Netherlands
The Journal of Medicine

Vasopressin: physiology and clinical use in patients with vasodilatory shock: a review

D.T. den Ouden*, A.E. Meinders

Department of General Internal Medicine, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, the Netherlands, e-mail: D.T.den_Ouden@lumc.nl, *corresponding author

ABSTRACT

Vasopressin is a nonapeptide synthesised in the hypothalamus and released upon stimulations such as hyperosmolality, hypotension and hypovolaemia. In acute shock states serum vasopressin levels increase rapidly and decrease in prolonged septic shock. The administration of vasopressin in healthy subjects has little effect, whereas in vasodilatory shock it increases the mean arterial pressure through V1 receptors and decreases the cardiac output. Vasopressin stimulates the V2 receptors in the kidney leading to reabsorption of water through aquaporin 2. However, in vasodilatory shock the antidiuretic effects are overcome by the effect vasopressin has on the kidneys: improvement of renal blood flow leading to water excretion. Twenty-four studies on the use of vasopressin in patients with vasodilatory shock are reviewed. They show that vasopressin potentiates norepinephrine effects, increases blood pressure significantly in patients with vasodilatory shock and may improve renal function. Side effects ranging from ischaemic skin lesions to possible intestinal ischaemia should not be underestimated. Above a dose of 0.04 U/min it may lead to cardiac arrest. Effects on mortality cannot be interpreted from these studies. Broad clinical use should await controlled trials to clarify its effects on clinical outcomes such as organ failure and mortality.

INTRODUCTION

In intensive care medicine vasopressin is reserved for patients with severe vasodilatory shock who are already receiving norepinephrine and still have hypotension, although it is used with the greatest caution because of the possible side effects.

In this review the physiology of vasopressin and its effects *in vitro* and in animal models are discussed. Thereafter a discussion is presented of the literature on studies with vasopressin treatment in patients with septic shock or vasodilatory shock of other origin. The goal of this review is to provide some insight into the current place of vasopressin in patients with vasodilatory shock.

PHYSIOLOGY AND EFFECTS OF VASOPRESSIN

Production and release of vasopressin

Vasopressin is a nonapeptide, which is synthesised in magnocellular neurons of the paraventricular and supraoptic nuclei in the hypothalamus.[1] Its production depends on vasopressin gene (chromosome 20p13) transcription, which increases on either hypertonic conditions, hypotension or hypovolaemia. From the magnocellular neurons the prohormone of vasopressin, consisting of vasopressin, vasopressin-associated neurophysin and a glycopeptide, is transported down long axons to the pars nervosa of the posterior pituitary where it is stored in granules. After stimulation, a generated action potential causes a calcium influx, followed by neurosecretory granule movement and release of vasopressin from the complex molecule with neurophysin and glycopeptide. The granules fuse with the cell membrane and extrude its contents into the perivascular space and the posterior pituitary capillary system.[2,3] The pituicytes surrounding axon terminals in the posterior

© 2005 Van Zuiden Communications B.V. All rights reserved.

pituitary remove an immediate barrier between the axons and the perivascular space by retracting, thus facilitating diffusion of peptides into capillaries.[4,5] Control of hormone synthesis resides at the level of transcription; after transcription the mRNA is increased and vasopressin released.[6,7] The axonal transport is a regulated process linked to vasopressin synthesis, as shown in rat models.[8]

Vasopressin release is mainly stimulated by hyperosmolality and hypotension or hypovolaemia, as well as acidosis, pain, hypoxia, hypercapnia and vomiting.[9] Low central venous pressure alone in for instance slightly dehydrated people is not a trigger for releasing vasopressin; at least a 10% reduction in circulating volume is necessary to release vasopressin.[1]

The amount of vasopressin stored is enough for several days; however it appears that during prolonged shock states the amount stored does not meet the amount of vasopressin required. In both animals and humans in shock, the vasopressin levels first rise to supranormal levels and then decrease as the shock state persists. Three reasons can be found for this: firstly the depletion of neurohypophyseal stores of vasopressin, secondly autonomic insufficiency or high concentrations of norepinephrine which both have a central inhibitory effect on vasopressin release[10,11] and thirdly the nitric oxide inhibiting vasopressin production.[12]

MRI scans have shown, in both animals and humans, that a decreased vasopressin production accounts for at least some part of the vasopressin shortage. In patients with septic shock and inappropriately low vasopressin levels, brain MRIs performed to exclude brain damage for other reasons showed a depletion of vasopressin stores in the posterior pituitary.[10] Also, in animal studies prolonged and intense stimulation of vasopressin release by dehydration or salt loading produced a depletion of stored hormone in the posterior pituitary.[7,13-16]

Vasopressin is rapidly metabolised by liver and kidney vasopressinases and has a half-life of 10 to 35 minutes.[17] Normal vasopressin levels are 0.5 to 5 pg/ml in overnight fasted, hydrated humans.[18,19] Water deprivation increases plasma osmolality and raises vasopressin to 10 pg/ml,[20] whereas in acute shock states the level rises to 100 to 1000 pg/ml (dogs, monkeys)[21-23] and decreases in prolonged septic shock to ±3.1 pg/ml in humans.[24] Gradual recovery of the vasopressin stores in the pituitary occurs over several days.[25]

Vasopressin acts on the different vasopressin receptors: the V1 receptor, mainly causing vasoconstriction, the V2 receptor, regulating the water balance, and the V3 receptor, which stimulates corticotropin (ACTH). This subject will be discussed in more depth in following paragraphs.

Baroreflex and vasopressin

There has been much research about the exact trigger that releases the (high) amounts of vasopressin in response to circulatory failure. Plasma vasopressin does not increase in severe hypovolaemia until it causes a steep fall in the arterial pressure. The evidence suggests that it is the sudden unloading of arterial baroreceptors that triggers the surge in vasopressin secretion. These high pressure arterial baroreceptors are located in the carotid sinus and aortic arch. Low-pressure volume receptors are present in the atria and pulmonary venous system.[26,27] Afferent signals from these receptors are carried from the chest to the brain stem through cranial nerves IX and X to the hypothalamus. It has been established that vasopressin release is higher if the tonic inhibitory baroreceptor input is diminished or absent. This is the case in animal laboratory studies in which baroreflex denervation was performed and in septic shock, where the baroreflex system is diminished or even abolished.[28] The administration of vasopressin in healthy animals with intact baroreflex receptors produced stable mean arterial blood pressure (MAP), lower cardiac output (CO) and higher peripheral resistance, whereas baroreflex denervated animals showed a remarkable increase in MAP and stable CO at low vasopressin concentrations (0.017 μU/kg) and remained stable until much higher infusion rates of vasopressin. These experiments led to the theory that baroreceptors and volume receptors normally inhibit magnocellular neurons and that absence of this counter-regulation results in the release of vasopressin.

A rise in vasopressin levels does not disrupt osmoregulation because hypotension increases the plasma osmolality-vasopressin relationship so that higher plasma vasopressin levels are required to maintain normal osmolality.[19,29] There is, however, animal experimental research that says that baroreceptor denervation produces a state of heightened osmotic sensitivity for vasopressin neurons with evidence for increased central vasopressin release to both direct and peripheral hypertonic saline stimulation.[30]

Blood pressure and vasopressin

Vasopressin has a vasoconstricting effect by four known mechanisms:[31] activation of V1 vascular receptors, modulation of ATP-sensitive K^+-channels (K_{ATP}), modulation of nitric oxide and potentiation of adrenergic and other vasoconstrictor agents. The effect of vasopressin through V1 receptors is mediated by the phosphotidylinositol pathway. *In vitro*, the action of vasopressin on different types of vessels varies with the particular type or location of the vessel by heterogeneity of the V1 receptor.[32] Under normal circumstances, vasopressin generally induces an endothelium-independent contraction of the vessels by acting on the smooth muscle myocyctes and potentiates the norepinephrine effect. In intracerebral arterioles of rats, increasing concentrations of vasopressin appeared to induce a triphasic response of vasodilatation, vasoconstriction and vasodilatation.[33] The vasodilatation was endothelium dependent, whereas the constriction was not.

Vasodilatation as found in the intracerebral arterioles of rats also occurred in experiments with human forearms, in human pulmonary arteries and veins, and isolated basilar and left circumflex coronary arteries of dogs.[34-36] Experiments indicated that the vasodilatory effect is nitric oxide (NO) dependent.

Sepsis causes a downregulation of V1 receptors, an effect mediated through proinflammatory cytokines.[37] Endotoxins, through cytokines, initiate a vasodilatory effect on the vessels, which is nitric oxide mediated, for the NO synthase inhibitor NMA attenuates the effect. If animals or vessels alone are subjected to an endotoxin load, the norepinephrine effect of vasoconstriction is quickly attenuated. The vasopressin vasoconstricting effect lasts several hours longer than norepinephrine and has a positive effect on the contracting abilities of norepinephrine.[38,39] The next mechanism through which vasopressin restores blood pressure is inhibition of K_{ATP} channels in the smooth muscle cells of the blood vessels. These channels are important in the development of hypotension and vasodilatation in response to decreases in cellular ATP and increases in the cellular concentration of hydrogen ion and lactate.[31]

In vivo vasopressin has little effect on blood pressure under normal circumstances at physiological concentrations. However, during hypovolaemia with decreasing arterial blood pressure the vasopressin release is heavily stimulated and strongly contributes to maintaining normal blood pressure. This is shown in experiments with haemorrhaging animals that develop hypotension and in animals with acute endotoxin shock, in which V1 receptor antagonists caused more profound hypotension.[40,41] Secondly, in hypotensive subjects strongly elevated levels of vasopressin are measured.[22,24] The haemodynamic responses on administered vasopressin in patients with advanced vasodilatory shock, however, are independent of baseline vasopressin concentrations,[42] suggesting that the vasopressin has a direct pharmacological effect, rather than the effect of only the replacement of the vasopressin deficiency. Despite the downregulation of the V1 receptors the vasopressin has vasoconstricting effects in these cases, which may be explained by the other three mechanisms through which vasopressin acts, as described above.

In situations where the baroreflex receptor system is impaired, for instance by cutting the nerve tracts or sepsis, the vasopressin effect is much more clear. The normally occurring leftward shift of the heart rate-arterial baroreflex curve through V1 receptors is absent and the vasopressin causes an increase in blood pressure, without increasing heart rate.[43,44]

In vivo in cases of septic shock, vasopressin is a powerful vasoconstrictor and potentiates the contracting abilities of epinephrine, which decrease in sepsis.[45] We will discuss the vasopressin effects in humans with vasodilatory shock in another paragraph.

The lungs and vasopressin

The lungs are organs on which vasopressin has a vasodilatory effect, in contrast to the rest of the body. Vasopressin significantly dilates arterial and venous lung segments in vasoconstricted rats through V1 receptors and NO.[46-48] Especially chronic hypoxic rats exhibited an augmented dilatory response to vasopressin compared with controls, which was due to enhanced dilation of precapillary segments.[49] Chronic hypoxia itself did not increase the NO synthase or vasodilatory effects. *In vitro* in canine pulmonary arteries and veins it was found that vasodilatation in veins is not only dependent on NO, but also prostaglandin I2.[50] A recent study by Leather in dogs, however, showed that vasopressin had a vasoconstricting effect in the lungs, leading to pulmonary hypertension.[51] So, although *in vitro* studies seem to show that vasopressin causes vasodilatation, this *in vivo* study shows possible pulmonary hypertension. Future long-term studies in humans will provide more insight into the reaction of the human pulmonary system to vasopressin.

The heart and vasopressin

As mentioned before, cardiac output decreases in the presence of vasopressin doses used in animals or humans with shock. Again, vasopressin acts through V1 receptors, which initiate coronary vasoconstriction and impaired cardiac relaxation, thus regulating cardiac function and myocardial perfusion.[52] V1 receptor activation probably has a positive inotropic effect due to an increase in calcium levels in the cardiac myocytes.[53] This seems contradictory to the fact that the CO decreases with vasopressin, but the positive inotropic effect might not be large enough to overcome the diminished coronary perfusion and impaired relaxation. If exposed to prolonged V1 receptor stimulation, the cardiomyocytes increase protein synthesis, leading to hypertrophy and cardiac remodelling.[54] Higher doses of vasopressin administered in vasodilatory shock in one study[55] led to cardiac arrest in six out of fifty patients. One case report mentions myocardial ischaemia intraoperatively in a hypotensive patient after administering 1 mg of terlipressin.[56]

The brain and vasopressin

Vasopressin has different effects on the several brain arteries. It is usually a powerful vasoconstrictor in larger cerebral arteries, acting through V1 receptors, as tested in isolated rings from medial cerebral arteries.[57] However, in experiments with dogs vasopressin and oxytocin dilated the basilar arteries through NO.[58] In experiments with rat intracerebral arterioles increasing concentrations of vasopressin induced the triphasic response of vasodilatation, vasoconstriction and vasodilatation, in which the vasodilatation was again endothelium and NO dependent.[33] It was hypothesised that vasopressin may constrict

smaller cerebral arterioles while dilating larger ones. Through the V3 receptor in the anterior pituitary gland vasopressin has a stimulatory effect on the release of corticotropin (ACTH), a process that also seems NO dependent. Corticotropin releasing factor (CRF), produced by the parvicellular division of the paraventricular nucleus, is necessary to maintain the ACTH secretion capacity.[59] Experiments in cattle showed that during induced sepsis, V3 and CRF1 receptor mRNAs are downregulated in the anterior pituitary, possibly resulting in a decreased ACTH secretion.[60] V3 receptors are also found in several peripheral tissues, such as kidney, adrenal medulla, pancreas, thymus, heart, lung, spleen, uterus and breast.[61] Its function there is not quite clear; it is however to be expected that there might be a local effect rather than a systemic one.

The kidneys, aquaporins and vasopressin

In the kidneys, water is mainly absorbed in the loop of Henle and the collecting duct, which is the more important site. In the collecting duct, vasopressin increases water permeability through V2 receptors, which are located on the principal cells of the collecting ducts. After stimulation of the V2 receptor, adenylate cyclase is generated, followed by an increase of intracellular c-AMP. c-AMP then causes fusion of aquaporin 2 (AQP-2) containing intracytoplasmic vesicles with the apical plasma membrane of the principal cell, thus reabsorbing water.[1,62,63] This system can be regulated quickly, depending on the amount of vasopressin secreted. If, however, the state of dehydration or shock with high levels of vasopressin persists, it will stimulate an increase in abundance of AQP-2 and AQP-3 water channels in the principal cells, allowing the ducts to achieve extremely high water permeability when necessary, and thus reabsorption of water.[64]

Throughout the literature, studies with vasopressin concerning renal blood flow seem to be inconsistent. These differences in outcome appear to be at least partly due to the wide range of doses used. Both afferent and efferent arterial diameters decrease significantly with vasopressin in low doses, which is a V1 receptor mediated effect.[65] Tamaki showed that vasopressin V1 stimulation led to a dose-dependent decreased lumen diameter of the afferent arterioles.[66] However, in the same article he mentions an increase in lumen diameter after adding vasopressin in norepinephrine constricted afferent arterioles through V2 receptors. Franchini showed in two studies a decrease in medullary flow of rat kidneys using a low vasopressin dose.[67,68] Another study[69] showed results of experiments on conscious rats in which kidney filtration decreased with low doses of vasopressin and increased with higher doses. Knowing these experimental results, one might be reluctant to use vasopressin in patients with already compromised kidney function, because it is not clear what the outcome will be. However, in patients with vasodilatory shock who received vasopressin, the urine production on average increased, counting for more than a vasoconstriction and water retention effect as described before. We will discuss this later.

VASODILATORY SHOCK AND VASOPRESSIN

Since 1997, several studies and case reports have been published about vasopressin effects in vasodilatory shock, either septic shock or vasodilatory shock after cardiopulmonary bypass (*table 1*). They were focused on short-term outcome such as haemodynamic effects and not designed to establish the effects on organ function or mortality.
A trial is now being conducted in Canada and the USA in patients with vasodilatory shock receiving vasopressin, aimed to evaluate organ function and mortality.
Studies already performed varied widely in the amount of vasopressin given, the duration of the vasopressin infusion and the measurements performed in the patient. It is therefore not simple to compare all these studies. Except for the randomised controlled trials, in most studies vasopressin was not given until norepinephrine dosages were very high or the patients' mean arterial pressure (MAP) decreased considerably. Vasopressin was therefore mostly used as 'last hope' medication. In the following section we will discuss the results of these studies.

Of the 24 studies, five were randomised controlled trials (*table 1*).[70-74] In these trials patients with vasodilatory shock were randomised to either the group receiving vasopressin added to norepinephrine (NE), or the group receiving increasing doses of norepinephrine only. Depending on the study protocol, the vasopressin improved the MAP and decreased the amount of NE necessary or it was possible to decrease the dose of NE while maintaining a stable MAP. Urine output and creatinine levels remained stable[71,72] or improved,[74] or were not mentioned.
In all studies, from single case reports to randomised controlled trials, the MAP increased significantly with a range of ΔMAP from 7 to 40 mmHg when vasopressin was added, without changing the administered dose and rate of catecholamines (*tables 1* and *2*). Some study protocols stated that the MAP should remain constant while adding vasopressin. Here the catecholamine administration could be decreased.
As mentioned before, vasopressin can exhibit a negative effect on the cardiac output, while increasing the MAP in vasodilatory shock. In the studies where the cardiac output or index was measured, vasopressin in general caused a decrease in cardiac output. This, however, did not seem to affect the rise in blood pressure.
Not all articles mention distinct features of organ perfusion,

Table 1

Overview of randomised controlled trials: vasopressin in vasodilatory shock

REFERENCE	STUDY	PATIENTS (TOTAL NO.; RANDOMISED TO AVP)	AVD DOSE (U/MIN)	DURATION AVP	ΔMAP MMHG	NE	ΔCI (*VS* NE)	SIDE EFFECTS MENTIONED (*VS* NE)	SURVIVAL (*VS* NE)	KIDNEY FUNCTION (*VS* NE)
70	RCT, crossover	Vasodilatory shock after LVAD implant (10/8)	0.1 0.1	1 h-7 d	↑ 27	↓ /stop	~	-	NR	NR
71	PRCT	Vasodilatory shock after CPB or in sepsis (48/24)	0.067	48 h	↑ 19 (0)	↓	↓ 10% (~)	New ischaemic lesions 7/24 (6/24); gastrointestinal perfusion better in AVP+NE than NE alone; bilirubin ↑	21/24 at 48 h	Creatinine stable
72	RCT	Septic shock (10/5)	0.04	>24 h	↑ 17	stop	↓ 7% (↓ 25%)	-	5/5 at 24 h (3/5)	Creatinine stable
74	DBRCT	Septic shock (24/13)	0.01-0.08	4 h	~	↓ ↓	↓ 8% (↓ 20%)	-	NR	UO doubled (~); creatinine clearance ↑ 75% (~)
73	DBRCT; prophylactic AVP	Vasodilatory shock after CPB (27/13)	0.03	6-72 h	-	AVP group 37% less NE	NR	Acute renal insufficiency 1/13 (1/14); right heart failure 1/13 (0); lethal haemorrhage 0 (1/14)	27/27 at 72 h	NR

AVP = vasopressin, MAP = mean arterial pressure, NE = norepinephrine, CI = cardiac index, RCT = randomised controlled trial, PRCT = prospective randomised controlled trial, DBRCT = double-blind randomised controlled trial, LVAD = left ventricular assist device, CPB = cardiopulmonary bypass, UO = urine output, NR = not reported. ↑ increase, ↓ decrease.

Table 2

Overview of other studies and cases: vasopressin in vasodilatory shock

REFERENCE	STUDY	PATIENTS	DOSE (U/MIN)	DURATION AVP	ΔMAP MMHG	NE	ΔCI	SIDE EFFECTS MENTIONED	SURVIVAL	KIDNEY FUNCTION
24	Matched cohort	Septic shock (19)	0.04	NR	↑ 27	↓	↓ 12%	-	NR	NR
55	Case series	Septic shock (50)	0.01-0.6	48 h	↑ ±10	↓33%	↓ 53%	6/50 cardiac arrest at AVP >0.05	8/50	UO ↑
75#	Case series	Vasodilatory shock after LVAD implant (50)	0.09±0.05	7±12 d	↑ 7	↓	ND	6% limb ischaemia in patient with CI <2 and AVP >10 U/h	50/50 (3d)	4/5 renal insuff. post-LVAD recovered
76	Case report	Septic shock (1); AVP 1st choice after dobutamine	0.04	23 h	↑ 23	No AVP	NR	Skin necrosis at peripheral infusion site	1/1	NR
78	Prospective clinical study	Septic shock (11)	0.04	4 h	↑ 7	~	~	↑ P(g-a)CO_2 gap	2/11	NR
79	Case series	Septic shock (12)	0.06-1.8	2-4 h	-	Stop	↓ 21%	↑ P(g-a)CO_2 gap	5/12	UO stable

AVP = vasopressin, MAP = mean arterial pressure, NE = norepinephrine, CI = cardiac index, LVAD = left ventricular assist device, CPB = cardiopulmonary bypass, dobu = dobutamine, milr = milrinone, SAP = systolic arterial pressure, UO = urine output, NR = not reported. ↑ increase, ↓ decrease, # includes 8 patients previously reported by Argenziano et al.[70]

Table 2 continued

REFERENCE	STUDY	PATIENTS	DOSE (U/MIN)	DURATION AVP	ΔMAP MMHG	NE	ΔCI	SIDE EFFECTS MENTIONED	SURVIVAL	KIDNEY FUNCTION
80	Case series	Septic shock (35), vasodilatory shock after cardiotomy (25)	0.067-0.1	0.5-384 h	↑ 22	↓	↓ 23%	↓platelets ↑liver enzymes ↑bilirubin	20/60	Creatinine stable
82	Case series	Septic shock (5)	0.04	1 h-21 d	↑ 25	↓/stop	↓ 11%	-	2/5	↑ /~
83	Case series	Vasodilatory shock after CPB (40)	0.1	1 h-6 d	↑ 24	↓	~	-	NR	NR
84	Case report	Vasodilatory shock after CPB (1)	Bolus 10 U; 0.23 U/min	2 d	↑ 40	↓	↓ 35%	-	1/1	UO ↑
85	Case series	Vasodilatory shock after cardiac transplant (20)	0.1	2 h-3 d	↑ 26	↓	↓ 17%	-	19/20	Creatinine stable
86	Case series, children	Vasodilatory shock after CPB (11)	0.0003-0.002 U/kg/min	6-144 h	↑ 15	↓	ND	-	9/11 at 2 wk	Creatinine stable
87	Case series	Vasodilatory shock in organ donors (10)	0.04-0.1	NR	↑ 18	↓/stop	ND	-	-	NR
88	Case series	Milrinone induced hypotension after CPB (3)	0.03-0.07	1-5 d	SAP ↑ 30-45	↓/stop	↓ 0-15%	-	2/3	UO ↑; Creatinine ↓
89	Case series	Milrinone induced hypotension in congestive heart failure (7)	0.03-0.07	>1 h	SAP ↑ 37	↓	~	-	NR	UO ↑
90	Case report	Septic shock, acute myocardial infarction (1)	0.02	5d	↑ 27	↓ ↓	↓ 24%	-	1/1	NR
91	Prospective case control	Septic shock (16)	0.04	16-284 h	↑ 4; 2/16 hypotension refractory	↑ (2/16 ↓)	~	-	9/16	UO ↑
92	Case series	Septic shock (7)	0.08±0.06	NR	NR	6/7 ↑ dobu/milr	↓ 31%	↓CI	NR	NR
93	Case series	Septic shock (8); terlipressin	1-2 mg	Bolus; effect ≥5 h	↑ 20	↓	↓ 21%	-	4/8	NR

AVP = vasopressin, MAP = mean arterial pressure, NE = norepinephrine, CI = cardiac index, LVAD = left ventricular assist device, CPB = cardiopulmonary bypass, dobu = dobutamine, milr = milrinone, SAP = systolic arterial pressure, UO = urine output, NR = not reported. ↑ increase, ↓ decrease, # includes 8 patients previously reported by Argenziano et al.[70]

such as kidney function. Some studies mentioned serum creatinine concentrations and/or urine output; in most cases, serum creatinine remained stable and the urine output increased. No patients are reported in whom kidney function deteriorated. Morales reported that in 18 out of 22 patients with renal insufficiency who received a left ventricular assist device (LVAD), the kidney function improved while administering vasopressin. It is not excluded that this effect resulted from the LVAD itself, but four out of five post-LVAD renal insufficiencies recovered with vasopressin, which makes a specific effect of vasopressin likely.[75] In Patel's double-blind randomised controlled trial (DBRCT), however, in patients with septic shock the urine output doubled and creatinine clearance improved by 75% compared with standard treatment.[74]

The reason for the stable or even improved kidney function in vasodilatory shock during vasopressin therapy is not apparent at first hand. Normally, one would expect that high doses of vasopressin stimulate the reabsorption of water through aquaporin-2, therefore creating lower diuresis. However, during hypotension or shock the kidneys are not well perfused, and are therefore not capable of building up the peritubular osmotic gradient through which urine can normally be concentrated. In the first period of vasopressin administration an improvement of renal blood flow is obtained with apparently increased glomerular filtration and thus an increase in water and electrolyte excretion. Secondly, due to better flow, the peritubular osmotic gradient will normalise, making it possible to reabsorb water and concentrate the urine.

There was no alteration in the plasma concentration of sodium or other electrolytes in the patients with vasodilatory shock, when treated with vasopressin.

Survival cannot be interpreted in most studies as they often do not report how seriously ill the patients are. In the RCTs the results varied and were not always mentioned: vasopressin *vs* NE resulted in at least the same survival, with sometimes slightly better survival for vasopressin at short term (Malay *et al.* mention survival of 5/5 at 24 hours for vasopressin *vs* 3/5 for norepinephrine).[72] All RCTs that mention survival rates measured them at 24 to 72 hours after start of trial, so it would be difficult to draw conclusions for longer-term survival.

SIDE EFFECTS

Seven out of the 24 studies mention side effects besides decreased cardiac index, whereas the others mention none. Side effects include limb ischaemia in a patient with impaired cardiac output and a vasopressin dose >10 U/h which resolved after discontinuing the vasopressin.[75] Six out of 50 patients suffered from cardiac arrest at doses >0.05 U/min.[55] Skin necrosis developed at the peripheral infusion site of vasopressin in one case report.[76] In a study by Dunser[77] in retrospective analysis in 63 critically ill patients with vasodilatory shock, 30% developed ischaemic skin lesions. There was no relationship between the vasopressin dose or length of infusion and the development of these lesions. Increased gastric regional partial pressure of pCO_2, which could be indicative of intestinal ischaemia, was found in two recent studies with a total of 23 patients.[78,79] Only one study found that gastrointestinal perfusion seemed to be better in patients with vasodilatory shock with vasopressin and NE than NE alone.[71] There was no report of actual intestinal ischaemia.

Dunser found a remarkable increase of plasma bilirubin in two studies in patients with vasodilatory shock who received vasopressin.[71,80] There was no obvious explanation. Since there were no other reports mentioning this side effect, results should be carefully interpreted and more research needs to be done.

One study showed that patients with vasodilatory shock receiving only NE developed significantly more new-onset tachyarrhythmias than patients receiving NE and vasopressin.[71] This seemed to be associated with the fact that the last group received lower doses of NE, which is known to have cardiotoxic and proarrhythmic effects.[81]

DISCUSSION ON THERAPEUTIC USE OF VASOPRESSIN

In nonacute vasodilatory shock there is a shortage of serum vasopressin and patients are in need of catecholamines. The standard treatment of vasodilatory shock is, in general, norepinephrine if blood pressure decreases, after proper fluid replacement. Studies with vasopressin show that it potentiates norepinephrine effects and increases blood pressure significantly in patients with vasodilatory shock. It also seems to preserve or sometimes restore renal blood flow and urine output. Doses used in studies vary but there seems to be a critical upper dose – 0.04 U/min – above which side effects increase. Studies performed are, however, short-term studies, so side effects may increase with longer use of vasopressin. Side effects noticed are ischaemic skin lesions, bilirubin increase and possible intestinal ischaemia. Theoretically, vasopressin seems to be a promising drug in patients with vasodilatory shock, and in short-term studies it improves blood pressure and renal blood flow. As mentioned earlier, a study aimed at long-term effects of vasopressin is being carried out, so definite statements on the use of vasopressin in these patients should at least wait until these results are published. Until then, vasopressin should still be reserved for those patients with severe vasodilatory shock in whom other vasopressors fail; it should be used with the greatest caution, preferably in a trial setting, with doses between 0.01 and 0.04 U/min.

Terlipressin use is not advisable because it is a long-acting (2 to 8 hours) drug and possible serious side effects cannot be reversed. In the mean time, we await the long-term randomised controlled trials.

REFERENCES

1. Robinson AG, Verbalis JG. Posterior Pituitary Gland. In: Williams Textbook of Endocrinology. Larsen PR, Kronenberg HM, Melmed S, et al. (editors). Philadelphia, Pennsylvania: Saunders, 2003. p. 281-9.
2. Giovannucci DR, Stuenkel EL. Regulation of secretory granule recruitment and exocytosis at rat neurohypophysial nerve endings. J Physiol 1997;498(Pt 3):735-51.
3. Nowycky MC, Seward EP, Chernevskaya NI. Excitation-secretion coupling in mammalian neurohypophysial nerve terminals. Cell Mol Neurobiol 1998;18(1):65-80.
4. Deleuze C, Duvoid A, Hussy N. Properties and glial origin of osmotic-dependent release of taurine from the rat supraoptic nucleus. J Physiol 1998;507(Pt 2):463-71.
5. Stern JE, Armstrong WE. Reorganization of the dendritic trees of oxytocin and vasopressin neurons of the rat supraoptic nucleus during lactation. J Neurosci 1998;18(3):841-53.
6. Majzoub JA, Rich A, van Boom J, Habener JF. Vasopressin and oxytocin mRNA regulation in the rat assessed by hybridization with synthetic oligonucleotides. J Biol Chem 1983;258(23):14061-4.
7. Zingg HH, Lefebvre D, Almazan G. Regulation of vasopressin gene expression in rat hypothalamic neurons. Response to osmotic stimulation. J Biol Chem 1986;261(28):12956-9.
8. Roberts MM, Robinson AG, Hoffman GE, Fitzsimmons MD. Vasopressin transport regulation is coupled to the synthesis rate. Neuroendocrinology 1991;53(4):416-22.
9. Leng G, Brown CH, Russell JA. Physiological pathways regulating the activity of magnocellular neurosecretory cells. Prog Neurobiol 1999;57(6):625-55.
10. Sharshar T, Carlier R, Blanchard A, et al. Depletion of neurohypophyseal content of vasopressin in septic shock. Crit Care Med 2002;30(3):497-500.
11. Zerbe RL, Henry DP, Robertson GL. Vasopressin response to orthostatic hypotension. Etiologic and clinical implications. Am J Med 1983;74(2):265-71.
12. Reid IA. Role of nitric oxide in the regulation of renin and vasopressin secretion. Front Neuroendocrinol 1994;15(4):351-83.
13. Fujisawa I, Asato R, Kawata M, et al. Hyperintense signal of the posterior pituitary on T1-weighted MR images: an experimental study. J Comput Assist Tomogr 1989;13(3):371-7.
14. Kurokawa H, Fujisawa I, Nakano Y, et al. Posterior lobe of the pituitary gland: correlation between signal intensity on T1-weighted MR images and vasopressin concentration. Radiology 1998;207(1):79-83.
15. Sato N, Tanaka S, Tateno M, Ohya N, Takata K, Endo K. Origin of posterior pituitary high intensity on T1-weighted magnetic resonance imaging. Immunohistochemical, electron microscopic, and magnetic resonance studies of posterior pituitary lobe of dehydrated rabbits. Invest Radiol 1995;30(10):567-71.
16. Zingg HH, Lefebvre D, Almazan G. Regulation of poly(A) tail size of vasopressin mRNA. J Biol Chem 1988;263(23):11041-3.
17. Czaczkes JW. Physiologic studies of antidiuretic hormone by its direct measurement in human plasma. J Clin Invest 1964;43:1625-40.
18. Cowley AW Jr, Cushman WC, Quillen EW Jr, Skelton MM, Langford HG. Vasopressin elevation in essential hypertension and increased responsiveness to sodium intake. Hypertension 1981;3(3 Pt 2):I93-100.
19. Robertson GL. The regulation of vasopressin function in health and disease. Recent Prog Horm Res 1976;33:335-85.
20. Morton JJ, Padfield PL, Forsling ML. A radioimmunoassay for plasma arginine-vasopressin in man and dog: application to physiological and pathological states. J Endocrinol 1975;65(3):411-24.
21. Arnauld E, Czernichow P, Fumoux F, Vincent JD. The effects of hypotension and hypovolaemia on the liberation of vasopressin during haemorrhage in the unanaesthetized monkey (Macaca mulatta). Pflugers Arch 1977;371(3):193-200.
22. Cowley AW Jr, Switzer SJ, Guinn MM. Evidence and quantification of the vasopressin arterial pressure control system in the dog. Circ Res 1980;46(1):58-67.
23. Wang BC, Flora-Ginter G, Leadley RJ Jr, Goetz KL. Ventricular receptors stimulate vasopressin release during hemorrhage. Am J Physiol 1988;254(2 Pt 2):R204-11.
24. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95AB(5):1122-5.
25. Fitzsimmons MD, Roberts MM, Sherman TG, Robinson AG. Models of neurohypophyseal homeostasis. Am J Physiol 1992;262(6 Pt 2):R1121-30.
26. Hainsworth R. Reflexes from the hearts. Physiol Rev 1991;71(3):617-58.
27. Thrasher TN. Baroreceptor regulation of vasopressin and renin secretion: low-pressure versus high-pressure receptors. Front Neuroendocrinol 1994;15(2):157-96.
28. Bishop VS, Thames MD, Schmid PG. Effects of bilateral vagal cold block on vasopressin in conscious dogs. Am J Physiol 1984;246(4 Pt 2):R566-9.
29. Quillen EW Jr, Cowley AW Jr. Influence of volume changes on osmolality-vasopressin relationships in conscious dogs. Am J Physiol 1983;244(1):H73-9.
30. Callahan MF, Ludwig M, Tsai KP, Sim LJ, Morris M. Baroreceptor input regulates osmotic control of central vasopressin secretion. Neuroendocrinology 1997;65(4):238-45.
31. Holmes CL, Landry DW, Granton T. Science review: vasopressin and the cardiovascular system part 2 – clinical physiology. Crit Care 2004;8(1):15-23.
32. Altura BM. Dose-response relationships for arginine vasopressin and synthetic analogs on three types of rat blood vessels: possible evidence for regional differences in vasopressin receptor sites within a mammal. J Pharmacol Exp Ther 1975;193(2):413-23.
33. Takayasu M, Kajita Y, Suzuki Y, et al. Triphasic response of rat intracerebral arterioles to increasing concentrations of vasopressin in vitro. J Cereb Blood Flow Metab 1993;13(2):304-9.
34. Katusic ZS, Shepherd JT, Vanhoutte PM. Vasopressin causes endothelium-dependent relaxations of the canine basilar artery. Circ Res 1984;55(5):575-9.
35. Tagawa T, Imaizumi T, Endo T, et al. Vasodilatory effect of arginine vasopressin is mediated by nitric oxide in human forearm vessels. J Clin Invest 1993;92(3):1483-90.
36. Vanhoutte PM, Katusic ZS, Shepherd JT. Vasopressin induces endothelium-dependent relaxations of cerebral and coronary, but not of systemic arteries. J Hypertens Suppl 1984;2(3):S421-2.
37. Bucher M, Hobbhahn J, Taeger K, Kurtz A. Cytokine-mediated downregulation of vasopressin V(1A) receptors during acute endotoxemia in rats. Am J Physiol Regul Integr Comp Physiol 2002;282(4):R979-84.

38. Hamu Y, Kanmura Y, Tsuneyoshi I, Yoshimura N. The effects of vasopressin on endotoxin-induced attenuation of contractile responses in human gastroepiploic arteries in vitro. Anesth Analg 1999;88(3):542-8.
39. Noguera I, Medina P, Segarra G, et al. Potentiation by vasopressin of adrenergic vasoconstriction in the rat isolated mesenteric artery. Br J Pharmacol 1997;122(3):431-8.
40. Schwartz J, Reid IA. Effect of vasopressin blockade on blood pressure regulation during hemorrhage in conscious dogs. Endocrinology 1981;109(5):1778-80.
41. Wilson MF, Brackett DJ, Hinshaw LB, Tompkins P, Archer LT, Benjamin BA. Vasopressin release during sepsis and septic shock in baboons and dogs. Surg Gynecol Obstet 1981;153(6):869-72.
42. Dunser MW, Hasibeder WR, Wenzel V, et al. Endocrinologic response to vasopressin infusion in advanced vasodilatory shock. Crit Care Med 2004;32(6):1266-71.
43. Cowley AW Jr, Monos E, Guyton AC. Interaction of vasopressin and the baroreceptor reflex system in the regulation of arterial blood pressure in the dog. Circ Res 1974;34(4):505-14.
44. Montani JP, Liard JF, Schoun J, Mohring J. Hemodynamic effects of exogenous and endogenous vasopressin at low plasma concentrations in conscious dogs. Circ Res 1980;47(3):346-55.
45. Medina P, Acuna A, Martinez-Leon JB, et al. Arginine vasopressin enhances sympathetic constriction through the V1 vasopressin receptor in human saphenous vein. Circulation 1998;97(9):865-70.
46. Eichinger MR, Walker BR. Segmental heterogeneity of NO-mediated pulmonary vasodilation in rats. Am J Physiol 1994;267(2 Pt 2):H494-9.
47. Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. Chest 1993;103(4):1241-5.
48. Walker BR, Haynes J Jr, Wang HL, Voelkel NF. Vasopressin-induced pulmonary vasodilation in rats. Am J Physiol 1989;257(2 Pt 2):H415-22.
49. Eichinger MR, Walker BR. Enhanced pulmonary arterial dilation to arginine vasopressin in chronically hypoxic rats. Am J Physiol 1994;267(6 Pt 2):H2413-9.
50. Sai Y, Okamura T, Amakata Y, Toda N. Comparison of responses of canine pulmonary artery and vein to angiotensin II, bradykinin and vasopressin. Eur J Pharmacol 1995;282(1-3):235-241.
51. Leather HA, Segers P, Berends N, Vandermeersch E, Wouters PF. Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. Crit Care Med 2002;30(11):2548-52.
52. Maturi MF, Martin SE, Markle D, et al. Coronary vasoconstriction induced by vasopressin. Production of myocardial ischemia in dogs by constriction of nondiseased small vessels. Circulation 1991;83(6):2111-21.
53. Walker BR, Childs ME, Adams EM. Direct cardiac effects of vasopressin: role of V1- and V2-vasopressinergic receptors. Am J Physiol 1988;255(2 Pt 2):H261-5.
54. Tahara A, Tomura Y, Wada K, et al. Effect of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced protein synthesis in neonatal rat cardiomyocyte. Cardiovasc Res 1998;38(1):198-205.
55. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. Intensive Care Med 2001;27(8):1416-21.
56. Medel J, Boccara G, van de Steen E, Bertrand M, Godet G, Coriat P. Terlipressin for treating intraoperative hypotension: can it unmask myocardial ischemia? Anesth Analg 2001;93:53-5.
57. De Aguilera EM, Vila JM, Irurzun A, Martinez MC, Martinez Cuesta MA, Lluch S. Endothelium-independent contractions of human cerebral arteries in response to vasopressin. Stroke 1990;21(12):1689-93.
58. Oyama H, Suzuki Y, Satoh S, et al. Role of nitric oxide in the cerebral vasodilatory responses to vasopressin and oxytocin in dogs. J Cereb Blood Flow Metab 1993;13(2):285-90.
59. Antoni FA. Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. Front Neuroendocrinol 1993;14(2):76-122.
60. Qahwash IM, Cassar CA, Radcliff RP, Smith GW. Bacterial lipopolysaccharide-induced coordinate downregulation of arginine vasopressin receptor V3 and corticotropin-releasing factor receptor 1 messenger ribonucleic acids in the anterior pituitary of endotoxemic steers. Endocrine 2002;18(1):13-20.
61. Lolait SJ, O'Carroll AM, Mahan LC, et al. Extrapituitary expression of the rat V1b vasopressin receptor gene. Proc Natl Acad Sci USA 1995;92(15):6783-7.
62. Borgnia M, Nielsen S, Engel A, Agre P. Cellular and molecular biology of the aquaporin water channels. Annu Rev Biochem 1999;68(425):458.
63. Nielsen S, Chou CL, Marples D, Christensen EI, Kishore BK, Knepper MA. Vasopressin increases water permeability of kidney collecting duct by inducing translocation of aquaporin-CD water channels to plasma membrane. Proc Natl Acad Sci USA 1995;92(4):1013-7.
64. Ecelbarger CA, Terris J, Frindt G, et al. Aquaporin-3 water channel localization and regulation in rat kidney. Am J Physiol 1995;259(5 Pt 2):F663-72.
65. Edwards RM, Trizna W, Kinter LB. Renal microvascular effects of vasopressin and vasopressin antagonists. Am J Physiol 1989;256(2 Pt 2):F274-8.
66. Tamaki T, Kiyomoto K, He H, et al. Vasodilation induced by vasopressin V2 receptor stimulation in afferent arterioles. Kidney Int 1996;49(3):722-9.
67. Franchini KG, Cowley AW Jr. Renal cortical and medullary blood flow responses during water restiction: role of vasopressin. Am J Physiol 1996;270(6 Pt 2):R1257-64.
68. Franchini KG, Cowley AW Jr. Sensitivity of the renal medullary circulation to plasma vasopressin. Am J Physiol 1996;270(3 Pt 2):R647-53.
69. McVicar AJ. Dose-response effects of pressor doses of arginine vasopressin on renal hemodynamics in the rat. J Physiol 1988;404:535-46.
70. Argenziano M, Choudhri AF, Oz MC, Rose EA, Smith CR, Landry DW. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997;96(9 suppl):II-90.
71. Dunser MW, Mayr AJ, Ulmer H, et al. Arginine Vasopressin in Advanced Vasodilatory Shock. A Prospective, Randomized, Controlled Study. Circulation 2003;107(18):2313-9.
72. Malay MB, Ashton RC Jr, Landry DW, Townsend RN. Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 1999;47(4):699-703.
73. Morales DL, Garrido MJ, Madigan JD, et al. A double-blind randomized trial: prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. Ann Thorac Surg 2003;75(3):926-30.
74. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 2002;96(3):576-82.
75. Morales DL, Gregg D, Helman DN, et al. Arginine vasopressin in the treatment of 50 patients with postcardiotomy vasodilatory shock. Ann Thorac Surg 2000;69(1):102-6.
76. Kahn JM, Kress JP, Hall JB. Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. Crit Care Med 2002;30(8):1899-901.

77. Dunser MW, Mayr AJ, Tur A, et al. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. Crit Care Med 2003;31(5):1394-8.
78. Van Haren FMP, Rozendaal FW, van der Hoeven JG. The effect of vasopressin on gastric perfusion in catecholamine-dependent patients in septic shock. Chest 2003;124:2256-60.
79. Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hellmann A. High-dose vasopressin is not superior to norepinephrine in septic shock. Crit Care Med 2003;31(11):2646-50.
80. Dunser MW, Mayr AJ, Ulmer H, et al. The effects of vasopressin on systemic hemodynamics in catecholamine- resistant septic and postcardiotomy shock: a retrospective analysis. Anesth Analg 2001;93(1):7-13.
81. Podrid PF, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation 1990;82(suppl):I103-13.
82. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. Crit Care Med 1997;25(8):1279-82.
83. Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg 1998;116(6):973-80.
84. Overand PT, Teply JF. Vasopressin for the treatment of refractory hypotension after cardiopulmonary bypass. Anesth Analg 1998;86(6):1207-9.
85. Argenziano M, Chen JM, Cullinane S, et al. Arginine vasopressin in the management of vasodilatory hypotension after cardiac transplantation. J Heart Lung Transplant 1999;18(8):814-7.
86. Rosenzweig EB, Starc TJ, Chen JM, et al. Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. Circulation 1999;100(19 suppl):II182-6.
87. Chen JM, Cullinane S, Spanier TB, et al. Vasopressin deficiency and pressor hypersensitivity in hemodynamically unstable organ donors. Circulation 1999;100(19 suppl):II244-6.
88. Gold JA, Cullinane S, Chen J, Oz MC, Oliver JA, Landry DW. Vasopressin as an alternative to norepinephrine in the treatment of milrinone-induced hypotension. Crit Care Med 2000;28(1):249-52.
89. Gold J, Cullinane S, Chen J, et al. Vasopressin in the treatment of milrinone-induced hypotension in severe heart failure. Am J Cardiol 2000;85(4):506-8, A11.
90. Lim TW, Lee S. Vasopressin effective in reversing catecholamine-resistant vasodilatory shock. Anaesth Intensive Care 2000;28(3):313-7.
91. Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA, III. Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock. Crit Care Med 2001;29(3):487-93.
92. Jackson WLJ, Shorr AF. Vasopressin and cardiac performance. Chest 2002;121(5):1723-4.
93. O'Brien A, Clapp L, Singer M. Terlipressin for norepinephrine-resistant septic shock. Lancet 2002;359(9313):1209-10.