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Role of vasopressin in current anesthetic practice

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Arginine vasopressin (AVP), also known as antidiuretic hormone, is a peptide endogenously secreted by the posterior pituitary in response to hyperosmolar plasma or systemic hypoperfusion states. When administered intravenously, it causes an intense peripheral vasoconstriction through stimulation of V_1 receptors on the vascular smooth muscle. Patients in refractory shock associated with severe sepsis, cardiogenic or vasodilatory shock, or cardiopulmonary bypass have inappropriately low plasma levels of AVP ('relative vasopressin deficiency') and supersensitivity to exogenously-administered AVP. Low doses of AVP and its synthetic analog terlipressin can restore vasomotor tone in conditions that are resistant to catecholamines, with preservation of renal blood flow and urine output. They are also useful in the treatment of refractory arterial hypotension in patients chronically treated with renin-angiotensin system inhibitors, cardiac arrest, or bleeding esophageal varices. In the perioperative setting, they represent attractive adjunct vasopressors in advanced shock states that are unresponsive to conventional therapeutic strategies.

Key Words: Arginine vasopressin, Hemorrhagic shock, Refractory hypotension, Septic shock, Terlipressin, Vasodilatory shock.

Introduction

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a nonapeptide produced in the hypothalamus and secreted into the circulation through the posterior pituitary gland. It was first discovered from the extract of the posterior pituitary by Oliver and Schafer in 1895 [1] and named for its vasoconstrictive properties. Its antidiuretic effects remained largely unknown until 1913, when it was renamed as ADH based on its strong antidiuretic effects in the kidney and beneficial actions in diabetes insipidus [2]. In the early 1950s, Vincent du Vigneaud characterized the structure of AVP and eventually synthesized it, for which he won the Nobel Prize in 1955 [3]. Until about 25 years ago, AVP had been used to treat diabetes insipidus and to reduce blood loss in gastrointestinal bleeding.

Although AVP is secreted in response to stress or shock states, its circulating levels are inappropriately low in patients with refractory hypotension associated with severe sepsis, hypovolemia, cardiogenic shock, or cardiac arrest ('relative vasopressin deficiency') [4,5], which is thought to contribute to the hypotension of shock. While beneficial effects of AVP in shock patients were first noted in a brief report in 1957 [6], it was not until the mid-1990s that AVP emerged as a potentially useful therapeutic for refractory shock [7]. In refractory shock, endovascular AVP is depleted [4,8] and exogenous AVP exerts profound vasopressor effects even at doses that would not affect arterial blood pressure in normal subjects [9].

The pressor effects of AVP are relatively preserved during hypoxemic and acidemic conditions [2], making it useful in refractory circulatory shock and cardiopulmonary resuscitation (CPR) [10]. Moreover, it may be cardio- and nephroprotective in patients with vasodilatory shock [11,12]. This review is aimed to explain the physiology and pharmacology of AVP, and its thera-

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peutic applications and safety in a broad range of cardiovascular compromise conditions, including septic shock, postoperative vasodilatory shock, cardiac arrest, and cardiogenic shock.

Physiology

Elaboration and synthesis of AVP

Human AVP consists of nine amino acids, the eighth of which is arginine; thus, it is called AVP to distinguish it from other analogs. Pre-pro-AVP is synthesized in magnocellular neurosecretory neurons (also known as neurohypophyseal neurons) in the supraoptic and paraventricular nuclei (known as osmoreceptors) of the anterior hypothalamus. It migrates along the supraoptic-hypophyseal tract to the posterior pituitary gland, where it is stored in neurosecretory vesicles [7]. In response to appropriate stimuli (e.g., hyperosmolar plasma/urine, hypotension, and hypovolemia), about 10–20% of the total AVP pool within the posterior pituitary is rapidly released initially, and it is then secreted at a greatly reduced rate. The entire process of AVP synthesis, transport, and storage in the posterior pituitary gland takes 1–2 h. Normal plasma concentrations are < 4 pg/ml. It has a half-life of 10–35 min [13,14].

Vasopressin receptors and signal transduction

Vasopressin receptors are classified according to their location and second messenger pathways into three subtypes: V_1 (formerly known as V_{1a}), V_2, and V_3 (formerly V_{1b}) receptors (Table 1). V_1 and V_2 receptors are expressed peripherally and are involved in the modulation of arterial blood pressure and renal function, respectively. V_1 and V_3 receptors are expressed in the central nervous system. The distribution and density of these receptors account for the potentially beneficial pharmacological effects [15].

They are G protein-coupled receptors, having seven transmembrane domains. V_1 receptors are Gq protein-linked and are expressed in vascular smooth muscle, hepatocytes, kidney, platelets, myometrium, bladder, adipocytes, and spleen. When activated, phosphatidylinositol bisphosphate is hydrolyzed to inositol triphosphate and diacylglycerol by phospholipase C, resulting in increases in intracellular Ca^{2+} concentrations, potentiating the interaction of actin-myosin chains, and leading to vasoconstriction. Other effects include the endothelial release of nitric oxide (NO) that causes vasodilation in the coronary and pulmonary vasculature [16,17]. They are also expressed in many regions of the brain, exerting effects in the regulation of social behaviors, blood pressure, memory, and body temperature.

V_2 receptors are Gs protein-linked and are expressed in the epithelial cells of the distal tubal and collecting ducts, controlling the antidiuretic effects of AVP. They activate adenylyl cyclase to increase cyclic adenosine monophosphate, leading to translocation and expression of aquaporin-2 in the principal cells along the renal collecting duct cells. V_2 receptors on vascular endothelium are also activated by vasopressin to release coagulation factor VIII and von Willebrand factor (vWF), which is important in binding platelets to the site of bleeding. They also mediate vasodilation through the release of NO in the kidney [18].

V_3 receptors activate Gq proteins to release intracellular Ca^{2+} after activation of phospholipase C and the phosphoinositide pathway. Their activation in the pituitary gland stimulates the secretion of adrenocorticotropic hormone (ACTH), growth hor-

Table 1. Subtype, Second Messenger, Localization, and Function of Vasopressin Receptor

Subtype	Signaling pathway	Location	Function
V_1	G protein-coupled, phosphatidylinositol/calcium	Vascular smooth muscle	Vasoconstriction
		Platelet	Platelet aggregation
		Liver	Glycogenolysis
		Myometrium	Uterine contraction
		Kidney	Efferent arteriolar constriction
		Brain	Temperature regulation
			Cognitive function (learning and memory)
			Emotional response (anxiogenic and depressive actions, stress adaptation)
			Social behavior (pair-bonding behavior, aggressive and affiliative behavior)
V_2	G protein-coupled, adenylate cyclase/cAMP	Kidney collecting duct cells	Insertion of aquaporin-2 channels
		Vascular endothelium	Release of vWF and factor VIII
V_3	G protein-coupled, phosphatidylinositol/calcium	Anterior pituitary lobe	Corticotropin, growth hormone, and prolactin secretion
		Brain	Stress adaptation, cognitive function, regulation of social behavior

cAMP: cyclic adenosine monophosphate, vWF: von Willebrand factor.

mone, and prolactin. They are also responsible for the actions of AVP in the central nervous system, such as regulation of social behavior [19].

AVP also has equal affinity with oxytocin for oxytocin receptors. Oxytocin receptors are observed predominantly on myometrium and vascular smooth muscle. Their activation by AVP increases intracellular Ca^{2+} via phospholipase C and the phosphoinositide pathway. They are also located on vascular endothelial cells, where they produce a calcium-dependent vasodilatory response via stimulation of NO synthase activity [20].

Physiological functions

AVP plays an important role in the regulation of osmolality, cardiovascular stability, blood coagulability, mood, and stress. It also releases ACTH and influences cognition, learning, and memory.

Osmotic control

AVP is released when central osmoreceptors in the hypothalamus and peripheral receptors near the portal vein detect very small increases, as little as 1% above normal, in extracellular fluid osmolality [21,22]. Even mild dehydration increases water reabsorption in the collecting ducts of the nephron, resulting in rapid antidiuresis, with increased urine osmolality up to 1,200 mOsm/kg, as plasma AVP levels rise to 5 pg/ml. AVP thereby maintains the plasma osmolality between 275 and 290 mOsm/kg H_2O. A much less sensitive trigger for the release of AVP is a decreased intravascular volume mediated by stretch receptors in the left atrium and great veins. The afferent arc is via the vagal and glossopharyngeal nerves to the solitary nucleus in the medulla oblongata (vasomotor center), and the efferent arc is from the vasomotor center to the hypothalamic nuclei [21]. Pain, stress, nausea, hypoxia, pharyngeal stimuli, and endogenous and exogenous chemical mediators also increase AVP release through central nervous inputs [2].

Cardiovascular control

Arterial blood pressure is maintained by an interaction among the sympathetic, renin-angiotensin, and AVP systems. However, under normal conditions and at normal physiological concentrations, AVP plays a minor role in arterial blood pressure regulation. When the sympathetic and renin-angiotensin systems are intact, the endogenous AVP system is not important for hemodynamic stability, and its effect is essentially negligible. Small hemodynamic changes cause only moderate changes in plasma AVP concentrations, and increases in response to hypotensive stimuli rarely exceed 20 pg/ml [23]. Moreover, potential cardiovascular effects of exogenous AVP are little when the two other systems are intact. In healthy volunteers, infusion rates of up to 4.6 pg/kg/min, achieving plasma levels of 34 ± 20 pg/ml, had no significant pressor effect [24]. In contrast to catecholamines, circulating AVP acting in the area postrema may augment baroreflex inhibition of efferent sympathetic nerve activity and thus counterbalance the increase in peripheral vascular resistance, resulting in minimal changes in blood pressure [25].

If the two other systems are compromised, such as during combined general and epidural anesthesia or in patients with orthostatic hypotension and autonomic insufficiency, even small increases in plasma concentrations of AVP (> 2 pg/ml) initiate an increase in peripheral vascular resistance, serving to maintain arterial blood pressure [14,24]. Epidural anesthesia (up to T2) often causes only a small decrease in blood pressure despite the widespread sympathetic block, even in the presence of an angiotensin-converting enzyme inhibitor (ACEI); however, additional blockade of V_1 receptors with a vasopressin antagonist produces profound hypotension [26]. In fact, AVP is a backup system for blood pressure control and cardiovascular sympathetic modulation.

In contrast, AVP may have a major impact during severe

Table 2. Vasopressin Plasma Concentrations in Different Conditions of Adult Patients

Condition	Plasma concentration (pg/ml)	Source
Healthy volunteers	2.0 ± 0.3	Baylis and Robertson [22]
Healthy volunteers after hypertonic saline infusion	14.8 ± 1.8	Baylis and Robertson [22]
Cardiac arrest before unsuccessful CPR	70.0 ± 9.0	Lindner et al. [29]
Cardiac arrest before successful CPR	193.0 ± 28.0	Lindner et al. [29]
Late septic shock	3.1 ± 1.0	Landry et al. [4]
Early cardiogenic shock	22.7 ± 2.2	Landry et al. [4]
Vasodilatory shock after CPB	12.0 ± 6.6	Argenziano et al. [59]
During CPB with non-pulsatile perfusion	198.0 ± 9.0	Levine et al. [58]
Unstable organ donor	2.9 ± 0.8	Chen et al. [32]
Late hemorrhagic shock	8.1 ± 5.1	Joseph et al. [80]
Early hemorrhagic shock	19.1 ± 6.7	Joseph et al. [80]

Data are mean ± SD. CPR: cardiopulmonary resuscitation, CPB: cardiopulmonary bypass.

hemodynamic instability (Table 2). By far the most potent trigger for AVP release is systemic arterial hypotension, mediated by aortic and carotid baroreceptors. In contrast to moderate changes in plasma AVP concentrations in subjects with an intact systemic circulation, they may be increased markedly during profound hypotension. It overrides all other triggers, and plasma AVP may reach levels 10- to 1000-fold greater than normal [21]. In animal models of hemorrhagic shock [27] and acute sepsis [28], plasma AVP increased to more than 319 pg/ml and 144 pg/ml, respectively. In patients with out-of-hospital cardiac arrest, AVP concentrations up to 193 pg/ml have been reported before CPR [29]. AVP causes substantial vasoconstriction in skin, skeletal muscle, fat, and mesenteric blood vessels, and predominantly increases systemic vascular resistance [30], shifting the blood flow from non-vital to vital organs as a passive effect. Moreover, low AVP concentrations have been reported to cause paradoxical vasodilation of a cerebral artery via release of NO through activation of V_1 receptors despite systemic vasoconstriction [31]. As such, AVP and its synthetic receptor agonists may be regarded as a humoral replenishment remedy for septic shock, intraoperative hypotension, and different types of vasodilatory shock [4,32]. They are also used as a vasopressor during CPR [10].

Corticotropin secretion and central regulatory function

AVP plays multiple regulatory roles via V_1 and V_3 receptors in the central nervous system and the anterior pituitary gland (ACTH secretion). It also exerts effects on the regulation of body temperature and cognitive/social behaviors (memory, anxiety, stress) [7,19,33].

Hemostasis

Like other stress hormones, AVP increases blood coagulation. In particular, AVP and desmopressin (DDAVP), a selective V_2 receptor agonist, increase plasma concentrations of vWF, which binds to collagen at sites of vascular injury to mediate platelet adhesion and aggregation, and serves as a carrier protein for coagulation factor VIII and, therefore, can decrease bleeding [34]. However, the wide variety of physiological actions provoked by AVP limits its use for treatment of bleeding disorders. DDAVP has few side effects and is used widely to manage bleeding diseases. In perioperative settings, patients with mild hemophilia A, type 1 von Willebrand disease, and congenital or acquired platelet disorders may benefit from hemostatic treatment with DDAVP via increases of factor VIII and vWF [35]. However, DDAVP increases the risk of arterial thrombosis [36].

Pharmacology

Exogenous AVP (8-AVP) must be given parenterally, because the peptide is hydrolyzed quickly by trypsin. It is not protein-bound and has a volume of distribution of 140 ml/kg. Its plasma half-life is 10–35 min, being rapidly metabolized by liver and kidney vasopressinases (35%) and excreted through the kidney (65%) [7]. Lysine vasopressin, or lypressin, is secreted endogenously in pigs and is often used as a therapeutic agent in humans. The development of synthetic AVP analogs with longer half-lives and receptor selectivity has greatly enhanced the clinical use of vasopressin [37].

Several AVP agonists and analogs are used currently (Table 3). Argipressin (Pitressin) acts on V_1, V_2, and V_3 receptors, and has been used for the treatment of refractory vasodilatory hypotension, cardiac arrest, and septic shock. Terlipressin (triglycyl-lysine vasopressin, TP) is a 12-amino-acid analog of lysine vasopressin, a precursor of AVP. The elimination half-life of TP is 50 min [38]. It is a prodrug and is metabolized by exopeptidases to yield the active metabolite lysine vasopressin in the circulation, having a longer biological half-life (6 h), which made it popular in the early 1990s. TP has been used in Europe and Asia for more than 20 years as the treatment of choice for bleeding

Table 3. Vasopressin Agonist and Synthetic Vasopressin Analogs

Name	Structure	Receptor affinity	Clinical application
Argipressin	8-arginine vasopressin (AVP)	V_1, V_2, V_3	CPR Intraoperative hypotension Severe hemodynamic instability Vasodilatory shock Septic shock
Desmopressin	Desamino-Cys-D-Arg vasopressin (DDAVP)	V_2	Central diabetes insipidus Bleeding disorders
Terlipressin	N3-triglycyl-8-lysin vasopressin	V_1	Intraoperative hypotension Bleeding gastric and esophageal varices Portal hypertension Septic shock

CPR: cardiopulmonary resuscitation.

esophageal varices.

Ornipressin has a specific affinity for V_1 receptors, thus mimicking the effects of AVP on vascular smooth muscle with limited antidiuretic effects. Desmopressin acetate (1-deamino-8-D-arginine vasopressin, DDAVP) is a synthetic agonist with V_2 receptor specificity and was initially devoted to the treatment of central diabetes insipidus. Through a direct action on endothelial V_2 receptors, DDAVP also increases factor VIII and vWF plasma concentrations in healthy subjects. This drug was approved for medical treatment in the United States in 1978.

Therapeutic Uses

Refractory arterial hypotension

The sympathetic, renin-angiotensin, and vasopressin systems are involved in the regulation of arterial blood pressure. By blunting sympathetic nervous activity on vascular tone, general anesthesia with most anesthetics may increase reliance on the renin-angiotensin and vasopressin systems to maintain blood pressure. ACEIs and angiotensin II receptor antagonists (AIIRAs) are used widely as first-line therapy for arterial hypertension [39]. In patients with long-term use of ACEIs/AIIRAs, intra-operative hypotension associated with general anesthesia may be refractory to treatment with norepinephrine, phenylephrine, and ephedrine [39]. In those whose sympathetic and renin-angiotensin systems have been blunted by general anesthesia and ACEIs/AIIRAs, TP (IV 1–2 mg) or AVP (IV 2–3 U) is an effective vasopressor if they are refractory to common adrenergic vasopressors [40-42]. In fact, because angiotensin II is a physiological stimulator of AVP release, perioperative hypotension in patients chronically treated with ACEIs is at least in part related to AVP deficiency [43].

Neuraxial anesthesia, especially high thoracic anesthesia, blocks sympathetic neural traffics both to the vasculature (T1-L2) and to the adrenal gland (T3-L3). Thus, renin release in response to hypotension may also be abolished, while AVP concentrations increase [26,44]. Consequently, patients with epidural anesthesia are at risk of hypotension, where exogenous AVP and TP may be suitable vasopressors. Resection of a massive pheochromocytoma may be complicated by catecholamine-resistant vasoplegic shock, although rare. Successful use of AVP (bolus of 10–20 U with continuous infusion at 0.1 U/min) has been reported [14,45].

Septic shock

Septic shock refers to life-threatening organ dysfunction due to a dysregulated host response to infection, accompanied by hypotension, requiring vasopressors to maintain the mean arterial pressure at 65 mmHg or greater and a serum lactate level greater than 2 mmol/L despite adequate fluid resuscitation [46]. Hypotension, in turn, triggers a cascade of neurohormonal responses involving sympathoadrenal activity, renin-angiotensin, and AVP, and thus profound peripheral vasoconstriction. However, vascular smooth muscle exhibits a decreased ability to contract, and the concomitant hypotension may be refractory to standard catecholamine therapy.

An exquisitely sensitive pressor response to exogenous AVP was first documented in refractory septic shock [6]. Landry et al. [4] also observed an unusually sensitive pressor response to exogenously infused AVP in septic shock despite the coinfusion of catecholamine. They found that plasma AVP levels were even lower than those in a cohort of patients in cardiogenic shock who also received catecholamines (3.1 ± 1.0 pg/ml vs. 22.7 ± 2.2 pg/ml, $P < 0.001$). AVP at doses of 2.4 U/h, less than one-tenth of that used for the management of bleeding esophageal varices, resulted in a dramatic increase in systolic blood pressure (92 to 146 mmHg) with withdrawal of catecholamine infusion. It was also noted that urine output was increased simultaneously in three of five patients, from an average of 30 to 110 ml/h [47]. In endotoxemia, an early increase from 14 to 144 pg/ml in plasma AVP was observed in animal models [28]. Similarly, in septic shock patients, AVP concentrations initially increased markedly and then declined progressively over 72 h to extremely low levels, representing relative AVP insufficiency [48].

A randomized trial of AVP versus norepinephrine in septic shock (the Vasopressin in Severe Sepsis Trial, VASST) divided septic shock patients (n = 778) into low-dose AVP (0.01–0.03 U/min) plus open label norepinephrine or norepinephrine [49]. It revealed no difference between the groups in mortality rates and major organ dysfunction at days 28 or 90. However, in patients with low severity of shock (defined as receiving baseline norepinephrine 5–15 μg/min), AVP decreased mortality by almost 10% (26.5% vs. 35.7%, $P < 0.05$). This study demonstrated the safety and efficacy of AVP and highlighted its role in reducing norepinephrine requirements in septic shock. Furthermore, Gordon et al. [12] performed a *post hoc* analysis of VASST to evaluate the role of AVP in patients with shock and acute kidney injury. They observed that in patients in the Risk category in the Risk, Injury, Failure, Loss, and End-Stage Renal Failure scoring system [50], a significantly smaller proportion of patients treated with AVP (21% vs. 40%) advanced to the Failure or Loss categories or needed dialysis (17% vs. 38%).

A recent systematic review and Bayesian network meta-analysis, including 2,811 patients from 14 randomized clinical trials, suggested that the combination of low-dose AVP to norepinephrine compared to dopamine was associated with an odds ratio for mortality in the short term of 0.69 (95% CI = 0.48–0.98) [51]. In contrast, another recently completed trial (Vasopressin vs.

Norepinephrine as Initial Therapy in Septic Shock) revealed no difference between the two drugs in renal function (the trial's primary outcome), shock duration, length of stay, or mortality, although the confidence interval included a potential clinically important benefit for AVP [52]. Thus, clinicians may consider a low dose AVP (up to 0.03 U/min) as an adjunct treatment to norepinephrine with the intent of raising mean arterial pressure to target or decreasing norepinephrine dosage, but not as the first-choice vasopressor in severe sepsis and septic shock, as recommended in the 2016 Surviving Sepsis Campaign Guidelines [53]. In sepsis, however, doses no higher than 0.04 U/min should be used, as higher doses may produce myocardial ischemia and cardiac arrest [53]. Infusion of AVP at 0.01 U/min raised plasma AVP levels to ~30 pg/ml, slightly higher than the level reported in patients with cardiogenic shock (~23 pg/ml), and at 0.04 U/min raised it to 100 pg/ml [2,4].

TP is also used increasingly as an adjunct vasopressor agent in the management of vasodilatory septic shock. Due to its higher selectivity for vascular V_1 receptors, compared with AVP, TP may have better cardiovascular effects and less systemic side effects (e.g., hyponatremia, thrombocytopenia, vascular leaks). It increases arterial blood pressure, reduces norepinephrine dose requirements, and improves kidney function (urine output and creatinine clearance) in septic shock [54]. Accordingly, TP (1.3 μg/kg/h) can be used as a rescue therapy for septic shock refractory to conventional treatments. Recently, selepressin, a short-acting selective V_1 receptor agonist, has emerged as a novel medication in the management of septic shock in animal studies. It may have advantages over AVP, because it causes pure vasoconstriction, has reduced antidiuretic effects, lacks thrombotic complication (because of reduced release of vWF), and provides better protection from increased permeability. Indeed, it was more effective than AVP in improving cardiovascular function and preventing vascular leaks in large animals with sepsis [55].

What, then, are the reasons underlying the increased pressor sensitivity to AVP in vasodilatory septic shock? In refractory vasodilatory shock, NO and metabolic acidosis may activate potassium channels (K_{ATP} and K_{Ca}) in the plasma membrane of vascular smooth muscle, and the resulting hyperpolarization prevents the Ca^{2+} that mediates adrenergic vasopressor-induced vasoconstriction from entering the cell [56]. Additionally, adrenoceptors are desensitized or down-regulated due to high circulating levels of catecholamines [57]. Consequently, hypotension and vasodilatation persist, despite high plasma concentrations of these agents [8]. AVP binds to V_1 receptors, causing vasoconstriction through several pathways, including modulation of K_{ATP} channel function and NO production, and enhancement of the vascular responsiveness to catecholamines [9]. Moreover, the number or affinity of V_1 receptors may be increased by the depletion of endogenous AVP. Taken together, the enhanced sensitivity to exogenous AVP may be attributable to its ability to block K_{ATP} channels, interfere with NO signaling, bind avidly to V_1 receptors, and potentiate the effects of adrenergic agents at the level of vascular smooth muscle in shock states [8,9].

Vasodilatory shock

Vasodilatory shock is defined as hypotension, increased cardiac index, and low systemic vascular resistance refractory to vasopressors, such as norepinephrine. It is the final common pathway for long-lasting and severe shock of any cause, and is also characteristic of the contact activation syndrome evoked by cardiopulmonary bypass or ventricular assist devices and hemodynamically unstable organ donors [8]. Cardiopulmonary bypass generally raises AVP plasma concentrations up to greater than 198 pg/ml when non-pulsatile flow is used [58]. Open heart surgery using bypass is often associated with vasodilatory hypotension requiring pressor support as part of a systemic inflammatory response. In these patients, low AVP plasma concentrations (12 pg/ml) are observed, representing AVP deficiency [59] (Table 2). Risk factors for post-bypass vasodilatory shock due to AVP deficiency are preoperative ejection fraction less than 0.35 and the use of ACEIs [59]. Post-bypass hypotension can be treated with low-dose AVP (0.01–0.03 U/min).

A recent single-center double-blinded clinical trial, "Vasopressin vs. Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery," randomized 330 patients with vasoplegic syndrome (defined as mean arterial pressure < 65 mmHg resistant to fluid challenge and postoperative cardiac index > 2.2 L/min/m^2) to receive AVP or norepinephrine as the initial drug [60]. In patients receiving AVP, the primary endpoint (mortality or severe complications including acute renal failure) occurred in 32%, compared with 49% in those receiving norepinephrine ($P = 0.001$), and atrial fibrillation was less frequent (64% vs. 82%, $P < 0.001$). It was suggested that AVP should be used as a first-line vasopressor in post-bypass vasoplegic shock to improve clinical outcomes.

In patients who developed post-bypass vasodilatory shock after placement of a left ventricular assist device, AVP (0.1 U/min) quickly and significantly raised arterial blood pressure secondary to increased systemic vascular resistance along with unchanged cardiac index [61]. Similarly, AVP (0.1 U/min) was useful in vasodilatory shock after cardiac transplantation [62]. Pretreatment with AVP (0.03 U/min) in high-risk patients undergoing cardiac surgery has yielded hemodynamic stability after cardiopulmonary bypass with an adrenergic agent sparing effect [63]. The efficacy and safety of AVP use (0.0003–0.002 U/kg/min) was also demonstrated in children after cardiac surgery [64].

Several studies have acknowledged a favorable impact of AVP

on renal function in septic shock and in vasodilatory syndrome after cardiac surgery. Animal studies in sepsis demonstrated improved creatinine clearance [65], and a preservation of renal function compared with norepinephrine [66]. In a *post hoc* analysis of the VASST trial, patients with acute kidney injury at baseline who were treated with AVP had a higher rate of renal recovery and lower mortality [12]. Holmes et al. [67], in a series of 50 septic patients, found that AVP infusion increased mean arterial pressure and diuresis.

The mechanisms by which AVP and its analogs protect against renal injury in vasodilatory shock states are poorly understood. One possible explanation may be due in part to its ability to raise low renal perfusion pressure back into the autoregulatory range, resulting in an increased glomerular filtration. Another more likely explanation is that, AVP even at high local concentrations, preferentially constricts the efferent arteriole, thereby improving the filtration fraction and glomerular filtration rate [68]. Moreover, AVP has been reported to cause afferent renal arteriolar vasodilation through V_2 receptors, which favors glomerular filtration [69]. In contrast, norepinephrine binds preferentially to the α-1 receptors of renal afferent arterioles, decreasing glomerular perfusion pressure and filtration [68].

Anaphylaxis is an allergic reaction, characterized by multisystem involvement, including the skin, airway, vascular system, and gastrointestinal tract. In severe anaphylactic shock, the airway is obstructed completely and the cardiovascular system is collapsed acutely due to vasodilation and leakage of plasma from capillaries, with resultant relative hypovolemia. For patients not in cardiac arrest, IV 0.05–0.1 mg epinephrine (5–10% of the dose used in cardiac arrest) has been used in patients with anaphylactic shock. Recently AVP has been used successfully in anaphylactic patients who did not respond to standard therapy, regardless of cardiac arrest [14,70]. The 2010 American Heart Association Guidelines on CPR also describe AVP administration as a potential therapy in cardiac arrest due to anaphylaxis that does not respond to epinephrine [71].

In brain-dead organ donor, when hemodynamic stability is not accomplished through the use of fluids, vasopressor agents should be considered. Dopamine is most commonly used in this situation. If a large amount of dopamine is required, then a second vasopressor agent can be added. AVP plasma concentrations decrease sharply after brain death [72], and thus are comparatively low (< 8 pg/ml) in hemodynamically unstable organ donors without clinical signs of diabetes insipidus [32]. AVP infusion at 0.04–0.1 U/min in these hypotensive subjects resulted in normal urine output, preserved renal function, and hemodynamic stability, along with reduced catecholamine requirements [73]. Indeed, AVP is recommended as the initial therapy of choice for potential heart donors by the American College of Cardiology [74].

Subsequently, hormonal therapy for hemodynamic stability was developed and recommended in brain-dead organ donors. The Cardiac Work Group, led by the United Network for Organ Sharing (UNOS), recommended the use of AVP as part of a hormonal resuscitation protocol (methylprednisolone, AVP, triiodothyronine or l-thyroxine, and insulin) for heart donors with a left ventricular ejection fraction less than 45% or with unstable hemodynamics [75]. UNOS multivariate studies on a hormonal resuscitation protocol (triiodothyronine or l-thyroxine, methylprednisolone, and AVP) in brain-dead donors revealed significant increases in the number of organs transplanted and in 1-year survival of kidneys and hearts [76]. In particular, thyroid hormone was shown to play a beneficial role in unusual cases of prolonged donor management: that is, longer than 24–48 h. Desmopressin has long been used to manage central diabetes insipidus in brain-dead organ donors due to its strong antidiuretic effects and prolonged duration of action. Nevertheless, decreased graft function due to its procoagulatory effects has been suggested as a side effect [36].

Uncontrolled hemorrhagic shock

Fluid resuscitation and catecholamine support are the standard therapeutic strategy for hemorrhagic shock. However, when the shock is prolonged, the response to both fluid and catecholamine vasopressors can be poor because of acidosis, desensitized receptors, persistent vasodilation, and/or NO release [8]. AVP improved survival, neurologic outcome, and enhanced hemodynamic performance in animal models in which severe uncontrolled blood loss was induced [27,77]. A recent systematic review and meta-analysis of randomized animal trials revealed that AVP and TP improved survival in the early phase of hemorrhagic shock, showing that AVP was more effective than all other treatment regimens including other vasopressor drugs [78]. In humans, low levels of AVP are observed after initial high plasma concentrations during significant hemorrhage that can respond to administration of exogenous AVP [79,80].

Recently, many physicians have used AVP when other inopressors have failed to have an effect in hypovolemic patients. The value of AVP may be related to the depletion of stored AVP during sustained profound hypotension. An animal study demonstrated almost complete depletion of radiolabeled AVP in the posterior pituitary following 1 h of hemorrhagic shock [8]. Several case reports have described successful results with AVP during hypovolemic shock that was unresponsive to conventional fluids, blood, and vasopressors [81,82]. However, the timing of application and AVP doses differed widely, with doses ranging from a 40 U bolus to a 0.04 U/min continuous infusion.

Cardiopulmonary resuscitation

Sudden cardiac arrest remains a leading cause of prehospital and in-hospital deaths. Outcomes after cardiac arrest remain poor more than a half a century ever since closed-chest CPR was first introduced. Epinephrine remains the vasopressor drug of choice in CPR. Its pressor action stems from its α1-adrenergic activity on peripheral vascular smooth muscles. Simultaneously, it stimulates β-receptors and increases myocardial oxygen consumption during CPR, causing myocardial dysfunction after restoration of spontaneous circulation (ROSC) [83].

On the other hand, AVP provokes vascular smooth muscle contraction through stimulation of V_1 receptors and enhances smooth muscle responsiveness to catecholamines. This agent lacks adrenergic stimulation and, as a result, causes limited increases in myocardial contractility, myocardial oxygen consumption, and metabolic demands. By virtue of these theoretical advantages, AVP has been suggested as an alternative, potent vasopressor in CPR. Moreover, it was noted that patients who were resuscitated successfully from cardiac arrest had higher plasma AVP concentrations compared with non-survivors (193 ± 28 pg/ml vs. 70 ± 9 pg/ml before CPR, $P < 0.001$) [29], which prompted research into the role of AVP in cardiac arrest. It has been suggested that AVP improves vital organ perfusion during CPR, post-ROSC survival, and neurological recovery in animal studies [84,85]. Even in a preliminary clinical study comparing epinephrine and AVP in patients with out-of-hospital ventricular fibrillation, a significantly larger proportion of patients treated with AVP than those treated with epinephrine was resuscitated successfully and survived for 24 h [86].

Despite the favorable animal and preliminary clinical results [84-87], prior, large, randomized, controlled trials comparing AVP and epinephrine have failed to demonstrate a clear, overall advantage of AVP [10,88,89]. Mentzelopoulos et al. [90] conducted a large meta-analysis involving six randomized controlled trials (n = 4,475) in which AVP was administered during CPR (with or without epinephrine), and evaluated its role in ROSC, as well as its role in long-term neurologic outcomes. They found that the use of AVP in patients in cardiac arrest was not related to any significant benefit or harm. The only long-term survival benefit was observed when AVP was administered to patients who were in asystole [10,90]. Use of one dose of AVP (40 U IV) as an alternative to the first or second dose of epinephrine was first included in the 2000 American Heart Association (AHA) Guidelines for CPR and Emergency Cardiovascular Care, based on observations that survivors of cardiac arrest had increased endogenous AVP levels for the treatment of unstable ventricular tachycardia and ventricular fibrillation [91].

In 2005, the AHA guidelines were revised to support the use of AVP in all cases of pulseless cardiac arrest, and this was continued up to 2010 guidelines [92]. However, AVP was removed from the 2015 AHA Guidelines for CPR and Emergency Cardiovascular Care to simplify the algorithm, because the combined use of AVP and epinephrine or AVP apparently offers no advantage over using standard-dose epinephrine [93].

Nevertheless, several studies have demonstrated the safety and efficacy of AVP and highlighted its role in prolonged cardiac arrest [10,90], suggesting that AVP is as safe as epinephrine in CPR, and thus still justifying the use of AVP in CPR. In pediatric cardiac arrests, evidence for using AVP is insufficient. As long as the cardiac arrest persists in children, epinephrine is the drug of choice. It is initially given in an IV or intraosseous dose of 0.01 mg/kg (0.1 ml/kg of a 1 : 10,000 solution), as in pulseless electrical activity related arrests. Further studies are required to define a more precise role for AVP in CPR and to determine the significance of the potential side effects.

Portal venous hypertension

Portal hypertension, due to liver cirrhosis, produces a hyperdynamic circulation: cardiac output is increased, systemic blood pressure is slightly below normal, and peripheral resistance decreases. Portosystemic shunting occurs, circumventing the hepatic filtering mechanism, thereby allowing drugs, nitrogenous waste, and toxins to enter the central circulation [94]. Because both AVP and TP bind to V_1 receptors, they constrict the mesenteric arteries, leading to reduced portal venous inflow and an ensuing reduction in portal pressure within minutes of administration. However, TP is more effective and may cause fewer systemic side effects than AVP. The agent has other advantages, including the convenience of a bolus injection, reduced cardiotoxicity, and a high cure rate of acute esophageal variceal bleeding (70%). Thus, TP (1–2 mg IV bolus every 4–6 h) has long been recommended to manage esophageal variceal bleeding in patients with portal hypertension [95].

Adverse Effects

AVP and TP act on V_1 receptors on vascular smooth muscle, leading to vasoconstriction, so that higher doses may be associated with increased side effects, such as gastrointestinal and myocardial ischemia [14,37]. Moreover, they reduce cardiac output, which may impair oxygen delivery, via reflex mechanisms mediated through baroreceptors reflex (aortic/carotid sinus baroreceptors). The reduced intestinal perfusion may cause tissue necrosis, with ensuing translocation of bacteria that promote the development of sepsis in the postresuscitation phase [96]. A case of myocardial ischemia requiring percutaneous coronary intervention after TP was reported in a patient with coronary artery disease [97]. Severe adverse reactions, such as myocardial

infarction and cardiac arrest, have also been reported even after local intramyometrial infiltration of AVP during gynecological surgery under general anesthesia [98,99]. Furthermore, an IV bolus of AVP, given to prevent beach chair positioning-induced hypotension under general anesthesia, was reported to decrease cerebral oxygenation, as measured by jugular venous oxygen saturation and near-infrared spectroscopy [42,100].

AVP activates V_2 receptors on endothelial cells, causing release of endothelial vWF, and enhances platelet aggregation, thereby increasing the risk of thrombosis [101]. Hyponatremia, anaphylaxis, bronchospasm, urticaria, abdominal cramps, angina, and chest pain have been reported [102]. AVP and TP should be used only at recommended dosages for indications that have been defined through clinical investigations, especially cautiously in patients with coronary artery disease or occlusive artery disease.

Vasopressin Antagonists

Vasopressin antagonists, the 'vaptan' drugs, produce aquaresis by their action on V_2 receptors in the collecting duct. They increase urine output and raise serum sodium concentrations. Several vaptans are already in clinical use or in clinical trials for the treatment of hyponatremia, congestive heart failure, cirrhosis, polycystic kidney disease, and nephrogenic diabetes insipidus. Tolvaptan is used in the United States and Europe for the treatment of hyponatremia. In Japan, it has been approved for the treatment of volume overload in patients with heart failure when other treatments fail to achieve an adequate response. Conivaptan is a high-affinity non-peptide antagonist of both V_2 and V_1 receptors that produces aquaresis. It was approved by the United States Food and Drug Administration in 2005 for the treatment of hyponatremia [103]. Lixivaptan is a selective V_2 receptor antagonist, which produces a significant increase in serum sodium levels [104]. Whereas conivaptan is administered intravenously, the other vaptans, like tolvaptan, and lixivaptan, are effective as oral medications.

Vaptans are also inhibitors of the liver enzyme cytochrome P450 3A4. Concurrent use of vaptans with drugs that are metabolized by cytochrome P450 3A4 has the potential for increased drug plasma concentrations and side effects [105]. In this regard, conivaptan is a relatively strong inhibitor and available only in parenteral form, and the recommended duration of therapy is limited to 4 consecutive days.

Conclusions

AVP and its synthetic receptor agonists are increasingly acknowledged as valuable adjunct vasopressors or alternatives to catecholamines for patients who have intraoperative refractory arterial hypotension, severe septic shock, and different types of vasodilatory shock. AVP is also used as a vasopressor during CPR. The rationale for their use is relative AVP deficiency in these situations, and exogenously administered AVP can restore vascular tone and blood pressure, thereby reducing the need for the use of catecholamines. The extent to which these therapies may improve patient outcomes remains a subject of ongoing research.

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