.e., benzodiazepines, opioids, vasopressors and antipsychotics) were associated with a higher risk of delirium in COVID-19 patients ($P \leq 0.04$) [13]. In the same study, family presence was associated with a lower risk of delirium ($P < 0.0001$). During the 21-day study period, patients were alive without delirium or coma for a median of 5 days (between 0 and 14 days). The results showed that older age, higher SAPS II scores at baseline, male sex, smoking or alcohol abuse, as well as the use of vasopressors on day 1, and invasive mechanical ventilation on day 1 were independently associated with fewer days alive and free of delirium and coma ($P < 0.01$). The mortality in this study was 29% within 28 days from admission, with most deaths occurring in the ICU [13].

Helms et al. conducted a cohort study including 140 patients from two ICUs in France between March and May 2020 [11]. In this study 84% of patients developed delirium presenting as acute attention, awareness, and cognition disturbances. The authors reported that nearly 70% of patients presented with an unexpected state of agitation despite high infusion rates of sedatives and neuroleptics, and 64% of patients had corticospinal tract signs. The authors also reported the results of brain magnetic resonance imaging (MRI) in 28 patients, with 61% demonstrating enhancement of subarachnoid spaces, 29% showing intraparenchymal white matter abnormalities, and 65% diagnosed with perfusion abnormalities. In 18/28 patients, cerebrospinal fluid (CSF) showed inflammatory disturbances, including oligoclonal bands with mirror pattern and increased levels of interleukin 6 (IL-6), whereas a SARS-CoV-2 reverse transcription polymerase chain reaction test (RT-PCR) in the

CSF was positive in only one patient. According to the authors, delirium was responsible for prolonged mechanical ventilation [11].

Jäckel et al. compared delirium in patients with acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 and influenza A and B viruses in a single-center retrospective register analysis [12]. Delirium was assessed by trained personnel using the Nursing Delirium screening scale (NuDesc) and RASS. Delirium was diagnosed in 65% of the patients with ARDS with a mean duration time of 5 days. According to Jäckel et al. there was no statistically significant difference in the prevalence of delirium, its type or intensity between patients with COVID-19 and those with influenza, therefore delirium in COVID-19 patients should be regarded as a complication of ARDS rather than being specific to SARS-CoV-2 infection [12].

23.3 Pathophysiology and Mechanisms

Delirium due to COVID-19, may be secondary to a variety of underlying pathobiological mechanisms, including direct invasion of the CNS by the virus, secondary to an inflammatory response, as a complication of severe COVID-19 infection, or due to environmental or other iatrogenic factors [3] (Fig. 23.1).

23.3.1 Delirium as a Result of Direct Neural Invasion

Delirium secondary to SARS-CoV-2 may arise as a direct result of neural invasion. In a case reported by Xu and colleagues, a 39-year-old man developed delirium 28 days after symptom onset along with progression of lung consolidations; by day 33 he had developed coma requiring mechanical ventilation; 3 days later he died as a result of diffuse brain edema and brain herniation [14]. At autopsy, the SARS-CoV antigen was detected in brain tissue by immunohistochemistry and viral RNA by *in situ* hybridization [14]. Other post-mortem examinations of brain tissue in patients (n = 4) who have died from COVID-19 have identified SARS-CoV in brain tissue [15].

SARS-CoV-1 and SARS-CoV-2 have a high affinity for angiotensin-converting enzyme (ACE) 2, using this as a potential pathway to gain entry into the pulmonary parenchyma and the brain, as shown in experimental animal models [16–18]. Additionally, SARS-CoV-2 may enter the CNS via the olfactory nerve, hematologic or lymphogenic access [19, 20]. Direct invasion of the CNS via the olfactory nerve may be one key entry-point for neuro-invasion and may explain why anosmia and ageusia rates are so high even in patients who are paucisymptomatic [21]. In experimental mice models, the coronavirus has been found in high quantities in the hippocampus and its presence is associated with development of a neurological disorder [17, 18].

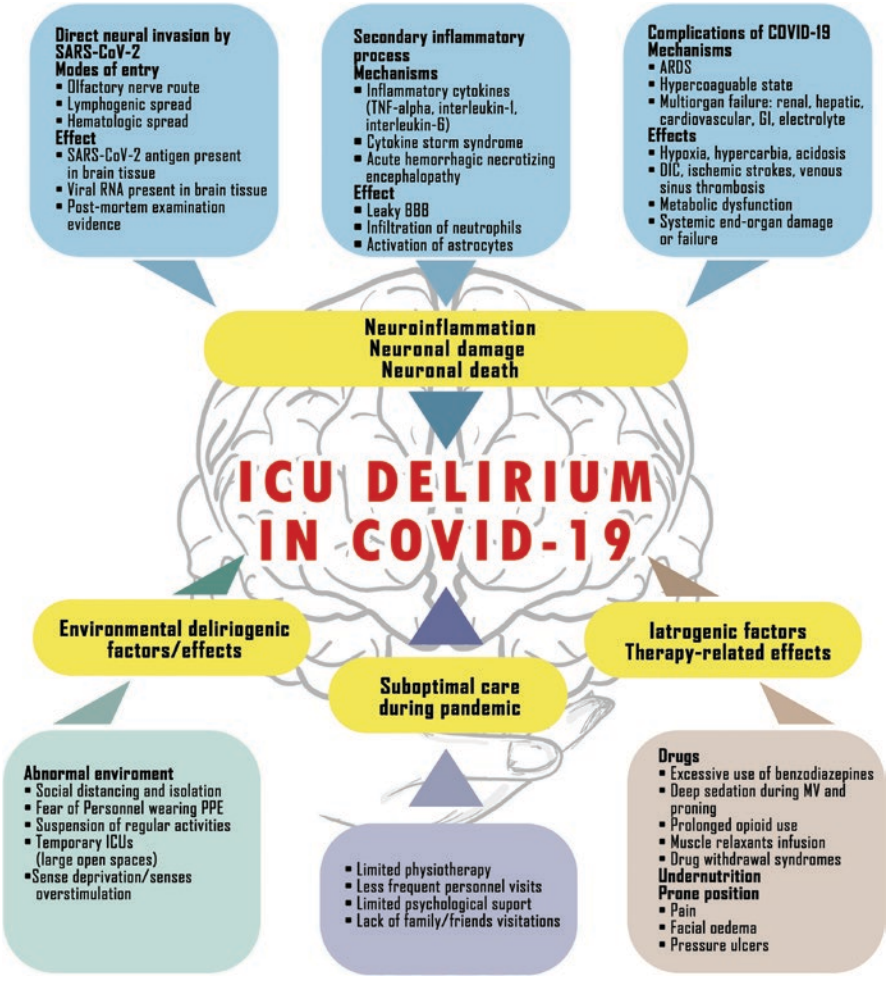

Fig. 23.1 Pathophysiology and mechanisms of intensive care unit (ICU) delirium in COVID-19. *ARDS* acute respiratory distress syndrome, *TNF* tumor necrosis factor, *GI* Gastrointestinal, *BBB* blood-brain barrier, *DIC* disseminated intravascular coagulation, *PPE* personal protective equipment

Meningioencephalitis associated with SARS-CoV-2 has been described in a patient with generalized fatigue, fever, neck stiffness and generalized seizures, who had a negative nasopharyngeal swab, but SARS-CoV-2 RNA was detected in the CSF [22]. A brain MRI showed hyperintensity along the wall of the right lateral ventricle as well as signal change in the right mesial temporal lobe and hippocampus, suggesting meningitis [22]. Although direct neural invasion by the virus may be one possible explanation for delirium in COVID-19 patients, it cannot be the only explanation, as reports have shown clear neurologic symptoms, including high

rates of delirium in patients with SARS-CoV-2 ARDS with no viral RNA as detected by PCR in CSF [10], suggesting secondary causes of delirium in COVID-19.

23.3.2 Delirium as a Result of an Inflammatory Process

Limited literature to date suggests a possible immune-mediated encephalopathy [23, 24]. Activation of inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, IL-1, IL-16, causes direct injury to the blood-brain barrier resulting in a 'leakiness' allowing for infiltration of inflammatory factors and blood, including the virus itself, especially in the temporal lobes where the blood-brain barrier is less robust [23, 25, 26]. These inflammatory cells may thereby release cytokines causing additional neuronal damage [27–32]. A subgroup of patients may experience a severe COVID-19 cytokine storm syndrome [33] or acute hemorrhagic necrotizing encephalopathy [34].

Direct neural invasion of the virus may lead to an unchecked neuroinflammatory process with activation of astrocytes and infiltration of neutrophils through the blood-brain barrier [17, 35], further leading to a cascade of neuron damage and death. In experimental mice models of picornavirus infection, inflammatory monocytes and neutrophils infiltrate the brain, specifically the hippocampus [36]. Experimental depletion of inflammatory monocytes but not neutrophils in the hippocampus preserved cognitive function, suggesting that the neurologic disorder seen as a result of acute infection and neuronal damage may be secondary to an inflammatory process [36].

23.3.3 Secondary Complications of COVID-19 Infection that may Cause Delirium

Complications of COVID-19 infection, such as pneumonia, ARDS, and multi-organ failure, as well as the interventions used to treat them (e.g., sedation for mechanical ventilation, prolonged hospitalization, etc.) are well described precipitating risk factors for delirium [37]. ARDS is characterized by a lung injury that causes fluid to build up in the alveoli, preventing the lungs from filling up with oxygen, which results in hypoxia, respiratory acidosis and respiratory failure, and in some cases disseminated intravascular coagulation and systemic end-organ damage or failure, all of which increase the risk for delirium. Patients with severe COVID-19 complications, including those with ARDS, often require prolonged hospital stays, sometimes requiring weeks of mechanical ventilation, and medications to support ventilation including sedatives, all of which might serve as precipitating factors for delirium [27].

Delirium resulting from COVID-19 complications may arise as a direct result of the treatment/management of critically ill patients or may arise as a downstream

consequence of the systemic effects of the virus. A variety of diffuse neurologic insults seen on imaging has been described in patients with COVID-19 with persistently diminished mental status, including confluent T2-hyperintensity and mild restricted diffusion in bilateral supratentorial deep and subcortical white matter and multiple punctate microhemorrhages in juxtacortical and callosal white matter [38]. The robust immune response to SARS-CoV-2 described earlier, may trigger a cytokine storm thereby increasing ferritin, C-reactive protein (CRP) and D-dimer, which may result in a hypercoagulable state, including peripheral blood clots and a higher prevalence of ischemic stroke and venous sinus thrombosis, which may in turn lead to delirium. In addition to the direct consequences of COVID-19 mentioned earlier, broader systemic complications, including renal, hepatic and cardiovascular derangements, may result in additional metabolic and other downstream complications, further potentiating the risk for delirium.

23.3.4 Environmental or Iatrogenic Causes of Delirium

Precautions put in place to slow the spread of COVID-19, such as social distancing, isolation procedures in the hospital limiting visitation and access to loved ones (who would typically be providing care, reorientation and reassurance directly at the bedside), as well as the widespread use of personal protective equipment (masks, face shields, gloves and gowns) may be upsetting or confusing to patients who are already confused (either due to administration of sedative medications or pre-existing neurocognitive disorders) [3].

23.4 Outcome

The spread of COVID-19 has caused respiratory failure in many patients and placed many of them in need of critical care. The experience of multi-level interventions and significant psychological difficulties in the ICU may impact their recovery course. It has been proven that delirium is associated with significant morbidity and mortality in critically ill patients with COVID-19 with a special emphasis on the elderly [39], and may have an impact on the functional outcome of ICU survivors. However, a recent review by Rogers et al. regarding psychiatric and neuropsychiatric presentations associated with severe COVID-19 infection [40] showed that apart from short-term delirium most people do not suffer from a psychiatric disorder following coronavirus infection. Nevertheless, all clinicians should be aware of the increased risk of depression, anxiety, fatigue or post-traumatic stress disorder (PTSD) in COVID-19 survivors. The probability of long-term consequences in COVID-19 ICU survivors are high due to organizational issues (restricted family contact) and high prevalence of ARDS resulting in deeper sedation with administration of benzodiazepines, deep sedation and prolonged mechanical ventilation.

23.5 Post-Intensive Care Syndrome and Post-Intensive Care Syndrome-Family

The post-intensive care syndrome (PICS) and PICS-family (PICS-F) may be particularly common during recovery of patients after COVID-19. Data regarding PICS in COVID-19 survivors is very limited as very few studies investigating neurocognitive deficits have been published [41, 42]. Martillo et al. collected data from a New York City Critical Care Recovery Clinic, assessing physical (Modified Rankin Scale, Dalhousie Clinical Frailty Scale, Neuro-Quality of Life Upper Extremity and Lower Extremity Function, Neuro-Quality of Life Fatigue) and psychiatric (Insomnia Severity Scale; Patient Health Questionnaire-9; and Posttraumatic Stress Disorder Checklist for *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition) domains, as well as cognitive testing (Telephone Montreal Cognitive Assessment) and the 3-Level Version of Euro-QoL-5D questionnaire [43]. In this study, 45 patients were included; 73% were males with a mean age of 54 years. According to the authors, 91% of COVID-19 ICU survivors fulfilled the diagnostic criteria for PICS, with 87% having impairments in the physical domain and 58% showing some degree of mobility impairment. In this group, 48% of patients had impairments in the psychiatric domain, whereas 38% were diagnosed with at least mild depression, 18% exhibited moderate to severe depression, and 18% presented PTSD. The Telephone Montreal Cognitive Assessment showed that 9% of patients had impaired cognition.

Depending on the methodology and the population studied, the incidence of PICS may still be underreported. Every opportunity should be taken to manage the secondary effects of SARS-CoV-2-associated critical illness to reduce the burden of PICS by promoting physical and cognitive rehabilitation and psychological adaptation. Healthcare systems dealing with survivors of COVID-19 should provide appropriate post-ICU care. Planning of inpatient and outpatient resources to support patients and their families might become one of the most difficult and expensive challenges imposed by the global pandemic on every country as long-term physical, psychological and functional disability may also lead to prolonged work absence.

The psychological stress for families and relatives of patients treated in the ICU is high because of restricted visitations and remote-only communication. In a study performed by Cattelan et al., psychological distress of reference persons of patients referred to the ICU for COVID-19 was evaluated on admission to the ICU, at discharge or death, and at 3 months afterwards [44]. In this study, out of 88 reference persons, 83% had anxiety and 73% depression, although 99% of the respondents expressed a feeling that the patient was safe, confident with the caregivers and satisfied with the information provided by the ICU staff. This underlines the fact that families and friends of ICU patients experience psychological distress related to remote-only communication with an overall negative experience.

23.6 Prevention and Management of ICU Delirium

Treatment of delirium in critically ill patients with COVID-19 should be based on clinical vigilance and general delirium management guidelines (the ABCDEF or A2F bundle) promoted by the Society of Critical Care Medicine (SCCM) in the ICU Liberation Collaborative [45]. Excessive workload and staff exhaustion during the COVID-19 pandemic may lead to suboptimal ICU care, including avoidance of using scales for pain or delirium assessment, downscaling non-critical interventions, limiting patient care or psychological burnout among personnel. Despite these difficulties, it should be stressed that delirium in critically ill patients receiving mechanical ventilation can be reduced dramatically by avoiding deep sedation and by early mobilization [46]. It is important to include adequate pain management as a priority in delirium management. Importantly, not only known sources of pain should be identified (intubation, intravenous access, drainage, etc.), but also pain unique to COVID-19 (e.g., headache, myalgia, peripheral neuropathies, pain associated with prone position, etc.) [47]. Recently, a study by Liu et al. focused on investigating the degree of implementation of evidence-based and supportive measures in ICUs treating patients with COVID-19, including the ABCDEF bundle, nutritional management or the use of ICU diaries [48]. Data were collected from 262 patients, with 47% of patients receiving mechanical ventilation and nearly 5% of the study population treated with extracorporeal membrane oxygenation (ECMO). Each element of the A2F bundle was evaluated within the following domains: A—analgesia (regular pain assessment) in 45% of patients; B (spontaneous awakening and breathing trials) in 28% of patients; C (regular sedation assessment) in 52% of patients; D (regular delirium assessment) in 35% of the study group; E (early mobility and exercise) in 47% of patients; and F (family engagement and empowerment) in only 16% of patients. The implementation of element E was only 4% for patients receiving mechanical ventilation and 8% for patients on ECMO. In this study cohort, adequate nutritional support was infrequent.

In conclusion, only a multilevel approach can provide success in delirium management with improvement of long-term survival, shorter mechanical ventilation time, shorter ICU and hospital lengths of stay, fewer re-admissions to the ICU, lower costs of care, reduction of PICS and PICS-F [49] (Fig. 23.2).

Ten simple rules for an effective ICU delirium approach are summarized below:

1. SCREENING: Delirium screening with a validated tool (CAM-ICU or ICDSC) can be performed in less than 1 min and should be performed in all patients.
2. CAUSES: Delirium identification should be a trigger to identify causes (e.g., hypoxia, infection/sepsis, medications, withdrawal syndromes), not to introduce pharmacological treatment.
3. GUIDELINES: Delirium management should follow well-established international guidelines (ABCDEF bundle).
4. PAIN: Adequate pain management, based on assessment by behavioral pain scales (Critical Care Pain Observation Tool [CPOT]/Behavioral Pain Scale [BPS]) should be a priority in sedated, mechanically ventilated patients.

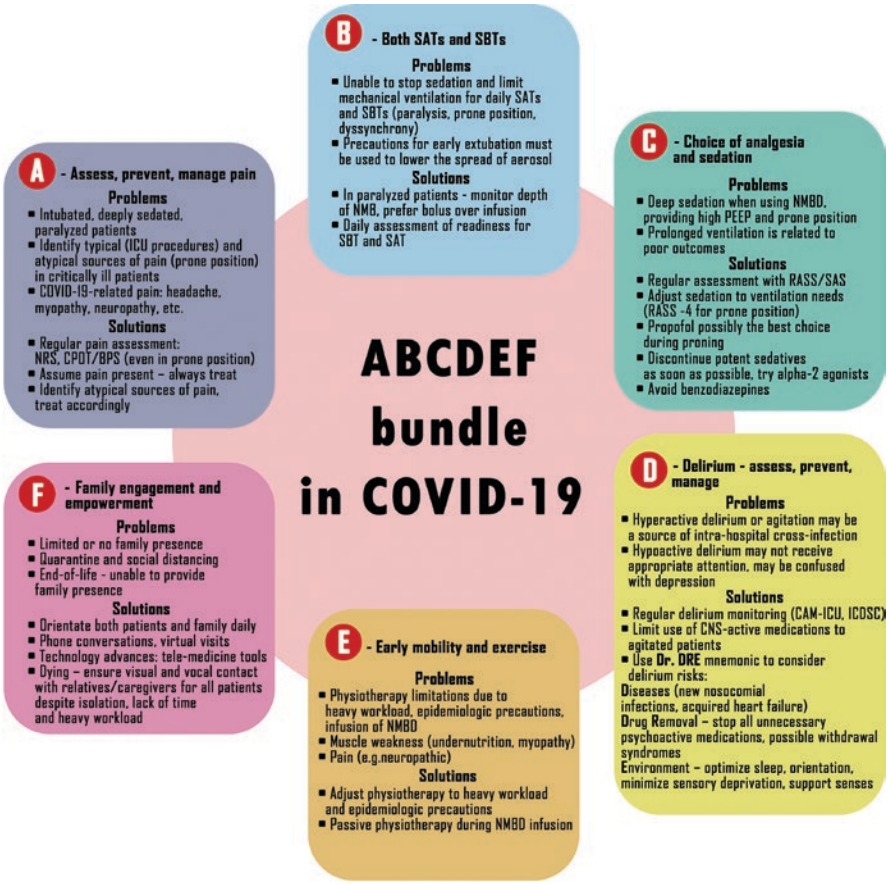

Fig. 23.2 ABCDEF bundle in COVID-19. *CNS* central nervous system, *ICDSC* Intensive Care Delirium Screening Checklist, *CAM-ICU* Cognitive Assessment Method for ICU, *RASS* Richmond Agitation–Sedation Scale, *SAS* Sedation-Agitation Scale, *PEEP* positive end-expiratory pressure, *NMBD* neuromuscular blocking drugs, *SBT* spontaneous breathing trial, *SAT* spontaneous awakening trial, *BPS* Behavioral Pain Scale, *CPOT* Critical Care Pain Observation Tool, *NRS* Numeric Rating Scale

5. SEDATION: Avoidance of excessive sedation, especially with the use of benzodiazepines.
6. DRUGS: No pharmacological interventions have yet been recommended for prevention or treatment of ICU delirium in COVID-19.
7. PHYSIOTHERAPY: Undue, prolonged immobilization should be avoided and regular physiotherapy must be implemented despite multiple challenges.
8. INTACT GI TRACT: Prevention of gastrointestinal problems (constipation) and adequate nutrition.

9. NON-PHARMACOLOGY: Standard non-pharmacological measures (e.g., regular orientation, restoration of senses, attention to wake-sleep cycle).
10. FAMILY & FRIENDS: Regular contact with family and caregivers, either in person or virtually has proven to be vitally important.

23.7 Conclusion

Acute brain dysfunction presenting as ICU delirium is highly prevalent, prolonged and severe in critically ill patients with COVID-19. It is a result of multiple predisposing factors and the neurotrophic potential of SARS-CoV-2 in the CNS. The use of benzodiazepines and limited family visits have been identified as modifiable risk factors for delirium. Only regular assessment with a validated delirium screening tool, identification of risk factors and early implementation of preventive measures may limit the prevalence of delirium. It is necessary to avoid factors previously recognized as associated with delirium and to extrapolate delirium management guidelines from other critically ill patient populations. Elements specific to the COVID-19 pandemic should focus on limiting periods of isolation, and ensuring the presence of family and friends, if not in person, then virtually. The mainstay of delirium management has been provided by the ABCDEF (A2F) bundle. Further research is needed to confirm the effectiveness of prevention and management measures to limit the prevalence and severity of COVID-19 delirium.

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Part VIII

Emergencies

Advanced Management of Intermediate-High Risk Pulmonary Embolism

24

T. Weinstein, H. Deshwal, and S. B. Brosnahan

24.1 Introduction

Pulmonary embolism is extremely common both in the general public and in hospitalized patients, but patients who have intermediate-high risk pulmonary embolism continue to pose significant treatment dilemmas. This is because the short-term mortality of a pulmonary embolus ranges from 2% in normotensive patients, 30% in patients with right ventricular (RV) dysfunction, and up to 65% in patients with cardiac arrest on presentation [1].

Understanding why a pulmonary embolism can pose such danger is anchored in the delicate balance that exists between the thrombus and obstructive shock. Once thrombus has formed in or embolized to the pulmonary artery, it acutely generates increases in pulmonary hypertension inducing right-sided heart failure. This is the primary driver of mortality in patients presenting with acute pulmonary embolism [2].

The increase in RV afterload is not simply from the physical obstruction of the pulmonary vascular bed but also the result of vasoconstrictive effects of thrombus-derived mediators such as thromboxane-A_2 and serotonin [3]. Although the right ventricle dilates to overcome the rise in pulmonary vascular resistance (PVR), eventually the dilation increases to the point of myocyte dysfunction and decreased strength of RV contraction. Additionally, the pressure overload in the right ventricle results in bowing of the intraventricular septum, decreasing left ventricular (LV) preload and negatively impacting cardiac output [4].

Treatment should be modified based on disease severity, but at present no perfect predictors exist to determine which patients will decompensate [5]. Clinical

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decision must be made by integrating clinical evaluation, often employing a pulmonary embolism score, in conjunction with imaging and laboratory markers that note RV dysfunction and injury. This method seems to correlate best with risk of decompensation [1, 6].

The Bova score was developed to determine which hemodynamically stable patients with pulmonary embolism had worse outcomes. Patients with a heart rate ≥110 beats/min, systolic BP 90–100 mmHg for at least 15 min, RV dysfunction, and elevated cardiac troponin had an increased risk of decompensation [7, 8]. Other scores, such as the Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI), combined with an assessment of RV function have been used to divide patients into intermediate-low risk and intermediate-high risk and help make treatment decisions [4, 9, 10]. In this chapter, we will review the evidence for various treatment modalities in patients with intermediate-high risk pulmonary embolism. Intermediate-high risk pulmonary embolism is best defined as a patient who has a pulmonary embolism, is hemodynamically stable, but has an elevated pulmonary embolism score and both radiographic and laboratory signs of right heart strain (Fig. 24.1) [11].

24.2 Treatment of High–Intermediate Risk Submassive Pulmonary Embolism

Once a diagnosis of pulmonary embolism is made, prompt initiation of anticoagulation is imperative as it has been shown to reduced mortality [12]. Similarly, conservative efforts to reduce the RV afterload, including oxygen supplementation and inhaled nitric oxide (iNO) to assist with pulmonary vasodilation can aid in preserving stability [13]. In cases of severe RV dysfunction, an inotropic agent such as dobutamine, should be initiated [14]. Supportive vasopressor therapy is required to keep mean arterial pressures (MAP) greater than 65 mmHg, with norepinephrine as the treatment of choice [15]. However, once dobutamine or vasopressors are used, the patient has progressed to a high-risk pulmonary embolism category and treatment algorithms can change. In significant pulmonary embolism, high afterload leads the right ventricle to dilate further. The use of extraneous intravenous fluid therapy can lead to acute RV decompensation by worsening septal shift and impacting LV preload [16]. In patients who are clinically deteriorating because of hypoxemia and respiratory distress, the decision to pursue invasive positive pressure ventilation is challenging due to concern for worsening RV afterload. The application of positive thoracic pressure can cause an acute decrease in RV preload. Therefore, an attempt to try conservative treatment, such as high flow nasal oxygen, should be considered prior to considering mechanical ventilation. If mechanical ventilation is pursued, hemodynamically neutral agents should be used for induction as the elevated PVR makes the right ventricle extremely preload sensitive. The use of propofol, a negative inotrope, has been associated with increased mortality in submassive pulmonary embolism and should be avoided [17].

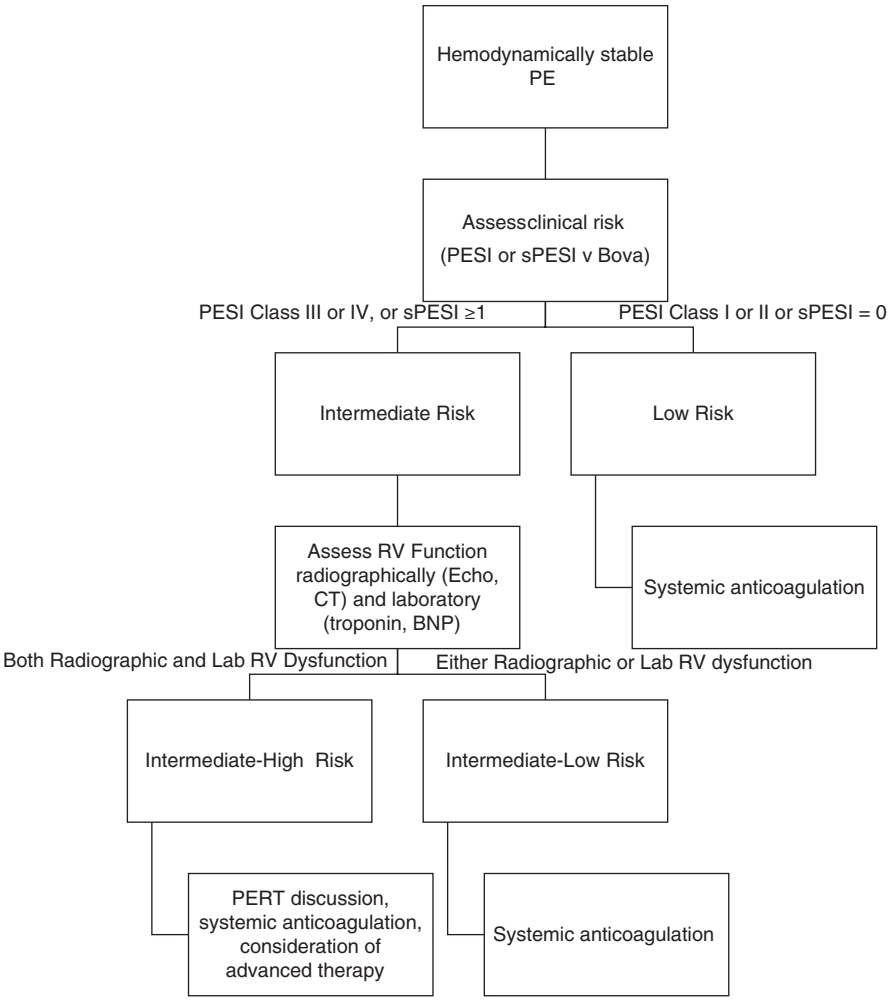

Fig. 24.1 Treatment algorithm for hemodynamically stable pulmonary embolism (PE). *BNP* brain natriuretic peptide, *PESI* Pulmonary Embolism Severity Index, *sPESI* simplified PESI, *RV* right ventricular, *CT* computed tomography, *PERT* pulmonary embolism response team. (Adapted from 2014 ESC guidelines [11])

24.2.1 Systemic Thrombolytic Therapy

While the use of systemic thrombolytic therapy is recommended in high-risk pulmonary embolism, defined as hemodynamically unstable patients or in patients after the return of spontaneous circulation, application in intermediate-risk pulmonary embolism is less well defined [15]. Patients with high-risk pulmonary embolism should undergo thrombolysis, in the absence of contraindications, as thrombolysis reduces mortality by almost 50% (3.9–2.2%) compared with anticoagulation alone

[18], yet this is counterbalanced by an increase in major bleeding (3.4–9.2%) and intracranial hemorrhage (0.2–1.5%). There is clear indication for use of systemic thrombolysis in the setting of rescue therapy for patients with submassive pulmonary embolism who have evidence of hemodynamic deterioration or who have not responded appropriately to anticoagulation [15]. When to use systemic thrombolysis in intermediate-risk pulmonary embolism poses a complex clinical dilemma with careful weighing of the risk-benefit ratio needed. This is because patients with intermediate-low risk pulmonary embolism will do well without escalation of therapy, and the addition of thrombolysis only adds risk without benefit. Several studies addressed below have looked at various dosages for systemic therapy with mixed results.

The European Pulmonary Embolism Thrombolysis (PEITHO) trial, the largest randomized controlled trial (RCT) to date, randomized 1004 patients with normotensive, submassive pulmonary embolism who had RV strain to weight-based tenecteplase with standard parenteral anticoagulation or parenteral anticoagulation alone [19]. Although the primary outcome was met, a decrease in the combination of death or decompensation, with decompensation making up most of the benefit, the study observed significant increases in major bleeding including intracranial hemorrhage in the tenecteplase group [19]. Nevertheless, the results solidified the role of tenecteplase in rescue therapy.

Another trial, TOPCOAT (Tenecteplase Or Placebo: Cardiopulmonary Outcomes At Three months), examined outcomes in patients with submassive pulmonary embolism randomized to low-molecular-weight heparin plus tenecteplase or placebo and demonstrated improvement in cardiopulmonary outcomes at 90 days with respect to dyspnea, quality of life scores, echocardiographic measures of RV function, and walk distance, but was not powered for mortality [20]. In meta-analysis, the stable hemodynamic subgroup has yet to show a clinically significant mortality benefit and given the increase in major bleeding, including intracranial hemorrhage, defining the exact subgroup that would benefit from more aggressive therapy remains elusive [21]. This is perhaps because intermediate-risk pulmonary embolism encompasses a large heterogeneous group of patients including those with low-intermediate risk and intermediate-high risk. The appropriate phenotyping of a patient becomes paramount when enrolling in trials to assess the true benefit of systemic thrombolysis. Because of this there remains a knowledge gap in managing patients with intermediate-high risk pulmonary embolism; currently treatment is guided mostly by a multidisciplinary and individualized approach.

Given the bleeding complications observed with conventional thrombolysis dosage, consideration was given to a ‘half-dose’ thrombolytic therapy. The rationale was that the lower dose would have the ability to maximize benefit of acutely lowering PVR while minimizing bleeding complications. The MOderate Pulmonary Embolism Treated with Thrombolysis trial, (MOPETT), was a single center study that aimed to determine whether half-dose recombinant tissue plasminogen activator (rtPA) would reduce rates of pulmonary hypertension (on echocardiogram) at 28 months. The incidence of pulmonary hypertension on echo was 57% in the anticoagulation group compared to 16% in the rtPA group and there was no increased

risk of bleeding. However, the 57% incidence of pulmonary hypertension in the control arm is disparate to known historical controls [22]. Therefore, there has been little change in clinical practice based on this study. At the present time, there is no convincing evidence to support ubiquitous use of systemic thrombolysis at any dose in hemodynamically stable patients and current guidelines do not recommend its use [15, 23, 24].

While a lower dosage may be ideal for some cases of pulmonary embolism, there are questions surrounding whether this approach is equivalent to higher doses in reducing PVR. We know that systemic thrombolytic therapy in patients with high-risk pulmonary embolism can be unsuccessful, as defined by persistent clinical instability or RV dysfunction up to 36 h after therapy, and accordingly the rate of inadequate response may increase as the thrombolysis dosage is lowered [25]. Analysis of a prospective single-center registry demonstrated higher mortality and higher recurrent pulmonary embolism in patients who had repeat-dose thrombolysis compared to surgical embolectomy, with similar bleeding risk. The study also noted that bleeding events in repeat dose therapy were all fatal [25]. To add to the discussion, the timing of the thrombolytic therapy can affect efficacy; thrombolysis is known to be most effective within 48 h of thrombosis generation. Early dosing offers the greatest benefit in reducing pulmonary artery pressure and RV dilation, yet delayed use for up to 2 weeks after symptoms has also shown some benefit [26]. Therefore, all applications of systemic thrombolysis may not be equal. With the advent of catheter-directed therapies, determining when to use systemic thrombolysis in intermediate-high risk PE has become further complicated. Catheter-directed therapies use less fibrinolytics but take longer to employ than systemic fibrinolytics.

24.2.2 Catheter-Directed Therapies

Percutaneous catheter-directed therapies offer an alternative to systemic thrombolysis, as well as a minimally invasive alternative to surgical thrombectomy for patients with high-intermediate risk pulmonary embolism at increased risk for decompensation. Several catheter-based treatment strategies have been utilized in clinical practice; however where catheter-directed therapies fit in the treatment algorithm for intermediate risk pulmonary embolism is still controversial.

Catheter-directed therapy can mean mechanical removal of clot alone or in conjunction with catheter-based thrombolysis. Mechanical therapies are good treatment options when a patient cannot tolerate fibrinolysis but has a physiologically significant thrombosis. The location of the clot dictates the utility of catheter-directed therapies as the pulmonary embolus must be proximal for the therapy to be effective. While there are larger vacuum-based therapies that require placement on extracorporeal oxygenation prior to their use, we will not review those as they would be unlikely to be used in intermediate-risk pulmonary embolism. Rheolytic thrombectomy, with devices such as AngioJet®, removes the thrombus by injecting a saline jet from the distal port under a high-pressure, thus creating a negative pressure force, while a separate catheter helps evacuate the thrombus [27]. Rheolytic

thrombectomy has become less popular, because as the thrombus breaks down there can sometimes be a sudden release of adenosine causing hemodynamic decompensation mostly evidenced by hypotension and bradycardia [28].

The FlowTriever® device has a suction catheter alongside three nitinol mesh disks that help remove residual clot after the initial thrombus is removed using suction. The advantage of the FlowTriever® device is that it offers a complete evacuation of proximal thrombi. The nitinol mesh disks are available in several sizes, allowing the proceduralist to choose an optimal size for each patient. The FLARE study demonstrated that the FlowTriever® results in significant improvement in the right ventricle to left ventricle ratio at 48 h. While no major bleeding or deaths were noted, the adverse event rate was 3.8%, including one pulmonary hemorrhage and three procedure-related clinical deteriorations [29]. The clinical use of FlowTriever® is often limited by the blood removed with the thrombus.

Mechanical catheter-directed therapy can be used in conjunction with catheter-directed thrombolysis or thrombolysis can occur on its own. Catheter-directed thrombolysis is when low-dose fibrinolytic agents are directly injected into the pulmonary artery at a slow infusion rate, often over the course of 12–24 h. The theoretical advantage of this technique is that the fibrinolytic infusion is at the site of thrombosis and a lower dose of fibrinolytics can be given despite longer exposure. There is conflicting evidence as to whether catheter-directed thrombolysis has less bleeding risk compared to systemic thrombolysis [30, 31].

Catheter-based therapies can help normalize the pressure in the right side of the heart more quickly than anticoagulation. The ULTIMA (ULTrasound Accelerated ThrombolysIs of PulMonAry Embolism) trial reported improvement in the right ventricle to left ventricle dimension ratio when ultrasound-assisted catheter-directed thrombolysis was used with unfractionated heparin compared to unfractionated heparin alone [32]. Although the study included only 59 patients, only three minor bleeding complications were noted in the ultrasound-assisted catheter-directed thrombolysis group compared to one in the heparin-only group. Similar results of reduced RV strain by decreasing pulmonary artery pressure, and no major bleeding complications were noted in two prospective single-armed studies: SEATTLE-II (A Prospective, Single-arm, Multi-center Trial of EkoSonic® Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) and PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, & Catheter Thrombolysis) trials [33, 34]. The OPTALYSE (Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism) trial reported that a shorter duration of 6–12 h of ultrasound-guided assisted catheter-directed thrombolysis with a lower dose of the fibrinolytic agent was also able to improve RV strain and decrease in RV afterload compared to longer durations and higher doses [35]. Given these studies, it seems like the optimal patient for catheter-directed therapies would be an intermediate risk patient with pulmonary embolism who is on the cusp of hemodynamic compromise; however, identification of this cohort remains a challenge.

The field of catheter-based treatment of intermediate-high risk pulmonary embolism continues to evolve. Its utility depends on the availability of an expert

proceduralist and the institution's access to use of an extracorporeal bypass circuit in the case of hemodynamic decompensation. The benefits, risks, and alternatives of the selected procedure must be discussed in a multidisciplinary manner and with the patient to improve outcomes and minimize complications.

24.3 Pulmonary Embolism Response Teams

The complexity of managing patients with intermediate-high risk pulmonary embolism calls for a multidisciplinary approach to decision-making as care may have to be individualized on a case-by-case basis. While echocardiography, biomarkers, and risk-stratification strategies help in decision making, it often becomes challenging to predict outcome in patients with intermediate-high risk pulmonary embolism. Institutions have developed pulmonary embolism response teams (PERTs) to assist in treatment strategies and the possible need for advanced therapies such as fibrinolysis versus catheter-based treatment versus surgical embolectomy on a case-by-case basis. While the composition of each team varies among institutions, they most often include some variation of pulmonologists, thoracic surgeons, cardiologists, interventional radiologists, and intensivists. It remains to be known whether PERTs improve outcomes, but they offer the best opportunity for a multidisciplinary approach to managing pulmonary embolism. The 2019 ESC guideline recommends forming an interdisciplinary team, such as a PERT, if resources are available [15]. Given the lack of hemodynamic predictors of these patients, we believe that PERTs represent the best method to weigh risk and benefit for each treatment option in patients not only with intermediate-high risk pulmonary embolism but also other pulmonary embolism conundrums.

24.4 Submassive Pulmonary Embolism: Rescue Therapy

24.4.1 Surgical Embolectomy

Surgical pulmonary embolectomy has classically been reserved for patients with massive pulmonary embolism who cannot receive fibrinolysis or remain unstable after administration, or for patients with intermediate-high risk pulmonary embolism who either fail thrombolysis or have an absolute contraindication [15]. Additionally, a definitive surgical approach is recommended for patients with high-risk thrombi, such as those with appreciable clot in the right heart near or through a patent foramen ovale [36, 37]. Surgical embolectomy can rapidly restore pulmonary blood flow and relieve acute obstruction. The surgical approach is through a median sternotomy and requires the patient to be placed on cardiopulmonary bypass (CPB), typically without aortic cross-clamping or cardioplegic arrest to avoid additional ischemic injury to an already stunned right ventricle. This is followed by an incision through the pulmonary trunk and the main pulmonary arteries with subsequent extraction of the acute clot [36, 38, 39]. All patients should have an echocardiogram

completed pre-operatively for an assessment of right and left sided heart function, and detection of a patent foramen ovale or an atrial septal defect, which helps to understand the risk of paradoxical embolism [39].

Systemic thrombolysis and catheter-directed therapies have emerged at the forefront of management to acutely relieve RV obstruction in intermediate-high risk pulmonary embolism as surgical pulmonary embolectomy has historically been associated with a higher mortality. However, over time, surgical technique has been revised and standardized to minimize perioperative mortality and thus sparked a renewed interest in expanding the scope of surgical interventions. Recent data from experienced surgical centers have shown in-hospital mortality as low as 11.7% in patients undergoing surgical embolectomy for acute high-risk pulmonary embolism. On deeper review of the data, it was noted that this value was largely driven by patients with massive pulmonary embolism and those with pre-operative arrest rather than patients in the intermediate-high risk pulmonary embolism category [40]. The safety of surgical embolectomy in submassive pulmonary embolism has been further underscored in other small single center studies, with one such study quoting no mortality in their cohort of patients [41]. In fact, the mortality from surgical pulmonary embolectomy in acute pulmonary embolism has been shown to be equivalent to that from thrombolysis. The New York State Registry, which included 174,322 patients hospitalized with pulmonary embolism between 1999 and 2013, revealed no difference in short-term mortality between surgical embolectomy and thrombolysis. Moreover, those who underwent surgical pulmonary embolectomy had lower rates of stroke, recurrent pulmonary embolism, and need for re-intervention [42]. Improvements in operative techniques and subsequent outcomes have highlighted that surgical pulmonary embolectomy is both safe and effective. This has led to garnered interest in perhaps expanding the criteria for surgical referral, particularly in cases of intermediate-high risk pulmonary embolism [40–42]. Nevertheless, this is not yet formally part of any guideline and likely requires a multidisciplinary discussion on a case-by-case basis.

24.4.2 RV Assist Devices

Mechanical circulatory support using RV assist devices as a bridge to or in combination with definitive therapy has been explored in patients who face high risk of RV decompensation and circulatory collapse. The Impella device is an 11-French catheter with a 22-French pump head that is percutaneously placed under fluoroscopy through the femoral vein and advanced into the pulmonary artery. The device pulls blood from an inlet that sits in the inferior vena cava and expels it directly into the pulmonary artery. It can maintain a perfusion of 4.4 l/ min for up to 2 weeks. The device has been best studied for its use in RV failure after a LV assist device, acute myocardial infarction, heart transplant, or open-heart surgery [43]. The data on use in acute pulmonary embolism are limited. Small retrospective case series have supported its use in high-intermediate risk and massive pulmonary embolism in terms of hemodyamic benefits, survival, and recovery of RV function after device

extraction [44]. Despite these appealing benefits, at present it has not been approved for use in RV failure in the setting of acute pulmonary embolism and is therefore not included in the current guidelines.

24.4.3 Extracorporeal Membrane Oxygenation

In patients who are hemodynamically compromised from an acute pulmonary embolism, venoarterial extracorporeal membrane oxygenation (VA-ECMO) can be considered as an alternative means of circulatory support. Current guidelines recommend utilization of ECMO as a means of mechanical support for patients with acute high-risk pulmonary embolism and refractory shock with the caveat that it is used in combination with definitive therapy, such as surgical embolectomy or catheter-directed therapy [15]. Additionally, ECMO may be helpful in the setting of cardiac arrest, though again, only as a bridge to definitive therapy [15].

There is currently a paucity of data surrounding ECMO as stand-alone therapy with anticoagulation and, thus, it is not a guideline-supported therapeutic avenue [45]. The data regarding ECMO in acute pulmonary embolism are limited to case reports and series, as well as smaller observational studies that are subject to variable bias [15, 45]. There are no RCTs assessing its use and limited information regarding outcomes. One recent review of 78 patients collected from case reports and series reported a 70% survival in patients using ECMO in massive and submassive pulmonary embolism. The authors further noted that this survival benefit was not associated with any one definitive treatment modality. Poorer outcomes were noted in patients where ECMO was instituted whilst in cardiopulmonary arrest and worsened further if initiated greater than 30 min from the time of arrest [45]. This suggests that, in the right patient and if initiated early, ECMO is a potentially life-saving therapeutic option that can provide clinical stability to allow for definitive therapy. However, it is important to underscore that ECMO is associated with a high incidence of complications, such as bleeding and infection, and outcomes are largely dependent on the experience of the center and patient selection [15].

24.5 Conclusion

While the optimal management of patients in the intermediate-high risk pulmonary embolism group remains to be defined, a combination of clinical variables, biomarkers and imaging studies may assist in identifying those patients that are most likely to benefit from a closely monitored setting [6, 18]. At present there are a large number of treatment options ranging from various thrombolysis dosages, catheter-directed therapies, surgical therapies, and peripherally inserted devices that can aid in augmenting cardiac output. Developing a superior method to determine who in the intermediate risk group would benefit remains paramount to investigating and further defining treatment for this group. While it is clear that there is benefit in aggressive treatment in the patient who needs it, if patients are not at true risk for

decompensation then aggressive treatment only comes with more risk. It is perhaps not the treatment of pulmonary embolism that needs defining but rather better individualized hemodynamic monitoring and prediction of decompensation that hold the key. Until a better characterization of this population can be made we assert that the best treatment intervention may be the implementation of PERTs so that an educated discourse can be made on a case by case basis.

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Enhancing Non-ICU Clinician Capability and ICU Bed Capacity to Manage Pandemic Patient Surge

25

H. Bailey and L. J. Kaplan

25.1 Introduction

Despite the global occurrence of critical illness, intensivist staffing in acute care facilities is not uniform. Shortages of trained intensivists permeate both low and middle income nations. Even in resource replete nations like the USA, nearly half of all acute care facilities are devoid of an intensivist [1]. Accordingly, critical care that is provided in such facilities often leverages multiple consultants, who guide patient care, but do not do so in a team-based fashion. Those with critical illness whose needs outstrip what may be provided at smaller critical access, rural or less well-resourced suburban facilities are commonly transferred to tertiary or quaternary facilities, the majority of which are academically driven or affiliated. Even in those acute care spaces, intensivist staffing may be limited based upon patient flow and competing time demands.

The current severe acute respiratory coronavirus 2 (SARS-CoV-2) pandemic has exacerbated shortages in all locations and created care crises in a global fashion. Patient surge into intensive care units (ICUs) further aggravated the intensivist shortage by creating a concomitant critical care bed shortage [2]. Innovative solutions were required to support patient flow from less well-equipped facilities to those with more resources, and to help safely manage the patient surge into advanced care sites. Linked strategies that created new bed spaces and trained non-ICU staff to help seasoned ICU staff care for the critically ill and injured helped achieve those

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paired aims [3]. This chapter will explore creating novel critical care spaces and training non-ICU clinicians as paired innovations to help manage pandemic-initiated health system challenges. It is important to recognize that these approaches are appropriate only when systems have enacted crisis standards of care.

25.2 Standards of Care

Understanding standards of care is essential as the standard under which the facility is operating helps guide expectations regarding the intensity and quality of care that may be rendered. That intensity reflects the interplay between facility resources and patient demand, including care acuity. While beds and staff are key elements, they will be addressed later in this chapter. There are three different standards of care—or capacities—that are readily identified: usual (conventional), contingency, and crisis [4]. Usual or conventional capacity indicates that resources, patients, and their dynamics are occurring in the usual daily workflow fashion. Disasters often trigger a move to contingency capacity, reflecting system stress. While resources may be in short supply, or highly utilized, the ability to provide usual quality care remains intact. Many resource-replete facilities can sustain contingency capacity for a sustained duration, but less replete ones only for a short time. When the intensity or volume of patients and their needs exceed the available resources, and the delivered quality of care cannot meet the usual standard, this state is termed crisis capacity. Care is generally considered adequate - or sufficient - for the clinical condition. It is during crisis capacity care that the concept of allocation of scarce resources must be considered and the notion of the greatest good for the greatest number guides that allocation. Often the decision to enact crisis capacity care relies on such a declaration from regional, state or governmental entities, rather than rendering the decision in a local fashion [5, 6].

25.3 Surge-Induced Issues

As the surge of critically and non-critically ill or injured patients flows into an acute care facility, both ICU and non-ICU spaces are apt to rapidly fill. The emergency department (ED) is the most common portal through which such patients are admitted, but direct transfer—especially to advanced centers—is another important channel of patient flow [7]. Facilities must articulate and adopt strategies to address the need to provide emergency care as well as pandemic-related care, all while continuing to address the needs of existing inpatients. During this pandemic, these needs were also impacted by acute illness or death of facility personnel (especially early on when shortages in personal protective equipment [PPE] were common), exit from the workforce to provide partner or child care, as well as normal attrition due to career change, relocation or retirement [8–10]. Adopted major strategies during this pandemic include but are not limited to: (1) cessation of elective procedures including surgery (reduced bed and staff utilization); (2) increased home care

management of non-critically ill patients (increase bed availability); (3) reduced or eliminated routine family visitation (PPE sparing); (4) reduced or eliminated trainee bedside presence (PPE sparing); and (5) reduced in-hospital subspecialist presence (PPE sparing) [11]. Reduced personnel and visitors also supported public health measures to reduce virus transmission. However, despite such approaches, many facilities consumed all of their licensed critical care beds. In the absence of a viable alternative strategy, sites would then have needed to explore scarce resource allocation approaches to ration care [12].

Fortunately, two alternative approaches were embraced. First, load-leveling, or patient distribution across sites within the same healthcare system helped with bed allocation [13]. Second, reducing all transfers into the system other than for unusual care (e.g., extracorporeal membrane oxygenation [ECMO] rescue) also reduced the rate of bed utilization [14]. Third, and perhaps most importantly, sites evolved novel ICU spaces to provide critical care in sites that were previously used for other kinds or levels of care [3, 15]. Since these beds were not part of the licensed bed allocation, the number could readily fluctuate, was difficult to track, and required a legal mandate to occur without penalty [16]. The expansion into novel ICU spaces drove the need for new staffing, administration, supplies, and bed management to provide safe and effective care.

25.4 Novel ICU Spaces

Once the need to craft novel critical care space is apparent, the process benefits from a team approach similar to that used for bedside ICU care. Novel spaces have been created using acute care floors, conference spaces, operating rooms (ORs), post-anesthesia care unit (PACU) beds, tents, and even *de novo* structures erected in parking lots [3, 17]. Regardless of where the space evolves, commonalities in terms of physical dimension, beds, power, water, suction, medical grade gas, monitors, alarms, supplies, computer access, line-of-sight access, as well as clean and soiled spaces are all common. The same structural accommodations that may have been placed in the traditional ICU should also be incorporated into novel ICUs. These include being able to position infusion pumps (and sometimes the ventilator) outside of the room to reduce the need for room entry for care titration, monitors that are visible through a glass panel, or are "slaved" to an external screen, alarms that ring outside of the room, as well as a host of other key reconfigurations of the structure of ICU care [3, 18]. While the above represent facility elements and are infrastructural in nature, the human elements are equally important.

In concert with the need for human staffing, there is an absolute imperative for overarching administration to direct patient admission, facilitate discharge, and interface with referring facilities. While these activities may be unit or service-line specific, it is more efficient to have all such activities governed by a single entity [19] (Fig. 25.1). In contrast, the guidance for each individual novel ICU space in terms of patient care, communication, data collection, supplies, and quality assessment benefits from local governance. Indeed, sourcing leaders in disciplines that reflect the

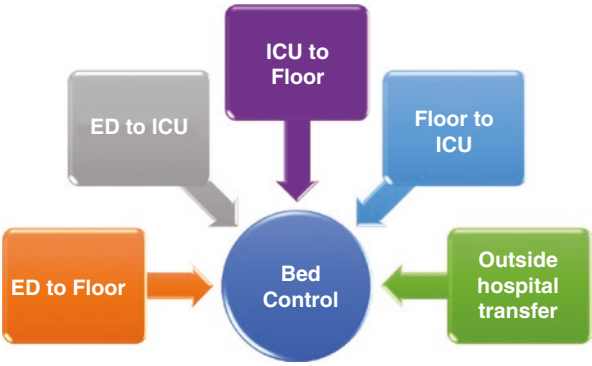

Fig. 25.1 This graphic demonstrates the multiplicity of inputs that could flow into a centralized bed control and allocation center to coordinate patient flow regardless of point of origin. *ED* emergency department, *ICU* intensive care unit

breadth of the ICU team may be problematic for facilities that have limited staffing with which to begin. More problematic is the staffing for bedside nurses, respiratory therapists, and pharmacists in particular, when establishing a novel ICU space. Facility leadership must also pay specific attention to managing the well-being of clinicians who work in the traditional ICU space as well as the novel ones. Burnout syndrome is a credible threat to clinician durability, viability and supply, especially given the duration of pandemic care [20]. Indeed, the Critical Care Societies Collaborative has recently issued a call to action as well as held a summit to address burnout syndrome in critical care using a multi-professional platform [21]. A recent Dutch study noted key factors that increase the likelihood of burnout syndrome in nurses and physicians, the two most studied groups in critical care [21].

25.5 Staffing Solutions to Expand ICU Clinician Supply

Since it is impossible to readily generate a large supply of appropriately trained intensivists within the context of a pandemic, other approaches must be engaged. There are four broad approaches to augmenting the supply of trained intensivists, one of which may also augment the workforce of the rest of the ICU team. First, pediatric intensivists may expand the age range for whom they provide care either in an adult facility, or within their pediatric facility in conjunction with their local facility leadership. Since pediatric ICUs (PICUs) often care for those with congenital anomalies well into the adult years, this is a viable and readily implementable strategy [22]. Second, those who provide critical care in some fashion outside of the traditional ICU may be adopted into the ICU clinician supply. A prime example would be anesthesiologists who work in acute care facilities and participate in emergency operative case management [23]. Third, if OR anesthesia ventilator devices are used to augment the ventilator supply in an ICU, certified registered nurse anesthetists may be used in place of respiratory therapists to manage those specific devices, augmenting the supply of respiratory therapists; this is anticipated to be relatively uncommon and not a major approach to staffing shortages [6, 23]. Fourth,

non-ICU clinicians may be trained to work in concert with seasoned ICU clinicians to care for the critically ill and injured [3, 6]. It is the fourth strategy that offers the greatest potential for workforce augmentation since it addresses every profession included in the ICU team and underpins a tier-staffing approach to surge management.

25.5.1 Non-ICU Clinician Training and the Tiered Staffing Strategy

The non-ICU clinicians who could be trained to work with seasoned ICU staff must be liberated from their usual workflow. The cessation of elective and semi-elective procedures in all disciplines is the dominant approach to rendering such individuals available for training and redeployment to novel ICU spaces [3, 5, 6, 23]. The tiered staffing strategy distributes seasoned individuals, such as intensivists, bedside critical care nurses, advanced practice providers, pharmacists (PharmD), and respiratory therapists, across novel spaces where they serve as leaders for those who do not normally work in an ICU. In this way, clinicians of virtually every parent specialty may be trained to participate in critical care as part of a larger team in which skilled individuals are interspersed [3, 5, 6, 23]. This model is presented in Fig. 25.2 and is derived from an approach to disaster care.

The training that may be provided to non-ICU clinicians to augment the critical care workforce in this way should not be conflated with education that leads to suitability for certification and credentialing to work as an intensivist to lead an ICU team, or as a team member to work within an ICU. Training that enables non-ICU clinicians to work with critical care clinicians is highly focused and represents only a small portion of the required core curriculum and skill sets to exclusively work in an ICU setting [24]. The phrase "just-in-time" training is often applied to

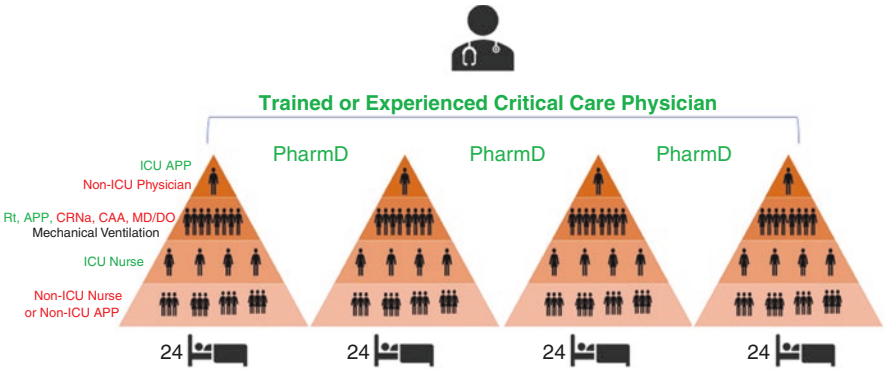

Fig. 25.2 Tiered staffing strategy for pandemic. *APP* advanced practice provider, *ICU* intensive care unit, *RT* respiratory therapist, *CRNA* certified registered nurse anesthetists, *CAA* certified anesthesiologist assistants, *DO* doctor of osteopathic medicine, *MD* doctor of medicine. Non-ICU-trained staff in red, trained and experienced ICU staff in green. (Reproduced with permission from the Society of Critical Care Medicine COVID-19 Rapid Resource Center [43])

such curricula. Since this kind of training has not been needed for vast numbers of individuals, a single best uniformly accepted approach did not exist. Instead, medical professional organizations combined already curated content that often formed the core of licensed and proprietary educational courses and combined them into an internally consistent whole. In order to make the conglomerated content accessible in a global fashion, a free, open access medical education (FOAMEd) approach unfenced the content from behind pay walls [25]. For example, the Society of Critical Care Medicine (SCCM) course, "Critical Care for the Non-ICU Clinician" has been downloaded more than 500,000 times and offers content from their Fundamentals suite of educational courses [26, 27]. Other societies, such as the European Society of Intensive Care Medicine (ESICM) has embraced a similar approach with their European Union supported coronavirus disease 2019 Skills Preparation Course (COVID-19 SPaCe) [27, 28].

25.5.2 Facility Level Accommodation

Of course, once an individual is trained to work in conjunction with a seasoned critical care professional, the facility must address local and temporary credentialing to allow such work to occur. Core supplemental education such as Advanced Cardiac Life Support, which is required for all working in an ICU, will not be feasible to achieve for the rapidly trained non-ICU clinician [29]. These deficits will require planning to preserve patient safety and may be managed in a host of successful fashions. Since the ICU-based work and workflow is generally unfamiliar to the rapidly trained individual, and certain common procedures may be even more unfamiliar, specialty teams may provide an ideal approach to supporting procedure timeliness, appropriateness, and safety [30]. Examples of such specialty teams include those focused on vascular access and invasive monitoring device placement, airway control, prone position therapy, as well as those related to aerosol generating procedures, such as therapeutic bronchoscopy or tracheostomy insertion [31, 32]. In many ways, such teams are congeners of the emergency response teams currently emplaced to aid in stroke, ST-elevation myocardial infarction (STEMI), cardiac arrest, trauma, and increasingly commonly, sepsis patient care [33]. Each of these new pandemic teams should have a relatively limited roster, be relieved of other duties, and be designed to reduce overall PPE utilization as well as room transit [34]. To do so, teams should evolve a workflow that addresses each step of their procedure with safety and preserving limited supply items as important goals.

25.6 Resuming Usual Care

As the pandemic surge ebbs, the need for novel ICU spaces may also fade. The facility must plan for the orderly 'deconstruction' of novel spaces and the reintegration of usual care within those locations and by the usual staff [3]. While so doing, certain structural modifications make sense to leave in place including windows in

doors, external screens that may display in-room monitor data, electrical outlets, as well as gas and suction ports since pandemic surge may recur. Moreover, the ability to 'flex' space to accommodate a disaster or a new infectious disease threat in the near future will benefit by maintaining durable structural advancements [3].

Reintegrating staff may offer additional challenges beyond simply reassigning work space. Given the duration of the pandemic, clinicians may be rather physically, mentally and emotionally stressed. Early on, there was intense patient flow, therapeutic and PPE shortages, as well as fear regarding virus acquisition and transmission, especially to family members [3, 35]. Later, as the first wave receded and many facilities resumed some or much of their usual care—alongside ongoing COVID-19 patient care—staff often transitioned without respite. The parallel COVID (+) and COVID (-) patients were initially 'cohorted', but patient volume often challenged a facility's ability to continue to do so, leading to cohorting within a single unit rather than cohorting in different units. Therefore, as the next wave crested, facilities were relatively full and then were asked to again evolve novel ICUs to provide accelerated volume COVID-19 patient care [36].

Without reductions in usual care, the staff to provide care using the previously leveraged tiered-staffing approach was then unavailable. They remained in their native units providing usual level care to patients with and without COVID-19. This more challenging circumstance was met with a variety of potential solutions, including but not limited to: solicitations for overtime, requests for reintegration into the workforce among retirees, changes in the usual nurse:patient ratios, and the uncapping of medical team patient care limits [36, 37]. These unusual approaches, many of which were viewed as potentially less safe than desired, underscore the need for a different approach to pandemic preparedness.

25.7 Potential Future Approaches

Two key elements that may be worthwhile to explore to support future pandemic—or other disaster—care address space as well as core critical care knowledge. Hospitals in most resource-replete nations rapidly filled, leading to bed shortages. Notable exceptions include China and Russia, which rapidly assembled entire facilities devoted to pandemic care [38]. While these new hospitals concentrated patients, they also concentrated clinicians, effectively relocating key pandemic care experts. Resource-replete nations could identify abandoned warehouses that could be converted into modular facilities and then serve as pandemic or disaster care sites. Between use for infectious disease outbreaks, they could be used for training for federal or public agencies, public health initiatives, or as test sites for specific technologies including those relevant for the ICU [17]. Such an undertaking could effectively liberate existing hospitals to continue usual care while concentrating unusual care in one location. It would also facilitate having a single type of medical record within the nation and create a viable platform from which to evaluate therapeutic interventions not beleaguered by lack of interoperability [39].

The extent to which critical care is integrated into trainee curricula is highly variable across disciplines whether medical, surgical, nursing, pharmacy or others relevant for the ICU [40]. Within each of those disciplines there is a 'blueprint' identifying the proportion of time spent in critical care during the training period. One way of enhancing competency in critical care when such skills are needed (as during the current pandemic) is to increase the time spent in critical care rotations. Not only should time be increased, but the year of training during which the exposure occurs is also important. Distributing exposure over early, middle and later years helps develop graded competency and enhances recall of essential knowledge [41]. Since the ED is the major portal of entry into the acute care facility for those with critical illness or injury, and this site is commonly overburdened with patients awaiting an inpatient bed (ED "boarding"), this discipline may be the optimal one with which to begin such a process [42]. The success of such a venture would guide expanding to other disciplines to increase critical care competency to support the ICU team and their patients during disaster or pandemic care.

25.8 Conclusion

The current SARS-CoV-2 pandemic underscored shortages in intensivists and in critical care beds. It also highlighted the ability to rapidly train non-ICU clinicians to function in concert with seasoned critical care professionals to expand ICU capacity in novel ICU spaces. The structural, administrative and human elements of such undertakings are vast and occur in a setting of accelerated stress over an expanded time frame. Future approaches to easing the burdens of pandemic care should address both space and staff in a thoughtful fashion to craft a nimble and feasible plan for future pandemics or disasters.

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