The role of vasopressin in cardiorespiratory arrest and pulmonary hypertension

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Summary

Vasopressin is a peptide synthesized in the hypothalamus whose primary role is in fluid homeostasis. It has recently gained interest as a potential agent in the treatment of cardiorespiratory arrest. Initial human studies have shown benefits with vasopressin in patients with out-of-hospital ventricular fibrillation and asystolic cardiac arrest. Animal studies have shown vasopressin to be a vasodilator in the pulmonary vascular system of rats, under normoxic and hypoxic conditions, with conflicting results in canines. Human studies have shown conflicting results with increases, decreases and no changes seen in pulmonary artery pressures of patients with a variety of clinical conditions. Research needs to be done in patients with pulmonary hypertension regarding the potential role of vasopressin during cardiac arrest in this subgroup.

Introduction

Vasopressin is a potential agent in the treatment of cardiorespiratory arrest. Initial human studies have shown benefits with vasopressin in patients with out-of-hospital ventricular fibrillation and asystolic cardiac arrest.1,2 These trials did not, however, include patients with pulmonary hypertension, who have a five-year mortality rate of 50%.3 and vasopressin may also be useful in this subgroup. We review the prospects for improving outcomes in cardiopulmonary resuscitation using exogenous vasopressin or its analogues, both in general use and in selected subgroups.

Vasopressin

Vasopressin is a nona-peptide, and is most commonly known as anti-diuretic hormone (ADH). It is synthesized in the paraventricular and supra-optic nuclei of the hypothalamus as a pro-hormone, and is then transported (bound to neurohypophysin) along the supraoptic-hypophyseal tract to the posterior pituitary gland. Approximately 10–20% is released initially; the remainder is secreted following various stimuli. The primary role of vasopressin is fluid homeostasis, and the strongest release stimuli are increasing plasma osmolarity and severe hypovolaemia.
Hyperosmolarity is detected by central and peripheral osmoreceptors. The central osmoreceptors are located in the subfornical organ nuclei in the brain and detect systemic changes. Peripheral osmoreceptors are located in the hepatic portal veins, and are able to detect osmolarity of ingested food and fluid. Afferent nerve impulses travel via the vagus nerve to the hypothalamus, stimulating synthesis and release. Hypovolaemia is detected by arterial baroreceptors found in the left atrium, aortic arch and carotid sinus, and results in increased vasopressin secretion. Other factors influencing secretion include pain, nausea, hypoxia, pharyngeal stimulation, and chemical mediators such as acetylcholine, histamine, prostaglandins and angiotensin (reviewed in reference 4).

Vasopressin has several important physiological functions, mediated by different G-protein-coupled receptors. $V_1$ receptors (previously called $V_{1a}$) mediate vasoconstriction via Gq protein activation of phospholipase C. This results in activation of inositol triphosphate and intracellular calcium release. These receptors are situated on vascular smooth muscle, and are found in the gastrointestinal tract, uterus, liver, adrenal cortex, platelets and the pituitary gland. $V_2$ receptors are linked to Gs protein, and stimulation results in activation of adenylate cyclase and increasing levels of cyclic adenosine monophosphate (cAMP). $V_2$ receptors are found on the renal distal tubule and collecting duct, and activation alters the water permeability of the collecting duct, resulting in reduced diuresis. $V_3$ receptors (previously known as $V_{1b}$) are located in the pituitary gland, and stimulation results in release of intracellular calcium via phospholipase C, which in turn stimulates adrenocorticotropic hormone secretion from the anterior pituitary (reviewed in reference 4). Vasopressin also acts at oxytocin receptors, situated in the umbilical vein, aorta and pulmonary artery, with low concentrations of vasopressin resulting in vasodilation via nitric oxide release.

The physiological effects of vasopressin were first described in 1895, and it was first synthesized in 1954. Current indications for its administration include treatment of diabetes insipidus (desmopressin); bleeding disorders, for example haemophilia; bleeding oesophageal varices (terlipressin) and more recently, cardiopulmonary resuscitation (CPR). This review focuses on this last indication.

In North America and Europe there are >600,000 sudden deaths annually, and optimal resuscitation treatment is continually being refined. Endogenous vasopressin levels appear significantly higher in successfully resuscitated patients than in patients who die, this observation prompted further research as to whether exogenous vasopressin administration would produce higher success rates following CPR.

**Vasopressin in cardiac arrest**

Initial animal studies used a pig model of ventricular fibrillation (VF). Lindner et al. showed that vasopressin (0.8 U/kg) caused significantly higher coronary perfusion pressures and total cerebral blood flow, compared to epinephrine (200 μg/kg). Coronary perfusion pressure during CPR increased from 10 ± 2 to 70 ± 5 and 47 ± 6 mmHg at 90 s and 5 min, respectively, after vasopressin treatment, vs. 12 ± 2, 36 ± 5 and 18 ± 2 mmHg in the epinephrine group ($p < 0.01$). Total cerebral blood flow in the vasopressin group was 78 ± 5 ml/min/100 g at 90 s, and 30 ± 3 ml/min/100 g at 5 min, vs. 38 ± 2 ml/min/100 g and 30 ± 3 ml/min/100 g in the epinephrine group ($p < 0.05$ and $p < 0.01$, respectively).

Prengel et al. also showed increased cerebral blood flow and oxygenation with vasopressin (0.4 U/kg) compared to epinephrine (200 μg/kg) in resuscitated pigs (51 ml/min/100 g at 90 s and 53 ml/min/100 g at 5 min in the vasopressin group, vs. 25 ml/min/100 g and 18 ml/min/100 g in the epinephrine group, $p < 0.05$). This increased cerebral blood flow also lasted longer in the vasopressin group (4 min vs. 1.5 min). Further, Wenzel et al. found improved survival following CPR in animals receiving vasopressin compared with epinephrine. In this study, after 4 min of VF, CPR was initiated and either vasopressin (0.4 U/kg) or epinephrine (45 μg/kg) given after 3 and 8 min of CPR, followed by either 0.8 U/kg vasopressin or 200 μg/kg epinephrine after 18 min of CPR. At 22 min of CPR, defibrillation was attempted, and this was successfully achieved in all pigs receiving vasopressin and none in the epinephrine group ($p < 0.05$). Subsequent magnetic resonance imaging (MRI) at 96 h showed no cerebral pathology in the survivors. Limitations with animal studies include the fact that these experiments were done under anaesthesia, and that lysine, not arginine vasopressin is the endogenous peptide in pigs. The applicability of the results to humans was thus uncertain, but recently, human studies have been done.

The first reported use of vasopressin in human CPR was in 1996, published eight case reports of patients who had failed resuscitation following cardiac arrest, with the use of epinephrine and defibrillation as per American Heart Association guidelines. These patients
were subsequently given 40 U of vasopressin intravenously, followed by defibrillation. All patients had return of spontaneous circulation, with three surviving to discharge from hospital. Further work by this group examined 40 patients who suffered out-of-hospital VF, and randomized them to either vasopressin (40 U) or epinephrine (1 mg) as primary drug treatment following initial failure of defibrillation. Subsequent resuscitation then followed Advanced Cardiac Life Support (ACLS) guidelines. Significantly more patients treated with vasopressin survived to 24 h (12 vs. 4, \( p = 0.02 \)) and more left hospital alive (8 vs. 3, \( p = 0.16 \)), with no difference in neurological outcome as measured by the Glasgow Coma Scale (GCS) \( p = 0.78 \).

A larger study was reported in 2001 of 200 patients with in-hospital cardiac arrest. Initial rhythms included pulseless electrical activity (PEA) (48%), asystole (31%), VT (3%) and VF (18%). Patients were randomized to either vasopressin (40 U) or epinephrine (1 mg) as the primary drug treatment. If there was no response to the study medication epinephrine 1 mg was given and resuscitation subsequently followed ACLS guidelines. There was no statistical difference in the survival to 1 h or to hospital discharge \( p = 0.66 \) and \( p = 0.67 \), respectively. Reasons for this apparent lack of benefit of vasopressin may be due to the time interval between the onset of CPR and giving the drug (7.8–8.6 min in Lindner’s study vs. 1.1–1.3 min in Stiell’s study) and also the different rhythms seen in the latter study.

The largest trial of vasopressin vs. epinephrine to date was reported in 2004. This was a randomized, double-blind study of 1186 patients who had suffered an out-of-hospital cardiac arrest, with initial rhythms of PEA, VF or asystole. Patients then received either up to two 1 mg doses of epinephrine or two 40 U doses of vasopressin. If further vasopressor drugs were needed, 1 mg epinephrine was used. Patients who presented in VF underwent three attempts at defibrillation before the drug was given. In patients with VF or PEA, there was no statistical difference between the two study drugs in survival to admission \( p = 0.48 \) and \( p = 0.65 \), respectively. However in patients with asystole, vasopressin was associated with higher rates of hospital admission \( 29\% \) vs. \( 20\% \), \( p = 0.02 \) and hospital discharge \( 4.7\% \) vs. \( 1.5\% \), \( p = 0.04 \), although in this latter group the confidence interval includes unity. There was also a higher rate of survival in the 732 patients in whom the initial two injections of vasopressin was unsuccessful in restoring spontaneous circulation and therefore subsequently had epinephrine, compared to the ‘epinephrine alone’ group (hospital admission 25.7% vs. 16.4%, \( p = 0.002 \); hospital discharge rate 6.2% vs. 1.7%, \( p = 0.003 \)). The study showed no significant overall difference between the groups in regard to cerebral performance. Further, in the subgroup with asystole, although 50% of patients in the vasopressin group had a cerebral performance rated severe or worse at hospital discharge, there were no survivors to hospital discharge in the epinephrine group. Although further work regarding outcomes with the use of vasopressin is required and the studies to date have differed in the time to drug use, total amount of drug used and patient population, the results so far have prompted the inclusion of vasopressin in the international CPR guidelines, but only as a secondary alternative.

### Pulmonary hypertension

One subgroup not included in the above studies is that of patients with pulmonary hypertension. Pulmonary hypertension is a rare disease of the pulmonary vasculature, defined as a mean pulmonary artery pressure >25 mmHg at rest or 30 mmHg with exercise. It has recently been reclassified by the WHO into five classes: (i) pulmonary arterial hypertension (PAH), of which idiopathic PAH (IPAH) is a subgroup (previously called primary pulmonary hypertension); (ii) pulmonary hypertension with left-sided heart disease; (iii) pulmonary hypertension with lung disease and/or hypoxaemia; (iv) pulmonary hypertension due to thrombotic and/or embolic disease (CTPH); and (v) miscellaneous.

IPAH characteristically presents with features of breathlessness, chest pain and syncope, with the mean age at diagnosis being 36 years, and is more common in women than in men (2:1). Treatment of PAH involves supportive therapies including warfarin, diuretics, digoxin and oxygen, while modern treatments are directed at the pulmonary vasculature, causing vasodilatation and reducing pulmonary vascular resistance. The current five-year mortality rate is approximately 50%, with the most common cause of death being right heart failure. However, sudden death may occur, and the frequency and outcome of CPR in this population was evaluated by retrospective analysis between 1997–2000. During this period, 3130 patients were treated in 17 referral centres in Europe and the USA, and 513 patients had circulatory arrest. CPR was only attempted in 132 (26%), and despite 96% of the attempts taking place in hospital only, 6% (8 patients) survived to 90 days, with all but one having an identifiable correctable cause for the arrest, e.g. digoxin toxicity, pericardial tamponade.
or vasovagal reaction. Vasopressin was not used during the CPR of these eight patients. One reason for the poor outcome from CPR, that was postulated by the authors was the high mean pulmonary vascular resistance, which was more than eight times the normal range, making chest compression highly unlikely to achieve adequate pulmonary blood flow and left ventricular filling. This fact combined with the use of epinephrine, which causes pulmonary vasoconstriction, gives a low probability of success of CPR in this group of patients.

**Vasopressin in the pulmonary circulation**

The effect of vasopressin in the pulmonary circulation has been studied in different animal species, under both normoxic and hypoxic conditions. In rats, isolated, perfused lungs were obtained and pre-constricted with the synthetic thromboxane analogue U46619. Following a bolus of arginine vasopressin (AVP), 66% of the vasoconstriction was reversed. In subsequent experiments the lungs were pre-treated with the nitric oxide synthesis inhibitor L-NNA, and the vasodilatory response was significantly diminished. The authors concluded that AVP vasodilates pre-constricted lungs, through a mechanism involving nitric oxide (NO) release. Subsequent work aimed at elucidating the mechanism of action of AVP vasodilatation used pre-treatment with K⁺ channel blockers. Again, AVP caused approximately 60% reversal of the vasoconstriction achieved with U46619, but there was no effect with the pre-treatment of K⁺ channel blockers, and therefore these channels are unlikely to be involved in AVP vasodilatation.

In conscious rats under normoxic conditions, constant infusion, as well as boluses, of AVP produced in a fall in both pulmonary artery pressure (PAP) and cardiac output, resulting in a constant calculated pulmonary vascular resistance. Acute hypoxia caused vasoconstriction and raised PAP, with a significantly greater response to bolus doses of AVP. In a second set of experiments using isolated, perfused rat lungs, acute hypoxia caused vasoconstriction, and the subsequent addition of AVP caused immediate vasodilatation whereas under normoxic conditions, AVP had no effect. Pretreatment with a specific V₁-receptor antagonist blocked the effects of AVP and the authors hypothesized that during hypoxic pulmonary vasoconstriction, AVP acts via V₁-receptors causing vasodilatation.

The effect of chronic hypoxia has also been studied in rats. After 4 weeks of hypoxia, pulmonary hypertension develops and this model seems the most applicable yet found to humans with the condition. Bolus injections and infusions of AVP caused reductions in mean PAP and increases in mean systemic arterial pressure in live rats, which was abolished by treatment with a V₁-receptor antagonist. Further experiments showed minimal vasodilatation to AVP in isolated, perfused chronic hypoxic lungs and also in pulmonary arterial rings pre-constricted with norepinephrine. These results suggested that AVP did not have a direct action on the pulmonary vasculature. In further work, the atrial natriuretic peptide (ANP) level was measured in conscious chronically hypoxic rats when given a bolus of AVP. Results showed a 7-fold increase in ANP in chronic hypoxic rats and a 5-fold increase in controls. This ANP release was abolished by pre-treatment with a V₁-receptor antagonist. It was concluded that the effects of AVP on the mean PAP in chronically hypoxic rats is due to V₁-receptor-mediated release of ANP.

Work done in dogs has centred on the acute effects of AVP in normoxic conditions. In conscious animals, AVP has no effect on pulmonary vascular resistance but increases pulmonary vascular pressure in one model simulating acute pulmonary hypertension (the use of a U46619 infusion in anaesthetized dogs, which increased mean PAP and total pulmonary resistance), the subsequent infusion of AVP further increased total pulmonary vascular resistance, and this was associated with a both negative inotropic effect on the right ventricle and increased right ventricular afterload. Canine pulmonary arteries segments mounted in an organ bath vasodilate to AVP, when preconstricted with phenylephrine. This effect was seen at lower concentrations of AVP in endothelium intact vessels, and interestingly, high concentrations of AVP caused an initial relaxation followed by vasoconstriction in endothelium-intact vessels, but only vasoconstriction was seen in endothelium-denuded vessels. The endothelium-dependent vasodilatation to AVP was inhibited by the nitric oxide synthase inhibitors L-NMMA and NO-Arg, and also a V₁-receptor antagonist. The authors hypothesized that endothelium-derived nitric oxide results in vasodilatation. This result was also reported by another group, who showed endothelium-dependent vasodilatation of canine pulmonary arteries, which was abolished by NG-nitro-L-arginine (L-NA).
**Human studies**

*In vivo* human studies have not consistently shown an effect of AVP on the pulmonary vasculature (Table 1). The first study was carried out in 1955 and examined the changes in pulmonary and systemic pressures in six normotensive and two hypertensive patients, by right heart catheterization. Intramuscular injection of a synthetic form of vasopressin (pitressin) caused an elevation in systemic pressure with no effect on pulmonary pressures. Ribot *et al.* studied the effect of vasopressin in patients with pulmonary tuberculosis (TB). The first group (*n* = 7) had advanced, diffuse pulmonary TB, while the second group (*n* = 5) had localized disease, involving fewer than two lung segments. Pulmonary pressures were measured by right heart catheterization prior to and following the intravenous infusion of pitressin. Results showed a significant rise in pulmonary artery pressure in the first group of patients. This was explained by pitressin causing vasoconstriction and causing a greater rise in mean PAP in vascular beds reduced by disease.

Further research on the effects of vasopressin in patients with cirrhosis of the liver and portal hypertension involved the measurement of systemic, pulmonary and splanchnic pressures. Segel *et al.* studied eight patients, and found that intravenous vasopressin reduced cardiac output, and increased pulmonary wedge and pulmonary arterial pressures, during the infusion. The authors suggested that this was due to a rise in left atrial pressure, and felt there was no direct effect on pulmonary pressure. Mols *et al.* studied 12 patients with liver cirrhosis, with similar results: cardiac output decreased and pulmonary artery pressures increased as a consequence of increased left heart filling pressures, and there was also no change in pulmonary vascular resistance. The most recent study in this subgroup of patients used the synthetic analogue terlipressin in 12 patients with liver cirrhosis. Echocardiography was used to assess PAP before and after 2 mg intravenous terlipressin. Results showed a significant decrease in PAP from 25.5 ± 3.6 to 22.5 ± 2.5 mmHg (p = 0.003). The limitations of these data mainly concern the patient groups used, including TB and liver cirrhosis, and the small numbers.

**Conclusions**

When vasopressin is used after VF arrest in animals, it causes increased coronary and cerebral blood flow, resulting in improved survival. In human studies, vasopressin improves outcome

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<th>Table 1</th>
<th>Summary of studies investigating the use of vasopressin in the human pulmonary vasculature</th>
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<tr>
<td>Patient group</td>
<td>Vasopressin administration</td>
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<tr>
<td>6 normotensive and 2 hypertensive patients</td>
<td>20–30 U Intra-muscular</td>
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<tr>
<td>7 patients with diffuse advanced pulmonary tuberculosis (TB), 5 patients with localized pulmonary TB</td>
<td>12–20 U Intravenous (IV)</td>
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<tr>
<td>8 patients with cirrhosis of the liver and portal hypertension</td>
<td>20 U IV</td>
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<tr>
<td>12 patients with liver cirrhosis</td>
<td>8 U IV</td>
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<tr>
<td>12 patients with liver cirrhosis</td>
<td>2 mg IV terlipressin</td>
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in out-of-hospital VF and asystolic arrest, such that the international CPR guidelines now include vasopressin as a second-line agent. The role of vasopressin in patients with pulmonary hypertension cannot be reliably assessed, and to date there have been no human vessel studies of the interaction between hypoxia and vasopressin response. As evidence on the use of vasopressin in CPR accumulates, it is important to study subgroups of the population, for example patients with pulmonary hypertension. The poor outlook in this group may potentially benefit from the use of vasopressin in CPR.

References


