

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 supra-optic 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

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 μ U/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 phosphatidylinositol 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 myocytes 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 study⁵⁵ led to cardiac arrest in six out of fifty patients. One case report mentions myocardial ischaemia intra-operatively 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 study⁶⁹ 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 Δ MAP 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 (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); right heart failure (1/13); lethal haemorrhage (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 >10 U/h	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 1 st 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.²⁰

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 cardiomy (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.²⁰

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 Dunser⁷⁷ 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 pCO₂, 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.

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