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REVIEW ARTICLE

Calcium and the anaesthetist

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Summary

Calcium plays a central role in a large number of physiological actions that are essential for life. It is important therefore that the anaesthetist understands calcium pathophysiology. In this review, the physiology, regulation, clinical features, causes and treatment of alterations in circulating calcium will be discussed. In addition, the effects that acid–base status, massive blood transfusion and cardiopulmonary bypass may have on circulating calcium will be highlighted. Finally, the role that calcium plays in ischaemic/reperfusion injury and myocardial stunning will be summarised.

Keywords *Calcium*: physiology; anaesthesia; drug reactions; reperfusion injuries.

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The calcium ion is essential for many biological processes that include cardiac automaticity; excitation–contraction coupling in myocardial, smooth and skeletal muscle; blood coagulation; neuronal conduction; synaptic transmission; hormone secretion and mitotic division. Calcium is also a major intracellular messenger needed for normal cellular function and required by many enzymes for full activity. Of particular relevance to the anaesthetist are the effects of calcium on the myocardium, vascular smooth muscle and blood coagulation.

Physiology

Myocardium

It has long been known that cardiac contraction and relaxation are primarily the result of repetitive phasic increases and decreases in the cytoplasmic calcium ion (Ca^{2+}) concentration [1]. These repetitive changes in the cytoplasmic Ca^{2+} concentration can be achieved by several mechanisms:

1 Opening and closing of calcium-specific or nonspecific channels on the cell membrane. The voltage-sensitive calcium channel in the surface membrane is the major route of entry of calcium, whose activation by depolarisation gives rise to the slow inward current. Calcium enters the cell by this route with each action potential and triggers the release of large amounts of Ca^{2+} from intracellular stores causing an immediate increase in cytosolic Ca^{2+} concentration.

2 The release and uptake of calcium by an intracellular calcium store, e.g. the sarcoplasmic reticulum. The sarcoplasmic reticulum Ca^{2+} release channel appears to be the major source for changes in cytoplasmic Ca^{2+} concentration required to produce cardiac contraction or relaxation in the mature heart. In the developing heart, the membranes of the sarcoplasmic reticulum are less abundant, which suggests that cardiac mechanics are regulated primarily by trans-sarcolemmal Ca^{2+} flux.

3 Chemical messengers such as hormones and neurotransmitters.

Each repetitive increase in cytoplasmic Ca^{2+} concentration increases Ca^{2+} binding to Troponin C, which results in an increase in the interaction between actin and myosin thereby producing cardiac contraction.

Cardiac relaxation occurs mainly when a protein of the sarcoplasmic reticulum, the Ca^{2+} ATPase pump, transports Ca^{2+} from the cytoplasm into the lumen of the sarcoplasmic reticulum membrane system, and when the Na^{+}–Ca^{2+} exchanger and the Ca^{2+} ATPase pump of the cell membrane transports Ca^{2+} from the cytoplasm to the interstitial space. The reduction in the cytoplasmic free Ca^{2+} concentration reverses the Ca^{2+} – Troponin C

binding equilibrium, so that Ca^{2+} dissociates from Troponin C. This reduces the interaction between actin and myosin and promotes active cardiac relaxation [2].

Vascular smooth muscle

Contraction of all smooth muscles is dependent on changes in the intracellular Ca^{2+} level [3]. This can occur as a result of inherent myogenic mechanisms that regularly depolarise the muscle fibres or from neural or hormonal actions. As a result of a rise in the cytoplasmic concentration of Ca^{2+}, more Ca^{2+} combines with the calmodulin regulatory protein to activate a protein kinase that phosphorylates myosin with subsequent activation of the smooth muscle actin–myosin complex.

In experimental tissue preparations, increase of intracellular calcium increases contractility in both cardiac and vascular muscle [4–7]. However, the overall haemodynamic response depends on the interplay between heart rate, preload, cardiac contractility and afterload.

Blood

Platelets

The cytoplasm of platelets contains contractile filaments of actin and myosin that enable activated platelets to change their shape and to release the contents of their granules. Increased concentrations of cytoplasmic Ca^{2+}, which occur as a result of thromboxane A2 formation from activated platelets, stimulate actin–myosin complexes with contractile responses that are thought to drive the change in shape, the release reaction and other events in platelet function [8].

Blood coagulation

Blood coagulation occurs as a result of a complex enzyme cascade. The end-stage is conversion of fibrinogen, a soluble plasma protein, into insoluble fibrin by the protease thrombin. There are two main pathways to fibrin formation:

The intrinsic pathway which commences when factor XII or 'Hageman factor' adheres to a negatively charged surface, e.g. collagen exposed by tissue injury, and becomes an active enzyme designated XIIa. Activation of a small amount of one factor catalyses the formation of larger amounts of the next factor, which catalyses the formation of still larger amounts of the next, and so on.

The extrinsic pathway, which is initiated by a substance generated by tissue damage and termed 'tissue factor' (sometimes called factor III), interacts with factor VII in the presence of calcium ions and phospholipid to activate factor X. The sequence then proceeds to the final step described above.

However, the two pathways are not entirely separate, because factor IXa and factor XIIa in the intrinsic pathway may interact with factor VIIa in the extrinsic pathway. Calcium and a negatively charged phospholipid are essential for the three final enzyme steps, i.e. for the action of:

Factor IX (intrinsic pathway) on Factor X
Factor VII (extrinsic pathway) on Factor X
Factor X on Factor II (thrombin).

Control

A normal 70-kg adult contains about 1.2 kg calcium, of which more than 99% is located in the bone. In the plasma, the normal total calcium concentration is about 2.25–2.55 $mmol.l^{-1}$ (9.0–10.2 $mg.dl^{-1}$). About 50% of this is free ionised calcium [8], about 10% is calcium combined with various anions (including bicarbonate, citrate, phosphate, lactate, and sulphate) [9] and the remaining 40% is bound to serum proteins, mainly serum albumin [10]. In the cell interior, the total concentration of calcium varies and may be as high as in the extracellular fluid [11]. However, the ionised calcium concentration in the cytoplasm is at least 1000 times lower than in extracellular fluid, ranging from 0.13 to 1.3 $\mu mol.l^{-1}$ [12]. It is maintained at this low level as the cell membrane permeability to Ca^{2+} is low and because cells have powerful mechanisms for extrusion, sequestration and buffering of calcium.

The free ionised calcium is the physiologically important component of the total calcium. In plasma, the ionised calcium concentration is normally maintained within a narrow range (1.0–1.25 $mmol.l^{-1}$), despite a widely varying input of calcium from the intestine and bone. Maintenance within this range is accomplished mainly by the action of three main calciotropic hormones: parathyroid hormone, calcitriol (1,25-dihydroxyvitamin D) and calcitonin.

Parathyroid hormone

Parathyroid hormone is released in increasing quantities in response to a decrease in the ionised calcium level, which it tends to correct by means of:

1 A direct action on bone (in concert with vitamin D) leading to release of skeletal mineral, including calcium and phosphate.

2 Direct actions on the kidney to promote calcium reabsorption by the distal renal tubule and inhibition of tubule phosphate reabsorption leading to an increase in plasma calcium concentration and acute phosphaturia. This phosphaturia prevents an increase in plasma phosphate concentration following release of calcium and phosphate from bone in conditions in which a rise in calcium concentration is required. In addition, in the

kidney, parathyroid hormone, together with other factors, including hypophosphataemia, increases the activity of the renal 25(OH) vitamin D 1-α hydroxylase enzyme in the proximal tubule and therefore increases the renal production of calcitriol, the most active metabolite of vitamin D.

Calcitriol

Calcitriol acts to increase calcium and phosphate absorption at the intestine level where calcium is believed to be absorbed by both passive diffusion and active transcellular transport, the latter being stimulated by calcitriol. It has dual effects on bone; it increases net bone resorption by increasing the metabolic activity of the osteoclasts and also plays a major role in facilitating bone formation. At the renal level, calcitriol promotes tubular reabsorption of calcium.

Calcitonin

Calcitonin is a 32-amino acid polypeptide hormone produced by the thyroid C cells. A negative feedback exists between serum calcium and calcitonin. A rise in serum calcium releases calcitonin, which subsequently influences bone and kidneys to decrease serum calcium. At the renal level, calcitonin tends to inhibit tubular reabsorption of calcium. At bone, calcitonin inhibits osteoclastic bone resorption. This acute inhibition of osteoclastic activity allows the continuing osteoblastic activity to increase net uptake of calcium by bone.

Clinical scenarios

Hypercalcaemia

Hypercalcaemia occurs when calcium influx into the extracellular fluid from the intestine and/or bone exceeds the efflux to intestine, bone and/or kidney. However, this usually happens when the influx of calcium from bone or the intestine exceeds the renal excretory capacity of calcium.

Clinical manifestations

The symptoms associated with hypercalcaemia generally correlate both with the magnitude and with the rapidity of the increase in serum calcium (Table 1). Mild hypercalcaemia, often observed with primary hyperparathyroidism, is generally asymptomatic. More severe hypercalcaemia of any aetiology can seriously disrupt normal gastrointestinal, neurological, cardiovascular and renal functions.

Gastrointestinal. Constipation, anorexia, nausea and vomiting are frequent. Poor fluid intake and fluid loss due to emesis are responsible for dehydration and may contribute to an acute hypercalcaemic crisis. Acute and chronic pancreatitis are also associated with hypercalcaemia and may transiently lower serum calcium.

Neurological. Central nervous system manifestations range from lethargy to confusion and coma. In some patients, headache is prominent. Generalised muscle weakness and hyporeflexia are characteristic findings in severe cases.

Cardiovascular. Hypercalcaemia decreases the plateau phase of the cardiac action potential. This is reflected in a shortened ST segment and consequently a reduced QT interval. Interestingly, with hypercalcaemia in excess of 4.0 $mmol.l^{-1}$ the T wave widens, tending to increase the QT interval. For this reason, the QT segment (distance from onset of QRS complex to onset of T wave) is a more reliable indication of hypercalcaemia. Arrhythmias may be common and serious. Fatal intra-operative cardiac arrest has occurred in a young man with a serum calcium level of 5.6 $mmol.l^{-1}$ despite attempts to reduce the level [13]. Acute elevation of serum calcium concentration may

Table 1 Clinical features of hypercalcaemia

Gastrointestinal:	Nausea and vomiting
	Anorexia
	Constipation
	Dehydration
Neurological:	Lethargy
	Fatigue
	Headache
	Muscle weakness and hyporeflexia
	Confusion
	Coma
Cardiovascular:	Hypertension
	ECG changes:
	Reduced QT interval
	Arrhythmias
	Digitalis sensitivity
	Cardiac arrest
Renal:	Polyuria
	Polydipsia
	↓ Renal blood flow
	↓ Glomerular filtration rate
	Interstitial nephritis
	Nephrocalcinosis
	Hypercalciuria
	Urolithiasis
Blood:	Thrombosis
Psychiatric:	Anxiety
	Dementia
	Depression
	Irritability
	Psychosis

cause a rise in blood pressure, possibly through direct vasoconstriction. However, the hypertension of chronic hypercalcaemia may also be due to renal damage. It is prudent to exercise caution when administering digitalis to hypercalcaemic patients as digitalis toxicity is exacerbated by a high serum calcium level.

Renal. Hypercalcaemia impairs renal function in several ways:

1 It causes polyuria and polydipsia by interfering with the action of antidiuretic hormone (ADH) on the collecting tubules.

2 It reduces renal blood flow and glomerular filtration rate as a consequence of vasoconstriction and dehydration.

3 It impairs proximal tubular function by deposition of calcium phosphate salts, with potential for producing focal scarring and inflammation (interstitial nephritis). In severe cases, nephrocalcinosis is visible on X-ray. Hypercalciuria and urolithiasis may also occur.

4 Superimposed urinary tract infection may aggravate hypercalcaemic nephropathy.

Blood. Calcium activates several factors in the clotting system. This may, in part, account for occasional reports of widespread thrombosis in hypercalcaemic patients [14].

Causes of hypercalcaemia

The commonest causes of hypercalcaemia apart from the artefactual causes are hyperparathyroidism and malignancy (Table 2). Sarcoidosis, thyrotoxicosis, vitamin D intoxication, thiazide diuretics and adrenal insufficiency are uncommon causes. Other causes such as immobilisation, end-stage renal disease and idiopathic hypercalcaemia of infancy are extremely rare.

Hyperparathyroidism. Primary hyperparathyroidism is the commonest cause of hypercalcaemia, accounting for more than 50% of cases. Often the patients are elderly females who are found to have a benign adenoma of a single parathyroid gland. Parathyroid carcinoma is a very rare cause. The excess parathyroid hormone leads to hypercalcaemia.

Table 2 Causes of hypercalcaemia

Hyperparathyroidism
Malignancy
Granulomatous diseases, e.g. sarcoidosis, tuberculosis
Thyrotoxicosis
Vitamin D intoxication
Thiazide diuretics
Adrenal insufficiency
Immobilisation
Exogenous calcium
End-stage renal diseases
Familial benign hypercalcaemia
Idiopathic hypercalcaemia of infancy
Lithium

Malignancy. Malignancy is the second commonest cause of hypercalcaemia and may be related to direct bone destruction or secretion of calcaemic factors by malignant cells. Hypercalcaemia occurs in about 10% of cancer patients [15]. The commonest causes are breast carcinoma, myeloma, bronchial and renal carcinomas. In general, the malignancy is already evident when patients present with hypercalcaemia.

Treatment of hypercalcaemia

Immediate treatment of the hypercalcaemia may be necessary in severely hypercalcaemic patients, especially in those who are symptomatic. Total serum calcium > 3.2 mmol.l^{-1} may be dangerous and urgent lowering of the level may be required. Rehydration, generally with intravenous saline solution, and early mobilisation are important initial steps. A rapid decrease of from 0.75 to 0.50 mmol.l^{-1} in total serum calcium concentration is typical after rehydration alone. In severely symptomatic patients, additional measures are often required. Forced saline diuresis can be performed safely using large amounts of isotonic saline (5–10 l.day^{-1}), together with potent diuretics, e.g. furosemide in doses of 100 mg every 2 h, but cardiovascular status and serum electrolyte concentrations must be monitored. It is prudent to seek assistance from a physician and, ideally, the patient should be managed in an intensive care or a high-dependency unit.

An elevated plasma calcium concentration secondary to myeloproliferative disorders can be decreased by the administration of the cancer chemotherapeutic drug plicamycin (previously termed mithramycin). Plicamycin is very effective but side-effects and toxicity limit the frequency of administration. A single dose of 25 μg.kg^{-1} corrected hypercalcaemia within 48 h in 30 of 41 cases of malignancy [16]. Intravenous etidronate may prove equally effective and is less toxic than plicamycin. Calcitonin has low toxicity but is not consistently effective in lowering hypercalcaemia. Glucocorticoids are effective in reducing calcium levels in patients with lymphoproliferative diseases and diseases associated with elevated calcitriol levels, e.g. granulomatous diseases, sarcoidosis and vitamin D toxicity. Intravenous phosphate, because of its potential acute toxicity, should only be used in life-threatening hypercalcaemia if etidronate disodium is ineffective and plicamycin is contraindicated.

Hypocalcaemia

Hypocalcaemia occurs when there is a net efflux of calcium from the extracellular fluid (i.e. calcium is lost from the extracellular fluid, often through renal mechanisms) in greater quantities than can be replaced by the intestine or bone. Falsely low levels of calcium due to hypoalbuminaemia should be excluded by measuring ionised calcium. The threshold level for the development of the symptoms of hypocalcaemia is not well defined. A variety of data suggest that life-threatening complications frequently occur when the serum ionised calcium concentration decreases to below 2 $mg.dl^{-1}$ (< 0.50 $mmol.l^{-1}$) [17].

Clinical manifestations

The symptoms generally correlate with the magnitude and rapidity of the decrease in serum calcium (Table 3). Hypocalcaemia may present with a variety of clinical signs and symptoms that relate to increased neuronal irritability leading to neurological, respiratory, cardiovascular and psychiatric manifestations.

Neurological. Manifestations of neuromuscular irritability predominate, and include paraesthesiae of the distal extremities and circumoral area, Chvostek's and Trousseau's signs, muscle cramps, tetany, and seizures. Dementia and movement disorders may also occur.

Table 3 Clinical features of hypocalcaemia

Neurological:	Paraesthesiae
	Chvostek's and Trousseau's signs
	Muscle cramps
	Tetany
	Muscle weakness
	Hyperactive reflexes
	Convulsions
Respiratory:	Laryngeal spasm
	Bronchospasm
Cardiovascular:	Hypotension
	Impaired contractility
	Bradycardia
	Arrhythmias
	Digitalis insensitivity
	Cardiac arrest
	ECG changes:
	QT and ST prolongation
	T inversion
Psychiatric:	Anxiety
	Dementia
	Depression
	Irritability
	Psychosis
	Confusion

Respiratory. Laryngeal spasm and bronchospasm may occur after surgery in patients following the removal of parathyroid adenomas secondary to acute hypocalcaemia. Muscle weakness may also develop and may precipitate respiratory failure.

Cardiovascular. Hypocalcaemia can result in hypotension (loss of vascular tone), cardiac failure (impaired cardiac contractility) and bradycardia. The electrocardiogram may demonstrate QT and ST interval prolongation and T wave inversion. However, it is important to note that the electrocardiogram may be normal during life-threatening hypocalcaemia and a normal ECG cannot therefore be relied upon to exclude this condition. Digitalis action depends upon extracellular calcium and hypocalcaemia can produce digitalis insensitivity. In addition, correction of hypocalcaemia in a patient with a therapeutic digitalis effect can precipitate digitalis toxicity. The generation of arrhythmias during hypocalcaemia is poorly studied. However, clinical observations suggest that cardiac irritability, e.g. premature ventricular contractions and ventricular fibrillation, can occur during severe hypocalcaemia.

Psychiatric. Anxiety, dementia, depression, irritability and psychosis can be observed in the awake patient in both hypocalcaemia and hypercalcaemia.

Causes of hypocalcaemia

Apart from apparent hypocalcaemia due to hypoalbuminaemia, the causes encountered in general hospital practice are, in approximate descending order of frequency: chronic and acute renal failure; vitamin D deficiency; magnesium deficiency associated with malabsorption or with alcoholism; acute pancreatitis; hypoparathyroidism; and infusion of phosphate, citrate or calcium-free albumin (Table 4). Among the surgical causes, the most common are parathyroidectomy, thyroidectomy and cardiopulmonary bypass. Hypocalcaemia is relatively common in critically ill adults [18] and children [19], particularly those with sepsis. It can also occur after a massive blood transfusion with citrate-anticoagulated blood, when the transfusion rate exceeds citrate metabolism, after the use of radiographic contrast media containing calcium chelators and during haemodialysis in patients with renal failure, depending on the calcium concentration of the dialysate. Maynard *et al.* [20] showed that the decrease in blood pressure induced by haemodialysis was reduced when a dialysate containing a high calcium concentration was used.

Treatment of hypocalcaemia

Patients with suspected hypocalcaemia should have an ionised calcium level performed to confirm the diagnosis.

Table 4 Causes of hypocalcaemia

Medical:	Chronic and acute renal failure
	Vitamin D deficiency
	Magnesium deficiency
	Acute pancreatitis
	Hypoparathyroidism
	Sepsis
Surgical:	Post-parathyroidectomy
	Post-thyroidectomy
	Post-cardiopulmonary bypass
Iatrogenic:	Massive blood transfusion infusion
	Phosphate, citrate or calcium-free albumin
	Radiographic contrast with calcium chelators

Mild degrees of hypocalcaemia with ionised calcium > 0.8 mmol.l^{-1} are usually asymptomatic and seldom require treatment. In more severe hypocalcaemia, it is more likely that the patient will experience hypocalcaemia-induced symptoms and therefore replacement therapy is appropriate. Serum ionised calcium concentrations < 0.50 mmol.l^{-1} are more frequently associated with life-threatening complications and constitute a medical emergency that necessitates intravenous calcium therapy. Initial therapy in adults consists of correction of any coexisting respiratory or metabolic alkalosis and the administration of a calcium bolus (100–200 mg of elemental calcium over 10 min), followed by a maintenance infusion of 1–2 mg.kg^{-1}.h^{-1} of elemental calcium. The serum calcium level usually returns to normal in 6–12 h with this regimen. Thereafter, the maintenance rate may need to be decreased to 0.3–0.5 mg.kg^{-1}.h^{-1}.

It is important to note that available preparations differ in their content of elemental calcium. There is no evidence that one form is clinically superior to another:

1 Calcium gluconate 10%: 10 ml = 9.3 mg of elemental calcium.

2 Calcium chloride 10%: 10 ml = 27.2 mg of elemental calcium.

Drugs contributing to hypocalcaemia should be discontinued. Calcium is irritating to veins and should be diluted before administration and all solutions are best administered through a central vein. Calcium should be given cautiously to patients receiving digitalis preparations, since it may induce digitalis-toxic arrhythmias or heart block.

Optimal therapy requires frequent monitoring of serum calcium, magnesium, phosphorus, potassium, and creatinine levels as well as the ECG and haemodynamic status. The therapeutic goal is to restore the serum calcium to near normal levels, which alleviate symptoms, and to avoid the complications of therapy, e.g. hypercalcaemia and hypercalciuria. Once the ionised calcium concentration is stable, calcium may be administered by the enteral route. Most patients require 1–4 g of elemental calcium per day in divided doses. When calcium alone is not sufficient for control of hypocalcaemia, vitamin D metabolites can be added. However, definitive treatment of hypocalcaemia involves recognition and correction of the underlying disorder.

Anaesthesia

During anaesthesia, several factors may alter the serum ionised calcium level, thus potentiating the adverse effects of hypo- and hypercalcaemia in susceptible patients. These factors are: the presence of malnutrition and low albumin; abnormal acid-base status and electrolytes; the drugs used during the peri-operative period; transfusion of large volumes of citrated blood; and the use of cardiopulmonary bypass. The anaesthetist should aim to prevent further changes in the plasma calcium concentration and to recognise and treat adverse effects of hypo- and hypercalcaemia, particularly those on the heart. Furthermore, current research suggests that the mechanism of action of many drugs used during anaesthesia is due, at least in part, to the calcium ion.

Premedication

Benzodiazepines are widely used in anaesthetic practice as premedication, a sedative-amnesic or induction agent. Animal studies have shown that haemodynamic alterations induced by benzodiazepines are mediated, in part, through inhibitory effects on the sympathetic nervous system [21] and via inhibition of voltage-dependent Ca^{2+} currents [22], preventing Ca^{2+} entry into vascular smooth muscle cells. Benzodiazepines are also able to relax airway smooth muscle. Studies on midazolam to determine the underlying mechanisms of this phenomenon have shown that midazolam directly relaxes airway smooth muscle by decreasing cytosolic Ca^{2+} via inhibition of the influx of extracellular Ca^{2+} with no effect on the release of stored Ca^{2+} [23]. Although the mechanisms by which benzodiazepines exert their effects on smooth muscle have been defined, clinical relevance in patients with low or high calcium has not been demonstrated.

Intravenous anaesthetic agents

Intravenous induction of anaesthesia is frequently associated with changes in cardiovascular function. The cellular mechanisms that mediate the cardiodepressant effects of intravenous anaesthetic agents remain undefined. *In vitro* studies have shown that such effects are due to a reduction in the availability of intracellular Ca^{2+}.

However, these effects are primarily apparent at supraclinical concentrations [24]. On the other hand, animal studies have shown that thiobarbiturates relaxed vascular smooth muscle independently of the intracellular Ca^{2+} concentration, while oxybarbiturates exerted their vasodilatory action via a reduction in the intracellular Ca^{2+} concentration [25]. These results may suggest that the vasodilatory effects of thiobarbiturates may not be accentuated in patients susceptible to alterations of calcium, as thiobarbiturates seemed to affect sites in the vascular smooth muscle distal to the regulation of intracellular calcium.

The physiological role of intracellular calcium in platelet aggregation has been established. The inhibitory effect of propofol on platelet aggregation has recently been studied [26] and has been found to be related to a reduction in the intracellular Ca^{2+} concentration. Propofol was found to inhibit the influx and the discharge of calcium ions, thus supporting the inhibitory effect of propofol on platelets. However, as there was no change in the bleeding time, it suggests that this inhibitory effect did not clinically impair haemostasis.

Inhalational anaesthetic agents

Inhalational anaesthetic agents may themselves be considered as nonspecific calcium antagonists. It is now reasonably well established that the myocardial depression [27] and vascular dilatation [28] caused to a varying extent by all modern volatile anaesthetic agents is related, at least in part, to alterations in calcium ion flux. Myocardial depression produced by inhaled anaesthetics has been shown to be potentiated by calcium channel blocking drugs due to the nonspecific calcium antagonism of volatile agents that can be reversed by calcium administration [29]. There are reports of impaired atrioventricular conduction, bradycardia and asystole in patients receiving verapamil and diltiazem under general anaesthesia. These interactions are more pronounced with enflurane and halothane than with isoflurane [30], and are mostly seen in patients with pre-existing ventricular compromise and, possibly, during open chest surgery [31].

Malsch *et al*. examined the depression of isometric contractile force caused by halothane in a myocardial muscle preparation and found an exaggerated response when the bathing medium was calcium deficient [32]. This may suggest that the negative inotropic effect caused by inhalational anaesthetics may also be potentiated in the presence of hypocalcaemia. Should bradyarrhythmias occur and profound hypocalcaemia be demonstrated, treatment should involve discontinuation of the volatile agent and cautious administration of a small dose of calcium salt.

Neuromuscular blocking agents

Neuromuscular blocking drugs are frequently an essential part of the anaesthetic technique. Calcium plays a central role in synaptic and neuromuscular transmission through changes in transmembrane calcium flux. However, calcium has a less immediate and dramatic effect on neuromuscular transmission than on cardiovascular function. It is nevertheless important that the role of calcium in synaptic transmission is understood. Calcium has two opposing actions in the neuromuscular transmission process. Presynaptically, it decreases the degree of depolarisation [33], which could antagonise a nondepolarising muscular block. Postsynaptically, it decreases the degree of depolarisation produced by acetylcholine [34], which could potentiate a nondepolarising block. The overall effect of calcium at the neuromuscular junction is therefore unpredictable. In general terms, responses to nondepolarising muscle relaxants seem to be potentiated both in hypo- and in hypercalcaemia, but are more obvious in the presence of muscle weakness and atrophy. A reduction in the duration of action of atracurium has been reported in a patient whose serum calcium was elevated secondary to hyperparathyroidism [35], indicating that monitoring of neuromuscular function is strongly recommended in patients with any calcium disorder.

After the administration of intravenous succinylcholine, some workers have found a decrease in the ionised calcium concentration in children during halothane anaesthesia, although the total calcium concentration remained unchanged [36]. These results may have been influenced to some extent by pH variations, as there was an inverse relationship between pH and ionised calcium. Others have reported a decrease in the total calcium concentration, possibly due to the migration of calcium ions within muscle cells during the fasciculations induced by succinylcholine [37] and to the formation of calcium complexes with anions, such as bicarbonate, phosphate, citrate and lactate.

Opioids

Classically, opioids inhibit Ca^{2+} entry via voltage-sensitive Ca^{2+} channels. This is generally accepted as part of the cellular basis of analgesia [38]. However, several recent reports have shown that opioids also stimulate Ca^{2+} influx [39]. Indeed, it has been proposed that opioid-induced increases in intracellular Ca^{2+} concentration may be involved in the biochemical events underlying analgesia [40]. Alternatively, there is evidence linking opioid-induced increases in intracellular Ca^{2+} concentration to the development of tolerance [39].

Currently, there appears to be no published information concerning the effects of opioids on serum Ca^{2+} concentration. However, changes in pH may occur if

respiratory depression ensues when opioids are used in spontaneously breathing patients. This can affect the binding of calcium to plasma proteins. Acidaemia will decrease protein binding with a subsequent increase in the ionised calcium [41].

Local anaesthetic agents

The mechanism by which bupivacaine may cause cardiotoxicity, if accidentally injected into the circulation, has been found to be related to changes in intracellular Ca^{2+} concentration [42]. The cardiodepressant effects of bupivacaine are seen *in vitro* as a reduction in the contraction force of heart tissue [43]. A determinant of the cardiodepression might be an inhibition of calcium current through L-type Ca^{2+} channels [42]. Inhibition of cardiac L-type Ca^{2+} channels by bupivacaine has been found to be more potent in the presence of calcium antagonists, although it is uncertain which drug potentiates the other [44]. This may suggest that the cardiotoxicity of bupivacaine may be increased in the presence of hypocalcaemia.

Animal studies comparing the inhibitory effects of local anaesthetics on L-type Ca^{2+} channels ranked potencies as follows: dibucaine > tetracaine > bupivacaine >> procaine = lidocaine, a sequence which seems to match the respective lipid solubilities. In addition, tetracaine was found to inhibit N- and T-type Ca^{2+} channels [45].

Maintenance of anaesthesia

The same principles applied during induction should continue during maintenance of anaesthesia. It is prudent to avoid significant changes in acid–base status due to mechanical ventilation. It is also wise to avoid massive blood transfusion in susceptible patients, the use of autologous blood being more beneficial. Blood loss can also be reduced using a hypotensive anaesthetic technique. Lastly, the measurement and correction of ionised calcium concentration in patients with calcium disorders during cardiopulmonary bypass is strongly recommended.

Acid–base status

It is generally recognised that the level of ionised calcium is affected by pH alterations. Isolated heart preparations have shown that decreasing the pH from 7.4 to 6.9 leads to an increased ionised calcium of 0.2–0.4 $mmol.l^{-1}$, which is large enough to increase contractile force by about 30% [46]. Acidosis decreases calcium binding to albumin thus increasing ionised calcium, while alkalosis increases binding (calcium shifts onto the albumin molecule), producing a subsequent reduction in the ionised calcium. Respiratory alkalosis may occur with acute hyperventilation, thus lowering ionised calcium. These changes in acid–base status tend to affect the ionised calcium concentration (the biologically important fraction) without changing the total calcium levels. Thus, the ionised calcium should be measured whenever possible to guide subsequent therapy.

Massive blood transfusion

When blood transfusions are given at about 30 $ml.kg^{-1}.h^{-1}$ and haemodynamic stability is maintained, compensatory mechanisms ensure that serum Ca^{2+} concentrations remain within normal limits [47]. More rapid rates of transfusion temporarily depress Ca^{2+} concentration, which recovers within 10 min if the infusion rate is decreased. However, clearance of citrate from the blood will be decreased during hypothermia if liver function is impaired and therefore rapid transfusion of relatively small volumes of citrate-containing blood products will cause a reduction of serum Ca^{2+} concentrations. This may be recognised clinically as a sudden decrease in arterial pressure that responds transiently to an intravenous injection of calcium salt. This reduction in arterial pressure has been found to be more severe in patients with underlying cardiac diseases [48]. Clearance of citrate from the blood should be encouraged by correcting the hypothermia, increasing the systemic and hepatic blood flow and by increasing urine output, since approximately 20% of citrate can be excreted in the urine [49].

Cardiopulmonary bypass

The initiation of cardiopulmonary bypass represents an exposure to a large volume of priming fluid and biochemical changes may occur as a result of haemodilution. Other aspects of bypass priming fluid such as protein content and acidity have been shown to influence ionised calcium [47]. Hypocalcaemia is common in small patients given large volumes of citrated blood [50]. An immediate decrease in ionised calcium has been reported in patients receiving citrated blood, and this reduction was greater than that found in patients receiving heparinised blood [51]. Large doses of heparin may also directly affect ionised calcium and cardiovascular stability [52]. Cardiovascular effects during bypass are difficult either to measure or to interpret, and studies of the effects of calcium therapy do not provide definitive therapeutic guidelines [51–53]. Nevertheless, the levels of ionised calcium should be monitored and corrected accordingly, particularly in view of the basic physiological relationship between ionised calcium and myocardial contractility.

Postoperative period

The factors that are responsible for altering ionised calcium levels continue during the postoperative period. Hypocalcaemia may present as laryngospasm in the

immediate postoperative phase, particularly after neck surgery, and may require re-intubation of the trachea. Furthermore, Zaloga *et al*. [54] found that laryngospasm associated with hypocalcaemia can be resolved with calcium repletion.

After cardiac surgery, the concurrent administration of calcium and catecholamines are used in an attempt to improve myocardial contractility. Indeed, it might be expected that calcium administration along with catecholamines would increase the effectiveness of catecholamines. Paradoxically, calcium was found to reduce the vasopressor action of epinephrine (adrenaline) in animals [55] and its inotropic action in humans [56]. Other studies demonstrated that calcium inhibits dobutamine's cardiac stimulating properties [57]. It is thought that calcium may inhibit the β-adrenergic action of epinephrine (adrenaline) by interfering with adenylate cyclase function. Conversely, drugs that produce their effects via mechanisms that do not involve activation of the β-adrenergic receptor such as amrinone (a phosphodiesterase inhibitor) and phenylephrine (an α-adrenergic agonist) were used in association with calcium in patients recovering from aortocoronary bypass surgery. In these patients, calcium did not augment or inhibit the cardiotonic actions of amrinone [57] or the hypertensive effects of phenylephrine [58]. Others found that calcium blunts the vasoconstrictor actions of norepinephrine (noradrenaline) [59, 60].

Controversies

Calcium and ischaemic injury

The mechanisms for cellular injury during ischaemia and reperfusion are under intense investigation. Most hypotheses for injury involve alterations in cellular calcium homeostasis [61]. The role of calcium in ischaemic cellular injury is particularly important considering the current use of exogenous calcium during and after cardiopulmonary bypass surgery, particularly in view of the advent of calcium channels blockers.

Early studies demonstrated that calcium was deposited in areas of tissue damage and it was suggested that calcium contributed to cellular injury. When calcium was removed from fluid bathing cardiac cells, the permeability of the cell membranes increased. With return of calcium to the bathing solution, there was an accelerated entry of calcium into the cell, cell contracture and death. The phenomenon became known as the Calcium Paradox [62]. Later, it was shown that ischaemic myocardium accumulated calcium during reperfusion. After 40 min of ischaemia (occlusion of the circumflex branch of the left coronary artery) and 10 min of arterial reperfusion, an 18-fold increase in myocardial calcium content was found. Furthermore, myocardium reversibly injured by 10 min of ischaemia and 20 min of reperfusion did not accumulate calcium [63, 64].

Increases in cytosolic calcium may be detrimental to cells by activating calcium-dependent phospholipase resulting in breakdown of cell membranes and generation of free radicals. Calcium may be harmful, potentiating the damaging effects of free radicals [65]. Calcium may also activate destructive proteases and nucleases and disrupt adenylate cyclase, sodium potassium ATPase activity, and other important calcium-regulated cellular enzymes [66]. If calcium is responsible for ischaemic damage, then intracellular free calcium concentrations should increase during both ischaemia and reperfusion. Cytosolic calcium can be measured using fluorescent techniques and nuclear magnetic resonance imaging. Most authors have detected increases in cytosolic calcium during ischaemia and reperfusion [65, 67]. However, the causes of increases in calcium during hypoxia, ischaemia and re-oxygenation remain uncertain. Changes in membrane potentials, inhibition of sarcoplasmic reticulum uptake of calcium and increased calcium influx could explain the changes [68].

In summary, calcium is implicated in the cellular damage produced by ischaemia and agents that increase calcium influx appear to be harmful during and after ischaemia, reperfusion, hypoxia and re-oxygenation. By contrast, agents that decrease calcium influx may ameliorate injury [69].

Myocardial stunning

Contractile dysfunction that occurs following a period of ischaemia and is not associated with necrosis is known as myocardial stunning [70]. This condition typically occurs after cardiac surgery, when the heart has sustained ischaemic-reperfusion damage during operation that may persist for hours to days. Evidence suggests that calcium influx during reperfusion may cause the stunning [71]. If this is true, the reduction of extracellular calcium during reperfusion should improve myocardial function, i.e. decrease stunning. Indeed, low calcium reperfusion of ischaemic hearts has been shown to prevent stunning [71]. The protective effect of low calcium reperfusion indicates a major role for cellular calcium overload in the pathogenesis of stunning. This also questions the common practice of administering intravenous calcium after ischaemia, e.g. after cardiopulmonary bypass. Initially, it was thought that myocardial stunning occurred only after ischaemia-reperfusion, but is now apparent that stunning can also be caused by hypoxia-reoxygenation. Neonates are not immune from such problems and as surgery for congenital heart lesions is now common, prevention and treatment of myocardial stunning are increasing in

importance for the paediatric cardiac anaesthetist. Compared with adults, neonatal myocardial stunning can develop in the absence of previous ischaemia, and therefore cyanotic neonates are at particular risk of 're-oxygenation injury'. Subsequent myocardial dysfunction thus occurs when cardiopulmonary bypass or extracorporeal membrane oxygenation is initiated rather than during reversal of ischaemia, as occurs in adults, suggesting that the methods used to prevent stunning in the neonate may need to vary from those used in the adult [72]. Generation of free radicals, resulting in damage to cellular proteins and phospholipids, with the disruption of intracellular calcium homeostasis, are the two nonmutually exclusive mechanisms responsible for this postinjury dysfunction [73]. Experimental studies have shown that hypoxia-reoxygenation may be even more injurious than a similar period of ischaemia-reperfusion [74, 75], suggesting that neonates undergoing surgery for a cyanotic heart condition may be more sensitive to the effects of this postinjury dysfunction.

Discussion

Hypercalcaemia

Hypercalcaemia is a metabolic disturbance with a clinical spectrum that ranges from an asymptomatic biochemical abnormality to a life-threatening disorder. Occasionally, a patient with hypercalcaemia may present for anaesthesia, and although an increase in serum calcium can cause a number of changes, the anaesthetist is particularly interested in its effects on the heart, circulation, muscle power and blood coagulation. Adequate pre-operative assessment and appropriate treatment should be initiated before elective surgery if the patient is symptomatic.

If anaesthesia has to be undertaken when hypercalcaemia exists, particular attention must be paid to the action of muscle relaxants. The duration of nondepolarising relaxants is likely to be prolonged, especially if muscle weakness coexists. Conversely, there is a report on reduction of duration of action of atracurium during hypercalcaemia [35]. However, a smaller dose than usual is recommended in the first instance, with further small increments being given according to the results of neuromuscular monitoring.

Patients with hypercalcaemia may benefit from hyperventilation and respiratory alkalosis in an attempt to shift calcium onto the albumin molecule. Nevertheless, this can only be recommended if life-threatening hypercalcaemia occurs while further measures to decrease ionised calcium are being employed. The cardiovascular and haemodynamic changes, although potentially lethal, are not commonly seen under anaesthesia, but, if required, therapy should be instituted to decrease the ionised calcium along the lines recommended earlier.

Hypocalcaemia

The anaesthetist is interested in the effects of hypocalcaemia on the heart, circulation, muscle power and blood coagulation. Adequate pre-operative assessment and appropriate treatment, if required, is essential before elective surgery.

If anaesthesia has to be administered when hypocalcaemia exists, particular attention must be paid to the potential additive effects on the heart and circulation of drugs commonly used in general anaesthesia, in particular the volatile anaesthetic agents. It must be remembered that greater myocardial depression and hypotension may occur and therefore, once the diagnosis has been made, calcium replacement may attenuate such responses.

The action of muscle relaxants may be prolonged and smaller doses may be required, with further increments administered in response to the results of neuromuscular monitoring. Hyperventilation should be avoided and normocapnia maintained throughout the procedure in order to prevent further decreases in ionised serum calcium. If hypocalcaemia develops during anaesthesia, the first indication may be the diagnostic changes in the ECG. A sample of blood could be taken for confirmation but, in view of the possible cardiac complications, the anaesthetist should probably interfere on the basis of the pharmacological principles previously outlined.

Conclusion

The calcium ion has a very important role to play in homeostasis. It is particularly relevant in physiological processes involved during the conduct of anaesthesia. It is also becoming a very important consideration during the conduct of cardiopulmonary bypass and the management of the critically ill patient on an intensive care unit. Current research also shows that the calcium ion is an integral part of the processes that produce both analgesia and anaesthesia. The main recommendation regarding the anaesthetist's role in managing patients with abnormal calcium metabolism is to try to restore and keep the ionised serum calcium within normal limits.

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