Review

Clinical review: Vasopressin and terlipressin in septic shock patients

Anne Delmas[1], Marc Leone[1], Sébastien Rousseau[1], Jacques Albanèse[1] and Claude Martin[2]

[1]MD, Department of Anesthesiology and Intensive Care Medicine, and Trauma Center, Marseilles University Hospital System, Marseilles School of Medicine, Marseilles, France
[2]Professor of Anesthesiology and Intensive Care, Department of Anesthesiology and Intensive Care Medicine, and Trauma Center, Marseilles University Hospital System, Marseilles School of Medicine, Marseilles, France

Corresponding author: Claude Martin, claude.martin@ap-hm.fr

Published online: 9 September 2004
This article is online at http://ccforum.com/content/9/2/212

Critical Care 2005, **9:**212-222 (DOI 10.1186/cc2945)

See commentary, page 134 [http://ccforum.com/content/9/2/134]

Abstract

Vasopressin (antidiuretic hormone) is emerging as a potentially major advance in the treatment of septic shock. Terlipressin (tricyl-lysine-vasopressin) is the synthetic, long-acting analogue of vasopressin, and has comparable pharmacodynamic but different pharmacokinetic properties. Vasopressin mediates vasoconstriction via V_1 receptor activation on vascular smooth muscle. Septic shock first causes a transient early increase in blood vasopressin concentrations; these concentrations subsequently decrease to very low levels as compared with those observed with other causes of hypotension. Infusions of 0.01–0.04 U/min vasopressin in septic shock patients increase plasma vasopressin concentrations. This increase is associated with reduced need for other vasopressors. Vasopressin has been shown to result in greater blood flow diversion from nonvital to vital organ beds compared with adrenaline (epinephrine). Of concern is a constant decrease in cardiac output and oxygen delivery, the consequences of which in terms of development of multiple organ failure are not yet known. Terlipressin (one or two boluses of 1 mg) has similar effects, but this drug has been used in far fewer patients. Large randomized clinical trials should be conducted to establish the utility of these drugs as therapeutic agents in patients with septic shock.

Introduction

The neurohypophysis contains vasopressin and oxytocin, which have very similar structures. In humans vasopressin is present in the form of an octapeptide called arginine vasopressin (AVP). The nomenclature of neurohypophysic hormones can be confusing. The name 'vasopressin' made it possible to refer to a hormone that is capable of both increasing arterial pressure in animals and triggering capillary vasoconstriction in humans. Such effects are only observed at high doses. At a low doses it inhibits urine output with no effect on the circulation, earning it the name 'antidiuretic hormone'.

The antidiuretic functions of vasopressin have been exploited clinically for many years for the treatment of diabetes insipidus. Its vasopressor properties are currently arousing interest and have been the subject of numerous studies [1–14]. These studies have suggested that vasopressin may have applications in several models of shock, particularly septic shock [1,3,6,8,9,15–19,21–26]. Septic shock is defined as circulatory failure and organ hypoperfusion resulting in systemic infection [27]. Despite improved knowledge of its pathophysiology and considerable advances in its treatment, mortality from septic shock exceeds 50% [28]. Most deaths are linked to refractory arterial hypotension and/or organ failure despite antibiotic therapy, fluid expansion, and vasopressor and positive inotropic treatment [29].

This general review analyzes data from the literature on the cardiovascular effects of vasopressin in septic shock so to define the position of this hormone for treatment of a pathological entity that remains one of the most preoccupying in the intensive care unit.

History

The vasopressor effect of an extract from the pituitary gland was first observed in 1895 [30], but the antidiuretic effect was not exploited in the treatment of diabetes insipidus until 1913 [31,32]. The neurohypophysic extracts administered to patients at that time reduced diuresis, increased urine density and intensified thirst. In the 1920s researchers demonstrated that local application of these extracts to animal capillaries

AVP = arginine vasopressin; MAP = mean arterial pressure; NO = nitric oxide; P_{CO_2} = partial carbon dioxide tension.

provoked vasoconstriction [5]. In 1954 vasopressin was isolated and synthesized [33].

Recently, many teams have become interested in the endocrine response of the organism during cardiac arrest and cardiopulmonary resuscitation [21–25]. It has been shown that circulating endogenous vasopressin levels are elevated in such patients [21–25]. This is of prognostic value in extreme cases of cardiovascular failure [7].

Studies on septic shock began in 1997, when Landry and coworkers [3] observed that vasopressin plasma concentrations had collapsed in these patients. Hence, the effects of exogenous vasopressin in shock became a focus for numerous research projects.

Biological characteristics

Structure and synthesis of vasopressin

Vasopressin is a polypeptide with a disulphide bond between the two cysteine amino acids [34]. In humans AVP is encoded by the mRNA for preproneurophysin II. After cleavage of the signal peptide, the resulting prohormone contains AVP (nine amino acids), neurophysin II (95 amino acids) and a glycopeptide (39 amino acids). The prohormone is synthesized in the parvocellular and magnocellular neurones of the supraoptic and paraventricular nuclei of the hypothalamus [35]. Cleavage of the prohormone yields the three components, including AVP. The final hormone is transported by the neurones of the hypothalamo–neuro–hypophyseal bundle of the pituitary gland to the secretion site, namely the posterior hypophysis. It is then stored in granule form. The whole process from synthesis to storage lasts from 1 to 2 hours (Fig. 1) [20].

Of the total stock of vasopressin, 10–20% can be rapidly released into the bloodstream [8]. Secretion diminishes if the stimulus continues. This kinetic action explains the biphasic course of vasopressin plasma concentrations during septic shock, with an early elevation followed by subsequent diminution [36].

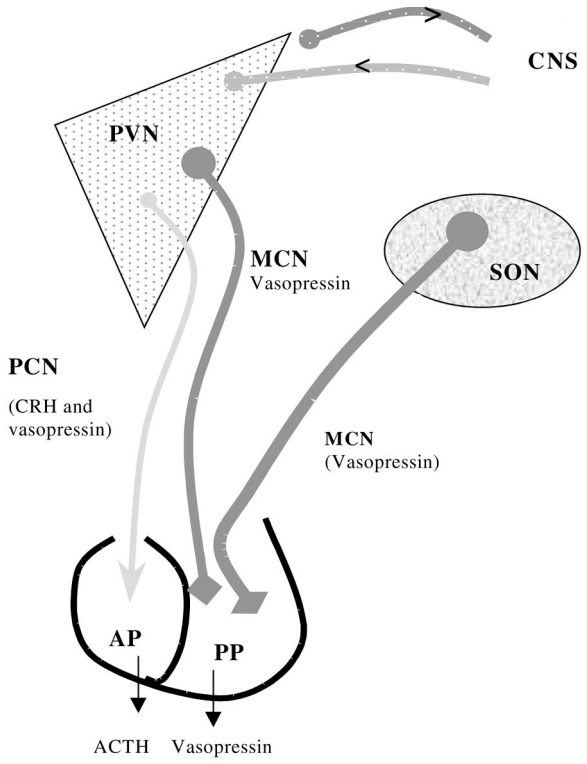
Vasopressin secretion

Vasopressin secretion is complex and depends upon plasma osmolality and blood volume.

Osmotic stimulus

Plasma osmolality is maintained by behavioural (hunger and thirst) and physiological (vasopressin and natriuretic hormones) adaptations. The central osmoreceptors that regulate vasopressin secretion are located near to the supraoptic nucleus in the anterolateral hypothalamus in a region with no blood–brain barrier [20]. There are also peripheral osmoreceptors at the level of the hepatic portal vein that detect early the osmotic impact of ingestion of foods and fluids [20]. The afferent pathways reach the magnocellular neurones of the hypothalamus via the vagal nerve. These neurones are depolarized by hypertonic conditions and hyperpolarized by hypotonic conditions [37].

Figure 1



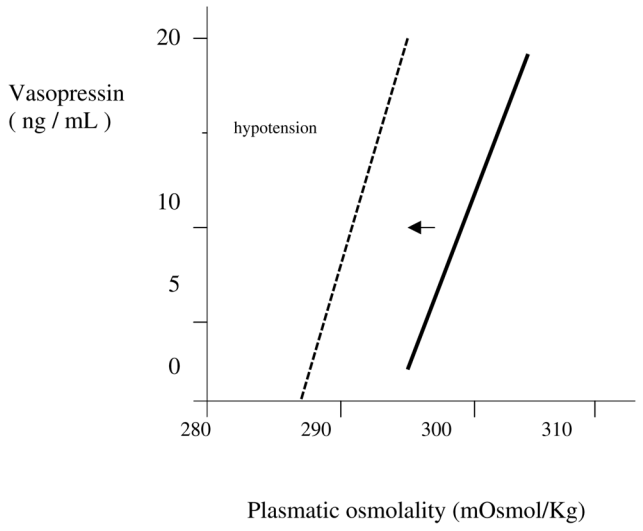
Pituitary secretion of vasopressin. The main hypothalamic nuclei release vasopressin and corticotrophin-releasing hormone (CRH), which stimulates the secretion of adrenocorticotrophic hormone (ACTH) via the anterior pituitary gland (AP). Magnocellular neurones (MCN) and supraoptic neurones release vasopressin, which is stored in the posterior pituitary gland (PP) before its release into the circulation. CNS, central nervous system; PCN, parvocellular neurones; PVN, paraventricular nucleus of hypothalamus; SON, supraoptic nucleus of hypothalamus. Modified from Holmes and coworkers [8].

The osmotic threshold for vasopressin secretion corresponds to a mean extracellular osmolality of 280 mOsmol/kg H_2O (Fig. 2). Below this threshold the circulating concentration is undetectable; above it the concentration increases in a linear relation to osmolality. If water restriction is prolonged then plasmatic hypertonia stimulates thirst, beginning at values of approximately 290 mOsmol/kg H_2O [20].

Volaemic stimulus

In contrast to osmotic stimulation, arterial hypotension and hypovolaemia stimulate vasopressin exponentially [8,20]. This secretion does not disturb osmotic regulation because hypotension modifies the relationship between plasmatic osmolality and the concentration of vasopressin; the slope of

Figure 2



Influence of plasma osmolality and hypotension on vasopressin secretion.

the curve is accentuated and the threshold lowered [38]. A greater concentration of vasopressin is therefore required to maintain normal osmolality (Fig. 2) [39–42].

Arterial hypotension is the principal stimulus for vasopressin secretion via arterial baroreceptors located in the aortic arch and the carotid sinus (Fig. 2) [6]. It is transported by the vagal and glossopharyngeal nerves toward the nucleus tractus solitarus and then toward the supraoptic and paraventricular nuclei. Inhibition of this secretion is principally linked to volume receptors located in the cardiac cavities [43]. In a physiological situation, inhibition is constant because of continuous discharge by these receptors. If stimulation diminishes then vasopressin secretion increases [44]. If central venous pressure diminishes, then these receptors first stimulate secretion of natriuretic factor, the sympathetic system, and renin secretion. Vasopressin is secreted when arterial pressure falls to the point that it can no longer be compensated for by the predominant action of the vascular baroreceptors [45–48].

Other stimuli

Other stimuli can favour secretion of vasopressin. These include hypercapnia, hypoxia, hyperthermia, pain, nausea, morphine and nicotine [49]. At the hormone level, numerous molecules are direct stimulators, including acetylcholine, histamine, nicotine, angiotensin II, prostaglandins, dopamine and, especially, the adrenergic system [36]. Noradrenaline (norepinephrine) has a complex effect on vasopressin secretion [49]. At low concentrations it increases activity. At high concentrations it inhibits the production of vasopressin [50]. Nitric oxide (NO), through cGMP, is a powerful neurohormonal inhibitor of vasopressin [8]. This pathway is of fundamental importance in the case of septic shock [6,8,20]. Opiates, alcohol, γ-aminobutyric acid, and auricular natriuretic factor are also inhibitors.

Metabolism

Vasopressin is rapidly metabolized by the aminopeptidases that are present in most peripheral tissues. Its half-life is approximately 10 min but can go up to 35 min in certain situations [51]. Its metabolic clearance greatly depends on renal and hepatic blood flows. In a physiological situation but without pregnancy, variations in metabolic clearance have little impact on the circulating concentration of vasopressin because of adaptation of neurosecretion [20].

Plasma concentrations of vasopressin in shock

In a healthy individual in a normal situation, the plasma concentration of vasopressin is less than 4 pg/ml. Blood hyperosmolarity increases this concentration to up to 20 pg/ml, but maximum urinary density occurs at levels of 5–7 pg/ml.

A biphasic response to a vasopressin concentration is observed in septic shock [3,10,12,14,19]. In the early phase elevated concentrations (sometimes >500 pg/ml) are detected. Subsequently, vasopressin secretion that is paradoxically insufficient with respect to the level of hypovolaemia has been observed [3,10,12,14,19]. In two cohorts of 44 and 18 patients, Sharshar and coworkers [52] evaluated the prevalence of vasopressin deficiency in septic shock. They found that plasma vasopressin levels are increased at the initial phase of septic shock in almost all cases, which could contribute to the maintenance of arterial blood pressure, and that the levels decreased afterward. A relative vasopressin deficiency (defined as a normal plasma vasopressin level in the presence of a systolic blood pressure <100 mmHg or in the presence of hypernatraemia) was more likely to occur after 36 hours from the onset of shock in approximately one-third of late septic shock patients [52].

In children with meningococcal septic shock high levels of AVP were measured [53]. The mean level was 41.6 pg/ml, with a wide range of individual values (1.4–498.6 pg/ml). AVP levels were not correlated with duration of shock, fluid expansion, or age-adjusted blood pressure and natraemia. AVP levels were higher in nonsurvivors but not significantly so [53]. Sequential measurements were not obtained in that study, and thus it was not possible to conclude that AVP administration is of little interest in children with meningococcal septic shock.

Plasma concentrations are close to physiological concentrations in the late phase of septic shock. The reasons for this phenomenon are not very clear. Recent studies have suggested that depletion of neurohypophysic stocks of vasopressin occurs after intense and permanent stimulation of the baroreceptors [8,20,54]. Some authors have attributed

Table 1

Site and molecular properties of vasopressin

Receptor	Tissues	Effects	Action
V_1 receptor	Smooth muscle cells of blood vessels, kidney, spleen, vesicle, testis, platelets, hepatocyte	Phospholipase C; release of intracellular calcium	Vasoconstriction
V_2 receptor	Renal collecting duct, endothelial cells	Via G protein, ↑cAMP	Increased permeability to water
V_3 receptor	Pituitary gland	Via G protein, ↑cAMP	↑ACTH secretion
OTRs (ocytocin receptors)	Uterus, breast, umbilical vein, aorta, pulmonary artery	Phospholipase C; ↑cytosolic calcium; release of nitric oxide	Vasodilatation

ACTH, adrenocorticotrophic hormone.

this to a failure of the autonomous nervous system [55]. The auricular mechanoreceptors, which may be stimulated by cardiac volume variations caused by mechanical ventilation, could slow down vasopressin secretion in a tonic manner [49]. An inhibitory effect of noradrenaline and NO in patients with septic shock is probable [50]. Moreover, a study conducted in rats with endotoxic shock demonstrated a reduction in the sensitivity of vasopressin receptors, which was probably linked to the actions of proinflammatory cytokines [56]. In humans, Sharshar and coworkers [52] concluded that the relative vasopressin deficiency probably results from a decreased secretion rate rather than from increased clearance from plasma.

Effects of vasopressin

Vasopressin acts through several receptors, the properties of which are summarized in Table 1. These receptors are different from those of catecholamines. Vasopressin has a direct vasoconstrictor effect on systemic vascular smooth muscle via V_1 receptors [8]. The same type of receptor was found on platelets, which are another storage location for vasopressin [57,58]. The V_2 receptors in the renal collecting tubule are responsible for regulating osmolarity and blood volume [8]. At certain concentrations, vasopressin provokes vasodilatation in some vascular regions. Vasopressin also acts as a neurotransmitter.

Vasoconstrictor effect

The vasoconstrictor activity of vasopressin, which is mediated by the V_1 receptors, is intense *in vitro*. There is also a probable indirect action on vascular smooth muscle cells by local inhibition of NO production [59]. However, under physiological conditions, vasopressin has only a minor effect on arterial pressure [26,60]. One experimental hypothesis is that the vasopressor effect of vasopressin is secondary to its capacity to inhibit smooth muscle cell K^+-ATP channels [61].

This moderate effect observed *in vivo* can be explained by the indirect bradycardic effect resulting from vasopressin's action on baroreflexes [62]. This effect on baroreflexes is mediated by the cerebral V_1 receptors [63]. It requires integrity of the cardiac baroreflexes because it disappears after administration of a ganglioplegic agent [63]. Vasopressin concentrations of approximately 50 pg/ml are required before any significant modification becomes apparent [64,65].

In shock the haemodynamic response to vasopressin becomes important in maintaining arterial pressure and tissue perfusion. Administration of V_1 receptor antagonists in animals in haemorrhagic shock increases hypotension [5,66]. Vasopressin concentrations increase during the initial phase of shock [41]. Thus, contrary to what is observed under physiological conditions, when the autonomous nervous system is deficient and baroreflexes altered the vasopressor effect becomes predominant and prevents severe hypotension [67]. However, its trigger differs from that of catecholamines on several levels. Vasopressin provokes a reduction in cardiac output and its vasoconstrictor activity is heterogeneous on a topographical level [5,6,8,68]. Its administration provokes vasoconstriction in skin, skeletal muscle, adipose tissue, pancreas and thyroid [5]. This vasoconstriction is less apparent in the mesenteric, coronary and cerebral territories under physiological conditions [68–70]. Its impact on digestive perfusion is under debate. Two studies conducted in patients with septic shock [18,19] demonstrated absence of impact of vasopressin on splanchnic circulation. In contrast, in a recent study conducted in animals in a state of endotoxaemic shock [71], a reduction in digestive perfusion with vasopressin administration was observed. Finally, contrary to catecholamines, whose effect can only be additive, vasopressin potentiates the contractile effect of other vasopressor agents [72].

Vasodilator effect

The vasodilatation of certain vascular regions with vasopressin is an further major difference from catecholamines.

This effect occurs at very low concentrations [2]. The literature is limited on this subject. Animal studies have been reported, but they were not conducted in the context of sepsis. Some authors reported vasodilatation at a cerebral level in response to vasopressin, with more marked sensitivity to vasopressin in the circle of Willis [2,73]. The mechanism of this vasodilatation can be explained by production of NO at the level of the endothelial cells [74,75]. The receptors involved have not been clearly identified.

It has been shown that vasopressin provokes vasodilatation of the pulmonary artery both under physiological and hypoxic conditions [77–79]. The V_1 receptors are involved and cause endothelial liberation of NO [80–82].

Renal effect

The renal effect of vasopressin is complex. In response to blood hyperosmolarity it reduces urine output through its action on the V_2 receptors, which induce reabsorption of water. Inversely, it has diuretic properties in case of septic shock [3,15,16,19] and congestive heart failure [83]. The mechanisms involved in the re-establishment of diuresis are poorly understood. The principal hypothetical mechanisms are a counter-regulation of the V_2 receptors [84] and selective vasodilatation of the afferent arteriole (under the action of NO) in contrast to vasoconstriction of the efferent arteriole [76,85].

Patel and coworkers [19] recently reported a randomized study in which there were significant improvements in diuresis and creatinine clearance in patients with septic shock under vasopressin treatment as compared with patients treated with noradrenaline. It has been shown in nonseptic rats that elevated concentrations of this hormone provoked a dose-dependent fall in renal blood output, glomerular filtration, and natriuresis [86,87]. All of the investigators who found a beneficial effect following treatment with vasopressin for septic shock used minimal doses, allowing for readjustment to achieve physiological concentrations [3,6,10,15–19].

Corticotrophic regulator effect

Vasopressin acts on the corticotrophic axis by potentiating the effect of the corticotrophin-releasing hormone on the hypophyseal production of adrenocorticotrophic hormone [88,89]. The ultimate effect is an elevation in cortisolaemia [90], which is of interest in the case of septic shock because cortisol levels can be lowered.

Effect on platelet aggregation

At a supraphysiological dose, vasopressin acts as a platelet-aggregating agent [91,92]. The coagulation problems in septic shock make this effect undesirable. However, the doses used are unlikely to provoke a significant aggregation effect [8].

The position of vasopressin in treatment of septic shock

The use of vasopressin in septic shock is based on the concept of relatively deficient plasma levels of AVP, but how robust is this concept? As discussed above, plasma AVP levels are low in septic shock – a phenomenon that does not occur in cardiogenic shock and not to such an extent in haemorrhagic shock. Are these low levels of AVP inappropriate? Applying the upper limit of AVP that is maintained in normotensive and normo-osmolar healthy individuals (3.6 pg/ml), Sharshar and coworkers [52] found that one-third of septic shock patients had levels of AVP that were inappropriate for the degree of osmolality of the volume of blood pressure. Because the upper limit changes with the level of blood pressure or osmolality, the incidence of vasopressin insufficiency would have been dramatically changed had the upper limit been based on expected vasopressin values for a given level of osmolality or blood pressure, or both. One way to overcome this problem would perhaps be to determine which AVP levels correlate with outcome, particularly survival.

Current treatments with a favourable haemodynamic effect, in increasing order of therapeutic use, can be listed as follows: catecholamines (dopamine at a dose >5 μg/kg per min, noradrenaline, then adrenaline) and corticosteroids (hydrocortisone 200 mg/day). Catecholamines have a vasopressor action that provokes local ischaemic phenomena [93–96]. The state of prolonged hyperkinetic shock is characterized by deficit and hypersensitivity to vasopressin [1]. Clinical trials of vasopressin in human septic shock are summarized in Table 2.

The first clinical study of the use of vasopressin in septic shock was that reported by Landry and coworkers in 1977 [3]. The patients studied had abnormally low concentrations of vasopressin in the constitutive period of shock. Administration of exogenous vasopressin at a low dose (0.01 U/min) to two of the patients caused a significant increase in these concentrations, suggesting a secretion defect. For the first time, that team observed a hypersensitivity to vasopressin in five patients whose plasma concentrations reached 100 pg/ml (infusion at 0.04 U/min) [1]. Systolic arterial pressure and systemic vascular resistance were significantly increased ($P<0.001$) and cardiac output was slightly reduced ($P<0.01$). A reduction of 0.01 U/min in vasopressin infusion rate caused the plasma concentration to fall to 30 pg/ml. Discontinuation of vasopressin triggered a collapse in arterial pressure. The hypersensitivity to vasopressin noted in these cases of vasoinhibitory shock is secondary to the dysautonomia that suppresses the bradycardic effect [97]. Although it has been demonstrated that suppression of the baroreflex increases considerably the vasoconstrictor power of vasopressin, this phenomenon is probably multifactorial [67,97]. A randomized placebo-controlled study was conducted in 10 patients with

Table 2

Published trials of low-dose vasopressin in human septic shock

Reference	Study design (*n*)	Observed effects
[1]	Case series (5)	A, B, C
[3]	Matched cohort (19)	A, B, D
[9]	Randomized clinical trial versus placebo (10)	A, B
[15]	Case series (16)	A, C
[16]	Case series (50)	A, B, C
[17]	Retrospective case series (38)	A
[18]	Randomized clinical trial: noradrenaline + vasopressin versus noradrenaline (48)	A, B, C, E, F
[19]	Randomized clinical trial: noradrenaline versus vasopressin (24)	B, C, D, F, G
[99]	Cases series (11)	H
[100]	Noradrenaline versus vasopressin (12)	A, F, H

A, significant increase in blood pressure; B, decrease in catecholamines related to an increase in blood pressure; C, increase in urine output; D, low doses of measured vasopressin; E, increase in systemic vascular resistance; F, absence of effect on mesenteric circulation; G, improvement in creatinine clearance; H, hypoperfusion of the gastric mucosa.

hyperkinetic septic shock [9]. The patients who received low-dose vasopressin (0.04 U/min) had a significant increase in systolic arterial pressure (from 98 to 125 mmHg; $P < 0.05$) and catecholamine weaning was performed. No variation in arterial pressure was noted in the placebo group, in which two patients died, whereas there were no deaths in the treated group. The cardiac index did not differ between the two groups.

Tsuneyoshi and coworkers [15] treated 16 patients with severe refractory catecholamine septic shock for 16 hours with 0.04 U/min vasopressin. In 14 of these patients haemodynamic status remained stable under vasopressin. Mean arterial pressure (MAP) increased from 49 to 63 mmHg and systemic vascular resistance from 1132 to 1482 dynes·s/cm^5 per m^2 ($P < 0.05$) 2 hours after the beginning of treatment. Cardiac index, pulmonary arterial pressures, cardiac frequency, and central venous pressure were not modified. ECG analysis of the ST segment showed no variation. Finally, diuresis was significantly increased in 10 patients ($P < 0.01$); the six others were in anuria from the beginning of the study.

Another study analyzed data from 50 patients in severe septic shock who had received a continuous vasopressin infusion for 48 hours [16]. MAP increased by 18% in the 4 hours after the beginning of the infusion, an effect which was maintained at 24 and 48 hours ($P = 0.06$ and $P = 0.08$, respectively). The coprescribed doses of catecholamines were reduced by 33% at hour 4 ($P = 0.01$) and by 50% at hour 48. It is of interest that five of the six patients who presented with cardiac arrest during the study had received vasopressin infusions greater than 0.05 U/min. The authors concluded that vasopressin administered during septic shock increased MAP and diuresis, and accelerated weaning from catecholamines. They also estimated that infusions greater than 0.04 U/min were accompanied by deleterious effects, without any gain in efficacy.

The first double-blind, randomized study comparing the effects of noradrenaline with those of vasopressin in severe septic shock was reported in 2002 [19]. Patients were receiving noradrenaline before the study (open-label phase). They were randomized to receive, in a double-blind fashion, either noradrenaline or vasopressin. The main objective of that study was to keep MAP constant. In the vasopressin group noradrenaline doses were significantly reduced at hour 4 (from 25 to 5 μg/min; $P < 0.001$). Vasopressin doses varied between 0.01 and 0.08 U/min. In the noradrenaline group, doses of noradrenaline were not significantly modified. MAP and cardiac index were not modified. Diuresis and creatinine clearance did not vary in the noradrenaline group but they were significantly increased in the vasopressin group. This observation is of great importance because diuresis increased in patients whose MAP was constant, which supports an intrarenal effect of vasopressin. The gastric carbon dioxide gradient and the ECG ST segment were unchanged in both groups. The authors concluded that administration of vasopressin made it possible to spare other vasopressor agents and significantly improve renal function in these patients with septic shock.

Another prospective, randomized controlled study was conducted in 48 patients with advanced vasodilatory shock [18]. Patients were treated with a combined infusion of AVP (4 U/hour) and noradrenaline or noradrenaline alone. AVP patients had significantly lower heart rate, noradrenaline requirement, and incidence of new onset tachyarrhythmia. MAP, cardiac index and stroke volume index were

significantly higher in AVP patients. Total bilirubin concentrations increased significantly in patients receiving vasopressin [18]. A significant increase in total bilirubin has been reported in patients treated with vasopressin [17]. However, direct AVP-induced hepatic dysfunction has not previously been described. Possible mechanisms for the increase in bilirubin may be an AVP-mediated reduction in hepatic blood flow [98] or a direct impairment in hepatocellular function. The authors concluded that AVP plus noradrenaline was superior to noradrenaline alone in treating cardiocirculatory failure in vasodilatory shock [18].

Despite its favourable effects on global haemodynamics and renal function (Table 2), little is known about possible adverse effects of AVP on organ function; in particular, gastrointestinal hypoperfusion – a common complication of septic shock – may be aggravated by this drug. Conflicting conclusions have been reported in humans. In a case series of 11 catecholamine-dependent septic shock patients, van Haren and coworkers [99] showed that vasopressin (0.04 U/min) was responsible for a significant increase in gastric–arterial partial carbon dioxide tension (P_{CO_2}) gap from 5 mmHg at baseline to 19 mmHg after 4 hours. There was a strong correlation between plasma levels of vasopressin and gastric–arterial P_{CO_2} gap. The authors concluded that vasopressin may elicit gastrointestinal hypoperfusion. Because all patients received high-dose noradrenaline in addition to AVP, an interaction between these two vasoconstrictive agents could not be excluded. In another study conducted in patients with advanced vasodilatory shock [18], a totally different conclusion was drawn. In the study patients, gastrointestinal perfusion was assessed by gastric tonometry and was better preserved in AVP-treated patients (who also received noradrenaline) than in patients treated with noradrenaline only; after 24 hours, gastric–arterial P_{CO_2} gap increased from 9 ± 15 to 17 ± 17 mmHg in the former group and from 12 ± 17 to 26 ± 21 mmHg in the latter group.

Similar descrepancies were reported in two studies reported in abstract form. In seven patients receiving 50 mU/kg per hour, ΔP_{CO_2} increased from 8 ± 6 to 48 ± 56 mmHg [100]. In another study conducted in 12 patients treated with noradrenaline, no change in pHi was observed when supplemental AVP was given [101].

At present it is difficult to draw firm conclusion on the effects of AVP on the gastrointestinal circulation in humans. Used in humans to replace noradrenaline (with MAP kept constant), vasopressin had mixed effects on hepatosplanchnic haemodynamics. Hepatoplanchnic blood flow was preserved, but a dramatic increase in gastric P_{CO_2} gap suggested that gut blood flow could have been redistributed to the detriment of the mucosa [102]. Similar confusion also exists in the experimental literature. In endotoxaemic pigs, vasopressin decreased superior mesentric artery and portal vein blood flow, whereas noradrenaline did not [103]. Mesenteric oxygen consumption and delivery decreased and oxygen extraction increased. Vasopressin increased mucosal–arterial P_{CO_2} gradient in the stomach, jejunum and colon, whereas noradrenaline did not [103]. In septic rats AVP infusion was accompanied by a marked decrease in gut mucosal blood flow, followed by a subsequent severe inflammatory response to the septic injury. The sepsis-associated increase in interleukin-6 levels was further increased by AVP infusion [104]. In an abstract reporting on the use of AVP in animals (not specified), a selective reduction in superior mesenteric artery flow was observed, associated with increased blood flow in the coeliac trunc and hepatic artery [71]. Future clinical trials with AVP should investigate the possibiity of adverse effects on the splanchnic circulation.

No clinical study of sufficient size has demonstrated a positive effect of vasopressin on survival in patients with septic shock. This treatment enables restoration of sufficient arterial pressure in cases in which it is impossible to achieve this goal using catecholamines or corticosteroids. The effect on organs requires further evaluation in a larger group of patients. In this context the results of large, prospective, randomized controlled studies are required before the routine use of vasopressin be can considered for symptomatic treatment of septic shock.

In an ideal world several concerns should be addressed before carrying out such a (probably huge) trial. The important questions to be addressed are as follows. Which type of septic shock should be considered – early or late (refractory)? Should only patients with documented inappropriate vasopressin levels be included? Which is the best comparator for AVP (dopamine, noradrenaline, phenylephrine)? Should a group of patients receive terlipressin (see below)? What should be the duration of AVP perfusion? Should the infusion rate be titrated against MAP or AVP levels? In addition to these questions, the following should be evaluated: the effect on oxygen metabolism (oxygen consumption being measured independent from oxygen delivery) and the oxygen delivery–consumption relationship; gastric mucosal perfusion and splanchnic and hepatic blood flows; renal function; and survival, which should be the primary end-point.

The potential side effects of vasopressin should be kept in mind, which include abdominal pain, headache, acrocyanosis, diarrhoea, bradycardia, myocardial ischaemia and ischaemic skin lesions.

The position of terlipressin in treatment of septic shock

All of the previously cited studies used arginine vasopressin, or antidiuretic hormone, which is the vasopressin that is naturally present in humans. This form is not available in all countries, and some hospital pharmacies have lysine vasopressin, or terlipressin (Glypressine®; Ferring Company,

Berlin, Germany), which is the form of vasopressin that is present in pig. The latter treatment is less manageable than the former because of its half-life and duration of action. Terlipressin (tricyl-lysine vasopressin) is a synthetic analogue of vasopressin. As a compound it is rapidly metabolized by endopeptidases to form the vasoactive lysine vasopressin. The half-life of terlipressin is 6 hours whereas that of vasopressin is only 6 min. In clinical practice the drug is administered as an intermittent bolus infusion to stop acute bleeding from oesophageal and gastric varices.

The first clinical trial of the efficacy of terlipressin in septic shock was performed in a small case series of eight patients [105]. Terlipressin was administered as a single bolus of 1 mg (the dosage used in gastroenterological practice) in patients with septic shock refractory to catecholamine–hydrocortisone–methylene blue. A significant improvement in blood pressure was obtained in these patients during the first 5 hours. Cardiac output was reduced, which might have impaired oxygen delivery. Partial or total weaning from catecholamines was possible. No other side effect was observed.

Another study was conducted in 15 patients with catecholamine-dependent septic shock (noradrenaline ≥ 0.6 μg/kg per min). An intravenous bolus of 1 mg terlipressin was followed by an increase in MAP and a significant decrease in cardiac index. Oxygen delivery and consumption were significantly decreased [106]. Gastric mucosal perfusion was evaluated by laser Doppler flowmetry and was increased after terlipressin injection. The ratio between gastric mucosal perfusion and systematic oxygen delivery was also significantly improved after terlipressin injection. These findings could be related to a positive redistribution effect of cardiac output on hepatosplanchnic circulation, with an increase in blood flow to the mucosa.

The adverse effects of terlipressin on oxygen metabolism were also emphazised in an experimental study conducted in sheep [107]. Terlipressin was given by continuous infusion (10–40 mg/kg per hour) and was responsible for a significant decrease in cardiac index and oxygen delivery. Oxygen consumption decreased whereas oxygen extraction increased. These modifications may carry a risk for tissue hypoxia, expecially in septic states in which oxygen demand is typically incrased. Terlipressin was also used in children [108] in a short case series of four patients with catecholamine-resistant shock. MAP increased, allowing reduction or withdrawal of noradrenaline. Two children died.

Conclusion

At present the use of vasopressin (and terlipressin) may be considered in patients with refractory septic shock despite adequate fluid resuscitation and high-dose conventional vasopressors [109]. 'Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first-line agent. If used in adults, it [vasopressin] should be administered at an infusion rate of 0.01–0.04 units/min' [109].

In accordance with current knowledge, the mechanism proposed to explain the efficacy of vasopressin (and probably that of terlipressin) is twofold. First, circulating vasopressin concentrations are inadequate in patients with septic shock; in this context exogenous vasopressin may be used to supplement the circulating levels of this hormone. Second, vasoconstriction is induced by vasopressin through receptors that are different from those acted upon by catecholamines, but the latter are desensitized in septic shock.

According to recent data reported the literature, the recommended dose of AVP should not exceed 0.04 UI/min. This dosing is for individuals who weigh 50–70 kg and should be scaled up or down for those who are outside this weight range. Injection of 1 mg terlipressin makes it possible to increase arterial pressure for 5 hours. For patients who weigh more than 70 kg, 1.5–2 mg should be injected. Cardiac output is decreased with vasopressin and terlipressin.

Vasopressin potentiates the vasopressor efficacy of catecholamines. However, it has the further advantage of eliciting less pronounced vasoconstriction in the coronary and cerebral vascular regions. It benefits renal function, although these data should be confirmed. The effects on other regional circulations remain to be determined in humans.

Vasopressin and terlipressin are thus last resort therapies in septic shock states that are refractory to fluid expansion and catecholamines. However, current data in humans remain modest, and properly powered, randomized controlled trials with survival as the primary end-point are required before these drugs can be recommended for more widespread use.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA: **Vasopressin pressor hypersensitivity in vasodilatory septic shock.** *Crit Care Med* 1997, **25:**1279-1282.
2. Okamura T, Toda M, Ayajiki K, Toda N: **Receptor subtypes involved in relaxation and contraction by arginine vasopressin in canine isolated short posterior ciliary arteries.** *J Vasc Res* 1997, **34:**464-472.
3. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA: **Vasopressin deficiency contributes to the vasodilation of septic shock.** *Circulation* 1997, **95:**1122-1125.
4. Gold J, Cullinane S, Chen J, Seo S, Oz MC, Oliver JA, Landry DW: **Vasopressin in the treatment of milrinone induced hypotension in severe heart failure.** *Am J Cardiol* 2000, **85:** 506-508, A11.
5. Laszlo FA, Laszlo F Jr, De Wield D: **Pharmacology and clinical perspectives of vasopressin antagonists.** *Pharmacol Rev* 1991, **43:**73-108.
6. Forrest P: **Vasopressin and shock.** *Anaesth Intensive Care* 2001, **29:**463-472.

7. Krismer AC, Wenzel V, Mayr VD, Voelckel WG, Strohmenger HU, Lurie K, Lindner KH: **Arginine vasopressin during cardiopulmonary resuscitation and vasodilatory shock: current experience and future perspectives.** *Curr Opin Crit Care* 2001, **7:** 157-169.
8. Holmes CL, Patel BM, Russell JA: **Physiology of vasopressin relevant to management of septic shock.** *Chest* 2001, **120:** 989-999.
9. Malay MB, Ashton RC Jr, Landry DW, Townsend RN: **Low dose of vasopressin in the treatment of vasodilatory septic shock.** *J Trauma* 1999, **47:**699-703.
10. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, Smith CR Jr, Rose EA, Landry DW, Oz MC: **Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent.** *Thorac Cardiovasc Surg* 1998, **116:**973-980.
11. 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, **Suppl:**II286-II290.
12. Argenziano M, Chen JM, Cullinane S, Choudhri AF, Rose EA, Smith CR, Edwards NM, Landry DW, Oz MC: **Arginine vasopressin in the management of vasodilatory hypotension after cardiac transplantation.** *J Heart Transplant* 1999, **18:**814-817.
13. Morales DL, Gregg D, Helman DN, Williams MR, Naka Y, Landry DW, Oz MC: **Arginine vasopressin in the treatment of 50 patients with post cardiotomy vasodilatory shock.** *Ann Thorac Surg* 2000, **69:**102-106.
14. Chen JM, Cullinane S, Spanier TB, Artrip JH, John R, Edwards NM, Oz MC, Landry DW: **Vasopressin deficiency and pressor hypersensitivity in hemodynamically unstable organ donors.** *Circulation* 1999, **Suppl:**II244-II246.
15. 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:**487-493.
16. 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:**1416-1421.
17. Dunser MW, Mayr AJ, Ulmer H, Ritsch N, Knotzer H, Pajk W, Luckner G, Mutz NJ, Hasibeder WR: **The effects of vasopressin on systemic hemodynamics in catecholamine-resistant septic and postcardiotomy shock: a retrospective analysis.** *Anesth Analg* 2001, **93:**7-13.
18. Dunser MW, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, Friesenecker B, Hasibeder WR: **Arginine vasopressin in advanced vasodilatory shock. A prospective, randomized, controlled study.** *Circulation* 2003, **107:**2313-2319.
19. Patel BM, Chittock DR, Russell JA, Walley KR: **Beneficial effects of short-term vasopressin infusion during severe septic shock.** *Anesthesiology* 2002, **96:**576-582.
20. Nicolet-Barousse L, Sharshar T, Paillard M, Raphael JC, Annane D: **Vasopressin: a hormone with multiple functions [in French].** Méd Thér Endocrinol 2001, **7:**757-764.
21. Prengel AW, Lindner KH, Ensinger H, Grunert A: **Plasma catecholamine concentrations after successful resuscitation in patients.** *Crit Care Med* 1992, **20:**609-614.
22. Lindner KH, Strohmenger HU, Prengel AW, Ensinger H, Goertz A, Weichel T: **Hemodynamic and metabolic effects of epinephrine during cardiopulmonary resuscitation in a pig model.** *Crit Care Med* 1992, **20:**1020-1026.
23. Schultz CH, Rivers EP, Feldcamps CS, Maronitz HB, Hevert CS: **A characterization of hypothalamic-pituitary-adrenal axis function during and after human cardiac arrest.** *Crit Care Med* 1993, **21:**1339-1347.
24. Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M: **Stress hormone response during and after CPR.** *Anesthesiology* 1992, **77:**662-668.
25. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG: **Release of endogenous vasopressors during and after cardiopulmonary resuscitation.** *Heart* 1996, **75:**145-150.
26. Schwartz J, Reid IA: **Role of vasopressin in blood pressure regulation in conscious water-deprived dogs.** *Am J Physiol* 1983, **244:**R74-R77.
27. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: **Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis.** *Chest* 1992, **101:**1658-1662.
28. Ruokonen E, Takala J, Kari A, Alhava E: **Septic shock and multiple organ failure.** *Crit Care Med* 1991, **19:**1146-1151.
29. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP: **Septic shock in humans: advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy.** *Ann Intern Med* 1990, **113:**227-242.
30. Oliver H, Shafer E: **On the physiological action of extracts of the pituitary body and certain other glandular organs.** *J Physiol (Lond)* 1895, **18:**277-279.
31. Farini F: **Diabetes insipidus and opotherapy [in Italian].** *Gazz Osped Clin* 1913, **34:**1135-1139.
32. von den Velden R: **Die nierenwirkung von hypophysenextrakten beim menshen.** *Berl Klin Wochenscgr* 1913, **50:**2083-2086.
33. Du Vigneaud V, Gash DT, Katsoyannis PG: **A synthetic preparation possessing biological properties associated with arginine vasopressin.** *J Am Chem Soc* 1954, **76:**4751-4752.
34. Barberis C, Mouillac B, Durroux T: **Structural bases of vasopressin/oxytocin receptor function.** *J Endocrinol* 1998, **156:** 223-229.
35. Paillard M, Froissard M, Blanchard A, *et al*: **Extracellular water and osnolarity [in French].** *Encycl Méd Chir* (Elsevier, Paris). Endocrinologie-Nutrition, 10-352-A10.1995: p11.
36. Sklar AH, Schrier RW: **Central nervous system mediators of vasopressin release.** *Physiol Rev* 1983, **63:**1243-1280.
37. Bourque CW, Oliet SH, Richard D: **Osmoreceptors, osmoreception, and osmoregulation.** *Front Neuroendocrinol* 1994, **15:** 231-274.
38. Robertson G, Athar S, Shelton R: **Osmotic control of vasopressin function.** In *Disturbances in Body Fluid Osmolality*. Edited by Andreoli TE, Grantham JJ, Rector FC Jr. Bethesda, MD: American Physiological Society; 1977:125-148.
39. Shrier RW, Berl T, Anderson RJ: **Osmotic and non osmotic control of vasopressin release.** *Am J Physiol* 1979, **236:**F321-F332.
40. Wood CE, Chen HG: **Acidemia stimulate ACTH, vasopressin, and heart rate responses in fetal sheep.** *Am J Physiol* 1989, **257:**R344-R349.
41. Robertson GL, Shelton RL, Athar S: **The osmoregulation of vasopressin.** *Kidney Int* 1976, **10:**25-37.
42. Quillen EW Jr, Cowley AW Jr: **Influence of volume changes on osmolality-vasopressin relationships in conscious dogs.** *Am J Physiol* 1983, **244:**H73-H79.
43. Leng G, Dyball RE, Russell JA: **Neurophysiology of body fluid homeostasis.** *Comp Biochem Physiol A* 1988, **90:**781-788.
44. Bisset GW, Chowdrey HS: **Control of release of vasopressin by neuroendocrine reflexes.** *Q J Exp Physiol* 1988, **73:**811-872.
45. Goldsmith SR, Francis GS, Cowley AW, Cohn JN: **Response of vasopressin and norepinephrine to lower body negative pressure in humans.** *Am J Physiol* 1982, **243:**H970-H973.
46. Norsk P, Ellegaard P, Videbaek R, Stadeager C, Jessen F, Johansen LB, Kristensen MS, Kamegai M, Warberg J, Christensen NJ: **Arterial pulse pressure and vasopressin release in humans during lower body negative pressure.** *Am J Physiol* 1993, **264:**R1024-R1030.
47. Trasher TN: **Baroreceptor regulation of vasopressin and renin secretion: low pressure versus high pressure receptors.** *Front Neuroendocrinol* 1994, **15:**157-187.
48. O'Donnell CP, Thompson CJ, Keil LC, Thrasher TN: **Renin and vasopressin responses to graded reductions in atrial pressure in conscious dogs.** *Am J Physiol* 1994, **266:**R714-R721.
49. Leng G, Brown CH, Russell JA: **Physiological pathways regulating the activity of magnocellular neurosecretory cells.** *Prog Neurobiol* 1999, **57:**625-655.
50. Day TA, Randle JC, Renaud LP: **Opposing α- and β-adrenergic mechanisms mediate dose-dependent actions of norepinephrine on supraoptic vasopressin neurones *in vivo*.** *Brain Res* 1985, **358:**171-179.
51. Czaczkes JW: **Physiologic studies of antidiuretic hormone by its direct measurement in human plasma.** *J Clin Invest* 1964, **43:**1625-1640.
52. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D: **Circulating vasopressin levels in septic shock.** *Crit Care Med* 2003, **31:**1752-1758.

53. Leclerc F, Walter-Nicolet E, Leteurtre S, Noizet O, Sadik A, Cremer R, Fourier C: **Admission plasma vasopressin levels in children with meningococcal septic shock.** *Intensive Care Med* 2003, **29:**1339-1344.
54. Sharshar T, Carlier R, Blanchard A, Feydy A, Gray F, Paillard M, Raphael JC, Gajdos P, Annane D: **Depletion of neurohypophyseal content of vasopressin in septic shock.** *Crit Care Med* 2002, **30:**497-500.
55. Zerbe RL, Henry DP, Robertson GL: **Vasopressin response to orthostatic hypotension: etiologic and clinical implications.** *Am J Med* 1983, **74:**265-271.
56. Bucher M, Hobbhahn J, Kurtz A: **Cytokine-mediated downregulation of vasopressin V1a receptors during acute endotoxemia in rats.** *Am J Physiol* 2002, **282:**R979-R984.
57. Thibonnier M, Roberts JM: **Characterization of human platelet vasopressin receptors.** *J Clin Invest* 1985, **76:**1857-1864.
58. Bichet DG, Razi M, Lonergan M, Arthus MF, Papukna V, Kortas C, Barjon JN: **Human platelet fraction arginine-vasopressin. Potential physiological role.** *J Clin Invest* 1987, **79:**881-887.
59. Kusano E, Tian S, Umino T, Tetsuka T, Ando Y, Asano Y: **Arginine vasopressin inhibits interleukin-1 beta-stimulated nitric oxide and cyclic guanosine monophosphate production via the OXT receptor in cultured rat vascular smooth muscle cells.** *J Hypertens* 1997, **15:**627-632.
60. Abboud FM, Floras JS, Aylward PE, Guo GB, Gupta BN, Schmid PG: **Role of vasopressin in cardiovacular and blood pressure regulation.** *Blood Vessels* 1990, **27:**106-115.
61. Wakatsuki T, Nakaya Y, Inoue I: **Vasopressin modulates K^+-channel activities of cultured smooth muscle cells from porcine coronary artery.** *Am J Physiol* 1992, **263:**H491-H496.
62. Reid I: **Role of vasopressin deficiency in the vasodilation of septic shock.** *Circulation* 1997, **95:**1108-1110.
63. Luk J: **Role of V1 receptors in the action of vasopressin on the baroreflex control of heart rate.** *Am J Physiol* 1993, **265:**R524-R529.
64. Cowley AW Jr, Switzer SJ, Guinn MM: **Evidence and quantification of the vasopressin arterial pressure control system in the dog.** *Circ Res* 1980, **46:**58-67.
65. Mohring J, Glanzer K, Maciel JA Jr, Dusing R, Kramer HJ, Arbogast R, Koch-Weser J: **Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic orthostatic hypotension.** *J Cardiovasc Pharmacol* 1980, **2:**367-376.
66. Schwartz J, Reid IA: **Effect of vasopressin blockade on blood pressure regulation during hemorrhage in conscious dogs.** *Endocrinology* 1981, **109:**1778-1780.
67. Jordan J, Tank J, Dietrich A, Clarck JP, Benton MD: **Vasopressin and blood pressure in humans.** *Hypertension* 2000, **36:**E3-E4.
68. Liard JF, Deriaz O, Schelling P, Thibonnier M: **Cardiac output distribution during vasopressin infusion or dehydration in conscious dogs.** *Am J Physiol* 1982, **243:**H663-H669.
69. 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:**413-423.
70. Kerr JC, Jain KM, Swan KG, Rocko JM: **Effects of vasopressin on cardiac output and its distribution in the subhuman primate.** *J Vasc Surg* 1985, **2:**443-449.
71. Martikainen TJ, Tenhunen JJ, Uusaro A, Ruokonen E: **Vasopressin causes selective intestinal hypoperfusion and lactate release in lethal endotoxin shock [abstract].** *Intensive Care Med* 2002, **28:**S65.
72. Karmazyn M, Manku MS, Horrobin DF: **Changes of vascular reactivity induced by low vasopressin concentrations: interactions with cortisol and lithium and possible involvement of prostaglandins.** *Endocrinology* 1978, **102:**1230-1236.
73. Suzuki Y, Satoh S, Oyama H, Takayasu M, Shibuya M: **Regional differences in the vasodilator response to vasopressin in canine cerebral arteries *in vivo.*** *Stroke* 1993, **24:**1049-1053.
74. Thibonnier M, Conarty DM, Preston JA, Plesnicher CL, Dweik RA, Erzurum SC: **Human vascular endothelial cells express ocytocin receptors.** *Endocrinology* 1999, **140:**1301-1309.
75. Okamura T, Ayajiki K, Fujioka H, Toda N: **Mechanisms underlying arginine vasopressin-induced relaxation in monkey isolated coronary arteries.** *J Hypertens* 1999, **17:**673-678.
76. Tamaki T, Kiyomoto K, He H, Tomohiro A, Nishiyama A, Aki Y, Kimura S, Abe Y: **Vasodilation induced by vasopressin V2 receptor stimulation in afferent arterioles.** *Kidney Int* 1996, **49:**722-729.
77. Jin HK, Chen YF, Yang RH, McKenna TM, Jackson RM, Oparil S: **Vasopressin lowers pulmonary artery pressure in hypoxic rats by releasing atrial natriuretic peptide.** *Am J Med Sci* 1989, **298:**227-236.
78. Walker BR, Haynes J Jr, Wang HL, Voelkel NF: **Vasopressin-induced pulmonary vasodilation in rats.** *Am J Physiol* 1989, **257:**H415-H422.
79. Eichinger MR, Walker BR: **Enhanced pulmonary arterial dilation to arginine vasopressin in chronically hypoxic rats.** *Am J Physiol* 1994, **267:**H2413-H2419.
80. Russ RD, Walker BR: **Role of nitric oxide in vasopressinergic pulmonary vasodilatation.** *Am J Physiol* 1992, **262:**H743-H747.
81. 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:**235-241.
82. Evora PR, Pearson PJ, Schaff HV: **Arginine vasopressin induces endothelium dependant vasodilatation of the pulmonary artery: V1-receptor-mediated production of nitric oxide.** *Chest* 1993, **103:**1241-1245.
83. Eisenman A, Armali Z, Enat R, Bankir L, Baruch Y: **Low dose vasopressin restores diuresis both in patients with hepatorenal syndrome and in anuric patients with end-stage heart failure.** *J Intern Med* 1999, **246:**183-190.
84. Aiyar N, Nambi P, Crooke ST: **Desensitization of vasopressin sensitive adenylate cyclase by vasopressin and phorbol esters.** *Cell Signal* 1990, **2:**153-160.
85. Edwards RM, Trizna W, Kinter LB: **Renal microvascular effects of vasopressin and vasopressin antagonists.** *Am J Physiol* 1989, **256:**F274-F278.
86. McVicar AJ: **Dose–response effects of pressor doses of arginine vasopressin on renal hemodynamics in the rat.** *J Physiol* 1988, **404:**535-546.
87. Harrison-Bernard LM, Carmines PK: **Juxtamedullary micro-vascular responses to arginine vasopressin in rat kidney.** *Am J Physiol* 1994, **267:**F249-F256.
88. Tucci JR, Espiner EA, Jagger PI, Lauler DP, Thorn GW: **Vasopressin in the evaluation of pituitary-adrenal function.** *Ann Intern Med* 1968, **69:**191-202.
89. Chrousos G: **The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation.** *N Engl J Med* 1995, **332:**1351-1360.
90. Antoni FA: **Vasopressinergic control of pituitary adrenocorticotropin secretion comes on age.** *Front Neuroendocrinol* 1993, **14:**76-122.
91. Leung FW, Jensen DM, Guth PH: **Endoscopic demonstration that vasopressin but not propranolol produces gastric mucosal ischaemia in dogs with portal hypertension.** *Gastrointest Endosc* 1988, **34:**310-313.
92. Haslam RJ, Rosson GM: **Aggregation of human blood platelets by vasopressin.** *Am J Physiol* 1972, **223:**958-967.
93. Martin C, Eon B, Saux P, Aknin P, Gouin F: **Renal effects of norepinephrine used to treat septic shock patients.** *Crit Care Med* 1990, **18:**282-285.
94. Fukuoka T, Nishimura M, Imanaka H, Taenaka N, Yoshiya I, Takezawa J: **Effects of norepinephrine on renal function in septic patients with normal or elevated serum lactate levels.** *Crit Care Med* 1989, **17:**1104-1107.
95. Martin C, Papazian L, Perrin G, Saux P, Gouin F: **Norepinephrine or dopamine for the treatment of hyperdynamic septic shock.** *Chest* 1993, **103:**1826-1831.
96. Ruokonen E, Takala J, Kari A, Saxen H, Mertsola J, Hansen EJ: **Regional blood flow and oxygen transport in septic shock.** *Crit Care Med* 1993, **21:**1296-1303.
97. Cowley AW, 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:**505-514.
98. Fasth S, Haglund U, Hulten L, Nordgren S: **Vascular responses of small intestine and liver to regional infusion of vasopressin.** *Acta Chir Scand* 1981, **147:**583-588.
99. 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:**2256-2260.

100. Bracco D, Cholero RL, Revelly JP: **Systemic and splanchnic heamodynamic effects of vasopressin administration in vasodilatory shock.** *Intensive Care Med* 2001, **27:**S137 (Abstract annual COngress Geneva, Switzerland).
101. Sladen RN, Kinstner C, Germann P, Ulrich R, Landry D: **Infusion of vasopressin enhances blood pressure and renal function while preserving cerebral, and splanchnic perfusion in patients in septic shock [abstract 349].** *Anesthesiology* 2002, **96:**1421.
102. 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:**2646-2650.
103. Martikainen TJ, Tenhumen JJ, Uusaro A, Ruokonen E: **The effects of vasopressin on systemic and splanchnic hemodynamics and metabolism in endotoxin shock.** *Anesth Analg* 2003, **97:** 1756-1763.
104. Westphal M, Freise H, Kehrel BE, Bone HG, Van Aken H, Sielenkamper AW: **Arginine vasopressin compromises gut microcirculation in septic rates.** *Crit Care Med* 2004, **32:**194-200.
105. O'Brien A, Clapp L, Singer M: **Terlipressin for norepinephrine-resistant septic shock.** *Lancet* 2002, **359:**1209-1210.
106. Morelli A, Rocco M, Conti G, Orecchioni A, De Gaetano A, Cortese G, Coluzzi F, Vernaglione E, Pelaia P, Pietropaoli P: **Effects of terlipressin on gastric mucosa in catecholamine-dependent septic shock.** *Intensive Care Med* 2004:in press.
107. Westphal M, Stubbe H, Sielenkamper AW, Borgulya R, Van Aken H, Ball C, Bone HG: **Terlipressin response in healthy and endotoxinemic sheep : impact on cardiopulonary performance and global oxygen.** *Intensive Care Med* 2003, **29:**301-308.
108. Rodriguez-Nunez A, Fernandez-Sanmartin M, Martinon-Torres F, Gonzalez-Alonso N, Martinon-Sanchez JM: **Terlipressin for catecholamine-resistant septic shock in children.** *Intensive Care Med* 2004, **30:**477-480.
109. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, *et al.*: **Surviving Sepsis campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32:**858-872.