Title: IMPORTANCE OF VASOPRESSIN AND UNIMPORTANCE OF RENIN-ANGIOTENSION IN RESPONSE OF AWAKE SWINE TO MODERATE HEMORRHAGE

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Introduction. The physiologic compensation for hemorrhage is complex. Several stimuli and reflexes result in activation of the sympathetic and renin-angiotensin systems, and in increased vasopressin secretion. The relative importance of the renin-angiotensin system and vasopressin in response to moderate hemorrhage has not been demonstrated in awake animals. We therefore examined the relative importance of these two during moderate hemorrhage in unmedicated swine.

Methods. Ten young 20-kg Landrace swine were randomly divided into two groups, briefly anesthetized with halothane, paralyzed, and ventilated to allow for percutaneous placement of a peripheral venous cannula, a thermodilution pulmonary artery catheter via the innominate vein, and an abdominal aortic cannula via a superficial femoral artery. Experimentation was begun when end-tidal halothane fell to less than 0.05 MAC. Ventilation was continued to maintain arterial PCO_2 at 40 torr throughout these experiments. The two groups were compared during normovolemia prior to the administration of any drug; following an intravenous injection of angiotensin II, 100 ng/kg; during an intravenous infusion of saralasin (a competitive inhibitor of angiotension II) 2μg/kg/min; and following another injection of angiotension II, 100 ng/kg, during the infusion of saralasin, to test for completeness of blockade. Animals were then bled by 30% of their blood volume through the arterial cannula, during a 30-minute period. During hypovolemia, the two groups were compared prior to administration of any drug, and after an intravenous injection of angiotensin II 100 ng/kg. In group I, saralasin 2 μg/kg/min was infused intravenously, and in group II, saline was infused intravenously at the same fluid volume rate (0.3 ml/min). Angiotensin II 100 ng/kg was again injected intravenously to test for presence or absence of blockade. Another eleven 20-kg Landrace swine were similarly instrumented and randomly divided into two groups. These animals were evaluated while awake, normovolemic; after an intravenous injection of arginine-vasopressin (AVP), 50 ng/kg; and after 30% hemorrhage, accomplished as above. While hypovolemic, in one group (III) the vascular response to AVP was blocked with an intravenous injection of [1-(B-mercapto-B, B-cyclopentamethylenepropionic acid), 2-(O-methyl) tyrosine] arginine^8-vasopressin, 10 ng/kg, dissolved in 1 ml saline. This compound is a specific antagonist of the vascular actions of vasopressin, but not of its antidiuretic activity. The other group (IV) was given 1 ml saline only. Groups were compared five minutes later. Data for group I and group II were compared by unpaired-t tests, as were data for groups III and IV. Statistical significance was accepted at $P < 0.05$.

Results. There were no differences between Groups I and II for mean aortic blood pressure (BPa), cardiac output (Q_t), systemic vascular resistance (SVR), right atrial pressure (RAP), pulmonary capillary wedge pressure (PAP_W), heart rate (HR), plasma epinephrine (E), norepinephrine (NE), and vasopressin concentrations, and plasma renin activity (PRA), during normovolemia. The two groups showed similar responses to iv angiotensin II; and saralasin infusion, which successfully blocked all cardiovascular responses to angiotensin II. 30% hemorrhage produced similar falls in BPa, Q_t, RAP, PAPW, and increases in E, NE, AVP, PRA, and SVR. After hemorrhage, both groups showed similar responses to iv angiotensin II; an increase in SVR and BPa. Infusion of neither saralasin nor saline changed any variable, and there were no differences between the two groups (Table 1). Angiotensin II, iv, produced the expected results in group II, but had no effect in group I, demonstrating that saralasin had successfully blocked the cardiovascular effects of AII. In the second series of experiments, during normovolemia there were no differences between groups III and IV for any measured variable. During normovolemia the two groups responded similarly to iv vasopressin, with increases in SVR and BPa, and decreases in Q_t. The two groups (III and IV) showed responses to hemorrhage which were not different from each other, or from groups I and II. AVP blockade (group III) resulted in a decrease in SVR and BPa, despite increases in E, NE and PRA, while saline (group IV) produced no changes in any variable (Table 2). The fall in SVR in group III was to a value not different from that prior to hemorrhage.

Conclusion From these data, we conclude that in awake swine (a) the renin-angiotensin system is not important in compensation for moderate hypovolemia, and (b) vasopressin is quite important in compensation for moderate hypovolemia.

Table 1: Response to saralasin (Group I) or Saline (Group II) after 30% hemorrhage

	Group I	Group II	P
BPa, torr	109 ± 7	111 ± 6	NS
Q_t, $ml \cdot min^{-1} \cdot kg^{-1}$	113 ± 11	122 ± 11	NS
SVR, units	998 ± 72	945 ± 70	NS
E, pg/ml	287 ± 126	341 ± 149	NS
NE, pg/ml	271 ± 59	254 ± 49	NS
PRA, ng $AII \cdot ml^{-1} \cdot hr^{-1}$	20 ± 7	25 ± 7	NS
AVP, pg/ml	26 ± 4	27 ± 11	NS

Table 2: Response to AVP blockade (Group III) or Saline (Group IV) after 30% hemorrhage

	Group III	Group IV	P
BPa, torr	51 ± 7	104 ± 9	<0.005
Q_t, $ml \cdot min^{-1} \cdot kg^{-1}$	101 ± 8	108 ± 13	NS
SVR, units	558 ± 26	1058 ± 175	<0.025
E, %hypovolemic control	239 ± 34	79 ± 16	<0.01
NE, %hypovolemic control	284 ± 28	96 ± 11	<0.001
PRA, %hypovolemic control	265 ± 37	90 ± 16	<0.005