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Management of Vasodilatory Shock
Defining the Role of Arginine Vasopressin

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Abstract

The rationale for an arginine vasopressin (argipressin) infusion was put forward after it was discovered that patients in shock states might have an endogenous arginine vasopressin deficiency. Subsequently, several investigations impressively demonstrated that arginine vasopressin can successfully stabilise haemodynamics even in advanced vasodilatory shock. We report on physiological and pharmacological aspects of arginine vasopressin, and summarise current clinical knowledge on employing a continuous arginine vasopressin infusion in critically ill patients with catecholamine-resistant vasodilatory shock of different aetiologies. In view of presented experimental evidence and current clinical experience, a continuous arginine vasopressin infusion of ~2 to ~6 IU/h can be considered as a supplemental strategy to vasopressor catecholamines in order to preserve cardiocirculatory homeostasis in patients with advanced vasodilatory shock. Because data on adverse effects are still limited, arginine vasopressin should be reserved for patients in whom adequate haemodynamic stabilisation cannot be achieved with conventional vasopressor therapy or who have obvious adverse effects of catecholamines that result in further significant haemodynamic deterioration. For the same reasons, arginine vasopressin should not be used as a single, alternative vasopressor agent instead of catecholamine vasopressors. Future prospective studies will be necessary to define the exact role of arginine vasopressin in the therapy of vasodilatory shock.

Vasodilatory shock may complicate severe disease in critically ill patients. Independently of the aetiology of vasodilatory shock, mortality rates are excessively high. Currently, catecholamines are the usual vasopressor agents used to support arterial blood pressure in order to ensure adequate organ perfusion in critically ill patients.[1] However, progressive hyposensitivity of arterial resistance vessels to catecholamines and, finally, loss of vasopressor effects may develop, with subsequent further increases required in catecholamine support and the development of toxic side effects.[2] Therefore, additional pharmacological agents that are able to restore vascular tone and arterial blood pressure would be of great clinical benefit.

Arginine vasopressin (argipressin) is a potent vasoconstrictor in numerous hypotensive states, including cardiac arrest,[3] the late phase of haemorrhagic shock,[4] and orthostatic[5] or haemodialysis-induced hypotension.[6] In recent years, several case reports and clinical trials have shown that haemodynamic stabilisation in catecholamine-resistant

vasodilatory shock can be achieved with a continuous infusion of arginine vasopressin.[7] This review article discusses physiological and pathophysiological aspects of arginine vasopressin, and summarises current clinical knowledge with continuous arginine vasopressin infusion in advanced vascular failure. Thus, the purpose of this article is to provide healthcare professionals managing patients with catecholamine-resistant vasodilatory shock with an in-depth review of continuous infusion of arginine vasopressin.

1. Pathophysiology of Vasodilatory Shock

Vasodilatory shock is characterised by low arterial blood pressure due to decreased systemic vascular resistance and sometimes a poor response to therapy with vasopressor drugs;[1] with sepsis and surgery requiring cardiopulmonary bypass being the most frequent causes.[8,9] However, vasodilatory shock may result from shock of any aetiology.[1] Prolonged tissue hypoperfusion can trigger excessive systemic inflammation leading to systemic vasodilatation and, finally, multiple organ dysfunction syndrome.[10] Thus, loss of vascular resistance may complicate cardiogenic or haemorrhagic shock despite correction of the underlying illness.[1,4] Massive systemic inflammatory response syndrome due to other non-infectious triggers (e.g. pancreatitis),[11] can be associated with excessive systemic vasodilatation. In addition, systemic hypotension because of low peripheral vascular resistance may complicate hepatic failure[12] and glucocorticoid deficiency,[13] or occur after specific intoxications[14-16] and following brain death.[17,18]

Different mechanisms have been implicated in the pathogenesis of vasodilatory shock, such as open potassium-sensitive channels and nitric oxide (NO).[1] Subsequently, an imbalance of vasopressor and vasodilatory factors results in excessive dilatation of arteriolar resistance vessels. Although the exact reason for open potassium-sensitive channels in vascular smooth muscle cells (VSMCs) is not known, this effect leads to an efflux of potassium hyperpolarising the cell membrane, thus causing vasodilatation.[14] In addition to intracellular signalling pathways, ATP-sensitive potassium channels are activated by decreases in intracellular ATP,[19] and increases in intracellular hydrogen ions and lactate concentrations.[20,21] In addition, elevated serum concentrations of atrial natriuretic factor, calcitonin-gene related peptide, adenosine[22] and cyclic guanosine monophosphate (cGMP) may be involved as well.[23] Furthermore, NO production is excessively enhanced as a result of increased expression of the inducible form of nitric oxide synthase (iNOS).[1] Mechanisms that are responsible have not been fully identified as yet but proinflammatory cytokines seem to be involved.[24] In vasodilatory shock, one of the many potential ways that NO can relax vascular smooth muscle is mediated by cGMP-induced activation of myosin light-chain phosphorylase,[25] another is via opening of calcium-sensitive potassium channels in VSMCs.[26] Deficiency of endogenous hormones, primarily vasopressin and cortisol, as well as hyporesponsiveness to endogenous vasopressor hormones, may contribute to the loss of arteriolar vascular tone.[1] Administration of vasodilatory inotropics, such as phosphodiesterase III inhibitors, can further aggravate hypotension promoting vasodilatation.[27]

2. Current Therapy of Vasodilatory Shock

The current therapy of vasodilatory shock implies causal treatment of the underlying disease, as well as adequate volume resuscitation and use of vasopressor agents to increase arterial blood pressure and to improve organ perfusion.[28] Catecholamines are the mainstay for the management of severe hypotension. However, development of adrenergic hyposensitivity with loss of catecholamine pressor effects, resulting in catecholamine-resistant vasodilatory shock, is a complication of concern. Further enforcing catecholamine therapy, intensivists often enter a vicious cycle in which significant catecholamine toxicity may contribute to a further clinical deterioration. If vasodilatory

shock becomes resistant to catecholamine therapy, mortality rates usually approach 100%.[29] Tachyarrhythmias, pulmonary hypertension, increased myocardial oxygen demand, as well as metabolic derangements such as hyperglycaemia and hyperlactataemia, are adverse effects of excessively high catecholamine administration.[30,31]

Several mechanisms are responsible for adrenergic hyposensitivity in advanced vasodilatory shock. Down-regulation of adrenergic receptors on VSMCs and impairment of postreceptor signal pathways reduce pressor effects of catecholamines.[32] Excessive production of NO and other inflammatory mediators as well as metabolic acidosis further contribute to this phenomenon.[33,34] Although catecholamine-resistance is a well-known dilemma in critically ill patients, no general definition of catecholamine-resistance exists in the literature. In our institution, catecholamine resistance is defined as a failing effect of a stepwise increase of norepinephrine by 0.2 μg/kg/min over a 2-hour period on mean arterial pressure. Frequently, this phenomenon occurs in conjunction with obvious catecholamine toxicity. For example, catecholamine-induced atrial fibrillation may further deteriorate cardiocirculatory function as a result of a loss of atrial contraction, necessitating a significant increase in catecholamine dosages to maintain mean arterial blood pressure.

3. Arginine Vasopressin

3.1 Physiology

Arginine vasopressin is an endogenous hormone with osmoregulatory, vasopressor, haemostatic and central nervous effects. The hormone is produced in the magnocellular nuclei of the hypothalamus and stored in neurosecretory vesicles of the neurohypophysis. It is secreted upon osmotic, haemodynamic and endocrinological stimuli. Important haemodynamic signals for secretion are reduced atrial filling, as well as decreased arterial blood pressure. Any reduction in blood volume or venous return stimulates arginine vasopressin secretion via activation of stretch receptors located in the left atrium and pulmonary arteries (Gauer-Henry reflex). Activation of baroreceptors in the aortic and carotid sinus further augments arginine vasopressin secretion via the glossopharyngeus and vagal nerves.[35] However, baroreceptor-mediated arginine vasopressin secretion is the primary stimulation release in hypotensive states.[36]

In an animal study, Kasting et al.[37] demonstrated that endotoxin directly stimulates arginine vasopressin secretion independently of plasma osmolarity, blood pressure or intravascular volume status. Proinflammatory cytokines, such as interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α, may further enhance arginine vasopressin production.[38-40] Also, high angiotensin II and III levels increase arginine vasopressin secretion.[41-43] Clinical studies and case reports have shown that patients with chronic angiotensin-converting enzyme (ACE) inhibitor therapy are at increased risk to develop hypotension and vasodilatory shock during and after cardiac surgery.[44] Since plasma arginine vasopressin concentrations were found to be inadequately low, a causal relationship between long-term ACE inhibitor therapy and reduced arginine vasopressin secretion is possible. A continuous intravenous infusion of the ACE inhibitor enalaprilat significantly decreased plasma arginine vasopressin levels in critically ill patients.[45] Eyraud et al.[46] reported that the arginine vasopressin analogue terlipressin is an effective vasopressor in patients receiving chronic ACE inhibitor therapy who develop catecholamine-resistant hypotension during cardiac surgery. Aside from angiotensin II and III, endothelins,[47,48] norepinephrine and epinephrine[35] are physiological secretagogues of arginine vasopressin, whereas atrial natriuretic factor suppresses arginine vasopressin secretion.[49,50]

3.2 Pharmacokinetic Profile

In plasma, arginine vasopressin is bound to proteins; 10% at basal plasma levels, and up to 40% at higher levels. Normal plasma levels range from ~2 to ~8 ng/L and serum half-life varies between ~8 and ~15 minutes. Splanchnic and renal enzy-

matic degradation are the primary pathways of inactivation. Renal clearance of arginine vasopressin results from glomerular filtration, degradation or reabsorption in the proximal nephron, and additional secretion into the distal nephron. Ten percent of arginine vasopressin is excreted as active hormone. Renal clearance remains unaffected by changes in serum levels over a broad range.[51] Splanchnic clearance of arginine vasopressin is accomplished almost equally by the intestine and the liver.[52] Because the sum of splanchnic and renal elimination of arginine vasopressin is less than estimates of its metabolic rate, there seems to be a pharmacologically significant clearance of arginine vasopressin by other organs.[51]

3.3 Pharmacodynamic Profile

3.3.1 Hemodynamic Effects

Peripheral effects of arginine vasopressin are mediated by different vasopressin receptors; namely V_1-(V_{1a}), V_2-(V_2), and V_3(V_{1b})- vasopressin-receptors. V_1-receptors have been found in arterial blood vessels and induce vasoconstriction by an increase in cytoplasmic ionised calcium via the phosphatidyl-inositol-bisphosphonate cascade.[53] In contrast to catecholamine-mediated vasoconstriction, the effects of arginine vasopressin are preserved during hypoxia and severe acidosis.[54] However, arginine vasopressin-mediated vascular effects differ substantially within particular vascular beds.

Physiologically, most arterial beds exhibit vasoconstriction in response to arginine vasopressin.[55,56] Vasopressor effects are strongest in the splanchnic, muscular and cutaneous vasculature.[57] In a cardiopulmonary resuscitation model, Voelckel et al.[58] found a significantly lower blood flow in the superior mesenteric artery in pigs resuscitated with arginine vasopressin than with epinephrine; there were no differences in hepatic or renal blood flow. Similarly to oxytocin-mediated paradoxical vasodilatation of vascular smooth muscle, vasodilatation after arginine vasopressin has been described in the pulmonary, coronary and vertebrobasilar circulation.[59-61] The underlying mechanisms seem to be NO-dependent.[59] Russ and Walker[62] reported release of NO, presumably from the endothelium, after stimulation of V_1-receptors. Relaxation was blocked by competitive NOS (cNOS) inhibition and was reactivated by the addition of L-arginine.

Recently, there is increasing evidence of haemodynamically relevant V_1-receptors on cardiomyocytes. *In vitro* and animal experiments have demonstrated an increase of intracellular calcium concentration and inotropy after stimulation of myocardial V_1-receptors.[63,64] Furthermore, arginine vasopressin mediates prostacyclin production and atrial natriuretic factor secretion in rat cardiomyocytes.[65,66] Whereas calcium influx and membranous protein kinase C are required for arginine vasopressin-induced secretion of atrial natriuretic factor, prostacyclin production after arginine vasopressin stimulation is mainly regulated by protein kinase C.[65]

Just as arginine vasopressin pressor responsiveness varies between normotensive and vasodilatory shock states, it may also vary between vasodilatory shock and shock as a result of low flow states, such as hypovolaemic and cardiogenic shock. Furthermore, the regional effects of arginine vasopressin are likely to vary between these three states, which needs to be assessed in future studies.

3.3.2 Hemostatic, Metabolic and Other Effects

V_1-receptors are expressed on thrombocytes. Upon stimulation, they induce an increase in intracellular calcium, thereby facilitating thrombocyte aggregation.[67] Arginine vasopressin increases thrombocyte expulsion from the bone marrow.[68] Other haemostatic effects are V_2-receptor mediated. Prostacyclin generation is stimulated, and tissue-type plasminogen activator activity, factor VIII-related antigen activity, factor VIII coagulant activity and von Willebrand factor multimeres all increase upon V_2-receptor stimulation.[69] Arginine vasopressin and its analogue desmopressin induce coagulatory activity in healthy individuals, in patients with haemophilia,[69] renal and hepatic disease,[70] and after cardiac surgery.[71] Whether

arginine vasopressin promotes clinically relevant coagulatory effects in dosages used in vasodilatory shock is currently unknown and must be examined in future studies.

Stimulation of V_1-receptors on hepatocytes increases glycolysis and glycogenolysis, gluconeogenesis, esterification and oxidation of free fatty acids, as well as production of ketone bodies.[72]

In the kidney, V_2-receptors are located on distal tubules and collecting ducts. Upon stimulation, they facilitate integration of aquaporines into the luminal cell membrane, leading to increased resorption of free water via an adenylate cyclase-dependent mechanism.[35] Despite this antidiuretic effect, an increase of urine output has been reported during continuous arginine vasopressin infusion in vasodilatory shock.[73-75] One explanation for this observation is the selective V_1-receptor-mediated vasoconstriction of efferent glomerular arterioles resulting in a significantly increased glomerular filtration pressure.[73] This may actually indicate that kidney function may improve during arginine vasopressin infusion. We have less experience with this phenomenon, since ~80–90% of our patients with an arginine vasopressin were undergoing haemofiltration. V_2-receptor-associated natriuretic and diuretic effects, as well as release of the atrial natriuretic factor, may also be involved.[75]

V_3-receptors are found on the anterior hypophysis, and stimulation induces liberation of adrenocorticotrophic hormone (ACTH) and, consequently, enhanced cortisol secretion from the adrenal glands.[76] Accordingly, Kornberger et al.[77] reported significantly higher serum ACTH and cortisol levels in animals resuscitated from cardiac arrest with arginine vasopressin than with epinephrine. V_3-receptors are further expressed on pancreatic isle cells where they induce insulin secretion.[78] However, stimulation of insulin secretion by arginine vasopressin only seems to be relevant during moderate to severe hyperglycaemia.[79]

Additional physiological effects of arginine vasopressin on specific brain functions, temperature regulation and myometrical contractions have been reported.[35,80]

3.4 Vasopressin Analogues

In the past, a variety of vasopressin analogues with major differences in their pharmacological profile were developed. They also have different profiles with regard to vasopressor and antidiuretic action profiles (figure 1). Among these analogues, affinity of arginine vasopressin for the V_1-receptor is the highest.[81] Although ornipressin and ter-

Peptide	Simplified amino acid structure	Activity in relation to arginine vasopressin: Antidiuretic-effect	Activity in relation to arginine vasopressin: Vasopressor-effect	Comment
Arginine vasopressin	Cys-Tyr-Phe-Glu-Asp-Cys-Pro-**L-Arg**-Gly-(NH_2)	100	100	ADH/AVP Piressin®[a]
Lysine vasopressin	Cys-Tyr-Phe-Glu-Asp-Cys-Pro-**Lys**-Gly-(NH_2)	80	60	LVP Lypressin®[a]
Oxytocin	Cys-Tyr-**Ile**-Glu-Asp-Cys-Pro-**Leu**-Gly-(NH_2)	1	1	Induces myometrical contradictions
Ornithine vasopressin	Cys-Tyr-Phe-Glu-Asp-Cys-Pro-**Orn**-Gly-(NH_2)	22	90	POR 8®[a], esophageal varices
DDAVP	Cys-Tyr-Phe-Glu-Asp-Cys-Pro-**D-Arg**-Gly-(NH_2)	1200	0.39	Desmopressin®[a], increases Factor VIII

Fig. 1. Chemical structures and affinity of arginine vasopressin analogues. All peptides shown have disulfide bonds between amino acids on position one and eight. Terlipressin is degraded into lysine vasopressin. **a** Use of trade names is for product identification purposes only and does not imply endorsement. **ADH** = antidiuretic hormone; **AVP** = arginine vasopressin; **DDAVP** = 1-desamino-8-d arginine vasopressin; **LVP** = lysine vasopressin.[81]

lipressin are not as potent ligands as arginine vasopressin, case reports describing successful therapy of catecholamine-resistant hypotension have been published.[46,82]

Terlipressin is a prodrug, which is converted into lysine vasopressin after degradation of the N-terminal glycine. Therefore, the vasoconstrictive effects of terlipressin demonstrate a delayed onset but last longer (half-life 4–6 hours) than the effects of arginine vasopressin.[83] Terlipressin has already been used to treat intraoperative hypotension in patients receiving long-term ACE inhibitor therapy.[46] In an animal model, terlipressin effectively reversed haemodynamic changes after endotoxin infusion. The significant increase in mean arterial blood pressure was, however, accompanied by a significant increase in pulmonary vascular resistance which might limit its therapeutic use in septic shock.[84] Furthermore, another animal study by Westphal and coworkers[85] found no increase in mean pulmonary artery pressure during a continuous infusion of terlipressin in endotoxaemic sheep. However, when compared to arginine vasopressin, the authors observed less pronounced vasopressor effects and a ceiling effect during terlipressin infusion.

Few data exist about the clinical use of other arginine vasopressin analogues in advanced vasodilatory shock. Considering the potency of arginine vasopressin on the V_1-receptor, arginine vasopressin must be considered as the first-line vasopressin analogue to be used in vasodilatory shock.

3.5 Arginine Vasopressin in Vasodilatory Shock

Plasma arginine vasopressin levels are significantly elevated in the initial phase of haemorrhagic or septic shock because of baroreceptor-mediated stimulation.[1] During this phase, arginine vasopressin antagonists have been shown to lower arterial blood pressure.[86,87] In prolonged shock, however, initially high plasma arginine vasopressin levels may substantially decrease.[4,88] Accordingly, clinical studies report low or inadequately low plasma arginine vasopressin levels in patients with advanced vasodilatory shock.[89] Normotensive patients on cardiopulmonary bypass demonstrated plasma arginine vasopressin levels of 100–200 ng/L. In contrast, in patients with postcardiotomy shock, mean plasma arginine vasopressin levels were <20 ng/L.[44] Landry et al.[90] reported significantly lower plasma arginine vasopressin levels in patients with septic shock than patients with cardiogenic shock.

Dysfunction of the baroreceptor-reflex as well as depletion of arginine vasopressin stores during sustained hypotension have been discussed as responsible mechanisms for arginine vasopressin deficiency.[1,90,91] Arginine vasopressin stores of the neurohypophysis were found be depleted within a short time of intensive cardiovascular and osmotic stimulation.[1,92] Because low-dose administration of arginine vasopressin barely affects arterial blood pressure in normotensive volunteers with an intact arterial baroreflex, arginine vasopressin hypersensitivity of arterial resistance vessels has been postulated in vasodilatory shock and discussed as a precondition for the vasoconstrictive effects of arginine vasopressin.[44,90] However, a relationship between pressor response to arginine vasopressin and plasma levels of the hormone could not be demonstrated.[93] In addition, during acute cardiac arrest, a situation where arginine vasopressin deficiency seems to be unlikely, powerful vasoconstrictive effects of arginine vasopressin have been shown.[81] One possible explanation why low-dose arginine vasopressin administration demonstrates only minor pressor effects in normotensive patients may be the physiological buffering of elevated vascular resistance by baroreflex-mediated reduction of cardiac output.[94] In contrast, in vasodilatory shock, this baroreflex-mechanism seems to be either significantly reduced or absent, indicating autonomic insufficiency.[95]

In vasodilatory shock, additional mechanisms of arginine vasopressin-mediated vasoconstriction independent of the V_1-receptor have been described. Blockade of activated ATP-sensitive po-

tassium channels within VSMC membranes by arginine vasopressin facilitates myocyte depolarisation and thus vasoconstriction.[96] Arginine vasopressin attenuates endotoxin and IL-1β-stimulated generation of NO inhibiting excessive vasodilatation.[97,98] Moreover, arginine vasopressin directly decreases intracellular concentrations of the NO second messenger, cGMP.[99,100] During endotoxaemia, arginine vasopressin enhances adrenergic responsiveness.[101] This might be caused by partial reversal of adrenergic receptor down-regulation. Another possible mechanism of reversal of vasodilatation, which has to be discussed is an arginine vasopressin-induced increased production of ACTH and cortisol, both of which are significantly decreased in a substantial number of patients in septic shock.[102] An increase of plasma cortisol levels in human septic shock has been shown to reduce the time to cessation of vasopressor therapy and is associated with a trend to earlier resolution of sepsis-induced organ dysfunction.[103] In addition, arginine vasopressin stimulates synthesis of endothelin-I,[104,105] the most potent endogenous vasopressor yet found.[106]

Interestingly, at the molecular level of cell membrane receptors, the pressure response to arginine vasopressin is markedly suppressed in vasodilatory shock,[107] similar to that reported for catecholamines, angiotensin II and endothelin.[108] Hollenberg and coworkers[109] demonstrated reduced responsiveness of resistance vessels in septic rats in response to arginine vasopressin. Administration of a NOS inhibitor partially restored arginine vasopressin responsiveness indicating a NO-dependent mechanism for arginine vasopressin hyporesponsiveness. NO-mediated modulation of arginine vasopressin receptors includes quantitative reduction[110] and impairment of inositol lipid metabolism,[111] as well as perturbation of transmembrane signalling pathways.[112]

4. Clinical Experience with Arginine Vasopressin in Catecholamine-Resistant Vasodilatory Shock

4.1 Septic Shock

We performed a literature search of Medline with the key words 'arginine vasopressin', 'vasopressin', 'vasodilatory shock', 'septic shock' and

Table I. Clinical studies on the use of continuous infusion of arginine vasopressin (AVP) in patients with septic shock

Reference	Study type	Disease	No. pts	AVP effects
Landry et al., 1997[90]	Case series	Septic shock	10	Increase in SAP, DAP and SVR Decrease in CO
Landry et al., 1997[73]	Case series	Septic shock	5	Increase in SAP, DAP, MAP and SVR Increase in urine output
Malay et al., 1999[113]	Prospective, randomised, placebo-controlled	Septic shock	10	Increase in SAP, MAP and SVR Decrease in CI
Dünser et al., 2001[30]	Retrospective	Septic and postcardiotomy shock	60	Increase in MAP and SVR Decrease in HR, MPAP, CI and norepinephrine requirements
Tsuneyoshi et al., 2001[74]	Prospective, case-controlled	Septic shock	16	Increase in MAP, SVR and urine output
Holmes et al., 2001[75]	Retrospective	Septic shock	50	Increase in MAP and urine output Decrease in CI and pressor dosages
Bracco et al., 2001[114]	Prospective	Septic shock	7	Increase in MAP and SVR Decrease in norepinephrine dosages Increase in delta-pCO_2

CI = cardiac index; **CO** = cardiac output; **DAP** = diastolic arterial pressure; **delta-pCO_2** = gastric mucosal pCO_2 gradient; **HR** = heart rate; **MAP** = mean arterial pressure; **MPAP** = mean pulmonary arterial pressure; **SAP** = systolic arterial pressure; **SVR** = systemic vascular resistance.

'vasopressor' in order to identify reports about managing vasodilatory shock patients with arginine vasopressin; in addition, we carefully searched for citations in articles for references that were not on Medline. Accordingly, table I presents published studies, except for single case reports, on the employment of arginine vasopressin in septic shock.

In 1997, Landry et al.[73] reported first clinical experience with continuous arginine vasopressin infusion (1.8–3 IU/h) in five patients with septic shock. Upon initiation of an arginine vasopressin infusion, a significant increase in mean arterial blood pressure and systemic vascular resistance occurred. Subsequently, a norepinephrine infusion could be tapered off in four of five patients. Attempts to reduce arginine vasopressin resulted in deterioration of mean arterial blood pressure, which could be reversed by an increase of arginine vasopressin infusion. In three of five patients, a paradoxical increase of urine output after the start of the arginine vasopressin infusion was observed, which may be due to constriction of efferent glomerular arterioles maintaining glomerular filtration rate despite decreased renal blood blow.

In a small prospective, placebo-controlled, double-blind study including ten patients, Malay et al.[113] confirmed the results of Landry.[73,90] In patients with septic shock, arginine vasopressin significantly increased arterial blood pressure and allowed a simultaneous reduction of catecholamine vasopressor agents. The authors attributed the significant increase in arterial blood pressure to the correction of inappropriately low plasma levels by administration of arginine vasopressin at dosages resulting in plasma concentrations similar to those found in acute shock states. During a 24-hour observation period, no significant differences in base deficit, serum sodium or serum creatinine concentrations occurred between patients treated with arginine vasopressin or placebo. After 24 hours, two out of five patients receiving placebo died, whereas all patients treated with arginine vasopressin survived.

In a prospective, case-controlled study in 16 patients with catecholamine-resistant septic shock, Tsuenyoshi et al.[74] reported improved haemodynamics in response to low-dose arginine vasopressin infusion. In addition, a significant increase of urine output occurred in ten patients. Serum levels of atrial natriuretic factor, aldosterone, angiotensin II and renin were not altered, suggesting that the haemodynamic effects of arginine vasopressin are not mediated by changes in serum levels of these hormones.

In a retrospective study including 60 patients with catecholamine-resistant septic and postcardiotomy shock, our working group[30] could show that a continuous arginine vasopressin infusion (4–6 IU/h) significantly increased mean arterial blood pressure and significantly decreased heart rate as well as norepinephrine requirements. A simultaneous decrease in cardiac index may be explained by the significant reduction in heart rate; myocardial performance assessed by stroke volume index remained unchanged (table II). In this study, we observed a significant decrease in mean pulmonary artery pressure during arginine vasopressin infusion, which has not been described in humans before. The decrease was already present 4 hours after initiation of arginine vasopressin, suggesting a causal relationship with administration of this novel vasopressor. Experimental studies in animals have demonstrated that arginine vasopressin-induced pulmonary vasodilatation is probably mediated by a NO-dependent mechanism.[62,115] However, the simultaneous significant reduction in norepinephrine infusion may have contributed to the observed decrease in pulmonary artery blood pressure. Table III displays changes in acid-base status and other laboratory parameters during continuous arginine vasopressin administration. We observed a significant elevation of serum transaminases and bilirubin levels. The significant decrease in thrombocyte counts could be a marker of increased platelet consumption resulting from continuous disseminated intravascular coagulation or could reflect increased arginine vasopressin-induced thrombocyte aggregation.[67]

Table II to go here (landscape)

In a recent retrospective analysis of 50 patients in severe septic shock, Holmes et al.[75] reported a significant increase in mean arterial blood pressure and urine output, as well as a significant decrease in catecholamine requirements and cardiac index during arginine vasopressin infusion. There was no change in systolic pulmonary artery blood pressure. During the study period, six cardiac arrests were observed; five out of six patients were receiving arginine vasopressin therapy >0.03 IU/min. Therefore, the authors suggested that arginine vasopressin dosages exceeding 0.04 IU/min may be associated with adverse effects and should be avoided.

The question arises about how to guide a continuous arginine vasopressin infusion in patients with vasodilatory shock in order to achieve the maximum benefit, and to avoid complications or adverse effects of this treatment strategy. Namely, solutions could be either to infuse arginine vasopressin at a fixed rate[116] or after determining an endogenous arginine vasopressin deficiency, as Landry et al. suggests.[90] However, we found that the acute situation of haemodynamic instability may simply not allow the time window to so, indicating that the intensivist may be simply forced to start an arginine vasopressin infusion without knowing the exact underlying pathophysiology or possibly lose the patient because of collapsing blood pressure.

As Argenziano et al.[44] showed, an arginine vasopressin infusion was effective in both vasodilatory shock patients with normal, and in those with inadequately low, endogenous arginine vasopressin levels. Accordingly, initiating an arginine vasopressin infusion may be a pragmatic decision to stabilise a patient whose cardiocirculatory homeostasis can not be maintained with catecholamine vasopressors.

In the current resuscitation guidelines of both the American Heart Association and the European Resuscitation Council,[28] the approach is somewhat similar; as the guidelines state: '[t]he standard treatment of patients with vasodilatory septic shock includes antibiotics, extracellular volume

Table II. Changes in haemodynamic parameters and norepinephrine requirements during a continuous infusion of arginine vasopressin in patients with catecholamine-resistant septic and postcardiotomy shock[a] (reproduced from Dünser et al.[30] with permission from Lippincott Williams & Wilkins© 2001)

Parameter	Unit	Baseline	4h	12h	24h	48h	72h	p-value
No. of pts		60	54	42	32	25	19	
HR	(beats/min)	114 ± 21	102 ± 18[b]	99 ± 16[b]	93 ± 18[b]	93 ± 17	86 ± 10[b]	0.0001[c]
MAP	(mmHg)	59 ± 12	78 ± 11[b]	77 ± 11	75 ± 14	80 ± 10[b]	81 ± 10[b]	0.0035[c]
MPAP	(mmHg)	28 ± 7	27 ± 6[b]	26 ± 6[b]	26 ± 5[b]	25 ± 4[b]	25 ± 4[b]	0.0048[c]
PCWP	(mmHg)	16 ± 4	15 ± 4	15 ± 3	18 ± 3	15 ± 5	15 ± 4	NS
CI	($L/min/m^2$)	4.3 ± 1.8	3.7 ± 1.3	3.7 ± 1.2[b]	3.5 ± 1.1[b]	3.3 ± 1.2[b]	3.3 ± 1.1[b]	0.0008[c]
SVI	($ml/beat/m^2$)	36 ± 14.2	36 ± 12.6	37 ± 12	37 ± 10.4	36 ± 10.8	36 ± 10.9	NS
SVR	($dyn \bullet sec/cm^5$)	638 ± 301	886 ± 465[b]	870 ± 314[b]	906 ± 314[b]	998 ± 369[b]	988 ± 336[b]	0.0003[c]
NE	(μg/kg/min)	1.8 ± 1.7	0.98 ± 0.78[b]	0.75 ± 0.63[b]	0.59 ± 0.44[b]	0.51 ± 0.51[b]	0.43 ± 0.43[b]	0.0001[c]

a Mean values ± SD.

b Significant change vs baseline.

c Significant time effect.

CI = cardiac index; **HR** = heart rate; **MAP** = mean arterial pressure; **MPAP** = mean pulmonary arterial pressure; **NE** = norepinephrine requirements; **NS** = not significant; **PCWP** = pulmonary capillary wedge pressure; **SVI** = stroke volume index; **SVR** = systemic vascular resistance.

Table III to go here (landscape)

expansion, vasopressors, and drugs that increase myocardial contractility. Adrenergic catecholamines employed in this setting such as norepinephrine often have a diminished vasopressor action in vasodilatory shock; therefore, alternatives may be very useful. Patients with vasodilatory shock refractory to adrenergic vasopressors should receive continuous infusions of arginine vasopressin early (~2.4 to ~6 IU/h) in order to stabilize cardiocirculatory function (class IIb recommendation: alternative intervention, good evidence, safe)'.

4.2 Postcardiotomy Shock

Table IV presents all published studies, except for single case reports, on the use of arginine vasopressin in postcardiotomy shock. In postcardiotomy shock, beneficial haemodynamic responses similar to that observed in septic shock have been reported after initiation of an arginine vasopressin infusion (2–6 IU/h).[30,44,89,93,117] In all studies, a significant increase in arterial blood pressure due to an increase in systemic vascular resistance and a significant reduction of vasopressor catecholamines has been shown.

In a retrospective study in 40 patients with postcardiotomy shock, Argenziano et al.[44] observed an increase in mean arterial blood pressure proportional to the severity of vasodilatory hypotension after start of arginine vasopressin administration. Rosenzweig et al.[118] reported a significant improvement of haemodynamics in a paediatric patient population (age, 3 days – 15 years) with postcardiotomy shock during arginine vasopressin therapy. In a large retrospective study in 50 patients with left ventricular assist device and postcardiotomy shock, Morales et al.[89] pointed at possible clinical adverse effects during arginine vasopressin infusion (table V). However, as noted by the authors, these adverse effects may also be explained by the severity of the disease and/or complications of mechanical cardiac support, and can not necessarily be attributed to administration of arginine vasopressin.

None of these studies reported adverse effects of continuous arginine vasopressin infusion on

Table III. Changes in acid-base status and laboratory parameters during a continuous arginine vasopressin infusion in patients with catecholamine-resistant septic and postcardiotomy shock (mean ± SD)[30]

Parameter (unit)	Baseline	1h	4h	12h	24h	48h	72h	p-value
No. pts	60	58	54	42	32	25	19	
pH	7.27 ± 0.13	7.2 ± 0.15	7.26 ± 0.12	7.27 ± 0.13	7.32 ± 0.12[a]	7.36 ± 0.09[a]	7.41 ± 0.05[a]	0.0001[b]
Lactate (mg/dl)	50 ± 38	55 ± 45	59 ± 51	48 ± 35	38 ± 34	28 ± 32	19 ± 11	NS
Base excess (mmol/L)	–5.4 ± 5.9	–9.2 ± 6.8	–6.1 ± –6.3	–4.3 ± 5.6	–2 ± 4.7	0.3 ± 6.2	1.7 ± 4	NS
Creatinine (mg/dl)	2.3 ± 1.2	NM	NM	NM	2.4 ± 1	2.2 ± 1	2.5 ± 1.6	NS
AST (U/L)	105 ± 275	NM	NM	NM	327 ± 629[a]	126 ± 327	98 ± 198	0.0236[b]
ALT (U/L)	97 ± 344	NM	NM	NM	221 ± 408	132 ± 286	77 ± 152	0.0316[b]
Bilirubin (mg/dl)	2.4 ± 2.3	NM	NM	NM	3 ± 3.4[a]	3.9 ± 4.3[a]	4.5 ± 5.3[a]	0.0001[b]
Thrombocytes (1000 cells/L)	138 ± 113	NM	NM	NM	104 ± 90[a]	92 ± 72[a]	63 ± 60[a]	0.0001[b]
PaO_2/FiO_2	188 ± 91	NM	NM	NM	214 ± 90	224 ± 77	219 ± 68	NS

a Significant change vs baseline.

b Significant time effect.

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **FiO_2** = inspired oxygen fraction; **PaO_2** = partial arterial oxygen pressure (tension); **NM** = not measured; **NS** = not significant.

Table IV. Clinical studies on the use of a continuous infusion of arginine vasopressin (AVP) in patients with postcardiotomy shock

Reference	Study type	Disease	No. pts	AVP effects
Argenziano et al., 1997[93]	Prospective, randomised, placebo-controlled	Vasodilatory shock after LVAD placement	10	Increase in MAP and SVR
Argenziano et al., 1998[44]	Retrospective	Postcardiotomy shock	40	Increase in MAP and SVR Decrease in norepinephrine support
Argenziano et al., 1999[117]	Retrospective	Postcardiotomy shock after cardiac transplantation	20	Increase in MAP Decrease in CI and pressor support
Rosenzweig et al., 1999[118]	Retrospective	Paediatric patients with postcardiotomy shock	11	Increase in SAP Decrease in pressor support
Morales et al., 2000[89]	Retrospective	Postcardiotomy shock	50	Increase in MAP and SVR Decrease in norepinephrine support
Dünser et al., 2001[30]	Retrospective	Septic and postcardiotomy shock	60	Increase in MAP and SVR Decrease in HR, MPAP, CI and norepinephrine requirements
Dünser et al., 2002[119]	Retrospective	Postcardiotomy shock	41	Decrease in HR, inotropic and pressor support Increase in LVSWI, MAP and SVR Spontaneous cardioversion of 50% of tachyarrhythmias

CI = cardiac index; **HR** = heart rate; **LVAD** = left ventricular assist device; **LVSWI** = left ventricular stroke work index; **MAP** = mean arterial pressure; **MPAP** = mean pulmonary arterial pressure; **SAP** = systolic arterial pressure; **SVR** = systemic vascular resistance.

myocardial oxygen supply, such as development of myocardial ischaemia.

Recently, we examined the effects of a continuous arginine vasopressin infusion over 48 hours in dosages of up to 6 IU/h on haemodynamic parameters and, in particular, cardiac performance, in 41 patients with catecholamine-resistant postcardiotomy shock (table VI).[119] We observed no changes in cardiac and stroke volume index, whereas heart rate significantly decreased, while left ventricular stroke work index increased simultaneously with a significant reduction in norepinephrine- and milrinone-requirements by 55% and 18%, respectively.

4.3 Other Vasodilatory States

Table VII presents all published studies, except for case reports, investigating the employment of arginine vasopressin in other vasodilatory states. Encouraging experiences with arginine vasopressin in septic and postcardiotomy shock have been extended by numerous retrospective analyses and case reports about the use of arginine vasopressin in hypotension of different aetiology. Reversal of hypotension after the start of a continuous arginine vasopressin infusion has been reported during combined general/epidural anaesthesia,[82] continuous milrinone infusion,[27] in cardiac arrest[81] and in pancreatitis-associated vasodilatory shock,[120] as well as in orthostatic[5] or haemo-

Table V. Complications of a continuous infusion of arginine vasopressin in 50 patients after left ventricular assist device implantation (reproduced from Morales et al.[89] with permission from the Society of Thoracic Surgeons)

Complication	Incidence
Bleeding	19/50 (38%)
Infection	18/50 (36%)
Right heart failure	16/50 (32%)
Ventricular arrhythmias	7/50 (14%)
Gastrointestinal bleeding	2/50 (4%)
Neurologic complications	3/50 (6%)
Thromboembolic complications	2/50 (4%)
Liver insufficiency	7/50 (14%)
Gastrointestinal ischaemia	0/50 (0%)

Table VI to go here (landscape)

dialysis-induced hypotension.[6] Moreover, stabilisation of haemodynamics and reduction of vasopressor catecholamine requirements has repeatedly been demonstrated in haemodynamically unstable organ donors without clinically manifest diabetes insipidus,[17,18,121,122] in late phase haemorrhagic shock[4] and intraoperatively in patients receiving ACE inhibitors long-term.[46]

5. Adverse Effects of Arginine Vasopressin Administration in Vasodilatory Shock

5.1 The Heart

High dosages of arginine vasopressin used to control upper gastrointestinal bleeding were reported to exert significant adverse effects on the heart, such as negative inotropy or myocardial ischaemia.[123] In an early report by Ruskin,[124] arginine vasopressin was even used as a stress test to detect ischaemic heart disease. Therefore, intensivists often hesitate to infuse arginine vasopressin as an additional vasopressor in advanced vasodilatory shock.[125] Controversial studies exist about the effects of arginine vasopressin on the coronary vascular bed. Case reports in patients with upper gastrointestinal bleeding have definitely demonstrated the occurrence of negative inotropic effects, myocardial ischaemia and infarction during arginine vasopressin administration.[126,127] However, these patients received arginine vasopressin dosages that were about 5–20 times higher than those in catecholamine-resistant vasodilatory shock (2–6 IU/h).[123] The decrease in inotropy may also be explained by a baroreflex-mediated buffering of cardiac output, since autonomic insufficiency is usually absent in patients with acute upper gastrointestinal bleeding.[94]

Several *in vitro* and animal studies demonstrated vasoconstriction of coronary arteries due to stimulation of V_1-receptors.[128,129] In contrast, Okamura[60] and Vanhoutte[130] observed arginine vasopressin-mediated vasodilatation of coronary arteries, which could be reversed by a V_1-receptor-antagonist. Wenzel et al.[131] reported a significant

Table VI. Effects of a continuous infusion of arginine vasopressin on cardiac and systemic haemodynamic parameters in patients with catecholamine-resistant postcardiotomy shock (mean ± SD) [reproduced from Dünser M[119] with permission from Springer-Verlag © 2002]

Parameter	Baseline	1h	4h	12h	24h	48h	p-value
No. of pts	41	41	38	36	32	21	
HR (beats/min)	108 ± 19	102 ± 18	96 ± 15[a]	94 ± 16[a]	91 ± 17[a]	92 ± 16[a]	0.0001[b]
CI (L/min/m^2)	3.3 ± 1	2.9 ± 1	3.0 ± 1	3.0 ± 1	3.1 ± 1	2.8 ± 1	0.0895
SVI (ml/beat/m^2)	30 ± 10	30 ± 8	30 ± 8	31 ± 8	32 ± 8	30 ± 7	0.1578
LVSWI (g/m^2/beat)	17 ± 8	26 ± 8[a]	25 ± 8[a]	26 ± 8[a]	27 ± 7[a]	25 ± 6[a]	0.0001[b]
MAP (mmHg)	55 ± 12	82 ± 14[a]	78 ± 12[a]	78 ± 11[a]	76 ± 12[a]	78 ± 8[a]	0.0001[b]
Mil (μg/kg/min)	0.4 ± 0.2	0.4 ± 0.3	0.39 ± 0.2	0.35 ± 0.2	0.33 ± 0.2[a]	0.33 ± 0.2[a]	0.0205[b]
NE (μg/kg/min)	1.62 ± 1.9	1.13 ± 1.7	0.91 ± 1.5[a]	0.58 ± 0.9[a]	0.57 ± 1[a]	0.73 ± 1.6[a]	0.001[b]

a Significant change vs baseline.

b Significant time effect.

CI = cardiac index; **HR** = heart rate; **LVSWI** = left ventricular stroke work index; **MAP** = mean arterial pressure; **Mil** = milrinone requirements; **NE** = norepinephrine requirements; **SVI** = stroke volume index.

Table VII. Clinical studies on the use of a continuous infusion of arginine vasopressin (AVP) in other vasodilatory shock states

Reference	Study type	Disease	No. pts	AVP effects
Kochar, 1985[5]	Prospective	Chronic orthostatic hypotension	10	Increase in MAP and SVR
Yoshioka et al., 1986[122]	Prospective, controlled	Haemodynamically unstable organ donors	16	Increase in MAP and SVR
				Decrease in pressor support
				Prolonged survival time
Iwai et al., 1989[18]	Prospective, controlled	Haemodynamically unstable organ donors	25	Increase in SVR
				The increase in SVR was achieved with AVP in combination with an increased dosage of epinephrine
				Increase in MAP and CI
Lindberg et al., 1990[6]	Prospective	Refractory haemodialysis-induced hypotension	6	Increase in SAP, DAP and MAP
Eyraud et al., 1999[46]	Prospective	Intraoperative hypotension in patients receiving ACE inhibitors long-term	10	Increase in MAP, EDA, ESA and ESWS
				Decrease in HR
Chen et al., 1999[17]	Prospective	Haemodynamically unstable organ donors	10	Increase in MAP
				Decrease in norepinephrine support
Morales et al., 1999[4]	Case series	Late phase of haemorrhagic shock	2	Increase in SAP
				Decrease in norepinephrine support
Katz et al., 2000[121]	Retrospective, case-controlled	Paediatric, brain-dead patients	34	Increase in MAP
				Decrease in pressor support
De Kock et al., 2000[82]	Prospective, double-blind, randomised	Hypotension during general/epidural anaesthesia	60	Increase in SAP, DAP and gastric pCO_2
				Decrease in pressor support
Gold et al., 2000[27]	Case series	Milrinone-induced hypotension	3	Increase in SAP
				Decrease in norepinephrine support

CI = cardiac index; **DAP** = diastolic arterial pressure; **EDA** = end-diastolic area; **ESA** = end-systolic area; **ESWS** = end-systolic wall stress; **HR** = heart rate; **MAP** = mean arterial pressure; **pCO_2** = partial pressure (tension) of CO_2; **SAP** = systolic arterial pressure; **SVR** = systemic vascular resistance.

increase in vascular diameter of the left anterior descending artery after a bolus injection of 0.4 U/kg arginine vasopressin in pigs. This vasodilatation was present during sinus rhythm, ventricular fibrillation and after successful cardiopulmonary resuscitation. The authors suggested that arginine vasopressin-induced vasodilatation in coronary arteries is dependent on NO. Therefore, in clinical situations, arginine vasopressin-mediated effects on coronary vessels may depend on dosages applied, as it has been shown for the pulmonary vasculature in dogs.[132]

In a retrospective study by our group,[119] continuous arginine vasopressin infusion in catecholamine-resistant postcardiotomy shock was associated with a significant increase in left ventricular stroke work index and a significant decrease in heart rate as well as vasopressor and inotropic requirements. Simultaneously, cardiac and stroke volume index remained unchanged despite of a significant reduction of positive inotropic agents, suggesting a lack of negative inotropic effects or even some positive inotropic action of low-dose arginine vasopressin infusion in postcardiotomy shock. Levels of myocardial enzymes (creatine kinase-MB, troponin I) significantly fell in all patients with elevated serum levels at study entry, and remained low in all other patients. Similarly, Eyraud[46] and Overand[133] reported improvement of myocardial performance during arginine vasopressin infusion in catecholamine-resistant hypotension. Elevated coronary perfusion pressure,[134] arginine vasopressin-induced coronary vasodilatation,[60,130] reversal of adrenergic receptor down-regulation, decrease of excessive beta-stimulation[135] and direct positive inotropic effects of arginine vasopressin may have contributed to these findings.[63,64,136] In addition, Welt et al.[137] found significant venoconstrictive effects of arginine vasopressin in an animal study, which may enhance ventricular filling and thus increase cardiac output.

Another interesting observation was spontaneous cardioversion of tachyarrhythmias into sinus rhythm in approximately half of patients with new-onset tachyarrhythmias during arginine vasopressin infusion. It may be speculated that the significant reduction in norepinephrine and milrinone requirements, both of which have significant pro-arrhythmic effects,[138,139] together with an improvement of myocardial perfusion, has contributed to spontaneous cardioversion from tachyarrhythmias. Therefore, arginine vasopressin given as a continuous infusion not exceeding 6 IU/h seems to be devoid of adverse effects on the heart in patients with catecholamine-resistant vasodilatory shock. Under these pathophysiological conditions, arginine vasopressin may even improve myocardial performance.[119]

5.2 The Skin

Physiologically, an arginine vasopressin-mediated vasoconstriction is mostly expressed in the cutaneous vasculature.[140] Therefore, arginine vasopressin has been used to reduce intraoperative blood loss during surgical repair of burn wounds.[141] Development of ischaemic skin lesions have been reported in patients with upper gastrointestinal bleeding receiving high dosages of arginine vasopressin.[142,143]

In a recent investigation, we have analysed the incidence and possible risk factors for the development of ischaemic skin lesions during continuous arginine vasopressin infusion in 63 patients with catecholamine-resistant vasodilatory shock (unpublished observation). We found that ischaemic skin lesions were a common complication (~30%) in patients with catecholamine-resistant vasodilatory shock undergoing a continuous arginine vasopressin infusion; most of the ischaemic skin lesions were located in the distal extremities and the trunk. Lingual ischaemia developed in up to 20% of patients showing ischaemic skin lesions. Although it is suggested that arginine vasopressin may induce ischaemic skin lesions, we found that a continuous arginine vasopressin infusion of 2–6 IU/h was not associated with ischaemic skin lesions. In fact, the presence of septic shock and a history of peripheral arterial occlusive disease were independent risk factors for the development of ischaemic skin le-

sions in our patients, which may be an epiphenomenon of the severe underlying disease.

Although not proven beyond a reasonable doubt, the risk of skin lesions may be lower in patients undergoing arginine vasopressin infusion in a hyperdynamic state versus a low flow state. In our experience with patients with catecholamine-resistant vasodilatory shock receiving an arginine vasopressin infusion, if normovolaemia was achieved and stroke volume index was <25 ml/beat/m^2 or cardiac index was <2 L/min/m^2, we started a milrinone infusion in order to improve perfusion.

5.3 The Gastrointestinal Tract

When considering the central role of the gastrointestinal tract as a possible source or engine of multiple organ dysfunction syndrome,[144] concern about possible adverse effects of arginine vasopressin on the gastrointestinal circulation have been raised.[145] When used in high single doses (~4–16 IU) to control upper gastrointestinal bleeding, arginine vasopressin significantly decreases gastrointestinal blood flow; accordingly, gut ischaemia following arginine vasopressin infusion has been reported.[123]

During haemorrhage, arginine vasopressin and angiotensin were shown to exert intense intestinal vasoconstriction in cats.[146] In addition, several animal studies demonstrated a role of arginine vasopressin in the development of splanchnic ischaemia during different experimental conditions.[147,148] For example, Varga et al.[149] observed endogenous vasopressin to be implicated in gastrointestinal mucosal injury in endotoxaemic rats, as arginine vasopressin strongly potentiated endogenous and exogenous catecholamine-mediated vasoconstriction in the splanchnic vascular bed.[147] In addition, Sun et al.[150] observed a significant decrease in superior mesenteric artery blood flow in arginine vasopressin-treated animals than in animals receiving norepinephrine infusion. Interestingly, concurrent enteral nutrition was able to prevent the decrease in superior mesenteric artery blood flow in rats.[151] Concerning hepatic circulation, Jenkins et al.[152] showed an increase in hepatic arterial blood flow, and a decrease in portal venous blood flow during systemic arginine vasopressin infusion in animals. In contrast, Fasth et al.[153] found only a short-lasting decrease of total hepatic blood flow during continuous infusion of arginine vasopressin into the hepatic artery in animals.

In 60 patients receiving arginine vasopressin therapy because of catecholamine-resistant vasodilatory shock,[30] we observed an increase in serum transaminases and bilirubin levels, which could represent a potential adverse effect of arginine vasopressin on gastrointestinal perfusion. However, the observed changes may have also resulted from progression of severe multiple organ dysfunction syndrome. In a prospective, randomised, placebo-controlled study including 60 hypotensive patients during combined general/epidural anaesthesia, continuous ornipressin administration significantly increased the end-tidal to gastric mucosal partial pressure of CO_2 (pCO_2) gradient, suggesting a development of slight splanchnic hypoperfusion. However, a non-significant increase in end-tidal to gastric mucosal pCO_2 gradient was also noted in norepinephrine-treated patients.[82] In seven patients with catecholamine-resistant vasodilatory shock, Bracco et al.[114] recently reported a significant increase in the end-tidal to gastric mucosal pCO_2 gradient, indicating a decrease in gastric mucosal perfusion. The authors recommended a close monitoring of gut perfusion using gastric tonometry if arginine vasopressin is applied; however, maximum dosages used in this study were greater than 6 IU/h, which we do not recommend. In addition, up to two bolus injections of 0.05 IU/kg of arginine vasopressin were applied.

In summary, concern about splanchnic hypoperfusion during continuous arginine vasopressin and its analogues has to be taken seriously but it has to be taken in proper perspective as well. For example, the vasopressor and antidiuretic function of arginine vasopressin[73] and ornipressin[82] are significantly different (figure 1), and therefore have to be adequately interpreted. Furthermore,

when discussing hypoperfusion of the gut, it has to be considered that vasopressin dosages that are usually administered in patients with bleeding oesophageal varices are about 3–5 times greater than in patients with catecholamine-resistant vasodilatory shock. Furthermore, the cardiocirculatory system in patients with bleeding oesophageal varices or undergoing routine anaesthesia usually represents autonomic sufficiency, which is significantly different to patients in vasodilatory shock whose cardiocirculatory system is usually autonomic insufficient. Accordingly, when infusing vasopressin continuously, we have to carefully consider both the setting and underlying pathophysiology. Thus, larger, prospective, randomised clinical trials are needed to exactly evaluate the effects of a continuous arginine vasopressin infusion on the gastrointestinal circulation in patients with advanced vasodilatory shock.

6. Limitations and Conclusions

The exciting news about arginine vasopressin studies in vasodilatory shock can not cover the fact that many issues have not yet been addressed, at least partially because commercial interest is lacking as a result of an expired patent from approximately 50 years ago. For example, a dose-response investigation has not been performed to date and most clinical studies have been conducted employing a continuous arginine vasopressin infusion of 2–6 IU/h. Secondly, as discussed in previous sections of this manuscript (specifically, section 5.3), arginine vasopressin may decrease gut perfusion; whether this may cause adverse effects in patients with diffuse mesenteric hypoperfusion is unknown at this point in time and needs to be addressed in future studies. Thirdly, we are unable to definitely determine whether ischaemic skin lesions during arginine vasopressin infusion were due to severe underlying disease and/or subsequent arginine vasopressin infusion. Fourth, although our entry criteria to initiate an arginine vasopressin infusion made sense in our observations, we do not want to exclude the possibility that better entry criteria could be formulated. Finally, the majority of evidence stems from retrospective studies, and more prospective, randomised controlled trials employing a continuous infusion of arginine vasopressin in patients with vasodilatory shock are definitely necessary to put this new strategy on more solid ground.

In conclusion, catecholamine-resistant vasodilatory shock is associated with excessive mortality rates. In recent years, several investigations impressively demonstrated that an infusion of ~2–6 IU/h arginine vasopressin can successfully stabilise haemodynamics even in patients with advanced vasodilatory shock. In view of the presented experimental evidence and current clinical experience, a continuous arginine vasopressin infusion can be considered as a supplement to vasopressor catecholamines in order to preserve cardiocirculatory homeostasis in advanced vasodilatory shock. Because data on adverse effects are still limited, arginine vasopressin should be reserved for patients in whom adequate haemodynamic stabilisation cannot be achieved with conventional vasopressor therapy or in whom obvious adverse effects of catecholamines promote further significant haemodynamic deterioration. For the same reasons, arginine vasopressin should not be used as a single, alternative vasopressor agent instead of catecholamine vasopressors.

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