Role of vasopressin in maintenance of potassium homeostasis in severe hemorrhage

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Uyehara CF, Sarkar J. Role of vasopressin in maintenance of potassium homeostasis in severe hemorrhage. Am J Physiol Regul Integr Comp Physiol 305: R101–R103, 2013. First published May 15, 2013; doi:10.1152/ajpregu.00206.2013.—Uncontrolled elevation in plasma potassium within minutes of rapid blood volume loss is associated with mortality and distinguishes nonsurvivors of severe hemorrhage from survivors. In a pig model of severe hemorrhage, we discovered that along with a sharp increase in plasma potassium coincident with a shut down of urine flow, nonsurvors also had an insufficient vasopressin response to hemorrhage. In contrast, survivors did have elevated vasopressin levels in response to hemorrhage and maintained plasma potassium within normal limits. While it has been demonstrated for some time that vasopressin can influence secretion of potassium in the distal nephron, the magnitude of this effect and conditions under which this contributes to physiological modulation of potassium excretion has yet to be defined. In this review, we assess the evidence that would suggest that vasopressin plays a key role in modulating potassium excretion and is important in the regulation of potassium homeostasis during hemorrhage.

hyperkalemia; potassium excretion; hypotension; potassium secretion; shock

HYPERKALEMIA has been directly associated with cardiovascular collapse in severe hemorrhagic shock (8, 13). The immediate increase in circulating potassium within minutes of large blood volume loss has been described but is not well understood. Suggested mechanisms include intracellular to extracellular potassium shifts (11), selective changes in cell membrane permeability (10), and disruptions of the Na+/K+ pump in myocardial cells (12). Regardless of the mechanism, uncorrected posthemorrhagic hyperkalemia is clearly correlated with increased mortality (6, 8, 14). With the onset of hyperkalemia, the potassium shift from the intracellular to extracellular compartment needs to be corrected, and an increase in urinary potassium excretion should occur to maintain potassium homeostasis (5). This suggests that when patients develop severe hyperkalemia in hemorrhagic shock, the normal renal mechanisms to excrete excess potassium may be impaired or insufficient to deal with the magnitude and rapidity of increasing potassium levels.

In a pig model of severe hemorrhagic shock, we found that about 20% of the animals died within 60 min from the start of hemorrhage; whereas all animals rapidly developed renal failure, nonsurvors were distinguished from survivors by severe progressive hyperkalemia. In our study, pigs underwent rapid blood volume loss at 3 ml·kg⁻¹·min⁻¹ for 7 min followed by 1 ml·kg⁻¹·min⁻¹ until a goal hemorrhage of 30 ml/kg shed blood volume was reached within 30 min, to mimic a bleeding pattern of uncontrolled hemorrhage followed by a period of relative hemostasis typically seen during trauma. This resulted in equivalent oxygen debt accumulation and hypotension, and no difference in blood gases or lactate levels, between survivors and nonsurvors before the decompensation of nonsurvors. In both survivors and nonsurvors, urine flow immediately decreased within the first 10 min of hemorrhage along with a 50% drop in blood pressure (Fig. 1).

In nonsurvivors, plasma potassium levels increased dramatically compared with survivors. Hyperkalemia in nonsurvivors occurred almost immediately after initiation of rapid hemorrhage, and plasma potassium was significantly elevated within 10 min of shock even before other early markers such as oxygen debt and lactate. In the nonsurvivor group, progressive hyperkalemia caused cardiac arrhythmias and eventually arrest. The hyperkalemia we observed in the nonsurvivors of hemorrhage are similar to that observed by Niemann and Cairns (7) where high potassium levels occurred within minutes of ventricular fibrillation in animals that could not be resuscitated; hyperkalemia was not seen in animals that did respond to resuscitation.

Upon closer examination, we found that the hyperkalemia in nonsurvivors was associated with an insufficient vasopressin response to hemorrhage. In accordance with the known vasopressin action of inducing potassium secretion in the distal nephron, this observation of insufficient vasopressin may account for the absence of a compensatory increase in urinary potassium excretion, and thus an accumulation of plasma
potassium to levels that caused cardiac arrhythmias in the nonsurvivors. While plasma potassium increased in the survivors, the levels stabilized within normal limits despite decreased renal output, perhaps because the increased vasopressin levels in the survivors could stimulate potassium secretion to rid the extracellular fluid compartment of excess potassium.

**Role of Vasopressin in Potassium Homeostasis**

The release of endogenous vasopressin is known to be primarily triggered by hypovolemia (via cardiopulmonary and arterial baroreceptors) and increased extracellular osmolarity. However, the increase in endogenous vasopressin associated with maintenance of normokalemia in our survivor group suggests that serum potassium may be a specific trigger and target for vasopressin release.

Micropuncture and microperfusion studies by Field et al. (4) have demonstrated vasopressin influence on renal potassium secretion in the late distal nephron. They showed that despite potassium excretion being a typically flow-dependent process, when urine flow was suppressed by the antidiuretic actions of vasopressin, potassium secretion was maintained independently of flow rate. This suggested that vasopressin has a physiological function of regulating potassium homeostasis during different states of hydration. Thus in states of antidiuresis, flow rate-dependent potassium retention may be counteracted by simultaneous vasopressin stimulation of potassium secretion in the distal nephron. Amorim and Malnic (1) also demonstrated that there appears to be an endogenous vasopressin effect on a basal tone of potassium secretion via V1 receptor-mediated action on the luminal surface of the initial cortical collecting duct that could be blocked with a V1 specific antagonist.

**Pharmacological Potential of Exogenous Vasopressin in Hemorrhagic Shock**

Vasopressin administered exogenously has been shown to induce urinary potassium secretion. For example, in rabbits administered extra water and vasopressin for a week, hypokalemia developed due to significantly elevated potassium excretion compared with controls (2). Although hemodilution was a potential contributing factor, this study suggests that exogenous vasopressin may have also increased potassium excretion. In a sheep model, pharmacological doses of vasopressin allowed rates of potassium urinary excretion to increase with increased plasma potassium concentrations (3). Thus, in situations of high potassium levels such as with severe hemorrhage, it is likely that pharmacological administration of vasopressin as a pressor agent to manage hypotension will have the added effect of maximizing potassium excretion to prevent hyperkalemia, although further investigation is needed.

**Perspectives and Significance**

Collectively, prior studies that have described vasopressin action on potassium secretion, along with our observation of uncontrolled hyperkalemia in pigs with an insufficient vaso-
pressin response to hypovolemia, suggest a distinctive role of vasopressin in blood pressure control. In addition to restoring mean arterial pressure through its vasoconstrictive action, it appears that vasopressin plays an equally important role in maintaining potassium homeostasis in severe volume loss via stimulation of potassium secretion in the distal nephron.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: C.F.T.U. conception and design of research; C.F.T.U. and J.S. performed experiments; C.F.T.U. and J.S. analyzed data; C.F.T.U. and J.S. interpreted results of experiments; C.F.T.U. and J.S. prepared figures; C.F.T.U. drafted manuscript; C.F.T.U. and J.S. edited and revised manuscript; C.F.T.U. and J.S. approved final version of manuscript.

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