

# Latest Version: 6.0

## Question: 1

A 35-year-old man, a victim of a motor vehicle accident, was found to have massive intracranial haemorrhage on computed tomography of his brain. He has been in a coma for the last 3 days in the intensive care unit and is currently on ventilator support.

After talking to the family members, a decision was made to follow regarding brain death testing is correct?

- A. Sedative drugs should be administered
- B. During apnoea testing, breathing is absent despite an arterial PCO<sub>2</sub> of
- C. Four-vessel angiography is required to establish intracranial blood flow
- D. Upgoing plantar responses excludes a diagnosis of brain death
- E. There should be a minimum 2-h observation and mechanical ventilation

**Answer: B**

Explanation:

The Australian and New Zealand Intensive Care Society (ANZICS) has established clinical guidelines to determine brain death.

These should be carried out by two 426 Intensive care medicine medical practitioners with the requisite knowledge, skills and

experience. Some states in Australia require the medical practitioners to have at least 5 years of working experience and at least

one person being a specialist not involved in organ retrieval. In Australia and New Zealand, whole brain death is required for the

legal determination of death. This contrasts with the United Kingdom, where brain-stem death is the standard. Determination of

brain-stem death requires unresponsive coma, the absence of brain-stem reflexes and the absence of respiratory centre function

in the clinical setting in which these findings are irreversible. In particular, there must be definite clinical or neuro-imaging

evidence of acute brain pathology (e.g. traumatic brain injury, intracranial haemorrhage, hypoxic encephalopathy) consistent with

the irreversible loss of neurological function. Certain preconditions have to be met before brain death testing:

- Absence of hypothermia (temperature is  $>35^{\circ}\text{C}$ )
- Adequate blood pressure (e.g. systolic blood pressure  $>90\text{ mmHg}$ , mean arterial pressure  $>60\text{ mmHg}$  in an adult)
- Sedative drug effects are excluded
- No severe electrolyte, metabolic or endocrine disturbance
- Intact neuromuscular function
- It is possible to examine the brain-stem reflexes (including at least one ear and one eye) • It is possible

to perform apnoea testing. For clinical testing there should be a minimum of 4 h observation and mechanical ventilation during which the patient has unresponsive coma (Glasgow coma score of 3), with pupils non-reactive to light, an absent cough/tracheal reflex and no spontaneous breathing efforts. 1. No motor response in the cranial nerve distribution to noxious stimulation of the face, trunk and four limbs, and no response in the trunk or limbs to noxious stimulation within the cranial nerve distribution 2. No pupillary responses to light 3. Absence of corneal reflexes 4. Absence of gag (pharyngeal) reflex 5. Absence of cough (tracheal) reflex 6. No vestibulo-ocular reflexes on ice-cold caloric testing 7. Breathing is absent [despite arterial  $\text{PCO}_2 > 60 \text{ mmHg}$  (8 kPa) and arterial  $\text{pH} < 7.30$ ] 8. Specify  $\text{PCO}_2$  in mmHg or kPa and pH at end of apnoea. To determine brain death when clinical examination cannot be done, the absence of intracranial blood flow needs to be demonstrated by either intraarterial angiography or another reliable method, but is not a routine part of testing.

## Question: 2

Which one of the following should be included in the parenteral nutrition for critically ill patients?

- A. Carbohydrate as glucose of 0.5 g/kg ideal body weight/day
- B. Amino acid mixture 0.3–0.5 g/kg ideal body weight/day
- C. Lipid emulsions 1–2 g/kg ideal body weight/day
- D. Weekly multivitamins and trace elements
- E. Separate infusions of lipid from amino acid-containing mixtures

**Answer: C**

Explanation:

In the intensive care unit (ICU), patients have increased metabolic needs related to stress, which are likely to accelerate the development of malnutrition, a condition associated with poorer clinical outcomes. Therefore, it is recommended that all patients who are not expected to be on normal nutrition within 3 days should receive parenteral nutrition within 24–48 h if enteral nutrition is contraindicated or if they cannot tolerate enteral nutrition (Singer et al., 2009). The minimal amount of carbohydrate required is about 2 g/kg of glucose/day. Hyperglycaemia (blood glucose  $> 10 \text{ mmol/L}$ ) contributes to death in critically ill patients and should be avoided to prevent infectious complications. Studies have shown conflicting outcomes in ICU patients when blood glucose is maintained between 4.5 and 6.1 mmol/L. There is a higher incidence of severe hypoglycaemia in patients treated to the tighter

limits, but clear recommendations are lacking. A balanced amino acid mixture of 1.3–1.5 g/kg ideal body weight/day should be administered and should include 0.2–0.4 g/kg/day of L-glutamine. Lipids should be an integral part of parenteral nutrition for energy and to ensure essential fatty acid provision in long-term ICU patients. Essential fatty acids are not synthesised within the human body and must be supplied. All parenteral nutrition prescriptions should include a daily dose of multivitamins and of trace elements. Previously, lipid emulsions were given separately but it is becoming more common for a single solution of glucose, proteins and lipids to be administered.

### Question: 3

Which one of the following is correct concerning patient management after successful resuscitation for ventricular fibrillation cardiac arrest?

- A. Early post-resuscitation electrocardiography accurately identifies acute
- B. Oxygen supplementation should be administered to achieve oxygen saturation
- C. Mechanical ventilation should be adjusted to achieve normocarbida
- D. Myocardial dysfunction after arrest is usually irreversible
- E. Pyrexia after cardiac arrest is self-limiting and does not require

**Answer: C**

Explanation:

Care after cardiac arrest and return of spontaneous circulation (ROSC) substantially influences patient outcomes (Nolan et al., 2012). An 'ABCDE' (airway, breathing, circulation, disability and exposure) approach can be used to identify and treat organ failure. 'Exposure' refers to the need for a comprehensive head-to-toe assessment. The inspired oxygen concentration immediately after ROSC should be adjusted to achieve normal arterial oxygen saturation (94–98%) when measured by pulse oximetry and arterial blood-gas analysis. Ventilation should be adjusted to achieve normocarbida and monitored using the end-tidal carbon dioxide with waveform capnography and arterial blood gases. In the setting of cardiac arrest, an early post-resuscitation 12-lead electrocardiogram (ECG) is less reliable for diagnosing acute coronary occlusion than in patients without cardiac arrest. Performing immediate coronary artery angiography in all patients with out-of-hospital cardiac arrest and no obvious non-cardiac cause of arrest, regardless of ECG changes, is becoming increasingly common. Post-cardiac arrest myocardial dysfunction can be severe, but usually resolves after 48–72 h, but this depends on pre-existing dysfunction. In patients with severe cardiogenic shock, an intra-aortic balloon pump should be considered. Recovery of brain function can be maximised by using targeted

temperature management, optimising cerebral perfusion, and controlling seizures and blood glucose levels. Pyrexia associated with systemic inflammatory response is common in the first 48 h after cardiac arrest, and is associated with poor outcome.

Therefore, post-cardiac arrest pyrexia should be actively treated and prevented where possible. Mild hypothermia improves outcome after a period of global cerebral hypoxia–ischaemia and it also decreases the cerebral oxygen requirements.

## Question: 4

Which one of the following statements is true concerning pulmonary artery catheters?

- A. The pulmonary artery wedge pressure is a measure of left atrial
- B. The use of pulmonary artery catheters is associated with improved intensive
- C. There is an increased incidence of ventricular arrhythmias
- D. Left bundle branch block is a common complication
- E. The normal pulmonary artery wedge pressure is 20–25 mmHg

**Answer: A**

Explanation:

The following parameters can be measured with a pulmonary arterial catheter: temperature, central venous pressure, right atrial pressure, right ventricular pressures, pulmonary artery pressures, pulmonary artery occlusion pressure, cardiac output and mixed venous sampling. The pulmonary artery wedge pressure (PAWP) tracing is obtained by inflating the balloon at the distal tip of the catheter, allowing the balloon to obstruct blood flow through a branch of the pulmonary artery. This creates a column of blood between the catheter tip and the left atrium, equilibrating pressure between them so that the pressure at the distal end of the catheter (the PAWP) is equal to that of the left atrium. The PAWP, which is also known as the pulmonary capillary wedge pressure or pulmonary artery occlusion pressure, varies from 6 to 15 mmHg, with a mean of 9 mmHg. The PAWP can estimate the left ventricular end-diastolic pressure (i.e. the left ventricular preload) if there is no obstruction to flow between the left atrium and left ventricle. A variety of haemodynamic and clinical problems can reduce the reliability of this estimate, including mitral valve disease, reduced left ventricular compliance and pulmonary disease. In intensive care unit patients, heart failure patients and patients undergoing high-risk surgery, the use of pulmonary artery catheters has not been shown to improve survival. Right bundle branch block is a complication of catheter insertion, placing patients with pre-existing left bundle branch block at risk of complete heart block. Ventricular and supraventricular tachycardias are well-recognised complications.

### Question: 5

In adult comatose patients after cardiac arrest, which one of the following parameters predicts a poor outcome?

- A. E. computed tomography (CT) scan showing cerebral infarction
- B. Absence of vestibulo-ocular reflexes at 12 h
- C. Glasgow coma scale (GCS) of less than 5 at 12 h
- D. Presence of myoclonus
- E. A computed tomography (CT) scan showing cerebral infarction

**Answer: A**

Explanation:

It is impossible to predict accurately the degree of neurological recovery during or immediately after a cardiac arrest. The neurological examination during cardiac arrest is not helpful in predicting outcome and should not be used. Furthermore, there are no clinical neurological signs that reliably predict poor outcome less than 24 h after cardiac arrest. After cessation of sedation (and/or induced hypothermia), the probability of awakening decreases with each day of coma. In adult patients who are comatose after cardiac arrest, and who have not been treated with hypothermia and who do not have confounding factors (such as hypotension, sedatives or neuromuscular blockers), the absence of both pupillary light and corneal reflex at 72 h or longer reliably predicts a poor outcome. Absence of vestibulo-ocular reflexes at 24 h or longer and a Glasgow coma motor score of 2 or less at 72 h or longer are less reliable. Other clinical signs, including myoclonus, are not recommended for predicting poor outcome. The presence of myoclonus status in adults was strongly associated with poor outcome, but rare cases of good neurological recovery have been described and accurate diagnosis was problematic. There is insufficient evidence that neuro-imaging or blood tests can accurately predict outcome.

### Question: 6

other medical problems included type 2 diabetes, chronic kidney disease (CKD) with serum creatinine of 178  $\mu$ mol/L due to diabetic nephropathy, hypertension and anaemia with a haemoglobin of 85 g/L. He was transferred to the intensive care unit 2 h after admission because of severe urosepsis (APACHE II score 30) and persistent hypotension (blood pressure 85/50 mmHg).

despite intravenous fluid resuscitation. Which one of the following statements concerning treatment options is correct?

- A. Blood should be transfused to maintain a haemoglobin level above
- B. High-dose steroids should be administered
- C. Patients should be placed in the supine position
- D. Blood glucose level should be strictly controlled between 4.5 and
- E. There is no clear benefit of colloid over crystalloid fluid resuscitation

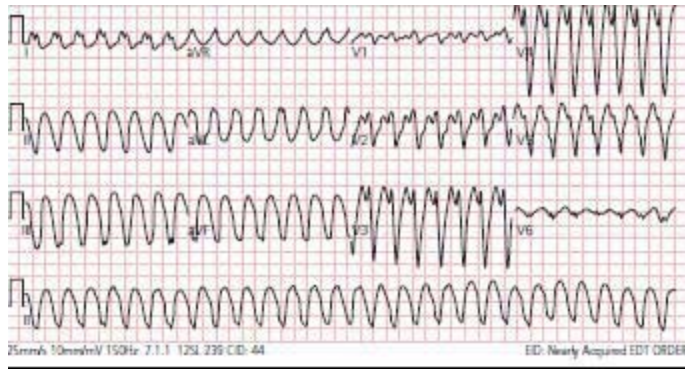
**Answer: E**

Explanation:

There is good evidence that early resuscitation in patients with severe sepsis or septic shock improves outcome (Annane et al., 2005; Dellinger et al., 2008). Supine body positioning is a risk factor for nosocomial pneumonia in mechanically ventilated patients, a semi-recumbent position reduces the risk. Studies show that transfusion of blood to critically ill patients to maintain a haemoglobin level of greater than 100 g/L does not improve outcome. However, a haemoglobin concentration of less than 70 g/L has become a more widely accepted threshold after the Transfusion Requirements in Critical Care (TRICC) trial. This trial randomised 838 critically ill patients to either a restrictive transfusion strategy (transfusion threshold of <70 g/L) or a liberal transfusion strategy (threshold of <100 g/L) and found that the restrictive strategy decreased in-hospital mortality. Whilst glycaemic control is important, an intensive insulin regimen to keep the level between 4.4 and 6.0 mmol/L has not shown a beneficial effect on mortality. In critically ill patients, a target blood glucose of 4.4–6.1 mmol/L increased the incidence of severe hypoglycaemia, and either increased mortality or had no effect on mortality, when compared to the more permissive blood glucose ranges of 7.8–10 mmol/L. Studies do not support the routine use of steroids in septic shock, but some advocate their use in patients with increasing vasopressor requirements and failure of other therapeutic strategies. There is no clear benefit of colloid over crystalloid fluid resuscitation, but crystalloid redistributes rapidly into the whole extracellular volume, hence larger volumes must be given for intravascular resuscitation.

## Question: 7

A 60-year-old man presents with sudden onset of palpitations. He is alert below. Which one of the following medications is contraindicated in this patient to correct the rhythm disturbance?



- A. Amiodarone
- B. Lignocaine
- C. Verapamil
- D. Magnesium
- E. Procainamide

**Answer: C**

**Explanation:**

All these medications can be useful agents in the treatment of ventricular tachycardia (VT), except for verapamil. Verapamil is contraindicated in this case because it can cause the blood pressure to fall due to negative inotropic action (RobertsThomson et al., 2011). The initial management of a patient with sustained monomorphic VT caused by underlying structural heart disease is determined by the patient's symptoms and haemodynamic state. Direct-current cardioversion is warranted for sustained VT, which produces symptomatic hypotension, pulmonary oedema or myocardial ischemia. Reversible causes of VT, such as electrolyte imbalances, acute ischaemia, hypoxia and drug toxicities, should be corrected. In patients who are haemodynamically stable, pharmacological reversion of VT can be attempted. Lignocaine can be useful in VT associated with ischaemia or myocardial infarction. However, in patients with slow and stable VT, the efficacy of lignocaine is limited. Intravenous procainamide is an appropriate therapy in these patients, as it rapidly slows and terminates VT. Although procainamide is successful for acute arrhythmia termination in around 75% of patients with sustained monomorphic VT, its use can be limited by hypotension, which occurs in approximately 20% of these individuals. Amiodarone is also useful, but its onset of action is slower than that of lignocaine or procainamide, and the results of acute termination studies have been variable. Transvenous catheter pace termination, by application of ventricular pacing at a faster rate than the VT ('overdrive'), can also be performed to treat

sustained VT. The most common form of idiopathic VT is focal VT arising from the right ventricular outflow tract, which accounts for approximately 60–70% of idiopathic VTs. These focal VTs can manifest as recurrent premature ventricular contractions or paroxysmal monomorphic VT, usually with left bundle branch block morphology and a marked inferior axis. Patients, who are typically aged 30–50 years, often present with palpitations and, occasionally, presyncope. The treatment of patients with focal VT depends on the frequency and severity of symptoms, as this condition has a benign course in the vast majority, with a low incidence of sudden cardiac death. Patients with minimal symptoms do not necessarily need treatment. For those with severe symptoms or those who have developed a tachycardia-mediated cardiomyopathy, the options include pharmacological therapy or radiofrequency catheter ablation. Acute termination of focal VT can be achieved by vagal manoeuvres, such as carotid sinus massage.

### Question: 8

Which one of the following factors is associated with increased chances of a successful spontaneous-breathing trial after prolonged mechanical ventilation?

- A. Pneumonia as cause of respiratory failure
- B. Chronic heart failure
- C. Upper airway stridor at extubation
- D. Partial pressure of arterial carbon dioxide of greater than 45 mmHg after
- E. Daily interruption of sedative infusion

**Answer: E**

Explanation:

Approximately 15% of patients in whom mechanical ventilation is discontinued require re-intubation within 48 h (McConville and Kress, 2012). Rates of extubation failure vary considerably among intensive care units (ICUs). For example, the average rate of failed extubation in surgical ICUs ranges from 5% to 8%, whereas it is often as high as 17% in medical or neurological ICUs.

Patients who require re-intubation have an increased risk of death, a prolonged hospital stay and a decreased likelihood of returning home, as compared with patients in whom discontinuation of mechanical ventilation is successful. Risk factors for unsuccessful discontinuation of mechanical ventilation include:

- Failure of two or more consecutive spontaneous-breathing trials
- Chronic heart failure
- Partial pressure of arterial carbon dioxide of greater than 45 mmHg after extubation



- More than one coexisting condition other than heart failure
- Weak cough
- Upper airway stridor at extubation
- Age 65 years or older
- Acute

Physiology and Chronic Health Evaluation (APACHE) II score of greater than 12 on the day of extubation

- Pneumonia as the cause of respiratory failure. Treatment approaches include a progressive reduction of ventilator assistance. Increasingly, tracheostomy is performed in patients who require prolonged weaning. However, the timing of tracheostomy remains controversial. Potential advantages of tracheostomy include easier airway suctioning and improvements in the patient's comfort

and ability to communicate. Although some studies have suggested that early tracheostomy might reduce short-term mortality, the

length of stay in the ICU and the incidence of pneumonia, others have not shown such benefits. A recent meta-analysis led to the

conclusion that there is insufficient evidence to warrant a recommendation for early tracheostomy.

Daily interruption of sedative

infusion has been associated with reduction of the duration of mechanical ventilation. Trials of spontaneous breathing assess a

patient's ability to breathe while receiving minimal respiratory support. To accomplish this, ventilators are switched from full

respiratory support modes, such as volume-assist control or pressure control, to ventilatory modes, such as pressure support,

continuous positive airway pressure (CPAP) or ventilation with a T-piece (in which there is no positive endexpiratory pressure).

Ideally, a trial of spontaneous breathing is initiated while the patient is awake and not receiving sedative infusions. For a spontaneous-breathing trial to be successful, a patient must breathe spontaneously with little or no ventilator support for at least

30 min without any of the following:

- Respiratory rate of more than 35 breaths/min for more than 5 min
- Oxygen saturation of less than 90%
- Heart rate of more than 140 beats/min

## Question: 9

A 50-year-old man with cirrhosis due to hepatitis C (from past intravenous drug use) and refractory ascites is being evaluated for

liver transplantation. His clinical condition is also complicated by porto-pulmonary hypertension. Which one of the following is an

absolute contraindication to orthotopic liver transplantation?

- A. A single hepatocellular carcinoma lesion of 3 cm in diameter
- B. Acute kidney injury due to hepatorenal syndrome

- C. Not responsive to interferon–ribavirin treatment
- D. Pulmonary artery pressure of 55 mmHg
- E. Refractory ascites

**Answer: D**

Explanation:

The ultimate treatment for cirrhosis and end-stage liver disease is liver transplantation (Schuppan and Afdhal, 2008). Once

decompensation has occurred in all types of liver disease, mortality without transplantation is as high as 85% over 5 years. Portopulmonary

hypertension (defined by the co-existence of portal and pulmonary hypertension) is rare, but occurs in up to 16–20%

of patients with refractory ascites. The development of porto-pulmonary hypertension seems to be independent of the cause of

portal hypertension. Although most patients with porto-pulmonary hypertension have cirrhosis as the underlying disease, the

syndrome has been described in patients with portal hypertension due to non-hepatic causes, such as portal venous thrombosis in

the absence of chronic hepatic disease. Thus, portal hypertension seems to be the required driving force of pulmonary

hypertension. The mechanisms by which portal hypertension causes pulmonary hypertension remain incompletely understood.

The development of severe pulmonary hypertension in patients who have cirrhosis is an ominous prognostic sign. The condition is

deemed irreversible and a pulmonary artery pressure of more than 40 mmHg precludes liver transplantation. Other absolute

contraindications include:

- Extrahepatic malignant disease
- AIDS responding poorly to highly active anti-retroviral therapy
- Cholangiocarcinoma
- Severe uncontrolled systemic infection
- Multiorgan failure
- Active substance abuse. The Milan criteria

suggest that the mortality and recurrence of hepatocellular carcinoma is acceptable if liver transplantation is done for either a

single tumour of less than 5 cm in diameter, or no more than three tumours with the largest being less than 3 cm in diameter.

Recurrence of infection with hepatitis C virus is universal following liver transplantation, with an accelerated natural history compared with hepatitis C infection in immunocompetent patients.

## Question: 10

Which one of the above is administered in the management of pulseless ventricular tachycardia that persists after three shocks?

- A. Adenosine
- B. Epinephrine (adrenaline)
- C. Amiodarone
- D. Atropine
- E. Calcium chloride (10%)
- F. Flecainide
- G. Lignocaine

**Answer: C**

Explanation:

Amiodarone is an anti-arrhythmic drug with complex pharmacokinetics and pharmacodynamics. It has effects on sodium, potassium and calcium channels, as well as alpha- and beta-adrenergic blocking properties. Two randomised trials demonstrated the benefit of amiodarone over conventional care, which included lignocaine in 80% of cases, or routine use of lignocaine for shock refractory, recurrent ventricular tachycardia (VT) or ventricular fibrillation (VF), for the endpoint of survival to hospital admission, but not to survival to hospital discharge (Nolan et al., 2012). Additional studies have reported improvement in defibrillation response when amiodarone is given to patients with VF or haemodynamically unstable VT. In view of the short-term benefits, amiodarone should be considered for refractory VF or VT. There is little evidence to suggest a survival-to-discharge advantage with any anti-arrhythmic drug used during resuscitation from out-of-hospital or in-hospital cardiac arrest. Amiodarone is given intravenously with an initial dose of 300 mg. An additional dose of 150 mg could be considered. This may be followed by an infusion at a rate of 15 mg/kg over 24 h. Amiodarone is recommended following the third shock; however, in situations where two or three stacked shocks are given in the first 'round', amiodarone is not given until two further shocks, with 2 min of cardiopulmonary resuscitation in between each round, have been given.

## Question: 11

Which one of the above is used in the management of torsades de pointes?

- A. Adenosine
- B. Epinephrine (adrenaline)
- C. Amiodarone
- D. Atropine
- E. Calcium chloride (10%)
- F. Flecainide
- G. Lignocaine

**Answer: H**

Explanation:

Magnesium is an electrolyte that is essential for membrane stability. Hypomagnesaemia causes myocardial hyperexcitability, particularly in the presence of hypokalaemia and digoxin. Compared with placebo, magnesium has not been shown to increase return of spontaneous circulation (ROSC) or survival for patients in VF in the pre-hospital, intensive care and emergency department settings. Magnesium should be given for hypomagnesaemia and torsades de pointes, but there is insufficient data for or against its routine use in cardiac arrest.

## Question: 12

Which one of the above should be administered to a patient experiencing palpitations caused by rapid atrial fibrillation (AF) with an accessory pathway?

- A. Adenosine
- B. Epinephrine (adrenaline)
- C. Amiodarone
- D. Atropine
- E. Calcium chloride (10%)
- F. Flecainide
- G. Lignocaine

**Answer: F**

Explanation:

The goals of acute drug therapy for rapid atrial fibrillation (AF) with an accessory pathway are prompt control of the ventricular response and stabilisation of the haemodynamic state (Link, 2012). Treatment of AF with an accessory pathway requires a parenteral drug with rapid onset of action that lengthens antegrade refractoriness and slows conduction in both the AV node/His-Purkinje system and the accessory pathway. Treatment is not to differentially block the AV node as this may increase antegrade conduction down the accessory pathway and accelerate the ventricular rate. Flecainide is effective at slowing conduction through both normal pathways as well as accessory pathways, and is therefore less prone to diverting conduction toward the accessory path. It also has greater effect at higher atrial rates. It is a potent inhibitor of sodium channels and

therefore slows conduction. The effect of flecainide can be seen as lengthening of the PR interval and widening of the QRS complex on the electrocardiogram. Flecainide is also known to be negatively inotropic and may result in bradycardia and hypotension. Other side effects include visual blurring and oral paraesthesiae. Cardioversion is required for haemodynamically unstable patients.

### Question: 13

Which one of the above should be administered to a patient who develops ventricular tachycardia at the onset of his regular haemodialysis with pre-dialysis biochemistry showing a potassium level of 7.0 mmol/L (3.4–4.5 mmol/L)?

- A. Adenosine
- B. Epinephrine (adrenaline)
- C. Amiodarone
- D. Atropine
- E. Calcium chloride (10%)
- F. Flecainide
- G. Lignocaine

**Answer: E**

Explanation:

Calcium is essential for normal muscle and nerve activity. It transiently increases peripheral resistance, myocardial excitability and contractility. Calcium may have toxic effects on an ischaemic myocardium. Therefore, it is to be given only to patients with hypocalcaemia, hyperkalaemia or who have overdosed on a calcium antagonist. Randomised controlled trials and observational studies have demonstrated no survival benefit when calcium was given to in-hospital or out-of-hospital cardiac arrest patients. In ventricular fibrillation, calcium did not restore spontaneous circulation. Hyperkalaemia raises the resting membrane potential, causing a narrowing between resting membrane potential and threshold potential for action potential (AP) generation. Calcium restores this initial narrowing back towards 15 mV by raising the threshold potential to being 'less negative'. APs generated from less negative voltages are slower since sodium channels in phase 0 are voltage dependent for velocity ( $V_{max}$ ). Calcium restores  $V_{max}$ , resulting in improvement in ECG changes within minutes of administration.