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The Vasopressin System

Physiology and Clinical Strategies

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Vasopressin, synthesized in the hypothalamus, is released by increased plasma osmolality, decreased arterial pressure, and reductions in cardiac volume. Three subtypes of vasopressin receptors, V1, V2, and V3, have been identified, mediating vasoconstriction, water reabsorption, and central nervous system effects, respectively. Vasopressin and its analogs have been studied intensively for the treatment of states of "relative vasopressin deficiency," such as sepsis, vasodilatory shock, intraoperative hypotension, and cardiopulmonary resuscitation. Infusion of vasopressin (0.01–0.04 U/min) decreases catecholamine requirements in patients with sepsis and other types of vasodilatory shock. Bolus application of 1 mg terlipressin, the V1 agonist, reverses refractory hypotension in anesthetized patients and has been studied in patients with septic shock and chronic liver failure. During cardiopulmonary resuscitation, a 40-U bolus dose of vasopressin may be considered to replace the first or second bolus of epinephrine regardless of the initial rhythm. The side effects of vasopressin and its analogs must be further characterized.

VASOPRESSIN, an extensively studied hormone, is crucial for osmoregulation, cardiovascular control, and homeostasis and therefore has substantial relevance for anesthesia and intensive care therapy. Although vasopressin or its analogs have been used traditionally to treat upper gastrointestinal bleeding, central diabetes insipidus, and bleeding disorders, recent studies suggest new indications. These include cardiopulmonary resuscitation (CPR), septic shock, intraoperative hypotension, and portal venous hypertension. Furthermore, inadequately low vasopressin plasma concentrations have been postulated as a cause for hemodynamic instability.

This review provides an update on the vasopressin system from its physiologic basis to the latest clinical applications and also describes therapeutic strategies using vasopressin receptor agonists and antagonists.

This article is accompanied by an Editorial View. Please see: Dünser MW, Lindner KH, Wenzel V: A century of arginine vasopressin research leading to new therapeutic strategies. ANESTHESIOLOGY 2006; 105:444–5.

Physiologic Functions and Regulation of Vasopressin

Synthesis and Release

Vasopressin, also known as antidiuretic hormone (ADH), is a nonapeptide synthesized in the hypothalamus. Because the human hormone contains arginine, it is specifically called *arginine vasopressin* (AVP) to distinguish it from analogs (fig. 1).

Two different types of hypothalamic neurons, magnocellular and parvocellular, synthesize AVP. The magnocellular neurons are mainly located in the supraoptic and paraventricular nucleus. Each neuron gives rise to a single axon into the posterior pituitary gland, where its neurosecretory endings release AVP. Because the capillaries within the pituitary gland do not have a blood–brain barrier, AVP released in close proximity to the capillaries easily enters the bloodstream.[1] Similarly, neurons from the parvocellular division of the paraventricular nucleus send axons to the external zone of the median eminence of the pituitary gland, where AVP is secreted into the pituitary portal circulation.[2] AVP is also released somatodendritically within the nuclei of its origin to regularize the phasic firing pattern of the neurons[3,4] (fig. 2).

The most important stimuli that evoke vasopressin release are increased plasma osmolality, decreased arterial pressure, and reduced cardiac filling, *i.e.*, decreased blood volume.[5] Therefore, vasopressin, like adrenergic agonists or renin/angiotensin, can be considered a stress hormone, acting to maintain homeostasis and milieu intérieur.

AVP Receptors and Signal Transduction

Three subtypes of vasopressin receptors, V1, V2, and V3, have been identified (table 1). V1 receptors are

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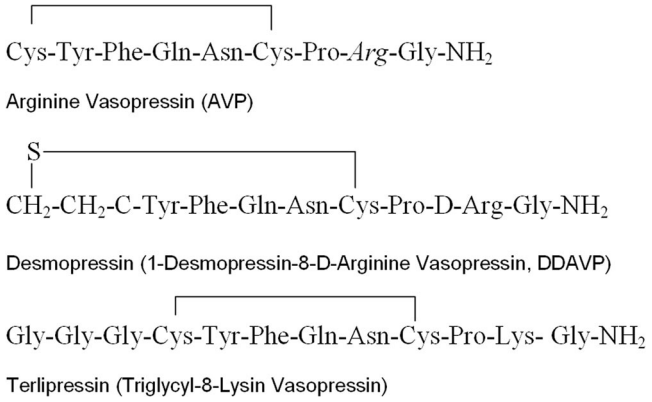

Fig. 1. Amino acid sequence of vasopressin and synthetic vasopressin agonists.

found on various cells including vascular smooth muscle, and V1 stimulation causes vasoconstriction. Kidney collecting duct cells express V2 receptors, which mediate water retention. V3 receptors are mainly found on cells within the central nervous system, especially in the adenohypophysis; their stimulation modulates corticotropin secretion. Vasopressin receptors are heptahelical membrane proteins coupled to specific G proteins for intracellular signal transduction.[6] A variety of signaling pathways have been shown to be associated with the V1 receptor. Activation of V1 and V3 receptors stimulates phospholipase C, which mediates the hydrolysis of inositol 4,5-bisphosphate to inositol 1,4,5-trisphosphate and diacylglycerol. These second messengers activate enzymes, such as protein kinase C, and mobilize intracellular calcium stored in the endoplasmic reticulum (fig. 3). Emptying of calcium stores activates *trp* cationic channels that allow extracellular calcium to enter the cells. V2 receptors interact with adenyl cyclase and generate cyclic adenosine monophosphate as a second messenger,[7,8] which stimulates protein kinase and causes insertion of aquaporin-2 into the luminal wall of collecting duct cells in the kidney. Binding of AVP to the V2 receptor causes receptor internalization and degradation.[9] However, details of regulation of vasopressin re-

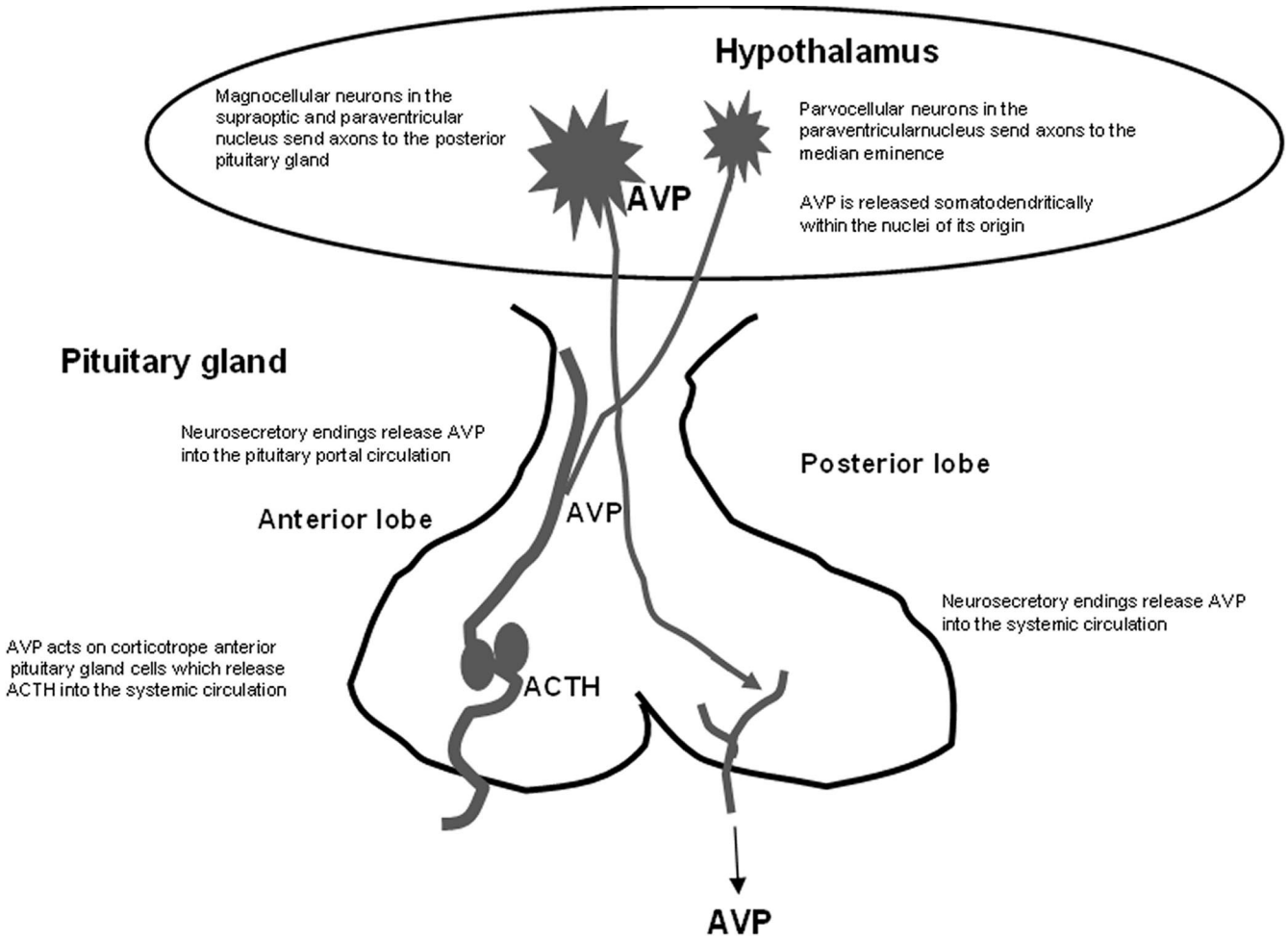

Fig. 2. Scheme of vasopressin release within the central nervous system. Vasopressin is synthesized in the hypothalamus in magnocellular and parvocellular neurons. Magnocellular neurons are mainly located in the supraoptic and paraventricular nucleus. Their axons release arginine vasopressin (AVP) into the systemic circulation in the posterior pituitary gland. Axons from parvocellular neurons in the paraventricular nucleus release AVP into the pituitary portal circulation. AVP is also released somatodendritically within the nuclei of its origin. ACTH = corticotropin.

Table 1. Localization of Vasopressin Receptor Subtypes and Mediated Functions

Receptor Subtype	Tissue	Main Function
V1	Liver, smooth muscle vascular cells, platelets, most peripheral tissues, central nervous system	Vasoconstriction
V2	Kidney collecting duct cells	Osmoregulation, water retention
V3	Central nervous system (adenohypophysis)	Corticotropin secretion

ceptor expression, potential genetic aspects, and possible feed back mechanisms have yet to be investigated.

Pharmacokinetics

Intravenous administration of exogenous AVP has effects within minutes. AVP rapidly distributes from plasma into the extracellular fluid volume. It is metabolized in the liver and kidneys, and a small proportion is eliminated with the urine. The plasma half-life is 4–20 min, so that continuous infusion is necessary for maintenance of effects. Exogenous AVP must be administered parenterally, because the peptide is quickly hydrolyzed by trypsin.[10,11]

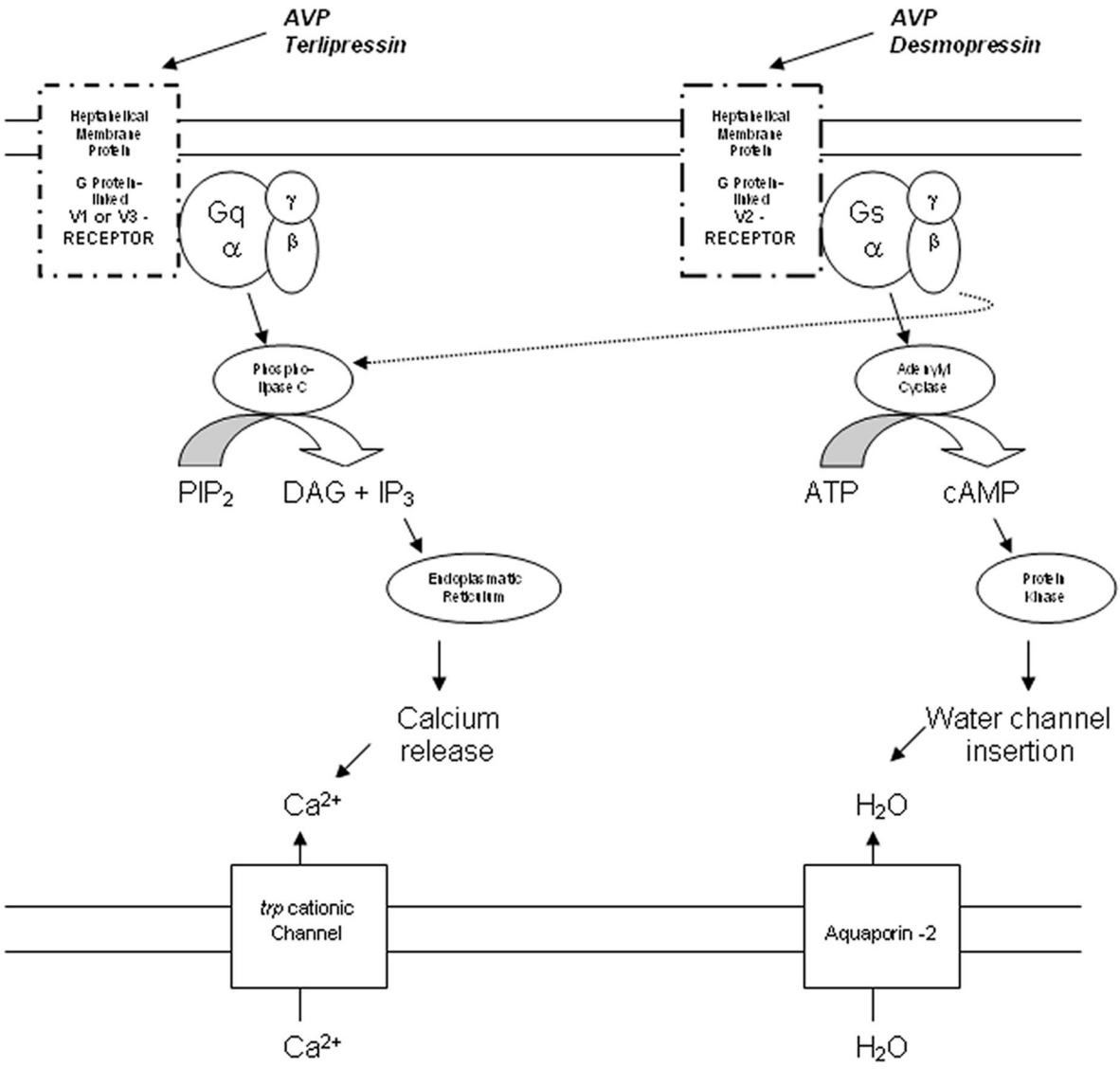

Fig. 3. Scheme of vasopressin's signal transduction. The *left* portion of the figure depicts V1 and V3 receptors on various cells; the *right* portion of the figure depicts V2 receptors on kidney collecting duct cells. *Arrows* indicate activation of pathways; the *dotted arrow* indicates a possible activation. ATP = adenosine triphosphate; AVP = arginine vasopressin; cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; Gq/Gs α, β, γ = G protein subunits; IP_3 = inositol (1,4,5) trisphosphate; PIP_2 = phosphatidylinositol (4,5)-bisphosphate.

Table 2. Vasopressin Agonists

Name	Structure	Receptor Affinity	Clinical Application
Argipressin	8-Arginine vasopressin (AVP)	V1, V2, V3	CPR, intraoperative hypotension, severe hemodynamic instability, vasodilatory shock
Desmopressin	Desamino-Cys-D-Arg vasopressin (DDAVP)	V2	Central diabetes insipidus, bleeding disorders
Terlipressin	N3-triglycyl-8-lysin vasopressin	V1	Intraoperative hypotension, gastrointestinal bleeding, portal hypertension

CPR = cardiopulmonary resuscitation.

Physiologic Functions

Vasopressin is important for osmoregulation, cardiovascular stability, and homeostasis but also serves as a corticotropin secretagogue and influences cognition, learning, and memory.

Osmoregulation. In healthy humans, plasma osmolality is sensed by osmoreceptors in the hypothalamus and is physiologically controlled within a very small range (285–290 mOsm/kg H_2O). Vasopressin-releasing magnocellular neurons directly function as such osmoreceptors, responding to increased osmotic pressure in their extracellular environment by increased firing rate and concomitant vasopressin release into the circulation.[1,12] In the kidney, the effects on vasopressin on collecting duct cells are mediated *via* V2 receptors, with V2 receptor activation evoking increased reabsorption of water.[13] As a result, vasopressin causes a decrease in plasma osmolality.[14,15]

Vasopressin plasma concentrations range between 0 and 20 pg/ml, depending on hydration and osmolality. For example, AVP plasma concentrations in euhydrated volunteers were 5 ± 1 pg/ml (mean ± SD) and increased to 30 ± 10 pg/ml with hyperosmolality (304 ± 2 mOsm/kg H_2O) evoked by infusion of hypertonic saline.[16] Even a low AVP concentration of approximately 2 pg/ml results in enhanced vascular smooth muscle contraction and increased systemic vascular resistance.[17]

Water permeability of cell membranes in the renal collecting duct is determined by aquaporin water channels. Activation of V2 receptors increases intracellular cyclic adenosine monophosphate, which in turn stimulates the vasopressin-regulated aquaporin-2 (AQP2) gene transcription and protein incorporation into the cell membrane. Accordingly, water permeability of the apical cell membrane increases markedly. Water exits the cell through other aquaporin channels at the basolateral membrane and returns into the systemic circulation, thus decreasing osmolality.[18]

Defects within this system are called *diabetes insipidus* and result in excessive loss of water. Diabetes insipidus is caused by lack of vasopressin release. Mutations of the V2 receptor system of kidney cells can cause renal (peripheral) diabetes insipidus.[15,19] In contrast, central diabetes insipidus with decreased vasopressin release can be either idiopathic or secondary due to head trauma, brain ischemia, or cerebral tumors which disturb the osmoregulatory function of vasopressinergic neurons.[20]

Accordingly, osmoregulatory functions of vasopressin can be substituted therapeutically with a synthetic selective V2 receptor agonist, desmopressin (desamino-Cys-D-Arg vasopressin [DDAVP]), as depicted in figure 1 and table 2. DDAVP is not digested by trypsin and hence can be administered orally, but nasal application is most commonly used for treatment of diabetes insipidus. Individual dosages for nasal application range from 5 to 40 μg. Antidiuretic effects of desmopressin are measurable after approximately 15 min and last for 8–12 h. Nasal dosages, therefore, are administered once or twice per day.[21]

Cardiovascular Control. To understand the role of vasopressin in circulatory regulation, it is necessary to examine the interplay between the three main vasopressor systems, *i.e.*, the sympathetic, renin–angiotensin, and vasopressin systems. Interestingly, despite widespread sympathetic block, epidural anesthesia often causes only a small decrease in blood pressure, even in the presence of an angiotensin-converting enzyme inhibitor. Only with additional blockade of vasopressin V1 receptors does blood pressure decrease significantly (fig. 4).[22,23] Therefore, as long as the other neurohumoral vasopressor systems are intact, endogenous vasopressin is not critical for hemodynamic stability, and its effects go unnoticed. However, if other systems are compromised, *i.e.*, during combined general and epidural anesthesia or in patients with orthostatic hypotension and autonomic insufficiency (fig. 5), even small increases in vasopressin plasma concentrations (> 2 pg/ml) serve to maintain blood pressure or initiate its increase by increasing peripheral vascular resistance.[24–26] Vasopressin causes substantial vasoconstriction in skin, skeletal muscle, and mesenteric blood vessels[27,28] mediated *via* V1 receptors. Interestingly, some studies also suggest vasodilatory effects of low vasopressin concentrations in selected vascular beds, including coronary, pulmonary, and cerebral arteries.[29,30] Endothelium dependence and nitric oxide–mediated mechanisms of V2 mediated vasodilation need further investigation.[31–33]

On the other hand, with neurohumoral systems intact,

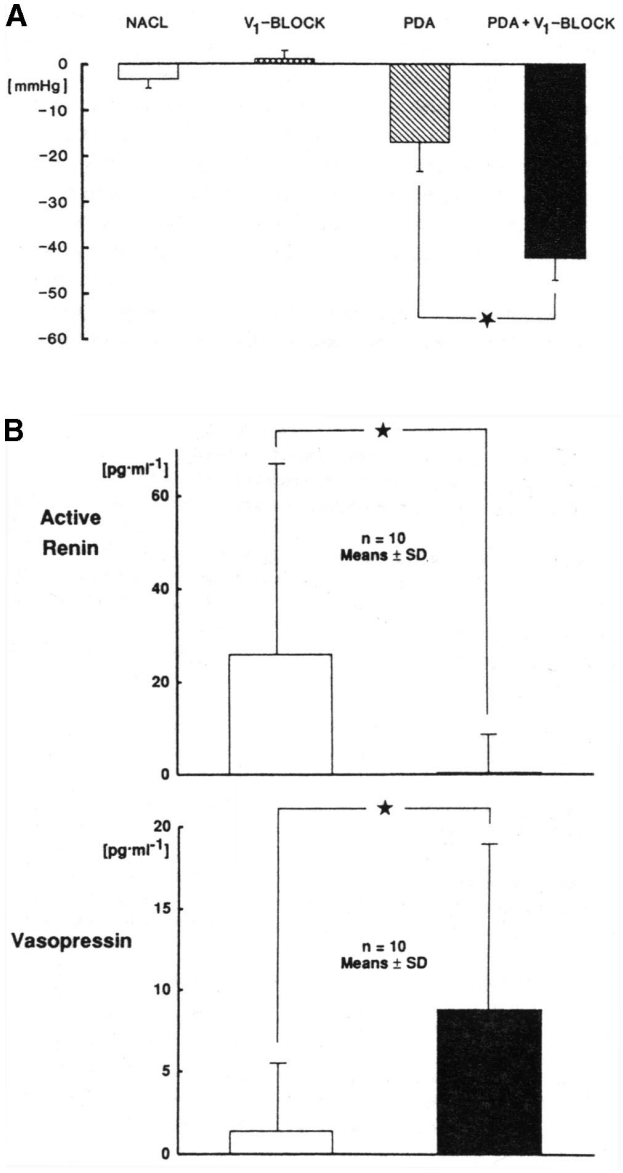

Fig. 4. Interplay between the sympathetic, renin–angiotensin, and vasopressin systems. (*A*) Maximum change in arterial blood pressure from baseline in conscious dogs after epidural saline (*open column*), vasopressin V1 receptor blockade alone (*column with crosses*), sympathetic blockade by epidural anesthesia alone (*striped column*), and epidural anesthesia in the presence of vasopressin V1 receptor blockade (*solid column*). Vasopressin receptor blockade alone has no impact on arterial pressure, whereas vasopressin receptor blockade markedly augments the decrease in arterial pressure during sympathetic blockade. Together with increased vasopressin concentrations observed with widespread sympathetic blockade, this indicates that the vasopressin system supports arterial pressure when both the sympathetic and the renin–angiotensin systems are impaired by sympathetic blockade. PDA = peridural anesthesia. From Peters *et al.*[22]; with permission. (*B*) Changes in plasma renin and vasopressin concentrations in response to induced arterial hypotension both before and during sympathetic block by epidural anesthesia (sensory blockade T1–T11) in humans. Hypotension was induced by intravenous infusion of sodium nitroprusside titrated to decrease mean arterial blood pressure by at least 25%. An increase in renin concentration is seen with the sympathetic nervous system intact, whereas sympathetic blockade suppresses renin release in response to hypotension but evokes vasopressin release. From Hopf *et al.*[66]; with permission. *Stars* indicate statistically significant differences.

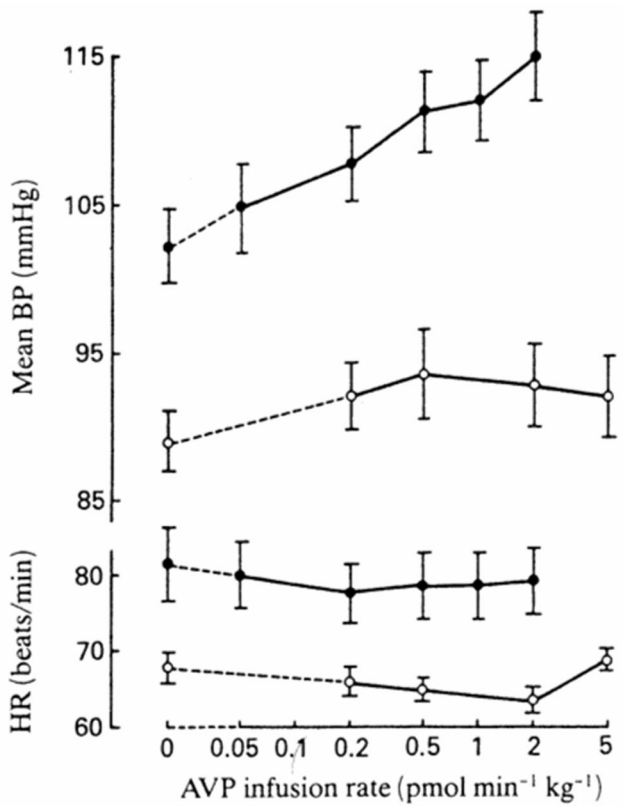

Fig. 5. Effect of incremental intravenous infusion of arginine vasopressin (AVP) on mean arterial blood pressure (BP) and heart rate (HR) in patients with autonomic insufficiency (*filled dots*) compared with healthy volunteers (*open dots*). AVP does not affect blood pressure in healthy volunteers, whereas it shows marked pressor effects in patients with autonomic insufficiency attesting to the buffering effect of an intact sympathetic nervous system. From Williams *et al.*[26]; with permission.

potential cardiovascular effects of exogenous vasopressin are buffered. In healthy volunteers, vasopressin infusion to plasma concentrations of up to 300 pg/ml does not change arterial blood pressure. Only moderate increases in central blood volume accompanied by a minor increase in central venous pressure and mild bradycardia are observed (fig. 5).[26] In fact, circulating AVP, by acting *via* specific V1 receptors in the area postrema, modulates central cardiovascular regulation by augmenting baroreflex inhibition of efferent sympathetic nerve activity and thus counterbalances its increase in peripheral resistance.[34,35] In addition, there is growing evidence for AVP receptors located on presynaptic terminals of central sympathetic efferents in the spinal cord, the stimulation of which may decrease sympathetic excitability.[36,37]

Therefore, vasopressin is an important backup system for blood pressure control and cardiovascular sympathetic modulation.[38]

Accordingly, with other regulatory systems intact, small hemodynamic changes cause only moderate changes in vasopressin plasma concentrations, and AVP increases in response to hypotensive stimuli rarely exceed 20 pg/ml.[39–41]

Table 3. Comparison of Vasopressin Plasma Concentration in Adults

Condition	Plasma Concentration, pg/ml
Healthy euhydrated volunteers[16]	5 ± 1
Healthy volunteers with infusion of hypertonic saline[16]	30 ± 10
Patients with cardiac arrest before unsuccessful CPR[45]	70 ± 9
Patients with cardiac arrest before successful CPR[45]	193 ± 28
Hypotensive patients in septic shock[46]	3 ± 1
Hypotensive patients in cardiogenic shock[46]	23 ± 2
Patients in vasodilatory shock after cardiopulmonary bypass[104]	8 ± 2
Patients during cardiopulmonary bypass[103]	198 ± 19

Data are mean ± SD.

CPR = cardiopulmonary resuscitation.

In volunteers, different stimuli for AVP release might be responsible for different responses of vasopressin plasma concentrations. Because it is difficult to selectively unload either cardiopulmonary or arterial baroreceptor afferents, cardiovascular reflex control of vasopressin releasing neurons is still not completely understood. Evidence suggests that cardiac rather than arterial baroceptor unloading is primarily responsible for vasopressin secretion in humans.[42] Animal studies also show an influence of adrenomedullin, a regulator of thirst and blood volume, on vasopressin production and release.[43] This suggests that AVP release is linked more closely to volume homeostasis than to arterial pressure control.

In contrast to moderate increases of vasopressin plasma concentrations observed in many volunteer studies, extensive AVP increases are observed during profound hypotension. In hemorrhagic shock, plasma AVP can increase to more than 180 pg/ml,[44] and in patients with out-of-hospital cardiac arrest, vasopressin concentrations of up to 193 pg/ml have been reported to occur before CPR, suggesting a major role of vasopressin during severe hemodynamic instability.[45]

Interestingly, several studies show comparatively low vasopressin concentrations in patients with vasodilatory shock or in hemodynamically unstable potential organ donors. Considering potential beneficial effects of endogenous vasopressin release, such AVP concentrations can be interpreted as inadequately low (table 3). Several clinical states of "relative vasopressin deficiency" have been proposed.[46,47]

Consequently, exogenous vasopressin can be used as a vasopressor when endogenous vasopressin concentration is inadequately low to maintain blood pressure. Vasopressin has been introduced into clinical practice as a vasopressor in several settings. Based on the concept of a relative vasopressin deficiency, vasopressin and synthetic vasopressin receptor agonists are used to treat intraoperative hypotension, different types of vasodilatory shock, and patients with sepsis (table 4). Vasopressin is also used as a vasopressor during CPR.

Corticotropin Secretion and Central Regulatory Functions of AVP. Corticotropin secretion is mainly regulated by corticotropin-releasing hormone (CRH) in response to decreased plasma cortisol concentrations. CRH neurosecretory cells send their axons from the paraventricular nucleus into the median eminence and release CRH into the pituitary portal circulation, activating corticotrope cells of the anterior pituitary. Vasopressin is also secreted into the pituitary portal circulation from parvocellular neurons in the paraventricular nucleus. Evidence suggests that CRH neurons also contain AVP.[2] Although CRH is the main corticotropin secretagogue, both hormones bind to anterior pituitary gland cells and regulate corticotropin release. Interestingly, the combined effect of the two hormones is far in excess of the added effect of each single hormone. In humans, concurrent administration of AVP and CRH produced a 30-fold increase of corticotropin as compared with administration of CRH alone.[2] Thus, vasopressin amplifies the effect of CRH on corticotropin release. These findings indicate the involvement of AVP in various stress responses.[48,49]

Vasopressin effects on anterior pituitary cells are mediated *via* specific V3 receptors (previously termed V1b).[6] Studies also show a wide distribution of these receptors throughout the central nervous system.[50] The consequences of these findings have yet to be fully elucidated, but vasopressin has been shown to influence thermoregulation, cognition, and memory as well as behavioral regulation. The CRH/AVP ratio, for example, seems to influence the pathophysiology of depression.[51,2]

Interestingly, increased plasma cortisol concentrations during CPR are associated with improved outcome. Therefore, corticotropin secretion stimulated by exogenous vasopressin might be one of the factors contributing to the successful use of vasopressin during CPR.[52]

Hemostasis. Blood collected during "stress" clots more rapidly.[53] Like other stress hormones, vasopressin enhances blood coagulation. In particular, AVP increases factor VIII and von Willebrand factor (vWF) plasma con-

Table 4. Doses of Desmopressin, Terlipressin, and AVP in Adults

Substance	Indication	Dose	Comment
Desmopressin	von Willebrand disease, mild hemophilia A	0.3 μg/kg intravenously	Clinical use since 1977 and clear evidence for efficacy
	Central diabetes insipidus	5–40 μg nasally or 1–4 μg/day intravenously or 0.3–0.6 mg/day orally	Clinical use since 1976 and clear evidence for efficacy
Terlipressin	Refractory intraoperative hypotension	1 mg intravenously	Three clinical trials with total of 60 patients, one case report on myocardial ischemia after terlipressin application
	Refractory hypotension in septic shock	1–2 mg intravenously every 4–6 h	One prospective study comparing terlipressin with norepinephrine, effects on outcome not yet evaluated
	Bleeding from esophageal varices in portal hypertensive patients	1–2 mg intravenously every 4–6 h	Evidence for efficacy, 34% relative risk reduction in mortality
	Hepatorenal syndrome	1–2 mg intravenously every 4–6 h	Several small nonrandomized studies with consistent results of improved renal function and systemic hemodynamics
AVP	CPR in adults	40-U bolus may replace first or second bolus of epinephrine	2005 AHA Guidelines on CPR, no recommendation for use in children
	Refractory hypotension in septic shock	0.01–0.04 U/min	Doses > 0.1 U/min may increase serious side effects
	Anesthesia for resection of neuroendocrine tumors	10- to 20-U bolus plus 0.1 U/min	Only two case reports published
	Vasodilatory shock after cardiopulmonary bypass	0.1 U/min	
	Anaphylactic shock	Bolus range from 2 to 40 U	Few case reports published
	Hemorrhagic shock	From 0.04 U/min to 40-U bolus	Few case reports published

AHA = American Heart Association; AVP = arginine vasopressin; CPR = cardiopulmonary resuscitation.

centrations.[53] However, the wide range of physiologic actions evoked by AVP limits its use for treatment of bleeding disorders. Desmopressin (DDAVP), the selective V2 receptor agonist, also increases factor VIII and vWF. Desmopressin has few side effects and is widely used to treat bleeding disorders. However, neither the receptor site nor the mechanisms by which desmopressin enhances platelet adhesion and increases factor VIII and vWF concentrations have been elucidated.[54] In perioperative settings, desmopressin is recommended to increase factor VIII and vWF concentrations in those patients with low but measurable concentrations, such as in patients with mild hemophilia A and type 1 von Willebrand disease.[55] Desmopressin can be administered nasally for treatment of diabetes insipidus. Nasal application is not recommended for treatment of bleeding disorders, and parental preparations are available for this indication. Intravenous application of 0.3 μg/kg desmopressin results in a 3- to 5-fold increase of coagulation factors VIII and vWF, with peak concentrations attained 30–60 min after intravenous injection and a plasma half-life of approximately 8 h.[53] Desmopressin has also been used perioperatively to attenuate hemorrhage in patients with congenital or acquired platelet disorders.[56] This indication remains controversial, because desmopressin increases the risk of arterial thrombosis[57] and other studies found no benefit of prophylactic desmopressin administration.[58]

Vasopressin Concentrations during Pregnancy

During pregnancy, plasma osmolality decreases by approximately 10 mOsmol/kg and is maintained on this lower value. Presumably, this is because the osmotic thresholds for thirst and for AVP release decrease in parallel. Thus, water intake increases and body fluids are diluted. Volume-sensing AVP release mechanisms also adjust to the new volume status,[59,60] and AVP plasma concentrations in pregnant women do not differ from values before pregnancy.

Therapeutic Strategies Using Vasopressin and Receptor Ligands

Refractory Arterial Hypotension during Anesthesia

Arterial blood pressure is maintained by the interplay of the sympathetic, renin–angiotensin, and vasopressin systems superimposed on circulatory mechanics. In turn, general anesthesia and most anesthetics interfere with cardiovascular regulation, resulting in a decrease in sympathetic neural drive and vascular smooth muscle tone. Perhaps ironically, vasopressin plasma concentration as a stress hormone during general anesthesia and surgery has been well studied, and modern anesthesia techniques aim to minimize stress hormone responses, including vasopressin release.[61] In addition, more patients are treated chronically with angiotensin-converting enzyme inhibitors or angiotensin II receptor (type 1)

antagonists, sometimes even combined with β-adrenoceptor blockade, impairing blood pressure maintenance.[62] In such patients, during anesthesia, hypotension refractory to repeated boluses of catecholamines has been described.[63] When anesthetized patients using AT-II receptor antagonists developed hypotension and did not respond to three boluses of epinephrine or phenylephrine, intravenous administration of the selective V1 vasopressin receptor agonist terlipressin (1 mg, triglycyllysin vasopressin) resulted in a significant and long-lasting increase in arterial blood pressure within 1 min.[64] Although no serious side effects were reported,[64] in one investigation, a case of myocardial ischemia requiring percutaneous transluminal coronary angioplasty after terlipressin was reported in a patient with coronary artery disease.[65] In this context, it should be remembered that some decades ago, AVP injection served as a stress test to uncover coronary artery disease by precipitating angina. Coronary artery disease is a contraindication for terlipressin, as outlined in the package insert.

Epidural anesthesia, especially thoracic epidural anesthesia, blocks neural traffic both to the vasculature and to the adrenal gland and also hormone responses including renal renin release, whereas AVP concentrations increase.[23,66] Therefore, patients with epidural anesthesia, especially when combined with general anesthesia and positive pressure ventilation, are at risk for hypotension. Exogenous AVP may be considered a suitable vasopressor in these patients. However, no data are available.

Therefore, terlipressin in a single 1-mg dose is an optional treatment for intraoperative hypotension refractory to catecholamines, especially in patients using renin–angiotensin system inhibitors.[67,68] Terlipressin (fig. 1 and table 2) is a synthetic vasopressin analog that is administered intravenously and converted into lysine vasopressin, resulting in a vasopressor effect lasting approximately 8 h. However, because terlipressin decreases splanchnic perfusion and oxygen delivery,[69] it should be used very cautiously, especially in patients with occlusive artery disease, until further studies are available.

Obstetric Anesthesia. No data exist on the use of exogenous vasopressin for the treatment of hypotension during obstetric anesthesia. Exogenous vasopressin significantly decreases uterine blood flow in the nonpregnant state as well as in pregnancy.[70,71] Therefore, vasopressin does not seem to be a suitable vasopressor for obstetric anesthesia during pregnancy or labor.

Anesthesia for Resection of Neuroendocrine Tumors. Pheochromocytoma is usually characterized by ectopic catecholamine secretion resulting in hypertension. However, pheochromocytoma releasing vasopressin has been described as well. In both types of tumors, feedback mechanisms could possibly down-regulate the neurohypophyseal vasopressin synthesis or release, but this has not been tested.[72,73] Patients with pheochromocytoma usually receive preoperative pharmacologic blockade of adrenoceptors. Thus, after tumor removal, maintenance of blood pressure by exogenous catecholamines can be impaired even when adequate fluid load is achieved. Exogenous vasopressin may be helpful in these patients. Two cases have been published describing exogenous vasopressin (AVP bolus of 10–20 U followed by 0.1 U/min) being used to restore blood pressure in a patients after pheochromocytoma resection.[74,75]

Vasopressin in Sepsis

Septic shock is characterized by vasodilatation and hypotension despite increased catecholamine concentrations and activation of the renin–angiotensin system. While nitric oxide is known to be responsible for vasodilation, failure of vascular smooth muscle to constrict may in part also be due to low vasopressin plasma concentrations.[76] In patients with septic shock, significantly lower vasopressin plasma concentrations have been measured compared with patients in cardiogenic shock, despite similar hypotension (*i.e.*, 3.1 *vs.* 22.7 pg/ml).[46] In the initial phase of septic shock, vasopressin concentrations almost always increase, but decrease to a significantly lower concentration after onset of septic shock.[77] This relative vasopressin deficiency may be caused by early depletion of hypothalamic AVP stores as revealed in magnetic resonance imaging by the loss of the T1-weighted signal, which is characteristic for the vasopressin content of the posterior pituitary lobe in patients with septic shock.[78] However, inhibition of cardiopulmonary afferents by volume loading or high catecholamine concentrations could also contribute to the comparatively low vasopressin concentrations observed in vasodilatory shock.[44] In addition, animal studies suggest that vasopressin V1 receptor gene expression in liver, lung, kidney, and heart is decreased as a result of cytokine-mediated down-regulation during endotoxemia, which may further aggravate the hemodynamic situation.[79]

Exogenous vasopressin has been used in patients with septic shock in several studies. AVP infusion (0.01 U/min) in patients with septic shock increased plasma concentrations of vasopressin to approximately 30 pg/ml, indicating that enhanced vasopressin degradation cannot account for low AVP plasma concentrations in sepsis.[46] Furthermore, AVP infusion (0.01–0.04 U/min) increased peripheral vascular resistance and arterial blood pressure within minutes of application.[80] No increase in pulmonary vascular resistance or pulmonary artery pressure was reported in patients treated with low-dose vasopressin (0.04 U/min), nor were cardiac complications or changes in electrolyte, blood and urine osmolality, or metabolic variables (fig. 6).[81] In fact, urine

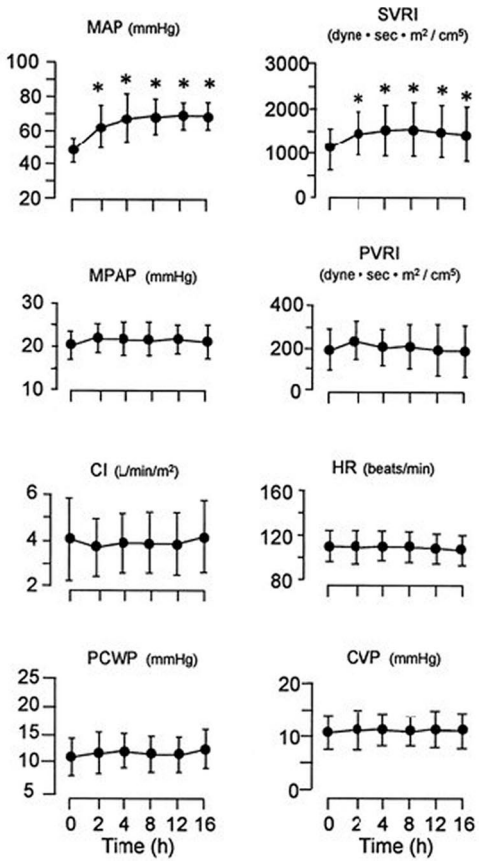

Fig. 6. Effect on hemodynamic variables of vasopressin infusion in patients with septic shock. Vasopressin significantly increases mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) within minutes of application. It does not significantly influence pulmonary vascular resistance index (PVRI), mean pulmonary artery pressure (MPAP), cardiac index (CI), heart rate (HR), wedge pressure (PCWP), or central venous pressure (CVP). From Tsuneyoshi *et al.*[81]; with permission.

output and creatinine clearance increased significantly in vasopressin-treated patients, if not anuric before treatment.[82] However, dosage should be limited to prevent adverse outcomes. In a retrospective analysis of 50 patients in severe septic shock receiving AVP for more than 2 h in an open-label fashion as a rescue therapy, 6 patients experienced cardiac arrest, 5 of them with a vasopressin infusion of more than 0.03 U/min.[83] Gastrointestinal perfusion can be reduced by vasopressin infusion,[84] but moderate doses of AVP (0.04 U/min) do not severely impair blood flow. Higher doses (exceeding 0.1 U/min) may induce ischemia in the mesenteric and renal circulation and decrease cardiac index, oxygen delivery, and oxygen uptake.[85,86] When AVP is used as a single vasopressor, high doses (up to 1.8 U/min) are necessary to maintain blood pressure.[86] Further side effects of AVP infusion were reported, such as significant decreases in platelet count and a significant increase in liver enzymes and total bilirubin concentration,[87–89] and suggest induction of platelet adhesion and reduction of liver perfusion, respectively. Despite decreases in platelet count, however, overall coagulation does not seem to be impaired in patients receiving AVP in advanced septic shock.[88,89] Severe ischemic skin necrosis after extravasation of vasopressin has also been reported.[90]

Alternatively, single bolus administration of 1–2 mg terlipressin, the selective V1 receptor agonist, has been reported to increase mean arterial blood pressure for approximately 5 h without serious side effects in eight patients with septic shock after other treatments had failed.[91,92] However, terlipressin is a potent intestinal vasoconstrictor, and evidence suggests decreased intestinal perfusion with terlipressin infusion.[93,94]

In summary, AVP is a potent vasopressor in septic shock, and its administration results in increased arterial blood pressure and decreased catecholamine requirements in the majority of patients, including children.[95,96] AVP infusion in advanced vasodilatory shock can be considered as a supplementary vasopressor. Low AVP doses (0.01–0.07 U/min) combined with norepinephrine are an optional treatment to stabilize cardiovascular function.[97]

Few data are available to evaluate side effects, dose limits, and mortality in comparison with conventional treatments. Therefore, further studies will be of great interest.

Vasopressin during Hemorrhage

Fluid resuscitation is the standard of care for hemorrhagic shock. However, in cases of prolonged hemorrhagic shock, the response to both volume and catecholamine vasopressors can be poor because of persistent vasodilation, acidosis, receptor down-regulation, and/or nitric oxide release. Animal data show promising effects of AVP infusion on restoration of circulation and survival in severe hemorrhagic shock.[98,99] Recently, AVP was demonstrated to restore circulation when used as an adjunct vasopressor in intractable hypotension due to hemorrhagic shock.[100–103] However, timing of application and AVP doses differed greatly, with dosages ranging from a 40-U bolus to a 0.04-U/min continuous infusion. In selected patients who would possibly die otherwise, AVP application may provide an option to stabilize cardiocirculatory function. However, data are very limited, and further research is needed.[104]

Vasopressin in Vasodilatory Shock

Apart from sepsis, vasopressin has been used also to increase arterial blood pressure in several other vasodilatory shock states, such as shock after cardiopulmonary bypass, or in hemodynamically unstable organ donors.

Cardiopulmonary bypass typically increases vasopressin plasma concentrations to more than 100 pg/ml.[105] Some patients develop postbypass hypotension as part of a systemic inflammatory response. These patients often need vasopressors for postbypass hypotension. In these patients, low AVP plasma concentrations (< 10 pg/ml) have been found, and this has been hypothesized

to represent vasopressin deficiency[106] (table 3). Risk factors for postbypass shock with inappropriately low AVP plasma concentrations are low ejection fraction and use of angiotensin-converting enzyme inhibitors.[107] In patients receiving a left ventricular assist device, AVP rapidly and significantly increased arterial pressure due to increased systemic resistance while cardiac index remained unchanged. Similarly, vasopressin (0.1 U/min) was effective in vasodilatory shock after cardiac transplantation.[108] In fact, vasopressin infusion (0.1 U/min) in patients with postcardiotomy hypotension enabled discontinuation of catecholamine administration in some patients. Prophylactic use of vasopressin in high-risk patients undergoing cardiopulmonary bypass has also been successful.[109] The effective and safe use of vasopressin ($0.0003–0.002\ U \cdot kg^{-1} \cdot min^{-1}$) has also been shown in children after cardiac surgery.[110,111] Case reports also suggest that vasopressin is effective in the treatment of hypotension due to phosphodiesterase inhibitors in patients with heart failure.[112]

In severe anaphylactic shock, cardiovascular collapse results from vasodilation and increased capillary permeability and relative hypovolemia. Vasopressin has been shown to restore blood pressure after catecholamine administration was ineffective in several cases of anaphylactic shock. Dosages ranged from 2 to 40 U as a bolus administration. The 2005 American Heart Association Guidelines on CPR mention vasopressin administration as a potential therapy for severely hypotensive patients in anaphylactic shock, but no dosages are recommended.[113]

Desmopressin, the V2 receptor agonist, has long been used to treat central diabetes insipidus in brain-dead organ donors, and its use, although not causing hemodynamic changes, is critical in these patients. Studies on side effects suggest decreased graft function due to its procoagulatory effects.[114–116] In contrast, early reports demonstrated that AVP in polyuric brain-dead organ donors resulted in normal urine output, preserved kidney function, and hemodynamic stability. Therefore, use of vasopressin in organ donors with diabetes insipidus has been proposed to increase the quality and number of organs for transplantation.[117] Comparatively low vasopressin plasma concentrations (< 8 pg/ml) were reported in hemodynamically unstable organ donors without clinical signs of diabetes insipidus.[47] AVP infusion (0.04–0.1 U/min) in these hypotensive patients restored blood pressure and significantly decreased catecholamine requirements. Further studies are needed to assess the influence of vasopressin on graft function.

Vasopressin during Cardiopulmonary Resuscitation

Patients with subsequent cardiac arrest have vasopressin plasma concentrations of up to 193 pg/ml before CPR.[48] Interestingly, patients in whom spontaneous circulation could be restored had significantly higher vasopressin concentrations both before and during CPR than those without return of spontaneous circulation.[45] Given the importance of vasopressin for circulatory stability, vasopressor effects of AVP might have contributed to resuscitation by improved vital organ blood flow. Therefore, exogenous vasopressin has been used during CPR in humans and in animal experiments. After unsuccessful CPR with epinephrine, vasopressin increased coronary perfusion pressure in a subgroup of patients.[118] Many studies in animals after evoked ventricular fibrillation or ventricular tachycardia have reported beneficial effects on outcome after vasopressin administration. In experimental CPR protocols including randomized treatment with either vasopressin or epinephrine, vasopressin was superior to epinephrine in increasing vital organ blood flow, including cerebral blood flow, and significantly more animals were resuscitated.[119–123] Vasopressin during CPR increases coronary artery cross-sectional area.[124] AVP (40 U) can be administered intravenously, as well as endobronchially or *via* the intraosseous route.[125,126]

Although case reports have described restoration of spontaneous circulation in humans after vasopressin when previous intravenous administration of epinephrine administration and defibrillation had failed,[127] only two prospective studies on the use of AVP for human CPR as the initial vasopressor agent are available. Of 40 patients with out-of-hospital ventricular fibrillation resistant to electrical defibrillation and treated with either epinephrine (1 mg intravenously) or AVP (40 U intravenously), a significantly larger number was successfully resuscitated and survived for 24 h after vasopressin.[128] In contrast, in 200 patients randomly assigned to receive either epinephrine (1 mg intravenously) or AVP (40 U intravenously) during in-hospital CPR, regardless of initial rhythm, no differences in restoration of spontaneous circulation or survival rate were reported.[129] Possibly, the difference in results between these studies relates to a marked difference in the study population (in-hospital *vs.* out-of-hospital arrest) and in time to start of CPR. Recently, the European Resuscitation Council gave a class IIb recommendation for the use of 40 U vasopressin as an initial vasopressor in adults with shock-refractory ventricular fibrillation as an alternative to 1 mg epinephrine.[130] The 2005 American Heart Association Guidelines on CPR recommend either to use repeated 1-mg boluses of epinephrine every 3–5 min or to replace the first or second dose of epinephrine with one dose of 40 U vasopressin intravenously or intraosseously (class indeterminate).[113] Vasopressin (40 U bolus) during CPR with initial rhythms other than ventricular fibrillation/ventricular tachycardia may also be considered to replace the first or second bolus of epinephrine. In a comparison of vasopressin and epinephrine in 1,186 patients with out-of-hospital CPR, there was no significant difference in outcome between vasopressin and epinephrine in pa-

tients with ventricular tachycardia or pulseless electrical activity but a significantly better outcome among patients with asystole receiving vasopressin treatment.[131]

A retrospective case series of children with cardiac arrest suggests beneficial effects of AVP when administered after failure of conventional CPR.[132] In contrast, after asphyxia in swine, used as a model for pediatric CPR, epinephrine (200 μg/kg) was found to be superior to vasopressin (0.8 U/kg) with regard to coronary perfusion pressure, left ventricular myocardial blood flow, and return of spontaneous circulation.[133] AVP in 0.4-U/kg boluses was reported to be equipotent to 45 μg/kg epinephrine.[134] In contrast, 0.4 U/kg vasopressin was found to be superior to 45 μg/kg epinephrine in the same setting, when cardiac arrest was evoked by ventricular fibrillation.[135] Taken together, there is inadequate data about the use of vasopressin for CPR in infants and children, and no active recommendations exist.[113] Further studies are necessary to determine the role of AVP during human CPR, in particular in patients with coronary artery disease.

Vasopressin and Portal Venous Hypertension

Vasoconstriction mediated *via* V1 receptors decreases mesenteric blood flow. The selective V1 agonist terlipressin also mediates arteriolar vasoconstriction in the splanchnic vascular bed.[136] Both vasopressin and terlipressin can decrease hepatic blood flow. Although both agents decrease blood flow and pressure in esophageal varices, vasopressin is less efficient and may cause more systemic side effects than terlipressin. Therefore, terlipressin (1- to 2-mg intravenous bolus every 4–6 h) has long been used to treat bleeding from esophageal varices in patients with portal venous hypertension.[137,138] Recently, new indications for the use of terlipressin in patients with chronic liver disease have been investigated because portal hypertension is often associated with a hyperdynamic circulation with increased cardiac output, heart rate, and plasma volume, as well as decreased blood pressure and systemic vascular resistance. Terlipressin (2-mg intravenous bolus) in patients with liver cirrhosis and portal hypertension increases arterial blood pressure and systemic vascular resistance, whereas cardiac output and heart rate decrease and portal pressure and hepatic blood flow are diminished.[94] Thus, terlipressin significantly attenuates the hyperdynamic circulation in chronic liver disease with portal hypertension.[94] Furthermore, portal hypertension with functional renal failure, *i.e.*, hepatorenal syndrome, has a high mortality and is also characterized by decreased systemic vascular resistance and hypotension. Terlipressin was suggested to improve renal function and survival in patients with hepatorenal syndrome.[139–141] Terlipressin (0.5- to 2-mg intravenous bolus every 4 h or 6 mg/24 h, respectively) combined with colloid infusion was found to reverse the hepatorenal syndrome in most patients.[142,143] Thus, terlipressin is a promising drug for patients with chronic liver disease.

Vasopressin Receptor Antagonists

Patients with chronic heart failure have increased plasma vasopressin concentrations, which may contribute to their clinical syndrome of fluid retention. Because AVP regulates vascular tone and water reabsorption *via* V1 and V2 receptor subtypes, respectively, these receptors are a potential neurohormonal target in the treatment of chronic heart failure. Two vasopressin antagonists, tolvaptan (oral V2 receptor antagonist)[144] and conivaptan (oral dual V1 and V2 receptor antagonist)[145–147] are currently under clinical evaluation. Both drugs have potent diuretic effects and are useful for treatment of the syndrome of inappropriate antidiuretic hormone secretion and other states of hyponatremia and water retention, *e.g.*, liver cirrhosis.[148,149]

Selective V1 antagonists are being studied for their effects on human vascular smooth muscle cells and tested in patients with essential hypertension and Raynaud phenomenon.[150–152]

Selective V3 antagonists are also under evaluation for anxiolytic and antidepressant effects in the treatment of stress-related disorders.[153,154] All of these approaches deserve further evaluation.

Summary

Vasopressin, a hypothalamic peptide, is crucial for fluid homeostasis and cardiovascular control, acting *via* three different receptor subtypes (V1, V2, and V3). Diabetes insipidus, defined as lack of vasopressin release or its renal effects, and resulting in excessive loss of water, can be treated using the V2 agonist desmopressin. Desmopressin also increases factor VIII and vWF concentrations and, therefore, can decrease bleeding. AVP and terlipressin, a V1 agonist, increase blood pressure by vasoconstriction and are used to treat intraoperative hypotension, portal venous hypertension, and septic and other (post–cardiopulmonary bypass) types of vasodilatory shock and to restore circulation during CPR. Side effects must be further investigated, and more studies are required.

Vasopressin receptor antagonists decrease vascular smooth muscle contraction (V1 antagonists) and have diuretic effects (V2 antagonists). They are currently under clinical investigation mainly for treatment of chronic heart failure.

References

1. Leng G, Brown CH, Russell JA: Physiological pathways regulating the activity of magnocellular neurosecretory cells. Prog Neurobiol 1999; 57:625–55

2. Scott LV, Dinan TG: Vasopressin and the regulation of hypothalamic-pituitary-adrenal axis function: Implications for the pathophysiology of depression. Life Sci 1998; 62:1985–98

3. Gouzenes L, Desarmenien MG, Hussy N, Richard P, Moos FC: Vasopressin regularizes the phasic firing pattern of rat hypothalamic magnocellular vasopressin neurons. J Neurosci 1998; 18:1879–85

4. Chevaleyre V, Moos FC, Desarmenien MG: Interplay between presynaptic and postsynaptic activities is required for dendritic plasticity and synaptogenesis in the supraoptic nucleus. J Neurosci 2002; 22:265–73

5. Goldsmith SR: Baroreceptor-mediated suppression of osmotically stimulated vasopressin in normal humans. J Appl Physiol 1988; 65:1226–30

6. Thibonnier M, Berti-Mattera LN, Dulin N, Conarty DM, Mattera R: Signal transduction pathways of the human V1-vascular, V2-renal, V3-pituitary vasopressin and oxytocin receptors. Prog Brain Res 1998; 119:147–61

7. Birnbaumer M: Vasopressin receptors. Trends Endocrinol Metab 2000; 11:406–10

8. Barberis C, Mouillac B, Durroux T: Structural bases of vasopressin/oxytocin receptor function. J Endocrinol 1998; 156:223–9

9. Robben JH, Knoers NV, Deen PM: Regulation of the vasopressin V2 receptor by vasopressin in polarized renal collecting duct cells. Mol Biol Cell 2004; 15:5693–9

10. Baumann G, Dingman JF: Distribution, blood transport, and degradation of antidiuretic hormone in man. J Clin Invest 1976; 57:1109–16

11. Beardwell CG, Geelen G, Palmer HM, Roberts D, Salamonson L: Radioimmunoassay of plasma vasopressin in physiological and pathological states in man. J Endocrinol 1975; 67:189–202

12. Mason WT: Supraoptic neurones of rat hypothalamus are osmosensitive. Nature 1980; 287:154–7

13. Bankir L, Fernandes S, Bardoux P, Bouby N, Bichet DG: Vasopressin-V2 receptor stimulation reduces sodium excretion in healthy humans. J Am Soc Nephrol 2005; 16:1920–8

14. Bankir L: Antidiuretic action of vasopressin: Quantitative aspects and interaction between V1a and V2 receptor-mediated effects. Cardiovasc Res 2001; 51:372–90

15. Birnbaumer M: The V2 vasopressin receptor mutations and fluid homeostasis. Cardiovasc Res 2001; 51:409–15

16. Mann SE, Fresquez M, Ross MG: A simplified index of the plasma sodium threshold for arginine vasopressin secretion-morning fasting, euhydrated sodium levels. Am J Obstet Gynecol 2000; 183:933–6

17. Ebert TJ, Cowley AW Jr, Skelton M: Vasopressin reduces cardiac function and augments cardiopulmonary baroreflex resistance increases in man. J Clin Invest 1986; 77:1136–42

18. Knepper MA: Molecular physiology of urinary concentrating mechanism: Regulation of aquaporin water channels by vasopressin. Am J Physiol 1997; 272:F3–12

19. Sangkuhl K, Rompler H, Busch W, Karges B, Schoneberg T: Nephrogenic diabetes insipidus caused by mutation of Tyr205: A key residue of V2 vasopressin receptor function (case report). Hum Mutat 2005; 25:505

20. Pivonello R, De Bellis A, Faggiano A, Di Salle F, Petretta M, Di Somma C, Perrino S, Altucci P, Bizzarro A, Bellastella A, Lombardi G, Colao A: Central diabetes insipidus and autoimmunity: Relationship between the occurrence of antibodies to arginine vasopressin-secreting cells and clinical, immunological, and radiological features in a large cohort of patients with central diabetes insipidus of known and unknown etiology. J Clin Endocrinol Metab 2003; 88:1629–36

21. Robinson AG: DDAVP in the treatment of central diabetes insipidus. N Engl J Med 1976; 294:507–11

22. Peters J, Schlaghecke R, Thouet H, Arndt JO: Endogenous vasopressin supports blood pressure and prevents severe hypotension during epidural anesthesia in conscious dogs. ANESTHESIOLOGY 1990; 73:694–702

23. Carp H, Vadhera R, Jayaram A, Garvey D: Endogenous vasopressin and renin-angiotensin systems support blood pressure after epidural block in humans. ANESTHESIOLOGY 1994; 80:1000–7

24. Aylward PE, Floras JS, Leimbach WN Jr, Abboud FM: Effects of vasopressin on the circulation and its baroreflex control in healthy men. Circulation 1986; 73:1145–54

25. Saad CI, Ribeiro AB, Zanella MT, Mulinari RA, Gavras I, Gavras H: The role of vasopressin in blood pressure maintenance in diabetic orthostatic hypotension. Hypertension 1988; 11:I217–21

26. Williams TD, Da Costa D, Mathias CJ, Bannister R, Lightman SL: Pressor effect of arginine vasopressin in progressive autonomic failure. Clin Sci (Lond) 1986; 71:173–8

27. Cowley AW Jr, Liard JF: Vasopressin and arterial pressure regulation: Special lecture. Hypertension 1988; 11:I25–32

28. Knotzer H, Pajk W, Maier S, Ladurner R, Kleinsasser A, Wenzel V, Dunser MW, Ulmer H, Hasibeder WR: Arginine vasopressin reduces intestinal oxygen supply and mucosal tissue oxygen tension. Am J Physiol Heart Circ Physiol 2005; 289:H168–73

29. Abboud FM, Floras JS, Aylward PE, Guo GB, Gupta BN, Schmid PG: Role of vasopressin in cardiovascular and blood pressure regulation. Blood Vessels 1990; 27:106–15

30. Walker BR, Haynes J Jr, Wang HL, Voelkel NF: Vasopressin-induced pulmonary vasodilation in rats. Am J Physiol 1989; 257:H415–22

31. Hirsch AT, Dzau VJ, Majzoub JA, Creager MA: Vasopressin-mediated forearm vasodilation in normal humans: Evidence for a vascular vasopressin V2 receptor. J Clin Invest 1989; 84:418–26

32. Rudichenko VM, Beierwaltes WH: Arginine vasopressin-induced renal vasodilation mediated by nitric oxide. J Vasc Res 1995; 32:100–5

33. Suzuki Y, Satoh S, Oyama H, Takayasu M, Shibuya M, Sugita K: Vasopressin mediated vasodilation of cerebral arteries. J Auton Nerv Syst 1994; 49 (suppl): S129–32

34. Hasser EM, Cunningham JT, Sullivan MJ, Curtis KS, Blaine EH, Hay M: Area postrema and sympathetic nervous system effects of vasopressin and angiotensin II. Clin Exp Pharmacol Physiol 2000; 27:432–6

35. Grindstaff RR, Cunningham JT: Cardiovascular regulation of vasopressin neurons in the supraoptic nucleus. Exp Neurol 2001; 171:219–26

36. Hallbeck M, Larhammar D, Blomqvist A: Neuropeptide expression in rat paraventricular hypothalamic neurons that project to the spinal cord. J Comp Neurol 2001; 433:222–38

37. Oz M, Kolaj M, Renaud LP: Electrophysiological evidence for vasopressin V(1) receptors on neonatal motoneurons, premotor and other ventral horn neurons. J Neurophysiol 2001; 86:1202–10

38. Bishop VS, Hay M: Involvement of the area postrema in the regulation of sympathetic outflow to the cardiovascular system. Front Neuroendocrinol 1993; 14:57–75

39. Goldsmith SR: The effect of moderate hypotension on vasopressin levels in normal humans. Am J Med Sci 1989; 298:295–8

40. Gabrielsen A, Warberg J, Christensen NJ, Bie P, Stadeager C, Pump B, Norsk P: Arterial pulse pressure and vasopressin release during graded water immersion in humans. Am J Physiol Regul Integr Comp Physiol 2000; 278: R1583–8

41. 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:R1024–30

42. Giannattasio C, Del Bo A, Cattaneo BM, Cuspidi C, Gronda E, Frigerio M, Mangiavacchi M, Marabini M, De Vita C, Grassi G, Zanchetti A, Mancia G: Reflex vasopressin and renin modulation by cardiac receptors in humans. Hypertension 1993; 21:461–9

43. Taylor MM, Baker JR, Samson WK: Brain-derived adrenomedullin controls blood volume through the regulation of arginine vasopressin production and release. Am J Physiol Regul Integr Comp Physiol 2005; 288:R1203–10

44. Holmes CL, Patel BM, Russell JA, Walley KR: Physiology of vasopressin relevant to management of septic shock. Chest 2001; 120:989–1002

45. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG: Release of endogenous vasopressors during and after cardiopulmonary resuscitation. Heart 1996; 75: 145–50

46. 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; 95:1122–5

47. 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; 100:II244–6

48. Aguilera G, Rabadan-Diehl C: Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: Implications for stress adaptation. Regul Pept 2000; 96:23–9

49. Tanoue A, Ito S, Honda K, Oshikawa S, Kitagawa Y, Koshimizu TA, Mori T, Tsujimoto G: The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. J Clin Invest 2004; 113:302–9

50. Hernando F, Schoots O, Lolait SJ, Burbach JP: Immunohistochemical localization of the vasopressin V1b receptor in the rat brain and pituitary gland: Anatomical support for its involvement in the central effects of vasopressin. Endocrinology 2001; 142:1659–68

51. Dinan TG, O'Brien S, Lavelle E, Scott LV: Further neuroendocrine evidence of enhanced vasopressin V3 receptor responses in melancholic depression. Psychol Med 2004; 34:169–72

52. Kornberger E, Prengel AW, Krismer A, Schwarz B, Wenzel V, Lindner KH, Mair P: Vasopressin-mediated adrenocorticotropin release increases plasma cortisol concentrations during cardiopulmonary resuscitation. Crit Care Med 2000; 28:3517–21

53. Mannucci PM: Desmopressin (DDAVP) in the treatment of bleeding disorders: The first twenty years. Haemophilia 2000; 6 (suppl 1):60–7

54. Cattaneo M: Desmopressin in the treatment of patients with defects of platelet function. Haematologica 2002; 87:1122–4

55. Cattaneo M: Review of clinical experience of desmopressin in patients with congenital and acquired bleeding disorders. Eur J Anaesthesiol Suppl 1997; 14:10–4

56. Kobrinsky NL, Israels ED, Gerrard JM, Cheang MS, Watson CM, Bishop AJ, Schroeder ML: Shortening of bleeding time by 1-deamino-8-D-arginine vasopressin in various bleeding disorders. Lancet 1984; 1:1145–8

57. Girolami A, Vettore S, Fabris F: Selection of both normal and bleeding patients is indicated before desmopressin administration (letter). Thromb Haemost 2005; 93:1198

58. Pleym H, Stenseth R, Wahba A, Bjella L, Tromsdal A, Karevold A, Dale O: Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. Anesth Analg 2004; 98:578–84

59. Lindheimer MD, Davison JM: Osmoregulation, the secretion of arginine vasopressin and its metabolism during pregnancy. Eur J Endocrinol 1995; 132: 133–43

60. van der Post JA, van Buul BJ, Hart AA, van Heerikhuize JJ, Pesman G, Legros JJ, Steegers EA, Swaab DF, Boer K: Vasopressin and oxytocin levels during normal pregnancy: Effects of chronic dietary sodium restriction. J Endocrinol 1997; 152:345–54

61. Brinkmann A, Seeling W, Wolf CF, Kneitinger E, Schonberger C, Vogt N, Orend KH, Buchler M, Radermacher P, Georgieff M: Vasopressor hormone response following mesenteric traction during major abdominal surgery. Acta Anaesthesiol Scand 1998; 42:948–56

62. Bertrand M, Godet G, Meersschaert K, Brun L, Salcedo E, Coriat P: Should the angiotensin II antagonists be discontinued before surgery? Anesth Analg 2001; 92:26–30

63. Brabant SM, Bertrand M, Eyraud D, Darmon PL, Coriat P: The hemodynamic effects of anesthetic induction in vascular surgical patients chronically treated with angiotensin II receptor antagonists. Anesth Analg 1999; 89:1388–92

64. Meersschaert K, Brun L, Gourdin M, Mouren S, Bertrand M, Riou B, Coriat P: Terlipressin-ephedrine *versus* ephedrine to treat hypotension at the induction of anesthesia in patients chronically treated with angiotensin converting-enzyme inhibitors: A prospective, randomized, double-blinded, crossover study. Anesth Analg 2002; 94:835–40

65. 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

66. Hopf HB, Schlaghecke R, Peters J: Sympathetic neural blockade by thoracic epidural anesthesia suppresses renin release in response to arterial hypotension. ANESTHESIOLOGY 1994; 80:992–9

67. Boccara G, Ouattara A, Godet G, Dufresne E, Bertrand M, Riou B, Coriat P: Terlipressin *versus* norepinephrine to correct refractory arterial hypotension after general anesthesia in patients chronically treated with renin-angiotensin system inhibitors. ANESTHESIOLOGY 2003; 98:1338–44

68. Eyraud D, Brabant S, Nathalie D, Fleron MH, Gilles G, Bertrand M, Coriat P: Treatment of intraoperative refractory hypotension with terlipressin in patients chronically treated with an antagonist of the renin-angiotensin system. Anesth Analg 1999; 88:980–4

69. Morelli A, Tritapepe L, Rocco M, Conti G, Orecchioni A, De Gaetano A, Picchini U, Pelaia P, Reale C, Pietropaoli P: Terlipressin *versus* norepinephrine to counteract anesthesia-induced hypotension in patients treated with renin-angiotensin system inhibitors: Effects on systemic and regional hemodynamics. ANESTHESIOLOGY 2005; 102:12–9

70. Sjoquist PO, Bjellin L, Carter AM: Effect of a vasopressin analogue (Nalpha-glycyl-glycyl-glycyl-[8-lysine]-vasopressin) on organ blood flow in the pregnant guinea pig. Acta Pharmacol Toxicol (Copenh) 1977; 40:369–77

71. Sjoquist PO, Bjellin L, Carter AM: Effect of 1-deamino-6-carba-(8-arginine)-vasopressin on organ blood flow in the female guinea pig. Eur J Pharmacol 1977; 46:25–30

72. Boccara G, Mann C, Guillon G: Secretion of vasopressin from a human pheochromocytoma (letter). Ann Intern Med 1998; 128:1049

73. Kay J, Minkel DT, Gustafson AB, Skelton M, Cowley AW Jr, Wilson SD: Elevated plasma vasopressin (AVP) levels during resection of pheochromocytomas. Surgery 1986; 100:1150–3

74. Augoustides JG, Abrams M, Berkowitz D, Fraker D: Vasopressin for hemodynamic rescue in catecholamine-resistant vasoplegic shock after resection of massive pheochromocytoma. ANESTHESIOLOGY 2004; 101:1022–4

75. Tan SG, Koay CK, Chan ST: The use of vasopressin to treat catecholamine-resistant hypotension after phaeochromocytoma removal. Anaesth Intensive Care 2002; 30:477–80

76. Reid IA: Role of vasopressin deficiency in the vasodilation of septic shock. Circulation 1997; 95:1108–10

77. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D: Circulating vasopressin levels in septic shock. Crit Care Med 2003; 31:1752–8

78. 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

79. 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:R979–84

80. Malay MB, Ashton RC Jr, Landry DW, Townsend RN: Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 1999; 47:699–703

81. 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; 29:487–93

82. Patel BM, Chittock DR, Russell JA, Walley KR: Beneficial effects of short-term vasopressin infusion during severe septic shock. ANESTHESIOLOGY 2002; 96: 576–82

83. 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; 27:1416–21

84. van Haren FM, 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

85. Malay MB, Ashton JL, Dahl K, Savage EB, Burchell SA, Ashton RC Jr, Sciacca RR, Oliver JA, Landry DW: Heterogeneity of the vasoconstrictor effect of vasopressin in septic shock. Crit Care Med 2004; 32:1327–31

86. 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; 31:2646–50

87. 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

88. Dunser MW, Fries DR, Schobersberger W, Ulmer H, Wenzel V, Friesenecker B, Hasibeder WR, Mayr AJ: Does arginine vasopressin influence the coagulation system in advanced vasodilatory shock with severe multiorgan dysfunction syndrome? Anesth Analg 2004; 99:201–6

89. Luckner G, Dunser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Mayr AJ, Friesenecker B: Arginine vasopressin in 316 patients with advanced vasodilatory shock. Crit Care Med 2005; 33:2659–66

90. Kahn JM, Kress JP, Hall JB: Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. Crit Care Med 2002; 30:1899–901

91. O'Brien A, Clapp L, Singer M: Terlipressin for norepinephrine-resistant septic shock. Lancet 2002; 359:1209–10

92. Albanese J, Leone M, Delmas A, Martin C: Terlipressin or norepinephrine in hyperdynamic septic shock: A prospective, randomized study. Crit Care Med 2005; 33:1897–902

93. Westphal M, Freise H, Kehrel BE, Bone HG, Van Aken H, Sielenkamper AW: Arginine vasopressin compromises gut mucosal microcirculation in septic rats. Crit Care Med 2004; 32:194–200

94. Moller S, Hansen EF, Becker U, Brinch K, Henriksen JH, Bendtsen F: Central and systemic haemodynamic effects of terlipressin in portal hypertensive patients. Liver 2000; 20:51–9

95. Masutani S, Senzaki H, Ishido H, Taketazu M, Matsunaga T, Kobayashi T, Sasaki N, Asano H, Kyo S, Yokote Y: Vasopressin in the treatment of vasodilatory shock in children. Pediatr Int 2005; 47:132–6

96. 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; 30:477–80

97. Dunser M, Hasibeder WR, Wenzel V, Mayr AJ: Lessons learned from high-dosage vasopressin infusion in septic shock (letter). Crit Care Med 2005; 32:1433

98. Morales D, Madigan J, Cullinane S, Chen J, Heath M, Oz M, Oliver JA, Landry DW: Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. Circulation 1999; 100:226–9

99. Stadlbauer KH, Wagner-Berger HG, Raedler C, Voelckel WG, Wenzel V, Krismer AC, Klima G, Rheinberger K, Nussbaumer W, Pressmar D, Lindner KH, Konigsrainer A: Vasopressin, but not fluid resuscitation, enhances survival in a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. ANESTHESIOLOGY 2003; 98:699–704

100. Sharma RM, Setlur R: Vasopressin in hemorrhagic shock. Anesth Analg 2005; 101:833–4

101. Tsuneyoshi I, Onomoto M, Yonetani A, Kanmura Y: Low-dose vasopressin infusion in patients with severe vasodilatory hypotension after prolonged hemorrhage during general anesthesia. J Anesth 2005; 19:170–3

102. Haas T, Voelckel WG, Wiedermann F, Wenzel V, Lindner KH: Successful resuscitation of a traumatic cardiac arrest victim in hemorrhagic shock with vasopressin: A case report and brief review of the literature. J Trauma 2004; 57:177–9

103. Krismer AC, Wenzel V, Voelckel WG, Innerhofer P, Stadlbauer KH, Haas T, Pavlic M, Sparr HJ, Lindner KH, Koenigsrainer A: Employing vasopressin as an adjunct vasopressor in uncontrolled traumatic hemorrhagic shock: Three cases and a brief analysis of the literature. Anaesthesist 2005; 54:220–4

104. Stadlbauer KH, Wenzel V, Krismer AC, Voelckel WG, Lindner KH: Vasopressin during uncontrolled hemorrhagic shock: Less bleeding below the diaphragm, more perfusion above. Anesth Analg 2005; 101:830–2

105. Levine FH, Philbin DM, Kono K, Coggins CH, Emerson CW, Austen WG, Buckley MJ: Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass with and without pulsatile flow. Ann Thorac Surg 1981; 32:63–7

106. 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:II-286–90

107. 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. J Thorac Cardiovasc Surg 1998; 116:973–80

108. 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 Lung Transplant 1999; 18:814–7

109. Morales DL, Garrido MJ, Madigan JD, Helman DN, Faber J, Williams MR, Landry DW, Oz MC: A double-blind randomized trial: Prophylactic vasopressin

reduces hypotension after cardiopulmonary bypass. Ann Thorac Surg 2003; 75:926–30

110. Rosenzweig EB, Starc TJ, Chen JM, Cullinane S, Timchak DM, Gersony WM, Landry DW, Galantowicz ME: Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. Circulation 1999; 100:II182–6

111. Lechner E, Dickerson HA, Fraser CD Jr, Chang AC: Vasodilatory shock after surgery for aortic valve endocarditis: Use of low-dose vasopressin. Pediatr Cardiol 2004; 25:558–61

112. 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; 28:249–52

113. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005; 112:IV1–203

114. Keck T, Banafsche R, Werner J, Gebhard MM, Herfarth C, Klar E: Desmopressin impairs microcirculation in donor pancreas and early graft function after experimental pancreas transplantation. Transplantation 2001; 72:202–9

115. Banafsche R, Keck T, Diener M, Gebhard MM, Klar E: Desmopressin impairs hepatic microcirculation: Impact on liver graft quality. Transplant Proc 2002; 34:2310–1

116. Marques RG, Rogers J, Chavin KD, Baliga PK, Lin A, Emovon O, Afzal F, Baillie GM, Taber DJ, Ashcraft EE, Rajagopalan PR: Does treatment of cadaveric organ donors with desmopressin increase the likelihood of pancreas graft thrombosis? Results of a preliminary study. Transplant Proc 2004; 36:1048–9

117. Kinoshita Y, Yahata K, Yoshioka T, Onishi S, Sugimoto T: Long-term renal preservation after brain death maintained with vasopressin and epinephrine. Transpl Int 1990; 3:15–8

118. Morris DC, Dereczyk BE, Grzybowski M, Martin GB, Rivers EP, Wortsman J, Amico JA: Vasopressin can increase coronary perfusion pressure during human cardiopulmonary resuscitation. Acad Emerg Med 1997; 4:878–83

119. Wenzel V, Linder KH, Augenstein S, Prengel AW, Strohmenger HU: Vasopressin combined with epinephrine decreases cerebral perfusion compared with vasopressin alone during cardiopulmonary resuscitation in pigs. Stroke 1998; 29:1462–7

120. Wenzel V, Lindner KH, Prengel AW, Maier C, Voelckel W, Lurie KG, Strohmenger HU: Vasopressin improves vital organ blood flow after prolonged cardiac arrest with postcountershock pulseless electrical activity in pigs. Crit Care Med 1999; 27:486–92

121. Wenzel V, Lindner KH, Krismer AC, Miller EA, Voelckel WG, Lingnau W: Repeated administration of vasopressin but not epinephrine maintains coronary perfusion pressure after early and late administration during prolonged cardiopulmonary resuscitation in pigs. Circulation 1999; 99:1379–84

122. Johansson J, Gedeborg R, Rubertsson S: Vasopressin *versus* continuous adrenaline during experimental cardiopulmonary resuscitation. Resuscitation 2004; 62:61–9

123. Raedler C, Voelckel WG, Wenzel V, Krismer AC, Schmittinger CA, Herff H, Mayr VD, Stadlbauer KH, Lindner KH, Konigsrainer A: Treatment of uncontrolled hemorrhagic shock after liver trauma: Fatal effects of fluid resuscitation *versus* improved outcome after vasopressin. Anesth Analg 2004; 98:1759–66

124. Wenzel V, Kern KB, Hilwig RW, Berg RA, Schwarzacher S, Butman SM, Lindner KH, Ewy GA: Effects of intravenous arginine vasopressin on epicardial coronary artery cross sectional area in a swine resuscitation model. Resuscitation 2005; 64:219–26

125. Wenzel V, Lindner KH, Augenstein S, Voelckel W, Strohmenger HU, Prengel AW, Steinbach G: Intraosseous vasopressin improves coronary perfusion pressure rapidly during cardiopulmonary resuscitation in pigs. Crit Care Med 1999; 27:1565–9

126. Wenzel V, Lindner KH, Prengel AW, Lurie KG, Strohmenger HU: Endobronchial vasopressin improves survival during cardiopulmonary resuscitation in pigs. ANESTHESIOLOGY 1997; 86:1375–81

127. Lindner KH, Prengel AW, Brinkmann A, Strohmenger HU, Lindner IM, Lurie KG: Vasopressin administration in refractory cardiac arrest. Ann Intern Med 1996; 124:1061–4

128. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG: Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet 1997; 349:535–7

129. Stiell IG, Hebert PC, Wells GA, Vandemheen KL, Tang AS, Higginson LA, Dreyer JF, Clement C, Battram E, Watpool I, Mason S, Klassen T, Weitzman BN: Vasopressin *versus* epinephrine for inhospital cardiac arrest: A randomised controlled trial. Lancet 2001; 358:105–9

130. Kern KB, Halperin HR, Field J: New guidelines for cardiopulmonary resuscitation and emergency cardiac care: Changes in the management of cardiac arrest. JAMA 2001; 285:1267–9

131. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH: A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004; 350:105–13

132. Mann K, Berg RA, Nadkarni V: Beneficial effects of vasopressin in prolonged pediatric cardiac arrest: A case series. Resuscitation 2002; 52:149–56

133. Voelckel WG, Lurie KG, McKnite S, Zielinski T, Lindstrom P, Peterson C, Krismer AC, Lindner KH, Wenzel V: Comparison of epinephrine and vasopressin in a pediatric porcine model of asphyxial cardiac arrest. Crit Care Med 2000; 28:3777–83

134. Nozari A, Rubertsson S, Wiklund L: Differences in the pharmacodynamics of epinephrine and vasopressin during and after experimental cardiopulmonary resuscitation. Resuscitation 2001; 49:59–72

135. Voelckel WG, Lurie KG, McKnite S, Zielinski T, Lindstrom P, Peterson C, Wenzel V, Lindner KH, Benditt D: Effects of epinephrine and vasopressin in a piglet model of prolonged ventricular fibrillation and cardiopulmonary resuscitation. Crit Care Med 2002; 30:957–62

136. Heinemann A, Wachter CH, Fickert P, Trauner M, Stauber RE: Vasopressin reverses mesenteric hyperemia and vasoconstrictor hyporesponsiveness in anesthetized portal hypertensive rats. Hepatology 1998; 28:646–54

137. Freeman JG, Cobden I, Lishman AH, Record CO: Controlled trial of terlipressin ("Glypressin") *versus* vasopressin in the early treatment of oesophageal varices. Lancet 1982; 2:66–8

138. Ioannou G, Doust J, Rockey DC: Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev 2003; CD002147

139. Moreau R, Durand F, Poynard T, Duhamel C, Cervoni JP, Ichai P, Abergel A, Halimi C, Pauwels M, Bronowicki JP, Giostra E, Fleurot C, Gurnot D, Nouel O, Renard P, Rivoal M, Blanc P, Coumaros D, Ducloux S, Levy S, Pariente A, Perarnau JM, Roche J, Scribe-Outtas M, Valla D, Bernard B, Samuel D, Butel J, Hadengue A, Platek A, Lebrec D, Cadranel JF: Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. Gastroenterology 2002; 122:923–30

140. Halimi C, Bonnard P, Bernard B, Mathurin P, Mofredj A, di Martino V, Demontis R, Henry-Biabaud E, Fievet P, Opolon P, Poynard T, Cadranel JF: Effect of terlipressin (Glypressin) on hepatorenal syndrome in cirrhotic patients: Results of a multicentre pilot study. Eur J Gastroenterol Hepatol 2002; 14:153–8

141. Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK: Beneficial effects of terlipressin in hepatorenal syndrome: A prospective, randomized placebo-controlled clinical trial. J Gastroenterol Hepatol 2003; 18:152–6

142. Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jimenez W, Arroyo V, Rodes J: Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: Results of a prospective, nonrandomized study. Hepatology 2002; 36:941–8

143. Saner F, Kavuk I, Lang H, Biglarnia R, Fruhauf NR, Schafers RF, Malago M, Broelsch CE: Terlipressin and gelafundin: Safe therapy of hepatorenal syndrome. Eur J Med Res 2004; 9:78–82

144. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J, Orlandi C: Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. JAMA 2004; 291:1963–71

145. Doggrell SA: Conivaptan Yamanouchi. Curr Opin Investig Drugs 2005; 6:317–26

146. Conivaptan: YM 087. Drugs R D 2004; 5:94–7

147. Russell SD, Selaru P, Pyne DA, Ghazzi MM, Massey KD, Pressler M, Serikoff A, Coats AJ: Rationale for use of an exercise end point and design for the ADVANCE (A Dose evaluation of a Vasopressin ANtagonist in CHF patients undergoing Exercise) trial. Am Heart J 2003; 145:179–86

148. Goldsmith SR: Vasopressin antagonists in CHF: Ready for clinical trials? Cardiovasc Res 2002; 54:13–5

149. Gattone VH II, Wang X, Harris PC, Torres VE: Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nat Med 2003; 9:1323–6

150. Hayoz D, Bizzini G, Noel B, Depairon M, Burnier M, Fauveau C, Rouillon A, Brouard R, Brunner HR: Effect of SR 49059, a V1a vasopressin receptor antagonist, in Raynaud's phenomenon. Rheumatology (Oxford) 2000; 39:1132–8

151. Serradeil-Le Gal C, Herbert JM, Delisee C, Schaeffer P, Raufaste D, Garcia C, Dol F, Marty E, Maffrand JP, Le Fur G: Effect of SR-49059, a vasopressin V1a antagonist, on human vascular smooth muscle cells. Am J Physiol 1995; 268: H404–10

152. Thibonnier M, Kilani A, Rahman M, DiBlasi TP, Warner K, Smith MC, Leenhardt AF, Brouard R: Effects of the nonpeptide V(1) vasopressin receptor antagonist SR49059 in hypertensive patients. Hypertension 1999; 34:1293–300

153. Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, Scatton B, Maffrand JP, Soubrie P: Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. Proc Natl Acad Sci U S A 2002; 99:6370–5

154. Serradeil-Le Gal C, Derick S, Brossard G, Manning M, Simiand J, Gaillard R, Griebel G, Guillon G: Functional and pharmacological characterization of the first specific agonist and antagonist for the V1b receptor in mammals. Stress 2003; 6:199–206