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Article

Vasopressors for cardiopulmonary resuscitation.

Does pharmacological evidence support clinical practice?

Peter E. Penson, William R. Ford and Kenneth J. Broadley

Division of Pharmacology, Welsh School of Pharmacy, Cardiff University, King

Edward VIII Avenue, Cathays Park, Cardiff, CF10 3NB, UK

Corresponding author. Tel.: +44-29-20-875832; fax +44-29-20-874149

E-mail address: BroadleyKJ@Cardiff.ac.uk. (K.J.Broadley)

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Abstract

Adrenaline (epinephrine) has been used for cardiopulmonary resuscitation since 1896; the rationale behind its use is thought to be its α-adrenoceptor-mediated peripheral vasoconstriction, causing residual blood-flow to be diverted to coronary and cerebral circulations. This protects these tissues from ischaemic damage and increases the likelihood of restoration of spontaneous circulation. Clinical trials have not demonstrated any benefit of adrenaline over placebo as an agent for resuscitation. Adrenaline has deleterious effects in the setting of resuscitation, predictable from its promiscuous pharmacological profile. This article discusses the relevant pharmacology of adrenaline in the context of cardiopulmonary resuscitation. Experimental and clinical evidence for the use of adrenaline and alternative vasopressor agents in resuscitation is given, and the properties of an ideal vasopressor are discussed.

Keywords

Adrenaline, Adrenoceptor Agonists, Advanced Cardiac Life Support, Cardiopulmonary Resuscitation, Epinephrine, Vasopressors.

Abbreviations

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

1 Introduction

1.1 Historical aspects

Cardiac arrest is the ultimate medical emergency and resuscitation has occupied the minds of people throughout the ages. History records numerous bizarre and probably unhelpful resuscitation techniques. These included rolling the victim around on top of a barrel or pumping tobacco smoke into his rectum (Hermreck 1988). Artificial ventilation was first attempted in the 16th century, and electrical defibrillation was initially investigated in the 18th. Cardiac massage and the use of adrenal gland extract, were both innovations of the 19th century (Hermreck 1988). Although myocardial infarction is the most common cause of cardiac arrest, it has been estimated that between 10% and 34% of cardiac arrests presenting in hospital are of non-cardiac origin (Grubb *et al.* 1995; Fischer *et al.* 1997; Kuisma and Alaspaa 1997; Weston *et al.* 1997; Engdahl *et al.* 2003). Commonly occurring non-cardiac causes of cardiac arrest include haemorrhage, trauma, pulmonary embolism, near drowning and intoxication (Kuisma and Alaspaa 1997). Cardiac arrest can also be precipitated by electrolyte abnormalities, sepsis (Hess *et al.* 2007) electrocution (Beers and Berkow 1999a) and iatrogenic effects (Brembilla-Perrot *et al.* 2003).

1.2 Current clinical practice

In order to achieve successful resuscitation and to prevent damage to the vital organs (in particular the heart and the brain), blood-flow must be rapidly restored to allow these vulnerable tissues to be reperfused. The International Liaison Committee on Resuscitation has issued guidelines for 'Advanced Cardiac Life Support'. They

suggest the use of adrenaline (epinephrine) in the treatment of all major types of rhythm disturbances presenting with cardiac arrest (International Liaison Committee on Resuscitation 2005). This includes the so called 'shockable' rhythms (ventricular fibrillation and pulseless ventricular tachycardia) which are treated with cardiopulmonary resuscitation (CPR) (ventilation and chest compressions) interspersed with defibrillator shocks, designed to restore the normal cardiac rhythm and adrenaline. 'Non shockable' rhythms (asystole and pulseless electrical activity) should also be treated using CPR and adrenaline. As the name suggests, defibrillation is not used as treatment for these rhythms. The distribution of the adrenaline around the circulatory system is achieved by the closed-chest cardiac massage element of CPR (International Liaison Committee on Resuscitation 2005) (Figure 1).

In Britain, it is recommended that 1mg of adrenaline should be given intravenously every three minutes during cardiac arrest (Mehta 2006) although international guidelines suggest dosing every three to five minutes (International Liaison Committee on Resuscitation 2005). This disparity probably reflects the fact that the guidelines are based on best practice and collective wisdom rather than evidence based medicine. Adrenal gland extract was first used for the purpose of resuscitation in 1896 (Gottlieb 1896; Crile and Dolley 1906) and adrenaline was used clinically initially as an intracardiac injection (Pearson and Redding 1963; Pearson and Redding 1964a) and subsequently as an injection into a peripheral vein followed by a saline flush and continuing chest compressions (Mehta 2006).

1.3 Mechanism of action of chest compressions in CPR

In order to aid recovery of a patient in cardiac arrest and to ensure perfusion of the vital organs, some method of ensuring a degree of circulation is required. This is achieved by repeated manual compressions of the chest. There are two (not mutually exclusive) theories as to how chest compressions lead to circulation of the blood. The 'thoracic pump' theory reasons that the intrathoracic pressure generated by chest compressions drives blood from the thorax into the general circulation, venous valves prevent backflow of blood, and thus repeated compressions can pump the blood around the circulation. The increased intrathoracic pressure would also assist venous return into the ventricles by compressing the vena thoracic vena cava and pulmonary vein. The 'cardiac pump' theory assumes that compression of the ventricles causes closure of the atrioventricular valves, and ejection of blood into the pulmonary artery and aorta. This has been extensively reviewed elsewhere (Andreka and Frenneaux 2006). It is important to note that distribution of any drug injected into the circulatory system during cardiac arrest is dependent upon, and limited by the blood-flow generated by CPR.

1.4 Rationale for the use of adrenaline in CPR

Interestingly, although the recommendations for the administration of adrenaline to a patient in cardiopulmonary arrest have changed little over the past century, the supposed rationale for the use of adrenaline have altered more than once. Crile and Dolley (1906) are quite clear about *"The value of adrenalin in raising the blood pressure, by its action upon the vascular walls in the state of suspended animation"*. However, Pearson and Redding cite the coronary arteries as the site of action (Pearson and Redding 1963)

and later it is suggested that the benefit of adrenaline lies in it increasing the amplitude of fibrillation and associated contractions prior to the application of a defibrillating electric current (Livesay *et al.* 1978). Studies in dogs carried out in the 1980s have led to the currently held view that peripheral arteriolar vasoconstrictor effects of adrenaline account for any beneficial effects seen at resuscitation. Constriction of peripheral circulation ensures that blood-flow generated by CPR is thus directed to coronary and cerebral circulation. Vasopressors are thought to prevent arterial collapse as intrathoracic pressure is raised by chest compressions (Michael *et al.* 1984). Aortic diastolic pressure, an important determinant of coronary blood-flow is increased (Michael *et al.* 1984; Brown and Werman 1990). Maintenance of coronary blood-flow is the most important factor in enabling return of spontaneous circulation (ROSC) or successful defibrillation (Kern *et al.* 1988; Paradis *et al.* 1990; Paradis *et al.* 1991; Babbs *et al.* 2001; Zhong and Dorian 2005)

It is interesting to note that one historical resuscitation method was to throw cold water at the face of the victim. (Hermreck 1988). History does not record the effectiveness of this technique, however it may have activated the human dive reflex which causes bradycardia and peripheral vasoconstriction (Levick 2003)

The peripheral vasoconstrictor effects of adrenaline are as a result of the activation of α-adrenoceptors, particularly in arterioles in the kidney, mucosa and skin and also in many veins (Hoffman 2001; Hoffman and Taylor 2001). The receptor subtypes involved will be discussed below in section 3.1.1. Catecholamines such as adrenaline do not penetrate the blood-brain-barrier (Dahlgren *et al.* 1980) and cannot act on central adrenoceptors when given systemically. Changes in systemic blood pressure,

therefore, largely dictate alterations in cerebral blood flow (Dahlgren *et al.* 1980; Hoffman 2001). Thus, the increased blood pressure achieved by peripheral vasoconstriction improves blood-flow in the coronary and cerebral circulations, protecting the most vital organs from ischaemic damage and improving the chances of achieving ROSC.

Despite its widespread use, a large body of experimental evidence from animal studies suggests that adrenaline may have no effect or even a detrimental effect on various measures of well-being and survival during resuscitation (Brown *et al.* 1988; Wenzel *et al.* 1999; Klouche *et al.* 2003; Niemann and Garner 2005; Schwartz and Lagranha 2006) . High doses do not seem to improve survival and may increase adverse effects (Ditchey and Lindenfeld 1988; Lindner *et al.* 1991b; Lindner *et al.* 1991a; Hornchen *et al.* 1993; Hilwig *et al.* 2000; Voelckel *et al.* 2000). These concerns have been upheld by the results of several clinical trials (Marwick *et al.* 1988; Olson *et al.* 1989; Herlitz *et al.* 1995; Woodhouse *et al.* 1995; Sherman *et al.* 1997; Behringer *et al.* 1998; Holmberg *et al.* 2002). See section 6 below. The most recent international guidelines, issued in 2005 concluded:

"Despite the widespread use of adrenaline during resuscitation, and several studies involving vasopressin, there is no placebo-controlled study that shows that the routine use of any vasopressor at any stage during human cardiac arrest increases survival to hospital discharge. Current evidence is insufficient to support or refute the routine use of any particular drug or sequence of drugs. Despite the lack of human data, the use of adrenaline is still recommended, based largely on animal data."
(International Liaison Committee on Resuscitation 2005).

This paper will review the evidence for and against the use of adrenaline for resuscitation. The focus will be on the pharmacological basis for the use of various agents and how this translates into success in the clinical setting. Often, agents which show promise experimentally yield disappointing results in the clinic. Experimental models used in this field of research are briefly described and their strengths and weaknesses discussed. The results of clinical trials in resuscitation are then discussed in detail.

2 Pathophysiology of cardiac arrest and ischaemic damage to the heart.

2.1 Time course of cardiac arrest

In order to treat cardiac arrest effectively, the mechanism by which ischaemic damage progresses must be understood. Pearson and Redding (1964b) recognised the importance of the different requirements of treatment before and after ROSC. This is particularly interesting in the light of the discovery that after periods of ischaemia, tissues can be further damaged by reperfusion (Heyndrickx *et al.* 1975) and that the mechanisms of ischaemic damage to tissue are different from those of reperfusion injury (Carden and Granger 2000) (Figure 2). More recently a three-phase model of the pathophysiology which occurs during cardiac arrest has been suggested (Weisfeldt and Becker 2002). This model divides the pathophysiology and treatment of cardiac

arrest into the following phases: (1) the electrical phase (up to four minutes after the cardiac arrest begins); (2) the circulatory phase (from four to ten minutes); and (3) the metabolic phase (after 10 minutes). According to the model, electrical defibrillation is most successful during the electrical phase and should be attempted if possible. If treatment is not begun until the circulatory phase, then interventions designed to supply oxygen to the vital organs (such as chest comprssions, artificial ventilation and vasopressor administration) should be carried out prior to attempted defibrillation. If treatment is not initiated until the metabolic phase has begun, chances of survival are poor. During this phase, gut bacteria release endotoxins into the circulatory system and if resuscitation is successful, severe reperfusion damage in all body tissues is likely (Weisfeldt and Becker 2002). It was suggested that adrenaline is most useful during the circulatory phase, where increases in coronary flow increase the likelihood of successful defibrillation. During the metabolic phase, the vasoconstriction elicited by adrenaline may cause ischaemia in various organs and therefore have a detrimental effect (Weisfeldt and Becker 2002).

This model has important implications for the way in which cardiac arrest is treated. Currently, guidelines for the treatment of cardiac arrest do not make any reference to the length of ischaemia prior to treatment; however this model challenges the current approach. For instance, it seems likely that different requirements might apply when resuscitation takes place within a hospital (and access to a physician is presumably rapid) and out-of hospital resuscitation when there may be a delay in obtaining medical assistance. Of interest, one clinical trial including 650 patients noted poor rates of survival when a high dose of adrenaline was given later than 10 minutes after

cardiac arrest (Stiell *et al.* 1992). Further analysis of time-course data is required to determine the significance of such observations.

2.2 Overview of ischaemic damage and reperfusion injury

Ischaemia plays a dual role in cardiac arrest; because the heart is a pump which supplies blood to all parts of the body (including itself, via the coronary artery), myocardial ischaemia inevitably occurs during sudden cardiac death and other immediate causes of cardiac arrest. However, myocardial ischaemia and infarction are also the most common causes of cardiac arrest (Camm 2002). Infarction follows thrombus formation in a coronary artery leading to ischaemic damage of the myocardium, infarct formation and subsequent electromechanical dysfunction (Beers and Berkow 1999c).

Rapid reperfusion of the tissue in question has traditionally been the treatment for ischaemia, although it is now known that at reperfusion, damage occurs over and above that sustained during ischaemia. This discovery led to the concept of 'reperfusion injury' (Braunwald and Kloner 1985). The paradox that reperfusion is both necessary for survival and damaging has lead to it being described as a 'double-edged sword'(Braunwald and Kloner 1985). Reperfusion injury is an important consideration from a clinical perspective because whilst it is almost impossible to predict when cardiac arrest will occur, reperfusion can happen as a result of a medical intervention (e.g. defibrillation and thrombolysis) and therefore is more amenable to therapeutic interventions (Piper *et al.* 2004). Various pharmacological agents including adenosine and opioids have been demonstrated to attenuate reperfusion injury in animal models. This has been extensively reviewed by Gross and Gross

(2006). Such agents have the potential to be administered at the time of defibrillation or thrombolysis, in order to minimise the damaged caused by reperfusion. Thus, if it is to be of use as a model for advancing clinical treatments of cardiac arrest, a reperfusion phase would be a useful addition to the three-phase model of Weisfeldt & Becker (2002).

Cardiac arrest can be associated with numerous presenting rhythms. Ventricular fibrillation is the most common presenting rhythm, occurring in 70% of cases of cardiac arrest. Co-ordination of cardiac contraction is lost and cardiac output is negligible. Pulseless electrical activity (also known as electromechanical dissociation or non-perfusing rhythm) refers to a situation whereby the pattern of electrical depolarisation within the heart is normal, but contraction does not occur. Asystole is an absence of both electrical and mechanical activity. (Beers and Berkow 1999c).

The remainder of this review will discuss the relevant pharmacology of adrenaline and other vasopressors, and the consequences of administration of these agents during resuscitation from cardiac arrest.

3 Pharmacodynamic and pharmacokinetic properties of adrenaline.

Adrenaline is a non-selective α-and β-adrenoceptor agonist, released by the adrenal medulla in response to stress. The cardiovascular effects of adrenaline are complex due to the fact that several subtypes of adrenoceptors are present in the heart and in the vasculature and physiological responses are usually the result of a combination of

effects. Table 1 summarises some general features and indicates their relevance to CPR.

The onset of myocardial ischaemia triggers the release of adrenaline from the adrenal medulla, as a result of fear and anxiety (if the patient is conscious) and the massive fall in blood pressure accompanying cardiac arrest (Schoemig and Richard 1991). An increase in sympathetic discharge also results in the release of noradrenaline from sympathetic neurones within the heart (Foley *et al.* 1987; Kern *et al.* 1989; Lindner *et al.* 1996a). In ischaemic regions, metabolic alterations during prolonged ischaemia lead to the emptying of neuronal noradrenaline vesicles into the cytoplasm. A reversal of the uptake transporter for noradrenaline releases the neurotransmitter into the synaptic cleft where it is able to accumulate. This noradrenaline release is independent of neuronal activity. Some synaptic noradrenaline spills over into the circulation. (Schoemig and Richard 1991). Hence cardiac arrest results in a raised plasma catecholamine state which is maintained long after resuscitation (Niemann and Garner 2005). The administration of adrenaline during cardiac arrest is therefore a mimic of the natural response, however high levels of endogenous catecholamines during CPR are correlated with poor survival (Lindner *et al.* 1996a) and to further increase concentrations may prove detrimental.

3.1 Pharmacology of adrenaline relevant to CPR

The introduction of adrenaline into the intact circulatory system of man causes an increase in cardiac output and blood pressure. This is brought about by constriction of arterioles, increase in venous return and by positive chronotropic and inotropic effects on the heart (Lichtenstein *et al.* 1987). Adrenaline causes vasodilatation by activation

of β_2-adrenoceptors in the coronary artery, liver and skeletal muscle, but vasoconstriction (mediated by α-adrenoceptors) elsewhere (Ganong 2001).

3.1.1 Actions on vascular adrenoceptors

As described above, beneficial effects of adrenaline are thought to be mediated by peripheral vasoconstriction. Classically, in humans, α_1-adrenoceptors are considered to be the main mediators of arteriolar vasoconstriction and α_2-adrenoceptors whilst having a lesser role in arteriolar vasoconstriction, are important mediators of venous vasoconstriction. Contraction in response to neuronal action potentials in arterial smooth muscle is almost exclusively mediated by α_1-adrenoceptors which are close to the sites of noradrenaline release at the synapse (Guimaraes and Moura 2001). Prejunctional α_2-adrenoceptors are found on post-ganglionic sympathetic neurones. When activated by noradrenaline, they attenuate the further release of noradrenaline initiating a negative-feedback mechanism. However, α_2-adrenoceptors are also present extrasynaptically, on smooth muscle cells and can contribute to vasoconstriction. The α_{2A} subtype is probably the most important in this respect (Kanagy 2005).

There is some debate over the relative importance of the receptor subtypes involved in mediating contractile responses to circulating catecholamines, which can cause vasoconstriction via α_1- and via α_2-adrenoceptors (Guimaraes and Moura 2001). One study in mice, using prazosin to block α_1-adrenoceptor-mediated responses, estimated that between 55 and 68% of the vasopressor response to injected noradrenaline was mediated through α_1-adrenoceptors (Duka *et al.* 2000). However, this study may have been flawed, because prazosin is also known to act as an antagonist to some extent at

α_{2B}- and α_{2C}-adrenoceptors (Kanagy 2005). There is some evidence that several pathophysiological features of cardiac arrest can increase the importance of α_2-adrenoceptor-mediated arteriolar vasoconstriction.

In healthy subjects, the vasoconstrictor response to α_2-adrenoceptor activation on smooth muscle is opposed by activation of endothelial α_2-adrenoceptors which initiates the release of nitric oxide and other endothelium-derived vasodilator agents. Indeed, in rat aorta, treatment with a nitric oxide synthase inhibitor is required to unmask the vasoconstrictor response to α_2-adrenoceptor stimulation (Kanagy 2005). This led to the suggestion that in intact arteries, the vasodilator (endothelial) effects of α_2-adrenoceptor activation might outweigh the vasoconstrictor (smooth muscle) effects. There is a paucity of information regarding the relative vasodilator and vasoconstrictor responses to α_2-adrenoceptor agonists in the arterioles, where vasopressors are intended to act during resuscitation. However, cardiovascular disease is likely to disrupt the balance of vasodilatation and vasoconstriction. Damage to the vascular endothelium is an important component of the pathophysiology of cardiovascular disease. Ischaemia also causes severe damage to the endothelium (Sapienza *et al.* 1996). Endothelial damage results in reduced endothelial vasodilator responses (Sapienza *et al.* 1996; Melo *et al.* 2004) and thus in patients presenting with cardiac arrest, the vasoconstrictor properties of α_2-adrenoceptors may dominate over the endothelial vasodilator effects (Kanagy 2005).

Vasoconstriction mediated by activation of α_2-adrenoceptors can be readily demonstrated in animal models *in vivo* (Timmermans and Van Zwieten 1980; Van Meel *et al.* 1981). However, this vasoconstriction is difficult to replicate in isolated *ex*

vivo blood vessels. It has been suggested that this is due to the fact that α_2-adrenoceptors predominate in small resistance vessels, whereas larger arteries, often used for such studies are abundant in α_1-adrenoceptors (McGrath 1982). This may have led to an underestimate of the importance of α_2-adrenoceptors as vasoconstrictors. Studies of the locations of post-junctional α_2-adrenoceptors in the porcine circulation have found them in arterioles, in cutaneous veins and arteries (Roberts *et al.* 1998) and in human omental arteries. In humans, there appears to be an inverse relationship between lumen diameter, and density of α_2-adrenoceptors (Nielsen *et al.* 1991). Vasoconstrictor responses to α_2-adrenoceptor stimulation have also been demonstrated in other small human arteries (Nielsen *et al.* 1991). Vasoconstriction in the human coronary circulation is mediated by both α_1-adrenocqeptors (in large vessels) and α_2-adrenoceptors (in the microcirculation) (Gregorini *et al.* 1999; Gregorini *et al.* 2002) and reduces the blood supply to the myocardium. Thus, whilst α-adrenoceptor agonists cause peripheral vasoconstriction which is beneficial during cardiac arrest, the overall effect may be detrimental if myocardial blood-flow is reduced.

It has been demonstrated, using human skeletal muscle arteries that ischaemia increases the vasoconstrictor response elicited by α_2- (and α_1-) adrenoceptors (Jarajapu *et al.* 2001). This may be another factor in allowing α_2-adrenoceptor agonists to have an enhanced vasoconstrictor role during resuscitation.

Vasodilatation of skeletal muscle vasculature is a classic 'fight or flight' response of adrenaline. The mechanism of the vasodilatiation is via the activation of β-adrenoceptors. This vasodilator effect of adrenaline opposes the beneficial α-

adrenoceptor-mediated vasoconstriction described above (Guimaraes and Moura 2001).

3.1.2 Action on cardiac adrenoceptors.

In ventricular myocardium and the sino-atrial node, adrenaline acts predominantly on β_1-adrenoceptors in the heart to mediate positive chronotropic and inotropic effects. This leads to an increase in oxygen demand in the myocardium. In the ischaemic heart, activation of β-adrenoceptors can therefore lead to a worsening of ischaemia. Carvedilol, an α_1- and β-adrenoceptor antagonist, has been demonstrated to have beneficial effects during myocardial ischaemia (See section 4.2 below).

The stimulation of α_1-adrenoceptors may be undesirable in resuscitation because they are also found in the heart, where they mediate a positive inotropic effect, leading to an increased oxygen demand in the myocardium. This has been demonstrated both in the rat (Williamson and Broadley 1989; Broadley *et al.* 1999) and in human subjects (Landzberg *et al.* 1991). Although it should be noted, that when a non-selective adrenoceptor agonist such as adrenaline is given, the predominant effect on inotropy is likely to be through β-adrenoceptors. Despite the apparent contraindications to α_1 stimulation, some investigators have studied the possibility of using methoxamine, an α_1-adrenoceptor agonist in the resuscitation setting. Two studies compared the use of this agent with adrenaline. In a canine model of resuscitation, methoxamine was found to be superior to adrenaline (Roberts *et al.* 1990), however in a clinical study adrenaline was superior (Olson *et al.* 1989).

Preliminary results from our laboratory demonstrate the adverse effects of adrenaline on myocardial stunning in rat isolated ventricular strips when adrenaline is given shortly prior to and during reperfusion (Figure 3). We are currently examining whether α-, β- or both adrenoceptor subtypes are involved in this deleterious effect.

3.1.3 Vasopressors after ROSC.

The resuscitated myocardium is likely to be stunned and thus pumping blood sub-optimally. Positive inotropes such as dobutamine are clinically used to increase cardiac output (Mehta 2006). Selective vasopressors may be of use in directing residual cardiac output to the vital organs (Livesay *et al.* 1978). A recent analysis of clinical trial data has demonstrated a positive correlation between blood pressure after myocardial infarction and survival (Mayer and Schunkert 2007; Yap *et al.* 2007). This may seem surprising initially; however it highlights the importance of ensuring adequate perfusion of organs after myocardial damage.

3.2 Miscellaneous properties of adrenaline relevant to resuscitation

Adrenaline has a promiscuous pharmacological profile, being an agonist for at least nine different receptor subtypes. It has numerous effects which may detract from any beneficial effects in the resuscitation setting, these are discussed below.

3.2.1 Coronary vasoconstriction

The haemodynamics of adrenaline are complicated because it can cause vasoconstriction (α-adrenoceptors) and vasodilatiation (β-adrenoceptors). However

high-doses of adrenaline can result in coronary vasoconstriction (Karch 1989). This presents a major limitation to the use of adrenaline in resuscitation.

3.2.2 Platelet aggregation

It has been established experimentally that stimulation of α_2-adrenoceptors induces platelet aggregation which will initiate blood clotting mechanisms (Cameron and Ardlie 1982). This occurs via the release of the pro-aggregatory thromboxane A_2 (Shah *et al.* 2000). At a concentration of 14.3 μg/kg (the standard 1mg dose of adrenaline given to a 70 Kg patient), platelet aggregation is approximately 10% (Poullis 2000). However, at higher doses of adrenaline used in some studies (Wenzel *et al.* 1999) platelet aggregation might be in the region of 75% (Poullis 2000). Given that it is occlusion of a coronary artery by thrombus formation and subsequent myocardial ischaemia that results in the tissue damage of myocardial infarction, and, that thrombolytic drugs, such as streptokinase must be given to restore blood-flow, the rationale behind giving a prothrombotic agent in these patients seems questionable. If it is the α_2-adrenoceptor which also has the beneficial effects in resuscitation, this fact could potentially limit the effectiveness of agents for resuscitation directed at this receptor (Table 2). However, the significance of this prothrombotic action may only be slight given that all myocardial infarction patients receive thrombolytic drugs as a matter of urgency (Mehta 2006).

3.2.3 Oxidation of catecholamines

Adrenaline can be oxidised *in vivo* by ceruloplasmin, a plasma α-globulin, by polymorphonucleocytes and by cytochrome oxidase (Behonick *et al.* 2001). Oxidation

products of adrenaline, of which adrenochrome is the main example (Green and Richter 1937) have been demonstrated to inhibit catechol-o-methyl transferase, an enzyme responsible for the inactivation of catecholamines (Abbs *et al.* 1967). This has the potential to further increase the concentrations of active catecholamines.

The oxidation products of catecholamines have been known for some time to cause damage to myocardial tissue (Yates and Dhalla 1975; Dhalla *et al.* 1978) although it is not known if they are more or less harmful than adrenaline itself (Bindoli *et al.* 1992; Behonick *et al.* 2001). It has been demonstrated that oxidation of catecholamines is partially responsible for the increased levels of free radicals observed during ischaemia. High levels of oxygen radicals are partly responsible for post-ischaemic contractile dysfunction because they cause peroxidation of membrane phospholipids, disrupting the structure of the membrane and increasing its permeability. This leads to cell death by necrotic mechanisms (Lazzarino *et al.* 1994; Moens *et al.* 2005). This suggests that non-catecholamine adrenoceptor agonists may prove more useful, although since endogenous catecholamine levels are greatly raised during ischaemic insult to the heart, the significance of this is hard to judge.

3.2.4 Adrenoceptor desensitisation

Adrenoceptors undergo desensitisation when exposed to high agonist concentrations. Adrenoceptors of the α_1 subtype are particularly prone to desensitisation during cardiac arrest (Sun *et al.* 2001), and, together with the potentially deleterious effects of α-adrenoceptor activation during resuscitation, this has been used as an argument for the use of selective α_2-adrenoceptor agonists for resuscitation (Sun *et al.* 2001).

3.2.5 Interactions with drugs concomitantly taken by patients.

Many patients who present with acute myocardial infarction will have been prescribed drugs for existing cardiovascular conditions. These may include α-adrenoceptor antagonists such as prazosin and doxazosin and β-adrenoceptor antagonists and drugs which act as antagonists at both α- and β-adrenoceptors. Drugs acting on α-adrenoceptors are used for a number of other conditions ranging from depression to benign prostatic hyperplasia (Hieble 2000). This potentially complicates the effects of giving adrenaline for resuscitation, in an unpredictable manner.

3.2.6 Consequences of exposure to adrenaline at reperfusion

Whilst the vasopressor actions of adrenaline may be of use in restoring circulation, the detrimental effects of clinically administered and endogenously released adrenaline may extend into reperfusion. The arrhythmogenic effects of α_1-adrenoceptor activation have been described above. It has also been demonstrated that β-adrenoceptors have functional importance during the period of reperfusion. β_1- and β_2-adrenoceptors may have differential effects on the stunned heart. It is reasonably clear that β_1-adrenoceptor stimulation is detrimental, as evidenced by the fact that the β_1 selective antagonists, metoprolol (Feuerstein *et al.* 1998) and bisoprolol (Gao *et al.* 2000) reduced infarct size in a rabbit model of the ischaemic heart when antagonists were given five minutes prior to reperfusion. However, isoprenaline, a non-selective β_1- β_2-adrenoceptor agonist did not alter infarct size although it did provide inotropic support (LaBruno *et al.* 1998). This has led to the suggestion that non selective β-adrenoceptor agonists exert beneficial effects due to β_2-adrenoceptor activation, but this is negated by harmful β_1 mediated effects (Broadley and Penson 2004) . An

overall detrimental effect of adrenaline on contractile recovery was shown in isolated rat ventricles when administered for five minutes at the end of a period of simulated ischaemia, and for the first fifteen minutes of reperfusion (Figure 3). Thus, further work is required to examine the effects of β_2-adrenoceptor activation at reperfusion.

3.2.7 Hypokalaemia induced by β-adrenoceptor activation

Activation of β-adrenoceptors has been implicated in mediating the hypokalaemia which is seen upon administration of adrenaline in humans. Hypokalaemia can result in arrhythmias (Beers and Berkow 1999b), hence is undesirable in the treatment of cardiac arrest (Roffey *et al.* 2003). Adrenaline infusion has been shown to initiate electrocardiographic changes in man via a β_2-adrenoceptor-induced hypokalaemia. It is not clear whether the timecourse of these effects would be relevant during cardiac arrest and resuscitation. However, in another study, low concentrations of adrenaline (up to 0.06 μg/kg/min) were infused into healthy men. The infusion resulted in hypokalaemia and disturbed repolarisation. However, when the plasma potassium was held constant via a potassium infusion, the electrophysiological disturbances remained. The authors attributed this result to a direct effect on the myocardium causing a lengthening of the QTc interval (Lee *et al.* 2003). It has also been shown in a cell-based model that adrenaline shortens the refractory period of the cardiac action potential, thus promoting fibrillations (Tovar and Jones 1997).

3.2.8 Pulmonary ventilation/perfusion mismatching

It has been demonstrated in an experimental study using dogs, that adrenaline has detrimental properties on pulmonary gas exchange during resuscitation. When regions of the lung become hypoxic (such as after respiratory arrest), hypoxic vasoconstriction in such areas directs blood-flow to better ventilated regions of the

lung. This vasoconstriction may be reversed by the activation of β-adrenoceptors by adrenaline, thus preventing the beneficial effects of this autoregulatory mechanism by diverting blood-flow away from better ventilated areas (Tang *et al.* 1991).

3.2.9 Distribution of adrenaline.

If the widely held theory that adrenaline exerts its beneficial effects through vasoconstriction in peripheral arterioles is correct (see section 1.4 above), the intravenous route of administration of adrenaline presents drug distribution problems. The poor cardiac output generated by chest compressions is not conducive to the rapid distribution of drugs. Additionally, before adrenaline can reach its site of action, it must pass through the heart and lungs, therefore it is likely to be present at higher concentrations in these organs, where a detrimental effect of adrenaline is predicted, rather than at its intended site of action in peripheral arterioles. Pharmacokinetic considerations in cardiac arrest have been extensively reviewed elsewhere (Pentel and Benowitz 1984).

3.2.10   Effects of adrenaline on mast cells

There is some evidence to demonstrate that the mast cell degranulation that occurs during ischaemia and reperfusion is mediated by activation of α_1-adrenoceptors on the mast cells. The subsequent release of cytotoxic degranulation products such as mast cell peroxidase, leads to myocardial dysfunction (Parikh and Singh 1999).

4 Possible alternatives to the use of adrenaline

The poor clinical outcome with adrenaline (Holmberg *et al.* 2002) has led to research being directed at developing alternative vasopressors for use in resuscitation. As described above, it has been suggested that stimulation of the α_2-adrenoceptor and resultant vasoconstriction produces a beneficial effect during resuscitation, whilst responses mediated by other adrenoceptors are theoretically detrimental. This has provoked the suggestion that better results might be achieved by the use of more selective adrenoceptor agonists, of by directing the response to adrenaline selectively towards desirable receptor subtypes by the use of antagonists. Attempts have also been made to use non-adrenergic vasopressors in experimental and clinical models of cardiac arrest. These strategies are discussed below.

4.1 Selective α-adrenoceptor agonists

The promiscuous pharmacological profile of adrenaline has led to the suggestion that subtype-specific adrenoceptor agonists might prove more beneficial. The possibility of using selective α_2-adrenoceptor agonists as vasopressor agents in resuscitation has been examined experimentally. The argument given is that activation of β-adrenoceptors is detrimental in resuscitation, because they increase the energy requirements of the heart, as do α_1-adrenoceptors to a lesser extent. The latter also become rapidly desensitised during ischaemia (Sun *et al.* 2001). Clonidine is unsuitable as it causes a paradoxical fall in blood pressure. This is due to activation of α_2-adrenoceptors in the central nervous system causing a fall in blood pressure (Kanagy 2005).

The supposedly selective α_2-adrenoceptor selective agonist, α-methylnoradrenaline has been suggested for use in resuscitation and it has proved promising in animal models of ischaemia reperfusion for the reasons outlined above. However, one small but well designed study in humans has cast doubt upon the usefulness of this drug because it showed no vasoconstrictor activity until β-adrenoceptors were blocked, suggesting that this agent acts additionally on β-adrenoceptors, opposing its beneficial vasoconstrictor response (Schafers *et al.* 1999).

As described above, post-junctional smooth muscle α_2-adrenoceptors cause vasoconstriction, whereas pre-junctional α_2-adrenoceptors prevent neuronal noradrenaline release and the resulting vasoconstriction (Table 1). Endothelial α_2-adrenoceptors cause vasodilatation by a nitric-oxide mediated mechanism. The effect of adrenaline on endothelial α_2-adrenoceptors is likely to counteract the beneficial vasopressor effects of α_2-adrenoceptor agonists. It is by no means clear whether activation of pre-junctional α_2-adrenoceptors would be beneficial or detrimental during resuscitation. High levels of endogenous catecholamines during resuscitation have been linked with a poor chance of survival, and thus it has been argued that stimulation of pre-junctional α_2-adrenoceptors to inhibit neuronal noradrenaline release would be expected to be advantageous (Sun *et al.* 2001). One possible approach to developing a new vasopressor for resuscitation would be to use a selective agonist with exclusively vasoconstrictor properties. Such an approach would prove challenging as the same subtype of adrenoceptor (α_{2A}) appears to mediate both vasoconstriction (via receptors located on smooth-muscle) and vasodilatation (via endothelial receptors).

One major limitation of this approach has been highlighted by a study in dogs, which demonstrated that when the coronary circulation is under-perfused, activation of α_2 adrenoceptors leads to a profound vasoconstriction in coronary arterioles. If this effect were to occur in humans, it would seem to preclude the use of α_2-adrenoceptoer agonists for resuscitation (Chilian 1991).

An intriguing possibility, that does not seem to have been considered elsewhere is that the α_2 adrenoceptors agonist effects of adrenaline are beneficial, but through venous rather than arteriolar constriction. It is possible that constriction of capacitance vessels would increase venous return and improve right atrial filling. Although there is no direct evidence to support this theory, it is interesting to note a beneficial effect of devices which compress veins i.e. cause mechanical venoconstriction. 'Military antishock trousers' have been shown to improve coronary and cerebral blood-flow during CPR (Lilja *et al.* 1981; Warren *et al.* 1983). The theory behind these devices is that they prevent venous pooling in the lower extremities and essentially perform an 'autotransfusion of blood'. The same theory lies behind the G-suits used by fighter pilots to prevent blacking out during high-speed manoeuvres. Interestingly the idea can be traced back to George Crile, one of the first investigators to use adrenaline in CPR (Sternbach 1984).

4.2 Directing endogenous and administered adrenaline towards α_2- adrenoceptors with antagonists.

Directing the effects of adrenaline towards specific receptor subtypes by the concurrent administration of subtype-specific adrenoceptor antagonists has been

suggested. The advantage of this approach is that it may reduce the deleterious effects of the massive endogenous release of catecholamines which takes place during cardiac ischaemia (Niemann and Garner 2005).

Based on the theory that α_2-adrenergic receptors would be beneficial at resuscitation (Sun *et al.* 2001), one study treated rats with carvedilol, an antagonist at α_1- , β_1- and β_2- adrenoceptors, prior to adrenaline treatment. It was demonstrated that after induced ventricular fibrillation and adrenaline administration during resuscitation, carvedilol pre-treated animals had significantly better myocardial and neurological function than controls. Importantly, survival was also significantly increased from 45 ± 22 hours to 71 ± 1 hour (Huang *et al.* 2006).

Carvedilol improves efficiency of energy production hence prevents build up of oxygen free radicals which frequently occur upon reperfusion. This effect has been demonstrated to be independent of the antioxidant properties of carvedilol and is thus probably receptor mediated (Monteiro *et al.* 2003). This could be confirmed by comparing the (+) and (-) stereoisomeric forms of carvedilol, both isomers presumably having equal non-receptor properties such as antioxidant activity. However, no clinical studies using adrenaline after carvedilol treatment appear to have been performed.

4.3 Non adrenergic vasopressor agents.

Vasopressin, alternatively known as anti-diuretic hormone, is released from the posterior pituitary in response to dehydration and has a two-fold effect on blood

pressure. It increases the permeability of the kidney tubule, increasing re-absorption of water and hence expanding blood volume. It also has a vasoconstrictor action on peripheral arterioles (Ganong 2001). Experimental results show a benefit over adrenaline (Johansson *et al.* 2004). Clinical results are described below (section 6.4). Endothelin-1 has also been investigated in a swine model of resuscitation. It was shown to increase coronary perfusion pressure but did not affect the likelihood of ROSC. (DeBehnke *et al.* 1996; DeBehnke 2000; DeBehnke and Benson 2000). As yet, no clinical studies using this agent appear to have been carried out.

However, a major contra-indication exists to the use of either of these agents in the resuscitation setting. They are both strong coronary vasoconstrictors (Martinez *et al.* 2003). This effect may outweigh any increase in coronary flow achieved by peripheral vasoconstriction.

4.4 Ideal properties of resuscitation vasopressor

Many vasopressor drugs are available, although relatively few have been extensively tested as candidates for use in CPR. It is possible that an as yet unexamined vasopressor may be more beneficial than any current agent. The ideal compound would improve the chance of ROSC and would improve long-term survival. When deciding which drugs to put forward for further testing in this field, it is suggested that a vasopressor with the following 'ideal' properties is sought. The drug or combination of drugs should:

- Constrict peripheral arterioles.
- Not constrict coronary or cerebral vessels (coronary vasodilator would be beneficial).

- Not increase myocardial oxygen consumption.

- Not increase platelet aggregation or blood coagulation.

- Have a relatively long plasma half-life to allow infrequent dosing during resuscitation.

- Not yield any metabolites that oppose the beneficial effects or have toxic properties.

- Protect against the harmful effects of raised levels of endogenous catecholamines but spare any beneficial properties.

- Not have any adverse effects upon reperfusion injury.

4.5 General effects of vasopressors which may limit usefulness during resuscitation

Ischaemic damage and reperfusion injury in the heart have been discussed above, however the mechanisms involved are applicable in various tissue types throughout the body. Because of the lack of blood flow, ischaemia of an organ or tissue causes the accumulation of waste products of metabolism locally. Upon reperfusion, these can be released into the general circulation and have deleterious consequences on distant organs. For example, tumour necrosis factor-α, a pro-inflammatory cytokine released into the circulation from all ischaemic tissues can compromise cardiac function and increase reperfusion injury (Blancke *et al.* 2005). This has been extensively reviewed elsewhere (Tisi and Shearman 1999). Ischaemia and reperfusion in a limb can cause a systemic reaction in which the function of multiple organs is disrupted (Yassin *et al.* 2002). Theoretically therefore, causing vasoconstriction in

peripheral blood vessels could worsen the ischaemic damage and consequent events at reperfusion. However, given that peripheral tissues are probably minimally perfused during CPR, the relevance of vasoconstriction may be minimal.

Vasopressors, by their very nature constrict blood vessels. This can prevent drug distribution in the circulatory system. Indeed, adrenaline is often given in combination with local anaesthetics to reduce local blood flow thus decreasing the amount of systemic absorption and prolonging local anaesthetic effects (Mehta 2006). Thus, when intended for systemic effects as in resuscitation, it may be difficult for vasopressors to reach their site of action, unless they have a high selectivity for particular peripheral vascular beds.

Case reports suggest that adrenaline administration can lead to intracranial haemorrhage (Choudhary *et al.* 1999; Cartwright and Reynolds 2005; Kwon *et al.* 2007). This is likely to result from its vasopressor effect, and may be of concern immediately after the ROSC, when circulating levels of the vasopressor drug may still be high.

5 Experimental models

A variety of experimental models have been used to study the effects of drugs on ischaemic damage and reperfusion injury. Laboratory methods have proved useful in preclinical investigation of drugs used during resuscitation and are extensively employed, although there is often a disparity between experimental findings and

clinical results. To date, no model has been validated, such that it can reliably predict the results of an intervention in the clinical setting.

5.1 In vivo experiments

In vivo models provide the most realistic tool for the experimental study of resuscitation. Various species have been used including rats (Klouche *et al.* 2003; Kolarova *et al.* 2005), dogs (Roberts *et al.* 1990) and pigs (Pellis *et al.* 2003; Niemann and Garner 2005). There is a wide distribution in the extent of coronary collateral circulation between species, meaning that selection of an appropriate species is essential. The collateral flow can be determined after the occlusion of a major coronary artery. It is defined as the amount of flow received by an ischaemic area of myocardium, as a percentage of that received by a non ischaemic region. In guinea pigs the collateral flow is close to 100%, whereas in dogs, it is less than 20%, and in rats less than 10% (Hearse 2000). In humans, the extent of coronary collateral circulation is very variable, however it is positively correlated with the degree of coronary artery stenosis (Fujita and Tambara 2004). Therefore, patients presenting with cardiac arrest following quite a long period of ischaemic heart disease, are likely to have well developed collateral circulation. The most common method of induction of cardiac arrest in experimental models is the application of a 60 Hz alternating current to the ventricular tissue or the thorax. This is a poor model for the majority of cardiac arrests, which usually result from coronary thrombosis leading to infarct formation (Camm 2002). This fact may go some way to explaining the discrepancy between the results obtained *in vivo* and *in vitro*. More clinically relevant results may be obtained when ischaemic cardiac arrest is initiated by coronary ligation. Whilst this technique has been used in the study of ischemia and reperfusion injury, it does not seem to have been applied to the study of resuscitation. Of interest, one group has

recently developed a model of cardiac arrest following chronic myocardial ischaemia following experimental coronary constriction. However, even in this model, cardiac arrest was initiated by electric shock (Fang *et al.* 2006). Developments such as this, which bring the experimental setting closer to reality may improve the reliability of experimental results in predicting outcomes in the clinic.

Despite their limitations, *in vivo* models have manifold advantages over *in vitro* experiments. When *in vivo* models are used, pharmacological agents are subject to similar metabolic processes that exist in the clinic. These models also replicate the conditions of arrested blood-flow during cardiac arrest and the subsequent difficulties in achieving drug distribution. Agents can be introduced into the circulatory system at the time of resuscitation, thus replicating the clinical situation. *In vivo* models provide a platform for the study of the survival of experimental animals over a relatively long term.

5.2 *In vitro isolated organs and cell culture methods*

In vitro laboratory methods usually rely on simulating ischaemia in whole perfused isolated hearts, isolated atria, ventricular strips, papillary muscles or even cultured cardiomyocytes before reperfusing the tissues and measuring the recovery in terms of the contractile function of the myocardium or by measuring the levels of cardiac damage indirectly. Drugs or interventions can be introduced at various points during ischaemia and reperfusion, and their effects on ischaemic damage and reperfusion injury examined.

Such reductionist approaches can be extremely useful in separating out the mechanism of action of a drug with complex pharmacological effects, such as

adrenaline. However the limitations of such techniques must be borne in mind. Firstly models using isolated hearts or cardiac tissues do not include the peripheral vasculature where adrenaline and other vasopressors are supposes to exert their beneficial effects. Such models will only demonstrate the myocardial and coronary vascular effects of these interventions, which may not always be beneficial (see Figure 3). Secondly, the tissues inevitably become ischaemic whilst they are being removed from the animal and prior to set up. This ischaemia may be sufficient to activate ischaemic preconditioning, a cardioprotective phenomenon whereby short periods of ischaemia initiate pro-survival signalling within cells and protect against the damage caused by subsequent ischaemic episodes (Murry *et al.* 1986; Awan *et al.* 1999; Yellon and Downey 2003). Thirdly, isolated cardiac preparations are rarely viable for long enough to determine whether any myocardial dysfunction is due to permanent cell death or reversible stunning.

5.3 Cardioactive properties of agents used in experimental models

Care needs to be taken in the interpretation of many *in vivo* and *ex vivo* experiments in the field of ischaemia and reperfusion injury. In order to carry out surgical procedures in animals as part of *in vivo* studies anaesthetic must be given. Similarly, when setting up the isolated perfused heart model, it is common to kill the animal using an overdose of pentobarbital followed by exsanguination; heparin is also commonly given to prevent thrombus formation in the heart. However, both anaesthetics (Weber and Schlack 2005) and heparin (Kilgore *et al.* 1999) have been demonstrated to exert

cardioprotective effects during ischaemia thus reducing the potential window of opportunity upon which cardioprotective interventions can act.

5.4 Why are models a poor representation of the clinical situation?

No experimental model of resuscitation has so far provided realistic predictions of clinical performance of an intervention. As a general trend, treatments which seem promising in experimental settings often prove disappointing in the clinic. A number of factors may be individually or collectively responsible for these discrepancies.

It is reasonable to expect in-vivo models, especially in larger animals such as pigs and dogs to give a good indication of how an intervention will perform in the clinic. This has not been the case. For instance, in their ground-breaking work, Pearson and Redding proudly announced

"*with no drug, or with sodium bicarbonate (2mEq. per kg.) we could restore circulation in only 10-20% of cases. With adrenaline we could restore circulation in 95-100%". (Pearson and Redding 1964a)*

Sadly, the rate of survival to discharge from hospital in patients suffering cardiac arrest out of hospital is less than 3% (Gueugniaud *et al.* 1998) and may reach 16 % when cardiac arrest occurs in hospital (Cooper *et al.* 2006) but is, in any case, rather less than Pearson and Redding's confident predictions.

Another problem is that most investigators utilise young healthy animals in their research, rather than animals which accurately reflect the multiple pathologies which are present in elderly patients who present with cardiac arrest secondary to myocardial infarction. Differences in blood pressure and the extent of coronary collateral circulation between young and old animals may have a major effect on the experimental results obtained.

Endpoints in experimental models have included ROSC (Hilwig *et al.* 2000), 24 hr survival (Kern *et al.* 1988; Hilwig *et al.* 2000), coronary perfusion pressure (Kolarova *et al.* 2005) and ventricular ectopic activity (arrhythmias) (Kolarova *et al.* 2005). Clinical end points have included ROSC, survival to hospital admission (where treatment was given outside hospital), survival to hospital discharge, neurological outcomes and survival to various other temporal endpoints. The variety of end points chosen and the manifold number of different protocols employed make the comparison of results from different studies very difficult indeed.

It could be argued that when investigating CPR where chest compressions are given in addition to pharmacological agents, the use of small animals may not provide a very realistic model. Animals of approximately the same size as humans, such as pigs may give better predictions of clinical outcomes.

6 Clinical evidence

Numerous clinical trials of adrenaline have been carried out in the resuscitation setting. Trials have been designed to answer one or more of the following questions:

Is adrenaline more effective than placebo control in CPR? Does high dose adrenaline produce better results than the standard dose? Are subtype-specific adrenoceptor agonists superior to adrenaline? Is the response to adrenaline improved when specific antagonists are given concurrently? Do non-adrenergic vasopressors produce better results than adrenaline? The designs and outcomes of these questions will be discussed below. Additionally a number of studies have examined the role of adrenaline in paediatric resuscitation, although this subject is outside the scope of this review and will not be discussed.

Although a large number of studies have been carried out, interpretation of the results is difficult because of the variety of endpoints used in studies. These have ranged from the most basis studies which used the ROSC as the endpoint (taking no account of the fate of the patient thereafter) to complex studies which have monitored survival over a number of months and have included monitoring of patients neurological function. Most studies have been conducted on a small scale, presumably due to limited funding and facilities; these studies have had limited power to detect differences between treatment groups. Many studies have included inherent scientific weaknesses, such as not being blinded to the physician or not including a placebo control. Several studies that were blinded included a direction that adrenaline be administered to the patient if the trial drug failed. These aspects of trials have been included on the basis of sound ethical reasoning, however they make it difficult to draw definitive conclusions.

Numerous studies have examined the effects of high and standard doses of adrenaline. The current guidelines for the administration of adrenaline allow for the repeated

administration of the drug (Figure 1), and this too was the case for experimental agents. Where doses of drug are cited in the text below, they refer to the dose given in each individual bolus rather than the total dose administered, except where stated otherwise.

6.1 Comparison of standard-dose adrenaline and placebo

For ethical reasons, no blinded randomised trials of adrenaline in the resuscitation setting have included a placebo control group (American Heart Association 2005). Several investigators have compared the outcome of groups of patients treated with adrenaline, with those not treated with adrenaline. This comparison is, however, inherently biased, because patients treated with adrenaline are more likely to be complicated cases, who do not respond to initial defibrillation. This makes interpretation of the data very difficult.

A retrospective study was carried out in Sweden examining the role of adrenaline in treating out-of-hospital cardiac arrest over a twelve year period. The records of 1360 patients were examined. Adrenaline was given to 35% of patients and did not result in any change in the survival of patients to hospital discharge compared with untreated patients. However, as the authors conceded the trial was not randomised, and a major confounding factor was that the patients treated with adrenaline were generally those who presented with more complicated clinical conditions (Herlitz *et al.* 1995)

A later, larger (10966 patients) prospective evaluation of adrenaline in CPR was carried out by the same group of researchers. A more clinically useful endpoint, survival to 1 month after cardiac arrest, was employed. Using multivariate analysis,

the use of adrenaline was found to be independently correlated with poor survival, especially in patients presenting with non-shockable cardiac rhythms (Holmberg *et al.* 2002). This study was also limited by the lack of randomisation, and differences in baseline variables between patient groups.

An Australian group, also claim to have compared both high- and standard-dose adrenaline with placebo in cardiac arrest. They found no difference in survival to hospital discharge between the groups and the overall hospital discharge rate was 0.9%. This trial in 339 patients probably represents the best attempt at conducting a placebo-controlled clinical trial of adrenaline in CPR to date. However, the results must be taken with caution, as the trial was neither randomised nor blinded, and the results demonstrated a bias of physicians for treating certain patient groups with standard-dose adrenaline. (Woodhouse *et al.* 1995).

One study recruited 199 patients in ventricular fibrillation who had failed to respond to one defibrillation attempt. The patients were randomised to receive endotracheal adrenaline or lidocaine to compare the effectiveness of these two drugs in resuscitation. These patients were compared with a group of 630 historical controls, treated with only sodium bicarbonate. The results of this study are hard to determine, as the number of patients available for analysis was reduced by poor compliance with study protocol. Survival to hospital discharge was significantly smaller (16%) in patients treated with adrenaline, than in patients treated with sodium bicarbonate or no drug (38%) (Olson *et al.* 1989)

In conclusion, no trial has identified a benefit of adrenaline over placebo in CPR, although is should be borne in mind, that the quality of the investigations carried out to date is rather poor.

6.2 High-dose adrenaline

The standard dose of 1mg adrenaline was taken directly from Redding and Pearson's early studies in dogs. More recently, concern was raised that due to the difference in mass between the dogs used in the study and an adult human, the dose of adrenaline used in the study was too small. Additionally, it was shown that at doses above 1mg, a dose-dependent vasopressor relationship existed to adrenaline in human beings during CPR (Gonzalez *et al.* 1989). In other words, at 1mg the dose was submaximal. In dogs, it was shown that the peripheral vasoconstrictor effects of adrenaline were responsible for the beneficial effects (Michael *et al.* 1984). Thus numerous trials have been carried out to compare the effects of high-dose adrenaline (up to 10 mg) with standard protocol. Some of these trials are of a high standard, being both randomised and blinded.

In the 1990s Barton and Callaham published a series of papers investigating treatment of cardiac arrest with standard- and high-dose adrenaline. They initially carried out a small trial on 49 patients. Apart from its small size, the trial suffered considerable weaknesses, in that it was not blinded, not randomised and the data was gathered retrospectively. However a trend towards a higher rate of ROSC was seen in high-dose treated patients (Barton and Callaham 1991).

These investigators set out to determine whether high-dose adrenaline was associated with a higher incidence of complications than normal dose. 68 patients with non-traumatic cardiac arrest were recruited into the study. The study was not randomised and physicians treated as they saw fit. Patients were retrospectively allocated to the high dose or low dose group, depending on whether they had received greater or less than 2.8 μg kg^{-1} min^{-1}. Additionally those patients who had received a bolus of 50 μg kg^{-1}were included in the high dose group (Callaham *et al.* 1991). The study was therefore somewhat flawed as it was not comparing two distinct doses, rather it was looking at a sliding scale with an arbitrary dividing line. The only significant difference between the two trials in terms of complications was a greater depression of serum calcium in the high dose adrenaline group. No significant difference was seen in survival to hospital discharge, although 30 % of patients in the standard dose group survived, compared with 18 % of high-dose treated patients. Although no conclusions can be drawn in the absence of statistical significance, the trial was probably underpowered to detect a survival difference, and the results of the low-dose treated group seem more promising.

The same group of investigators went on to carry out a randomised clinical trial of high-dose adrenaline and standard dose adrenaline in pre-hospital cardiac arrest. The study enrolled 816 patients. Noradrenaline was also examined as a vasopressor in this trial, and the results are discussed elsewhere. In addition to ROSC, additional outcome measures were included. These were survival to hospital admission, survival to hospital discharge and their Cerebral Performance Category score (a measure of mental function and capacity) whilst in hospital. High dose adrenaline increased the probability of achieving ROSC. In the high dose group, circulation was restored in

13% of patients, compared with 8% for standard dose adrenaline. However no statistically significant increase to hospital discharge was noted, although this trial was probably underpowered to detect any such change (Callaham *et al.* 1992).

At around the same time another group carried out a randomised trial of standard and high-dose adrenaline, specifically in asystole and electromechanical dissociation. The trial included 68 adult patients and was blinded. Survival to hospital discharge was taken to be the endpoint. There was a trend towards a higher rate of discharge in the high-dose adrenaline group, although this did not reach statistical significance. Blood pressure was, however higher at 1 and 5 minutes post-resuscitation, the rate of initial restoration of circulation was better in high dose treated groups (57 % v. 15 %) and there was no difference in the incidence of adverse effects between groups (Lindner *et al.* 1991a).

Paradis' group have long been interested in resuscitation. In one early study they examined the effects of coronary perfusion pressure on the ROSC. The trial was relatively small, recruiting 100 patients. In addition to the main focus of the study, the investigators also analysed some data relating to patients in the study who had been treated with high-dose rather than standard dose adrenaline. No difference was seen in terms of achievement of ROSC and no patients in either group survived to hospital discharge. Results from the trial gave some indication that high coronary perfusion pressures were correlated with good rates of ROSC, confirming data seen elsewhere in animal models. It was tentatively suggested that a coronary perfusion pressure of 15 mmHg might be a cut-off point below which ROSC was unlikely or impossible (Paradis *et al.* 1990). The group therefore went on to carry out a small (32 patients)

clinical trial, designed to address specifically the question of how high- and low dose adrenaline affected coronary perfusion pressure during CPR. They discovered that high dose adrenaline was more effective than standard dose at raising the coronary perfusion pressure above their previously defined critical level and hence they tentatively concluded that high-dose adrenaline may be more effective at achieving ROSC than the standard dose.(Paradis *et al.* 1991)

The 'Multicenter High-Dose Epinephrine Study Group' performed a large trial comparing standard and high dose adrenaline in cardiac arrest outside the hospital. 1280 patients were randomised to receive either 0.02 mg/kg or 0.2 mg/kg intravenously. The study included patients presenting with any presenting rhythm and examined multiple endpoints including ROSC, survival to hospital admission, survival to hospital discharge and neurological outcome. No difference could be found between the two groups with respect to any of these outcomes. The authors attributed this failure to the delay in reaching the patient, and the extensive ischaemic damage already occurred (Brown *et al.* 1992).

At one hospital, the resuscitation protocols were radically altered. Initially no adrenaline was used in resuscitation, however guidelines then changed and suggested physicians use high dose (10 mg adrenaline). A retrospective analysis was then carried out; investigating the success of resuscitation before and after the protocol was changed. Immediate survival was 43% in patients who did not receive adrenaline, but only 22% in high-dose treated patients. This difference was statistically significant (Marwick *et al.* 1988). The weakness of the study was that, as a retrospective analysis, it could not be randomised, however, the study focused on patients presenting with

ventricular fibrillation after failure to respond to initial defibrillation, and was thus more focussed than other studies. Of 210 patients, 77 received high dose adrenaline and the rest received no drug. Multiple logistic regression showed adrenaline to be an independent predictor of poor outcome but no significant difference was seen in survival to hospital discharge, although as the authors pointed out, the number of patients to survive to discharge was too small.

One study attempted to determine whether high dose adrenaline could exert any beneficial effects after the failure of standard therapy (Sherman *et al.* 1997). Although small (140 patients), this study had the advantage of being blinded and randomised. No benefit of high-dose adrenaline was seen in terms of any of the outcome measures. It should be remembered, that the ischaemic damage to the heart, and other organs are likely to be very high after initial treatments have been tried and have failed. It would be surprising if any intervention could be of benefit at this stage.

The 'European Epinephrine Study Group' conducted a large (3327 patients) multi-centre randomised trial comparing the use of high dose (5mg) and standard dose (1 mg) adrenaline in cardiac arrest outside the hospital (Gueugniaud *et al.* 1998). The investigators found a small increase in the likelihood of restoring circulation when high dose adrenaline was used (40.4% v. 36.4 %). Analysis of subgroups revealed that high-dose adrenaline improved the chances of restoring circulation in patients with asystole, but not when ventricular fibrillation was the presenting rhythm. No difference was seen between the groups in terms of survival to hospital discharge or in terms of neurological outcome.

One group carried out a randomised, blinded trial comparing standard (1mg) and high (10mg) doses of adrenaline in asystole. The investigators did not find any difference in survival between the groups in terms of survival, although the study was extremely small, recruiting only 40 patients, and was thus vastly underpowered to detect any such changes (Lipman *et al.* 1993).

A retrospective study of 178 patients in ventricular fibrillation showed that high cumulative doses of adrenaline given during resuscitation were correlated with poor neurological outcome as assessed by the cerebral performance score (Behringer *et al.* 1998).

In conclusion, it seems that high dose adrenaline is more efficient at achieving a ROSC than the standard dose, but no trial has shown an increase in survival to hospital discharge, or any improvement in long-term neurological function in survivors. On this basis, the use of high dose adrenaline may be unwarranted; the benefit to the patient, of achieving ROSC but dieing soon after certainly seems negligible. One interpretation of this data is that the increased benefit from the additional vasopressor effect of high dose adrenaline, is counterbalanced by increased adverse effects

6.3 Other Adrenergic agents

Noradrenaline has been compared with adrenaline in one randomised clinical trial of out of hospital resuscitation. No significant difference was seen between standard dose adrenaline and noradrenaline (11mg). However there was a trend towards a

better initial achievement of ROSC but worse neurological recovery in patients treated with noradrenaline (Callaham *et al.* 1992).

One randomised study including 102 patients set out to compare adrenaline with the α_1-adrenoceptor selective agonist, methoxamine, in resuscitation from ventricular fibrillation (Olson *et al.* 1989). The study was carefully designed and equipressor doses of each drug were given. Methoxamine was less effective at achieving ROSC than was adrenaline. However this study was very interesting, since the dose of adrenaline given was 0.5 mg. This is half the clinically recommended dose. However, 19.6 % of patients in the adrenaline group were discharged alive from hospital, a reasonably high figure by the standards of resuscitation trials . This result should be followed up with a larger comparison of standard and low dose adrenaline and ideally a placebo group, to discover firstly, whether or not adrenaline is beneficial in resuscitation, and if this is the case, to enable the optimal dose of adrenaline to be discovered.

6.4 Non adrenergic vasopressors

After initial successes in animal models and the observation that vasopressin can increase coronary perfusion pressure during human cardiopulmonary resuscitation (Morris *et al.* 1997), several studies of resuscitation using vasopressin in humans have been carried out, despite the fact that this drug is known to be a coronary vasoconstrictor (Martinez *et al.* 2003).

In a small (8 patients) early study, it was shown that vasopressin may be more effective than adrenaline at achieving ROSC from cardiac arrest (Lindner *et al.*

1996b). This group went on to echo their findings in a larger (40 patient) study (Lindner *et al.* 1997) which recruited patients in ventricular fibrillation, and showed a benefit of vasopressin over adrenaline in initially restoring circulation.

Stiell carried out a randomised, triple blind, controlled trial, comparing adrenaline (1mg) or vasopressin (40U) in cardiac arrests which occurred in the hospital. 200 patients were recruited into the study, which found no difference between the patient groups in terms of 1 hour survival or survival to hospital discharge. The authors concluded that vasopressin should not be recommended for CPR (Stiell *et al.* 2001)

In the biggest comparison of vasopressin and adrenaline carried out so far, 1219 patients who had suffered cardiac arrest outside the hospital were randomised to receive either adrenaline (1mg) or vasopressin (40U). One of the endpoints uses was survival to hospital admission. Whilst no overall difference was seen between the groups, the large number of patients recruited into the study enabled analysis of subgroups to be carried out. It was found that when the presenting rhythm was asystole, patients treated with vasopressin were more likely to survive to hospital discharge than adrenaline treated patients. (Wenzel *et al.* 2004)

6.5 *Vasopressor combinations*

One study, including 298 patients, found that administering adrenaline together with vasopressin resulted in a greater rate of success then when adrenaline was used alone. The authors suggested that the synergistic vasopressor effects of the two drugs allowed smaller then usual doses of each to be given, thus reducing adverse effects. In

fact, in this trial the same total dose of adrenaline (3.8 mg) was given to both groups of patients (Guyette *et al.* 2004).

6.6 Conclusions from clinical trials

There are no studies that show adrenaline to be better than placebo in terms of survival. Higher than standard adrenaline doses do not lead to better results, and may in fact lead to worse outcomes. The results of some studies suggest that vasopressin may be more effective than adrenaline; one study even suggests that it may improve survival to hospital discharge in patients with asystole (Wenzel *et al.* 2004). However the results of the clinical trials must be taken with caution, many published data were analysed retrospectively, and hence were not randomised. Several trials recruited a wide variety of patients (different presenting rhythms, different duration of cardiac arrest etc.) and simply did not include a sufficient number of patients to detect the differences they were attempting to measure. A major conclusion from clinical trials is that more clinical trials are needed. If relatively small trials (<1000 patients) are carried out, they should be focused to answer a very specific question such as "is standard dose adrenaline superior to placebo in improving the survival to hospital discharge in patients with ventricular fibrillation of less than 10 minutes duration?". There therefore appears to be an urgent need for large multinational trials with the power to detect differences between the many different subtypes of patients.

7 Conclusions

There is a mounting body of evidence to suggest that adrenaline is less than ideal as a vasopressor agent when used in CPR. In answer to the question posed by the title of this review, the pharmacological basis for current clinical practice, the use of adrenaline as a vasopressor in resuscitation, is extremely limited. It certainly does not stand up to the rigour of 'evidence based medicine'. In the context of CPR, adrenaline raises blood pressure and increases coronary and cerebral perfusion by causing systemic vasoconstriction, an effect thought to be mediated by α_2-adrenoceptors. However, it also stimulates α_1, β_1 and β_2 adrenoceptors leading to potentially detrimental effects during ischaemia and upon the reperfusion of the myocardium and other tissues which occurs with the ROSC.

Adrenaline was introduced as an agent for CPR at a time when our knowledge of pharmacology was extremely limited. Indeed it preceded by over fifty years, Ahlquist's description of the α and β effects of adrenaline (Ahlquist 1948). With our modern understanding of receptor subtypes, it is probable that more selective adrenoceptor agonists, or indeed non adrenergic vasopressor agents could be used to much greater effect. However, in clinical trials, newer agents have not been proven conclusively to be any more effective than adrenaline and the recommendation of its use has remained largely unchanged since 1906.

Some clinical evidence seems to suggest that different presenting arrhythmias respond better to different treatments. For example, vasopressin seems to be more effective than adrenaline in treating asystole. (Wenzel *et al.* 2004). When more evidence

regarding such patterns emerges, it may be possible to recommend different vasopressor agents for different arrhythmic states rather than using the current 'one-size-fits-all' approach. Further to this, the time for which the heart has been ischaemic prior to resuscitation may have a bearing on the optimum treatment. Pearson & Redding suggested in the 1960s that there are two phases to cardiovascular resuscitation (before and after ROSC) (Pearson and Redding 1964b), however, the more sophisticated three-phase model of cardiac arrest recently proposed by Weisfeldt and Becker (2002), may prove more useful in directing therapies to achieve optimum results.

Care must be taken when interpreting the outcomes of clinical trials, particularly with respect to the endpoints used. Several studies have claimed benefit of a particular agent or protocol on the basis that it improved the likelihood of restoration of circulation, without an improvement in the rate of hospital discharge. It has been argued that this endpoint is valid, because many factors apart from the resuscitation protocol influence whether or not the patient is discharged alive (Callaham *et al.* 1992). However, one has to question whether initial resuscitation, followed soon after by death is of any benefit to the patient.

Vasopressor agents should be screened for compliance to the 'ideal' properties for vasopressor resuscitation agents listed above. Careful attention should be paid to the experimental models used in evaluating novel drugs, to enable useful medicines to be taken forward into the clinic. However, it should be borne in mind that the poor results of all agents used in clinical trials may indicate that arteriolar vasopressors are not a suitable treatment for cardiac arrest. A balance needs to be struck between

maintaining sufficient coronary flow to allow ROSC, and preventing ischaemic damage to tissues caused by vasopressors (and subsequent systemic effects at reperfusion). A further problem with vasopressors is that they prevent their own distribution in the circulatory system.

Given that the survival rate to hospital discharge after cardiac arrest may be less than 3% (Gueugniaud *et al.* 1998), there is great scope for improvement of current treatment protocols. One serious problem holding back progress in this field is a reluctance of physicians, for ethical reasons to participate in clinical trials, or to enter patients into trials when one arm of the trial constitutes a placebo, or a new drug not recommended in the guidelines (Woodhouse *et al.* 1995). This has led to many studies being underpowered. Taking into account the multitude of evidence that suggests that adrenaline is not beneficial during resuscitation, and the potential number of lives that could be saved by an improvement in resuscitation protocol, there is a strong argument that clinical trials in this field are ethical. This concern has been expressed by the 2005 International Consensus Conference on CPR *"Further research is needed in virtually all facets of CPR... Ethics committees must empower investigators to challenge the unproven dogma that we have tolerated for far too long"* (Nolan *et al.* 2005). However, results with vasopressin have proved equivocal, and no other vasopressor agents have shown much promise to date. The onus is therefore on those involved in laboratory research to direct their work urgently to finding a beneficial alternative to adrenaline and to produce sufficient data to convince clinicians to participate in clinical trials.

8 Acknowledgement

9 References

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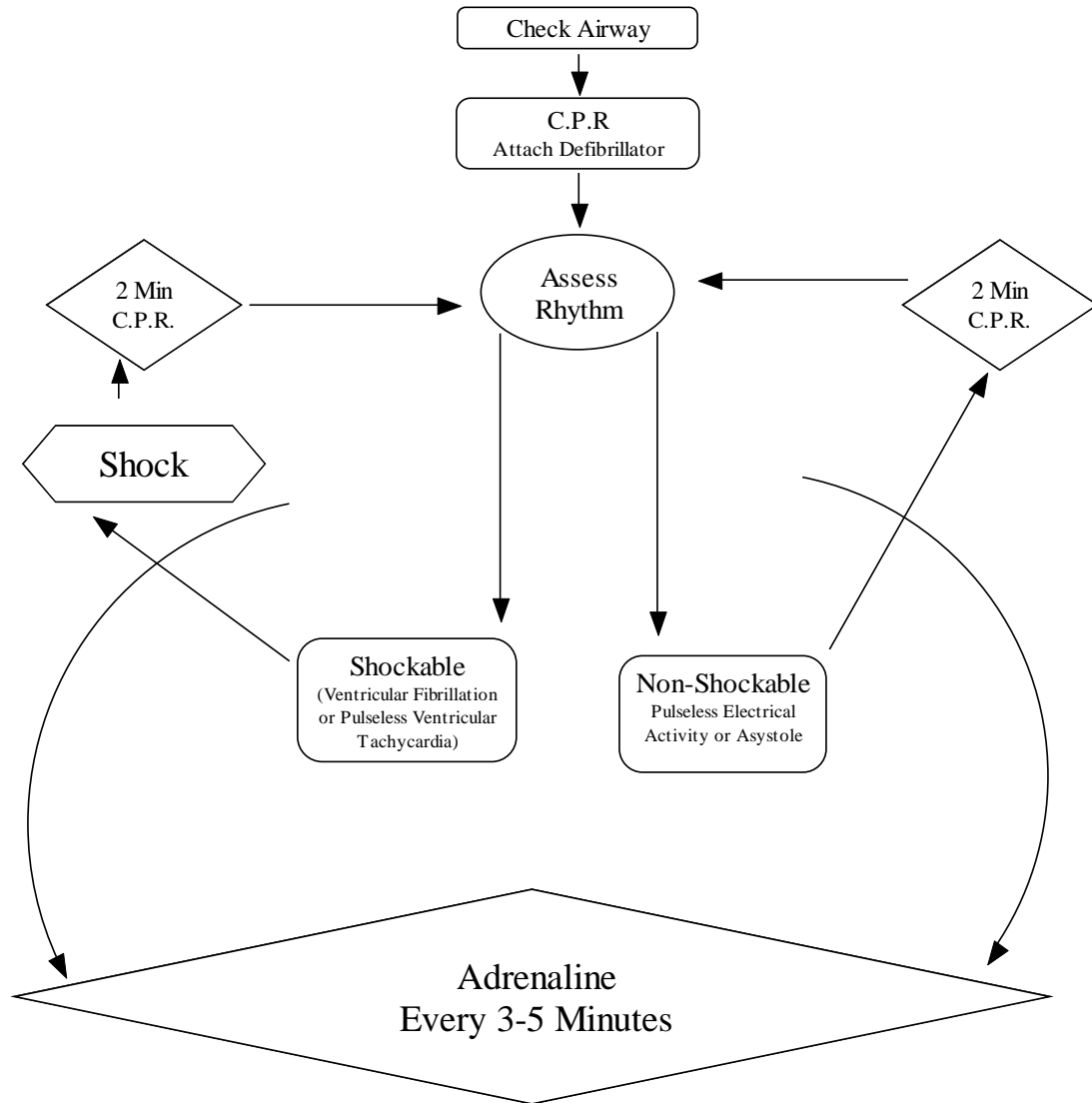
10 Figures and Tables

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                              │   Check Airway   │
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                              ┌──────────────────┐
                              │      C.P.R       │
                              │ Attach Defibrillator │
                              └──────────────────┘
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Figure 1: Algorithm for Advanced Life Support. Modified from International Liaison Committee on Resuscitation (2005)

Check Airway

C.P.R
Attach Defibrillator

2 Min
C.P.R.

Assess
Rhythm

2 Min
C.P.R.

Shock

Shockable
(Ventricular Fibrillation
or Pulseless Ventricular
Tachycardia)

Non-Shockable
Pulseless Electrical
Activity or Asystole

Adrenaline
Every 3-5 Minutes

Figure 1: Algorithm for Advanced Life Support. Modified from International Liaison Committee on Resuscitation (2005)
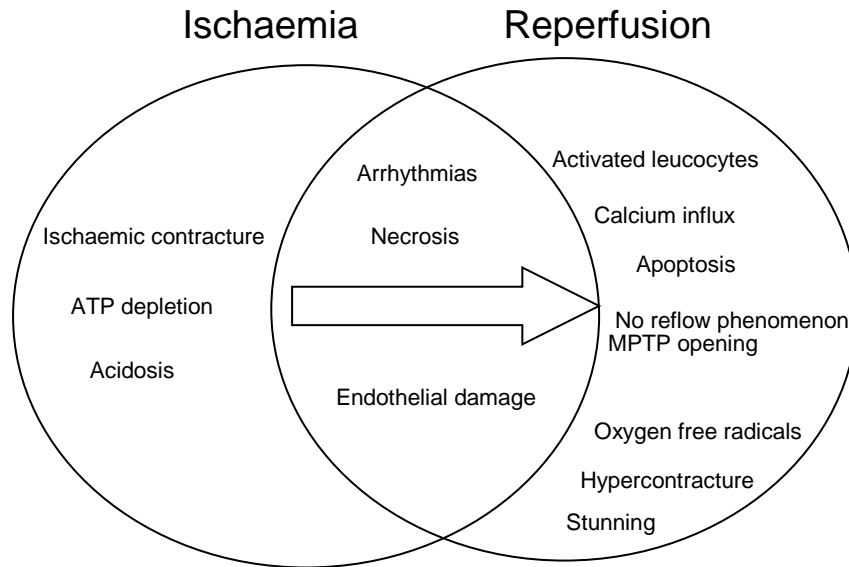
Figure 2. Pathophysiological factors involved in reperfusion injury. The overlap between the circles indicates the shared mechanisms between ischaemic damage and reperfusion injury. MPTP, mitochondrial permeability transition pore.
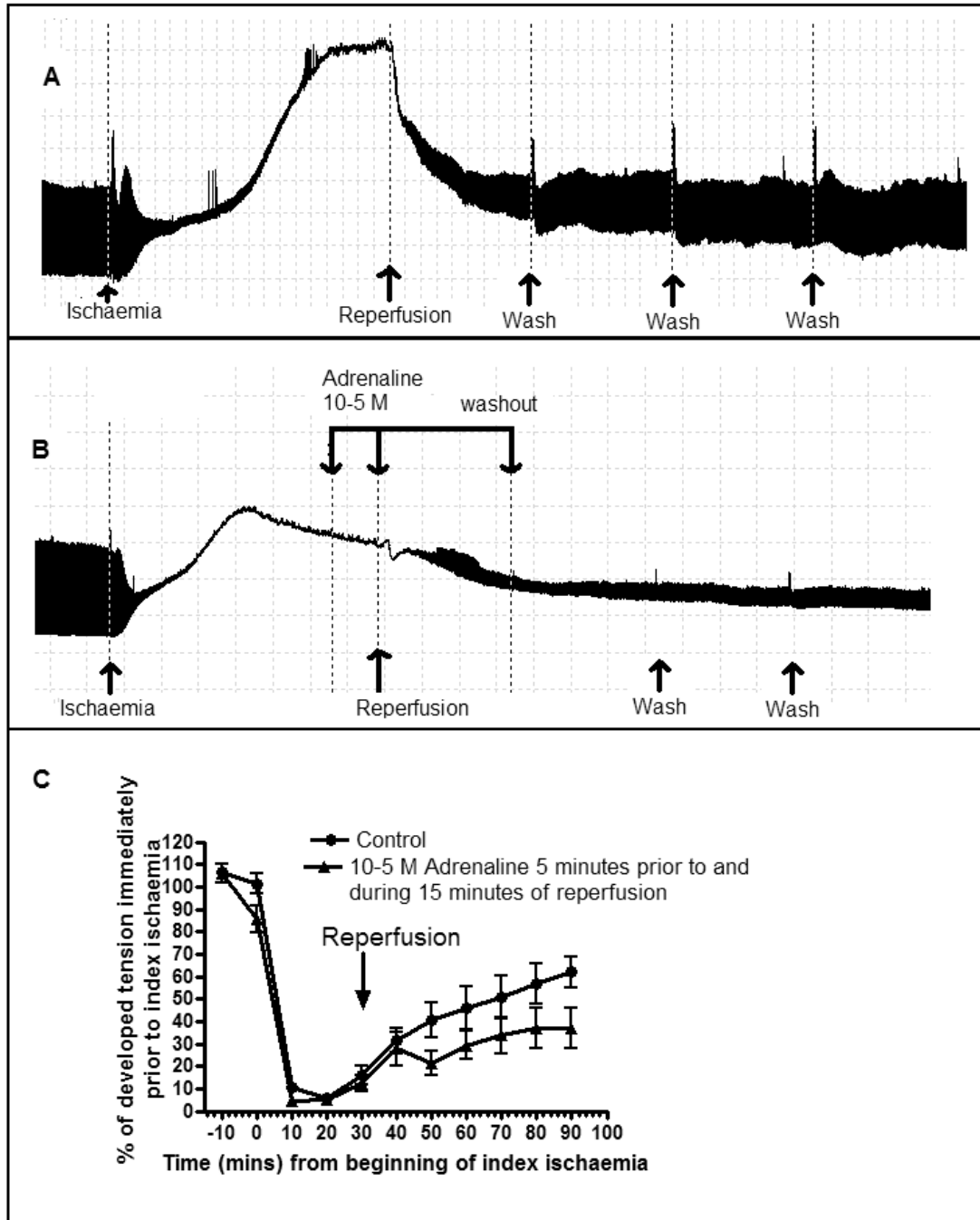
Figure 3: Ischaemia and reperfusion in the isolated right ventricle of the rat. A and B are representative traces from individual traces showing developed tension before, during and after simulated ischaemia (induced by removal of glucose from the bathing solution and gassing with 95% N_2 / 5% CO_2 instead of 95% O_2 / 5% CO_2). In A, the tissue was untreated (control) whereas B shows a tissue treated with adrenaline (10^{-5} M) for the final five minutes of ischaemia and the first 15 minutes of reperfusion as a mimic of resuscitation. C shows mean results ± S.E.M (n=6).

Table 1: Cardiovascular effects of adrenoceptor subtypes in humans. The responses stated refer to actions on postsynaptic smooth muscle receptors unless otherwise stated in brackets. Where one receptor subtype appears to dominate functionally in a particular vascular bed, this is also indicated. ☺ indicates potential beneficial effect during CPR ☹ indicates potential detrimental effect during CPR.

Receptor Subtype	Major Transduction Mechanism	Vascular Effects			Cardiac effects	
		Large arteries	Arterioles	Veins	Chronotropy	Inotropy
A_{1A}	$G_{q/11}$	Vasoconstriction - coronary arteries ☹	Vasoconstriction ☺	Vasoconstriction ☺	+ve ☹	+ve ☹
A_{1B}	$G_{q/11}$	Vasoconstriction ☺	Vasoconstriction ☺	Vasoconstriction ☺	+ve☹	+ve ☹
A_{1D}	$G_{q/11}$	Vasoconstriction ☺	Vasoconstriction ☺			
A_{2A}	$G_{i/o}$	Vasoconstriction ☺ Vasodilatation (endothelium) ☹	Vasodilatation (endothelium) ☹	Vasoconstriction ☺		-ve (pre-synaptic) ☺
A_{2B}	$G_{i/o}$	Vasoconstriction – coronary ? ☹	Vasoconstriction			
A_{2C}	$G_{i/o}$	Prevents NA release (presynaptic) ☺	Cold-induced vasoconstriction	Vasoconstriction ☺		-ve (pre-synaptic) ☺
B_1	G_s	Vasodilatation - coronary arteries ☺	Vasodilatation ☹		+ve ☹	+ve ☹
B_2	G_s	Vasodilatation ☹	Vasodilatation ☹		+ve ☹	+ve ☹
B_3	$G_{i/o}$	Vasodilatation ☹	Vasodilatation ☹			-ve ☹