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Vasopressin

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Arginine vasopressin (hereafter referred to as “vasopressin”), also known as antidiuretic hormone, is essential for survival as attested by its teleological persistence. Oxytocin and vasopressin-like peptides have been isolated from 4 invertebrate phyla and 7 major vertebrate families, representing more than 120 species.¹ Although oxytocin differs from vasopressin by only one amino acid (80% homology), they have clearly divergent physiological activities. The vasopressor effect of pituitary extract, first observed in 1895, was attributed to the posterior lobe of the gland.² It wasn't until 18 years later that the antidiuretic effect of neurohypophyseal extract was demonstrated. After isolation and synthesis of vasopressin in the 1950s, it was proven that the same hormone in the posterior pituitary possessed both antidiuretic and vasopressor effects.³ The importance of vasopressin in osmotic defense is fundamental. Indeed, the antidiuretic effect of vasopressin has been exploited clinically for over half a century to treat diabetes insipidus. Only recently has vasopressin emerged as a therapy for shock states, renewing an interest in its cardiovascular effects.

Vasopressin mechanisms

The actions of vasopressin are mediated by stimulation of tissue-specific G protein-coupled receptors (GPCRs) currently classified into:

- V₁ vascular (V₁R)
- V₂ renal (V₂R)
- V₃ pituitary (V₃R)
- oxytocin (OTR) subtypes,⁴ and
- P₂ purinergic receptors (P₂R).⁵

The actions of vasopressin are signaled through pathways that are similar to extracellular agents such as hormones (glucagon, luteinizing hormone, and epinephrine), neurotransmitters (acetylcholine, dopamine, and serotonin), and chemokines. Whether vasopressin causes vasoconstriction or vasodilation depends on the vascular bed studied, which may in turn, depend on the receptor density (eg, V₁R vs OTR), the model studied, the dose of vasopressin,⁶ and the duration of exposure to the hormone.⁷ Indeed, the opposing influences of the various pathways that determine the functional state of vascular smooth muscle is an area for further study. The important question is whether vasopressin can cause simultaneous vasoconstriction of some vascular beds and vasodilation of others.

The V₁ vascular receptor (V₁R)

V₁Rs are found in high density on vascular smooth muscle and cause vasoconstriction by an increase in intracellular calcium via the phosphatidyl-inositol-bisphosphate cascade. Cardiac myocytes also possess V₁Rs and are discussed in a subsequent section. Additionally, V₁Rs are located in the brain, testes, superior cervical ganglion, liver, blood vessels, and renal medulla.⁸ The exact physiologic role of vasopressin in many of these diverse tissues remains unknown. Platelets express the V₁R which, upon stimulation, induces an increase in intracellular calcium, thus facilitating thrombosis;⁹ however, there appears to be a tremendous variability in the aggregation response of normal human platelets to vasopressin.¹⁰

V₁Rs are also found in the kidney where they occur in high density on medullary interstitial cells, vasa recta, and epithelial cells of the collecting duct. Vasopressin acts on the medullary vasculature via the V₁R to reduce blood flow to the inner medulla without affecting blood flow to the outer medulla.¹¹ V₁Rs on the luminal membrane of the collecting duct – probably exerted through V₁R receptors located on the luminal membrane – limit the antidiuretic effects of vasopressin.¹¹ In addition, vasopressin selectively causes contraction of efferent arterioles,¹² likely via the V₁R, but not afferent arterioles. This selectivity, not shared by catecholamine vasopressors, would tend to increase the glomerular filtration rate (GFR), likely accounting for the paradoxical increase in urine output observed when this antidiuretic hormone is administered to subjects in vasodilatory shock.^{13,14}



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The V_2 renal receptor (V_2R)

The well-known antidiuretic effect of vasopressin occurs via activation of the V_2R . Vasopressin regulates water excretion from the kidney by increasing the osmotic water permeability of the renal collecting duct, an effect that is explained by coupling of the V_2R with a pathway that activates cAMP (cyclic adenosine monophosphate).¹⁵ Indeed, most cases of diabetes insipidus can be explained by mutations of the V_2R gene, located on chromosome region 10q28.¹⁶

The V_3R pituitary receptor (V_3R)

The human V_3R (previously known as $V_{1b}R$) is a pituitary receptor that, due to its scarcity, was only recently characterized. However, the V_3R has a pharmacological profile that distinguishes it from the human V_1R and activates several signaling pathways, depending on the level of receptor expression.¹⁷ Interestingly, the V_3R is also overexpressed in ACTH-hypersecreting tumours.

The oxytocin receptor (OTR)

The OTR can be considered a “non-selective” vasopressin receptor. The OTR has equal affinity for vasopressin and oxytocin, whereas the V_1R has a 30-fold higher affinity for vasopressin than for oxytocin.¹⁸ OTRs have been localized to a variety of reproductive and nonreproductive tissues. Importantly, OTRs exist in high density on vascular endothelium, mediating nitric oxide-dependent vasodilation.¹⁹ Recently, the oxytocin/OTR system has been discovered in the heart. Activation of cardiac OTR stimulates the release of the atrial natriuretic peptide (ANP) that is involved in natriuresis, regulation of blood pressure, and cell growth.²⁰ Embryonic stem cells exposed to oxytocin exhibit increased ANP mRNA, abundant mitochondria, and express sarcomeric myosin heavy chain, consistent with the promotion of cardiomyocyte differentiation.²¹

The purinergic receptors (P_2R)

Recently, vasopressin has been demonstrated to act on the P_2 class of purinoceptors (P_2R).⁵ P_2R s may also have an important role in cardiac contractility. ATP released by platelets, endothelial cells, and damaged myocardium activates the P_2R , causing a large increase in cytosolic calcium and myocyte contractile amplitude.²² ATP is also released as a co-transmitter with norepinephrine from sympathetic nerve endings and acts in a synergistic manner with β -adrenergic agents, increasing myocardial contractility.²³ In contrast to β -adrenergic agents, inotropy is not accompanied by a positive chronotropic effect. It is speculated that a P_2R agonist-stimulated increase in contractility could occur without the expense of a rate-related increase in myocardial oxygen demand.²² Recently, vasopressin has been shown to exert cardiac effects through activation of P_2R s expressed on cardiac endothelium. Further study is necessary to ascertain the significance of vasopressin P_2R activation in the human heart, but the discovery that vasopressin acts on P_2R s is intriguing.

Cardiovascular effects of vasopressin

Vasopressin restores vascular tone in vasoplegic (catecholamine-resistant) shock states by at least 3 known mechanisms through activation of V_1R s: modulation of K_{ATP} channels, modulation of nitric oxide, and potentiation of adrenergic and other vasoconstrictor agents.²⁴

Vasopressin, norepinephrine, and angiotensin II act on cell surface receptors to effect vasoconstriction. Vasopressin inter-

acts with V_1 receptors, found in high density on vascular smooth muscle. Activation of these receptors stimulates phospholipase C and intracellular second messengers that, in turn, activate protein kinase C and elevate intracellular free calcium to initiate contraction of vascular smooth muscle. In contrast, vasodilators (eg, atrial natriuretic peptide [ANP] and nitric oxide [NO]) activate a cyclic guanosine monophosphate (cGMP)-dependent kinase that, by interacting with myosin phosphatase, dephosphorylates myosin and thus prevents muscle contraction.²⁵ The opposing influences of these pathways are important in determining the functional state of vascular smooth muscle and the integration of this signaling is a key component in vascular homeostasis.

Potassium (K^+) channels

A key mechanism by which vascular smooth muscle tone is controlled is through K^+ channels. The resting membrane potential of vascular smooth muscle ranges from -30 to -60 mV; however, a more positive potential (depolarization) opens voltage-gated calcium channels, increasing cytosolic Ca^{++} concentration and inducing vasoconstriction. Conversely, hyperpolarization closes these channels, decreases cytosolic Ca^{++} concentration, and induces vasodilation.²⁴ The membrane potential of vascular smooth muscle is controlled by a number of ion transporters and channels, particularly K^+ channels. The opening of K^+ channels allows an efflux of potassium, thus hyperpolarizing the plasma membrane and preventing the entry of calcium into the cell, even in the presence of vasoconstrictor agents.²⁶

Four types of K^+ channels have been described. Of these, the ATP-sensitive K^+ channel (K_{ATP}) is the best understood and has a critical role in disease states such as vasodilatory shock. K_{ATP} channels are physiologically activated by decreases in cellular ATP and by increases in the cellular concentrations of hydrogen ions and lactate. This activation prevents the opening of voltage-gated Ca^{++} channels and contributes to the vasoplegia (resistance to catecholamines) seen in shock states. Activation of K_{ATP} channels is a critical mechanism in the hypotension and vasodilation characteristic of vasodilatory shock. Agents that close K_{ATP} channels (eg, the sulfonylureas) have been shown to increase arterial pressure and vascular resistance in vasodilatory shock due to hypoxia,²⁷ in septic shock²⁷ and in the late vasodilatory phase of hemorrhagic shock.²⁸ An important mechanism through which vasopressin restores vascular tone in vasoplegic (catecholamine-resistant) shock states may be its ability to close K_{ATP} channels.²⁹

Nitric oxide modulation

Another mechanism by which vasopressin exerts vascular control is through modulation of nitric oxide (NO). Nitric oxide contributes to the hypotension and resistance to vasopressor drugs that occurs in vasodilatory shock. The vasodilating effect of NO is mediated mainly by activation of myosin light-chain phosphatase. However, NO also activates K^+ channels in vascular smooth muscle.³⁰ Agents that block NO synthesis during septic shock, increase arterial pressure and decrease the doses of vasoconstrictor catecholamines required to maintain arterial pressure.³¹ Vasopressin may restore vascular tone in vasodilatory shock states by blunting the increase in cGMP that is induced by NO³² and ANP,³³ and by decreasing synthesis of inducible NO synthase that is stimulated by lipopolysaccharide.³²

Vasopressin potentiates the vasoconstrictor effects of many agents, including norepinephrine³⁴ and angiotensin II.³⁵ Vaso-

pressin has been demonstrated to cause vasodilation in numerous vascular beds, a feature not shared by other vasoconstrictor agents. It has been demonstrated that the mechanism of vasodilation is due to activation of oxytocin endothelial receptors that in turn trigger activation of endothelial isoforms of NO synthase.¹⁹

Vasopressin and the heart

The actions of vasopressin on the heart are complex and studies are seemingly contradictory. Depending on the species studied, the dose used, and the experimental model, vasopressin can cause coronary vasoconstriction or vasodilation, and exert positive or negative inotropic effects. In addition to the vascular effects on coronary blood flow, vasopressin also has mitogenic and metabolic effects on the heart.

Coronary vascular tone

The effect of vasopressin on the coronary vascular bed is controversial. Several investigators have demonstrated a V_1 R-mediated coronary vasoconstrictor response to vasopressin,³⁶ an effect that appears to be dose-dependent and intensified by removal of endothelium.³⁷ In contrast, coronary vasodilation in response to vasopressin has been demonstrated in isolated canine³⁸ and primate³⁹ coronary arteries. Recently, vasopressin was demonstrated to cause coronary vasodilation in an intact animal model. A bolus injection of vasopressin significantly increased the vascular diameter of the left anterior descending artery in pigs; this vasodilation was present during sinus rhythm, ventricular fibrillation, and after successful cardiopulmonary resuscitation.⁴⁰ Vasopressin likely affects coronary vasodilation through control of endothelial tone,³⁸ as demonstrated in the pulmonary vasculature.⁴¹

Several preclinical studies have evaluated vasopressin in animal models of cardiac arrest.^{42,43} These studies suggest that vasopressin leads to superior resuscitation rates compared to epinephrine. The improvement in restoration of spontaneous circulation is partially ascribed to an improvement in coronary blood flow.⁴⁴ However, in the setting of cardiac arrest, the improvement in coronary blood flow is likely mediated by an improvement in coronary perfusion pressure as opposed to vasopressin-mediated coronary vasodilation.

Inotropy

Studies of the inotropic effects of vasopressin are also controversial and again, seem to depend on the dose used and the model studied. Indeed, in many experimental studies, it is difficult to isolate the effects of vasopressin on inotropy from its effects on coronary blood flow. The net effect of vasopressin on cardiac function in an intact preparation seems to depend on the concentration of vasopressin as well as the relative balance of its effects on coronary perfusion pressure (diastolic blood pressure), coronary vascular tone, and any direct effects on the inotropic state of the myocardium.

The clinical observation that vasopressin greatly increases afterload in vasodilatory shock (systemic vascular resistance (SVR) nearly doubles), but depresses cardiac output relatively little (14%), led to speculation that vasopressin at low doses might have positive inotropic effects.⁴⁵ Furthermore, in a small trial of vasopressin in patients with heart failure and vasodilatory hypotension due to the phosphodiesterase inhibitor, milrinone, vasopressin increased SVR, but did not depress cardiac output,⁴⁶ again suggesting a positive inotropic action. However, these conclusions are speculative since it is difficult to isolate the

effects of vasopressin on contractility from its effects on coronary perfusion, heart rate, and ventricular preload. Of more importance is the net clinical benefit of these often-contradictory actions. An observational study of critically ill humans specifically examined the effects of low-dose vasopressin infusion on hemodynamics and cardiac performance.⁴⁷ In 41 patients with catecholamine-resistant post-cardiotomy shock, continuous infusion of vasopressin 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.⁴⁷ Cardiac index and stroke volume remained unchanged despite a significant reduction in the requirement for inotropic agents. Interestingly, myocardial enzymes significantly decreased in all patients and in many with atrial arrhythmias converted on infusion. The authors concluded that low-dose vasopressin improved myocardial performance in this group of patients.

Classically, it has been thought that the effects of vasopressin on the heart were mediated via the V_1 R (vascular smooth muscle/calcium-dependent effect) or the oxytocin receptor (endothelial/nitric oxide effect). Neonatal rat cardiomyocytes possess V_1 Rs⁴⁸ and vasopressin causes dose-dependent increases in intracellular calcium, which is dependent on extracellular magnesium and calcium concentrations, and secondary to V_1 R activation and phospholipase-mediated inositol triphosphate (IP_3) generation.⁴⁹ The V_1 R also mediates prostacyclin and atrial natriuretic factor release from cultured rat cardiomyocytes exposed to vasopressin.⁵⁰ Oxytocin receptors have been identified in isolated rat heart and oxytocin causes increased ANP release in perfused rat heart preparations.²⁰ The negative inotropic and chronotropic effects of oxytocin may be mediated by these cardiac oxytocin receptors. Blockade of cholinergic receptors and NO production attenuated the negative effects of oxytocin on cardiac function.⁵¹ Recently, it has been suggested that the cardiac effects of vasopressin are due to selective activation of intravascular purinoceptors and that an intermediary of these effects is ATP.⁵ Adenoviral gene transfer of the V_2 R into cardiomyocytes was shown to modulate the endogenous cAMP signal cascade and increase contractility of rat cardiomyocytes.⁵²

In the setting of primary cardiac dysfunction, however, it is the effect of vasopressin on systemic vascular resistance that may counter any potential beneficial effects on cardiac inotropy. In fact, antagonism of vasopressin receptors has been advocated as therapy for congestive heart failure. Certainly, both animal models of congestive heart failure and early clinical studies support the notion that antagonism of V_1 and V_2 receptors leads to improvement in cardiac function, likely mediated through reductions in cardiac afterload.⁵³

Clinical applications of vasopressin in shock

In health, the role of vasopressin in the maintenance of resting arteriolar tone and systemic blood pressure is minor, and high concentrations of vasopressin are required before vasoconstrictor effects are seen. It is only during shock states that the role of vasopressin in the maintenance of systemic blood pressure is seen. Indeed, vasopressin deficiency and hypersensitivity to its pressor effects appear to be a hallmark of vasodilatory shock states.²⁴ These states include vasodilatory septic shock,^{13,45,54-56} vasodilatory shock post-cardiopulmonary bypass,⁵⁷⁻⁶¹ vasodilatory shock due to phosphodiesterase inhibition in the treatment of heart failure,⁴⁶ hemodynamically unstable organ donors,⁶² and the late, so-called "irreversible" phase of volume-treated hemorrhagic shock.⁶³ The reason for the reduction in

Table 1: Clinical trials of low-dose vasopressin in vasodilatory shock states

Reference	Date	Trial	N	Patients	Findings
Landry DW ⁵⁴	1997	Case Series	5	Septic shock	A, B, C
Landry DW ⁴⁵	1997	Matched Cohort	19	Septic shock	A, B, D in
			12	Cardiogenic shock	Septic Group
Malay MB ⁵⁵	1999	RCT	10	Septic shock – Trauma	A, B
Patel BM ⁵⁶	2000	RCT	24	Septic shock	A, B, C, D
Dunser MW ⁷⁶	2001	Retrospective	60	Septic and post-cardiotomy shock	A, B, _ in CI
Tsuneyoshi ⁷⁷	2001	Prospective, Case-controlled	16	Septic shock	A, B, C
Argenziano M ⁵⁸	1998	Retrospective Case series	40	Post-bypass vasodilatory shock	A, B, D
Argenziano M ⁵⁷	1997	RCT Placebo: N/S	10	Vasodilatory shock Post-LVAD implant	A, B in treatment arm D in all
Argenziano M ⁶⁰	1999	Case series	20	Vasodilatory shock post-cardiac transplant	A, B
Rosenzweig EB ⁶¹	1999	Case series	11	Pediatric – vasodilatory shock post-bypass	A, B, D
Morales DL ⁷⁸	2000	Retrospective Case series	50	Vasodilatory shock post-LVAD implantation	A, B
Dunser MW ⁴⁷	2002	Retrospective	41	Post-cardiotomy shock	A, B
Chen JM ⁶²	1999	Case series	10	Organ donors with vasodilatory shock	A, D
Gold J ⁴⁶	2000	Case series	7	Milrinone-hypotension	A, B, C

A: Increase in blood pressure; B: Decrease or discontinuance of catecholamines; C: Increase in urine output; D: Low plasma vasopressin levels in subjects. CI = cardiac index

circulating concentrations of vasopressin has not been fully determined; however, depletion of neurohypophyseal stores has been observed in profound shock states.⁶⁴

The clinical use of vasopressin followed observations that exogenous administration of vasopressin during shock is capable of restoring systemic blood pressure. Landry and co-workers first demonstrated this property in 5 patients with advanced septic shock.⁵⁴ Since their initial observations, several uncontrolled trials have demonstrated that vasopressin can restore blood pressure during septic shock, following cardiopulmonary bypass, and following adrenaline resistant cardiac arrest (Table 1). Few controlled studies, however, have been performed to properly evaluate the effectiveness of vasopressin in shock. This is a critical point since it cannot be inferred that if an agent restores blood pressure, it will also lead to an improvement in outcome. An increase in blood pressure may be obtained at the expense of perfusion to critical organs or it may worsen cardiac performance by impairing ventricular output through an increase in ventricular afterload. Consequently, organ injury could worsen in the face of blood pressure restoration. A case in point is the manner in which nitric oxide synthase (NOS) inhibition was embraced to treat shock in septic patients.⁶⁵ In fact, NOS inhibitors have clinical effects that are similar to vasopressin and several reports have documented increased blood pressure, reduced pressor requirements, and an attendant reduction in cardiac output (a profile that resembles vasopressin) in patients with septic shock.^{66,67} However, a recent randomized controlled trial of an NOS inhibitor in septic shock was halted because of higher mortality in the group that received treatment.⁶⁸

At the present time, the only blinded, systematic evaluation of vasopressin in sepsis is a recent study by Patel and co-workers.⁵⁶ In a controlled fashion, they compared the effects of vasopressin to norepinephrine in 24 patients with septic shock who required vasopressor infusions. Patients who received vasopressin had a significant (80%) reduction in vasopressor requirements. Interestingly, patients in the vasopressin arm experienced a doubling in urine output and a 75% increase in creatinine clearance. Based on current

information, it appears that replacement of vasopressin at a fixed dose can eliminate the need for catecholamine pressors in many patients.

Vasopressin has also been evaluated in the setting of hypotension following the induction of anesthesia in patients who are chronically treated with angiotensin converting enzyme (ACE) inhibitors.^{69,70} One study compared terlipressin (a vasopressin agonist) plus ephedrine (n=21) versus ephedrine alone (n=19) in patients following induction of anesthesia.⁶⁹ The second study evaluated vasopressin (n=13) compared to placebo (n=14) in patients following cardiac bypass.⁷⁰ Both studies demonstrated that the vasopressin agonist led to better hemodynamic stability and less catecholamine use. Consequently, in patients who are refractory to conventional vasopressors (owing to chronic blockade of their renin angiotensin system [RAS]), vasopressin may offer some clinical benefit in improving hemodynamics. In fact, the study by Morales and co-workers demonstrated that the vasopressin group of patients chronically treated with ACE inhibitors had a shorter ICU stay following induction of anesthesia.⁷⁰ These studies bear repeating in order to evaluate these highly relevant endpoints and confirm the safety of vasopressin before its widespread clinical use is recommended.

Vasopressin increased arterial and coronary perfusion pressure compared with clinical doses of epinephrine in animal models of cardiac arrest. Interestingly, like adrenaline, vasopressin may be administered via the endotracheal tube. In fact, vasopressin had better hemodynamic effects than intratracheal adrenaline in one study of a canine model of cardiac arrest.⁷¹ Based on these favourable reports, vasopressin has been advocated for use in cardiac arrest.

In 1997, Lindner and co-workers reported the effects of 40 units of vasopressin versus 1 mg of adrenaline in patients not responding to 3 counter-shocks in the field.⁷² Fourteen (70%) of patients in the vasopressin group versus 7 (35%) of patients in the adrenaline group survived to hospitalization. However, a more recent study by Steill et al of vasopressin in cardiac arrest found no benefit over adrenaline.⁷³ This study evaluated vasopressin versus

adrenaline as the first agent given to 200 patients suffering an in-hospital cardiac arrest. It found no advantage for either agent in 1-hour survival or survival to hospital discharge. Importantly, there was no difference between the groups in mini-mental status exam or cerebral performance category scores. The reason for the discrepancy between these 2 studies is unclear. One explanation is that the 2 populations evaluated were different; ie, Lindner studied patients who suffered a cardiac arrest out-of-hospital, while Steill evaluated hospitalized patients who may have a different prognosis after cardiac arrest than their counterparts in the community. Similarly, the etiology of cardiac arrest may have differed between the 2 groups, with more patients having a primary cardiac event in the community.

Administration of vasopressin to patients with low-flow states (ie, in cardiogenic or hypovolemic shock) is strongly contraindicated because cardiac output is severely depressed by the increase in afterload in these states. Indeed, blockade of V_1 and V_2 receptors has been advocated for treating congestive heart failure. In a rat model of congestive heart failure, a single oral dose of conivaptan (a V_1 R and V_2 R blocker) increased urine volume and decreased urine osmolality in a dose-dependant manner.⁷⁴ Furthermore, conivaptan attenuated the changes in left ventricular end-diastolic pressure, lung, and right ventricular weight. The authors stressed that vasopressin plays a significant role in elevating vascular tone via vasopressin V_1 Rs and plays a major role in retaining free water through V_2 Rs in this model of congestive heart failure.

Summary

Vasopressin is a unique vasoactive hormone that is important for controlling vascular tone and it has potentially important myocardial effects. Vasopressin can restore vascular tone in refractory vasodilatory shock states due to V_1 R activation of K_{ATP} channels, inhibit NO, and potentiates endogenous vasoconstrictors. In refractory shock states, administration of vasopressin in low physiological doses has been associated with an impressive stabilization of hemodynamics. In addition, vasopressin at a low dose (0.04 units/min) is not associated with a substantial decline in cardiac output. Vasopressin is gaining popularity for use in septic shock and vasodilatory states associated with cardiac anesthesia and surgery. It is important to stress that clinical studies to date have been small, have focused on physiological outcomes, and data on adverse effects are limited. Therefore, vasopressin as first-line therapy of vasodilatory shock is not recommended. Future prospective studies are necessary to define the role of vasopressin in the therapy of vasodilatory shock and it is hoped that, unlike early trials of NO synthase inhibition in sepsis, the more favourable hemodynamic profile of vasopressin will translate into clinical benefits. In addition, its selective constriction of renal efferent over afferent arterioles could spare renal function in shock. The results of a multicentre, randomized, controlled evaluation of vasopressin in patients with septic shock are eagerly awaited.⁷⁵ Patients are eligible for this study if they have hypotension (refractory to fluids and are receiving > 5 μ g/min of levophed or equivalent for 6 hours) secondary to sepsis and suspected or confirmed infection. Patients are randomized to receive either vasopressin or levophed. This study is novel in that the control

arm will be receiving an active pressor. The use of an active control arm was mandated in order to reduce the risk of unblinding investigators as to the contents of the study infusion. This study has currently enrolled just over 200 patients and should be completed in the next 2 years.

Cheryl L. Holmes, MD, is a Consultant in critical care in Kamloops, British Columbia. Dr. Holmes has completed several studies and scientific reviews defining the role of vasopressin in septic shock and has been one of the lead investigators in the multicentre clinical trial of vasopressin in septic shock.

Donald W. Landry, MD, is a physician in the Department of Medicine, Columbia University, New York. Dr. Landry has provided some of the early work supporting the use of vasopressin in septic shock. His work spawned clinical interest in this area.

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