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Artificial Organs

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ISBN 978-1-84882-281-8 e-ISBN 978-1-84882-283-2
DOI 10.1007/978-1-84882-283-2

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Control Number: 2009920379

Printed on acid-free paper

Springer Science+Business Media
springer.com

Foreword

Artificial organs have come a long way since the first dialysis machine, the rotating artificial kidney, was invented in 1944 by Willem Johan Kolff, who is known as the "father of artificial organs". At that time he met stiff resistance from his hospital superiors but his persistence paid off and a million saved lives have been attributed to his first invention. He was indeed the first to mix medicine and engineering. An artificial organ is any machine, device, or other material that is used to replace the functions of a faulty or missing organ or other parts of the human body. Some body parts are more of a challenge than others. The heart has one purpose and it is to pump blood; however, the liver has biochemical and physiological functions which are difficult to simulate. The implantation of an artificial organ is critical because of the patient life dependency on the artificial organ itself. The treatment of choice is organ transplantation, however, transplant candidates face a long waiting time and many die while on the waiting list. In addition there are patients who are excluded from transplantation because of age or presence of other diseases. This book presents an overview of the current state of knowledge of artificial organs including the liver, pancreas, kidney, heart, cochlea, skin, stem cells, composite tissue allograft, and sphincters. It is designed for students interested in the field of organ replacement and bioartificial organs and it promotes an understanding of the designs and materials required for successful implants. It fulfills a useful place in the medical literature. The editors have gathered together experts in a variety of different fields both from the experimental and clinical aspects. Research in the field of artificial organs will lead to a closer relationship between science and technology and provides a stepping stone for the future.

Professor the Lord Darzi of Denham KBE

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Management of Multiorgan Failure After Artificial Organ Implantation

Michael Devile, Parind Patel and Carlos MH Gómez

Cardiovascular Failure

The requirements of hemodynamic support in patients with artificial organs follow the same principles as for any other patient. Ultimately the need for such support will arise if the patient is in shock. The key disturbance in shock is the inability of the tissues and cells to obtain and utilize enough oxygen for their aerobic respiratory needs, ultimately resulting in cell death.

Classification

Shock is classified into four types based on the underlying pathophysiological mechanism: hypovolemic, cardiogenic, obstructive, and distributive. (Table 1-1). The patient with artificial organs will have a higher risk of all of the above mechanisms at various stages of the peri and postoperative process and extra vigilance is therefore necessary. The management of shock should nevertheless follow basic critical care principles: re-establishing perfusion to vital organs while treating the underlying condition.

Hypovolemic Shock

This can often present as an emergency (due to massive hemorrhage for instance) or in a more indolent manner leading to slow organ hypoperfusion (due to a mismatch of fluid input and output). Initial resuscitation should consist of restoring intravascular volume, but more importantly reversing the cause (bleeding vessels, coagulopathy, reversing gastrointestinal losses). The choice of fluid should be based on the fluid type that has been lost. For example, blood and blood products should replace blood and crystalloid should be used for vomiting and dehydration. For mild to moderate blood loss similar to that expected in a routine renal transplant crystalloid (2–3 times the lost blood volume) or colloid (1–2 times the lost blood volume) is usually appropriate.

The debate of crystalloids versus colloid has not been resolved; there exists numerous conflicting trials, meta-analysis, and opinions. The crystalloids of choice in resuscitation are normal saline or lactated Ringer's solution because their osmolality is similar to that of the intravascular volume. In large-volume resuscitation, however, excessive normal saline infusion may produce hyperchloremic metabolic acidosis. As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points and results in more edema. Crystalloids are less expensive. The current choice of colloids includes hydroxyethyl starch, gelatins, and albumin all of which offer more efficient intravascular volume expansion. The administration of hydroxyethyl starch may increase the risk of acute renal failure, although newer preparations appear to be less problematic. Previous concerns of albumin resuscitation leading to increased mortality has recently been dispelled by the SAFE study indicating that albumin administration was safe and as effective as crystalloid. With any fluid there is inevitable dilution of blood (red blood cells) and coagulation factors which needs to be considered.

N. Hakim (ed.), *Artificial Organs*, New Techniques in Surgery Series 4, DOI 10.1007/978-1-84882-283-2_1,

Table 1-1. Causes of Shock

Type of shock	Signs	Hemodynamic variables	Causes relevant to artificial organs
Hypovolemic	Weak pulse	↓CVP/PAOP	Massive hemorrhage
	Narrow pulse pressure	↓CO	Gastrointestinal fluid loss
	Poor peripheral perfusion	↑SVR	Diuresis
Cardiogenic	Pulmonary/peripheral edema	↑CVP/PAOP	Acute coronary syndrome
	Gallop rhythm, arrhythmias, & murmurs	↓CO	Valvular heart disease/dysrhythmias
	Poor peripheral perfusion	↑SVR	Cardiomyopathy
Obstructive	Distended neck veins	↑CVP/PAOP	Tension pneumothorax
	Poor peripheral perfusion	↓CO	Cardiac tamponade
	Respiratory failure	↑SVR	Pulmonary embolism
Distributive	Pyrexia	↓CVP/PAOP	Sepsis/SIRS
	Warm and vasodilated peripheries	↑CO	Anaphylaxis
	Edema	↓SVR	Acute liver failure

Whatever the fluid, the therapy should be titrated to re-establish normal blood pressure, pulse, cardiac output, and end-organ perfusion.

Cardiogenic Shock

Cardiogenic shock essentially refers to the failing pump. The blood flow to the vital organs and peripheries is decreased due to an intrinsic defect in cardiac function. This can be due to pathology affecting the heart muscle, rhythm, or the valves.

The most common cause, both generally and within transplant medicine and artificial organs, is myocardial ischemia. As in all types of shock, treating must be the priority: in cardiogenic shock this is achieved by reversing the ischemia (with angioplasty, thrombolysis, or emergency coronary artery bypass grafting), correcting the dysrhythmias, or simply supporting the circulation while allowing time for the stunned myocardium to recover while preserving perfusion. The early introduction of such measures has resulted in a significant improvement in ischemia induced cardiogenic shock and mortality.

In terms of hemodynamic support, various inotropic agents exist (Table 1-2) which act via modulation of the sympathetic nervous system either as direct agonists (dobutamine, dopexamine, dopamine, adrenaline) or indirectly by inhibiting phosphodiesterase III (e.g., milrinone). Both mechanisms result in an increase in cAMP, an intracellular modulator of myocardial contractility and arteriolar vasodilation. Often the inotropes, because of the arterial vasodilatory effects or the concurrent systemic inflammatory response syndrome that may occur with cell death, are combined with vasopressors to maintain overall perfusion pressure in general and coronary artery perfusion pressure in particular. Although the use of these agents is thought of as essential to the care of a hemodynamically unstable patient, there is great variability within countries and centers as to the optimum agent. It is also notable that the role of

Table 1-2. Vasoactive Drugs in Sepsis and the Usual Hemodynamic Responses

Drug	Dose	Principal mechanism	Cardiac output	Blood pressure	SVR
Dobutamine	2–20 mcg/kg/min	Beta 1	++	+	+
Dopamine	2–10 mcg/kg/min	Dopamine→Beta 1→Alpha	++	+	+
Dopexamine	0.25–4 mcg/kg/min	Dopamine + Beta 2	++	+/–	–
Epinephrine	0.01–1 mcg/kg/min	Beta 1+ Beta 2 + Alpha	++	+	+
Milrinone	0.3–0.7 mcg/kg/min	Phosphodiesterase inhibitor	+	+/–	–
Norepinephrine	0.01–1 mcg/kg/min	Alpha > beta 1, beta 2	+	++	++
Phenylephrine	0.2–2.5 mcg/kg/min	Alpha	+	++	++
Vasopressin	0.4–0.10 U/min	V1 receptor	+	+	++

sympathetic nervous system stimulation is of questionable benefit in the failing heart where the underlying cause of failure has not been addressed.

Recently Levosimendan, an inotropic agent that acts independently of the sympathetic nervous system by sensitizing the myocardial contractile proteins to calcium has been shown to improve hemodynamics and cardiac output in patients with cardiogenic shock following ACS as well as after coronary bypass surgery. This may prove useful as a pharmacological bridge during myocardial stunning, possibly with fewer (sympathetically mediated) detrimental effects.

Combined with revascularization, mechanical support with IABP counterpulsation improves outcome in patients with cardiogenic shock following acute coronary syndrome. Specific to cardiogenic shock, the use of ventricular assist devices may transiently improve hemodynamics but this has not yet been translated into mortality benefits and presently is reserved as a salvage strategy in centers where it exists and other measures have failed. The same can be said of extracorporeal membrane oxygenation, although both of these techniques are more useful following cardiac transplantation.

It must also be remembered that hypovolemia may also play a significant part in cardiogenic shock, requiring the careful administration of fluid to improve cardiac output via the Frank–Starling principle. Simultaneous monitoring for fluid overload via central venous, pulmonary artery pressures, and signs of pulmonary edema must be undertaken.

Distributive Shock

Distributive shock occurs when peripheral vascular dilatation causes a fall in systemic vascular resistance. As a result cardiac output is often increased but the perfusion of many vital organs is compromised because the blood pressure is too low and the body loses its ability to distribute blood properly

The most common cause is septic shock, but a similar picture can be seen in anaphylaxis and acute adrenal insufficiency. In addition a significant organ reperfusion induced systemic inflammatory response syndrome (SIRS) immediately follows transplantation which can mimic distributive shock. However, newer immunosuppressive agents have dramatically reduced the rates of acute graft rejection over the last decade but instead have exacerbated the problem of post-transplant infections. Although clinical features include warm peripheries bounding pulses, the significant alterations in the microcirculation results in tissue and organ dysfunction. The longer the distributive shock remains the greater the organ failure and mortality. As a result of the persistently high mortality from septic shock, the Surviving Sepsis Guidelines have been acknowledged and implemented across the world. Incorporated within these are the essential themes of early and appropriate administration of antibiotics and early goal directed shock resuscitation. In the initial stage, because of capillary leakage, hypovolemia contributes significantly to the shock. Hence fluid resuscitation should be initiated as in hypovolemic shock. Simultaneously, vasopressor therapy is required to maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved. Below a certain mean arterial pressure, autoregulation in various vascular beds can be lost and perfusion can become linearly dependent on pressure. A mean arterial pressure of 65 mmHg is generally accepted as a target to preserve tissue perfusion. However, in those who have hypertension, as in many renal transplant patients, autoregulation will occur at a higher point and hence greater MAP will be needed.

Fluids and vasopressors are targeted to hemodynamic variables along with assessment and trends of regional and global perfusion such as urine output, conscious level, acidemia, and blood lactate concentrations.

As shown in Table 1-2 many vasopressors are available. Norepinephrine may have advantages over epinephrine in causing less compromise to the splanchnic circulation and lactatemia. Dopamine may cause unwanted tachycardia and arrhythmias and provides no advantage in preventing renal failure. Concerns also exist about the immunosuppressive effects of dopamine. Vasopressin may be an alternative to norepinephrine or in patients with norepinephrine resistance, although again there is little data to support its routine use and certainly in higher doses cardiac, digital, and splanchnic ischemia have been reported.

To complicate matters, there is significant cardiac dysfunction directly related to sepsis that may require combination therapy with inotropic agents as for cardiogenic shock.

Finally, steroids remain controversial: they probably have significant effects in reversing shock, but long-term side effects such as neuropathy and recurrent infections are thought to be at least in part responsible for the observed lack of mortality benefit.

Obstructive Shock

The treatment of obstructive shock is relatively simple in principle although may prove to be difficult in practice.

Relief of the obstruction is achieved by

- Urgent pericardiocentesis in cardiac tamponade. This is a relatively likely complication following cardiac transplant, but less likely in other solid organs although anticoagulation or coagulopathy that may occur can lead to tamponade.
- Needle thoracostomy followed by formal chest drain in tension pneumothorax. This may occur perioperatively secondary to diaphragmatic damage or as a complication of central venous catheterization or positive pressure ventilation.
- Thrombolysis, pulmonary embolectomy, or surgical removal of a massive pulmonary embolism should be considered in any post-transplant patient presenting with sudden dyspnoea and hypoxia. The condition along with fat embolism is more frequent following lung transplant.

Maintaining a high preload may help with obstructive shock, with fluid resuscitation improving the patient's cardiac output and hypotension temporarily while buying time for definitive intervention.

Conclusion

Shock is one of the most frequent situations encountered in critical care patients. Post-transplant and/or artificial organ insertion shock is associated with poor outcome unless rapidly treated and reversed. In any shocked patient, hemodynamic therapy should be targeted to achievable goals. This includes

- Find and treat the cause: this is the most difficult and yet crucial aspect as the diagnosis of the underlying problem may be difficult to establish. Without addressing the ischemia or hemorrhage the remaining targets would be pointless.
- Establish adequate intravascular volume resuscitation: this is relevant to hypovolemic but also to other forms of shock in order to optimize cardiovascular function.
- Establish an adequate blood pressure: this may require the use of vasopressors and inotropes, often in combination.
- Ensure organ function by targeting the above therapy to maintain and preserve function of all systems and prevent the situation cascading into multi-organ failure.

The challenge is to reverse the patient's deteriorating condition rapidly to achieve an overall successful outcome.

Respiratory Failure

Respiration is the complex process involving ventilation, pulmonary gas exchange, oxygen delivery by the circulation, and oxygen utilization by the tissues for the production of cellular high-energy phosphate. By convention, respiratory failure is used in a clinical context to mean failure of ventilation and/or pulmonary gas exchange.

Respiratory support in a transplant patient may be required immediately postoperatively or at a later occasion for indications similar to that of the general population.

The principle of the management of respiratory failure should begin primarily with the diagnosis and treatment of the underlying pathology, often simultaneously with respiratory support.

Definition

Type 1

This is defined as hypoxemia without hypercapnia, indeed the CO_2 level may be normal or low. It is typically caused by a ventilation/perfusion mismatch; the air flowing in and out of the lungs is not matched with the flow of blood to the lungs.

This type is caused by conditions that affect oxygenation like:

- Parenchymal disease
- Diseases of vasculature and shunts.

Type 2

This is defined as build up of carbon dioxide from energy utilization. The underlying causes include

- Reduced breathing effort (in the fatigued patient)
- Increased resistance to breathing (such as in asthma)
- A decrease in the area of the lung available for gas exchange (such as in emphysema).

There are of course situations in which both mechanisms coexist in varying degrees such as asthmatics who develop chest infections.

Causes of Respiratory Failure

Many of the causes (Table 1-3) have specific treatments. Respiratory support may become necessary due to either continued deterioration of the primary cause or development of acute lung injury. Table 1-4 outlines some factors known to precipitate lung injury.

Mortality from acute respiratory failure is approximately 40%, but rises significantly if associated with failure of other organs.

Management of Respiratory Failure

Treating the underlying cause must be the priority. Ventilation, either non-invasive or invasive, merely supports the respiratory function of the lungs while they are recovering from the primary pathology.

Table 1-3. Causes of Respiratory Failure

Pulmonary dysfunction
Asthma
Chronic obstructive pulmonary disease
Pneumonia
Pneumothorax
Hemothorax
Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)
Cystic fibrosis
Cardiac dysfunction
Pulmonary edema
Valve pathology
Other
Fatigue due to prolonged *tachypnoea* in *metabolic acidosis*
Intoxication with drugs (i.e., *morphine, benzodiazepines*) suppresses respiration.
Coma
Neuromuscular disease

Table 1-4. Precipitating Conditions Relevant to Transplant Medicine

Direct	Indirect
Pneumonia	Massive transfusion
Lung contusion	Sepsis
Aspiration of gastric contents	Pancreatitis
Fat embolism	Cardiopulmonary bypass
Toxic inhalation	Burns
Pulmonary surgery	Bone marrow transplant
Reperfusion injury	Drugs and toxins

Initial supportive management may consist of supplemental oxygen progressing to non-invasive ventilation. The effectiveness of NIV will depend on the underlying condition and is now considered as a first-line intervention in patients with COPD exacerbation. In acute cardiogenic pulmonary edema, NIV either as continuous positive airway pressure (CPAP)or as Bi-level positive airway pressure (BiPAP) will improve gas exchange, reduce respiratory rate, and the need for intubation. Its use in other causes of respiratory failure (pneumonia, asthma, acute lung disease, and neuromuscular disease) are less well defined , but at the very least may provide time to prepare for intubation or more definitive treatment.

The indications for intubation and mechanical support are also difficult to describe as they depend not only on the degree of hypoxia and/or hypercarbia but also on the clinical observations. These include trends in respiratory rate, use of accessory muscles, ability to cough and talk, and changes in mental state.

Once ventilated, the emphasis should continue with treatment of the predisposing cause of respiratory failure, as well as avoidance of ventilator induced lung injury and ventilator-associated pneumonia. The causes of respiratory failure (Table 1-3) may also lead to acute lung injury directly or as a result of prolonged mechanical ventilation.

Acute Lung Injury

Definition

Acute lung injury and its more severe form, acute respiratory distress syndrome (ARDS) are an inflammatory response of the lung. The insult

may be direct (pulmonary) or indirect (non-pulmonary) and the result is characterized by:

- Acute onset
- Bilateral infiltrates on chest radiograph
- Clinical or measurable absence of left atrial hypertension
- Hypoxemia: Pa O2/FiO2 of <40 kPa for ALI and < 26.7 kPa for ARDS

Epidemiology

The reported incidence of ALI is variable. A recent population-based study from Washington showed an incidence of acute lung injury of 78.9 per 100,000 person-years.. The mortality does appear to be declining. In the late 1980s, the reported mortality was around 60–70% (1995). The KCLIP study shows the in-hospital mortality rate for ALI of 38.5% and ARDS of 41%. The incidence of acute lung injury increased with age from 16 per 100,000 person-years for those 15 through 19 years of age to 306 per 100,000 person-years for those 75 through 84 years of age. Mortality increased with age from 24% for patients 15 through 19 years of age to 60% for patients 85 years of age or older. It is estimated that there are 190,600 cases of acute lung injury in the United States which are associated with 74,500 deaths and 3.6 million hospital days.

There is no data regarding the incidence of ALI or ARDS following artificial organ implantation, although it seems likely the incidence is greater as patients are more susceptible to many of the causes, in particular infection and sepsis.

Pathogenesis

The initial insult to the lungs results in an inflammatory response which causes alveolar deposition of fibrin and collagen, pulmonary microthrombi, and acute destruction of the alveolo-capillary membrane leading to increased permeability and widespread inflammatory alveolar exudate.[28] There may follow a fibrotic response characterized by repair and proliferation of fibroblasts and type II pneumocytes.

The consequences of such changes are alveolar edema and collapse, reduced lung compliance, increased venous admixture, and hypoxemia. There is also pulmonary vasoconstriction, which increases alveolar dead space, exacerbates the ventilation-perfusion mismatch and may lead to pulmonary hypertension and increased right ventricular work with consequent failure.

Management

Continuous positive airways pressure (CPAP) may be of benefit in mild cases, however, most patients will require early intubation and mechanical ventilation. Indications include hypoxemic or hypercarbic respiratory failure, acidemia, exhaustion, and reduced or altered consciousness. Profound sedation is usually required for ventilation as struggling or coughing can cause loss of recruited lung and worsening oxygenation. Paralysis may be necessary if sedation alone does not settle the patient.

The aim of ventilation is to improve oxygenation without causing further damage to the lungs. Difficulties arise as some alveoli are normal and open while others are stiff and collapsed. It is therefore necessary to try to open the collapsed alveoli without damaging the normal areas. The main causes of ventilator-induced lung damage are over-distension, alveolar collapse, capillary leak as well as cyclical opening and closing.

Lung Protective Ventilation

"Lung-protective" ventilation strategies use smaller tidal volumes and pressures in an attempt to protect the lung from both overdistension (VILI – "Ventilator Induced Lung Injury") and dampen or prevent the release of inflammatory mediators that may drive the inflammatory response. If respiratory acidosis develops through the use of low tidal volumes, this is often tolerated ("permissive hypercapnia"). The ARDSnet conducted a multicenter, prospective, randomized, controlled trial from 1996 to 1999 to determine whether the use of low tidal volumes would improve clinical outcomes in ARDS. The trial compared "traditional ventilation" (tidal volume of 12 ml/kg of predicted body weight and a plateau airway pressure of $<$50 cm H_2O) with "low tidal volume" ventilation (tidal volume of 6 ml/kg of predicted body weight and a plateau pressure of $<$30 cm H_2O). The lower tidal volume group displayed a significantly reduced mortality rate, 31 versus 40%. The debate continues as to whether the low tidal volumes were beneficial or the high tidal

volumes were harmful. Nevertheless it appears common practice to ventilate patients on lower tidal volumes (<10 mls/kg).

Fluid Strategy

The management of acutely unwell patients is faced with many dilemmas and ALI is no exception. ALI is characterized by increased pulmonary vascular permeability and some would argue that fluid restriction should decrease alveolar lung edema and improve oxygenation and ventilation. However, this may in turn render the patient hypovolemic, thus reducing cardiac output, oxygen delivery, and organ perfusion. Recent evidence showed restrictive fluid strategy was associated with improved gas exchange and ventilator free days without any detriment to other organs, although without any impact on mortality. Guiding fluid therapy with the use of a pulmonary artery flotation catheter has also shown no benefit in a heterogeneous group of critically ill patients. A simple titration of the least amount of fluid required to maintain general perfusion appears to be the favored strategy at present in ALI patients, particularly with other organ failures.

Positive End Expiratory Pressure

The issue of positive end expiratory pressure (PEEP) is also a source of varying results with large studies showing no benefit but others reporting large beneficial effects on survival and lung physiology. These differences are, in addition to nuances of trial design, probably also reflective of the difficulty in separating PEEP from other ventilatory interventions. There is good evidence to suggest that certain patients with ALI/ARDS have more recruitable lungs and that these certainly are more responsive to PEEP. Current best practice is to set PEEP somewhere above the lower inflection point of the pressure–volume curve and to then perform a PEEP trial in which PEEP is increased so long as there is no corresponding increase in plateau pressure.

PEEP has been applied in ARDS and acute lung injury in an attempt to improve oxygenation and prevent lung shear-stress injury associated with the cyclical opening and closing of collapsed alveoli ("atelectrauma"). In the face of ARDS, most clinicians would apply a PEEP of 5–10 cm H_2O. However, it is important to balance the beneficial effect of PEEP on arterial oxygenation and its adverse effects such as cardiovascular compromise and increased airway pressures and over-distension. The ARDS-net group performed a randomized, controlled trial to determine whether higher levels of PEEP would improve clinical outcomes in patients with ARDS. All patients received mechanical ventilation with a tidal-volume goal of 6 ml/kg of predicted body weight and an end-inspiratory plateau-pressure limit of 30 cm H_2O. Mean PEEP was 8.3 cm H_2O in the lower group and 13.2 cm H_2O in the higher group. There were no significant differences between the groups in the mortality rate or number of ventilator-free days, ICU-free days, or organ-failure free days

Corticosteroids

Corticosteroids have no role in the acute management of ARDS. However, a small trial in only 25 patients (Meduri) suggested a survival benefit if high-dose methylprednisolone is given as a treatment for the later "fibroproliferative" phase. Recently the ARDS Network performed a large multi-center randomized trial to reproduce the previous findings. Although, overall, 60-day mortality was similar between the two groups, methylprednisolone was associated with significantly increased 60- and 180-day mortality rates among patients enrolled at least 14 days after the onset of ARDS. Methylprednisolone therapy increased the number of ventilator-free and shock-free days during the first 28 days, in association with an improvement in oxygenation, with fewer days of vasopressor therapy. When compared with placebo, methylprednisolone did not increase the rate of infectious complications but was associated with a higher rate of neuromuscular weakness. Despite the improvement in cardiopulmonary physiology, the results of this study do not support the routine use of methylprednisolone for persistent ARDS. In addition, starting methylprednisolone therapy more than 2 weeks after the onset of ARDS may increase the risk of death.

Inhaled Pulmonary Vasodilators

Inhaled nitric oxide can selectively vasodilate the pulmonary vascular and reduce pulmonary

hypertension, decrease shunting, and improve gas exchange in ARDS. There are no systemic effects because nitric oxide is scavenged rapidly by hemoglobin. However, numerous large clinical trials have failed to demonstrate that the improvements in oxygenation seen in patients treated with nitric oxide translate into improved outcome. Current expert opinion suggests that nitric oxide should not be used routinely but be reserved for patients in whom adequate oxygenation cannot be achieved by lung protective mechanical ventilation and prone positioning.

Inhaled prostacyclin vasodilates the pulmonary bed as effectively as nitric oxide but does not result in the same improvements in oxygenation. Again mortality benefits have not been proven.

Prone Ventilation

The benefits of prone ventilation are explained by an improvement in ventilation perfusion matching, recruitment of atelectasis, and the delivery of more homogenous ventilation to all parts of the lung. Two large randomized trials have compared the effects of prone positioning on mortality from ARDS. In both trials, there was a significant improvement in oxygenation when patients were turned prone. However, this did not translate into improved clinical outcome. The rates of displacement of endotracheal tubes, vascular catheters, and thoracotomy tubes were similar in the two groups in one trial but increased in the prone group in the other trial. Consensus appears to be that prone positioning is only useful in severe ARDS with dependent disease and refractory hypoxemia.

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) is, in theory, a "lung-protective" mode of ventilation. HFOV provides efficient gas exchange by using very low tidal volumes and high respiratory rates. The application of a constant mean airway pressure in HFOV allows the maintenance of alveolar recruitment while avoiding low end-expiratory pressure and high peak pressures. The mean airway pressure generated by HFOV is usually higher than that generated by conventional ventilation (tidal volumes of 10 ml/kg). A randomized controlled comparing HFOV with a conventional ventilation strategy in 148 adults with ARDS confirmed that HFOV is effective and safe and not associated with significant hemodynamic effects. However, there was no significant difference in mortality between the groups. One of the limitations of this (and almost all of the other older studies of ventilation strategy) was that HFOV was not compared with the current gold standard low*-tidal volume approach used by the ARDSnet trial.

Extracorporeal Support

Extracorporeal membrane oxygenation (ECMO) proposes to provide the gas exchange via veno-venous bypass while maintaining the lungs at rest. The main advantage is that the lungs are not exposed to injurious ventilatory strategies. Again there have been no advantages demonstrated in randomized clinical trials thus far and the technique is only contemplated in refractory hypoxemia in specialist units. Retrospective single center series reported 67% rate of patients weaned of ECMO with a 52% hospital survival (Hemmila. *Ann Surg*. 04;240:595–607). Results of a prospective controlled study (CESAR Trial) are awaited. Preliminary results suggest a relative risk (survival or severe disability) in favor of ECMO in adults with severe acute respiratory failure of 0.69. Modifying the technique to pumpless extracorporeal carbon dioxide while employing a fully protective lung ventilation strategy may be of benefit where hypercapnia is the major manifestation of ARDS.

In summary, there is good evidence to support the following ventilation strategy: low tidal volumes of 6 ml/kg and plateau pressures not higher than 30 cm H_2O, appropriate PEEP as discussed, target arterial oxygen saturations of 90%, pH above 7.2 and judicious fluid administration.

Disadvantages of Ventilation

Although mechanical ventilation is regarded as life-saving support, there are many potential complications including pneumothorax, airway injury, alveolar damage, and ventilator-associated pneumonia, among others. To tolerate endotracheal intubation patients need to be sedated which in turn has many unwanted effects such

as hypotension and gastro-intestinal stasis. Positive pressure ventilation reduces venous return and increases afterload of the right ventricle which in turn may fail and lead to cardiovascular collapse. Patients should be considered for weaning from ventilation at the earliest opportunity

Non-invasive Ventilation (NIV)

This is the use of positive pressure ventilation through specially designed face masks rather than endotracheal tubes. The two most widely used ventilatory modes are continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). It is in general less effective in delivery of pressure ventilation than invasive (endotracheal) ventilation but requires less or no sedation and can be administered in properly equipped units outside intensive care.

It is potentially advantageous in cardiogenic pulmonary edema, a condition in which many clinicians find it useful to undertake a" trial of CPAP" accompanied by conventional pharmacological afterload reduction and diuresis. Recently, a meta-analysis pointed to a reduction in the need for endotracheal intubation and mortality in this group of patients.

Some clinicians advocate non-invasive ventilation as a useful tool to facilitate early extubation. Indeed a randomized controlled trial in predominantly medical patients showed reduced length of ventilation, intensive care stay, tracheostomy requirement, and morality in patients receiving NIV.

NIV is widely established as an important component of the treatment of acute exacerbations in chronic obstructive pulmonary disease. Evidence from pooled randomized controlled trials points to improvements in mortality, length of stay, and intubation rate with early introduction of NIV in addition to usual medical treatment. Many groups also use NIV in the treatment of obesity hypoventilation and obstructive sleep apnea syndromes.

NIV in acute lung injury is neither favored by many clinician nor supported by evidence.

Weaning

Withdrawal from mechanical ventilation should be considered at the earliest opportunity, but only if the patient can support there own ventilation and oxygenation. There are several objective parameters to look for when considering withdrawal, but there is no specific criteria that generalizes to all patients. The objective criteria include

- Adequate oxygenation (e.g., 8 kPa on $FIO_2 >$ 0.4; PEEP $<$5–10 cm H_2O; PO_2/FIO_2 $>$300 mmHg (40 kPa))
- Stable cardiovascular system (e.g., HR $<$140; stable BP; no (or minimal) pressors or inotropes
- No significant respiratory or metabolic acidosis
- Adequate conscious level (e.g., arousable, GCS $>$13, obeying commands, no continuous sedative infusions)
- Adequate cough to clear respiratory secretions
- The acute disease process that led to the patient needing mechanical ventilation must also have been reversed or resolved.

Finally, weaning is a complex and disputed area of critical care medicine in which, however, there is evidence of benefit from a multidisciplinary approach, consistency and simplicity, aggressive treatment of infection and heart failure, nutrition, daily weaning trials, and persistence.

Conclusion

The causes of respiratory failure are multiple. Each will have its own specific treatment, but advances in both non-invasive and invasive ventilatory support have had a significant impact on the outcome of such a life-threatening condition. The most notable benefit is time for the diagnosis and treatment of the underlying condition to occur.. ALI or ARDS as a cause of respiratory failure or consequence of the underlying illness and the need for mechanical ventilation also has a dramatic impact on outcome. Despite greater understanding of the cellular and molecular mechanisms, specific therapies do not exist. However, much has been learnt from salvage therapies and the importance of protective ventilation strategies.

Acute Renal Failure

Epidemiology

Acute renal failure (ARF) is a common complication following major surgery. After major

surgery, incidences can range from 10% for uncomplicated non-cardiac solid organ transplants and artificial organs to 50% in cardiac transplantation and extracorporeal circulatory support.

Its presence carries a high mortality – ranging from 15% with simple pre-renal azotemia to greater than 60% in those requiring renal replacement therapy (RRT).

The most common etiology of ARF in the critically ill transplant patient is in the context of multi-organ failure. The initial insult is usually pre-renal, with renal hypoperfusion occurring from either vasodilation in severe sepsis or hypovolaemia during the peri and immediate postoperative period, e.g., intra-operative hemorrhage or marked extracellular fluid shifts.

Progression from this initially reversible rise in serum creatinine and urea concentrations leads to acute tubular necrosis (ATN). Pre-renal azotemia and ischemic ATN constitute a continuum of the same pathophysiological processes, and together account for 75% of the cases of acute renal failure. Intrinsic damage from renal disease accounts for around 30% of cases in the post-transplant patient (Table 1-5) and is most likely due to chemical/pharmacological injury. Foremost among these are radiocontrast media, nephrotoxic antibiotics, immunosuppressives, and non-steroidal anti-inflammatory drugs.

Table 1.5. Causes of Acute Renal Failure in the Critically ill Post Transplant Surgery Population [After Cosgrove et al. 2007 *Ann R Coll Surg Engl*. **89**:22–29]

Pre-renal
- Hypotension; sepsis
- Hypovolemia: dehydration, blood loss, acute pancreatitis
- Reduced cardiac output: cardiac tamponade
- Intra-abdominal compartment syndrome

Renal
- Acute tubular necrosis
- Drugs: aminoglycosides, non-steroidal anti-inflammatory drugs, radiographic contrast medium
- Toxins: endotoxins
- Hepatorenal syndrome
- Intra-abdominal compartment syndrome
- Pigment nephropathy (myoglobinuria): drug-induced rhabdomyolysis

Post-renal
- Ureteral obstruction: stones, surgical,
- Bladder dysfunction: surgical
- Urethral obstruction: traumatic/prostatic hypertrophy

Obstructive renal failure is less common (10% approximate incidence) in critically ill patients and may follow complications associated with abdominal surgery.

Establishing the underlying cause of acute renal dysfunction in this group of patients is vitally important for the rapid initiation of effective treatment, maximizing the prospect of reversing any acute renal disease. It is also important for prognostic reasons as mortality in acute tubular necrosis can be as high as 65%, compared with 5–20% for those patients with ARF as part of a multisystem disease.

Risk Factors

The most commonly identified risk factors for the development of renal failure are impaired preoperative renal function. Transplant and artificial organ patients also suffer from other factors known to be associated with renal failure, such as hypertension, hyperlipidemia, atherosclerosis, and diabetes. Patients with pre-existing renal dysfunction are at highest risk of developing postoperative renal failure. Renal dysfunction is particularly common in patients awaiting liver transplantation (and/or receiving artificial liver support) and is well documented as an important determinant of outcome. In these patients, quantification of the severity of renal function is complicated by the impact of hepatorenal dysfunction. This is usually present to some degree by the time these patients require transplantation, even when it has not progressed to the full blown hepatorenal syndrome (HRS). None of the studies of long-term renal function in these patients has factored in the potential impact of post-transplant HRS from poor liver graft function and only a few have segregated patients with recurrent hepatitis C or hepatitis B, who may additionally have hepatitis-associated glomerulonephritis.

The measurement of serum creatinine, however, seems to have a limited ability to identify patients with preoperative renal dysfunction because of its variation with age, sex, and muscle mass. Calculated creatinine clearance as an alternative measure of renal function is probably much better at estimating renal reserve, thereby identifying those at greater risk of needing postoperative renal replacement therapy.

Postoperative renal failure requiring (RRT) seems to increase markedly when creatinine

clearance decreases below 60 ml/min, even if the serum creatinine lies in the normal range. Thus, the incorporation of this threshold into the preoperative assessment may help to identify high-risk patients for the early institution of aggressive renal protective therapies, such as volume expansion, use of vasopressors, and/or specific pharmacological therapies.

Age-related predisposition to acute renal failure arises due to a combination of reduced renal reserve, susceptibility to volume depletion, and a reduced ability of the kidney to conserve salt and concentrate urine. Body mass index (BMI) has also been identified as a preoperative predictor of ARF, independent of associated comorbidities such as diabetes and hypertension.

Pathophysiology

Pre-renal Dysfunction and ATN: Renovascular Hemodynamics

Pre-renal disease arises due to either a true hypovolaemia (e.g., acute haemorrhage) or a drop in the effective circulating volume (e.g., fall in cardiac output, widespread systemic vasodilation, or intrarenal vasoconstriction). It arises because, although the normally high renal blood flow exceeds the organ's usual oxygen requirements, only 10% of this passes to the renal medulla, where the P_aO_2 is only 1.2–2.2 kPa. These very metabolically active medullary cells are therefore markedly susceptible to underperfusion and consequent cellular hypoxia.

Autoregulation

Initially the kidney responds by maintaining GFR and renal blood flow to a relatively constant level, through autoregulation. Net filtration pressure and renal perfusion pressure are preserved through an angiotensin II-mediated constriction of the efferent arteriole, accompanied by an intraluminal myogenic compensatory vasodilation of the afferent pre-glomerular arteriole, principally through the paracrine actions of prostaglandins. The net result is maintenance of a near constant renal blood flow within a wide range of mean arterial pressures, from around 60 to 160 mmHg.

Drugs that interfere with this autoregulatory process include antagonists of the renin angiotensin system and cyclo-oxygenase inhibitors such as non-steroidal anti-inflammatory drugs. Another important group of drugs that cause acute constriction of the afferent arteriole after their first postoperative dose is calcineurin inhibitor immunosuppressives (CNI), principally ciclosporin and tacrolimus. These agents cause an acute reduction in renal perfusion by interfering with autoregulation, the effects of which are particularly apparent in situations of hypovolaemia or reduced cardiac output. This is particularly relevant in the immediate postoperative period, where the altered physiological milieu depends on this autoregulatory response.

Postoperative sepsis also directly and specifically interferes with renal hemodynamics through the release of pro-inflammatory cytokines. These interfere with autoregulation through stimulation or antagonism of various mediators, resulting in glomerular endothelial dysfunction and consequent aggravated renal ischemia.

Despite this, pre-renal dysfunction is often reversible if the factors causing the renal hypoperfusion are corrected. The severity and duration of renal ischemia which causes fixed post-ischemic ATN is not well established and variable given different patient characteristics, but there is usually an interval that defines the transition from functional pre-renal to post-ischemic ARF. During this early functional stage, vigilant recognition and aggressive optimization of renal blood flow, through volume expansion and/or cautious systemic vasoconstriction, can restore renal function to normal.

Histological Changes

Histologically, ischemia-induced renal failure in animals includes loss of the proximal tubular brush border, blebbing of apical membranes, and cellular and mitochondrial swelling. With advanced injury, tubular cells detach from the basement membrane and contribute to intraluminal aggregation of cells and proteins leading to tubular obstruction.

It is not clear though, whether this model applies to the critically ill. It has been postulated that in sepsis, cellular malfunction arises through immune-mediated cellular apoptosis. However, post-mortem evidence does not support this, nor do situations where recovery of renal function ensues within days, far quicker than that required for regeneration of renal tubular cells.

An alternative explanation may be that in sepsis cellular energetics are altered due to impaired mitochondrial respiration – a failure of oxygen utilization rather than delivery. This model fits well with the relative paucity of histological tubular changes in septic patients and may account for the occasionally rapid restoration of renal function seen in some critically ill patients.

Renal Optimization After Artificial Organ Implantation

The importance of maintaining adequate hydration and renal perfusion cannot be overstated. The most effective prevention of ARF is stabilization of systemic hemodynamics, optimization of cardiac output and blood pressure and the avoidance of specific risk factors such as nephrotoxic drugs – ensuring meticulous maintenance of immunosuppressive and antibiotic levels. When possible, a CNI should be withheld until renal function has improved, particularly in patients with renal failure from HRS or congestive cardiac failure.

Obstruction to the lower urinary tract should always be excluded and, in postoperative abdominal surgical patients, intra-abdominal hypertension must be considered a contributing factor.

Early recognition and effective management of any acute precipitant can minimize its severity, allowing natural reversal of the pathophysiology. This may include control of surgical bleeding, radiological, or surgical drainage of a septic focus, relief of ureteric and/or urethral obstruction and abdominal decompression to treat abdominal compartment syndrome.

Indeed, the evolution of clinical ATN has been divided, rather arbitrarily, into four stages: (1) initiation, (2) extension, (3) maintenance, and (4) recovery. It is suggested that most of the preventative interventions during ATN should be active during the extension phase.

During the extension and maintenance phases of established ATN, a variety of interventions and drugs have been used either to prevent injury or to hasten recovery of ischemic and/or toxic ATN (e.g., endothelin receptor blockers, growth factors adenosine and adenosine antagonists, nitric oxide synthase inhibitors). Although some of these interventions are effective in altering the course of experimental ATN, all but a few have shown clinical benefit. Unfortunately overall treatments remain largely supportive, with the exception of N-acetylcysteine in radiocontrast-induced renal failure and activated protein C in sepsis. Supportive stabilization of general hemodynamics and optimization of cardiac output are best achieved in critical care with volume expansion, usually followed by vasopressors.

Volume Expansion

Initially volume expansion aimed to achieve supranormal cardiac index values comparable to those shown by survivors and normal values for mixed venous oxygen saturation. More recently, however, less severe organ dysfunction has been demonstrated with early institution of treatment to increase central venous oxygen saturation to 70% or higher as well as avoidance of unnecessarily high increases in cardiac work, especially in individuals observed to have decreased cardiopulmonary reserve.

The importance of volume therapy and hydration may also help to prevent radiocontrast media and amphotericin-induced ATN, as well as drug-induced intrarenal tubular precipitation of crystals following high doses of methotrexate, sulfonamides, or acyclovir.

Vasopressors

When appropriate volume expansion fails to restore adequate mean arterial pressures, vasopressors are indicated. Although there is concern that these may cause intrarenal vasoconstriction and counter any beneficial effects of increased blood pressure, vasopressor administration does improve renal blood flow, especially in patients with sepsis characterized by systemic vasodilation and impaired autoregulation.

Diuretics

Loop diuretics are commonly used in volume control and boast the theoretical benefit of reducing medullary oxygen demand and protecting against ischemic injury. Beyond experimental models, however, renal protection has never been clinically demonstrated. They do not accelerate renal recovery, reduce the need for dialysis, or decrease mortality and although some