Review

Science Review: Vasopressin and the cardiovascular system part 2 – clinical physiology

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Abstract

Vasopressin is emerging as a rational therapy for vasodilatory shock states. In part 1 of the review we discussed the structure and function of the various vasopressin receptors. In part 2 we discuss vascular smooth muscle contraction pathways with an emphasis on the effects of vasopressin on ATP-sensitive K^+ channels, nitric oxide pathways, and interaction with adrenergic agents. We explore the complex and contradictory studies of vasopressin on cardiac inotropy and coronary vascular tone. Finally, we summarize the clinical studies of vasopressin in shock states, which to date have been relatively small and have focused on physiologic outcomes. Because of potential adverse effects of vasopressin, clinical use of vasopressin in vasodilatory shock should await a randomized controlled trial of the effect of vasopressin's effect on outcomes such as organ failure and mortality.

Keywords adrenergic agents, antidiurectic hormone, cardiac inotropy, hypotension, nitric oxide, oxytocin, physiology, potassium channels, receptors, septic shock, smooth muscle, vascular, vasoconstriction, vasodilation, vasopressin

Introduction

Vasopressin is a hormone that is essential for both osmotic and cardiovascular homeostasis. A deficiency in vasopressin exists in some shock states and replacement of physiologic levels of vasopressin can restore vascular tone. Vasopressin is therefore emerging as a rational therapy for shock. Preliminary studies [1–12] show that infusion of low-dose vasopressin in patients who have vasodilatory shock decreases norepinephrine (noradrenaline) dose requirements, maintains blood pressure and cardiac output, decreases pulmonary vascular resistance, and increases urine output. Thus, low-dose vasopressin could improve renal and other organ function in septic shock. Paradoxically, vasopressin has also been demonstrated to cause vasodilation in some vascular beds, distinguishing this hormone from other vasoconstrictor agents.

The present review explores the vascular actions of vasopressin. In part 1 of the review we discussed the signaling pathways, distribution of vasopressin receptors, and the structural elements responsible for the functional diversity found within the vasopressin receptor family. We now explore the mechanisms of vasoconstriction and vasodilation of the vascular smooth muscle, with an emphasis on vasopressin interaction in these pathways. We discuss the seemingly contradictory studies and some new information regarding the actions of vasopressin on the heart. Finally, we summarize the clinical trials of vasopressin in vasodilatory shock states and comment on areas for future research.

Vascular smooth muscle contraction pathways and vasopressin interaction

Vasopressin restores vascular tone in vasoplegic (catecholamine-resistant) shock states by at least four known mechanisms [13]: through activation of V_1 vascular receptors (V_1Rs); modulation of ATP-sensitive K^+ channels (K_{ATP}); modulation of nitric oxide (NO); and potentiation of adrenergic

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ANP = atrial natriuretic peptide; IP_3 = inositol trisphosphate; K_{ATP} = ATP-sensitive K^+ channel; NO = nitric oxide; NOS = nitric oxide synthase; OTR = oxytocin receptor; SVR = systemic vascular resistance; V_1R = V_1 vascular receptor; V_2R = V_2 renal receptor.

and other vasoconstrictor agents. A short discussion of vascular smooth muscle contraction pathways is necessary to understand the interaction of vasopressin.

All muscle cells use calcium as a signal for contraction. Vascular smooth muscle cells are regulated by a variety of neurotransmitters and hormones; these interact with a network of signal transduction pathways that ultimately affect contractility either by affecting calcium levels in the cell or the response of the contractile apparatus to calcium. Calcium levels are increased by extracellular entry via voltage-gated calcium channels and by release from intracellular stores. At high cytosolic concentrations, calcium forms a complex with calmodulin that activates a kinase, which phosphorylates the regulatory light chain of myosin. Phosphorylated myosin activates myosin ATPase by actin and the cycling of myosin cross-bridges along actin filaments, which contracts the muscles. Vasodilation occurs when a kinase interacts with myosin phosphatase, which dephosphorylates myosin and prevents muscle contraction [14].

Vasopressin, norepinephrine, and angiotensin II act on cell surface receptors that couple with G-proteins to effect vasoconstriction. Vasopressin interacts with V_1Rs, which are found in high density on vascular smooth muscle, through the $G_{q/11}$ pathway to stimulate phospholipase C and produce the intracellular messengers inositol trisphosphate (IP_3) and diacylglycerol. These second messengers then activate protein kinase C and elevate intracellular free calcium to initiate contraction of vascular smooth muscle. In contrast, vasodilators such as atrial natriuretic peptide (ANP) and NO activate a cGMP-dependent kinase that, by interacting with myosin phosphatase, dephosphorylates myosin and thus prevents muscle contraction [14]. The opposing influences of these pathways are important in determining the functional state of vascular smooth muscle, and integration of this signaling is a key component in vascular homeostasis [15].

A key mechanism by which vascular smooth muscle tone is controlled is through K^+ channels [16]. The resting membrane potential of vascular smooth muscle ranges from $-30\,mV$ to $-60\,mV$. A more positive potential (depolarization) opens voltage-gated calcium channels, increasing cytosolic Ca^{2+} concentration, and induces vasoconstriction. Conversely, hyperpolarization closes these channels, decreases cytosolic Ca^{2+} concentration, and induces vasodilation [13]. The membrane potential of vascular smooth muscle is controlled by a number of ion transporters and channels, particularly K^+ channels. The opening of K^+ channels allows an efflux of potassium, thus hyperpolarizing the plasma membrane and preventing entry of calcium into the cell [16], even in the presence of vasoconstrictor agents [17].

Four types of K^+ channels have been described (Table 1) [16]. Of these, the K_{ATP} channel is the best understood and plays a critical role in disease states such as vasodilatory shock. K_{ATP} channels are physiologically activated by decreases in cellular ATP and by increases in the cellular concentrations of hydrogen ion and lactate [18,19]. This activation prevents opening of voltage-gated Ca^{2+} channels and contributes to the vasoplegia (resistance to catecholamines) that is seen in shock states.

Activation of K_{ATP} channels is a critical mechanism in the hypotension and vasodilation that are characteristic of vasodilatory shock. Agents that close K_{ATP} channels (such as sulfonylureas) have been shown to increase arterial pressure and vascular resistance in vasodilatory shock due to hypoxia [20], in septic shock [20–22], and in the late, vasodilatory phase of hemorrhagic shock [23]. An important mechanism by which vasopressin restores vascular tone in vasoplegic (catecholamine-resistant) shock states may be its ability to close K_{ATP} channels [24].

Another mechanism by which vasopressin exerts vascular control is through modulation of NO. The latter contributes to the hypotension and resistance to vasopressor drugs that occurs in vasodilatory shock. The vasodilating effect of NO is mediated mainly by the activation of myosin light-chain phosophatase. However, NO also activates K^+ channels in the vascular smooth muscle [25,26]. Agents that block NO synthesis during septic shock increase arterial pressure and decrease the doses of vasoconstrictor catecholamines needed to maintain arterial pressure [27]. Vasopressin may restore vascular tone in vasodilatory shock states by blunting the increase in cGMP that is induced by NO [28] and ANP [29], and by decreasing the synthesis of inducible nitric oxide synthase (NOS) that is stimulated by lipopolysaccharide [28]. This inhibition occurs via the V_1R [30,31].

Vasopressin potentiates the vasoconstrictor effects of many agents, including norepinephrine [32,33] and angiotensin II [34–36]. The underlying mechanism of this is unknown but possibilities include coupling between G-protein-coupled receptors [36], interaction between G-proteins, and interference with G-protein-coupled receptor downregulation through arrestin trafficking.

Vasopressin has been demonstrated to cause vasodilation in numerous vascular beds [37–44] – a feature not shared by other vasoconstrictor agents. The mechanism of vasodilation has been demonstrated to be due to activation of endothelial oxytocin receptors (OTRs) [45], which in turn trigger activation of endothelial isoforms of NOS.

Whether vasopressin causes vasoconstriction or vasodilation depends on the vascular bed studied [46], which may, in turn, depend on the receptor density (V_1R versus OTR), the model studied, the dose of vasopressin [47], and the duration of exposure to the hormone [48]. Indeed, the opposing influences of various pathways that determine the functional state of vascular smooth muscle is an area for further study. For

Table 1

Potassium modulation of arterial smooth muscle tone

Channel	Vasoconstriction: close		Vasodilation: open	
	Effector	Artery	Effector	Artery
K_V	Angiotensin II	Pulmonary	Prostacyclin	Cerebral
	Histamine	Coronary	β-Adrenoreceptor	Portal vein, cerebral
	Hypoxia	Pulmonary		
K_{ATP}	Vasopressin	Mesenteric	Adenosine	Coronary
	Angiotensin II	Mesenteric and coronary	Calcitonin-GRP	Mesenteric, coronary and renal
	Endothelin	–	Acidosis, lactate	Cerebral
	Norepinephrine	–	Nitric oxide	–
	Histamine	–	Vasactive intestinal peptide	–
	Serotonin	–	Prostacyclin	–
	Neuropeptide Y	–	Hypoxia	Coronary
	Hypoxia	Pulmonary		
BK_{Ca}	Angiotensin II	Coronary	β-Adrenoreceptor	Coronary, aorta
	Thromboxane a_2 agonist	Coronary	Nitric oxide	Basilar
	Endothelin	Coronary	Atrial natriuretic peptide	–
			C-type natriuretic peptide	–
K_{IR}			Potassium	Cerebral, coronary

K^+ channels contribute importantly to the resting membrane potential of smooth muscle and thus regulate the intracellular calcium level. When K^+ channels are closed (depolarized), voltage-gated calcium channels open and cytosolic calcium concentrations rise, leading to vasoconstriction. Agents that open (hyperpolarize) K^+ channels cause vasodilation through inactivation of voltage-gated calcium channels and a decrease in intracellular calcium concentration [13]. Four types of K^+ channel have been described in vascular smooth muscle: voltage-activated K^+ channels (K_V); ATP-sensitive K^+ channels (K_{ATP}); Ca^{2+}-activated K^+ channels (BK_{Ca}); and inward rectifier (K_{IR}) channels [16]. The table summarizes what is known regarding the modulation of K^+ channels by vasoconstrictors and vasodilators on the various vascular beds. Note that hypoxia causes vasoconstriction of the pulmonary vasculature through K_V and K_{ATP} channels, and yet vasodilation of other vascular beds through K_{ATP} channels. K_{ATP} channels are particularly important in vasodilatory shock states and are hyperpolarized by pathologic conditions such as hypoxia, acidosis, and increased nitric oxide [13]. K_{ATP} channels can be depolarized (closed) by vasoconstrictors such as vasopressin and angiotensin II [16]. GRP, gene-related protein.

example, prolonged exposure to cAMP inhibits both angiotensin II and vasopressin-stimulated phosphoinositide hydrolysis and intracellular calcium mobilization [49]. Adenylyl cyclases present a focal point for signal integration in vascular smooth muscle, and type III adenylyl cyclase has been proposed as a key subtype for cross-talk between constrictor and dilator pathways [50]. The important question is whether vasopressin can cause simultaneous vasoconstriction of some vascular beds and vasodilation of others.

Vasopressin and the heart

The actions of vasopressin on the heart are complex and the studies are seemingly contradictory. Depending on the species studied, the dose used, and the experimental model, vasopressin can cause coronary vasoconstriction or vasodilation and exert positive or negative inotropic effects. In addition to its vascular effects on coronary blood flow, vasopressin also has mitogenic and metabolic effects on the heart.

Coronary vascular tone

The effect of vasopressin on the coronary vascular bed is controversial. Several investigators have demonstrated a V_1R-mediated coronary vasoconstrictor response to vasopressin [51–54] – an effect that appears to be dose dependent [55,56] and intensified by removal of endothelium [46]. In contrast, coronary vasodilation in response to vasopressin has been demonstrated in isolated canine [57,58] and primate [44] coronary arteries. More recently, vasopressin was demonstrated to cause coronary vasodilation in an intact animal model. A bolus injection of vasopressin significantly increased the vascular diameter of the left anterior descending artery in pigs [59]. This vasodilation was present during sinus rhythm, ventricular fibrillation, and after successful cardiopulmonary resuscitation. Vasopressin probably effects coronary vasodilation through control of endothelial tone [58], as has been demonstrated in the pulmonary vasculature [39].

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A difference between the 'normal' and stressed heart in their responses to vasopressin has been reported, with vasoconstriction seen in normoxic state and vasodilation seen during hypoxia [60]. Using an isolated working rat heart model, high-dose vasopressin (777 ± 67 pg/ml) reduced coronary flow by 38.4 ± 2.6% in normoxic hearts. Myocardial function was also significantly decreased by vasopressin. In contrast, the same dose of vasopressin administered to hypoxic hearts resulted in a smaller decrease in coronary blood flow (−11.5 ± 2.8%) and an improvement in myocardial function. Interestingly, in hearts treated first with vasopressin and then with hypoxia, there was a greater degree of coronary vasodilation as compared with that observed in hearts treated with hypoxia alone. These results indicate that the vasoconstrictor effect of vasopressin on the coronary vessels, as well as its effect on the myocardium, may be dependent on oxygen tension and possibly on the redox state of the cell. In addition, vasopressin-constricted vessels appear to retain considerable vasodilatory reserve, despite evidence of ischemic conditions [60].

Several preclinical studies have evaluated vasopressin in animal models of cardiac arrest [61–64]. These studies suggested that vasopressin leads to superior resuscitation rates as compared with epinephrine (adrenaline). The improvement in restoration of spontaneous circulation is partially ascribed to an improvement in coronary blood flow [65]. However, in the setting of cardiac arrest, the improvement in coronary blood flow is probably mediated by an improvement in coronary perfusion pressure as opposed to vasopressin-mediated coronary vasodilation.

Inotropy

Studies of the inotropic effects of vasopressin are also controversial, and the effects appear to depend on the dose used and the model studied. In a study of an isolated working rat heart model, investigators found that high-dose vasopressin (878 pg/ml) produced significant decreases in coronary flow, myocardial oxygen consumption and left ventricular peak systolic pressure, and a small decrease in cardiac output [55]. Similarly, intracoronary infusion of vasopressin-dextran (a method employed to keep the vasopressin in the vascular compartment) in isolated perfused guinea pig hearts caused coronary vasoconstriction and negative inotropy – effects that were blocked with vasopressin antagonists and P_2 purinergic receptor antagonist [66]. These results were duplicated in conscious dogs, in which an infusion of low-dose vasopressin (15 pg/ml) caused significant increases in left ventricular end-systolic pressure, end-systolic volume, total systemic resistance, and arterial elastance, whereas the heart rate and stroke volume were decreased. There was no significant change in coronary sinus blood flow. Vasopressin decreased the slope of the left ventricular end-systolic pressure–volume relation, the maximal first derivative of left ventricular pressure/end-diastolic volume relation, and the stroke work–ventricular end-diastolic relation, and shifted the relations to the right, indicating a depression of left ventricular performance

[67]. The relevance of these observations in the setting of vasodilatory shock in humans, however, is not known.

It is often difficult to isolate the effects of vasopressin on inotropy from its effects on coronary blood flow. Indeed, when attempts were made to study the effects of vasopressin on the heart independently of coronary blood flow, the effects of vasopressin on inotropy were strikingly different. By maintaining constant coronary flow, the direct cardiac effects of vasopressin on an isolated rat heart preparation were determined, independent of changes in myocardial oxygen delivery elicited by coronary vasoconstriction [56]. Myocardial function was assessed at vasopressin concentrations of 0, 10, 25, 50, 100, 200, 400, and 500 pg/ml. Progressive coronary vasoconstriction was observed with increasing vasopressin concentration. In contrast, peak ventricular pressure and the first derivative of left ventricular pressure (dP/dt_{max}) increased at 50 and 100 pg/ml vasopressin but fell at 400 and 500 pg/ml. The maximal peak ventricular pressure and dP/dt_{max} responses were at 50 pg/ml, whereas at 500 pg/ml both peak ventricular pressure and dP/dt_{max} were reduced below control. Pretreatment with a specific V_1R antagonist totally blocked both the coronary vasoconstrictor and contractility responses to vasopressin. These data suggest that, although vasopressin causes dose-related coronary vasoconstriction and negative inotropy at high vasopressin concentrations, the hormone may exert a net positive inotropic effect at low doses. It appears that the net effect of vasopressin on cardiac function in an intact preparation will depend on the concentration of vasopressin as well as on the relative balance of its effects on coronary perfusion pressure (diastolic blood pressure), coronary vascular tone, and any direct effects on the inotropic state of the myocardium.

The clinical observation that vasopressin greatly increases afterload in vasodilatory shock (systemic vascular resistance [SVR] nearly doubles) but depresses cardiac output relatively little (14%) led to speculation that vasopressin at low doses might have positive inotropic effects [3]. Furthermore, in a small trial of vasopressin in patients with heart failure and vasodilatory hypotension due to the phosphodiesterase inhibitor milrinone, vasopressin increased SVR but did not depress cardiac output [68], again suggesting a positive inotropic action. However, these conclusions are speculative because it is difficult to isolate the effects of vasopressin on contractility from its effects on coronary perfusion, heart rate, and ventricular preload. Of more importance is the net clinical benefit of these often contradictory actions. An observational study conducted in critically ill humans specifically examined the effects of low-dose vasopressin infusion on hemodynamics and cardiac performance [69]. In 41 patients with catecholamine-resistant postcardiotomy shock, continuous infusion of vasopressin was associated with a significant increase in left ventricular stroke work index and a significant decrease in heart rate, as well as vasopressor and inotropic requirements. Cardiac index and stroke volume remained

unchanged despite a significant reduction in the requirement for inotropic agents. Interestingly, myocardial enzymes significantly fell in all patients and many patients with atrial arrhythmias converted on infusion. The authors concluded that low-dose vasopressin improved myocardial performance in this group of patients.

Classically, the effects of vasopressin on the heart were thought to be mediated through the V_1R (vascular smooth muscle/calcium-dependent effect) or OTR (endothelial/NO effect). Neonatal rat cardiomyocytes possess V_1Rs [70], and vasopressin causes a dose-dependent increase in intracellular calcium, which is dependent on extracellular magnesium and calcium concentrations, secondary to V_1R activation and phospholipase-mediated IP_3 generation [71]. The V_1R also mediates prostacyclin and ANP release from cultured rat cardiomyocytes exposed to vasopressin [72]. OTRs were also identified in isolated rat heart, and oxytocin causes increased ANP release in perfused rat heart preparations [73]. The negative inotropic and chonotropic effects of oxytocin may be mediated by these cardiac OTRs. Blockade of cholinergic receptors and NO production attenuated the negative effects of oxytocin on cardiac function [74]. More recently it was suggested that the cardiac effects of vasopressin are due to selective activation of intravascular purinoceptors and that an intermediary of these effects is ATP [66]. Indeed, adenoviral gene transfer of the V_2 renal receptor (V_2R) into cardiomyocytes was shown to modulate the endogenous cAMP signal cascade and increase contractility of rat cardiomyocytes [75].

In the setting of primary cardiac dysfunction, however, it is the effect of vasopressin on SVR that may counter any potential beneficial effects on cardiac inotropy. Indeed, antagonism of vasopressin receptors has been advocated as therapy for congestive heart failure; both animal models of congestive heart failure and early clinical studies support the notion that antagonism of V_1Rs and V_2Rs leads to an improvement in cardiac function, probably mediated through reductions in cardiac afterload [76–78].

Cardiac hypertrophy

Vasopressin promotes cardiac hypertrophy in neonatal rat hearts via direct effects on cardiomyocyte protein synthesis secondary to IP_3-mediated intracellular calcium release [79]. In the adult rat heart, vasopressin directly increased the rate of protein synthesis via the V_1R, which was sensitive to amiloride – a mechanism that differs from the cAMP-dependent mechanism that is responsible for the cardiac hypertrophy induced by pressure overload [80].

Summary

V_1R-mediated coronary vasoconstriction is a dose-dependent phenomenon that may be attenuated by the endothelial vasodilating properties of vasopressin action via the OTR or P_2 purinergic receptor. When cardiac contractility is studied independently of coronary perfusion, vasopressin may have a positive inotropic effect at low doses. Further work is necessary to determine the significance of these observations in human hearts in both health and disease states.

Clinical application of vasopressin in shock

In health, vasopressin's role in the maintenance of resting arteriolar tone and systemic blood pressure is minor. Indeed, high concentrations of vasopressin are required before vasoconstrictor effects are seen. It is only during shock states that vasopressin's role in the maintenance of systemic blood pressure is seen. Indeed, vasopressin deficiency and hypersensitivity to the hormone's pressor effects appear to be a hallmark of vasodilatory shock states [13]. These states include vasodilatory septic shock [1–5], vasodilatory shock post-cardiopulmonary bypass [6–9,81], vasodilatory shock due to phosphodiesterase inhibition in the treatment of heart failure [12,68], hemodynamically unstable organ donors [11], and the late, so-called 'irreversible' phase of volume treated hemorrhagic shock [82]. The reason for the reduction in circulating concentration of vasopressin has not been fully determined. However, depletion of of neurohypophyseal stores has been observed in profound shock states [83].

The use of vasopressin clinically has followed observations that exogenous administration of vasopressin during shock is capable of restoring systemic blood pressure. Landry and coworkers [4] first demonstrated this property in five patients with advanced septic shock. Since their initial observations, several uncontrolled trials have demonstrated that vasopressin can restore blood pressure during septic shock, following cardiopulmonary bypass and following epinephrine-resistant cardiac arrest (Table 2). However, few controlled studies have been performed to evaluate properly the effectiveness of vasopressin in shock. This is a critical point because it cannot be inferred that if an agent restores blood pressure then it will also lead to an improvement in outcome. An increase in blood pressure may be being obtained at the expense of perfusion to critical organs, or it may worsen cardiac performance by impairment of ventricular output through an increase in ventricular afterload. Consequently, organ injury could worsen in the face of a restoration of blood pressure. A case in point is the manner in which NOS inhibition was embraced to treat shock in septic patients [84]. Indeed, NOS inhibitors have clinical effects that are similar to those of vasopressin. Several reports have documented an increase in blood pressure, reduction in pressor requirement, and attendant reduction in cardiac output [84–86] (a profile that resembles that of vasopressin) in patients with septic shock. However, a recent randomized controlled trial of a NOS inhibitor in septic shock was halted because of higher mortality rates in the group that received treatment [87].

At present the only blinded, systematic evaluation of vasopressin in sepsis is that recently reported by Patel and coworkers [2]. In a controlled manner, they compared the effects of vasopressin with those of norepinephrine in

Table 2

Clinical trials of low-dose vasopressin in vasodilatory shock states

Reference	Year	Trial	*n*	Patients	Findings
[4]	1997	Case series	5	Septic shock	A, B, C
[3]	1997	Matched cohort	19 12	Septic shock Cardiogenic shock	A, B, D in septic group
[5]	1999	RCT	10	Septic shock – trauma	A, B
[2]	2000	RCT	24	Septic shock	A, B, C, D
[94]	2001	Retrospective	60	Septic and postcardiotomy shock	A, B, ↓CI
[95]	2001	Prospective, case-controlled	16	Septic shock	A, B, C
[7]	1998	Retrospective case series	40	Postbypass vasodilatory shock	A, B, D
[6]	1997	RCT Placebo: N/S	10	Vasodilatory shock post-LVAD implant	A, B in treatment arm; D in all
[8]	1999	Case series	20	Vasodilatory shock post-cardiac transplant	A, B
[9]	1999	Case series	11	Pediatric – vasodilatory shock postbypass	A, B, D
[10]	2000	Retrospective case series	50	Vasodilatory shock post-LVAD implantation	A, B
[69]	2002	Retrospective	41	Postcardiotomy shock	A, B
[11]	1999	Case series	10	Organ donors with vasodilatory shock	A, D
[68]	2000	Case series	7	Milrinone – hypotension	A, B, C

Findings are classified as follows: A, increase in blood pressure; B, decrease or discontinuance of catecholamines; C, increase in urine output; and D, low plasma vasopressin levels in subjects. CI, cardiac index; LVAD, left ventricular assist device; N/S, normal saline; RCT, randomized controlled trial.

24 patients with septic shock who required vasopressor infusions. Patients who received vasopressin had a significant (80%) reduction in vasopressor requirement. Interestingly, patients in the vasopressin arm experienced a doubling in urine output and a 75% increase in creatinine clearance. Based on current information, it appears that replacement of vasopressin at a fixed dose can eliminate the need for catecholamine pressors in many patients.

Vasopressin was also evaluated in the setting of hypotension following induction of anesthesia in patients chronically treated with angiotensin-converting enzyme inhibitors [88,89]. One study compared terlipressin (a vasopressin agonist) plus ephedrine (*n*=21) versus ephedrine alone (*n*=19) in patients following induction of anesthesia [88]. The second study evaluated vasopressin (*n*=13) compared with placebo (*n*=14) in patients following cardiac bypass [89]. Both studies demonstrated that the vasopressin agonist led to better hemodynamic stability and less catecholamine use. Consequently, in patients who are refractory to conventional vasopressors (owing to chronic blockade of their renin–angiotensin system), vasopressin may offer some clinical benefit in improving hemodynamics. Indeed, the study conducted by Morales and coworkers [89] demonstrated that, among those patients chronically treated with angiotensin-converting enzyme inhibitors, the group that received vasopressin had a shorter duration of stay in the intensive care unit following induction of anesthesia. These studies must be repeated in order to evaluate these highly relevant end-points and to confirm the safety of vasopressin before widespread clinical use of this agent can be recommended.

Vasopressin has also been demonstrated to increase arterial and coronary perfusion pressure as compared with clinical doses of epinephrine in animal models of cardiac arrest. Interestingly, like epinephrine, vasopressin may also be administered via the endotracheal tube. In fact vasopressin had better hemodyamic effects than did intratracheal epinephrine in one study of a canine model of cardiac arrest [90]. Based on these favorable reports, vasopressin has been advocated for use in cardiac arrest. In 1997, Lindner and coworkers [91] reported the effects of 40 units of vasopressin versus 1 mg epinephrine in patients who had not responded to three counter-shocks in the field. Fourteen (70%) patients in the vasopressin group versus seven (35%) patients in the epinephrine group survived to hospitalization. However, in a more recent study of vasopressin in cardiac arrest, no benefit over epinephrine was found [92]. That study evaluated vaso-

pressin versus epinephrine as the first agent given in 200 patients who suffered in-hospital cardiac arrest. The investigators found that there was no advantage with either agent with respect to 1-hour survival or survival to hospital discharge. Importantly, there was no difference between groups in Mini Mental Status Examination or cerebral performance category scores. The reason for the discrepancy between the two studies is unclear. One explanation is differences between the two populations evaluated. Lindner and coworkers [91] evaluated patients who suffered a cardiac arrest out of hospital, whereas Steill and coworkers [92] evaluated hospitalized patients. Hospitalized patients may have a different prognosis after cardiac arrest than that of their counterparts in the community. Similarly, the etiology of the cardiac arrest may also have differed between the two groups, with more patients having a primary cardiac event in the community.

Administration of vasopressin to patients in low flow states (i.e. cardiogenic or hypovolemic shock) is strongly contraindicated because in these states cardiac output is severely depressed by the increase in afterload. Indeed, blockade of V_1Rs and V_2Rs has been advocated for treating congestive heart failure. In a rat model of congestive heart failure a single oral administration of conivaptan (a V_1R and V_2R blocker) increased urine volume and decreased urine osmolality in a dose-dependant manner [77]. Furthermore, conivaptan attenuated the changes in left ventricular end-diastolic pressure, and lung and right ventricular weight. The investigators stressed that vasopressin plays a significant role in elevating vascular tone through vasopressin V_1Rs and plays a major role in retaining free water through V_2Rs in this model of congestive heart failure.

In summary, the use of vasopressin at a low dose (0.04 units/min) is not associated with substantial decline in cardiac output. Vasopressin does not constrict the pulmonary circulation, and thus vasopressin may be preferred for patients with pulmonary hypertension. In this respect vasopressin differs from NOS inhibitors. It is hoped that, unlike early trials of NOS inhibition in sepsis, vasopressin's more favorable hemodynamic profile will translate into clinical benefit. Also, vasopressin's selective constriction of renal efferent over afferent arterioles could spare renal function in shock. Hopefully, the results of an active multicenter randomized controlled evaluation [93] will help to determine the role of vasopressin in septic shock.

Conclusion

Vasopressin is a unique vasoactive hormone that is important in control of vascular tone and has myocardial effects. Vasopressin can restore vascular tone in refractory vasodilatory shock states due to V_1R activation of K_{ATP} channels, inhibitory action on NO, and potentiation of endogenous vasoconstrictors. Although animal and *in vitro* studies suggest that vasopressin may have negative inotropic and coronary vasoconstrictor properties, clinical studies of low-dose vasopressin to date do not demonstrate adverse cardiac effects of vasopressin. In refractory shock states, administration of vasopressin in low, physiologic doses has been associated with impressive stabilization of hemodynamics. Vasopressin is gaining popularity in diverse states such as septic shock and vasodilatory states associated with cardiac anesthesia and surgery. We stress that the clinical studies to date have been small and have focused on physiologic outcomes, and data on adverse effects are limited. Therefore, we do not recommend vasopressin as first-line therapy for vasodilatory shock. Future prospective studies are necessary to define the role of vasopressin in the therapy of vasodilatory shock.

Competing interests

None declared.

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