Special reviews

Antiarrhythmic and Haemodynamic Effects of the Commonly Used Intravenous Electrolytes

J. REDMAN, L. I. G. WORTHLEY

Department of Critical Care Medicine, Flinders Medical Centre, Adelaide, SOUTH AUSTRALIA

ABSTRACT

Objective: To review the physiology and cardiovascular effects of the commonly used intravenous electrolytes.

Data sources: Abstracts, articles and published reviews of studies reported from 1966 to 2000 and identified through a MEDLINE search on cardiac arrhythmias and electrolytes.

Summary of review: While isotonic saline solutions are used to improve the haemodynamic status in critically ill patients who are hypotensive and hypovolaemic, other intravenous solutions including potassium chloride, calcium chloride, magnesium sulphate and sodium or potassium phosphate as well as hypertonic saline and sodium bicarbonate have unique and often therapeutically useful haemodynamic and antiarrhythmic effects.

Potassium chloride solutions are used to treat hypokalaemia with a maximum speed of correction in an adult of 20 mmol per 30 minutes when an acute myocardial infarct is present. A greater infusion rate may be necessary when ventricular or supraventricular tachyarrhythmias are present although close ECG monitoring will be required. Magnesium sulphate (2 - 20 mmol) has been used for hypomagnesaemic and normomagnesaemic cardiac arrhythmias (particularly when digoxin induced) and calcium chloride (3.4 - 6.8 mmol) is used to treat hyperkalaemic and hypermagnesaemic cardiac arrhythmias. Both hypertonic sodium bicarbonate and sodium chloride solutions have antiarrhythmic effects that may be beneficial in conditions that include tricyclic poisoning, hyperkalaemia and bupivacaine toxicity, although sodium bicarbonate is generally used for tricyclic cardiotoxicity. Low cardiac output states and arrhythmias have also been reported in hypophosphataemic patients that are reversed by infusions of potassium or sodium phosphate.

Conclusions: Intravenous potassium chloride, calcium chloride, magnesium sulphate, sodium and potassium phosphate, sodium bicarbonate and hypertonic saline can be used effectively to alter the haemodynamic status and manage cardiac arrhythmias. However, their indications are selective and complications may occur, so careful administration and monitoring are required with their use. (Critical Care and Resuscitation 2001; 3: 22-34)

Key words: Myocardial action potential, magnesium sulphate, potassium chloride, calcium chloride, sodium bicarbonate, hypertonic saline, sodium phosphate, potassium phosphate

Excitability of myocardial tissue depends upon the intracellular and extracellular concentrations of electrolytes including potassium, sodium, magnesium and calcium, with myocardial excitability varying with

Correspondence to: Dr. L. I. G. Worthley, Department of Critical Care Medicine, Flinders Medical Centre, Bedford Park, South Australia 5042 (e-mail: lindsay.worthley@flinders.edu.au)
changes in concentrations of these electrolytes.

The cardiac cell membrane (i.e. sarcolemma) is an ion-impermeable lipid bilayer composed of phospholipid molecules that separate the myocardial extracellular fluid (ECF) and intracellular fluid (ICF) compartments. With the appropriate stimulus, macromolecular proteins that traverse the lipid bilayer (i.e. channels), selectively permit ions to move from one side of the sarcolemma to the other. These channels are selectively permeable to different ionic species and are controlled by ‘gates’ which may be voltage sensitive, time sensitive and receptor operated. Flow through the channel for a particular ion depends upon the driving force (i.e. the difference between the transmembrane potential and the equilibrium potential for that ion) and the ease with which the ion passes through the channel (i.e. the conductance). The differences in ionic concen-trations, or more precisely ionic activities, across the sarcolemma establish the electrochemical gradients. Concentration gradients for K\(^+\), Na\(^+\) and Ca\(^{2+}\) cause K\(^+\) to move from the intracellular to the extracellular compartment, and Na\(^+\) and Ca\(^{2+}\) from the extracellular to the intracellular compartment. Energy-dependent ionic pumps are required to maintain the differential ionic concentrations across the membrane.

While abnormal concentrations of these electrolytes in the ECF may alter the excitability and contractility of myocardial cells, the ECF concentrations of the electrolytes may also be altered for therapeutic effect. We review the physiology of myocardial excitability and the effects of altered concentration of these electrolytes on the excitability and contractility of myocardial cells, as well as the therapeutic effects of an increase in their ECF concentrations.

The resting membrane potential

The resting membrane potential (RMP) is the potential difference across the cell membrane during electrical diastole. For the myocardial muscle fibre this is about 90 mV (i.e. the ICF has a negative potential when compared with the ECF). The RMP is largely determined by the K\(^+\) gradient across the cell membrane. As K\(^+\) is about 20 times more permeable than Na\(^+\), it tends to move down its concentration gradient leaving the interior of the cell negative. If, at rest, the sarcolemma was more permeable to Na\(^+\) than K\(^+\), then Na\(^+\) would tend to move to the interior of the cell and cause a positive RMP (this movement of sodium is only facilitated during phase 0 of the action potential).

If one assumes the cell membrane is permeable to potassium only, the RMP may be derived from the Nernst equation. However, the membrane potential at any given time depends upon the distribution of all fluid ions and the cell membrane permeabilities to these ions at that point in time. The Goldman constant field equation expands the Nernst equation to consider the effects of sodium, chloride and other ions as well as potassium on the trans-membrane potential. Nevertheless, at rest, potassium plays the major role in determining the resting membrane potential (RMP) thus the RMP is often derived from the Nernst equation which is represented as:

$$E_K = 61.5 \times \log [K^+]_o / [K^+]_i,$$

Where $$E_K = \text{RMP (equilibrium potential for } K^+)$$

$$[K^+]_o = \text{K^+ concentration outside the cell}$$

$$[K^+]_i = \text{K^+ concentration inside the cell}$$

The Nernst equation reveals that the extracellular K\(^+\) has a greater effect on RMP than intracellular K\(^+\). An increase in ECF K\(^+\) reduces the RMP, inactivating the fast response and reducing the conducting velocity, all of which cause the electrocardiogram changes of, prolongation of the PR interval and QRS wave, which in the extreme may lead to sinus arrest and broad wave slow ventricular tachycardia, respectively. An increase in the ECF K\(^+\) also accelerates repolarisation, producing tall peaked T waves. A decrease in ECF K\(^+\) hyperpolarises the cell membrane, although as the permeability of the membrane to K\(^+\) reduces with hypokalaemia, the hyperpolarisation is smaller than that expected from the Nernst equation.

The resting membrane potential is set largely by the inward rectifier K\(^+\) channels ($$I_{K1}$$).\(^2\)

The myocardial cell action potential

This has been divided into four phases which are largely determined by the selective alterations in ion permeabilities of the sarcolemma (Figure 1).

**Phase 0.** This represents the initial fast depolarisation phase due to a rapid inward sodium current ($$I_{Na}$$) which is initiated by a stimulus that elevates the RMP from -90 mV to a threshold value of -60 mV, increasing the membrane permeability to Na\(^+\). The stimulus also decreases the membrane permeability to K\(^+\) (as depolarisation activates the inward rectifier $$I_{K1}$$ channels). Both of these changes cause the cell to reverse its polarity, with the interior of the cell changing from -90 to +30 mV. The deactivation of the inward rectifier $$I_{K1}$$ channels is prolonged and is reactivated again during phase 3.

The rapid inward current ($$I_{Na}$$) is dependent upon the RMP. If the RMP is less negative than -90 mV, before the stimulus, the rate of depolarisation is slow and the impulse is conducted slowly. The rapid inward current is blocked by a RMP of less than -60 mV, which may
occur with a high external (e.g. ECF) concentration of K⁺. If the RMP is more negative than -90 mV before the stimulus, then the rate of depolarisation is rapid and the impulse is conducted rapidly.

Phase 1. Phase 1 represents an initial period of rapid repolarisation due to closure of sodium channels and a transient outward current (Iₒ) caused by a rapid activation (i.e., increase in K⁺ permeability) then inactivation of outward potassium channels.⁴

Phase 2. Phase 2 is a plateau period of repolarisation which results from an increase in the sarcolemmal K⁺ permeability, due to activation of the delayed rectifier potassium channels (Iₚ) and a ‘slow’ inward current due to an inflow of Ca²⁺ (and Na⁺) ions through a ‘slow’ channel. This ‘slow’ channel is known as the calcium channel as it is 100 times more selective for Ca²⁺ than Na⁺, even though both Ca²⁺ and Na⁺ ions flow through it and Na⁺ ions account for nearly one-third of the slow inward current (due to a higher ECF Na⁺ in comparison with Ca²⁺).⁵,⁶

During phases 1 and 2, there is a gradual return of the intracellular potential toward zero, due to an increase in Ca²⁺ permeability triggered initially by the inward sodium current. This slow inward calcium current is also responsible for the coupling of the excitation of the cell membranes to the activation of the contractile proteins and is sensitive to the ECF Ca²⁺ concentration.

An important feature of many calcium channels is their sensitivity to control by sarcolemmal receptors. In cardiac muscle, β₁ agonists, and in vascular smooth muscle α-adrenergic agonists increase Ca²⁺ influx via the slow inward current. In both cases, the increase in Ca²⁺ flux appears to be due to recruitment of an additional number of active calcium channels rather than an increase in the size of the channel or alteration in the rates at which the gates open or close. The calcium channels are also divided into two broad groups (i.e. voltage-sensitive or receptor operated) depending on the stimulus required to achieve the activated state. Channels which are activated in response to an appropriate change in the membrane action potential are known as voltage-sensitive channels. The receptor-operated channel is dependent for its activation on an interaction between cell surface receptors and specific neurotransmitters (e.g. acetylcholine, noradrenaline, histamine and adenosine).

Phase 3. This represents a relatively fast period of repolarisation with a slow return of the intracellular potential to the RMP of -90 mV due to a delayed increase in K⁺ permeability (due to a reactivation of the inward rectifier IK channels and deactivation of the delayed rectifier IK channels) and decrease in Ca²⁺ permeability.

Phase 4. The action potential of the myocardial conducting tissue (with the exception of the mid atrioventricular nodal region) has an unstable resting membrane potential due to a steady inward current (Iₒ) carried by Na⁺ through a relatively nonspecific channel activated by polarisation to high membrane potentials in the sinoatrial (SA) and atrioventricular (AV) nodal cells and His-Purkinje cells.⁷ This channel is strongly modulated by neurotransmitters and is responsible for the tissue’s pacemaker activity. Acetylcholine decreases the slow inward current by activating the receptor operated muscarinic K⁺ channels (Kₐch). This channel is
also opened by activation of the purinergic (adenosine) receptor. The speed with which the RMP reduces to the threshold potential, determines the rate at which the tissue discharges.

The SA and upper AV node have a diastolic depolarisation phase (i.e. phase 4), a maximum RMP of -70 to -50 mV, and a threshold potential (with depolarisation) which is -40 mV, i.e. the slow inward current is activated when the fast inward current is inactivated, implying that an action potential can occur in partially depolarised cells in which the fast Na⁺ channels have been inactivated. The action potential of the AV node is due to the slow inward Ca²⁺ current alone, as it is resistant to Tetrodotoxin (a fast sodium channel inhibitor), and is sensitive to verapamil and manganese (i.e. slow calcium channel inhibitors).⁶

\[ I_{\text{K(ATP)}} \] is a K⁺ current carried through a channel which is opened by intracellular ADP (and other intracellular nucleoside diphosphonates) and blocked by ATP (an effect which is inhibited by adenosine, ADP and other intracellular nucleoside diphosphonates). The channel is not blocked by extracellular ATP. This channel contributes to the shortening of the action potential during myocardial ischaemia and has been associated with the cardioprotective mechanism of ischaemia related preconditioning.⁸

The unique action potential of myocardial tissue provides the properties of: conductivity (i.e. the ability to conduct an impulse, the speed of which is related to speed of depolarisation), automaticity (i.e. the property of spontaneous impulse formation), excitability (i.e. the property of all myocardial tissue which relates to an ability to respond to a stimulus) and refractoriness (i.e. a period of reduced ability of the myocardium to respond to a stimulus).

CARdiovascular EFFECTS of ELECTrolytes

Potassium

The extracellular K⁺ concentration is largely responsible for the resting membrane potential and therefore has a large influence on myocardial tissue excitability. Intravenous potassium is often used to treat hypokalaemic cardiac arrhythmias as the cardiac effects of hypokalaemia include excitability and contractility changes. For example:

ECG changes. Hypokalaemia causes the U wave to become prominent, the T wave to flatten and invert, the ST segment to become depressed and the PR interval to increase. The QTc interval does not change although it may be mistaken for the QU interval or be prolonged due to an associated hypomagnesaemia.

Arrhythmias. Hypokalaemia can cause atrial tachyarrhythmias (e.g. paroxysmal supraventricular tachycardia, multifocal atrial tachycardia) and ventricular tachyarrhythmias (e.g. torsades de pointes,¹⁶,¹⁷ ventricular tachycardia, ventricular fibrillation) in the absence of underlying cardiac disease.¹¹ Hypokalaemia (but not hypomagnesaemia¹²) is also a risk factor of ventricular tachycardia (VT) and ventricular fibrillation (VF) in the early post myocardial infarction period,¹³,¹⁴ which may be due to stress-related adrenaline secretion, rather than hypokalaemia per se.¹⁵-¹⁷ The increase in adrenaline secretion associated with an acute myocardial infarction causes hypokalaemia by inducing a β₂ receptor mediated influx of K⁺ (largely in skeletal muscle cells¹⁸). Potassium supplementation reduces the incidence of VF in these patients.²⁰ The risk of primary cardiac arrest is greater in hypertensive patients treated with thiazide diuretics, than in patients who are treated with a combination of thiazide and potassium-sparing diuretic agents.²¹

Myocardial inotropic effects. A reduction in concentration of extracellular potassium has a mild positive inotropic effect due to an associated increase in intracellular Na⁺, which activates a Na/Ca exchange and increases the intracellular Ca²⁺ concentration.²²

Standard treatment of hypokalaemia usually involves administration of intravenous or oral potassium chloride, particularly when hypokalaemia is associated with metabolic alkalosis, although potassium may be replaced as a chloride, phosphate, citrate or acetate salt. If the patient has renal tubular acidosis and hypo-kalaemia, then potassium acetate or citrate is required. When phosphate depletion also exists, then potassium phosphate may be administered, although phosphate can only be infused slowly (e.g. maximum rate 2 - 6 mmol/hr/70 kg²³,²⁴) and is usually administered to correct a phosphate deficiency rather than potassium deficiency.

A linear relationship describing a decrease in plasma potassium of 0.27 mmol/L/100 mmol deficit/70 kg body weight, has been described.²⁵ However, this estimate should only be used as a guide. When replacing potassium, intravenous administration should normally not exceed 40 mmol/hr and plasma potassium levels should be monitored at 1 to 4-hourly intervals.²⁶,²⁷ In patients who have acute myocardial infarction and hypokalaemia, intravenous potassium is recommended at a rate of no greater than 10 mmol/30 min (in 50 - 100 mL of 5% dextrose), and repeated as necessary (rechecking the potassium level every hour) until the serum potassium is 4.0 - 4.5 mmol/L (or plasma potassium is 3.5 - 4.0 mmol/L).²⁸ However in patients with severe hypokalaemia, administration of potassium
salts should be either as an undiluted solution through a central venous line or diluted in 0.9% saline, as potassium in dextrose solutions have been reported to initially worsen the hypokalaemia.29

Some have advocated an antiarrhythmic dose of 2 mmol as a bolus30 or 6 mmol over 1 minute (to increase the plasma potassium by 2 mmol/L)31 to manage hypokalaemic tachyarrhythmias; however even with such a low dose, it is conceivable that in patients with low cardiac outputs, a dangerously high level of plasma potassium might occur transiently to cause sudden sinus arrest, AV block or asystole.32

Magnesium supplementation may also be required in patients with hypokalaemia because hypokalaemia and hypomagnesaemia commonly coexist. Moreover, renal potassium wasting may occur with hypomagnesaemia (particularly if the plasma magnesium is < 0.5 mmol/L),33 thus hypomagnesaemia may impede the correction of hypokalaemia.27 Spironolactone, triamterene, amiloride or ACE inhibitors are of use in preventing renal potassium loss rather than an adjunctive measure during the correction of an existing deficit.27

While there have been no studies that have shown that potassium has an antiarrhythmic effect in normokalaemic patients, in patients who have resistant ventricular tachyarrhythmias, plasma potassium levels of > 4.0 - 4.5 mmol/L are often preferred.

Calcium
Ionised Ca²⁺ in ECF is needed for myocardial contraction and excitation-contraction coupling. Calcium chloride (or gluconate) is used to treat the life-threatening cardiovascular effects of hyperkalaemia, hypomagnesaemia and hypocalcaemia.

Hyperkalaemia
In the severely hyperkalaemic patient, calcium does not reduce plasma potassium; it is used to counter the toxic cardiac effects (and reverse the ECG changes) of hyperkalaemia by increasing the intracellular calcium34 causing the threshold potential to be less negative.35 The cardiac effects of hyperkalaemia include:

**ECG changes**: Hyperkalaemia characteristically causes, a tall slender, peaked or ‘tented’ T wave at plasma K⁺ concentrations of 6 mmol/L or greater (due to an increase in repolarisation rate), a prolongation of the P wave, QRS wave and the PR interval at plasma K⁺ concentrations of 7 mmol/L or greater, a diminution in the amplitude of the P wave, which may progress to sinus arrest, and a diminution in R wave and widening of the QRS complex (caused by a reduction in conduction velocity, producing a slow idioventricular rhythm) at plasma K⁺ concentrations of 8 mmol/L or greater, and ‘sine-wave’ VT or VF at a plasma K⁺ level of 9 mmol/L or greater.

**Arrhythmias**: While a progressive rise in plasma K⁺ can produce ‘sine-wave’ VT or VF, an abrupt rise in plasma K⁺ may produce sinus arrest, AV nodal block, first-, second- or third- degree heart block and asystole.

**Myocardial inotropic effects**: Hyperkalaemia exerts a negative inotropic effect, which is caused by the decrease in duration of the action potential (and thus the duration of the slow calcium current) causing a reduction in intracellular Ca²⁺ and hypotension.

For mild hyperkalaemia (i.e. plasma K⁺ > 4.5 and < 5.5) treatment usually includes reducing the potassium intake, correcting renal failure and treating the cause (e.g. ceasing non-steroidal anti-inflammatory drugs, potassium sparing diuretics or angiotensin converting enzyme inhibitors).

Treatment of severe hyperkalaemia (i.e. plasma K⁺ > 5.5 mmol/L) includes reducing the plasma potassium (by shifting potassium into the ICF and enhancing potassium excretion) and reducing the cardiac effects of hyperkalaemia (e.g. intravenous calcium salts). The administration of intravenous glucose and insulin, and sodium bicarbonate will reduce the ECF potassium,36 although nebulised salbutamol (10 - 20 mg) may also be useful (due to a β₂ adrenergic effect activating the Na⁺K⁺-ATPase), as it can reduce the plasma potassium by 0.6 - 1 mmol/L, after 20 - 30 min and will last for 2 hr.37 Resonium A (sodium polystyrene sulfonate) has the capacity to bind 3.1 mmol of potassium per gram by releasing 3.1 mmol sodium. However, its onset is slower (e.g. maximum effect in 4 hours) and while it may be given rectally, in the unconscious hyper-kalaemic critically ill patient it probably has little place.

In severe hyperkalaemia, calcium salts should be given first (3.4 - 6.8 mmol or 5 - 10 mL of 10% calcium chloride), followed by insulin and glucose. However, glucose is only necessary with insulin if there is normoglycaemia and should be infused over 5 - 10 minutes as a sudden increase in tonicity due to hyperglycaemia may temporarily increase the plasma potassium by 0.1 - 0.6 mmol/L, for each 10 mosmol/kg increase in tonicity.38 This may then be followed by sodium bicarbonate 50 - 100 mmol and nebulised salbutamol. As all of the methods to reduce the plasma potassium are only temporary, treatment should also be aimed at the underlying cause which may include dialysis.

Class I antiarrhythmic agents (and probably magnesium sulphate) are contraindicated in patients with hyperkalaemia as they potentiate myocardial conduction abnormalities (e.g. sinus arrest, AV nodal block, first-, second- or third- degree heart block and asystole).
**Hypertension.**

As severe hypertension (i.e. > 5 mmol/L) can produce a generalised depression of cardiac conduction causing, junctional or sinus bradycardia, sinoatrial block, AV block, and asystole, treatment of severe hypertension (as well as increasing excretion of the ion, which may require dialysis) may require intravenous calcium chloride (3.4 - 6.8 mmol) to rapidly manage the cardiac conduction defects.

**Hypocalcaemia.**

While the cardiac effects of hypocalcaemia have included the ECG changes of a prolonged and shortened QT, with hypocalcaemia and hypercalcemia respectively, many of the early studies which described this association were performed in patients who had chronic hyper- or hypocalcaemia, and the Ca\(^{2+}\) measurements were of plasma total calcium rather than plasma ionised Ca\(^{2+}\).\(^{40,44}\) It is now recognised that hypocalcaemia severe enough to cause myocardial depression (e.g. an ionised calcium level of 0.5 mmol/L or less) may be associated with a normal QT, interval\(^{42,43}\) and therefore a normal QT, interval does not exclude hypocalcaemia.

Hypocalcaemia per se rarely if ever causes an arrhythmia.\(^{44,45}\) Chronic hypocalcaemia, however, may cause cardiac failure.\(^{46-49}\) In chronic renal failure patients receiving haemodialysis with varying concentrations of ionised Ca\(^{2+}\) in the dialysate, ha have had varying effects recorded. Some studies have found that left ventricular contractility varied directly with the plasma ionised Ca\(^{2+}\);\(^{50,51}\) other studies have noted no effect on the left ventricular systolic function with an increase in serum calcium caused by a rise in concentrations of ionised Ca\(^{2+}\) in the dialysate.\(^{52,53}\) An acute rise in serum calcium, however, has been found to impair diastolic function (i.e. negative lusitropy).\(^{54}\)

Intravenous Ca\(^{2+}\) is often used to increase blood pressure in patients who have a low ionised calcium level (usually < 0.8 mmol/L) which it does by causing peripheral vasoconstriction and increasing cardiac contractility. The predominant haemodynamic response may depend upon the patients initial ionised Ca\(^{2+}\) level\(^{55}\) and the presence or absence of underlying heart disease. Peripheral vasoconstriction predominates if the patient’s plasma ionised Ca\(^{2+}\) is normal and there is no underlying cardiac disease. Enhancement of myocardial contractility predominates if the patients plasma ionised Ca\(^{2+}\) is low and the patient has underlying cardiac disease, because the myocardial performance is often correlated directly with ECF Ca\(^{2+}\) in the presence of β-receptor down regulation\(^{56}\) (i.e. in patients who have chronic heart disease or prolonged exposure to beta-agonists) or in the presence of beta-blockade.\(^{56}\) If the vasoconstrictive response predominates, then the rise in blood pressure tends to be transient; if an increase in contractility predominates, then the rise in blood pressure tends to be more prolonged.\(^{57}\) Critically ill trauma and septic patients often have low ECF Ca\(^{2+}\) levels which may only respond transiently to intravenous Ca\(^{2+}\) administration\(^{6,59}\) and it is thought that some of the ECF Ca\(^{2+}\) that moves intracellularly to increase cardiac contractility may, in the long term, be harmful.\(^{59,60}\) If intravenous calcium is considered necessary (i.e. to keep the ionised calcium > 0.8 mmol/L),\(^{61}\) then a continuous calcium infusion rather than a bolus dose is recommended.\(^{62,63}\)

**Vasoconstrictive agent: intravenous Ca\(^{2+}\) increases systemic blood pressure by increasing peripheral resistance\(^{64}\) (particularly in the presence of hypomagnesaemia) due to a direct effect of the Ca\(^{2+}\) ion and an increase in catecholamine release at both the sympathetic nerve ending and the adrenal medulla.\(^{57}\)

**Inotropic agent: intravenous Ca\(^{2+}\) increases myocardial contractility by increasing the amount of ECF Ca\(^{2+}\) available for myocardial contraction. Calcium also reverses the negative inotropic effect of a high ECF K\(^+\) level.\(^{55}\)**

Either calcium chloride or calcium gluconate may be used.\(^{56}\) Both are often packaged as 10 mL ampoules of a 10% solution. The 10% calcium chloride solution contains 0.68 mmol/mL of calcium, the 10% calcium gluconate solution contains 0.225 mmol/mL of calcium. As the clinical advantages of one salt when compared to the other have not been documented,\(^{57}\) and as recent clinical studies have shown rapid and equal dissociation of Ca\(^{2+}\) from both the chloride and gluconate salt\(^{64,67}\) (even in the absence of hepatic function\(^{65}\)), it would seem that either salt may be used.

Either 3 - 5 mL of 10% calcium chloride or 10 mL of 10% calcium gluconate may be administered under ECG control over 2 - 5 min. No more than 10 mL of the 10% calcium chloride solution should be given without measuring ionised Ca\(^{2+}\) levels to guide therapy. The mean plasma Ca\(^{2+}\) level in cardiac arrest patients was found to be 3.82 mmol/L, 5 min after a bolus of 5 mL of calcium chloride, which decreased to a mean level of 2.79 mmol/L after 10 min, and returned to normal after 15 min.\(^{61}\) If a continuous infusion of calcium is deemed necessary, then calcium chloride 10%, 1 - 5 mL/hr (i.e. 0.7 - 3.5 mmol/hr, to keep the plasma ionised calcium > 0.8 mmol/L and monitoring plasma ionised calcium 4-hourly) may be used.\(^{61}\) The clinical effects of intravenous Ca\(^{2+}\) are nausea, vomiting and generalised feeling of warmth and tingling, which may make the patient intensely uncomfortable. Acute administration of intravenous calcium may cause AV dissociation,
ventricular ectopies, VT and VF, particularly in the presence of digoxin toxicity or hypokalaemia.\textsuperscript{77,80,84}

Other effects
While there have been case reports where intravenous calcium salts have been used as pre-treatment of verapamil therapy that have caused reversion of paroxysmal supraventricular tachycardia\textsuperscript{80} (an effect which was probably was due to the concomitant elevation in blood pressure and reflex increase in cardiac parasympathetic tone that slowed atrioventricular conduction), reports of ventricular fibrillation have also been published.\textsuperscript{70}

Magnesium
Magnesium has been described as ‘nature’s physiological calcium blocker\textsuperscript{82}, inhibiting Ca\textsuperscript{2+}-induced muscle contraction by inhibiting the release of Ca\textsuperscript{2+} from the sarcoplasmic reticulum, increasing the uptake of Ca\textsuperscript{2+} by the sarcoplasmic reticulum (by stimulating the Ca\textsuperscript{2+}-ATPase activity) and by competing with Ca\textsuperscript{2+} at certain binding sites on troponin C and myosin.\textsuperscript{71} Unlike the synthetic calcium-blockers, increasing extracellular Mg\textsuperscript{2+} has not been shown to block the entry of Ca\textsuperscript{2+} into the cell through the slow channel,\textsuperscript{71} although increasing intracellular magnesium experimentally inhibits calcium entry through the dihydropyridine-sensitive channels.\textsuperscript{72}

In normomagnesaemic patients, intravenous magnesium sulphate causes coronary and systemic vasodilation (reducing coronary artery spasm and blood pressure, respectively), inhibits platelet function, and has antiarrhythmic effects when used to elevate plasma concentrations up to 2 mmol/L.\textsuperscript{73} It also causes a slight decrease in heart rate, a prolongation of the PR interval (due to an increase in the PA and AH interval without altering the HV interval), with no effect on the QRS (except at high doses) or QTc duration.\textsuperscript{74,77} Magnesium also decreases the sympathetic tone by causing a sympathetic ganglia blockade\textsuperscript{78} and reducing noradrenaline release and storage in the postganglionic sympathetic nerve fibres\textsuperscript{79,80} (although in normal individuals it increases plasma noradrenaline and neuropeptide-Y-like activity\textsuperscript{83} and may also enhance parasympathetic tone).\textsuperscript{82} At plasma levels < 10 mmol/L, Mg\textsuperscript{2+} has no negative inotropic effects.\textsuperscript{83}

Magnesium sulphate has been used as an antiarrhythmic agent to treat both hypomagnesaemic and normomagnesaemic cardiac arrhythmias.\textsuperscript{84}

Hypomagnesaemia
The cardiac effects of hypomagnesaemia include ECG changes (e.g. prolongation of the QTc segment and U waves, although U waves are most likely due to an associated hypokalaemia), arrhythmias (e.g. ventricular and atrial tachycardias\textsuperscript{44,85,86}, negative myocardial inotropic effects (e.g. cardiac failure,\textsuperscript{87} cardiogenic shock\textsuperscript{88}) and coronary ischaemia.\textsuperscript{98-92} Intravenous magnesium sulphate has been used in the treatment of:

Arrhythmias. Both bolus and continuous intravenous infusions of magnesium sulphate have been used to treat ventricular ectopies and VT,\textsuperscript{85,93} even in the absence of overt hypomagnesaemia.\textsuperscript{94,95} It is the treatment of choice of alternating VF and asystole during cardiac arrest\textsuperscript{96} and is also effective in the treatment of halothane,\textsuperscript{97} digoxin\textsuperscript{98-106} or hypomagnesaemia\textsuperscript{101,102} -induced cardiac arrhythmias, torsades de pointes\textsuperscript{94,103} and multifocal atrial tachycardia\textsuperscript{104,105} (Figure 2 and Figure 3). In one study, magnesium sulphate was more effective than amiodarone in converting acute atrial tachyarrhythmias in critically ill patients.\textsuperscript{106} However, in a prospective randomised controlled study of in-hospital cardiac arrest, magnesium (8 mmol bolus followed by 32 mmol over the next 24 hours), did not improve immediate or long-term morbidity or mortality.\textsuperscript{107}

Hypertension. Continuous infusions have been used to treat hypertension associated with pre-eclampsia or tetanus. Intravenous magnesium sulphate causes a direct peripheral arteriolar vasodilation which may be associated with a generalised warm and tingling sensation and reduction in blood pressure.\textsuperscript{98}

Cardiac failure. Intravenous infusions of magnesium sulphate do not have a direct effect on myocardial contractility in normal individuals.\textsuperscript{83} However, in hypomagnesaemic patients, cardiac failure\textsuperscript{87} and cardiogenic shock\textsuperscript{88} have been corrected with intravenous magnesium sulphate infusions.

Acute myocardial infarction. An infusion of intravenous magnesium sulphate has been reported to be associated with a decrease in mortality in normomagnesaemic patients with acute myocardial infarction\textsuperscript{73,86,109,110} even when thrombolytic and aspirin therapy were used, mortality was reduced by a further 25% (i.e. by 2.5 patients per 100 patients).\textsuperscript{73} The time of intravenous magnesium administration in acute myocardial infarction may be critical, as magnesium given at a mean of 3 hours after the onset of chest pain appears to be beneficial whereas magnesium given at a mean of 8 hr is not.\textsuperscript{111} In the fourth international study of infarct survival (ISIS-4), no significant advantage was recorded with intravenous magnesium sulphate (8 mmol in 15 min followed by 72 mmol in 24 hr) in any patient group (e.g. with or without thrombolytic therapy, and in those in whom it was infused before thrombolytic reperfusion had probably occurred).\textsuperscript{112} However, the optimal 24 hr dose of magnesium may be between 50 to 65 mmol and that doses of > 75 mmol (ISIS-4 used 80 mmol/24 hr) may increase mortality (due to an increase in bradyarrhythmias and heart failure),\textsuperscript{113} accordingly some
believe that the use of magnesium in myocardial infarction may warrant reexamination.

Unstable angina. In patients with unstable angina, an infusion of intravenous magnesium sulphate (8 mmol bolus followed by 3 mmol/hr for 24h) has been reported to be associated with a reduction in CK-MB release, a more rapid regression of T wave changes and reduced adrenaline excretion, when compared with a placebo.

Post cardiac surgery. In one study of post cardiac surgery patients an intravenous infusion of 8 mmol of magnesium chloride (over 20 min) decreased the incidence of ventricular arrhythmias and increase the cardiac index, although it does not alter the incidence of atrial fibrillation in post coronary artery bypass patients. Intravenous magnesium sulphate (2 - 8 mmol bolus over 2 - 5 min, up to 30 - 40 mmol during the first 12 hr post operative period) may also be used to control hypertensive episodes (and episodes of shivering and tachycardia). It also reduces postoperative analgesic requirements and promotes normal sleep.

Magnesium sulphate may be administered as an 8 mmol intravenous bolus (over 5 min), followed by an infusion of 65 mmol in 50 - 500 mL of 5% dextrose over 24 hr, which increases, on average, the serum magnesium concentration to 1.55 mmol/L, in patients without renal failure. If the bolus is not followed by an infusion, the serum magnesium level returns to normal after 20 min.

While some believe that a rationale exists for the use of intravenous magnesium in patients with high plasma potassium levels, magnesium can potentiate myocardial conduction abnormalities (e.g. sinus arrest, AV nodal block, first-, second- or third-degree heart block and asystole) and therefore is probably contraindicated in patients with hyperkalaemia. In hyperkalaemia associated with digoxin poisoning however, intravenous magnesium sulphate may eliminate refractory ventricular tachycardia and decrease the serum potassium.

Other effects of intravenous magnesium sulphate include an unpleasant flushing, and nausea and vomiting, particularly if administered too rapidly.

Sodium bicarbonate

Intravenous sodium bicarbonate as an 8.4% (1000 mmol/L) solution has been used for many acute cardiovascular disorders. For example:

Hyperkalaemia. While intravenous sodium bicarbonate (e.g. 100 mL of 8.4% or 100 mmol) is often used
in patients with hyperkalaemia and acidosis, in one study of patients with chronic renal failure, the effect of sodium bicarbonate was inconsistent and only reached significance at 4 hours after a constant administration. Therefore, severe cardiac dysfunction secondary to hyperkalaemia should be treated with intravenous calcium salts in the first instance.

*Tricyclic overdose.* Increasing arterial blood pH reduces free tricyclic blood levels. \[125\] Hyperventilation, to induce respiratory alkalosis, is often used first to treat respiratory acidosis, metabolic acidosis, and the ventricular arrhythmias associated with tricyclic antidepressant toxicity. \[124,125\] If ventricular arrhythmias persist, both hyperventilation and sodium bicarbonate are used to keep the plasma pH greater than 7.45. \[126\]

**Cardiac arrest.** Administration of intravenous sodium bicarbonate does not improve the ability to defibrillate \[127\] improve left ventricular contractility \[128\] increase the cardiovascular response to circulating catecholamines \[129,130\] or improve survival rates in cardiac arrest. \[130-133\] It is now no longer recommended in the routine management of cardiac arrest. \[134\]

**Hypertonic saline.**

Hypertonic saline may be used as a 3% (510 mmol/L), 7.5% (1275 mmol/L) or 20% (3400 mmol/L) solution (usually < 100 mmol as a bolus) and has many cardiovascular effects when infused. For example:

*Hyponatraemia.* Chronic hyponatraemia is associated with a positive inotropic effect, which is most likely due to an increase in the intracellular Na+ causing a Na+/Ca2+ exchange to increase the intracellular Ca2+. \[135\] While some studies have reported a negative inotropic effect with the acute administration of hypertonic saline, \[130,133\] other have reported an increase in cardiac output due to a positive inotropic effect, peripheral vasodilatation and increase in preload. \[138,139\] Hypertonic saline does not alter ischaemic injury associated with myocardial infarction and reperfusion. \[140\]

**Antiarrhythmic effects.** In an experimental model of tricyclic antidepression, hypertonic saline was more effective than sodium bicarbonate or hyperventilation in reversing prolongation of the QRS interval. \[141\] In other experimental models, hypertonic saline abolished ouabaine-induced arrhythmias, \[142\] and (with pretreatment) provided significant protection against bupivacaine-induced ventricular arrhythmias. \[143\]

**Phosphate.**

In one study of patients without clinical cardiac disease who had hypophosphataemia, significant ventricular ectopic activity was recorded which improved or disappeared after phosphate replacement. \[144\] In another study of patients with acute myocardial infarction, a low serum phosphate (< 0.84 mmol/L) was a significant predictor of ventricular tachycardia during the first 24 hr of hospitalisation. \[145\] Acute hypophosphataemia may be associated with a reversible form of cardiac failure. \[146\]

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