*David C. Warltier, M.D., Ph.D., Editor*

Anesthesiology 2006; 105:599–612 

# *The Vasopressin System*

## *Physiology and Clinical Strategies*

*Tanja A. Treschan, M.D.,* Jürgen Peters, M.D.†*

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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

* Assistenzärztin, † Professor of Anesthesiology and Intensive Care Therapy and Chairman, Klinik für Anästhesiologie und Intensivmedizin.

Received from the Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Essen, Germany. Submitted for publication August 22, 2005. Accepted for publication April 17, 2006. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Treschan: Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Hufelandstr. 55, Essen D-45122, Germany. tanja.treschan@uni-essen.de. 

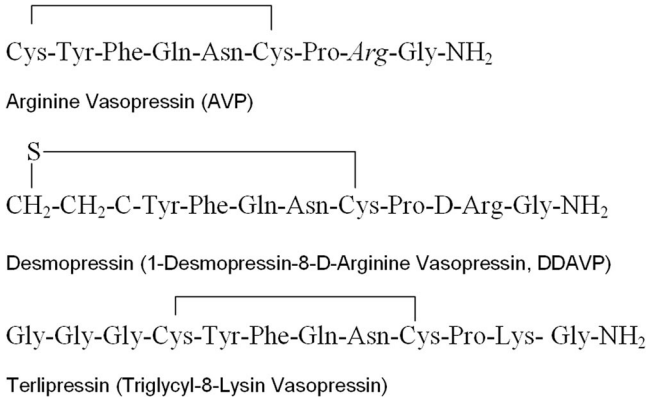


**Fig. 1. Amino acid sequence of vasopressin and synthetic vasopressin agonists.**

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-

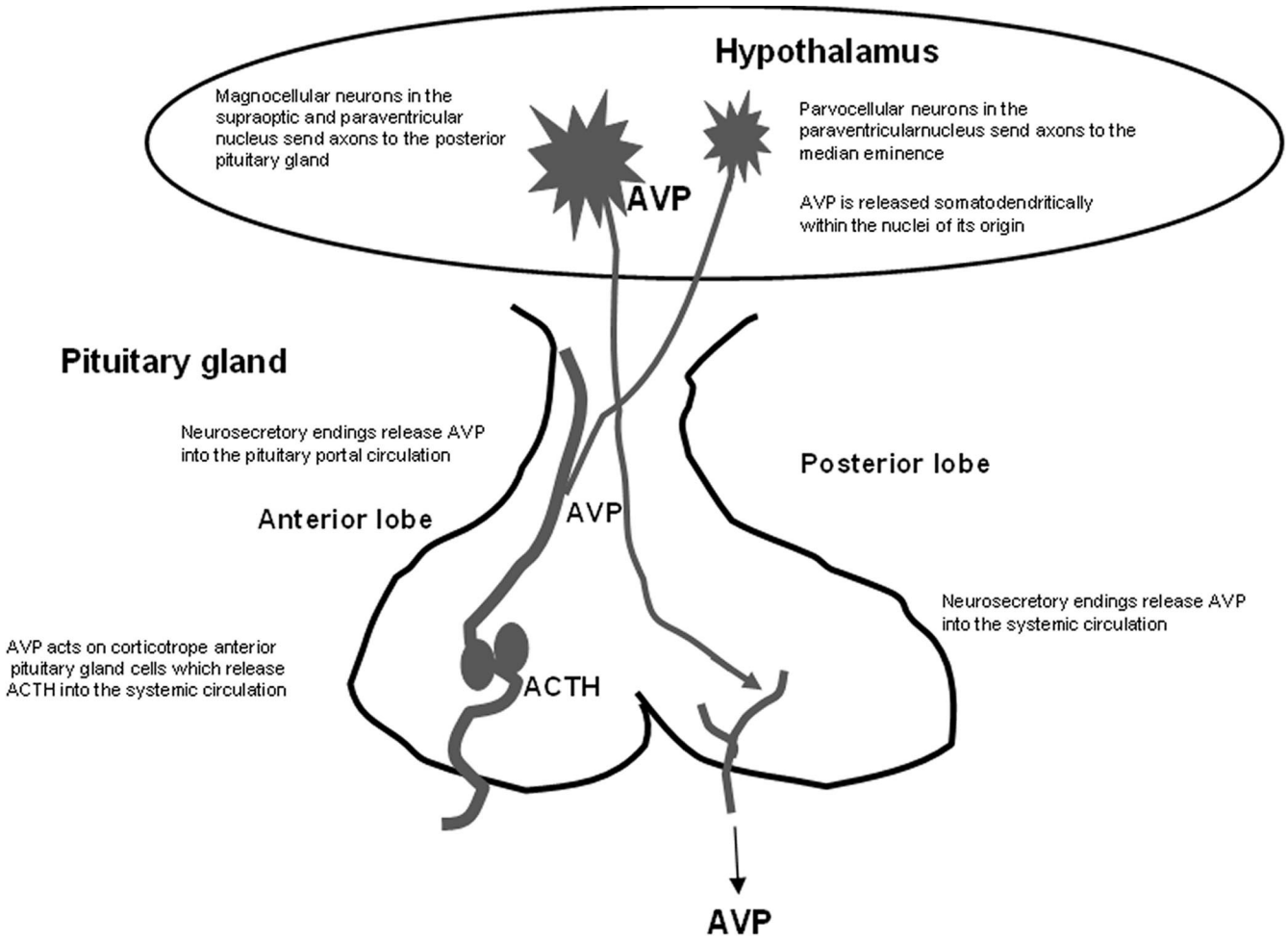


**Fig. 2. Scheme of vasopressin release within the central nervous system. Vasopressin is synthesized in the hypothalamus in magnocellular and parvocellular neurons. Magnocellular neurons are mainly located in the supraoptic and paraventricular nucleus. Their axons release arginine vasopressin (AVP) 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]

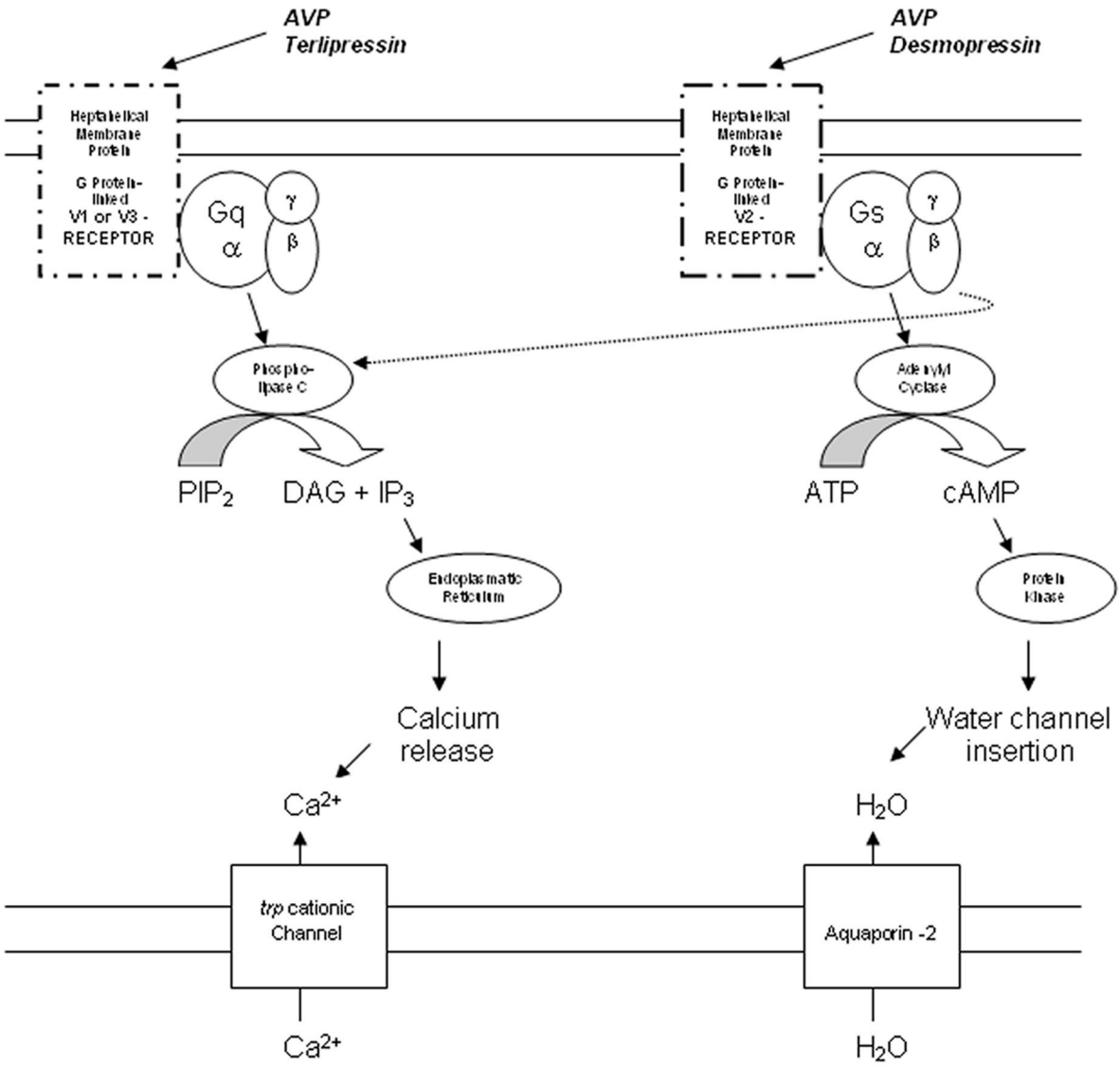


**Fig. 3. Scheme of vasopressin's signal transduction. The *left* portion of the figure depicts V1 and V3 receptors on various cells; the *right* portion of the figure depicts V2 receptors on kidney collecting duct cells. *Arrows* indicate activation of pathways; the *dotted arrow* indicates a possible activation. ATP = adenosine triphosphate; AVP = arginine vasopressin; cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; Gq/Gs $\alpha$, $\beta$, $\gamma$ = 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,

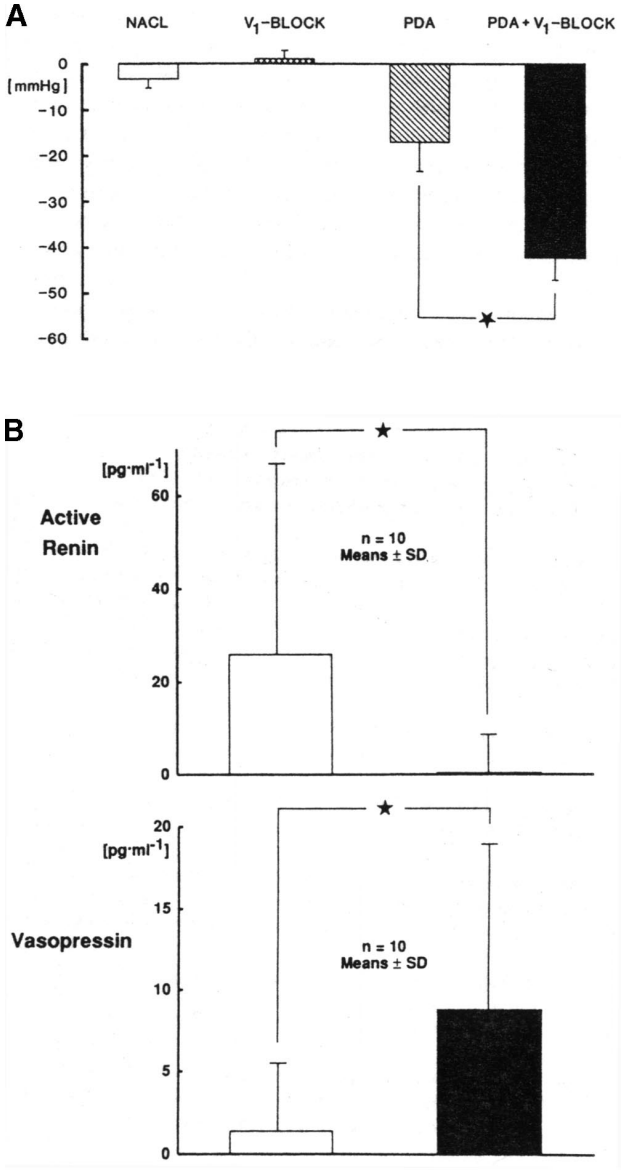


**Fig. 4. Interplay between the sympathetic, renin–angiotensin, and vasopressin systems. (*A*) Maximum change in arterial blood pressure from baseline in conscious dogs after epidural saline (*open column*), vasopressin V1 receptor blockade alone (*column with crosses*), sympathetic blockade by epidural 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.**

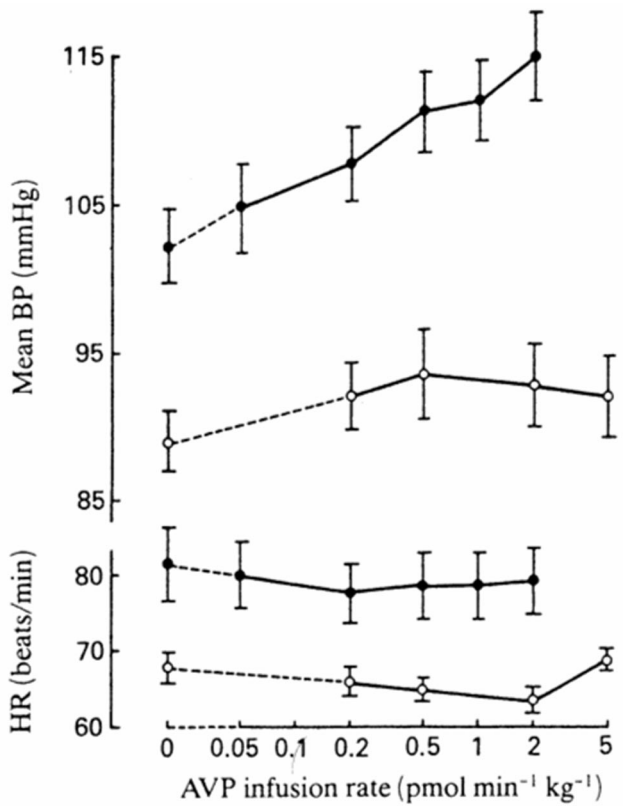


**Fig. 5. Effect of incremental intravenous infusion of arginine vasopressin (AVP) on mean arterial blood pressure (BP) and heart rate (HR) in patients with autonomic insufficiency (*filled dots*) compared with healthy volunteers (*open dots*). AVP does not affect blood pressure in healthy volunteers, 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

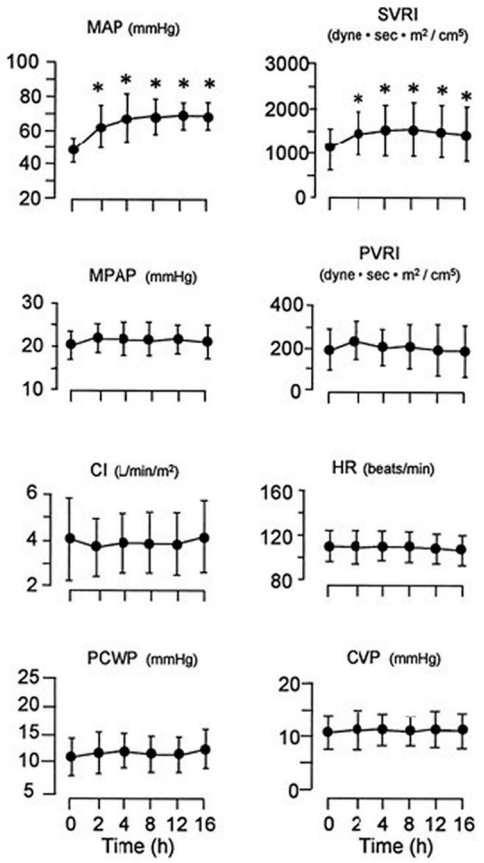


**Fig. 6. Effect on hemodynamic variables of vasopressin infusion in patients with septic shock. Vasopressin significantly increases mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) within minutes of application. It does not significantly influence pulmonary vascular resistance 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.

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