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## Confirming the Potential use of Vasopressin in Prehospital Cardiac Arrest

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## STUDENT CONTRIBUTION

### Confirming the Potential use of Vasopressin in Prehospital Cardiac Arrest

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This paper uses the term [primary health care practitioner] inline with current academic norm. The primary health care practitioner represents the following: *Ambulance Paramedic, Intensive Care Paramedic, Paramedic, Mobile Intensive Care Ambulance Officer, Advance Life Support Officer, Ambulance Officer and or anyone who practices prehospital emergency care.*

#### Introduction

Adrenaline is used as the initial drug in the pharmacological management of cardiac arrest in the prehospital setting by the Australian primary health care practitioner. Its use is supported by the Australian Resuscitation Council [ARC].<sup>1</sup> Despite modern resuscitative skills employed by practitioners the likelihood of surviving an out-of-hospital cardiac arrest remains poor. <sup>2</sup> It has been implied that out-of-hospital cardiac arrest survival within Australia could be as low as 3%,<sup>3</sup> this paper explores the possible use of vasopressin in cardiac arrest.

#### Cardiac Arrest - Definition

Cardiac Arrest [CA] is “a sudden cessation of cardiac output and effective circulation”.<sup>4</sup>

Cardiac Arrest is classified into two areas primary and secondary.<sup>5</sup> Primary CA can be caused by myocardial infarction, drug overdose, and electrocution. These can precipitate cardiac arrhythmias, the aberrant arrhythmia usually being Ventricular Fibrillation [VF], although other arrhythmias can occur for example Ventricular Tachycardia [VT], and Asystole the cardiac standstill rhythm.<sup>4, 5</sup>

Secondary Cardiac Arrest causes can be respiratory arrest, airway obstruction and severe haemorrhaging. Note there are many other causes of cardiac arrest and these are not just limited to the above mentioned. For example other causes may include trauma, hypothermia and electrolyte imbalances.<sup>6</sup>

#### Diagnosis

Diagnosis of CA is made by three determining factors:

1. Unconsciousness;

2. Absent respirations;
3. Non-identifiable carotid pulse.<sup>7</sup>

## **Prehospital Intervention**

Cerebral perfusion in the human body is dependant on adequate blood pressure and blood oxygenation. Because cardiac output is compromised in Cardiac Arrest it reduces the perfusion pressure causing cerebral hypoxia, and ultimately encephalopathy, this transpires in around four minutes.<sup>3, 6, 8</sup> To stabilise and maintain physiological parameters primary health care practitioners in essence follow the principles of Basic Life Support and Advance Life Support guidelines that have been formulated by the Australian Resuscitation Council. [Click here to see BLS Guideline](#)<sup>9</sup> [Click here to see ALS Guideline](#)<sup>10</sup>

Factors which influence cardiac arrest survival are age, pre-existing and current abnormal pathophysiology, patient's down time prior to Ambulance Service arrival, prehospital intervention, current cardiac rhythm and origin.<sup>11</sup>

## **Literature Review**

It is important to identify clinically advantageous prehospital pharmacotherapy interventions that can be used in resuscitation. It has been suggested by Wenzel & Lindner that vasopressin could improve CA patient outcomes this paper will further investigate research and literature to this effect.<sup>12</sup>

## **The Physiology and Pharmacology of Vasopressin**

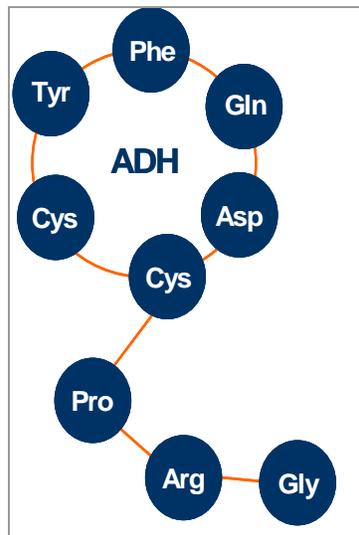
Vasopressin or antidiuretic hormone [ADH] is nine-amino-acid nonapeptide. Vasopressin is synthesised by the hypothalamus and is stored in secretory granules. From here they are then transported along the axon to the nerve ending and released by the posterior pituitary gland in response to stimuli.<sup>13, 14</sup> Figure.1 provides an overview of the ADH chain.

The stimulation of osmoreceptors in the supraoptic region of the hypothalamus releases vasopressin in response to raised plasma osmotic pressures for example a decrease in circulating blood volume or diuresis.<sup>13</sup> Vasopressin can be classified into two stimulant groups V<sub>1</sub> or V<sub>2</sub>.<sup>15</sup>

V<sub>2</sub> receptors are found in the basolateral membrane of the distal tubule. When Vasopressin is induced it begins to stimulate adenylyl cyclase activity. This causes an increase in cyclic adenosine monophosphate [cAMP]. From here an increase in water permeability at the distal convoluted tubule and collecting duct occurs. Thus an increase in urine osmolality, this produces a decrease in urinary flow rate, and increases the absorption of urea in the collecting duct.<sup>15, 16</sup>

When vasopressin V<sub>1</sub> is stimulated the effects on V<sub>1</sub> receptor causes calcium to release itself from sarcoplasmic reticulum located in smooth muscle cells ultimately this causes vasoconstriction in small arterioles which in turn decreases blood flow. The theory is that in a hemodynamically stable person this has little effect, however when hemodynamics are threatened vasopressin causes profound vasoconstriction of skin, skeletal muscle and intestine.<sup>16</sup> As a result there is less vasoconstriction at the coronary, renal and cerebral vasculature,<sup>16</sup> thus assisting in the maintenance of Cerebral Perfusion Pressure and oxygenation.

Figure.1 Antidiuretic Hormone Amino Acid Peptide Chain (Adapted from 17)



## Clinical Research

Kudenchuk & Racht [1999] state that pharmacological life support measures need to be proven, or new treatments devised for ALS treatment.<sup>18</sup> This is also supported by Lord. Lord advises “despite the significant emphasis placed on the use of medications in cardiac arrest, the Australian Resuscitation Council, reminds us that ‘no medication has been shown to improve long term survival in humans after cardiac arrest’”.<sup>19</sup>

## Search for Evidence

In a search for evidence Hogg investigated Medline [1966 to 2004]. The search discovered a total of 47 papers however only 3 papers compared the effects of adrenaline and vasopressin.<sup>20</sup> These were Lindner et al. [1997] Germany, Stiell et al. [2001] Canada, and Wenzel et al. [2004] European Resuscitation Council.<sup>20</sup> [Click here to see Review](#)

## Significant Literature

### Wenzel et al. [2004]

The recent study by Wenzel et al. in ‘Austria, Germany and Switzerland’ compared vasopressin ‘Pitressin’ with adrenaline ‘Supraenin’ [Wenzel V: personal communication] in out-of-hospital cardiopulmonary resuscitation.<sup>21</sup> According to Wenzel et al. current international guidelines advocate the use of adrenaline in cardiac resuscitation, and as a secondary measure vasopressin should be considered by the practitioner in a last ditch effort. <sup>21</sup>

The study was designed “as a double-blind, prospective, multicenter, randomised, controlled clinical trial; the primary end point was survival to hospital admission, and the secondary end point was survival to hospital discharge”.<sup>21</sup> It is thus far the largest clinical study in the

prehospital setting to demonstrate the potential benefits from the use of vasopressin in cardiac arrest.<sup>22</sup>

Admission methods into the study required the patient to be in cardiac arrest in the out-of-hospital environment, and present with VF, Pulseless Electrical Activity [PEA] or Asystole. At total of 1219 patients underwent randomisation.<sup>21</sup>

Researchers found that vasopressin had similar effects as that of adrenaline when it comes to managing VF and PEA.<sup>21</sup> The study found no significant difference in the rate of hospital admission with the use of vasopressin and adrenaline among patients who had VF [vasopressin 46.2%] versus [adrenaline 43.0%]  $p=0.48$ ; or PEA [vasopressin 33.7%] versus [adrenaline 30.5%]  $p=0.65$ .<sup>21</sup>

Most importantly vasopressin was superior to adrenaline in asystole, and confirmed a higher hospital admission rate [vasopressin 29.0%] versus [adrenaline 20.3%]  $p=0.02$ , the hospital discharge rate was also interesting with [vasopressin 4.7%] versus [adrenaline 1.5%]  $p=0.04$ .<sup>21</sup>

Furthermore is the fact that fewer patients underwent randomisation than initially projected by the researchers. The authors recognise this factor and state “the primary end point of survival to hospital admission was not optimal but realistic in a trial of this type”.<sup>21</sup>

Patients who had been given vasopressin were 40% better off in arriving to definitive care alive. The effectiveness of vasopressin with adrenaline occurred 25 minutes after initial cardiac arrest occurred. However increasing the dosage of adrenaline was not effective.<sup>22</sup> The authors conclude and note that vasopressin should supersede adrenaline in refractory cardiac arrest.<sup>21</sup>

#### Stadlbauer et al. [2003]

The Wenzel et al. study also makes aware that there was no significant difference in cerebral performance.<sup>21</sup> This result is contradicted in a study by Stadlbauer et al. who studied the effects of the combination of vasopressin and adrenaline in view of neurological recovery, and compared such effects with adrenaline and saline placebo alone in 17 porcine models of prolonged resuscitation.<sup>23</sup>

In this study 4 minutes of cardiac arrest ensued. Cardiopulmonary Resuscitation then occurred for 3 minutes. During the study the animals where given a combination of vasopressin and adrenaline, adrenaline or saline placebo. At the time interval of 22 minutes which included a total of 18 minutes of CPR defibrillation therapy was undertaken to achieve ROSC.<sup>23</sup> Spontaneous circulation occurred in the vasopressin and adrenaline group. However, adrenaline and the placebo porcine models died. The conclusions of this study found that the combination of vasopressin and adrenaline ensured long-term survivability with full neurological recovery.<sup>23</sup>

As pointed out by Turner animal studies have potential limitations due to the fact that porcine models have different vasopressin receptors that could cause a variation in human hemodynamics when arginine vasopressin is administered.<sup>11</sup> Also noted is the fact that the experimental animals are healthier compared to patients that present in the prehospital field with differing pathophysiological conditions.<sup>11</sup>

#### Steill et al. [2001]

In the Canadian study undertaken by Steill et al. compared the effects of vasopressin with adrenaline in patients that presented with myocardial ischemia. This study was a randomised controlled trial.<sup>24</sup> The study was conducted in the Emergency Department and Critical Care Unit

of three teaching Hospitals. The primary outcomes of the study were survival to hospital discharge and to one hour and neurological function.

During the study adults who suffered from cardiac arrest and required adrenaline where at random given 1mg of adrenaline or 40 units of vasopressin.<sup>24</sup> The researchers conclude that the trial did not show any benefit from vasopressin for any in-hospital cardiac arrest patients. This included patients with myocardial infarction and ischemia.<sup>24</sup>

#### Lindner et al. [1997]

Lindner et al. study randomly compared vasopressin with adrenaline in out-of-hospital VF. Patients were randomly either assigned vasopressin 40U IV or adrenaline 1mg IV. The study's endpoint consisted of successful resuscitation, this included admission to hospital, survival for 24 hours, survival to hospital discharge and neurological outcome assessed by the Glasgow Coma Scale. [Click here to view Glasgow Coma Scale](#) <sup>26</sup>

Forty patients were assessed in the out-of-hospital setting who were in VF and resistant to direct counter current shocks over an 18 month period.<sup>25</sup> The study found administered [adrenaline 35%] versus [vasopressin 70%]  $p=0.06$  in the group survived to hospital admission. At the period of 24 hours after admission [adrenaline 20%] versus [vasopressin 60%]  $p=0.02$  in the group were still alive. When it came to hospital discharge three [adrenaline 15%] versus [vasopressin 40%] survived. In respect to the neurological outcome the mean GCS at the point of hospital discharge was [adrenaline 10.7] versus [vasopressin 11.7]. <sup>25</sup>

#### Turner [2003] and Shock Refractory VF

Turner discusses three published clinical studies that have supported the use of vasopressin as a treatment option in prolonged or shock-refractory VF.<sup>11</sup> One significant study within the paper overviewed Chugh, Lurie, Lindner.<sup>27</sup> They observed that vasopressin secured a 24 hour survival rate [vasopressin 60%] versus [adrenaline 20%]  $p=0.02$ . <sup>27</sup> Survival to discharge [vasopressin 40%] versus [adrenaline 15%]  $p=0.16$ . When it came to ROSC to definitive care admission [vasopressin 70%] versus [adrenaline 35%]  $p=0.06$ .<sup>26</sup> Wenzel et al. concluded that vasopressin used in VF did not demonstrate to be more effective. <sup>21</sup>

#### **Other**

Vasopressin has also shown to be effective in special resuscitation circumstances, including hypothermia, anaesthesia-associated arrest, hypovolemia, and vasodilatory shock.<sup>28</sup>

#### **Benefits and Limitations of Vasopressin in Cardiac Arrest**

Vasopressin compared with adrenaline does not display any beta  $\beta$  adrenergic activity this means it does not produce skeletal muscle vasodilation and increased myocardial oxygen consumption.<sup>16, 2</sup> Vasopressin has a longer half-life, and is effective in maintaining coronary perfusion pressures above a threshold that correlates with ROSC and may increase cardiac contractility.<sup>28</sup> A reduction in cardiac index does occur in the post resuscitation period although this is transient and reversible.<sup>16</sup>

Vasopressin is a stimulator for Adrenocorticotropin Hormone [ACTH], and increases plasma cortisol levels, this may improve the likelihood of ROSC due to the fact that the hormones may enhance myocardial action and hinder circulatory collapse.<sup>11,29</sup> In an experiment undertaken by

Kornberger et al. it was found that animal ACTH and cortisol levels remained unchanged when given adrenaline, however the group that received vasopressin increased after administration.<sup>29</sup> The “clinical significance of the ACTH and cortisol concentrations remains unclear. The levels of these hormones have been low in failed resuscitation attempts”.<sup>11</sup>

Turner states cost as a potential downfall to the use of vasopressin. Vasopressin costs around \$70.00 [AUS] retail for 1 ampoule that is 20 units compared to 1 ampoule of adrenaline that costs 85 cents [AUS].<sup>11</sup> Therefore vasopressin could be seen by some professionals as expensive considering the cost of adrenaline.

There are significant study weaknesses which have been identified by Hogg, <sup>20</sup> as identified in Table.1.

Table.1 Vasopressin or adrenaline in cardiac resuscitation: Study weaknesses

<b>Lindner et al. [1997]</b>	<b>Stiell et al. [2001]</b>	<b>Wenzel et al. [2004]</b>
“Only looked at VF. Small patient sample. All out-of-hospital arrests with mean emergency team response times of 6 minutes”. <sup>20</sup>	“Powered only to show a 20% difference in 1 hour survival”. <sup>20</sup>	“4748 out of 5967 patients with out-of-hospital cardiac arrest were not randomised”. <sup>20</sup>  “The study was powered to show a 25% improvement in outcome. Evidence of a smaller benefit would require a much larger study”. <sup>20</sup>

A limitation in the use of vasopressin can be attributed to the lack of prehospital clinical trials with optimal and valid end-points. However, adrenaline has been used in the international setting of cardiopulmonary resuscitation for decades.<sup>30</sup> Additionally there may be some resistance by (medical, primary care practitioners, professional organisations) to change learned and practiced methods in the administration of adrenaline, especially when it involves clinical and theoretical re-education in the applications of vasopressin.

Selective information processing may also play a significant role in the practitioner’s resistance to change. Practitioners could be at fault of selectively processing information in defence of keeping their personal perceptions ‘of adrenaline’ intact. Ideologically, they may ignore information which challenges the norm of practice, especially when there is a significant shift in the way CA patients are treated.<sup>31</sup>

It is noted that vasopressin should be given cautiously to patients who suffer seizures, migraine asthma, renal disease and heart failure. Caution should be taken in pregnancy as high doses of vasopressin can have oxytocic effects and should clearly be used when needed.<sup>16</sup> Otherwise the substance is contraindicated in chronic nephritis, and should not be used.<sup>16</sup> At this current time there is inadequate data in particular in the administration of vasopressin to paediatric patients therefore the substance it is not recommended in refractory asystolic paediatric arrest until the efficacy and safety can be evaluated.<sup>28</sup>

## **Limitations of Adrenaline**

Adrenaline remains to be a Class IIb. drug according to the AHA, that is “A therapeutic option that is not well established by evidence, but may be helpful and probably not harmful”.<sup>32</sup> Adrenaline has been advocated in all cardiac arrests due to its vasopressor actions that assist in the maintenance of Cerebral Perfusion Pressure during the resuscitation period.<sup>2</sup>

A toxic adrenergic state can occur with the use of adrenaline pre and post-resuscitation. This includes arrhythmias, increase myocardial oxygen demand, ventilation perfusion mismatches, myocardial defects.<sup>15, 11</sup> Additional administration of adrenaline could increase hypoxemia and promote further acidosis. This in turn would additionally deteriorate the vasopressor effects of adrenaline. Therefore, adrenaline might be ineffective and possibly detrimental.<sup>2</sup>

The question remains – does adrenaline improve survival rates? A review of current literature suggests that the answer to this question is “no”.<sup>2, 21, 27, 33</sup> In fact according to Babbs et al. no pre-clinical or clinical studies that have compared vasopressin with adrenaline favour adrenaline.<sup>27</sup> The future of adrenaline remains unclear in cardiac arrest considering current evidence.

## **Discussion on Current Literature**

In the Wenzel et al. [2004] study neurological outcomes should be construed circumspectly. This is due to the fact that the research study undertaken “was not powered to compare the effect of vasopressin with that of adrenaline on brain function after cardiopulmonary resuscitation”.<sup>30</sup> What also needs to be highlighted here is that patients already had a dismal chance of survival with an electrocardiograph finding of asystole, bearing in mind asystole is an important outcome predictor in cardiac arrest with an unfavourable neurological outcome.<sup>30</sup> Wenzel, Arntz and Lindner state that “we must remember that the duration of ischemia reflects vital organ injury and that the necessary vasopressor dosage reflects, the response to the resuscitation efforts”.<sup>30</sup>

It appears that most health professionals are reluctant to value research into the effectiveness of prehospital intervention. Hutchinson points out that “one reason for such reluctance maybe that there is a fundamental difficulty in addressing the questions that everyone wants answered: what works, in what context, with which groups, and at what cost?”.<sup>34</sup> It should be noted that sometimes it not possible to answer all of these questions at once and further research needs to occur to investigate specific issues.

Rigorously designed research into the effectiveness of vasopressin and adrenaline in respect to neurological recovery needs to occur; an effective design will allow for future and potential research funding.<sup>33</sup> It has been suggested that larger studies will need to be conducted. Such studies need to be able to prove a benefit “of a minimum 25% increase in survival”.<sup>20</sup>

A future research design would ideally include a randomised controlled trial with a large study group in the Australian prehospital setting that would assess the effectiveness of vasopressin on neurological outcome and survivability.

Assessment of neurological outcome with post arrest follow up’s from one to six months, and six to twelve months. The study should include and assess neurological outcome through the use of the Disability Rating Scale [DRS] formed by Rappaport et al.<sup>35</sup> The scale detects and measures clinical changes in patients who have suffered from head trauma.

The DRS specifically assesses:

1. Arousability, awareness and responsivity,
2. Cognitive ability for self care activities;
3. Dependence on others;
4. Psychosocial adaptability.

[Click here to view the Disability Rating Scale](#) 36

McIntyre states “because of the size and power of the study by Wenzel et al, the dismal rate of resuscitation among patients with asystolic cardiac arrest, and the apparent absence of any added risk to patients who may be treated according to the new therapeutic sequences, practitioners should perhaps be encouraged to incorporate the use of vasopressin” in the resuscitative framework.<sup>2</sup>

An argument could be made in relation to the implementation of vasopressin into pharmacology guidelines as an interim measure this view is suggested by McIntyre.<sup>2</sup> One view would suggest that too many clinical procedures and pharmacological interventions over the years have proven to be ineffective and implemented immediately, based on very little scientific research or evidence. Although it seems that vasopressin is as efficacious as adrenaline.<sup>20, 21</sup>

Combining vasopressin and adrenaline is beneficial when vasopressin is administered *prior* to adrenaline, which was achieved in the Wenzel et al. study.<sup>30</sup> However, Wenzel, Arntz, Lindner advise that further investigation needs continue before confirming this, and that a study is currently being undertaken in France.<sup>30</sup>

## Pharmacotherapy Guideline

Based on the available theoretical and clinical information that this paper has explored, a pharmacotherapy guideline has been developed that could be implemented into a future research programme and the Australian Resuscitation Council’s guideline for Adult Advanced Life Support. This guideline maybe utilised by the primary health care practitioner in cases of prehospital asystolic refractory cardiac arrest. Drug dosages are based on the ARC Adult Advanced Life Support Medications Policy Statement and the Wenzel et al. study.<sup>1, 21</sup>

## Guideline Rationale

The emphasis on this guideline is the use of vasopressin in refractory asystole. For the purpose of this guideline refractory pertains “to a disorder that is resistant to treatment”.<sup>4</sup>

Vasopressin is superior to adrenaline in asystole. Vasopressin followed by doses of Adrenaline may be more effective in refractory cardiac arrest.<sup>21</sup> Vasopressin can cause high perfusion pressures.<sup>37</sup>

## Pharmacotherapy

If the patient is in confirmed asystole vasopressin pharmacotherapy should take precedence over adrenaline with 40u Arginine vasopressin to be given immediately NO REPEAT, followed on by 1mg adrenaline if no response to vasopressin every 3 minutes thereafter.<sup>21,1</sup>

## Guideline Refractory Asystolic Cardiac Arrest



### CARDIAC ARREST DIAGNOSIS

- Basic Life Support and Cardiopulmonary Resuscitation.**9,38**
- Establish Airway access ETT or LM.**39,40,41**
- Establish Intravenous access – Hartmanns 500ml TKVO.**41,42**
- Vasopressin [Arginine Vasopressin] [IV] 40u 1 dose only **NO repeat.****21**
- Adrenaline 1mg continuing incremental doses every 3 minutes.
- Other pharmacotherapy can be delivered after initial vasopressin and adrenaline
- Treatment at the discretion of the practitioner.**21**

### Recommendations

It is clear that more research needs to be undertaken in relation to vasopressin and its potential use in the Australian prehospital setting. Such information is pressing and warrants further investigation. A series suggested recommendations have been formulated based on current literature and research for the future.

Current evidence would suggest by Hogg that Vasopressin is as efficacious as adrenaline,**20** therefore a trial implementation using the formulated guideline that this paper has presented should occur with specific research exploiting vasopressin and adrenaline pharmacotherapy on neurological outcome in prehospital cardiac arrest.

This recommendation should include the formation of a collaborative investigative team that includes key industry representatives. This is supported and suggested by McIntyre.**2**

International guidelines that advocate vasopressin as an alternative to adrenaline in shock refractory VF should immediately be revised. This pharmacotherapy has been contraindicated by the Wenzel et al. [2004] study.**21**

### Conclusion

At this stage no Australian Ambulance Service undertakes the use and administration of vasopressin in cardiac arrest, nor does the Australian Resuscitation Council make any recommendation for use in their current guidelines.

It is clear that more research needs to be undertaken in relation to vasopressin and its potential use. However the significance of international research and literature cannot go unnoticed. In the view of this paper there is enough evidence to support the use of vasopressin in further research or in a last ditch attempt in refractory asystole.

The future use of adrenaline and vasopressin remains unclear within the Australian context, however it is hoped that this paper will formulate extensive discussion in the professional arena. It is indisputable that an extensive study needs to be formulated assessing vasopressin and adrenaline pharmacotherapy on neurological outcome. This should ultimately be the next stage. We need to identify whether or not vasopressin administration is going to be advantageous and not detrimental to long term survival and neurological outcome.

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