In 2010, David Bennett and Andy Rhodes set up an annual academic meeting in London. Their idea was to present and discuss controversies and innovations in intensive care medicine. The size and format of the meeting is designed to encourage thoughtful debate.

For this, our sixth meeting, we have asked the faculty of speakers to each write a book chapter that complements their invited presentation. The topics covered include state of the art reviews on cardiovascular, respiratory, renal and brain pathophysiology and ICU management, together with insightful commentaries on quality improvement, blood transfusion and the recent Ebola epidemic.

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6th Critical Care London Meeting

Critical Care London 2015

Andrew Rhodes, Jonathan Ball & Maurizio Cecconi

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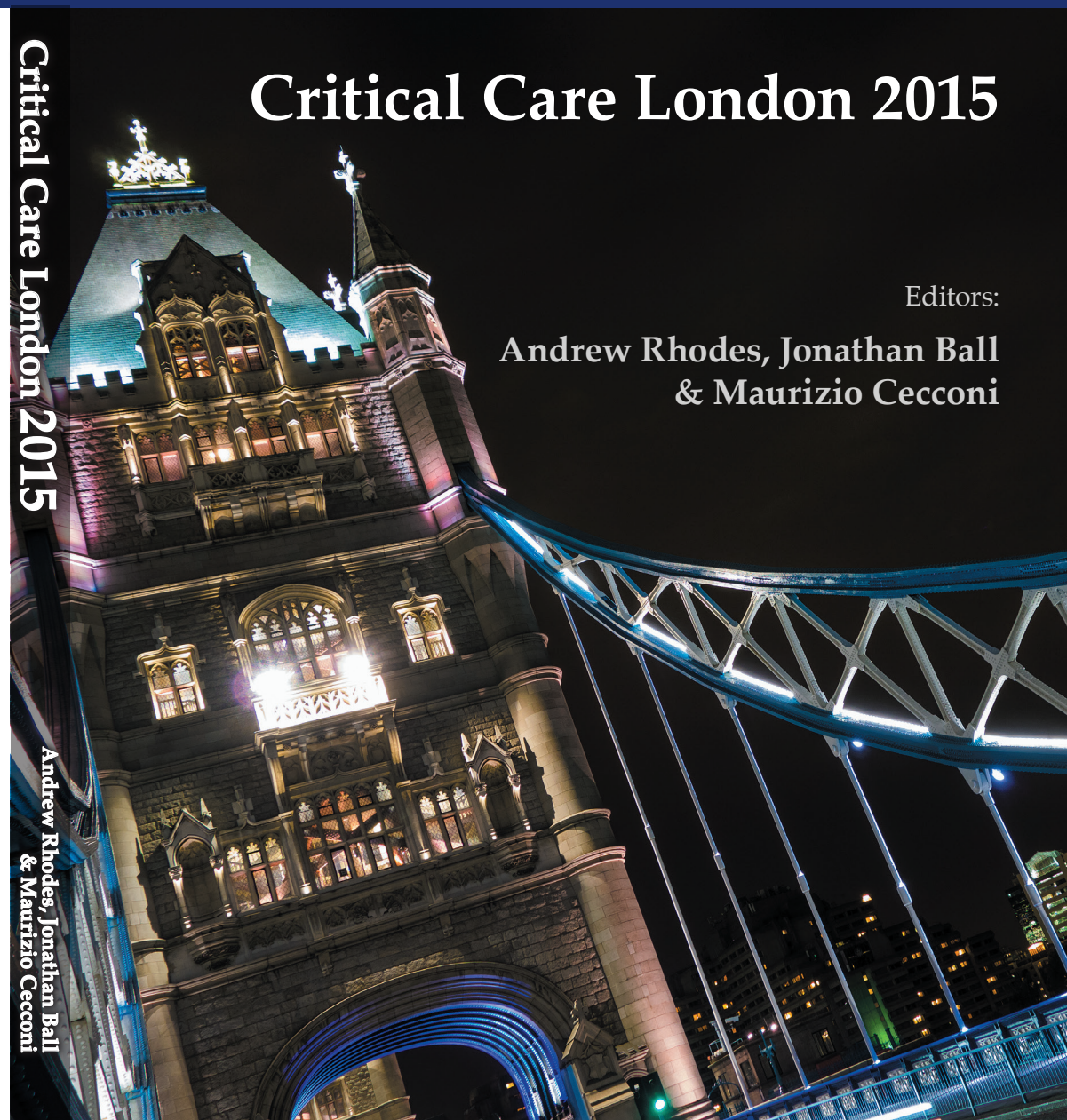

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Contents

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1.
Quality Improvement in Critical Care

Simon MacKenzie

We all aim to improve the care we deliver, and the GMC expects all doctors to demonstrate evidence of this, but in recent years 'Quality Improvement' has also become an area of practice with its own language, conferences and certainties. Much like intensive care. This carries the risk that clinicians think that quality improvement is something that only experts can do. Others may believe that it is all common sense and that quality improvement experts can teach us nothing. Neither view is very helpful. Any clinician can acquire the basic knowledge and skills to be a successful improver. The key is to question and challenge: to believe that, however good we are, we can be better.

Where does Quality Improvement fit in?

Quality Improvement fills a gap between what we mean to do and what we actually do. Research creates knowledge, education spreads it, exams test it, simulation helps us translate it and audit tells us whether we do what we think we do. All of these offer us the opportunity to improve but none guarantee it. In fact we know that quality of care is often not as good as it could, and should, be. Perhaps surprisingly, it is not around the cutting edge treatments that we let ourselves, and our patients, down - the problems are usually around the basics. This is where formal Quality Improvement can help. It provides two things: a distinct way of looking at things and specific tools to address challenges.

Quality Improvement is complimentary to, but fundamentally different from, Quality Assurance. We do need to report on whether we meet standards but, even when we do, we must always aim to be better. In describing a trilogy of quality control, quality planning, and quality improvement (Figure 1 1) Juran said that asking which was most important was like asking which leg of a three legged stool was most useful.

Figure 1-1: Juran Trilogy

How to do Quality Improvement

'In God we trust, all others must bring data'
~ W Edwards Deming

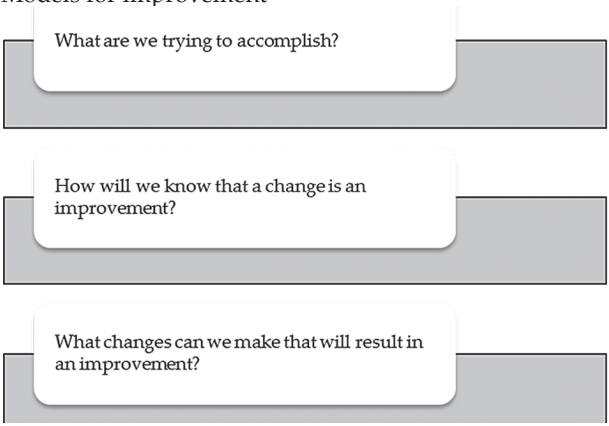
There are many different approaches to Quality Improvement, of which the Model for Improvement is probably the simplest (Figure 1 2). This incorporated the PDSA cycle, Plan, Do, Study, Act but it is essential not to overlook the three key questions at the start of the process:

- What are we trying to accomplish?
- How will we know a change is an improvement?
- What change can we make that will result in an improvement?

Don't start your improvement project until you can answer these questions.

Quality Improvement is therefore going to require data. Just as your research will be judged on the data, so will your QI. The tools for analysing will differ however and we will return to this.

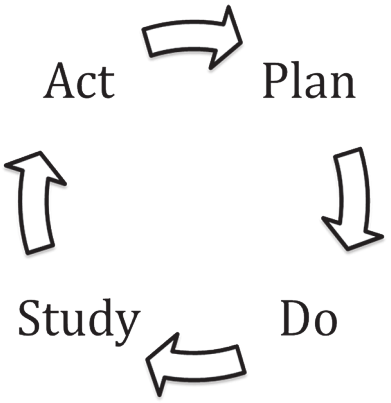
Figure 1-2: Models for improvement



Planning requires not just planning the intervention but deciding what data to collect, which will normally include 'balancing measures'. These are other things that might be adversely affected by what we plan to do.

- Doing is the part of the cycle when the intervention is undertaken, measurement are made and the data are collected
- Study involves looking at the change in the data associated with the intervention
- Acting means returning to the start of the cycle and either planning a new intervention or rolling out what has been done more widely.

Figure 1-3: PDSA cycle



Done properly this is scientific and rigorous but there are aspects that will make those who have undertaken medical research uncomfortable. The first is that the process is iterative. We will start with an intervention and assess both whether it can be implemented and whether it is effective. This means that we may start with one patient: after all if we cannot make our new process work for a single patient, there is no point in trying to do it across the whole unit until we fix that. Again this can be uncomfortable when we generally think that only large studies are of any value. Here we are looking for small scale but rapid feedback. Depending on what we are trying to improve, it may be possible to do several cycles rapidly (e.g. drug administration), in other cases cycles may be much longer.

In terms of what to measure it is important to include both measures of process and measures of outcome. This can be illustrated by a simple example.

What are we trying to achieve?	Reduced central line infections (CRBSI)	
How will we know change is an improvement?	Reduced incidence of CRBSI	Outcome
What change can we make that will result in an improvement?	Use chlorhexidine skin prep	Process

In this example the use of chlorhexidine is a means to an end, a process intervention. We may believe strongly that it will be effective but cannot assume that. If we only measured chlorhexidine use, and assumed that CRBSI must have improved because that is what the literature says we may fail to deliver actual improvement in outcome. If on the other hand we only measure the number of central line infections and not the use of chlorhexidine, we may attribute erroneously attribute improvement to our intervention. Alternatively, we might see no improvement and assume chlorhexidine is ineffective whilst failing to notice that we didn't actually change practice. Looking at process and outcome measures together is a powerful tool. One unit had implemented the Ventilator Bundle but recognised that there had been no reduction in the incidence of Ventilator Associated Pneumonia (VAP). This raised various possibilities: possibly the theory was wrong and the bundle is not effective in preventing VAP. Alternatively, the measurement of VAP might be poor or there might be some confounder. The Charge Nurse leading the project looked closely at what was actually happening on the unit and found that although staff members thought that they were implementing the bundle correctly they were not. The action that resulted was further training and in the next cycle VAP was successfully reduced.

Table 1-1: Understanding the link of process and outcome

Process changed **Outcome changed** • Successful improvement that is understood and can be sustained	**Process changed** **Outcome unchanged** • Theory incorrect, process and outcome not linked • Theory partly correct, however additional interventions required • Theory correct, but process has not actually changed
Process unchanged **Outcome changed** • Change in outcome due to other factors, known or unknown • Change in outcome is due to random variation and will probably not be sustained	**Process unchanged** **Outcome unchanged** • Understand reasons why intervention was not implemented and plan next cycle

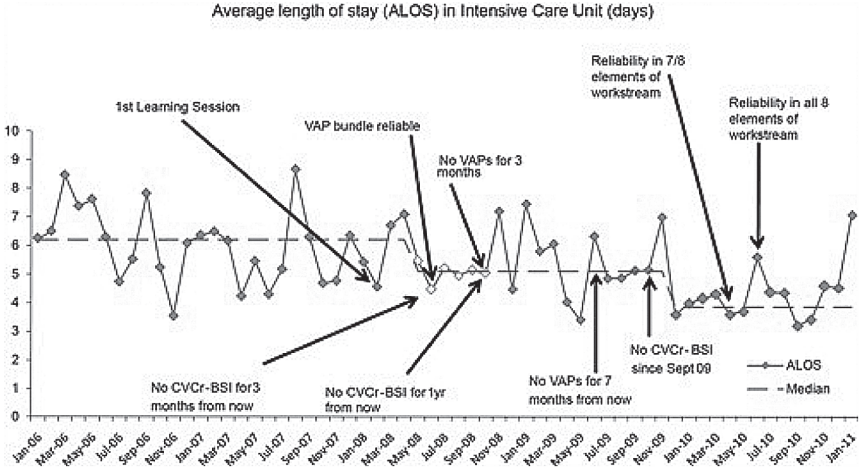
It will be clear from this iterative approach that a statistical approach which compares two study groups, to see if they are statistically significantly different in terms of an outcome is inappropriate. What is required is a way of looking at data over time that allows us to distinguish random variation from a true change and to test whether it is sustained. The simplest way to do this is with a 'run chart' where data points are plotted serially: we can then inspect visually, annotate to note interventions and apply pre-defined rules (Figure 1 4). It is important to plot observations in order, because a run chart can then help determine not only whether a change is real but whether it is related to our interventions or was happening anyway. A run chart is simple, reduces the chance of over interpreting a single result and allows us to see visually whether there is improvement and whether it is sustained. It is dynamic rather than static, but run chart rules can be used to determine whether changes are statistically significant. We would expect half of all observations to be above the median and half below, and there is less than a 0.05 probability that the following are due to random variation, the same test we conventionally use for statistical significance in research.

- Shift: six or more consecutive points that are either above or below the median.
- Trend: five or more consecutive points all increasing or all decreasing
- Run: A series of points either above or below the median. The expected number of runs can be calculated for a given number of observations

and either too few or too many runs indicates non-random variation (e.g. for 20 observations fewer than 6 runs or more than 16)
- Astronomical data point: this is subjective and is only used to describe an extreme outlier, not simply the highest or lowest point

More information on run charts is available at Perla *et al* [1]. There are other approaches that can be used including Control (SPC) and CUSUM charts.

Figure 1-4: Run chart of ICU Length of Stay (courtesy of Prof K Rooney)



The improvement methods and analytical approaches described here were originally developed by industry and a key goal is to reduce variation. Some clinicians object to both of these. They shouldn't. This is not about limiting clinical freedom, or treating patients like widgets. It is about recognising that there are many things that we do on a very regular basis, that we should do consistently unless there is a clear reason for not doing, but that we frequently do much less consistently than we intend. None of us would get on a plane knowing the pilot had assumed it had been fuelled 'because it always is', nor would we allow a surgeon to operate on us if we knew he had decided he didn't need to wear gloves.

In fact one of the important lessons from Quality Improvement in industry is that what we need to do is improve systems rather than focus on blaming individuals. The aim is to prevent mistakes before they occur rather than to detect them afterwards. This can be done in various ways, all of which are

based around making it easy to do the right thing and harder to do the wrong thing. These include the use of check lists, the creation of forcing functions, and building team work using tools such as crew resource management (CRM).

It is relatively easy to undertake QI in Critical Care. As a speciality we have a good evidence base for some of what we do, and good data since we have a relatively small number of patients who are closely monitored and in a defined geographical area. The consequences, for good or ill, of our interventions are often clearly apparent in a short timescale. Equally it used to be a place where Healthcare Associated Infection (HAI) was regarded as inevitable- one consultant referred to it as 'bug central'. Reduction, in some units the virtual elimination, of Catheter Related Blood Stream Infections is one of the success stories of the last decade. The story has some aspects that offer broader lessons. Pronovost *et al* [2] developed a package of measures at John Hopkins that eliminated CRBSI and showed that a statewide programme could deliver and sustain improvement across a range of units, a finding which has been replicated elsewhere including in the UK .

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Useful resources

www.ihi.org
www.qihub.scot.nhs.uk

2.
Prediction of Extubation Success and Failure.

Colette Coyle and Susannah Leaver

Introduction

Managing patients receiving mechanical ventilation is a key part of the Intensivist's role. The decision to cease ventilatory support and free the patient from the ventilator is complex and requires a comprehensive assessment of the patient's readiness for this. In 2005 an international consensus conference proposed six stages of mechanical ventilation see Figure 2-1 [1]. The patient's progress through these stages can be categorised into three groups depending on difficulty and duration (Table 2-1). Whilst between 60%-80% of patients fall in the 'simple weaner' category and extubate on the first attempt, the rest are difficult or prolonged weaners and as such are associated with an increased morbidity and mortality [1].

Within the above framework there are two components in the preparation for removing invasive mechanical ventilation. An assessment of readiness to wean followed by, if successful, the spontaneous breathing trial (SBT) to help determine the likelihood of successful extubation. The scope of this chapter is not to discuss all elements of weaning but will focus on:

- Why we need to assess readiness for potential liberation from the ventilator,
- How to assess readiness for cessation of ventilation,
- Common causes of weaning failure and diagnostics that can be used to help predict those likely to succeed while identifying those requiring a more prolonged individualised weaning strategy.

Table 2-1: Classification of weaning process (adapted from Boles *et al*. [1].) Percentage of patient in each group shown in parentheses

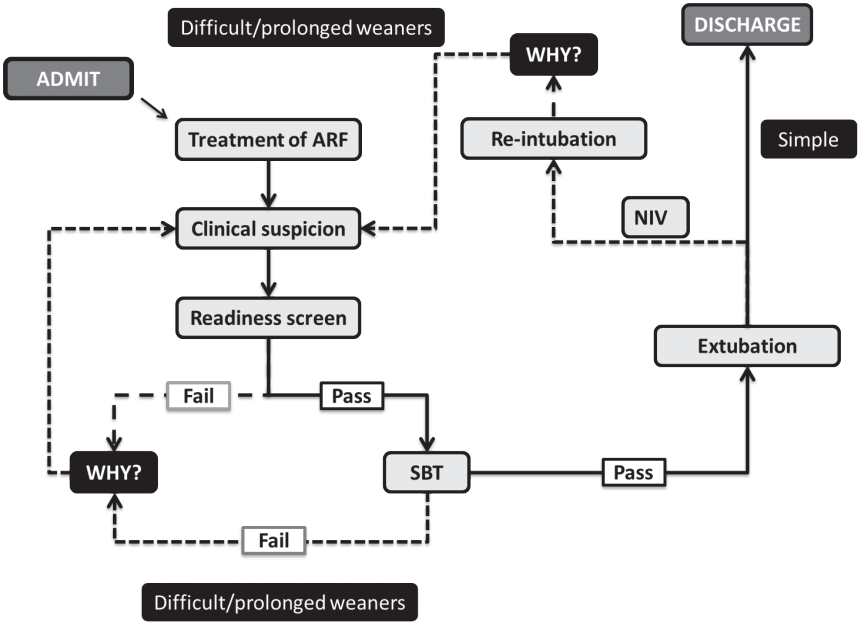
Simple weaning (60% patients) Successful extubation on the 1st attempt
Difficult weaning (30-40%) Require up to 3 SBTs and successfully weaned within 7 days from 1st SBT.
Prolonged weaning (5-15%) Fail more than 3 SBTs OR required more than 7 days of weaning from 1st SBT.
Long Term (5%) Require more than 6 hours ventilation a day for more than 21 days

Assessing Readiness for Removal of Mechanical Ventilation

Why do we need to do this?

Prolonged ventilation is associated with increased morbidity and mortality, thus once intubated patients require daily assessment to ensure duration of intubation is kept to the minimum required [2]. By contrast, despite meeting weaning criteria, failure of planned extubation occurs in 10-20% of cases requiring re-intubation, which is independently associated with increased mortality [2]. Whether this is due to selection of high-risk patients or the deleterious effects associated with re-intubation such as aspiration, atelectasis or pneumonia is unknown. Thus the assessment for readiness to extubate requires a balance between the increased mortality associated with delayed weaning with that attributed to re-intubation following failed extubation.

Figure 2-1: Stages of Weaning (adapted from [1]).



After admission the first stage (pre-weaning stage) is treatment of the underlying condition for which intubation was required. The next step is Clinical suspicion – this is when the treating physician first thinks there is a high probability that the patient can wean from the ventilator. This is followed by the Readiness screen (see text) and, if this passed, a Spontaneous Breathing Trial (SBT). If the patient passes the SBT they progress to the next stage Extubation and if successful they are discharged from the unit. The final stage is Re-intubation if extubation fails. The solid lines represent success and if this occurs on the first weaning attempt the patient is a 'simple' weaner. The broken lines represent failure and if the patient progresses along these routes they become by definition 'difficult or prolonged' weaners. Patients can fail at each stage. Whenever a patient fails the question should be WHY?. This will enable treatment to be put in place thus improving the chance of success at the next attempt. ARF acute respiratory failure; SBT Spontaneous Breathing Trial; NIV non invasive ventilation

Clinical judgment alone is often inaccurate in predicting those with the ability to breathe independently; a case -control study found that 50% of patients that self-extubated never required re-intubation [3]. Similarly, Girard *et al*. showed that only 31% of those who self-extubated following a paired spontaneous awakening

and spontaneous breathing trial required re-intubation [4]. Furthermore, between 65-85% of patients will successfully undergo extubation at the first assessment of readiness [5,6]. Therefore a daily structure for assessing the need for ventilation is required, not only to ensure the majority extubate at the earliest opportunity but also to identify those who are unlikely to wean readily and require a prolonged period of individualised weaning

How do you assess readiness?

The most common cause of delay is the failure to appreciate readiness to wean. Thus a daily sedation hold and assessment for readiness to wean is of paramount importance. Readiness to wean criteria are widely used but not universally agreed. These criteria are used to help identify those that can safely be liberated from the ventilator. One such criterion was devised at a clinical consensus conference in 2001 and is outlined in Table 2-2 [7]. It is split into those that are 'required' and those that are 'optional.'

Table 2-2: Readiness to Wean Criteria (adapted from Macintyre *et al* [7])

Required Criteria • Resolution of the underlying cause for respiratory failure • Pa 02/FiO_2 > 150mmHg/20kPa or Sp02 >90% on FIO_2< 0.4 and PEEP <5cm H_2O • pH >7.25 • Haemodynamic stability (no or low dose vasopressor medications) • Able to initiate an inspiratory effort
Optional Criteria • Haemoglobin > 70 to 100 g/L • Core temperature <38 to 38.5 degrees centigrade • Mental status awake and alert or easily rousable. • Able to cough

Common Causes for Weaning / Extubation Failure and Identification of High Risk Patients

There are a number of causes for weaning and extubation failure some of which are outlined below. The key to prevention is early identification and treatment enabling repeat readiness testing the following day.

Age and co-morbidities

Thille *et al*. identified patients over the age of 65 with pre-existing cardiac or respiratory disease as have much higher rates of reintubation [8]. Thus ensuring

optimal management of underlying co-morbidities is essential when dealing with these patients and a period of non-invasive ventilation immediately post extubation might be beneficial.

Unresolved / new pathology

Failure to ensure that the process for which intubation was required has resolved is a common cause of extubation failure. In addition, failure to recognise and treat a new process such as new onset of sepsis or further neurological insult can lead to prolonged ventilation. Thus the early detection and reversal of these processes is essential to reduce the amount of time the patient requires mechanical ventilation.

Cardiac failure and fluid balance

Attention should be paid to haemodynamic stability and fluid balance. A patient with significant vasopressor or inotropic reliance, or positive fluid balance is less likely to pass a trial of spontaneous breathing. Optimising cardiovascular function and fluid balance are therefore of paramount importance. The switch from positive to negative intra thoracic pressure that occurs with cessation of ventilation increases venous return, left ventricular after load, and increases myocardial oxygen consumption [1]. This can unmask latent left ventricular dysfunction. Indeed diastolic dysfunction demonstrated by echocardiogram during an SBT was associated with weaning failure [9]. Furthermore, in patients who passed an SBT, those with a significantly elevated BNP from baseline during SBT were more likely to fail extubation. A BNP rise of <20% was predictive of greater success [10]. In addition a positive fluid balance in the 24 hours immediately prior to extubation was associated with extubation failure [11]. Thus measuring BNP and performing an ECHO during an SBT can help unveil latent left ventricular dysfunction and prevent premature extubation in these patients. Optimising heart failure and setting a negative fluid balance should be instituted prior to re-testing the following day.

Obstructive sleep apnoea

The presence of obstructive sleep apnoea (OSA) and obesity are associated with a higher risk of extubation failure. Patients who are obese have reduced respiratory compliance and an increased work of breathing. The weaning process needs to be adapted accordingly to improve the success rate, for example by using non-invasive ventilation immediately post extubation.

Airway protection/ ability to cough

Being fully awake and alert is ideal for weaning but abnormal mentation does not preclude successful extubation. The following questions need to be asked and addressed:

- Is the patient co-operative?
- Is there significant agitation that may affect compliance with management post extubation?
- Is the patient in pain and could this be contributing to the agitation?
- Is there unexplained altered neurology?
- Does the patient have a good cough
- Can they manage their secretions?
- If the patient is still requiring frequent suction to clear secretions or has a weak cough then the risk of retention of secretions is high and subsequently reintubation is more likely.

Metabolic acidosis

A significant acidosis at time of the decision to wean from ventilation will have an effect on how the patient copes without respiratory support. A patient still trying to compensate for a marked metabolic acidosis is likely to fatigue more quickly and require reintubation. Addressing this with correction of the underlying process causing the acidosis such as treatment for diabetic ketoacidosis, renal replacement therapy for chronic or acute renal insufficiency will improve success. .

Anaemia

Severe anaemia is considered a contraindication to weaning particularly if acute. However haemoglobin levels of >70g/L as opposed to previously targeted levels of >100g/L are adequate and targeting higher thresholds has not been proven to be of any benefit [12].

Using Weaning Predictors

Weaning predictors measure different physiological aspects of respiratory function. They can be used as an adjunct to the above criteria, particularly in high-risk patients, to help identify patients likely to tolerate a SBT and hence extubation as well as those likely to fail. The indices described below are simple and can be carried out with equipment routinely available in the critical care environment.

Rapid shallow breathing index (RSBI)

The rapid shallow breathing index is the ratio of respiratory frequency to tidal volume and thus measures work of breathing. Patients still requiring ventilatory support have a high respiratory rate with shallow breathing and hence the index is high. An RSBI of <105 breaths/min/L was demonstrated to predict a successful SBT with a reported sensitivity of 0.97 and specificity of 0.65 [13]. Although RSBI has been measured in a number of weaning modes, in the original paper RSBI was measured without positive end expiratory pressure or pressure support.

After allowing one minute to enable stabilisation, RSBI should be measured in the subsequent minute and then the patient returned to the previous ventilator settings. The ventilator reading for RSBI should be used with caution as some ventilators report RSBI in real time (breath by breath) rather than averaged over the preceding minute.

Maximal inspiratory pressure / negative inspiratory force

The maximal inspiratory pressure (MIP) is an assessment of inspiratory muscle strength. The test was originally performed by attaching an aneroid manometer to the endotracheal tube and asking the patient to inspire maximally against an occluded airway. Most ventilators now have a function that enables MIP measurement. On some ventilators it is called Negative inspiratory force (NIF). Measuring MIP requires a co-operative patient. The patient is instructed following expiration to breathe in as deeply as possible, warning them that the effort may feel difficult during the procedure. Thus MIP measures the negative deflection in pressure during the patient's maximal effort to breathe during an expiratory hold manoeuvre at the end of a relaxed or forced expiration. MIP can be underestimated due to lack of effort from the patient, to negate this the valve can be occluded for up to 20 seconds, which will trigger the patient to maximal effort. A more negative (-30cm H_2O or less) value is associated with successful weaning. A MIP of -20cm H_2O or more positive has been associated with weaning failure [14]. On some ventilators the value appears as a positive reading in which case the higher the value the greater chance of successful extubation.

Occlusion pressure P0.1

The occlusion pressure P 0.1 is a non-volitional test and measures the airway pressure generated in the first 0.1 second (P0.1) during an inspiratory effort against an occluded airway. It is a measurement of the central respiratory drive and can be measured on most modern ventilators. Normal subjects have a P0.1 between -2 to-5cm H_2O. Patients with more negative P0.1 are more likely to fail an attempt at discontinuation from ventilation. Values of - 6cm H_2O have been associated with weaning failure [15]. Low values (< -2) are also useful indicating lack of respiratory drive secondary to brain injury or over sedation. Predictive accuracy of the P0.1 is higher when it is normalised for the MIP. The P0.1/MIP ratio relates the work of breathing to the inspiratory muscle power. A higher value being associated with weaning failure [16].

Peak cough flow

Peak cough flow is another useful tool in assessing readiness for extubation. The patient is asked to cough or cough induced with 2 mls normal saline. The flow in litres per minute can then be assessed by looking at the spike in the expiratory flow waveform. Absolute values can be measured but it also useful to track cough strength particularly in patient with neuromuscular weakness. Normal

peak cough flow in a spontaneous breathing patient is greater than 200L/min. However it is lower in an invasively ventilated patient as the endotracheal tube precludes glottis closure. An involuntary peak cough flow greater than 58.5 L/min was found to be associated with successful extubation [17].

Summary

Readiness testing, whilst not an exact science, is useful as a guide to help identify patients likely to successfully extubate thus avoiding unnecessary prolonged intubation. Of equal importance these tools can help identify those patients likely to fail thereby avoiding premature extubation. In practice clinical criteria are most commonly used and weaning prediction measures reserved for high-risk patients or those where there is clinical doubt. These tests are simple to use and can provide useful additional information when assessing your patient. In all ventilated patients a process should be in place to enable daily assessment limiting the exposure to the complications that prolonged ventilation can give rise to.

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3.
Extracorporeal Carbon Dioxide Removal

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Introduction

Respiratory failure - a condition in which the respiratory system is unable to maintain adequate gas exchange to satisfy metabolic demands - is the most common cause of admission to critical care, and because of the increase of life expectancy in industrialized countries, respiratory diseases will represent the third most common cause of death by 2025. An important syndrome leading to respiratory failure in critically ill patients is the acute respiratory distress syndrome (ARDS), which leads to poor lung function with hypoxaemia, hypercapnoea and low respiratory system compliance.

In these conditions, mechanical ventilation is often able to provide adequate oxygenation and CO_2 removal. However, the improvement of gas exchange commonly occurs at the expenses of a secondary injury to the lung (ventilator induced lung injury or VILI) due to inhomogeneous lung overdistension. VILI can lead to the release of inflammatory mediators that reach other organs causing multiple organ failure [1]. This has led to the concept of protective mechanical ventilation with limited tidal volume and plateau pressure [1-10]. Application of protective ventilator strategies is associated with decreased serum cytokine levels [2], decreased extra-pulmonary organ dysfunction [7] and decreased mortality [10].

In the last 15 years it has become evident that targets of mechanical ventilation traditionally considered 'protective' are often unable to offer lung protection particularly in the more severe cases of lung injury. This has led to the concept of an 'ultra protective' ventilation strategy which employs even lower tidal volumes; a lower respiratory rate; lower driving pressures and lower plateau pressures while maintaining an adequate mean airway pressure to avoid a reduction in functional residual capacity.

Ultra-protective ventilation strategies are likely to lead to hypercapnea and its deleterious consequences including systemic and cerebral vasodilatation, cardiovascular depression, arrhythmias, and pulmonary vasoconstriction with an increase in pulmonary arterial pressure. Acute pulmonary hypertension increases RV afterload and causes acute cor pulmonale which is associated with

high mortality rates [3]. The need to correct hypercapnoea without exposing the lung to mechanical trauma has resulted in a renewed interest in extracorporeal technologies that facilitate extracorporeal CO_2 removal (ECCOR).

Definition

$ECCO_2R$ is a technique of partial respiratory support that achieves removal of CO_2 from the blood though a low blood flow (0.4–1 L/min) extracorporeal circuit, without significant effect on blood oxygenation. Through $ECCO_2R$ a proportion of the total CO_2 production is cleared to allow reduction of mechanical ventilation and allow 'lung rest' [4]. Although the original purpose for $ECCO_2R$ was to provide additional CO_2 clearance in patients with severe ARDS to allow reduction in tidal volumes and inspiratory pressures, its applications are extending to include patients with Chronic Obstructive Pulmonary Disease (COPD), and as a bridge to transplant or in order to facilitate thoracic surgery.

$ECCO_2R$ Gas Exchange Physiology

The oxygenation of blood and the removal of carbon dioxide (CO_2) are physiologically different. Oxygen is mainly transported bound haemoglobin with only limited dissolved oxygen, and the mixed venous blood generally has a high saturation (65-70%), which limits the amount of oxygen per litre that can be added to the blood perfusing the natural or the extracorporeal lung. This makes blood oxygenation dependent on blood flow (on average 4–7 L/min). In contrast, CO_2 exchange depends on ventilation or in the case of a membrane, gas flow (termed sweep gas flow). The sweep gas contains little or no CO_2 and is passed through the membrane on the other side of a semipermeable membrane to the blood, thereby creating a diffusion gradient, which allows CO_2 removal. By using a sweep gas of up to 100 % oxygen at high flows, the gradient in partial pressure of oxygen and CO_2 across the membranes separating the blood from gas can be significantly higher than the gradient across the capillary and alveolar wall in the native lungs.

Considering that 1 L of blood is transports around 500 mL of CO_2 (double the CO_2 production per minute - about 200-250 mL/min), in a perfectly efficient system a flow of 0.5L/min would be sufficient to remove all of the CO_2 produced [5-8]. However, in practice CO_2 removal at any given blood flow depends upon the gas flow, blood CO_2 content and hemoglobin [9] as well as the efficiency of the gas exchange membrane. These limit the amount of CO_2 removed from the blood and $ECCO_2R$ is usually able to remove up to 25% of carbon dioxide production [4]. Blood flow is of course also important and CO_2 removal also

varies with changes in blood flow through the device [10]. Apart from the fact that CO_2 removal is proportional to the $PaCO_2$, sweep gas flow and blood flow, it also exhibits biphasic removal kinetics, exemplified by the initial rapid decline in $PaCO_2$ secondary to removal of the dissolved CO_2, and then followed by a more steady removal of CO_2, liberated from bicarbonate [11].

Description of $ECCO_2R$ Systems

$ECCO_2R$ systems vary in characteristics, technology and ability of gas exchange. They range from renal dialysis systems (low blood flow and low priming volume) to partial extracorporeal support ($ECCO_2R$), up to systems capable of full ECMO support with the capability of removing all CO_2 production and providing flows high enough to increase oxygen delivery and therefore provide blood oxygenation. An $ECCO_2R$ circuit consists of a percutaneously placed drainage cannula placed in a large central vein (or artery), a membrane lung and a return cannula into the venous system. In the case of arterio-venous systems (AV), the patient's blood pressure provides the driving pressure across the membrane. Veno-venous systems require a pump to be placed within the circuit.

Access cannulae

Access to the circulation is gained either through separate arterial and venous cannulae (AV systems) or using double lumen cannulae (VV systems). The AV system requires two single lumen wire-reinforced cannulae, one in the femoral artery to access blood and one in the femoral vein to return the blood to the venous side. The venous cannula is usually larger than the arterial cannula in order to reduce resistance to blood flow. The key disadvantage of the AV approach is the need for arterial cannulation with the potential side effects of arterial injury and limb ischaemia. In reported series distal ischaemia occurs in 11-24% of cases [12, 13]. The risk of ischaemia relates directly to the diameter of the arterial cannula. It is recommended that ultrasound of the artery takes place prior to cannulation to ensure that the arterial lumen is at least 1.5 times the size of the arterial cannula. Arterial injury is reported to occur in 7.5%-10% of cannulations [12, 14] for $ECCO_2R$ and is thought to relate to operator experience, patient factors including peripheral vascular disease and size of arterial cannula. In the AV approach, flow is of course directly related to arterial cannula diameter and the risk of inadequate blood flow has to be balanced against the risk of arterial injury and limb ischemia.

Cannulae for VV $ECCO_2R$ are conceptually identical to dialysis catheters. They are wire-reinforced, double lumen coaxial cannulae between 13 and 19 Fr. Some cannulae have heparin coatings to reduce the risk of thrombosis. They can be placed in any large central vein although the jugular and femoral approaches

are most commonly used [15]. The cannulae used for $ECCO_2R$ have the same complications as any central venous cannula, including risk of vessel perforation leading to bleeding or damage to surrounding stuctures, e.g. pneumothorax or arterial injury [16].

Regardless of the approach chosen, cannulae are inserted using a percutaneous Seldinger technique. Ultrasound has been shown to reduce the risk of complications relating to central venous and ECMO cannula insertion and it would seem prudent to use ultrasound guidance for $ECCO_2R$. Similarly it would seem prudent to observe strict aseptic technique during cannula insertion as this has been demonstrated to reduce complications relating to central venous cannula insertion. Not all cannulae are heparin bonded and either flushing with a heparinized saline solution or systemic anticoagulation with heparin will be required at the time of cannulation to prevent thrombosis of the cannula.

The membrane lung

The concept of placing a barrier between blood and air began with the observation that gas exchange occurred across cellophane tubing in hemodialysis machines [5, 17]. Indeed the membrane lung is conceptually very similar to modern haemodialysis filters using capillary tubules to carry blood through the oxygenator and separate tubules to carry the sweep gas. Recently, non-microporous poly-4-methyl-1-pentene (PMP) has been used; it provides superior gas exchange, better biocompatibility, lower resistance and is less susceptible to plasma leak [5]. Modern membrane lungs achieve adequate gas exchange with surface areas of 1 to 3 m^2. The gas exchange membrane is connected to air or oxygen which acts as a "sweep gas" to remove CO_2 that has diffused out of the patient`s blood. The flow rate of oxygen is increased in a stepwise fashion up to a maximum of 12 L/min.

The pump

Blood flows through the $ECCO_2R$ circuits can occur in two ways:

1) using the patient's own arterial blood pressure (***pumpless systems***) - where arterial blood is accessed through an arterial cannula and returned to the venous system via a venous cannula. These systems (arterio-venous, or A-V $ECCO_2R$) have the advantage of not requiring a mechanical pump. They therefore tend to be simpler and cheaper, but have the disadvantage of requiring arterial cannulation with the potential side effects of arterial injury and limb ischaemia. The AV-$ECCO_2R$ circuit introduces a low resistance iatrogenic shunt between the arterial and venous systems thereby reducing systemic vascular resistance and a compensatory increase in cardiac output to maintain systemic arterial perfusion pressure. In addition, the proportion of the cardiac output that flows through the $ECCO_2R$ system is not involved in

peripheral perfusion; hence the patient's effective cardiac output is reduced. Furthermore, for optimal functioning, a mean arterial pressure of 70 mm Hg and a cardiac index >3 l/min/m^2 is required [18]. For that reason patients with cardiac failure, severe haemodynamic instability and severe peripheral vascular disease are a contraindication to AV-$ECCO_2R$.

2) Alternatively, blood flow can be achieved through a ***mechanical pump***. The pump and the membrane can be separate components or can form a single console. Pumps can be *roller* or *peristaltic* (older systems) or rotary pumps, which can be 'diagonal' or 'centrifugal' where a rotating impeller creates a suction vortex that draws blood into the centre of the pump and propels it outwards the outlet.

Experimental Evidence for Efficacy of CO_2 Removal

Regardless of whether the AV or VV approach is used, $ECCO_2R$ devices can remove enough CO_2 to allow a 50% reduction in minute alveolar ventilation [19], with significant reduction in $PaCO_2$ and consequent reduction in pulmonary artery pressure and improvement in RV-arterial coupling even with flows as low as 0.6-0.7 L/min and average sweep gas flow of 8 L/min [20]. Livigni *et al.*, in an adult sheep model, were able to obtain a constant removal of arterial CO_2, with an average 20% reduction in CO_2, with extracorporeal blood flow of 300 mL/min (around 5% of cardiac output) [21]. Other animal studies have demonstrated that the devices can maintain consistent CO_2 removal for over 7 days using a low flow VV approach [22]. Novel methods to maximize CO_2 removal, such as regional blood acidification which increases the bioavailability of CO_2 by unbinding it from the bicarbonate ion in circulating blood, are also under investigation [23, 24].

Clinical Evidence for Efficacy of CO_2 Removal

In the mid-late 1970's Kolobow, Gattinoni and Pesenti pioneered the use of veno-venous $ECCO_2R$ for partial-to-total CO_2 removal to allow low-frequency ventilation and lung rest [25-27]. In addition, these authors showed that the removal of one third of the basal CO_2 production though the extracorporeal circuit at flows of 400-600 mL/min allowed reduction of tidal volumes and the switch to non-invasive ventilation [28, 29]. Early clinical trials however, did not show positive outcomes and the complication rate – particularly bleeding – was elevated [30-33]. In 1980, Gattinoni *et al.* showed that ECMO with a blood flow as low as 1.3 L/min drastically reduced ventilation needs (respiratory frequency of 2-3 breaths/min) thus limiting ventilator-induced lung injury [27]. A subsequent observational study of 23 patients with severe ARDS [34], demonstrated the

ability of $ECCO_2R$ to allow reduction in respiratory rate and inflation pressures while maintaining CO_2 clearance and supporting oxygenation. Bleeding was significant in this series and was the reported cause of death in 4/23 patients.

More recent series in humans have demonstrated consistent evidence that $PaCO_2$ can be reduced and arterial pH due to respiratory acidosis improved using both the $ECCO_2R$ [35]. AV $ECCO_2R$ has also been shown to reduce minute ventilation in an uncontrolled cohort of 159 patients over 10 years showed [18]. Similarly VV-$ECCO_2R$ can effectively reduce $PaCO_2$ in patients with ARDS and can facilitate a reduction in both tidal volume and airway pressures [5, 8].

Current Evidence

ARDS

Besides the general improvement in the standard of care provided in the intensive care units (ICUs), the only specific management that has consistently been shown to reduce mortality in ARDS is the provision of mechanical ventilation with static inspiratory pressures (plateau pressure) of less than 30 cmH_2O and low tidal volumes normalised to predicted body weight (PBW) according to a concept known as 'lung-protective ventilation' (LPV). This strategy has been shown to reduce ventilator induced lung injury (VILI), and is linked to improvements in short and long term outcomes for the majority of patients [36].

However, despite this global improvement in survival, there is a cohort of patients with severe hypoxaemia (PaO_2/FiO_2 < 13.3kPa) and hypercapnoea (leading to a pH <7.20) who offer a significant therapeutic challenge. This group of patients, even when managed with optimal recruitment and LPV, have a significantly higher mortality than patients with a higher PaO_2/FiO_2 ratio or lower $PaCO_2$ for any given minute ventilation [37-39]. It is likely that the identification of this subgroup of patients with 'severe' ARDS, will be made more explicit in the new 'Berlin definition of ARDS' [40], allowing for targeted therapeutic interventions and further clinical studies.

One of the potential rationale for the poorer outcomes in patients with more severe ARDS is that due to the extent of lung consolidation and alveolar injury, the available lung volume is small. Hence the use of conventional low tidal volume ventilation (6 mL/Kg ideal body weight) when administered into a smaller available lung volume will yield excessive lung strain. Terragni *et al.* [41] demonstrated that up to one third of patients receiving LPV had evidence of tidal hyperinflation and hence lung injury. One of the reasons for maintaining a conventional lung protective ventilation approach is to limit the hypercapnoea and consequent respiratory acidosis that will develop with very

low minute ventilation. Although permissive hypercapnoea has been advocated, hypercapnoea may cause significant physiological instability including pulmonary hypertension and right ventricular failure leading to a global low cardiac output state. In these patients, the addition of $ECCO_2R$ may allow control of hypercapnic respiratory acidosis and facilitate ultra-protective ventilation thereby limiting end-inspiratory lung stretch. It is possible that this approach may improve patient outcome.

In 1994, Brunet *et al*, used extracorporeal CO_2 removal combined with low frequency positive pressure ventilation ($ECCO_2R$ -LFPPV) in severe ARDS. They showed that $ECCO_2R$ improved gas exchange and prevented lung overinflation [42]. However, the same year Morris *et al*., in a randomized trial showed that in patients with severe ARDS full $ECCO_2R$ (meaning 100% CO_2 removal) compared to conventional mechanical ventilation had a lower mortality of 33% versus 42% for the control group which failed to achieve statistical significance, The authors did not recommend extracorporeal support as a therapy for ARDS outside controlled clinical trials [43]. Subsequent studies, have confirmed efficacy of $ECCO_2R$ in removing CO_2 allowing reduction in tidal volumes to and below 4 mL/kg [44] but with high mortality and complications [12, 45]. Similarly, Zimmerman *et al* showed that when $ECCO_2R$ was used as rescue in more severe ARDS (PaO_2/FiO_2 ratio <200 mm Hg, and/or pH <7.25 after a 24 hour period of optimized ventilation) it achieved marked removal in arterial carbon dioxide allowing a rapid reduction in tidal volume (<or= 6 ml/kg) and inspiratory plateau pressure. Adverse events occurred in six patients (11.9%) [13]. The high mortality and disappointing effect of $ECCO_2R$ in the early use of $ECCO_2R$ were likely to be due to the complex extracorporeal systems with high flow resistances and large surface areas (3.5 m^2), the use of occlusive roller pumps (with high haemolysis rate) and a less biocompatible membrane requiring high anticoagulation levels. In addition mechanical ventilation was in the pre-ARDSNet era and employed high tidal volumes and peak pressures.

Terragni *et al.* used VV-$ECCO_2R$ in 32 ARDS patients to facilitate 'ultraprotective' ventilation of 4 ml/kg [46]. VV-$ECCO_2R$ treated the hypercapnic acidosis and allowed the plateau pressure to be reduced to 25 cmH_2O to deliver 4 ml/kg ideal body weight tidal volume. Importantly the reduction in tidal volume did lead to tidal derecruitment and higher oxygen fraction, consequently there was a need for higher levels of positive end-expiratory pressure (PEEP) to maintain lung recruitment and functional residual capacity. The reduction in airway pressures seems to have reduced pulmonary inflammation as demonstrated by a reduction in bronchoalveolar inflammatory cytokines. In the prospective randomized 'Xtravent-study', Bein *et al*. [47] demonstrated that use of very low tidal volumes (3 ml/kg PBW) combined with ECCO2R with an arterio-venous configuration, was safe and beneficial in patients with severe ARDS in terms of 28 and 60 days

ventilator-free days, but not mortality. A *post hoc* analysis showed increase in ventilation free-days at 60 days in patients with severe hypoxemia (PaO_2/FiO_2 < 20 kPa) [47]. A recent systematic review of 14 studies (495 patients, two RCTs and 12 observational studies) with equal split between AV and VV $ECCO_2R$, showed that $ECCO_2R$ was feasible, facilitating the use of lower tidal volume ventilation [16], and post hoc analysis of data shows an increase in ventilator-free days in more severe ARDS although there has been no demonstrable mortality benefit to date.

Therefore, although the addition of $ECCO_2R$ to ultraprotective ventilation is appealing for patients with moderate to severe ARDS, at this time the effect of this approach on survival remains inconclusive [15,42,45]. Clearly the potential risk-benefit relationships still need to be defined, with the advantages of tidal volume/airway plateau pressure minimization being balanced against this risks associated with $ECCO_2R$ and derecruitment [16]. Finally we do not currently know which patient cohort is the key population to target. Patients with more severe respiratory failure (PaO_2/FiO_2 <20 kPa) may be an appropriate population of patients, as according to UK Intensive Care National Audit and Research Centre (ICNARC), this cohort has a 40% ICU mortality and around 50% hospital mortality. Clearly further research is required before this approach can be advised outside of clinical trials.

COPD

Patients who present with an acute hypercapnic respiratory failure due to a severe exacerbation of COPD often require hospitalization and non-invasive respiratory support (NIV) [3]. However, NIV fails to improve 25–50% of COPD patients who then require invasive positive pressure ventilation [48, 49]. These patients have prolonged weaning, and in-hospital mortality is as high as 25–39% [4–8, 50]. Concerningly, the mortality for patients who require invasive MV after failing NIV has been shown to be higher than those who are treated at the outset with invasive MV [4]. It is not clear why this is the case, however ventilator associated pneumonia is common in COPD patients requiring invasive mechanical ventilation and this has been shown to be an independent predictor of increased ICU mortality with mortality as high as 60–64%, and VAP [51, 52].

In severe COPD exacerbations, high airway resistance, ventilation/perfusion mismatch, dynamic hyperinflation and increased work of breathing with increased CO_2 production lead to hypercapnia. Given the outcomes of patients requiring mechanical ventilation its avoidance in this population is potentially of clinical benefit. For this reason, $ECCO_2R$ is being considered as an adjunctive therapy to NIV to facilitate the withdrawal of NIV, avoid intubation or facilitate early extubation. The feasibility of using venovenous $ECCO_2R$ for

acute hypercapnic respiratory failure due to COPD exacerbations has been demonstrated in several recent cases and cohort studies [50, 53-55].

A recent retrospectively propensity matched cohort study found that AV $ECCO_2R$ was able to consistently reduce $PaCO_2$, improve respiratory acidosis and reduce respiratory rate in 21 patients suffering from acute hypercapnic respiratory failure (mainly COPD) who were failing NIV [56]. In this retrospectively matched cohort study 90% of the patients treated with AV $ECCO_2R$ did not require intubation and invasive mechanical ventilatory support, and that there was a trend in this group towards a reduced length of hospital stay, but not mortality.

Another recent study by Burki and colleagues, reported on VV $ECCO_2R$ using a dual lumen venous catheter in COPD patients with hypercapnic respiratory failure. Three groups of patients were studied: patients with a high likelihood of requiring intubation; patients who had failed two weaning attempts from continuous NIV support and did not wish to be intubated; or to assist weaning in patients already on invasive ventilation [54]. $PaCO_2$ and pH improved within 6 hours and there were minimal major complications of the technique. All patients in whom the goal was intubation avoidance or weaning from NIV achieved remained ventilator free and separated from NIV. The approach was less successful in patients where early extubation was the goal in this study. However a feasibility study by Abrams *et al.* [50], enrolled five patients with acute respiratory acidosis in the setting of COPD exacerbations who had failed NIV and required IMV were initiated on $ECCO_2R$ to facilitate endotracheal extubation and mobilization. All five patients were successfully extubated within 24 h (median duration, 4 h) and ambulating within 48 h of $ECCO_2R$ support. Furthermore dyspnea improved as the respiratory acidosis resolved. This approach of using $ECCO_2R$ post-NIV failure was also used successfully in a small study by Roncon-Albuquerque *et al.* [53]. Finally there has been a recent retrospective cohort study using historical controls reported from Italy where 25 patients at high risk of NIV failure who received $ECCO_2R$ via a 14-Fr dual-lumen cannula in the femoral vein had lower intubation rates (HR 0.27) and a lower mortality [57]. Thirty-six percent of patients experienced device malfunctions and 12% of patients had bleeding complications, including one vessel perforation.

In summary the arguments for $ECCO_2R$ in exacerbations of COPD are compelling, although the evidence remains relatively weak. In patients who are failing NIV and who do not want intubation but also do not want palliative care $ECCO_2R$ seems a reasonable approach [58].

Thoracic surgery

A few case reports show that $ECCO_2R$ has been successfully applied to patients who underwent elective or emergency thoracic surgery, to allow surgery in patients who would not have tolerated one-lung ventilation [59].

Bridge to transplant

A further group of patients– those awaiting lung transplantation who develop life-threatening hypercapnoea - may benefit from $ECCO_2R$ as bridge to transplantation (LTX). In a study of 20 patients, the most common underlying diagnoses were bronchiolitis obliterans syndrome, cystic fibrosis, and idiopathic pulmonary fibrosis. Hypercapnoea and acidosis were effectively corrected in all patients within the first 12 h of $ECCO_2R$ therapy: Nineteen patients (95%) were successfully transplanted. Hospital and 1-year survival was 75 and 72%, respectively [60]. AV $ECCO_2R$. Devices have also been surgically implanted from the pulmonary artery to left atrium as a bridge to lung transplantation in patients with significant pulmonary hypertension [31]. Patients have similarly been successfully bridged to lung transplant using VV $ECCO_2R$ [44,59,60] reported successfully bridging 12 patients to lung transplant using VV $ECCO_2R$ [61].

Conclusions

Technological advances in $ECCO_2R$, together with the recognition that ventilation-induced lung injury can occur despite lung protective ventilation, have created the opportunity for an extended role of partial extracorporeal CO_2 removal. Future applications will involve smaller and more biocompatible $ECCO_2R$ systems, for patients with moderate-severe ARDS but also as a sole supportive modality in patients with hypercapnic respiratory failure. The potential complications of $ECCO_2R$ need to be evaluated when considering patients for extracorporeal support.

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4.
Mean Systemic Filling Pressure and the Venous Tone.

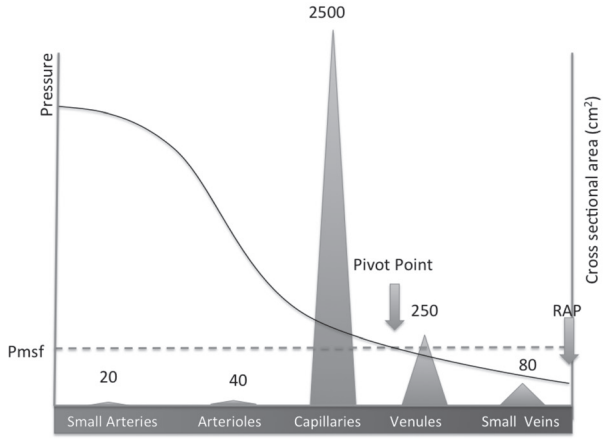
Hollmann Aya, Maurizio Cecconi and Andrew Rhodes

Introduction

Haemodynamic instability is a common cause of patient's referral to intensive care. This instability is often described as an inadequate arterial blood pressure, or as unspecific signs of inadequate perfusion of organs and tissues such as metabolic acidosis, hyperlactaemia, decreased urine output mottled skin and/or prolonged capillary repletion time. Under steady concentration of haemoglobin, cardiac output (CO) is the main determinant of oxygen delivery (DO_2). However, the CO is not primary controlled by the heart itself [1,2]. Instead, the rate of blood flow to each organ is almost always finely controlled by a combination of local signals in relation to tissue needs (such as the availability of oxygen and other nutrients, the accumulation of carbon dioxide and other waste products) and to sympathetic activity. Thus, CO is basically the sum of all the local tissue flows, which is in other words the venous return. Under steady conditions, the cardiac output and venous return are equal, and any parameter that determines venous return will therefore also determine cardiac output.

The venous system plays an important role in the maintenance of cardiovascular stability. It is not just a pipe to bring the blood back to the heart. It works as an adjustable blood reservoir that can modify blood flow in order to meet metabolic demands in changing situations. Veins contain 70% of total blood volume, whereas arteries contain only 13 -18%, and capillaries 7% [2,3]. Venous wall are thin, although with muscular fibres able to contract or expand, depending on the needs of the circulation. During hypovolaemia, sympathetic nervous reflexes cause venoconstriction, sending blood back to the central circulation. Actually, even after 20% of the total blood volume has been lost, the circulatory system functions almost normally because of this variable reservoir function of veins [2].

Figure 4-1: Pressures and cross -sectional area across cardiovascular system



Pmsf: mean systemic filling pressure. This is the pressure at all points in the cardiovascular system when the heart stops. During normal circulation, there is a point (pivot point) where the pressure equalise the Pmsf. At that point, the pressure is independent of flow, and theoretically localise at the venule territory. The drop in pressure is mainly related to the increase in the total cross-sectional area and the compliance of the vascular wall.

The heart pumps blood continuously into the aorta keeping the mean arterial pressure high, averaging 80 – 100 mmHg. This pressure decreases progressively as the blood flows into the systemic circulation, as low as the level of the right atrial pressure (RAP). This fall in pressure is mainly caused by the increasing total cross sectional area in each level of the vascular tree. When the heart stops, the arterial pressure falls down and the RAP progressively increases. At certain point, blood will not be flowing, and the pressure will be the same in all territories of the circulatory system. This pressure is the *mean systemic filling pressure (Pmsf)*. This pressure was described by Bayliss and Starling [4], and they figured that somewhere in the circulation there must be a point where the pressure is not changing when the heart stops. Actually, during a cardiac arrest, the pressure in the small veins (< 1 mm) and venules do not change substantially, they are the "pivoting point" of the system [5]. This pressure is less than the capillary pressure, close to the portal venous pressure and greater than the RAP. Its anatomic location it is not necessarily at the same venous branching level in the various organs. The importance of this pressure, rather than its anatomical location, is that it provides a quantitative measurement of the intravascular filling status independent from cardiac function: its value is equal to the Pmsf.

Let us imagine the "blood reservoir" as a distensible compartment. The volume required to fill a distensible tube, such as a tyre or a blood vessel, with no

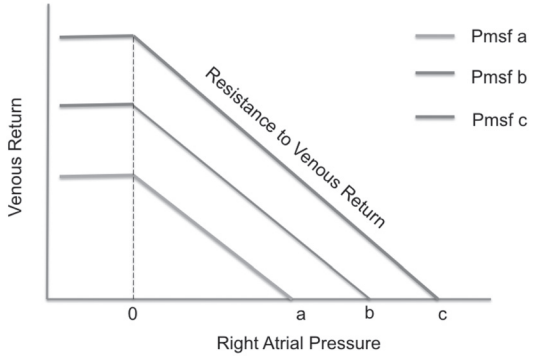
pressure rise is called the "unstressed" volume (V_o). Further volume expansion will imply necessarily a pressure rise and an elastic distension of the wall of the tube, which depends on the compliance (C) of the wall. This volume is the "stressed" volume (V_s) and is related to the pressure in the next equation:

$$Pmsf = V_s/C$$

Guyton [6,7] realised that is actually the difference in pressure between two points, not any single pressure at any point of the cardiovascular system, which determines the rate of flow. Given that most of blood is in the venous reservoir, the pressure at this point is particularly interesting. Guyton pointed out that venous return must be defined by three parameters: the mean systemic filling pressure (Pmsf), the right atrial pressure (RAP) and the resistance to venous return (RVR). This can be also mathematically represented as follow:

$$VR= (Pmsf-RAP)/RVR$$

Figure 4-2: Venous Return Curves



Pmsf: mean systemic filling pressure. Each curve represents different volume status. In order to move from the blue to the red curve, Pmsf must change from a to c without changes in resistance.

Guyton [9] drew venous return curves in recently dead dogs. The heart was replaced with a pump and the right atrial pressure (RAP) was controlled by increasing or decreasing the minute capacity of the pump. Increasing or decreasing the total quantity of blood controlled the mean circulatory filling pressure. From these curves one can spot that for a given RAP, the greater the Pmsf, the greater the venous return is. Importantly, under isovolumetric conditions the greater is the RAP, the lower is the venous return. Thus, given this lineal relationship, if venous return and RAP can be measured and changed

without changes in the volume status, the slope of the line could be calculated (the RVR) and the Pmsf could be estimated.

Control of Venous Tone

Certain parts of the venous system are particularly compliant: these include the spleen, the liver, the large abdominal veins and the venous plexus beneath the skin. Splanchnic and cutaneous veins have a high population of α1- and α2-adrenergic receptors, so they are very sensitive to adrenergic stimulation, contrary to skeletal and muscle veins [9]. The control of the venous system has been extensively studied in animal models. There are nerve terminations in the proximity of many small vein smooth muscles [10] but not in the veins of skeletal muscle [11]. However, circulating catecholamines can induce contraction of venules and veins of skeletal muscle and mesentery [10,11]. Thus, probably catecholamines released from the sympathetic nerve termination of the arterial side may pass through the capillary bed and affect the venous system.

Smooth muscle of the veins and arteries do not respond necessarily in the same way to chemical signals. Dihydroergotamine can activate the veins but not the arteries [12]. The venous system primarily has α-adrenergic receptors [13-16]. Stimulation of the β-adrenergic receptors of arterioles cause vasodilation but has little effect on the veins [17, 18]. Angiotensin can increase Pmsf [17,19]. Isoprotenerol, a β-adrenergic agonist, causes a decrease in Pmsf when veins are constricted with angiotensin. On the other hand, vasopressin has very little effect on Pmsf [20] or on vascular capacity once reflex blockade [21] and similar results were reported regarding natriuretic peptides [22].

Nitroglycerin and nitroprusside decrease Pmsf, increase unstressed blood volume but do not change vascular compliance in ganglion-blockade dogs [23]. Verapamil and Nifedipine increase venous return by reducing the resistance to venous return without changing the Pmsf whereas nitroglycerin in small doses can reduce Pmsf without changes in resistance to venous return [24]. Diltiazem reduce both resistance and Pmsf increasing CO.

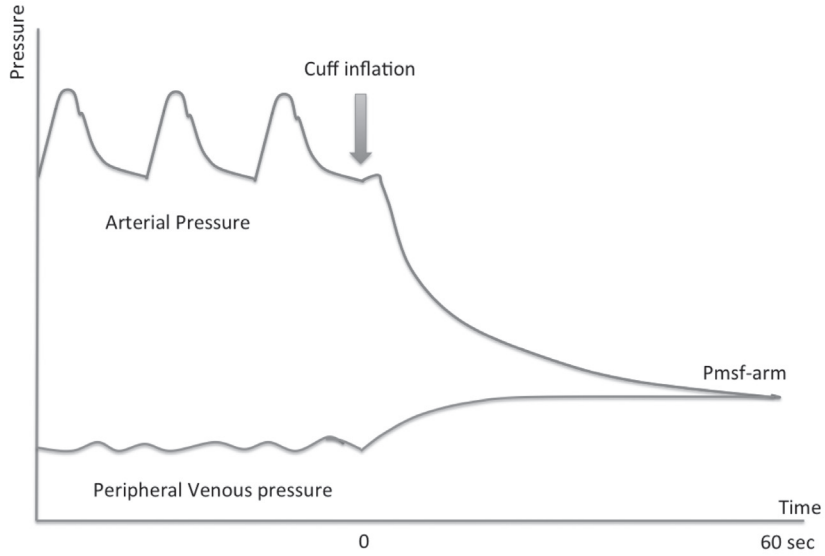
Moderate hypercapnea and hypoxia have little direct non-reflex effect on CO and Pmsf [25]. Severe hypercapnea ($PaCO_2$ to 114 mmHg (15.2 KPa)) caused an increase in Pmsf by 5.5 mmH, whereas a PaO_2 of 34 mmHg (4.5 KPa) caused an increase in Pmsf by 2.5 mmHg [26].

Measurement of Pmsf with Intact Circulation

The Pmsf is not easy to measure in patients with an intact circulation. Schipke *et al*. [27] performed a fibrillation – defibrillation sequence in 82 patients during cardioverter /defibrillator implantation to measuring the Pmsf over 13 seconds. A true equilibrium pressure was not achieved, and the arterial – central venous pressure difference was 13.2 ± 6.2 mm Hg and differences still persisted in sequences of 20 seconds.

Pinsky [28] proposed a model in animals with an intact circulation to construct venous return curves observing the relationship between isovolumetric changes in CO and RAP during intermittent positive pressure recruitment manoeuvres. Pmsf was estimated by calculation of the slope and extrapolation of the RAP value to zero CO. Pmsf calculated were found similar to Pmsf measured during circulatory arrest. Other studies [29-31] have confirmed this linear relationship between VR and CVP and derived Pmsf from the regression equation in animal models with intact circulation. Maas and colleagues [32] applied the same rationale to study the effect of a 12-second inspiratory hold manoeuvre to three different steady-state levels on central venous pressure (CVP) and blood flow (CO) measured via the pulse contour method during the last 3 seconds in mechanically ventilated postoperative cardiac patients. This study showed again a linear relationship between CVP and CO, and importantly, Pmsf could be estimated at bedside in intensive care patients with an intact circulation. Obviously this technique is only feasible in fully sedated patients under mechanical ventilation. Keller and colleagues [33] used this method to assess the changes on venous return with passive leg raising (PLR) manoeuvre: they observed nine postoperative cardiac patients at baseline, during PLR and after volume expansion (500 ml of Hydroxyetil starch). They reported a Pmsf at baseline of 19.7 mmHg. This increased to 22 mmHg after PLR and to 26.9 mmHg after volume expansion (VE). Although CO increased after PLR and VE, the gradient of pressure of venous return (difference between Pmsf and CVP) increased by 2 mmHg after PLR and by 5.8 mmHg after VE. This could explain why a PLR test does not consistently increase CO in fluid responsive patients [34], or even for a fluid challenge, the increased in Pmsf is an essential condition to effectively test the cardiac response.

Figure 4-3: Arterio-venous equilibrium model for measuring Pmsf-arm at bedside with a pneumatic torniquet.



After 60 seconds of occlusion arterial and venous pressure equilibrate

Parkin G. and Wright C.[35] proposed a method for estimating a mean systemic filling pressure analogue (Pmsa) using the mean arterial pressure (MAP), RAP, CO and anthropometric data. Pmsa algorithm is fully described in other publications [36]. In essence, they build a mathematical model to that use patient's data as predictors of Pmsa. The clinical validity of this approach was tested in ten patients in acute renal failure receiving continuous vein-venous hemofiltration [37]. Fluid replacement therapy was electro-mechanically controlled to a target value of Pmsa. This method was also used to analyse haemodynamic changes after a fluid challenge (250 ml of colloids or crystalloids in five minutes) in patients admitted to intensive care [38]: Pmsa increased similarly in responders and non-responders, as expected but interestingly CVP increased more in non-responders, neutralising the changes in the gradient of pressure of venous return as described by Guyton. Recently, Gupta *et al* [39] used Pmsa to investigate the performance of cardiac power (defined as the product of arterial pressure and cardiac output) relative to Pmsa (CP_{vol}). CP_{vol} represents a measurement of cardiac performance adjusted to the vascular tone. According to the authors, values below 0.047 of CP_{vol} have a high sensitivity (97%) and not so high specificity (57.5%) to predict fluid responsiveness.

Anderson [40] proposed a non-invasive technique to measure Pmsf by a rapid occlusion of the circulation in the arm (Pmsf-arm). Once the arterial (Pa) and venous pressures (Pv) in the arm equilibrate, the pressure measured would be Pmsf (Figure 4-3). Maas *et al* [41] compared these three methods in eleven postoperative cardiac surgery patients. Bland-Altman analysis for the difference between Pmsf-arm and Pmsf showed a bias of -1.0 (±3.1) mmHg (p = 0.06) and a coefficient of variation (CV) of 15%. Although there was a statistically non-significant bias, one may think that this is actually quite significant considering the small sample size of this study. Regarding the difference between Pmsf and Pmsa there was a bias of -6.0 (±3.1) mmHg (p< 0.001) and a CV of 17%. The three methods were useful to track changes after volume expansion.

The precision of the Pmsf-arm technique has been recently studied [42]. Four repeated measurements were performed in 20 patients after cardiac surgery. Pa and Pv equalised after 60 seconds of cuff inflation. For a single measurement, the coefficient error (CE) was 5% (± 2%) and the least significant change (LSC) was 14% (± 5%). Averaging two measurements the CE improves to 4% (± 1%), and the LSC was reduced to 10% (± 4%).

Clinical Application of the Venous Tone

Although the measurement of the vascular tone in the venous side of the circulation may have a lot of potential applications, there is still very little evidence about the clinical impact of this information on the management of critically ill patients.

Rangapa *et al* [43] investigated the potential of a computerised decision-support system (Navigator™, Applied Physiology, Sidney, Australia) to improve consistency of haemodynamic evaluation and treatment decisions by intensive care unit clinical staff with different levels of expertise and experience in 20 patients admitted after elective cardiac surgery. The authors concluded that this system improve consistency in decision-making.

Sondergaard *et al*. [44] carried out a small pilot clinical trial in 27 post-operative patients requiring goal-directed therapy to evaluate the efficiency of the Navigator™system in achieving haemodynamic targets (measuring the percentage time in target zone and the averaged standardized distance from the centre of the target (ASD) and time to achieve targets) and the level of concordance between the therapy suggested by the system and an expert clinician. The mean percentage time in the target zone was 36.7% for control and 36.5% for intervention and the ASD was 1.5 in control and 1.6 in intervention (no p value was reported). There was a high level of concordance between decision support

recommendation and anaesthetist action (84.3%). The authors concluded that the treatment recommended by the Navigator system mirrored that of a senior anaesthetist in the achievement of therapeutic goals. Unfortunately, this study is probably underpowered to show differences in the efficiency measurements, fluid balance or vasoactive medications. In addition, it is quite interesting that in both groups the percentage of time in the target zone was so low.

Some interesting studies demonstrated that useful information could be obtained by observing the Pmsf. The current consensus on circulatory shock and heamodynamic monitoring states that even in the context of fluid responsive patients, fluid management should be carefully titrated, especially in the presence of elevated intravascular filling pressures [45]. The similar principle applies to the Pmsf. A fluid challenge can be used to assess fluid responsiveness and also, as spotted by Maas and colleagues [46], to assess systemic compliance. In this study, systemic compliance is reported from fifteen postoperative cardiac surgery patients around 64 mL/mmHg. Systemic venous compliance could be very useful information to prioritise treatment: a high compliance after a fluid challenge may indicate the use of vasoconstrictors instead of infusion of a large amount of fluids. Another study [47] showed that administration of Noradrenaline increased CO in preload responsive patients. Noradrenaline increased Pmsf either by reducing venous compliance or by venoconstriction (reduction of venous capacity and shifting unstressed volume to stressed compartment, see Figure 4-2). Unfortunately, the authors did not assess the effect of noradrenaline on venous compliance. In the rest of patients, Noradrenaline had predominantly an arterial vasoconstrictive effect, increasing cardiac afterload. This study stressed the importance of monitoring venous tone and CO when using vasopressors.

Since venous return equals CO, in practice CO and CVP changes can provide most of the information about the Guytonian view of the circulation. However, without the understanding how the venous tone works, the values of CVP can be confusing. Proof of this is the number of studies that looked at the CVP as a preload index [48]. CVP preforms as the meeting point between Pmsf and cardiac function: a high CVP can be related to a high Pmsf or a low cardiac function or both. Thus, knowing Pmsf would helps clinicians to better understand the haemodynamic status of critically ill patients at bedside.

Conclusion

The venous system plays and important role in the haemodynamic stability. Most of blood volume is stored and regulated in the venous territory. The mean systemic filling pressure can be now measured and it is the pressure of the pivot point of the circulation, where the pressure is independent of blood flow. This pressure is the driving pressure of the circulation and affects, along with the cardiac function, venous return. Three methods have been described to measure Pmsf at bedside, in patients with intact circulation. This variable can be now integrated as another peace of information that helps to understand patient`s conditions and to guide haemodynamic therapy in accordance to patients' physiology.

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5.
How Can We Non-Invasively Assess Oxygen Delivery?

Azriel Perel

The oxygen delivery (DO_2) includes the cardiac output (CO), haemoglobin (Hgb) concentration, the O_2 saturation (SaO_2) and the partial pressure of O_2 (PaO_2). Deterioration in any of these components may lead to a life-threatening situation and death. Therefore many of our therapeutic decisions are aimed at the prevention, early identification or timely improvement of Hypovolaemia, Anaemia and Hypoxemia. At the same time, Fluids, Blood and Oxygen should be considered as drugs that need careful titration, since when administered in excess they may be associated with severe consequences. Newly introduced technologies that extend the capabilities of traditional pulse oximetry allow us to continuously and non-invasively assess the major components of DO_2 and facilitate bedside decision in this complex environment.

O_2 Saturation (SpO_2)

The role of pulse oximetry in clinical anaesthesia and in intensive care has evolved to the point where it is unlikely that we will ever be able to do without it [1]. Routine monitoring of SpO_2 helps identify hypoxemia in the operating room, the post-anaesthesia care unit (PACU) and the ICU. SpO_2 has also been recently suggested to play a role in the definition of ARDS both in paediatric [2] and adult [3] populations. Monitoring SpO_2 on the general ward may be of value for surgical patients who are at risk to develop postoperative respiratory failure [4]. The introduction of a pulse oximetry and respiratory rate-based patient surveillance system (SafetyNet, Masimo) into a general ward resulted in a significant decrease in rescue events and in ICU transfers [5]. And yet we have to remind ourselves that SpO_2 may be misleading in patients that receive supplemental oxygen, and may fail to detect ***ventilatory*** problems such as drug-induced respiratory depression [6]. A more effective mean of ventilatory monitoring, such as capnography or the monitoring of respiratory rate [7], should be used more frequently in all patients who are susceptible to develop respiratory depression.

Oxygen Reserve Index (ORI)

Although the partial pressure of O_2 (PaO_2) does not contribute significantly to DO_2 (except in anemia) it is frequently used to assess oxygenation status during supplemental oxygen administration, where the SpO_2 is no longer informative. This requires blood gas sampling and analysis that is intermittent and delayed. Between invasive sampling, changes in PaO_2 cannot be assessed and therefore unexpected hypoxia or unintended hyperoxia can occur.

The Oxygen Reserve Index (ORI) is a new feature of multiple wavelength pulse oximetry that provides real-time visibility to oxygenation status in moderate hyperoxic range (PaO_2 of approximately 100 to 200 mm Hg). The ORI is an "index" parameter with a unit-less scale between 0.00 and 1.00 that can be trended and has optional alarms to notify clinicians of changes in a patient's oxygen status. The ORI may make pre-oxygenation visible, may provide early warning when oxygenation deteriorates, and may facilitate a more precise setting of the required FiO_2 level.

Hemoglobin (SpHb)

Another major component of the DO_2 is the hemoglobin (Hb) concentration, which can now be measured via the pulse oximeter sensor [8]. The continuous non-invasive measurement of hemoglobin (SpHb) allows a real-time identification of changes in Hb concentration between invasive blood sampling. It may therefore prevent unnecessary transfusions and their associated complication, as well as identify undetected bleeding.

Most clinical practice guidelines recommend restrictive red blood cell (RBC). The rational for a restrictive strategy stems from the recognition of the associated potential complications and the significant cost that is involved. In spite of the recommendations to use restrictive transfusion strategies, it seems that many clinicians still use a more liberal transfusion strategy, often termed the "10/30 rule" (Hb of 10 g/dl, haematocrit of 30%) [9]. There may be a few reasons for this discrepancy. The first one, and probably the most common one, is the fear of severe anaemia especially when further bleeding is anticipated. A more forgiving attitude to blood transfusion in the perioperative period may also be due to the practice of goal-directed therapy (GDT) which advocates maximizing DO_2. For example, in the very recent POM-O study, in which achievement of preoperative DO_2 values in the postoperative phase was attempted in high-risk surgical patients, the number of patients in the GDT group that received blood transfusion intra- and postoperatively was nearly double than the number in the control group [10]. Other reasons for not adhering to a restrictive transfusion

regimen may include the growing perception that transfusion trigger in the individual patient is too complex and important to be guided by a single Hb value alone [11,12].

The introduction of continuous non-invasive SpHb monitoring may be helpful in preventing unnecessary transfusion as it may allow clinicians to more confidently manage patients at lower Hb levels with the knowledge that further drops into a critical anaemic range will become readily apparent [13]. Thus, a stable or a rising SpHb trend may convince the clinician that additional transfusion may be unnecessary, especially when there is a delay in receiving laboratory hemoglobin values [8]. Indeed many decisions to transfuse, especially in the operating room, are not preceded by Hb measurement [9,13]. Adding SpHb monitoring to standard of care blood management resulted in a significant decrease in blood utilization in high blood loss neurosurgery [14] and during elective orthopaedic surgery [13].

Additionally, and of more potential importance, is the ability of a dropping SpHb trend to alert the clinician to the possible presence of undetected bleeding [8,13-15].

Importantly, SpHb monitoring is not yet as accurate as laboratory haemoglobin, and it is therefore not intended today as its replacement. Its value-added benefits should be considered as supplementing intermittent, delayed laboratory values with continuous, real-time visibility of whether Hb is stable, increasing, or decreasing [16]. In addition, the accuracy of SpHb values may be improve by in-vivo adjustment using reference Hb values [17].

Fluid Responsiveness

New pulse oximeter sensors offer a continuous measurement of the Plethysmographic Variation Index (PVI), a measure of the respiratory-induced variations in the plethysmographic waveform, which, in mechanically ventilated patients and under certain conditions, may reflect fluid responsiveness (FR) [18,19]. FR, in turn, is the degree by which the cardiac output (CO) responds to a modification of preload [20,21].

Although the CO is a main determinant of DO_2 it is not measured very often in clinical practice due to issues of availability, invasiveness, cost, inaccuracy, and lack of belief in its value. In addition, a low CO value does not tell us what to do (fluids? inotropes?) nor does the CO predict FR [22]. Hence, to correctly interpret CO we need to combine several variables in order to decide whether CO is adequate and how it can be optimized in the most effective manner [23].

The maximization of CO has been the hallmark of 'classic' perioperative GDT. However, in spite of earlier evidence and appeal of GDT, many recent studies have failed to demonstrate its efficacy [10,24,25]. In a recent review I have pointed out that GDT may have failed to improve outcome because it was based on CO (or stroke volume) maximization only, without taking into account whether the patient is going to respond to fluids ***before*** the actual administration of fluids [26]. Indeed GDT has usually resulted in larger amounts of fluids, usually colloids, being given to the patients receiving GDT [10,24]. This problem has been inadvertently highlighted in a recent observational sub-study of the OPTIMISE trial [24], which included 100 of the 368 patients allocated to the CO–guided hemodynamic therapy algorithm [27]. According to the results of this study, only 28.6% of fluid challenges were associated with increased stroke volume, meaning that more than 70% of fluid challenges were administered to "non-responders". The significance of this report cannot be underestimated.

The use of dynamic parameters, such as the Systolic Pressure Variation (SPV), Pulse Pressure Variation (PPV) and Stroke Volume Variation (SVV), to assess FR in mechanically ventilated patients has become very prevalent in recent years [20]. The PVI is a dynamic parameter that can assess FR through the pulse oximeter sensor in the absence of an arterial line [28,29]. The PVI was shown to be similar to the PPV and SVV in its predictive ability of FR [19,30]. A higher PVI may be a first sign of occult hypovolemia [20,21] and is usually correlated with a greater response of the CO to volume expansion [19,30,31]. The benefit of using the PVI is demonstrated in 3 separate studies, in which intraoperative PVI-guided fluid management resulted in significantly less fluids being administered compared with the control standard therapy group [32-34]. Hence the PVI may prevent unnecessary and potentially damaging fluid overload as low PVI values mean that the patient is most probably not going to respond to fluids.

The PVI has the same limitations as all other dynamic parameters, the main ones being the presence of spontaneous ventilation, arrhythmias, too high or too low tidal volumes, and right heart failure [20]. However, excessive large variations in the plethysmographic waveform during spontaneous ventilation should not be ignored as they may be an important sign of increased respiratory effort. A high PVI value during spontaneous ventilation, termed sPVI, has been recently shown to be a most sensitive sign of upper airway obstruction [35]. Like with all other dynamic parameters, a good predictive ability necessitates a tidal volume of at least 7 ml/kg and will be reduced when lower tidal volumes are employed. In addition, the PVI may be less reliable than PPV and SVV for predicting FR in critically ill patients receiving norepinephrine [36].

Summary

The modern version of the pulse oximeter offers, in addition to SpO_2, new parameters such as the ORI, the SpHb and the PVI, which are all related to DO_2. However, each of these (and all other) parameter that we measure has inherent limitations, confounding factors and inaccuracies. It is only by combining these parameters together that we can make best use of our monitors. The combination of SpO_2 and the newly-introduced ORI allow a better assessment of the oxygenation status. The SpHb can greatly facilitate patient blood management, and yet transfusion decisions should take into account other factors as well. The PVI itself does predict FR and yet FR in and by itself is not an indication for fluid administration. The combination of all these parameters offers us a more holistic understanding of the pathophysiological status, facilitates crucial decisions in a timely manner, and helps prevent severe potential side-effects of our very potent therapies, namely fluids, blood and oxygen.

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6.
Monitoring the Microcirculation in Critically Ill Patients

Nasirul Ekbal & Mervyn Singer

Introduction

The primary role of the circulation is to deliver adequate oxygen to meet tissue metabolic demands [1]. Circulatory shock is a common condition in critical care and represents inadequate cellular oxygen supply (hypoxia), and/or impaired oxygen utilization (dysoxia). This can, if not corrected promptly, progress to organ dysfunction and failure. Early resuscitation regimens targeted toward pre-specified hemodynamic values improved outcomes in patients with severe sepsis or undergoing high-risk surgery [2,3]. This strategy does not however benefit patients in established organ failure [4,5]. Thus, a relatively narrow window of opportunity exists to provide tissues with sufficient oxygen to restore cellular metabolism and prevent/ameliorate further organ dysfunction.

Assessment of the adequacy of oxygen delivery and utilization is therefore key to early identification and intervention. Traditional markers such as urine output, heart rate and blood pressure remain in common use to evaluate tissue hypoperfusion, yet are non-specific and often change belatedly [6]. Newer techniques, while superior, still have limitations. For example, mixed or central venous oxygen saturation reflects the global oxygen supply-demand balance yet may not recognize any local mismatch, particularly in 'canary organs' whose perfusion may be compromised before others [7]. In addition, organs vary in their metabolic activity and the blood flow they receive. Biochemical markers such as lactate, the product of the imbalance between lactate production and metabolism, and arterial base excess are also frequently used as markers of tissue hypoperfusion. While sensitive, these too are somewhat non-specific markers of global tissue hypoxia [8].

Regional Perfusion

Recognition of the limitations of global 'whole body' monitoring has stimulated efforts to develop devices that evaluate regional tissue perfusion and oxygenation. For any monitor of a regional bed, an important consideration is whether it reflects changes occurring in other organs during a systemic insult. Preferably, this should occur concurrently or, ideally, beforehand to provide an early warning system enabling prompt intervention and correction of the problem. This is particularly pertinent when using an accessible site such as mouth (sublingual), bladder, muscle or subcutaneous tissue as a surrogate for deeper 'vital' organs such as liver, brain and kidney.

Key properties of an 'ideal' monitor for organ hypoperfusion

- Provides accurate and reproducible results
- High sensitivity & specificity delivered at an early point
- Easy to use
- Non- or minimally invasive, and causes no harm
- Provides continuous and interpretable data
- Reflects regional data and is also a useful early indicator of systemic hypoperfusion
- Provides information to guide therapeutic interventions

This chapter describes techniques available for real-time monitoring of the microcirculation, defined as vessels with diameters < 100μm (i.e. arterioles, capillaries and venules) tissue perfusion and metabolism, and highlights novel developments that may complement or even supersede current tools.

Microcirculation Measurements

Several techniques can monitor or visualize the microcirculation in situ and are available for patient use.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive optical technique based on passage of near infrared light (700-1000 nm) through biological tissues. By the Beer-Lambert law, the NIRS signal is limited to interrogating small vessels (<1 mm diameter) only. The amount of light recovered after illumination depends on the degree of scattering within the tissue and by the three molecules known to affect NIR light absorption, namely haemoglobin, myoglobin and mitochondrial cytochrome oxidase (COX). Differential absorption patterns depend on whether these chromophobes are oxygen-bound. Pre-defined algorithms generate

concentrations; as the contributions of myoglobin and COX to light attenuation is relatively minor; NIRS predominantly assesses microvascular oxy- and deoxyhaemoglobin. Some specialized machines can generate a COX signal (*q.v.*). 'Tissue O_2 saturation' (StO_2) is calculated from the spectrophotometric quantitation of oxy- and deoxyhaemoglobin. As 70% of blood within skeletal muscle is venous, the resting NIRS signal value mostly represents local venous oxyHb saturation, rather than 'tissue'. It thus reflects both local supply-demand balance and any arteriovenous shunting present.

NIRS-measured parameters may be directly calculated or derived indirectly. Directly calculated measurements use spatially resolved spectroscopy to determine absolute ratios of oxy-Hb and deoxy-Hb. This technique is most commonly used in cerebral oximetry systems. Cerebral activity leads to an increase in blood flow and leads to a change in the local oxy-Hb and deoxy-Hb. Brain StO_2 monitoring has been successfully applied in neonates [9] and animal models [10], but is more challenging in adults due to interference from scalp blood flow [11]. The thenar eminence, a superficial muscle of the hand with little interference from overlying fat and subcutaneous tissue, is the main site used for muscle StO_2 monitoring, as arterfact from oedema or adipose tissue provide measurement in even obese and critically ill patients [12]. However, an issue with thenar muscle monitoring is the wide range (52-98%) found in healthy subjects [13]. A further study has shown that a low StO_2 within 1 hour of admission identifies trauma patients requiring blood transfusion within the subsequent 24 hours [14]. NIRS values are also affected by age, body mass index, gender, race and smoking [15,16]. As changes in StO_2 reflect changes in flow and/or metabolism, a proportional change may leave StO_2 unaltered. This may explain why absolute values fell outside the normal range in severely shocked trauma patients [13] and in septic shock, only when oxygen delivery fell markedly [17,18]. More recently, changes in cerebral tissue oxygen saturation, detected by NIRS, have shown to correlate with physiological changes in cerebral oxygen delivery [19]. However, sufficient reliability at the single subject level remains to be elucidated and further research is required to ensure sufficient reproducibility [20].

Measures calculated indirectly are obtained from interventions to alter the circulation in the tissue being assessed. This is performed using arterial and/or venous occlusion, commonly known as the vascular occlusion test (VOT). By occluding blood flow, NIRS can assess dynamic changes in the rate of oxy-Hb and deoxy-Hb, with complex physical models allowing calculation of regional tissue oxygen saturation, oxygen consumption and blood flow. The rate of fall of StO_2, rate of reperfusion together with reactive hyperaemia following arterial and/or venous occlusion is decreased in shocked compared with non-shocked septic patients, or healthy volunteers [21]. The StO_2 recovery slope seen on reperfusion evaluates both the limb's oxygen content and the capacity to recruit

arterioles and venules ('microvascular reserve'). The slope may be altered by different pathologies or therapeutic interventions. In sepsis, the alterations seen suggest both microcirculatory dysfunction and impaired utilization of oxygen (mitochondrial dysfunction ± reduced metabolism) [22, 23]. More recent studies continue to show the discriminatory value of dynamic NIRS parameters, slower reperfusion rates were seen in trauma patients showed slower reperfusion rates compared to controls [24] and also predicted increased cardiac troponin levels in patients admitted with severe post-partum haemorrhage [25].

Laser Doppler flowmetry

Laser Doppler flowmetry (LDF) utilizes wavelengths of visible and infrared light to measure tissue perfusion by exploiting changes in wavelength frequency (Doppler shifts) that moving erythrocytes impart to light. The chosen wavelength is usually 780nm as this is near the isobestic point (800nm) where the absorption spectra of oxy- and deoxyhaemoglobin intersect; changes in blood oxygenation have little effect on measurement. Laser light is delivered fibreoptically and diffusely scattered by stationary tissue, with some being reflected back with no change in wavelength. However, photons that encounter moving red blood cells experience a Doppler shift, which is also detected. This signal is dependent on the flow of blood and represents red cell velocity through the microvasculature [26].

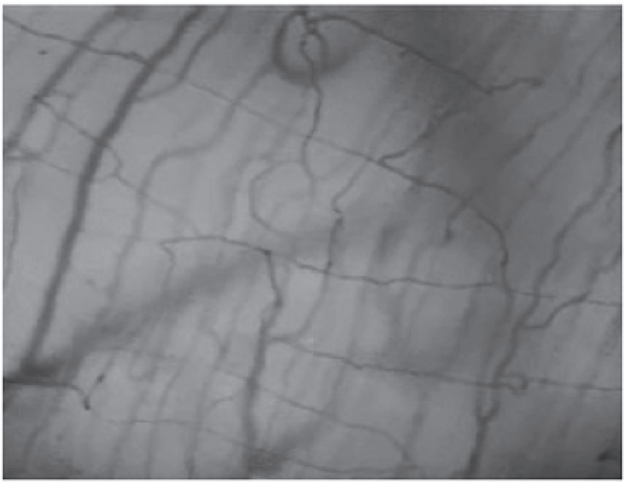
In porcine haemorrhagic shock, changes in skin LDF flux occurred earlier than heart rate, blood pressure, arterial lactate or base deficit [27]. After abdominal surgery or endotoxin administration, no effect was seen in intestinal microcirculation despite fluid resuscitation and norepinephrine to restore blood pressure and regional blood flow to baseline levels or above [28, 29]. By contrast, titrating norepinephrine to obtain a mean arterial pressure of 90 mmHg in patients with established septic shock significantly increased red cell flux to deltoid muscle [30].

LDF monitoring has several drawbacks. Outputs are obtained as arbitrary perfusion units and not absolute blood flow, thus only trends can be assessed. The result is a net vector flow in line with the direction of the incoming Doppler-shifted signal. As this signal may contain components from blood flowing through multiple vessels at varying angles to the probe, results may vary considerably. This may also be seen in tissues with a heterogeneous microcirculation. It is thus important to fix the probe in position, or to use a multi-fibre array to increase the surface area being captured.

Microvideoscopic techniques

Historically, intra-vital microscopy was considered the gold standard for microcirculation imaging. However, this is restricted to trans-illuminable tissues such as the nailfold bed, or requires specific dyes not licensed for human use. Videomicroscopic imaging devices such as sidestream dark-field (SDF) imaging have supplanted intra-vital microscopy as a clinical tool to visualize the microcirculation [31, 32]. Light is reflected by superficial tissue layers but absorbed by haemoglobin contained within erythrocytes. A 530 nm wavelength is usually chosen as this corresponds to another isobestic point in the absorption spectra of deoxy- and oxyhaemoglobin. Absorbed light is reflected back, allowing erythrocytes to be viewed as grey/black bodies moving against a white background (Figure 6-1). Tissue perfusion can be characterized in individual vessels, or averaged over an area within the device's field of vision. Studies have mainly focussed upon the sublingual circulation, though brain, eye and digestive tract have also been assessed in patient studies [33,34]. The microcirculation cannot be monitored continuously with SDF, though repeated images are generally obtainable and fairly reproducible. Recorded video-clips are measured offline using software that provides a semi-quantitative analysis. SDF is operator-dependent, so adequate training is needed to ensure that image acquisition is satisfactory and video-clips objectively analysed. A recent study found a third of recordings by a trained investigator were technically excellent whereas a further third showed pressure artefact from the probe on the tissue surface [35]. Design improvements may overcome such issues [36].

Figure 6-1: SDF image of the rat microcirculation



Notwithstanding these caveats, interesting data have been generated during surgery, in shocked patients and animal models. The sickest septic patients presenting to an emergency department had the greatest sublingual microcirculatory abnormalities which prognosticated for eventual outcome [37]. In a follow-up study investigating early goal-directed therapy resuscitation, an association was seen between microcirculatory improvement and better outcomes [38]. Of note, these data may have been confounded by greater norepinephrine use in poor outcome patients. In other human septic shock studies, no change in pre-existing sublingual microvascular flow abnormalities was seen with norepinephrine, though considerable inter-individual variation was reported [30, 39]. Hypoperfusion and increased flow heterogeneity (rather than the expected hyperdynamic flow pattern) are the main characteristics of the sublingual microcirculation in patients with established septic shock [40]. Similar changes were seen in a cardiogenic shock model though the cerebral microcirculation remained unaffected [41]. Differences were also seen between sublingual and intestinal microcirculations in septic patients [42]. Nitroglycerin in septic patients and fluid loading plus dopexamine in high-risk surgical patients improved microcirculatory flow yet no outcome benefit was forthcoming [43, 44]. The precise role of microcirculatory manipulations in affecting mortality and morbidity thus remains to be elucidated.

Summary

Alterations in oxygen transport and utilization are integral to the development of multiple organ failure. Therefore the ultimate goal of resuscitation in circulatory shock is to restore effective tissue oxygenation and cellular metabolism. Haemodynamic monitoring is currently the cornerstone of management and some prospective randomized trials have confirmed outcome benefit when pre-emptive or early treatment is directed towards maintaining or restoring adequate tissue perfusion. However, treatment end-points remain controversial, in large part due to current difficulties in determining what constitutes 'optimal'. Advances in technology are providing promising non- or minimally-invasive techniques. These however require initial validation to ensure reliability and to gain the necessary confidence that they can be used as surrogates reflecting or, better still, preceding changes in deeper, more vital organs. On satisfactory demonstration of the above, randomized controlled trials can assess their impact upon outcomes and this must occur before potential implementation into management guidelines.

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7.
Remote Ischaemic Conditioning. What We Know So Far.

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Definition

Remote ischaemic conditioning (RIC) refers to an endogenous occurrence in which repetitions of transitory non-lethal ischaemia applied to an organ provides a protective mechanism against ischaemic-reperfusion injury (IRI) to a distant organ [1,2].

From Coronary Arteries to a Broader Understanding of a Generalizable Phenomenon.

In 1986, Murray *et al* [3] utilised a canine model to apply 4 cycles of 5-minute intervals of coronary artery ischaemia alternating with 5 minutes of reperfusion, prior to applying a prolonged period of ischaemia,via the same coronary artery. They found that ischaemic preconditioning significantly reduced the extent of myocardial infarction. In 1993 Przyklenk *et al* [4] showed that ischaemic preconditioning could be applied to a branch of the coronary arteriesseparate from the one that was subsequently occluded, whilst still producing significant reductions in the volume of myocardial infarction. They postulated the concept of intra-myocardial protection secondary to a regional signalling pathway and hence the emergence of the concept of RIC. Whilst revolutionary, the research had limited clinical applicability in view of its invasive nature.

Since then, a number of preclinical studies have evaluated the protective effect of RIC on the ischaemic heart [5,6]. Several tissues and organs have been targeted as remote ischaemic stimuli, including limbs, mesenteric arteries and the infra-renal aorta,all providing a similar protective effect on prolonged ischaemia and reperfusion-exposed myocardium [7-10]. Controversial results in terms of cardio-protection have been noted using the brain as RIC stimulus [11, 12].

While the role of RIC was initially targeted at myocardial protection, our increasing knowledge on the phenomenon suggests that ischaemic conditioning has a more systemic and widespread effect, with studies revealing potential

benefits in a number of organs including the brain [13], kidneys and lung [14].. It is this ubiquitous nature of RIC that diverts our attention to its applicability in the systemic inflammatory response and to the patient with multi-organ dysfunction.

The use of remote ischaemic pre-conditioning and post-conditioning have both been utilised in preclinical studies, similarly showing significant improvements in the ischaemic reperfusion injury in the target organ(s), as long as 24 hours after the initial insult. This is of particular relevance and importance since most injurious events are unpredictable and the clinical applicability of post-conditioning will be limited. More preclinical data is required to elucidate when the optimal application of remote ischaemic post-conditioning (RIP) to obtain significant benefits and to delineate how long the protective effect lasts.

Over a decade later, the first clinical RIC study waspublished, when Guanydin *et al*. [15] applied RIC to the right upper limb of 8 male patients prior to undergoing coronary artery bypass grafting (CABG).The results confirmed an enhanced anaerobic glycolysis in the RIC group versus control, which they suggested was responsible for the observed myocardial protection in the interventional arm.

In the following years, several human studies have tested RIC in the context of elective coronary artery bypass grafting, elucidating no clear benefits in terms of myocardial infarct size reduction, decreased troponin I release or reduced mortality [16-19]. This discrepancy in observed benefit may be due to a number of study-related limitations including small sample groups, different techniques of RIC application and different anaesthetic techniques, specifically the use of volatile agents as compared with total intravenous anaesthesia. Kottenberg *et al*. have [20] recently evaluated the application RIC in CABG patients expressly comparing the use volatile anaesthetics with intravenous propofol, showing that in the propofol group the protective effect of RIC was abolished. Further investigation into the effects of anaesthetic technique on the benefits RIC is warranted.

Three Main Mechanisms have been Proposed to Explain the Effects of RIC

There are three prevalent theories employed to explain the mechanisms underlying RIC: neuronal, humoral and systemic response.

The neuronal pathway

The use of hexamethonium, a nicotinic receptor antagonist acting on preganglionic parasympathetic and sympathetic receptors, has been shows to obliterate the beneficial effects of RIC. This, in contrast to local ischaemic conditioning suggesting that the autonomic system is only involved in the propagation of protection from one organ to another, and that a separate pathway is responsible for loco-regional protection [6].

In the RIC organ, an increase in Calcitonin Gene-Related Peptide-Like Immunoreactivity (CGRP-LI) has been demonstrated [7]. Although the mechanism by which this confers protection is not clearly understood, it has been suggested that the increase in CGRP-LI would stimulate capsaicin-sensitive sensory nerves to release nitric oxide *(NO)* initiating a protective pathway.

Adenosine production is increased in ischaemia/inflammation and has been implicated in the activation of an afferent neuronal signalling pathway in the RIC organ, as the use of an adenosine receptor blocker would abolish the protective effect of RIC in the target organ [21]. Furthermore, adenosine is thought to regulate local perfusion through vasodilatation via A1 and A2a receptors in the target organ, providing more tolerance to an ischaemic stimulus.

The humoral pathway

Several substances and their receptors have been studied:
The application of RIC has been associated with a decrease in tachy-arrhythmias in myocardial ischaemia. Noradrenaline and prostacyclin levels increase in response to the application of ischaemic conditioning, irrespective of location. Administering reserpine, a vesicular monoamine transporter inhibitor resulting in catecholamine depletion, partially eliminated the antiarrhythmic benefits of RIC, suggesting that the release of noradrenaline prior to an ischaemic event conferred protection, although the underlying mechanism is still not well delineated [22].

It has been shown that activation of K-ATP channels in the inner mitochondrial membrane of target organ cells during RIC, optimises myocardial energy consumption and maintains a physiological pH during the ischaemic event [9].

It has also been demonstrated that activation of NO-synthase and NO production is increased during RIC, intimating that NO confers protection to the target organ by enhancing microcirculatory blood flow and reducing cell membrane damage secondary to the ischaemic insult [23].

Activation of protein kinase C (PKC) in the target organ is implicated as being a common part of the signalling transduction pathway involved in ischaemic conditioning [10].

The mitochondrial permeability transition pore (MPTP) is thought to be associated with cardiac necrosis, and a reduction of its activation by the increase in endogenous opiods through K-opiod receptor activation is thought to be an integral pathway explaining the protective benefits of RIC [24, 25]. Δ1-opioid receptor activation has been shown to be involved in myocardial protection, as its inhibition minimises the RIC protection effect. The signalling pathway of opioids is, at present, not clearly defined. One of the postulated mechanisms is through the generation of free radicals, which are shown to impart myocardial protection in RIC [26].

Cannabinoid receptor n.2 activation via the production of endogenous cannabinoids such as arachidonoylethanolamide (anandamide) and sn-2 arachidonoylglycerol has been demonstrated in ischaemic conditioning. The myocardial protective effect of endogenous cannabinoids is putatively exerted via the activation of the above receptor and its two G-protein coupled subunits [27].

It has been shown that the inhibition of mitogen-activated protein kinases (MAPKs) negates the cardio-protective benefit of RIC. The activation of MAPKs during RIC increased the phosphorylation of extracellular signal-regulated kinases (ERK-1, ERK-2) and jun n-terminal kinase (JNK-1), whilst reducing that of p38 in the RIC organ. This was not demonstrated in the target organ. The underlying mechanism is not yet understood [28].

HIF-P4H3 (*Hypoxia Inducible Factor*) inhibition has been noted to enhance RIC myocardial protection. It has been suggested that it could trigger a transduction pathway involving activation of NF-kB (*Nuclear Factor kappa-light-chain-enhancer of activated B cells*) [29].

Several efforts have been made in an attempt to detect the humoral molecules responsible for cardio-protection via proteomic analysis of RIC patients' blood samples. Although Shimizu at [30] in 2009 postulated that in vivo transient limb ischaemia releases a low-molecular-mass (<15 kDa) hydrophobic circulating factor(s) which induce(s) a potent protection against myocardial ischaemia-reperfusion injury, in Langendorff-perfused hearts and isolated cardiomyocytes of the same species, no clear > 8kDa protein has been detected so far [31].

The systemic inflammatory response syndrome (SIRS).

Contemporary research indicates that the systemic inflammatory response consists of unbridled pro-inflammatory and anti-inflammatory response mechanisms that most likely coexist. The inflammatory response is initiated by the body's recognition of abnormal self or exogenous material in the form of Damage-Associated Molecular Pattern molecules (DAMPs) and Pathogen-Associated Molecular Pattern molecules (PAMPs). Toll-like receptors (TLRs)

are cell-surface receptors that, when stimulated by DAMPs/PAMPs, trigger an intracellular avalanche of reactions, activating the MAP-kinase and NF-kB-signalling cascades via MyD88, and resulting in gene transcription and cytokine release, such as tumour necrosis factor α (TNFα), interleukins 1 and 6 (IL-1, IL-6) [32]. Increased presence of adhesive molecules and chemotactic factors causes the aggregation of leukocytes, increasing turbidity and reducing flow. Nitric oxide, the concentration of which is also significantly heightened during inflammation, results in vasodilatation causing further reduction in flow and increasing vascular permeability.Tissue dysoxia is the end-result of numerous complex and interdependent mechanisms, including microcirculatory dysfunction, an increase in interstitial fluid and shunting; but also, and notably, due mitochondrial dysfunction [33].

RIC has been shown to:

- Reduce the TNFα production and selectin exposure resulting in less PMN infiltration and endothelial damage [34-36].
- Increase the expression of anti-inflammatory genes (Hodhsc, Prdx4, Febp4, Hsp73), and decrease the expression of pro-inflammatory genes Egr-1 Dusp-1 and Dusp-6 [37]. This modulation of gene expression determines the reduction in tissue damage and endothelial permeability.
- Reduce the myeloperoxidase activity, IL-1β and CXC ligand 8 production in leukocytes via activation of Cannabinoid receptor n.2 [38].
- Scavenge free radicals and reduce endothelial adhesion molecules via haemoxygenase activation; reduction in TGF-β1 production [39].
- Increase recruitment of haemopoietic stem cells and homing of mesenchimal stem cells [40].
- Enhance anaerobic glycolysis, preserving the function of the endothelium via reduction of pro-inflammatory protein release, decreasing leukocyte chemotaxis, adhesion and exocytosis [15, 17,41].

The Roads Converge: RIC Shares Sepsis Pathophysiology

Sepsis is a systemic inflammatory response in the presence of an infective aetiological agent. This, in turn, determines microvascular injury, increased clotting risks, reduced perfusion of organs and, when severe, multi-organ failure [42].

In 1999, Mendez C *et al*. [43] showed that inducing a sub-lethal haemorrhage 24 hours prior to the administration of lipopolysaccharide (LPS), caused reduction of TNFα levels, reduced vascular lung injury and reduced overall mortality as compared with a control group. The mechanism proposed was similar to the one

suggested for RIC: ischaemic-reperfusion injury resulted in relative tolerance to the ensuing septic shock.

Recently, some researchers have applied the model of RIC to septic shock demonstrating, in animal models, that RIC cycles decrease macrophages infiltration, reduce the inflammatory response and the PMN infiltration, and improve renal function [35, 44]. Even though the instigating stimulus is different, these results preliminarily suggest that RICand sepsis share some of their pathophysiological mechanisms.

In an *injurious occurrence*:
a host local response is set in play including:

- pro-inflammatory cytokines,
- WBC activation,
- endothelial damage driven by the injurious agent or by leukocyte,
- increased adhesion and ROS production by leukocytes,
- tissue dysoxia;
- a systemic inflammatory response is mounted and the process may spread to other organs;
- the process evolves into resolution of the infection or to Multi Organ Failure.

In *RIC*, the same response is down-regulated:

- a host local response is set in play including:
- vasodilating factors,
- anti-inflammatory cytokines,
- reduced WBC activation;
- a systemic conditioning response is mounted: an anti-inflammatory tendency is established;
- the anti-inflammatory status eventually dissipates.

Whilst still in its youthful stages and its clinical relevance at present seems elusive, the application of RIC in the patient presenting with SIRS is an arena that shows promise for future research.

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8.
Postoperative Delirium: Review of Current Evidence

Suraj Yalamuri and Charles Brudney

Introduction

Central nervous system (CNS) complications after surgery are a major source of morbidity and mortality. With an average reported incidence of 36.8%, postoperative delirium is a complicated process that increases patient mortality, hospital length of stay, health care cost, and increases risk of long-term cognitive decline [1,2]. A recent systematic review showed a wide range in the incidence of delirium (10-89%) with specific at-risk populations: ICU patients (41%) and post-surgical elderly patients (89%) [3]. In the United States, the cost of delirium is estimated to be $38 - $152 billion [4]. Therefore, understanding the pathophysiology of postoperative delirium and identifying treatment strategies has the potential to significantly improve patient outcome while reducing resource utilization and healthcare cost.

The Diagnostic and Statistical Manual of Psychiatric Disorders (DMS-IV) defines delirium as a clinical diagnosis with an altered state of consciousness, change in cognition, and an acute fluctuating time course. There are three main subtypes: hyperactive (25%), hypoactive (50%), and mixed (25%). The hypoactive subtype is routinely missed and is associated with a higher mortality rate [5]. The majority of studies define postoperative delirium as occurring between 24-72 hours after surgery [1]. The Confusion Assessment Method (CAM) is the most often used diagnostic method with a reported sensitivity and specificity of 94% and 89% respectively [1-6]. While there are several risk prediction models for postoperative delirium, predictors most often used in the 37 identified models included age [20], preoperative Mini-Mental State Examination score [10], and preoperative increased alcohol use [7,6]. There is no direct evidence that current pharmacological and non-pharmacological treatments improve patient outcomes for those at higher risk of delirium as predicted by risk prediction models [3]. Additionally, the lack of standardization in the frequency of screening for delirium also accounts for the variability in outcomes [7]; however, early diagnosis and treatment of modifiable factors with current therapies do help patients recover from postoperative delirium [8].

Etiology

The multiple risk factors for postoperative delirium can be categorized according to the timing of the perioperative period [8]. Preoperatively, age >70, malnutrition (low serum albumin and dehydration), alcohol and drug abuse all carried an odds ratio of 3.3 of developing postoperative delirium. Pre-existing cognitive impairment, such as dementia and psychiatric disorders, had an odds ratio of 4.2. Other risk factors were decreased functional status (2.5) and electrolyte abnormalities (3.4) [9]. Another risk factor is type of surgery: orthopedic, abdominal aortic aneurysm repair, and cardiothoracic procedures have an increased odds ratio as high as 8.3 [10]. Risk factors intraoperatively include hypothermia, hypotension, and hypoxia [8]. Risk of developing postoperative delirium is 40% vs 19% with maintaining an increased depth of anesthesia as measured by BIS scores [11,12]. Postoperatively, the greatest risk factors were persistent hypercarbia and hypoxia (17.2%) and an increased hospital length of stay (14%) [10,13]. Benzodiazepine use is pervasive in the perioperative period and its use in the elderly population contributes to delirium in a significant manner. Each additional 1 mg of midazolam carries with it a 7% risk of developing delirium [13].

While some of the above risk factors are modifiable, the molecular basis of postoperative delirium is an area of ongoing research. Most of the models have a similar theme: a susceptible patient who endures an acute neurological insult. This leads to alterations in the levels of neurotransmitters or inflammatory mediators that lead to delirium. There are several implicated markers with the most common being gamma aminobutyric acid (GABA), dopamine, acetylcholine, inflammatory makers such as CRP, cortisol, and a multitude of interleukins (IL-6, IL-8, IL-10) [1]. In the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial, McGrane *et al* found a trend toward higher CRP in 87 post-surgical and ICU patients who developed postoperative delirium [14]. Patients who develop delirium after undergoing coronary artery bypass grafting have been found to have elevated cortisol levels and higher IL-6 levels. The same patient population also showed a correlation between lower intraoperative BIS scores and higher cortisol levels [15]. Cortisol has been found to mediate cognitive function through the glucocorticoid receptors in the hippocampus and frontal cortex.

Another area of interest is exploring the association between preexisting dementia and the risk of postoperative delirium. Patients with the epsilon 4 allele of apolipoprotein E (apoE4) are thought to be at a higher risk of developing delirium as it is also a risk factor for the development of Alzheimer's disease [1]. However, the evidence for this is equivocal: a study of 250 patients in the PACU showed no association between those with apoE4 and delirious patients whereas

Leung and van Munster suggested this to be a risk factor [16]. Comprehensively, the studies on delirium show the process to be multifactorial. While the definitive pathways of delirium are still being explored, there are proven treatment strategies to both treat and minimize patient risk.

Treatment

Since delirium has a complex pathophysiology, treatment should also be multimodal. Moreover, postoperative delirium presents in the context of other acute medical problems that also require treatment. Therefore, management demands thoughtful consideration and effective use of both pharmacologic and non-pharmacologic treatments. A recent systematic review and meta-analysis by Zhang *et al* found three beneficial interventions: 1) In patients requiring sedation, dexmedetomidine produced less delirium when compared to propofol, midazolam, or morphine; 2) both typical and atypical antipsychotics decreased delirium occurrence when compared to placebos; 3) multicomponent interventions (geriatrics consultation, patient specific non-pharmacologic interventions, and targeted education for staff managing patient's with delirium) were effective in preventing delirium [2].

Non-pharmacologic interventions

The mainstay of non-pharmacologic interventions is identifying the at-risk patient and intervening prior to the development of delirium. In patients undergoing orthopedic surgery, Marcantonio *et al* showed that early consultation with the geriatrics service and making patient targeted recommendations reduced the incidence and duration of delirium [17]. In addition, the number of patients with severe delirium was also reduced (11.3% vs 28.1%). This same benefit has been shown by other studies [4, 5, 18]. One area of interest is the restoration of sleep-wake cycle. Patients treated with diazepam/flunitrazepam/pethidine (DFP) had a lower incidence of delirium (5% vs 35%) [19]. Moreover, Taguchi and Ono both showed that patients exposed to bright light for 2 hours day during postoperative days 2-5 after thoracic surgery had a reduced incidence of severe delirium [20, 21]. While both studies showed a trend toward lower rates of delirium, none reached significance. Zhang *et al* performed a power regression and showed that the study was underpowered to detect the difference seen [2]. Cognitive stimulating activities, patient and staff education, and even music therapy have all shown a trend toward benefit, but most of these studies were small and underpowered [2]. While non-pharmacologic interventions alone might not be the answer, they should be incorporated into the comprehensive care plan when caring for a delirious patient.

Sedation

Dexmedetomidine is an alpha-2 agonist that is advantageous for sedation due to its lack of GABA mediation. This results in less cognitive impairment as its site of action is in the brainstem and not the cortex. In a 2009 study, cardiovascular patients requiring sedation in the ICU were randomized to dexmedetomidine vs propofol vs midazolam. Those receiving dexmedetomidine for sedation had both lower incidence of (10% vs 44% propofol/42.5% midazolam) and shorter duration of delirium (2d vs 3d propofol/ >5 days midazolam) [22]. In this case, sedation with a benzodiazepine not only increased the incidence of delirium, it also significantly lengthened the duration of delirium. Another set of commonly used sedative drugs in the ICU are opioids. Shehabi *et al* showed that patients after cardiac surgeries who were sedated with dexmedetomidine had lower rates of delirium (8.6%) compared to those sedated with morphine (15%). And similar to benzodiazepines, they also had a longer duration of delirium (2d vs 5d) [23].

Antipsychotics

The mainstay of pharmacologic treatment for delirium has been with antipsychotic medication. Kaneko and Wang have shown that haloperidol up to 5mg during POD 1-5 resulted in reducing the incidence of delirium [24, 25]. Interestingly, 0.5mg of haloperidol three times per day given for 3 days before the surgery did not reduce the incidence of postoperative delirium, but did reduce the severity and duration in those who developed delirium (5.4d vs 11.85d) [26]. The newer atypical antipsychotics are of interest due to their decreased extrapyramidal side effects. Atypical antipsychotics such as olanzapine, risperidone and quetiapine have been shown to reduce the rate, duration, and severity of delirium [27-29]. Antipsychotics should be included in the multicomponent intervention model of treating delirium and this is supported by the National Institute of Health guidelines [2].

Summary

Postoperative delirium is a complication with significant morbidity and mortality. In addition to increasing hospital length of stay and healthcare costs, delirium is associated with prolonged cognitive dysfunction and need for patient recovery in skilled nursing facilities. The wide range of incidence suggests that all the risk factors for developing delirium have not yet been elucidated. Elderly postsurgical patients with multiple medical comorbidities are at an increased risk of developing delirium. The pathophysiology of the disease state is currently under active investigation, but current evidence points to changes in neurotransmitters and neuroinflammatory mediators. Studies have shown an association between patients with pre-existing dementia and a higher risk of postoperative delirium.

Perioperative recognition of modifiable risk factors and treatment with both pharmacologic and non-pharmacologic methods provide the greatest benefit. Early geriatric consultations along with patient specific non-pharmacologic interventions are effective means of reducing the risk of developing delirium. The mainstay of pharmacologic therapy is currently haloperidol, although recent studies have shown atypical antipsychotics (with a lower side-effect profile) are equally effective. In patients requiring sedation, dexmedetomidine is associated with lower risk of delirium when compared with benzodiazepines or opioids. Benzodiazepines are particularly harmful with each dose carrying an incremental risk of developing delirium. It is important to recognize that treatment of delirium needs to be in the context of the patient's other medical problems including both acute and chronic and that treatment needs to incorporate a multi-modal approach.

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9.
Novel Biomarkers of Acute Kidney Injury – Ready for Clinical Practice?

Marlies Ostermann

Introduction

Acute kidney injury (AKI) is a syndrome which affects 13-18% of patients admitted to hospital. [1] It is particularly common in the elderly population and in patients in the Intensive Care Unit (ICU). The diagnosis is based on an acute rise in serum creatinine, fall in urine output or both. [2] Although serum creatinine and urine output are easily available at little cost, they are neither renal specific nor fully diagnostic or prognostic. [3] The main limitations are that serum creatinine can be affected by muscle mass, may change in response to drugs without an actual change in renal function (for instance after trimethoprim) and is not reliable in patients with liver disease. In addition, it provides no information about the underlying cause of AKI and may take 24-36 hours to rise after a definite renal insult. Similarly, urine output may persist until renal function almost completely ceases, can be manipulated by diuretics and may be appropriately reduced in case of hypovolaemia.

There is general consensus that better markers of renal function are needed to improve identification of patients at risk of AKI, allow earlier detection of AKI and to improve differential diagnosis and prognostication. [4] The hope is that with such an approach and earlier interventions, the outcome of patients with AKI can be improved.

Numerous novel biomarkers have been identified in serum and urine in different experimental and clinical settings. [4, 5] They are renal and non-renal derived molecules, which vary in their origin, physiologic function and time of release after renal injury and can be broadly divided into different types:

- Markers of glomerular function: small molecular weight proteins that are present in the systemic circulation and undergo glomerular filtration.
- Markers of tubular function: molecules that are usually reabsorbed by tubular cells.

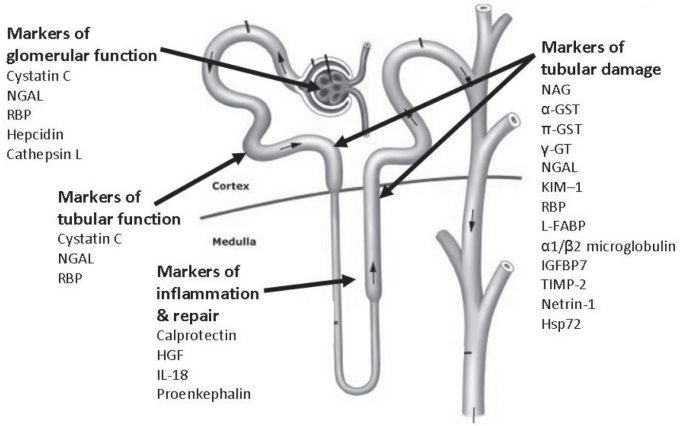
- Markers of tubular damage or repair: molecules that are released following tubular cell damage or gene up-regulation.
- Markers of inflammation: inflammatory mediators released by renal cells or infiltrating inflammatory cells in response to activation of inflammatory processes.

Different Biomarkers Evaluated in Clinical Trials

The most-studied biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, Kidney Injury Molecule 1 (KIM-1) and Interleukin (IL) 18. [7-20] The majority of studies have focussed on the ability of novel biomarkers to diagnose AKI before a detectable serum creatinine rise or to prognosticate an outcome, for instance need for renal replacement therapy (RRT) or mortality.

Most studies were conducted in well-defined settings where the timing of renal injury was known, i.e. after cardiopulmonary bypass surgery, coronary angiography or following organ transplantation. Furthermore, a large number of studies were undertaken in children where comorbidities such as chronic kidney disease (CKD), diabetes mellitus, chronic inflammatory diseases and malignancies are usually absent. As a result, not all studies can be easily generalised to adult critically ill patients in the emergency department (ED) or ICU where the exact onset of AKI is usually not known and important confounding factors are present.

Figure 9-1: Novel AKI Biomarkers



Abbreviations: AKI = acute kidney injury; GST =glutathione S-transferase; γ-GT = γ-glutamyl transpeptidase; NGAL = Neutrophil gelatinase-associated lipocalin; NAG = N-acetyl-β-D-glucosaminidase; KIM-1 = Kidney Injury Molecule-1; IL-18 = Interleukin 18; RBP = retinol binding protein; L-FABP = Liver-type fatty acid-binding protein; IGFBP7 = Insulin-like growth factor binding protein-7; TIMP-2 = tissue metalloproteinase-2; HGF = hepatocyte growth factor; Hsp = heat shock protein

Overall, the performance of different urinary and plasma biomarkers for AKI has been variable with an area under the receiver operating characteristics curve (AUC) between 0.3 – 1.0. [21] Studies with higher AUC values often included homogenous populations with a well-defined single renal insult. In more heterogenous populations including critically ill patients in the ICU or ED where the onset of renal injury is very variable, biomarkers tend to perform less well.

Early Diagnosis of AKI

The most common comorbidities associated with AKI are older age, hypertension, CKD, congestive heart failure, diabetes, chronic proteinuria and vascular disease. The most common high-risk exposures include sepsis, nephrotoxic drugs, hypotension and cardiopulmonary bypass surgery. Following a definite renal injury, serum creatinine rise lags 24-36 hours and a period of "subclinical AKI" can remain unrecognised. Many investigations have focussed on the role of biomarkers to diagnose AKI before a detectable serum creatinine rise in different clinical settings.

In the emergency department

The identification of patients with AKI at a time when serum creatinine is still in the normal range may be potentially be useful in patients presenting to the ED. However, existing data are conflicting. A study in ED patients with suspected sepsis showed that a plasma NGAL (pNGAL) level >150ng/ml had a sensitivity of 81% for predicting AKI but specificity was only 51% [15]. A different study in 635 patients admitted to hospital from the ED concluded that a single measurement of urinary NGAL (uNGAL) helped to distinguish AKI from normal renal function, pre-renal azotemia and CKD. In addition, it was predictive of the need for RRT and admission to ICU [20]. However, the mean serum creatinine of those with AKI was already elevated at 495 μmol/L (SD 486) at time of presentation in the ED. In contrast, a multicentre study in 665 ED patients admitted to hospital showed that serial pNGAL results in combination with clinical judgement improved the prediction of development of AKI [22].

Results of further studies are awaited before novel AKI biomarkers can be routinely adopted in the emergency setting.

Table 9-1: Most modern biomarkers from human studies (modified from reference 4)

AKI biomarker	Characteristics and site of origin	Renal handling	
Alanine aminopeptidase (AAP) **Alkaline phosphatase (ALP)** **γ-glutamyl transpeptidase (γ-GT)**	enzymes located on the brush border villi of the proximal tubular cells	released into urine after tubular injury	
Cystatin C	13 kDa cysteine protease inhibitor produced by nucleated human cells and released into plasma	freely filtered in glomeruli and completely reabsorbed by proximal tubular cells	
α glutathione S-transferase (α GST)	47-51 kDa cytoplasmic enzyme produced in proximal tubule	limited glomerular filtration; released into urine following tubular injury	
π glutathione S-transferase (π GST)	47-51 kDa cytoplasmic enzyme produced in distal tubules	limited glomerular filtration; released into urine following tubular injury	
Insulin-like growth factor-binding protein 7 (IGFBP7)	intracellular marker of cell-cycle arrest; present in several cells, including tubular cells	released in the early phase of tubular cell stress / injury	
Interleukin-18 (IL-18)	18 kDa pro-inflammatory cytokine	released from proximal tubular cells following injury	

	Biologic sample	Time of detection after kidney injury	Confounding factors
	urine	?	
	plasma and urine (detectable in urine only after tubular injury)	12-24 hours post renal injury	• systemic inflammation • malignancy • thyroid disorders • glucocorticoid disorders • smoking
	urine	12 hours	
	urine	12 hours	
	urine	<2 hours	
	plasma and urine	6-24 hours after renal injury	• systemic inflammation • sepsis • heart failure

AKI biomarker	Characteristics and site of origin	Renal handling	
Kidney Injury Molecule–1 (KIM-1)	transmembrane glycoprotein produced by proximal tubular cells after ischaemic or nephrotoxic injury; no systemic source	present in urine after ischaemic or nephrotoxic damage of proximal tubular cells	
Liver-type fatty acid-binding protein (L-FABP)	14 kDa intracellular lipid chaperone produced in liver, intestine, pancreas, lung, nervous system, stomach and proximal tubular cells	freely filtered in glomeruli and reabsorbed in proximal tubular cells; increased urinary excretion after tubular cell damage	
N-acetyl-β-D-glucosaminidase (NAG)	>130 kDa lysosomal enzyme produced in many cells including proximal and distal tubular cells	too large to undergo glomerular filtration; urinary elevations imply tubular origin	
Neutrophil gelatinase-associated lipocalin (NGAL)	25 kDa glycoprotein produced by epithelial cells throughout the body	plasma NGAL is filtered and completely reabsorbed by healthy tubular cells NGAL is also produced in distal tubular segments and released into urine after tubular damage	
Retinol binding protein (RBP)	21 kDa single-chain glycoprotein; specific carrier for retinol in the blood	filtered by glomeruli and reabsorbed but not secreted by proximal tubules; excretion into urine after decrease in tubular function	
Tissue inhibitor of metalloproteinases-2 (TIMP-2)	intracellular marker of cell-cycle arrest; present in several cells, including tubular cells	released in the early phase of tubular cell stress / injury	

	Biologic sample	Time of detection after kidney injury	Confounding factors
	urine	12-24 hours after renal injury	• renal cell carcinoma • chronic proteinuria • CKD • sickle cell nephropathy
	plasma and urine	1 hour after ischaemic tubular injury	• CKD • polycystic kidney disease • liver disease • sepsis
	plasma and urine	12 hours	• diabetic nephropathy
	plasma and urine	2-4 hours post AKI	• sepsis • malignancy • CKD • pancreatitis • COPD • endometrial hyperplasia
	plasma and urine	< 12 hours	• Type II diabetes • obesity • acute critical illness
	urine	<2 hours	

Post cardiac surgery

Several studies have focussed on the ability to diagnose AKI early after cardiac surgery and to predict outcomes, including progression to more severe AKI, need for RRT and mortality [23-28]. The most-studied biomarkers are those that are released by tubular cells following renal injury (such as NGAL and KIM-1) or markers which reflect an inflammatory process (such as IL-18). The majority of studies concluded that NGAL, IL-18, cystatin C, KIM-1 and Liver-type fatty acid-binding protein (L-FABP) indeed indicated AKI earlier than serum creatinine. For instance, urine IL-18 and urine and plasma NGAL peaked within 6 hours after admission to ICU [26]. In a different study, the addition of urine IL-18 and pNGAL levels to a clinical risk model based on age, gender, ethnicity, diabetes, hypertension, preoperative renal function and cardio-pulmonary bypass time increased the AUC to predict AKI from 0.69 to 0.76 and 0.75, respectively [27].

Other studies focussed on the role of new AKI biomarkers as indicators of severity and progression of renal injury. Measurement of 32 different biomarkers in 95 patients with AKI stage 1 after cardiac surgery showed that IL-18 was the best predictor for worsening AKI or death, followed by L-FABP, NGAL and KIM-1 [24]. A study in cardiac surgery patients who already had a raised serum creatinine showed that π glutathione S-transferase (π GST) was best at predicting the progression to AKI stage 3, followed by NGAL, cystatin C, hepatocyte growth factor and KIM-1 [25]. Of note, IL-18 was not measured. Markers of cell cycle arrest have also shown promising results after cardiac surgery [29]. Serial levels of urinary tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) were able to predict both early AKI and renal recovery.

During critical illness

AKI is common during critical illness, especially in patients with sepsis. Numerous studies have investigated the role of novel biomarkers in diagnosing AKI early and predicting outcome in ICU patients [7, 11-14, 17, 19, 30-37]. Studies investigating cystatin C, urine IL-18, uNGAL and pNGAL have shown mixed results, mainly as a result of heterogenous patient populations, differences in timing and frequency of measurements and use of different biomarker cut-offs. A study in 301 heterogenous ICU patients showed that pNGAL allowed the diagnosis of AKI up to 48 hours prior to AKI, with an AUC of 0.78 [30]. Of note, there was a strong association between pNGAL and overall disease severity regardless of the presence of AKI. A large prospective study in 1439 ICU patients admitted to multiple ICUs in Finland confirmed that IL-18 during the first 24 hours of ICU had only poor-to-moderate ability to predict AKI, RRT or 90-day mortality [11].

Some studies evaluated biomarker panels rather than individual markers. For instance, Endre *et al* measured 6 urinary biomarkers (NGAL, KIM-1, IL-18,

alkaline phosphatase, γ-GT and cystatin C) prospectively in 529 patients on admission to ICU and found that no biomarker had an AUC above 0.7 in the prediction of AKI, RRT or mortality [37]. In contrast, Doi *et al* measured urinary L-FABP, NGAL, Cystatin C, IL-18 and albumin in 339 critically ill adult patients on admission to a medical-surgical ICU and found that the best biomarker to detect AKI was L-FABP with an AUC of 0.75 (95% CI 0.69-0.80) [31]. Two studies in diverse populations of critically ill patients showed that the combination of urinary [TIMP-2] and [IGFBP7] was superior to other biomarkers at identifying patients at risk for imminent AKI [33, 34].

The decision how to utilise novel biomarkers in critically ill patients remains a challenge, in particular in light of the dynamics of critical illness, the presence of confounding factors and uncertainty regarding timing of measurements.

Prediction of Outcome

Different outcomes have been evaluated in clinical studies, including severity and progression of AKI, need for RRT and ICU and hospital mortality.

For the need for RRT

Some AKI biomarkers have the capacity, either alone or in combination with traditional renal function tests and clinical judgement to predict the need for RRT [4]. Higher biomarker concentrations are often associated with need for RRT, in particular plasma cystatin C, urinary KIM-1 and N-acetyl-β-D-glucosaminidase (NAG). However, most studies were confounded by the fact that the precise indications for RRT were not provided. In some studies, the use of a novel biomarker was only marginally better than prediction based on clinical parameters [38]. Finally, there are no data showing that AKI biomarkers are able to indicate the optimal time when to initiate and when to discontinue RRT.

For renal recovery

There is increasing recognition that AKI survivors are at risk of developing CKD and end-stage renal failure even if renal function initially recovers [39]. Although several pathways and mediators in renal recovery and the transition from AKI to CKD have been identified, the clinical data regarding the performance of these substances as biomarkers are limited [40].

For mortality

There is good evidence that some novel AKI biomarkers are predictive of mortality, in particular when used in critically ill patients. The most widely studied biomarker is NGAL but others have also demonstrated an association with hospital mortality, for instance cystatin C and IL-18 [4]. Some novel AKI biomarker even predict outcome beyond hospital discharge [41, 42]. The mechanisms that underlie the association between these markers and long-term mortality are not clear. It is possible that biomarkers of AKI reflect not only renal damage but also correlate with secondary effects on non-renal organs.

For renal function after transplantation

In the field of transplantation, the identification of early non-invasive biomarkers to monitor graft status and predict outcome is an important research area. However, existing data are variable and conflicting. A study in 99 consecutive deceased kidney donors in the ICU (176 recipients) found that increased donor uNGAL levels but not pNGAL levels predicted histological changes in subsequent donor kidney biopsies, a higher risk of delayed graft function (DGF) beyond 14 days and worse 1-year graft survival [43]. In contrast, a study in 41 deceased kidney donors concluded that pNGAL was better at predicting DGF [44].

In liver transplant recipients, uNGAL detected AKI at 4 hours and pNGAL at 8 hours after transplantation whereas glutathione S-transferase (GST) and KIM-1 failed to detect AKI [45]. In another study, elevated serum IL-8 and urine IL-18, NGAL, IL-6, and IL-8 were elevated within the first 24 hours following surgery in those patients who developed AKI [46].

To date, these novel biomarkers remain research tools until further confirmatory studies are available.

Application of new AKI biomarkers in clinical practice

Commercial biomarker kits are now available in the UK. However, their best use in clinical practice remains uncertain [47, 48]. There are several reasons:

1. Biomarker studies have shown inconsistent and sometimes conflicting results. This may be explained by the inclusion of heterogenous patient populations and the use of different biomarker cut-offs. [49] In addition, a major flaw of all studies is the fact that the performance of novel biomarkers is usually judged by the level of agreement with serum creatinine, a marker with well known limitations.

2. Ideally, any new diagnostic test should provide additional information that is not surmised from clinical evaluation and traditional investigations. Although numerous studies have confirmed that most novel biomarkers indeed predict AKI earlier than serum creatinine alone, their superiority over clinical models could not always be confirmed.

3. A single biomarker is unlikely to be useful in all clinical settings. Instead it is more likely that a panel of functional and damage biomarkers in combination with traditional markers of renal function and clinical judgement will be necessary. The exact panel which provides not only best results but is also affordable in routine clinical practice remains uncertain.

4. Evidence that the use of novel biomarkers influences the decision making process and improves patients' outcomes is still lacking.

Despite these persistent uncertainties, the discovery of new biomarkers for AKI has opened the doors to a better understanding of the processes involved in AKI. More research is necessary to improve our interpretation of biomarker values. Ultimately, clinical usefulness of a set of markers will be determined not only by accuracy and reliability in prediction but also by whether that information alters therapy and whether this translates into an improvement in clinical outcomes.

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10.
Scarred For Life: The Long Term Sequelae of Acute Kidney Injury During Critical Illness

James Doyle and Lui Forni

Introduction

The sequelae of renal injury are not limited just to the acute episode with considerable evidence supporting the observation that an episode of AKI may increase an individuals risk of both morbidity and mortality in the longer term [1]. Indeed, this increased risk is seen for up to 2 years after the index case [2]. This is of concern given the incidence of AKI in the general hospital setting is 15% and in critical care this increases to over 25%, whereas in paediatric practice the incidence varies depending on casemix but is quoted at 8-25% [3, 4].

Temporal trends are more reassuring with both the mortality rates of the critically ill reducing over the last two decades as well as a reduced risk of dialysis dependence after an episode of AKI. However this survival increase is reflected in the total annual cost of AKI-related inpatient care, which, in 2014 was estimated at £1.02 billion, or just over 1% of the NHS budget in the United Kingdom [5]. As a consequence it is no surprise that the long-term outcome for patients with AKI is not only focusing on mortality but morbidity as well as quality of life is now receiving appropriate attention [6, 7].

This article will highlight the long term outcomes of AKI, in doing so we will acknowledge the limitations in defining renal recovery, consider the effect of acute management on long term outcome and propose a more formal pathway for chronic care.

So What are the Long Term Sequelae of AKI?

There have been several studies supporting the observation that AKI and CKD may be associated but demonstration of a clear association does not necessarily confer causation [8-10]. The data that does exist demonstrates that following an episode of AKI during critical illness there is a:

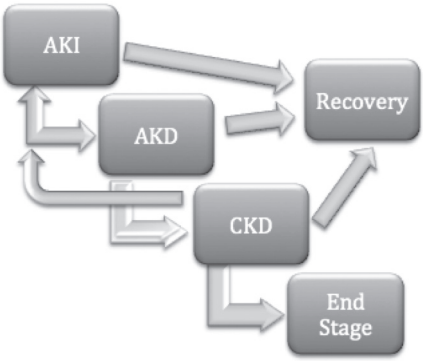
- increase in mortality [11].
- increase rate of adverse coronary events [12].
- increase rate of cerebrovascular accidents [13].
- increase in adverse renal outcomes [11].

As such the evidence does support long term follow up of patients who have suffered an episode of AKI [14]. Current prospective studies are underway focusing on the link between AKI and CKD [15]. If this is to affect clinical practice we need to define both a route of deterioration but also a route of recovery.

What is Meant by Renal Recovery?

It is fair to state that the presence or absence of AKI is now well established following the publication of the KDIGO guidelines which define AKI according to changes in serum creatinine and urine output and classifies AKI by stages 1,2 or 3 [16]. Similarly, chronic kidney disease (CKD) is also defined by KDIGO and reflects both chronic structural change to the kidneys as well as functional change [17]. Finally there is the concept of acute kidney disease (AKD) which describes the transition between the acute and chronic states [18]. It is important to recognize these three states do not occur in isolation nor necessarily in sequence as depicted in Figure 9-1. Furthermore renal recovery does not have a standardized definition making analysis of post-AKI epidemiology complex. A few studies have attempted to define recovery from AKI usually with regard to the necessity for renal replacement therapy a rather draconian end point and whilst convenient to describe recovery as the cessation of RRT the criteria for stopping are not uniform and open to bias [19]. Other methods of recovery include a return of the GFR to 20% of premorbid function, however this too has not been validated. Recovery needs to consider both the degree of recovery of renal function and the timing for this to occur, a consensus not yet agreed upon.

Figure 10-1: Acute Kidney Disease. The transition between acute and chronic disease states.



How is Renal Recovery Assessed?

At this point it is worth mentioning both the mechanism and limitations of current assessment of AKI. Creatinine is used as a surrogate for glomerular filtration rate (GFR) during AKI in critically ill unstable patients because the GFR is rarely measured in clinical practice. Equations have been developed which estimate the GFR (eGFR) from the serum creatinine where differences in age, sex and race are considered such as the MDRD and the CKD-EPI equations [20-22]. However creatinine is a biomarker for the GFR only under clinically *stable* conditions [23]. In the critically ill there is a significant overestimation of GFR owing in part to reduced creatinine generation and reduced muscle bulk. In sepsis particularly the former is found in 50% of patients with AKI [24-27]. Several studies have compared formal measurement of the GFR and eGFR with considerable disparity observed [28]. Finally there is a delay between renal injury and any observed rise in creatinine.

So what of alternative markers? Newer biomarkers may provide more timely information regarding renal status. For example a combination of biomarkers TIMP-2/IGFBP7 together with urine output and serum creatinine has been validated to be superior to predicting dialysis at 9 months in patients with AKI [29-32]. Many biomarkers, including some of the novel ones, have been observed to remain elevated years after an episode of AKI which is an issue when defining recovery [33]. However, recent evidence from animal studies suggest up-regulation of genes that code for biomarkers associated with renal injury may be surrogates for progressive renal injury following ischaemic insult [34]. Further studies have shown that renal recovery was slower in patients who had

increased concentrations of both plasma interleukin (IL)-8 and IL-18 and tumour necrosis factor receptor-I (TNFR-I) [35].

Aetiology of Acute Kidney Injury Affecting Outcome

Classically the aetiology of AKI is considered as pre-renal, renal or post-renal. Although in critical care the aetiology is more often multifactorial as a consequence of multi organ dysfunction. A recent study suggests that outcome is related to aetiology with sepsis associated AKI having the worst outlook [36]. In the post-operative patient, an episode of AKI carries a significant risk of recurrent AKI episodes and CKD [37]. Conversely AKI outcome has been improving in trauma and obstetric related cases [38].

The effects of acute management on long term outcome

Whilst there are guidelines for the management of AKI, the principles remain supportive to resolve concomitant volume overload, acidosis, electrolyte disturbances, and the impact on other organ function. There is no evidence supporting pharmaceutical intervention to-date to treat AKI.

Those acute treatments associated with improved outcome include:

- Avoidance of iatrogenic volume overload
- Use of a modality of continuous renal replacement therapy (RRT) when indicated, as opposed to intermittent RRT [39]
- Evidence does not support a survival benefit with RRT dosing, indeed an extended 4 year follow up of the RENAL study confirmed that both short (90 day) and long (4 year) mortality or the subsequent need for chronic dialysis was not affected by the dosing of RRT [2].
- Long term treatment options should remain in line with the management of CKD and include:
- Referral to a nephrology specialist. With evidence demonstrating a reduced all cause mortality in patients with severe AKI who undergo RRT. In addition early referral in patients with CKD also demonstrates a survival benefit [40, 41]
- Control of hypertension with manipulation of the renin -angiotensin-aldosterone system.
- Heavy proteinuric states should have more aggressive control of hypertension and use of antiproteinuric agents
- Consideration of the high risk nature of developing AKI in those with CKD during critical illness
- General cardiovascular health, lifestyle and dietary advice

Is There a Pathway to Reduce this Scarred Outcome?

If an episode of AKI during critical illness has a documented long term morbidity consequence it would be reasonable to expect a follow up management plan to mitigate potential morbidity. The current evidence of such a plan is scare with a recent UK based study of AKI requiring RRT demonstrating 57% of patients had appropriate post discharge investigations and only 12% of survivors received specialist nephrology follow up [42]. A US study demonstrated appropriate referral in less than 10% [43]. Validation is required for current risk prediction models. The management of CKD has robust recommendations regarding follow up which rely on the eGFR as well as the presence of proteinuria expressed as an albumin:creatinine ratio in mg/mmol (ACR). A model can be envisaged whereby these parameters along with clinical assessment and relevant investigation could be incorporated into a proposed patient pathway, which should ensure appropriate referral.

Figure 10-2 outlines such a proposed model and although this cannot possibly describe every potential clinical scenario it does provide a framework for referral and follows, in part, the CKD pathway described by KDIGO.

Figure 10-2: Proposed pathway for patient monitoring of AKD.

<table>
<tr><td colspan="3" rowspan="2"></td><td colspan="3">ACR Categories (mg/mmol)</td></tr>
<tr><td><3</td><td>3-30</td><td>>30</td></tr>
<tr><td colspan="3"></td><td>A2</td><td>A2</td><td>A3</td></tr>
<tr><td rowspan="6">eGFR ml/min/1.73m^2</td><td>>90</td><td>G1</td><td rowspan="3">No Features of Significant Renal Disease Measure eGFR at 90 Days</td><td rowspan="2">No Features of Significant Renal Disease Measure eGFR at 90 Days</td><td>No Features of Significant Renal Disease Measure eGFR at 90 Days</td></tr>
<tr><td>60-89</td><td>G2</td><td>Measure eGFR 2-4 weeks post discarge</td></tr>
<tr><td>45-59</td><td>G3a</td><td rowspan="3">Nephrology Referral</td><td rowspan="3">Nephrology Referral</td></tr>
<tr><td>30-44</td><td>G3b</td></tr>
<tr><td>15-29</td><td>G4</td><td rowspan="2">Nephrology Referral</td></tr>
<tr><td><15</td><td>G5</td><td></td><td></td></tr>
</table>

Features of significant renal disease include persistent proteinuria and haematuria; suspected glomerulonephritis; known structural renal disease (eg: APCKD); suspected urological disease and hypertension refractory to treatment.

ACR = alhumin : creatinine ratio
A1-A3 = ACR Categories
G1-G5 = GFR Categories

Summary

The long-term sequelae of AKI during critical illness is now apparent and an episode of AKI, particularly when necessitating RRT, confers considerable increased risks of mortality and morbidity. This is reflected in an increase incidence of CKD, cardiovascular events and stroke as well as significant effect on the quality of life of survivors. Mitigation of this scarring may be accomplished with early identification of patients at risk of CKD and targeted referral. The possibility of achieving this is now even more likely with novel biomarkers assessing renal recovery. The ability to quantify this improvement may be possible with a consensus statement defining renal recovery and perhaps give parameters as to the cessation of RRT during critical illness. The end-result of improving patient outcomes and offering considerable cost savings to the local health economy.

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11.
Update on Blood Transfusion Decisions in the ICU

Jean-Louis Vincent

Introduction

The first human-human blood transfusion is reported to have taken place in 1795 in Philadelphia [1]. Since then we have made considerable advances in the preparation, sterilization and storage of red blood cells (RBCs) for transfusion and this is considered a fairly safe intervention [2]. Indeed, some 14 million units of red blood cells are transfused very year in the United States [3]. In the intensive care unit (ICU), about 30% of patients will receive a blood transfusion during their ICU stay [4, 5].

In 1999, results from the randomized Transfusion Requirements in Critical Care (TRICC) study helped catalyse a change in clinical transfusion practice in ICUs around the globe. This study showed that critically ill patients had similar outcomes when transfused using a liberal (trigger hemoglobin [Hb] < 9 g/dl) or restrictive (trigger Hb < 7 g/dl) target [6]. However, when analyzed in more detail, several concerns became apparent, including the fact that many patients with risks related to the presence of anemia were not included and only 13% of the screened patients were enrolled - indeed, the study was stopped prematurely because of these difficulties in recruitment [6]; Moreover, despite apparently similar mortality rates in the two groups, in patients aged < 55 years and in those with Acute Physiology and Chronic Health Evaluation (APACHE) II scores of less than 20, mortality rates were actually higher in the liberal than in the restrictive arm. In a post-hoc review, patients with ischemic heart disease had lower mortality rates with liberal transfusion than when transfusions were restricted [7]. Taken more pragmatically, what this study actually suggested was that the decision to give a blood transfusion needs to be based not on a single hemoglobin value but that individual patient characteristics need to be taken into account. We will discuss this concept in a little more detail in the rest of this chapter.

Why Transfuse?

Blood transfusions may be given as a response to acute, life-threatening hemorrhage, but in ICU patients, they are more often given in an attempt to increase oxygen-carrying capacity in the presence of reduced hemoglobin levels and hence optimize oxygen delivery. Transfusions in this situation are generally just one part of a combined effort that also includes fluid administration and vasoactive agents. By increasing global oxygen delivery, it is hoped that regional delivery and oxygen uptake will also increase, thus reducing local tissue hypoxia and its detrimental effects on organ function. However, increasing global and even regional oxygen delivery does not necessarily lead to increased oxygen uptake by the tissues, which is dependent not only on oxygen delivery but also on local microcirculatory and metabolic factors, which are not yet completely understood [8, 9]. Blood viscosity is one of the key factors in the relationship between blood transfusion and tissue oxygen delivery and uptake. RBC transfusion increases blood viscosity, which, in turn can increase cardiac output and thus decrease oxygen delivery. On the other hand, increased viscosity may also help maintain functional capillary density thus potentially improving tissue oxygenation [10].

In this context, one of the difficulties in the clinical situation is that we do not yet have reliable tools to measure and monitor tissue perfusion or oxygenation or indeed local cellular metabolism. Blood lactate levels and mixed venous oxygen saturation provide clues as to the adequacy of underlying tissue oxygenation but are just surrogate measures of the actual value. Techniques such as orthogonal polarization spectral (OPS) and sidestream darkfield (SDF) imaging and near-infrared spectroscopy (NIRS) have been used to try and improve our understanding of the underlying physiology in volunteers and various patient populations, but these remain experimental. In 44 ICU patients, Creteur *et al*. showed that RBC transfusion did not affect NIRS-derived variables overall, but there was considerable interindividual variation and blood transfusion was associated with improved muscle oxygen consumption and microvascular reactivity in patients in whom these variables were impaired prior to transfusion [11]. Others have reported similar findings in patients with sepsis using OPS [12] and NIRS [13]. Kopterides *et al*. used microdialysis of subcutaneous adipose tissue to explore cellular metabolism before and after transfusion in ICU patients with sepsis [16]. In this retrospective study, RBC transfusion was associated with a decrease in the lactate/pyruvate ratio, which was correlated with the pre-transfusion ratio. The effectiveness of a blood transfusion to increase oxygen delivery may, therefore, depend on how severely impaired the microcirculation is. NIRS and SDF techniques have also been used to try and assess the different effects of transfusion with leukodepleted versus non-leukocyte-depleted blood [14] and of older versus fresher blood [15].

Risks of Anemia

Anemia, generally defined as a hemoglobin concentration < 12 g/dl, is common in ICU patients and associated with worse outcomes [4, 21]. Corwin *et al*. reported that a nadir hemoglobin concentration of <9 g/dL during the ICU stay was an independent predictor of increased mortality and prolonged hospital length of stay [4]. In surgical ICU patients, Sakr *et al*. [21] reported that lower hemoglobin levels were associated with higher disease severity, greater mortality rates, and longer ICU and hospital lengths of stay.

Anemia is particularly detrimental for the heart, because cardiac output increases in part by an adrenergic response with increase in heart rate and myocardial contractility, which may be poorly tolerated, especially when occurring over a relatively short period of time, by patients with coronary artery disease and elderly patients in general. Indeed, by reducing this adrenergic response, blood transfusions act a bit like beta-blocking agents!

Risks of Blood Transfusion

Although improvements in blood collection, typing, testing, treatment and storage have made blood transfusion a fairly safe intervention [2], it is still associated with complications. Simple adverse effects include allergic reactions and fever, more severe complications include transmission of infectious organisms, hemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion related cardiac overload (TACO), and transfusion-related immunomodulation (TRIM) [22]. Despite the large number of transfusions administered every day around the globe, the incidence of these complications has not been widely documented. In a recent hemovigilance study from the United States, the rate of transfusion-related adverse reactions was 205 per 100,000 total RBC units transfused. Allergic and non-febrile haemolytic reactions were the most frequent. TRALI occurred at a rate of 1.5/100,000 transuded RBC units and transfusion transmitted infections occurred at a rate of 0.3/100,000 [23]. Several early observational studies reported that blood transfusion was an independent risk factor for mortality [4, 20, 24, 25], and clinical trials in specific patient groups also suggested worse outcomes in transfused patients [26-29].

When to Transfuse?

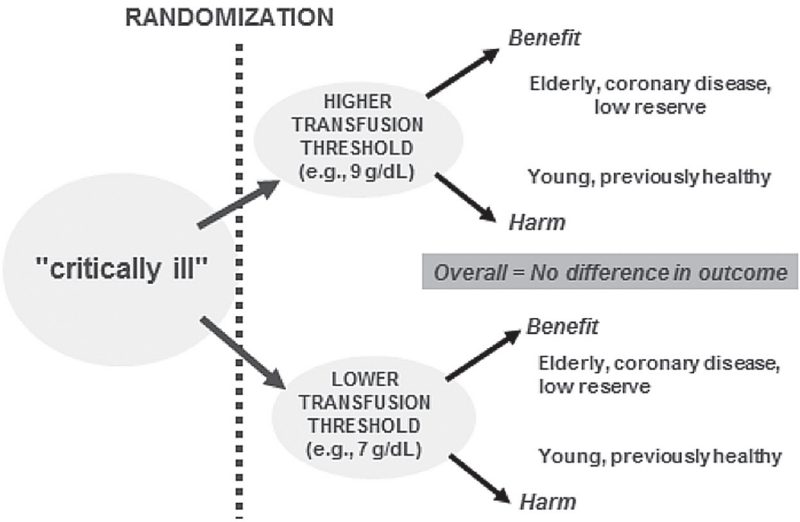
The decision to transfuse is, therefore, not an easy one, needing to balance the risks of anemia against those of transfusion. For many years, these decisions were guided by the "10/30" rule established essentially based on data from healthy volunteers [30]. This stated that transfusions should be given whenever the hemoglobin concentration decreased below 10 g/dl and/or the hematocrit < 30% [31]. However, patients, especially critically ill patients, are different to healthy volunteers: their microcirculation is altered as are their oxygen needs and their response to transfusion will also be different. Moreover, critically ill patients are very heterogeneous, being of different ages, and having different comorbidities, ongoing diagnoses, and concomitant medications. As such, it is unlikely that a single transfusion "trigger" would be ideal for all critically ill patients.

The TRICC study discussed earlier attempted to determine whether critically ill patients could be safely transfused at lower hemoglobin levels in view of increasing concerns about associated risks [6]. The study did indeed suggest that a more restrictive practice was safe in most patients. International guidelines and expert recommendations rapidly adopted the "new" trigger [32] and transfusion rates decreased in many units [33, 34], perhaps particularly in higher volume units [35]. There have been no other large randomized studies on transfusion strategies in general ICU populations since the TRICC study, largely because of problems with recruitment, with physicians finding it difficult to randomize certain types of patients to one or other transfusion strategy or the risk that they would deviate from protocol when patients failed to respond as hoped for [36].

Randomized studies have been conducted in more specific groups of critically ill patients and have given conflicting results [37-43]. In cardiac surgery patients, mortality was higher in patients randomized to restrictive (hemoglobin level <7.5 g/dl) compared to liberal (hemoglobin level <9 g/dl) transfusion (4.2 vs. 2.6%; hazard ratio 1.64, 95% CI 1.00 to 2.67; p=0.045), although the global composite outcome (serious infection, ischemic event, or acute kidney injury) was similar in the two groups [39]. In cancer patients undergoing major surgery, fewer patients met the composite endpoint of mortality or severe clinical complications in the liberal transfusion strategy (hemoglobin level <9 g/dl) group compared to the restrictive (hemoglobin concentration <7 g/dl) group (19.6% [95% CI 12.9 to 28.6%] versus 35.6% [27.0 to 45.4%], p=0.012) [40]. In patients with septic shock, 90-day mortality rates were similar in patients who received liberal (hemoglobin <9 g/dl) or restrictive (hemoglobin <7 g/dl) transfusions (43.0% versus 45.0%, p=0.44) [41]. Interestingly, in recent studies of early goal-directed therapy (EGDT) in patients with septic shock, in which blood transfusion formed part of the protocol if hematocrit was <30% and central venous saturation <70%, EGDT protocol-treated patients with sepsis received more transfusions but there were no differences in outcome among groups [44, 45].

What these RCTs have clearly demonstrated, rather than providing us with any simple solution to the "when to transfuse" question, is that different patients respond differently to receiving a blood transfusion. It is clear that there cannot be a single number trigger for blood transfusion that will meet be adequate for all patients [46]. ICU patients, even those in defined populations such as with sepsis or after cardiac surgery, are a heterogeneous group. For example, a young, previously healthy trauma patient is very different to an elderly patient with sepsis and known ischemic heart disease. It is difficult to imagine that in a randomized clinical trial, these two patients could fall into the same treatment arm. If randomized to the liberal group, the young patient will receive a transfusion that, in all likelihood, was not necessary and will not aid and may even harm his recovery. The elderly patient, randomized to the same group, will likely benefit from his/her transfusion. Similarly, if randomized to the restrictive group, the elderly patient will not receive the transfusion that would likely have been of benefit, while the young patient will benefit from not receiving an unnecessary transfusion. In each treatment arm, some patients will benefit and others will have no benefit or may be harmed, thus the study is overall unlikely to demonstrate a difference between the two treatment arms (Figure 11-1.) This heterogeneity is a major problem with all randomized controlled trials in critically ill patients, regardless of the intervention in question [47].

Figure 11-1: Schematic of a randomized clinical trial comparing two red blood cell transfusion triggers.



Schematic of a randomized clinical trial comparing two red blood cell transfusion triggers, showing that, in each arm, some patients will benefit and others will not, or will even be harmed, so that the overall result is unlikely to show a clear difference between the two groups.

Conclusion

Critically ill patients are heterogeneous in nature and use of a strict transfusion protocol based solely on a certain hemoglobin level may lead to inappropriately high rates of transfusion [41]. RCTs comparing transfusion strategies are limited by this heterogeneity and are non-informative. Observational data are of use but extensive analysis is needed to ensure all confounding factors are controlled for before definite conclusions can be reached regarding the effects of transfusions [48]. As with many other interventions in intensive care medicine, we may have been over-enthusiastic in our use of blood transfusions in the past, but a restrictive approach to all patients is not the answer to previous excesses. Rather the decision to transfuse must be made separately for each patient, based on hemoglobin concentration, but also on clinical characteristics such as age and presence of ischemic heart disease, underlying diagnosis, clinical status, and global and regional perfusion and oxygenation variables [46].

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12.
The 2014-5 Ebola Outbreak in West Africa: an Example of North-South Skills and Knowledge Transfer. But What Did We Learn?

Greg McAnulty and Tejshri Shah

Ebola in West Africa

Ebola or Ebola virus disease (EVD) was first identified as being present in West Africa after Médecins Sans Frontières (MSF) was asked to investigate a cluster of deaths in a remote rural area near Guéckédou, Guinea, in March 2014 [1]. The appearance of this high-mortality infectious disease in this area was apparently new. It subsequently spread more rapidly, further and infected an order of magnitude more people than earlier outbreaks in central Africa. The recognition that this outbreak of Ebola was a threat to regional and perhaps global health was at first limited but rapidly became very broad. The focus of much media attention and even that of developed world public health systems was on the potential for a pandemic in countries where this was never a real possibility and not on the suffering of the patients and their communities [2]. However, in the months following June 2014 the response from health workers and governments mainly in Europe and North America led to an impressive influx of organisational expertise, medical skill and money into the three most affected countries: Liberia, Guinea and Sierra Leone. The epidemic began to subside in the first months of 2015 which coincided with the arrival of the bulk of external expertise and the opening of many more designated Ebola management structures. This was not necessarily causally related but did mean that there was a considerable change in the capacity of health care systems to increase the intensity of their interventions for individual patients.

Viral haemorrhagic fevers (VHF) are caused by a number of different viruses. Among them are the filoviruses which include Ebola and Marburg. Another VHF, Lassa Fever, caused by an arenavirus usually contracted by contact with rodent urine and faeces but transmissible by contact with bodily fluids is endemic in rural West Africa.

The 2014-5 EVD epidemic was caused by Ebola virus (EBOV, formerly, Ebola Zaire, one of the five sub-types of the virus [3]). The disease characteristically appears in clusters of cases and is generally spread by direct or indirect contact with infected patients. The origin of many is probably contact with infected animals which form the reservoir of the disease. The virus itself is fragile in the environment and although case fatality rates are high, transmission rates are relatively low [4]. Until 2014, the largest outbreak of Ebola was just under 500 cases Uganda in 2001-2 [5].

Ebola is most likely to be transmitted in the later, symptomatic stages of the disease when viral concentrations in bodily fluids is high [6]. For this reason, health workers are particularly exposed and the use of personal protection equipment (PPE) has become emblematic of the response to the disease. Other strategies for preventing direct contact between suspected and confirmed patients and health staff are equally important [7].

The illness presents with non-specific symptoms: fever, vomiting, diarrhoea, headache, anorexia, weakness, abdominal pain, arthralgia and myalgia. Hiccoughs and dyspnoea are late signs. Haemorrhage from mucous membranes occurs in a minority. Delivery or miscarriage is likely to be associated with excessive blood loss [7]. Fever on presentation is not invariable. Clinical suspicion of a diagnosis is based on a patient presenting with a cluster of features which conform to the outbreak case definition. In the 2014-5 outbreak this was the presence of fever and a history of contact with an infected person, fever and the presence of at least three of ten defined symptoms, unexplained haemorrhage or miscarriage or otherwise unexplained death. The diagnosis is now confirmed with polymerase chain reaction (PCR) assay for viral components [8].

The case fatality rate for Ebola is reported to be up to 90%. It was put at approximately 38% in the 2014-5 outbreak but estimates of case rates vary considerably [9]. Children, the elderly and pregnant women are at significantly greater risk of dying [4, 10]. It is likely that there are a proportion of asymptomatic cases but in outbreaks where transmission is mainly from human to human this may be small [11].

The Impact of the Disease

The emergence of Ebola in West Africa occurred in a context which probably exacerbated its impact. First, the region is one of the poorest and least developed in the world. All countries have been severely affected by wars within the past 15 years, access to primary and secondary healthcare is very limited, particularly in rural areas, and maternal mortality is among the highest in the world ranking [12].

Malnutrition, endemic disease (in particular, malaria, typhoid and streptococcal infections and periodic outbreaks of cholera, measles, meningococcal disease, dysentery and other hemorrhagic fevers) present a considerable burden. In addition, road transport in rural areas is extremely difficult and transport for patients with a severe illness from their homes to diagnostic and treatment facilities is challenging, uncomfortable and may take many hours, especially in the rainy season. Similarly, access to remote communities by surveillance teams is difficult and time-consuming.

The traditional management of filovirus hemorrhagic fevers is founded on actions to reduce and contain the spread of the disease while reducing suffering and mortality by providing the best patient care possible. MSF is the organisation with the most experience in this field and has published comprehensive guidelines on how to achieve this [13]. Until 2014-5 Ebola and other filovirus outbreaks received little world media.

Although there was a delay in the West African outbreak being recognised by UN agencies (including the WHO) as an international emergency, by the latter part of 2014 it had become a major focus of the international media [14]. Much developed world media attention highlighted the potential for the spread of the disease outside the outbreak area. Less than 30 patients were treated for the disease in Europe and North America. Over 27,000 cases were confirmed by laboratory testing in the three most affected countries. Additionally, a small number of cases were confirmed in Nigeria, Senegal and Mali. Only a very small number of cases of Ebola were acquired outside West Africa [15].

For much of 2014, facilities for identifying, transporting and treating patients with Ebola in the three most affected countries were hopelessly inadequate and patients could be given little more than basic nursing and oral therapy once they reached a facility that had the capacity to provide medical care safely [16]. Although a number of novel therapies have been proposed and used in very limited numbers, there is no established treatment for Ebola beyond supportive care [17].

Consequences of the 2014-5 Outbreak

A positive outcome of the intense media, institutional and governmental interest in the second half of 2014 was that it stimulated the engagement of an unprecedented number of healthcare personnel who became willing and able to commit to being personally involved in the Ebola crisis. There are no official estimates of the total number of doctors, nurses, water and sanitation as well as logistics and administrative workers who travelled to West Africa in 2014-5 from countries outside the outbreak area in response to the crisis. It is likely to be in the

tens of thousands. This does not include several thousands of military personnel from Europe and North America. Many of those involved in the response were from other countries in Africa. Although the international response to the crisis was initially slow by the end of 2014 resources were beginning to match the need. In particular, it was no longer necessary for suspected patients to be transferred large distances to Ebola management centres (EMCs) and it became easier to adequately trace and monitor Ebola contacts in many areas. It also became possible to provide more intensive therapy for patients with Ebola but, ironically, this escalation coincided with a wave of expressions of dissatisfaction with the strategies used to treat patients with Ebola who were in the EMCs [18, 19].

The response to the 2014-5 Ebola outbreak uniquely involved large numbers of nursing and medical staff from resource-intensive backgrounds and this, perhaps, explains the rapid increase in the use of parenteral therapy as well as the frustrations with the perceived impediments to achieving better survival rates towards the latter half of the epidemic period. The question was frequently asked: could more have been done to improve the outcome for patients with Ebola? This was, no doubt, driven by a recognition that the care given to health workers and others who acquired the disease in West Africa but were repatriated and treated in developed world intensive care units was different from that available to most patients treated in EMCs in the three most affected countries.

The intervention into the 2014-5 Ebola outbreak was one of the most intensive (and expensive) in the history of humanitarian health emergencies. However, the difference between the reported level of care provided to those who were treated in developed world intensive care units (ICUs) [20] and those who were treated in EMCs in West Africa was odious. The vast majority of those who were treated for Ebola in developed world ICUs (and, indeed all repatriated health workers) survived compared with approximately 40% of those treated in EMCs in West Africa [9]. However, not all the survival benefit should be attributed to 'cutting edge' critical care. Repatriated health workers were not elderly, not children, not pregnant and, before departure to West Africa, were in good health. Moreover, the ICU treatments provided for most repatriated Ebola patients were modest although some received mechanical ventilation, convalescent serum, anti-viral, anti-bodies and haemofiltration [20, 21].

Although international organisations and donor governments played a large part in the response to the Ebola crisis, it should not be forgotten that the vast majority of the work of building, maintaining and operating the EMCs, as well as burying the dead, was done by workers from the local communities. Indeed, they bore the brunt of the risk [22]. As well, the EMCs were only part of the response. Outreach programmes which involved contact identification and tracing, follow up and rehabilitation of survivors was in many ways a far more

complex operation but received less media attention [23]. There were profound changes in social and burial practices in response to health promotion and, no doubt, to the consequences of communities being exposed to the realities of the outbreak. Despite these changes in behaviour, the outbreak has still not been contained in some districts.

Two, quite emotive, arguments were made for the role of parenteral fluids in improving a patient's chances of survival [17, 18]. At the time these were published the use of parenteral fluids was becoming more prevalent in many EMCs. However, the administration of intravenous fluids with limited supervision and haemodynamic monitoring l*et a*lone biochemical surveillance was problematic [24]. Certainly, some patients with Ebola died from remediable fluid and electrolyte deficits but, disappointingly, parenteral fluid administration did not appear to have been a panacea.

There did not seem to have been a marked survival advantage for patients treated aggressively in at least one centre [25] and mortality in the West African region from Ebola did not change very much from before the peak of the epidemic when there was little parenteral therapy given (36.9% of all recorded cases by week ending 5th November 2014) until later when parenteral fluids were commonly administered to patients unable to drink adequately (41.2% by week ending 27th May 2015) [26]. The findings of two recent analyses of fluid resuscitation in patients with severe malaria may add to caution about ascribing significant improvements in survival to broadly applied fluid therapy [27, 28]. When limited blood chemistry analysis became more widely available in January 2015 at a time when patient numbers were decreasing marked derangement in electrolytes were not a prevalent as had been expected [29].

Of course, case identification rates will have changed considerably between March 2014 and the middle of 2015. The effect of survivor bias is likely to have influenced EMC mortality rates early on. As well, likely earlier presentation in the latter part of the period of the outbreak will have complex influences produced both by proportional changes in illness severity and possible treatment effects.

Could We Have Done Better?

Yet, something else was missing. The separation and isolation of patients, the limiting of contact between staff and the communities, between staff in the health facilities and in their accommodation and the wearing of PPE were all part of strict biosecurity arrangements imposed by organisations responsible for managing EMCs. There is no doubt that this affected the way medical care was delivered. The restriction of the use of intravenous cannulae became a focus of

criticism of what was seen as less than ideal treatment [18] it may not have been the most important. Certainly, many patients benefited from the administration of parenteral therapy, others could have but the delivery of effective and safe care of the critically ill patient requires much more than fluid therapy.

Patients with Ebola died of the consequences of severe sepsis. Although there is evidence that in developed world critical care settings the mortality from severe sepsis is falling [30] it is not clear why. It is likely that the mechanism behind the success in reducing mortality is complex and involves organisational and team discipline in implementing care [31]. The role of many individual components of so-called 'care bundles', in particular aggressive fluid resuscitation, have been questioned [32] but it seems that the model of care established in critical care units has something to offer. The model of care for Ebola patients in EMCs was markedly different. Round the clock monitoring of vital signs and careful measurement of fluid balance did not happen. In fact, frequent and accurate recording of relevant clinical data was difficult partly because of the physical environment (although some possible solutions were developed late in the crisis [33]) but also partly because much of what was collected was based on WHO surveillance forms [34]. Although some illness severity scoring systems were developed in some EMCs these were never used widely and the monitoring of clinical features important for assessing the requirement for therapeutic interventions was basic, particularly early in the crisis. More important, perhaps, was that medical and nursing care was fragmented by the arrangements constructed around the over-riding need to maintain biosafety for staff.

One of the effects of the involvement of so many acute care doctors and nurses in the response to the outbreak was, perhaps, a distortion of focus towards acute care interventions. This may have been at the cost of a better understanding of the need for contact observation and support. Community-based, preventative action may not have been so engaging for the doctors and nurses involved in the EMCs. Could a better balance have been struck earlier?

For understandable reasons (which might also include high staff turnover and the unfamiliarity of the environment) more traditional clinical hierarchies were not established in the EMCs. Whilst, undoubtedly, individuals made deep personal commitments to patients clear, continuing individual clinical authority was not as strong as it would be in a developed world critical care environment where every patient has a specific clinician in charge of his or her case. Would this have made a difference to the number of patients who could have survived Ebola in EMCs? Perhaps. Even probably. But, perhaps, not as much as might be thought.

What Does the Future Hold?

We can dare to hope that the publication of an interim report of what seems to be a remarkably effective vaccine and vaccination strategy for the management of Ebola marks the beginning of the end of the prolonged epidemic in West Africa [35].

This is likely to change everything. But there is still much to consider, analyse and learn from the hard lessons of the efforts to control the spread of the disease before the arrival of a vaccine. We used tools of limited effectiveness and at times we lost sight of the needs of our patients as individuals.

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13.
Protecting the Brain from Long Term Damage

Jonathan Ball

Introduction

Brain injury is very common and is probably the most significant cause of long term acquired physical and cognitive disability. The most frequent mechanisms are trauma, global hypoxic-ischaemic injury, spontaneous haemorrhage and infarction. The concept that the acutely injured brain is vulnerable to a complex cascade of potentially modifiable secondary injuries is well established. Most of these secondary mechanisms are common to all types of primary injury. Over recent years, it has become clear that these secondary mechanisms can persist resulting in a chronic inflammatory, progressive, neurodegenerative pathology that clinically manifests as accelerated brain ageing, premature dementia and frailty [1]. As clinicians tasked with the early management of the most severely brain injured, what can we do to minimise secondary brain injury in the acute and early rehabilitation phases?

The State of the Art

Though predictable and clichéd, standard ABCDE management of the patient's airway, breathing, circulation, metabolic state (D for dextrose *et al*) and environment must be the first set of priorities. Failure and / or delays in doing so, is strongly associated with worse outcome in a large number of observational studies. Though much energy has been expended on how these interventions are best performed following brain injury the evidence base is weak [2]. Given that time is a critical factor, familiar practices are likely to be more efficient and safer than specialist recipes. What are easily lost sight of are the physiological targets of these interventions, which are perhaps best described as fulfilling the Goldilocks criteria - those being not too much or too little but just right. The physiological parameters covered by this paradigm include arterial oxygen content, carbon dioxide tension (but not pH - since a mild to moderate acidosis may increase oxygen delivery amongst other benefits); intravascular volume, cardiac output and all circulatory pressures. Ideally, all of these variables should be monitored and normalised within minutes. As time progresses, similar attention is

required to haemoglobin concentration, haematocrit, blood glucose and sodium concentrations, balanced coagulation (neither hypo- nor hyper-coaguable] and brain temperature (which may not necessarily be the same as core temperature - classically brain temperature is 0.5-1.0ºC higher than core body temperature). In short, to limit secondary injury in the acute aftermath of a brain injury, do the simple things well and pay close attention to detail - otherwise known as the first tenet of intensive care. With the recognition of the cumulative benefit of a series of marginal gains, there is persuasive evidence that delivering these comparatively simple interventions is associated with better outcomes [3].

As with all organ systems, supportive care for the brain should aim to maintain an adequate (but not excessive) supply of essential fuels (not just glucose) [4, 5] and oxygen whilst removing waste products before they reach toxic levels. This essentially depends upon the bulk convectional transport of the systemic circulation (that is flow and not pressure), the integrity and function of the distributive microcirculation (including in this scenario, the blood brain barrier) and the diffusion distance between cells and the circulation. In order to achieve these goals we ideally need continuous physiological monitoring of the whole brain with a high degree of temporal and spatial resolution. In addition, we need reliable tools to augment the systemic circulation, modify the microcirculation and reverse any interstitial oedema that limits diffusion. The current state of this art includes monitoring that provides very limited spatial but reasonable temporal resolution, though principally of surrogate markers of brain tissue health. Our interventions however, are strictly limited to blunt instruments capable of titrating systemic blood pressure and rescue interventions that attempt to limit global brain metabolism to mitigate against limited supply. Furthermore, most, if not all, of our interventions from intravenous fluids to mechanical ventilation have unwanted effects that we can often do little to minimise beyond being cognisant of them.

However, it should not be forgotten that brain tissue has a remarkable capacity to adapt to slow (minutes to hours) changes in almost all physiological parameters. Some of these adaptive changes permit continuing cellular function whilst others appear to induce a state akin to hibernation. With more rapid and / or extreme deviations from homeostasis, apoptosis may be induced (preferable to necrosis which is pro-inflammatory) and may, with future therapies, be halted and reversed. Therefore, it is biologically plausible to use interventions that control the rate of deviation from normal values rather than doggedly targeting fixed values regardless of trends, physiological adaptations and individual variability. Though our current ability to differentiate between physiological (pro-survival) adaptation and pathophysiology (changes that result in tissue injury) remains imperfect, there is emerging evidence of the value of post-injury conditioning [6], or more precisely, inducing / augmenting pro-survival physiological adaptation to post-injury conditions.

Monitoring the Brain

Reported symptoms and clinical signs of neurological dysfunction are the most sensitive and specific form of brain monitoring. They are augmented by structural brain imaging, most commonly CT. However, severe brain injury commonly has adverse effects on consciousness, which not only limits clinical assessment but also, often necessitates airway protection and sedative drugs. Plain CT, with some limitations, is able to demonstrate the presence and evolution of haemorrhage and structural change within the cranial cavity but the correlation with function is limited. Additionally, CT is constrained by the cumulative dose of ionising radiation and the logistics of having to transport patients to and from the scanner. Hence, continuous physiological brain monitoring is essential.

The most widely monitored parameter of brain physiology is intra-cranial pressure (ICP) from which cerebral perfusion pressure (CPP) is calculated by subtracting ICP from the mean systemic arterial pressure (MAP). ICP in the range 5-15mmHg (6.8-20.4cmH_2O) is considered normal. Current guidelines suggest that both ICP and CPP are targeted to minimise secondary injury. Critical thresholds for these parameters (associated with harm) are long established though remain controversial, being an ICP >20-25mmHg and a CPP <50 and >70mmHg [7].

The evidence to support the ICP threshold is reasonably robust when considered as the cumulative, intensity duration product [8] sometimes referred to at the "dose" of intra-cranial hypertension, though the relationship is probabilistic. There are two commonly employed methods for monitoring ICP, parenchymal fibre optic sensors and transduced ventricular drains. Both are invasive and can result in significant local complications. They may both result in significant measurement errors as the sample volume of parenchymal sensors is very small and that of ventricular drains global, albeit potentially confounded by obstructed CSF circulation, especially if unilateral or compartmental. Ventricular drains are more challenging to insert and maintain but have the advantage of facilitating the drainage of CSF. A recent observational study suggests that the ventricular drainage method of ICP monitoring (coupled with an ICP / CPP treatment algorithm] is associated with a significant survival advantage over parenchymal probes [9]. Whilst this trial cannot be considered definitive it certainly challenges some established practices.

In contrast, the established CPP thresholds are complicated by two major factors. The first is the lack of adherence to a standard anatomical reference level for the MAP (the heart verses the foramen of Monro) [7]. The difference in MAP between these two sites is exacerbated in taller patients, with varying angles of the head of the bed, and with different sites of arterial cannulation. The resulting

discrepancy can be in the clinically critical order of 15-20mmHg (heart > foramen of Monro).

The second factor is the preservation, change in the lower threshold or loss of "global" arterial cerebral autoregulation (cerebral arterial vasoconstriction in response to an increase in MAP to maintain a constant cerebral blood flow (CBF) [10]). In a normal adult brain the lower threshold of autoregulation is a CPP in the region of 50mmHg, below which, there is a proportional relationship between MAP and CBF. Thus, as CPP falls below 50mmHg, increasing degrees of ischaemia result. As with ICP, the cumulative, intensity duration product of CPP<50mmHg is reliably associated with poor outcome [8]. However, in the presence of intra-cranial hypertension, the lower threshold for autoregulation increases, thus targeting a CPP significantly greater than 50mmHg may be required to limit ischaemia [11]. In addition, if autoregulation is preserved, then targeting a CPP of >70mmHg might be beneficial, as CBF should be maintained with a reduced intra-cranial blood volume resulting in a fall in ICP, with a higher CPP causing a greater effect. However, if autoregulation is lost (especially in relation to an injured area], a CPP of >70mmHg is likely to increase intra-cerebral blood volume leading to an increase in ICP and a diminished CBF. In addition, the increase in hydrostatic pressure may increase local oedema. There is also an association between targeting a CPP >70mmHg and acute respiratory distress syndrome and myocardial injury. Finally, there are no trials that demonstrate a clear outcome benefit when a CPP >70mmHg is blindly targeted - the evidence is reviewed here [12].

The reasoning behind targeting a single value of ICP and CPP is too basic [13] and challenged by observable phenomena [14, 15]. Though familiar, the reasoning that underpins these ideas is worth reviewing. The brain is surrounded by a fluid cushion and encased in a rigid box. If some of the volume in the box becomes occupied by extravascular blood and / or interstitial (+/- cytotoxic] oedema then the ICP will rise. There is very limited compensation available through alterations in the volume and distribution of cerebrospinal fluid (CSF). Thus (the intra-vascular] intracranial blood volume has to diminish and cerebral perfusion pressure increase, in order to maintain intra-cranial pressure and cerebral blood flow. However, in almost all types of brain injury the pressure effects are not evenly distributed [16, 17]. Furthermore there is the unpredictable preservation of cerebrovascular autoregulation [13] and coupling of cerebrovascular blood flow to local metabolic demand [18]. Failure of these mechanisms may result in ischaemia or hyperaemia, both of which cause secondary injury. Beyond the focal / regional nature of these alterations, they also evolve over the first few and hours to days following an injury [19]. Finally, it is unreasonable to assume that venous drainage [20] and CSF production, circulation and resorption are unaffected by the brain injury, yet these critically interdependent variables are

partially or completely ignored. In short, the traditional treatment paradigm based upon static measures of ICP and CPP is grossly overly simplistic.

For these reasons, it is unsurprising that many trials, involving ~25,000 patients, have failed to demonstrate the value of standard ICP / CPP guided therapy [21]. Three trials published over recent years have dramatically challenged, and one would hope are changing, perceptions [22-24]. In short, blind adherence to a one-size-fits-all absolute critical threshold for ICP and CPP should be consigned to the ever-growing graveyard of accepted ICU practices [25]. The solution / innovation is the broad acceptance of multi-modal neurophysiological monitoring to guide and individualise therapy - for a detailed review and graded recommendations see [26]. What this means in real terms is using additional / complementary physiological variables, trend data and observing the dynamic relationships between variables [27]. Examples include: brain tissue oxygen tension (invasive sensor with small sample volume]; frontal oximtery (non-invasive using near infrared spectroscopy]; jugular venous bulb oximetry; cerebral microdialysis (invasive sensor with small sample volume) and continuous, quantitative (real-time computer analysis of derived variables) EEG. There are many limitations and challenges to the widespread adoption of multimodal monitoring. Cost, complexity and patient heterogeneity make research slow and fraught with confounding factors. Hopefully we have learned that we should individualise and dynamically adapt physiological targets despite inadequate and sometimes contradictory monitoring using our limited and blunt tools of physiological manipulations and therapies. Technological innovations in the integration of bedside monitoring holds significant promise [28].

Specific Interventions to Optimise Cerebral Perfusion

Pathological (as opposed to iatrogenic) cerebral hyperaemia is comparatively uncommon but may be injurious causing excessive intra-cranial blood volume / intra-cranial hypertension and vasogenic oedema. Therapeutic strategies include analgesia, sedation and anti-hypertensive agents such as labetalol. Venodilators, such as glyceryl tri-nitrate are relatively contra-indicated in the presence of an elevated ICP as in theory at least, such agents can increase intra-cerebral blood volume lending to further increases in ICP. More commonly, cerebral perfusion is low, usually in the context of an elevated ICP. Increasing cerebral perfusion can be achieved by a combination of increasing the MAP and / or decreasing the ICP. As detailed above multimodal monitoring should be used to determine the effectiveness of interventions.

Increasing the MAP is achieved using standard therapies; intravenous fluids and vasopressors / inopressors. There is a compelling argument that the

cardiovascular therapy of such patients requires continuous cardiac output monitoring to achieve stroke volume optimisation (not maximisation] together with the assessment and management of myocardial dysfunction. Any brain injury can result in so-called neurogenic stunned myocardium (a phenotype of Takotsubo cardiomyopathy) - the pathophysiology of which is reviewed here [29]. The optimal management of this myocardial dysfunction in concert with optimal cerebrovascular therapy remains to be determined, with some evidence to suggest that standard therapies are either ineffective or detrimental. Novel therapeutic approaches such as hyperinsulinaemic euglycaemia and levosimendan are being actively investigated.

Decreasing the ICP can be achieved by a number of means, which are often used in combination:

- Simple interventions include head elevation to 30-50° coupled with unobstructed cerebral venous drainage (neutral head position, appropriate endotracheal tube fixation and avoidance, if possible, of large bore jugular venous lines). Of note, until recently, the importance of cerebral venous drainage has probably been under appreciated [20, 31]. However, translation from this new found awareness to routine clinical measurement and intervention is seemingly a long way off [32].

- Analgesia-sedation delivered by continuous intravenous infusions of opiates and propofol and / or midazolam are routinely used to reduce ICP; blunt / obliterate patient responses to ICU care (such as coughing, gagging and ventilator dysynchrony); and reduce cerebral metabolic demand in the face of inadequate supply. However, there is conflicting evidence regarding the neurotoxicity and neuroprotection induced by all of these agents [33-36]. The most plausible explanation for these observations relates to the effects these drugs have on bioenergetic homeostasis [37] and the probability that they all have a relatively narrow therapeutic window. Furthermore, despite the high incidence of acute severe brain injury and the ubiquity of continuous sedation in the care of these patients there is an astounding lack of data on the efficacy, safety and effects of these agents on long-term clinical outcomes. There is no evidence that any one agent or combination is superior to any other [38, 39]. More recently, the practice of regular (4 hourly to daily) sedation holds in patients with acute severe brain injury has emerged [40, 41]. There is an argument that titrating these infusions to both clinical and neurophysiological parameters is more logical than blind adherence to continuous, fixed, high dose infusions. Well designed studies to address these issues are essential and long overdue.

- Taking sedation to its extreme, the use of barbiturate coma as a rescue strategy for refractory intracranial hypertension is common but has no evidence base [42]. There is only one published study from the modern era. It is a single US centre, retrospective case series, which paints a somewhat rose-tinted picture of functional survivors [43]. The cohort presented is a very select 54 patients from a pool of 4,934 patients admitted between April 1998 and December 2004, with an Abbreviated Injury Scale head score of 3 or greater. They had a mean age of 16.8 ± 8.6 years (range, 0.5–39). Of these 54, 19 survived to 1 year follow up, of whom 8 (15%] reported no disability and 5 had moderate disability (using the 5 point Glasgow Outcome Score). The remaining 6 were in a vegetative state. The optimal drug / drug combination, the physiological target (ICP and / or EEG burst suppression) and the duration of coma are unknown. Barbiturate coma is associated with a very high incidence of ICU complications, including myocardial depression, intestinal paresis and hospital acquired infections, most especially, ventilator associated pneumonia.

- Hyperosmolar therapy either with mannitol and / or hypertonic saline is commonly employed in the management of intracranial hypertension [44, 45]. There is unequivocal evidence to support the use of bolus mannitol therapy in the acute reduction of rapidly rising ICP to create a time window for definitive therapy [46]. Caution with this therapy is essential to avoid hypovolaemia / hypotension. However, repeated or continuous use of mannitol cannot be recommended and may be counterproductive due to accumulation within the injured brain causing rebound / refractory intracranial hypertension [47, 48]. Alternatively, hypertonic saline can be used as an acute bolus therapy [49, 50], as repeated doses or as continuous infusion [44]. However, despite its increasing popularity, caution should be employed with continuous infusions or targeted hypernatraemia (145-155mmol/l), neither of which are proven to be safe or efficacious [51, 52]. Various strengths and regimes of hypertonic saline have been employed but none established as clearly superior. Hypertonic sodium lactate maybe an equivalent or even superior therapy [53, 54]. Overall, on the basis of limited evidence hypertonic electrolyte solutions appear to be marginally superior to mannitol. However caution should be applied when using osmotherapy therapy beyond a temporising bridge to surgical intervention [55, 56]. Hyperoncotic therapy has no place in the routine management of intra-cranial hypertension.

- Steroid therapy, specifically, dexamethasone and methylprednisolone, are not recommended as therapies for intracranial hypertension

following acute brain injury (any cause) [57, 58]. The only circumstances in which dexamethasone is recommended for the treatment of intracranial hypertension is in the context of primary [58] or secondary brain tumours [59].

- "Lund" therapy is a holistic strategy that aims to minimise cerebral oedema and optimise brain perfusion [60]. The concept aims to continuously achieve normovolaemia, normal haematocrit (using pRBC Tx), normal plasma oncotic pressure (using hypertonic 20-25% albumin) and if possible, the use of β1-adrenoreceptor antagonists, α2-agonists and angiotensin II receptor blockers. The very limited published data appears to support this approach but it has not been compared to a more conventional strategy in a randomised controlled trial. For a pro-con debate see [61, 62].

- Insertion of an external ventricular drain (EVD) not only permits continuous, global, ICP monitoring, it also facilitates controlled drainage of CSF to maintain a target ICP [63]. However, EVDs are invasive, and are associated with a small but significant risk of local haemorrhage and ventriculitis [64]. There are no absolute indications and their use tends to depend on the preference of individual neurosurgeons. A recent trial (mentioned above] suggests a significant survival advantage of EVDs over parenchymal ICP probes [9].

- Therapeutic hypothermia is a recognised rescue therapy for refractory intracranial hypertension although its use remains controversial [65]. Its use has also been investigated as a pre-emptive strategy in patients with severe traumatic brain injury. Almost all aspects of this intervention remain controversial but the current best evidence suggests that the target temperature should be in the range 35.0-35.5ºC, the duration of therapy 4-6 days and that re-warming should occur at a maximum rate of 0.2ºC/hour [66]. It is the subject of the Eurotherm3235 study [67] that has now stopped recruiting despite not having enrolled the proposed target number of participants (http://www.eurotherm3235trial.eu/home/index.phtml). Two other large trials are still recruiting POLAR-RCT (NCT00987688), the HOPES Trial (NCT02064959).

- Surgical evacuation of any mass lesion is strongly indicated in the following situations [63]:

    - Acute extradural haematoma: volume >30cm3 as measured on CT scan

- Acute subdural haematoma: thickness >10mm or midline shift >5mm as measured on CT scan
- Acute subdural haematoma: thickness >10mm or midline shift >5mm but GCS score <9, which decreased by ≥2 points between injury and admission and / or presenting with fixed dilated pupils and / or ICP >20mmHg
- Intraparenchymal lesion: CT evidence of mass effect or increased ICP refractory to medical treatment or progressive neurological deterioration referable to lesion
- Frontal / temporal contusion: volume >50cm3 as measured on CT scan or GCS score 6–8 and volume >20cm3 and midline shift >5mm / compression of cisterns
- Posterior fossa lesion: mass effect on CT or neurological deterioration or deterioration referable to lesion

Lesions not fulfilling these criteria may be conservatively managed along with serial imaging and close monitoring

- Decompressive craniectomy (DC) is arguably the most effective and definitive treatment of acute intracranial hypertension. However, despite over 100 years of recorded procedures, controversy remains regarding all aspects of this intervention. Though the procedure (if sufficiently extensive] unequivocally controls ICP, it permits dramatic brain swelling that is associated with deleterious effects on perfusion, diffusion, cellular metabolism, axonal integrity and intercellular co-dependency [68]. Despite the potential for harm and a significant incidence of complications in survivors [69] there has been a growing enthusiasm for the procedure and a widening set of indications. To date, only one randomised control trial of DC has been published, though one other has completed recruitment (RESCUEicp http://www.rescueicp.com/frameset4.html) and others are underway. In the completed study, patients with severe, diffuse traumatic brain injury and refractory intracranial hypertension were randomised to either standard medical care (including osmotherapy and barbiturate coma] or standard care and a large bi-fronto-temporal decompressive craniectomy [70]. The study ran for 7 years and 5 months and recruited 155 patients from a screened pool of 3478, the majority being excluded as a consequence of having mass lesions (n=1222) or ICP controlled at <20mmHg (n=1105). The groups were reasonably well matched but the median age was 24. 70 of 73 patients randomised to DC and 4 of 82 in the control group actually underwent DC. Roughly one third of patients received barbiturates for ICP control prior to randomisation, whilst a third of the DC group and 77% of the control group received thiopentone post randomisation. Post

randomisation, the use and quantity of both mannitol and hypertonic saline was markedly higher in the control group. At 6 months follow up, 19% of the patients had died (equal proportions] and 6% had little or no disability (equal proportions]. Of the remaining 75% the functional outcomes were significantly better (albeit significantly disabled) in the control group. This unexpected result has generated many column inches, predominantly decrying the lack of generalisabilty of this study together with calls not to change current practice. Though DC undoubtedly has a place in a proportion of patients with refractory intra-cranial hypertension, that place is uncertain.

Adjunctive Interventions

Two additional components of standard neuro ICU care are also worthy of consideration in minimising secondary brain injury, packed red blood cell (pRBC] transfusion and prophylactic anticonvulsants.

Anaemia is associated with worse outcomes in all forms of critical illness including traumatic brain injury, spontaneous aneurysm subarachnoid haemorrhage and acute stroke [71]. Physiologically, anaemia causes two problems, a reduced haematocrit, which adversely effects functional capillary density, and, a reduced arterial oxygen content that requires an increase in cardiac output to maintain oxygen delivery. However, pRBC transfusion, though it may restore haemoglobin concentration, has myriad adverse effects including on the microcirculation and the immune system [72]. Accordingly, a large number of trials of pRBC transfusion have been conducted over recent years in diverse patient populations to determine the effects on clinical outcome. This evidence supports a haemoglobin concentration transfusion trigger of 70g/L [73]. Two recently published, large studies in patients with severe traumatic brain injury confirm the appropriateness of this threshold [74, 75]. Two follow-up publications from the epo and transfusion study group and a third study from a separate group provide biological explanations for the detrimental effects of pRBC transfusion following acute brain injury [76-78].

The incidence of post acute brain injury seizures varies widely and depends upon the nature, location and type of injury [79]. Younger patients (15-30 years of age] appear to have a higher risk. Such seizures are often classified as immediate (first 24 hours], early (day 2 - 7) and late (after 7 days). The incidence following severe traumatic brain injury is in the order of 4%. Prophylactic anticonvulsant therapy, through recommended in some guidelines is inconsistently applied. Phenytoin is considered the drug of choice based upon a single, 25 year old study that had an unprecedented early seizure rate in the control group - reviewed

here [80]. Phenytoin has poor pharmacokinetics, a narrow therapeutic window (requiring monitoring], causes both neuro and systemic toxicity (especially with prolonged use], is associated with rare but catastrophic adverse reactions and has many drug-drug interactions. If used for prophylaxis, it should be stopped after 7 days. Even with this short duration of therapy there are concerns about its adverse effects on long term functional outcomes. Levetiracetam is rapidly being adopted as an alternative. It appears to be equally effective but safer with less toxicity. Of note, there are no randomised, placebo control trials of prophylactic anticonvulsant use in the modern era.

Other Potential Therapies to Minimise Secondary Injury and Chronic Brain Inflammation

Our knowledge of the cascade of events from injury to neuronal cell death is extensive, if incomplete. As this knowledge has grown the question as to whether we can intervene and limit the damage with a specific therapy has been doggedly pursued. In excess of 140 separate compounds and strategies have been investigated for their potential neuro-protective effects [81, 82]. There has been much justified criticism of the poor quality of trials, which have arguably brought the field into disrepute [83]. Many therapies, that had shown initial promise in animal models, have failed to demonstrate any clinical benefit when trialled in patients. One potential explanation is that there are given too late in the clinical course of events, when the damage is irreversible. A second and related explanation is the failure of the cerebral-microcirculation, which results in inadequate delivery of the trial agent to the injured, but potentially salvageable, neuronal tissue. A third explanation is that no single agent is ever going to be effective as it cannot treat even a fraction of the myriad processes and cell types involved. Table 13-1 and Table 13-2, lists neuroprotective therapies under active investigation and gives key references for each. Table 13-3, lists recent neutral and negative neuroprotection studies.

Table 13-1: Neuroprotective therapies under active investigation

Therapy	Key reference(s)
(N-)acetylcysteine	RCT in mild TBI which shows benefit [84] Follow up proof of principal study in 2 animal models [85]
Amantadine	RCT in severe TBI which shows an increase in the pace of recovery [86]
Calorie restriction, ketogenic diet, and ketone bodies. BUT early feeding beneficial	Conceptual reviews [87-89]. Animal study [90]. Meta-analysis [91]
Cell cycle inhibitors - cyclin-dependent kinases Non-selective (Flavopiridol) Selective (Roscovitine)	Conceptual review [92]
Cell therapies	Conceptual review [93]
Cerebrolysin	Cochrane systematic review - "no evidence of benefit" [94] A retrospective, multi-centre cohort study which suggests benefit [95]
Citicoline*	Conceptual reviews [96, 97]
Gases Normobaric hyperoxia*, hyperbaric oxygen; hydrogen, carbon dioxide, nitric oxide, helium, argon, xenon, hydrogen sulfide and carbon monoxide.	Conceptual review [98]
Iron chelation	Conceptual review [99] Animal study [100]
Lactate, pyruvate and erythropoietin	Conceptual reviews [54, 101]

Therapy	Key reference(s)
Levetiracetam (pleiotrophic neuroprotectant)	Conceptual review [102]
Magnesium sulphate Montherapy In combination	Meta-analysis [103] With mannitol [104]; hypothermia [105]; polyethylene glycol [106]
Melatonin	Conceptual review [107]
Methamphetamine (low-dose)	Conceptual review [108]
Minocycline	Conceptual review [109]
Oestrogen, progesterone* and neuro-steroids	Conceptual reviews [110-112] NCT00973674 results awaited
Peroxisome proliferator-activated receptor (PPAR) agonists fenofibrate (PPAR-α agonist) pioglitazone and rosiglitazone (PPAR-γ agonists)	Conceptual review [113] Conceptual review [114]
Post conditioning	Conceptual reviews [6, 115]
Propranolol + / - clonidine	Retrospective cohort study which suggest benefit [116] Prospective RCT currently recruiting [117]
Sodium valproate (as a histone deacetylase inhibitor)	Conceptual review [118]
Statins*	Conceptual reviews [119, 120]
Tranexamic acid	CRASH3 trial in progress [121] Meta-analysis [122]
Trans-sodium crocetinate	Conceptual review [123] Animal study [124]

Table 13-2: Recent neutral or negative studies

Agent
Albumin - large, international RCT in stroke patients [125]
Citicoline - 2 recent large scale, international, multi-centre RCTs failed to show any benefit in either TBI or stroke patients [97].
Cyclosporine A - 3 recent neutral studies and one ongoing study [93]
Erythropoietin - negative study in acute ischaemic stroke [126]; neutral study (complex protocol RCT) [75]
Oxygen - normobaric hyperoxia associated with higher mortality and worse functional outcomes compared to normoxia [127]. However, small RCT of hyperbaric + normobaric episodic exposure showed benefit [128]. RCT of episodic hyperbaric therapy in mild traumatic brain injury > 4 months post injury demonstrated no effect [129].
Progesterone - 2 large multicentre RCTs showed no benefit in TBI [130].
Statins - Two recent large, multicentre RCTs showed no benefit in patients with aneurysmal subarachnoid haemorrhage [131, 132].

Conclusion

Brain injury is common and a major cause of death and disability. Protecting the brain from secondary injury is possible with the early delivery of best supportive care being the most effective intervention. Complex multi-modal monitoring of neurophysiology to individualise inventions that affect ICP and CPP is essential but challenging. A variety of therapies continue to be investigated that may, in the future, have positive effects on functional neurological outcome.

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