

## THE ATP-SENSITIVE POTASSIUM-CHANNEL INHIBITOR GLIBENCLAMIDE IMPROVES OUTCOME IN AN OVINE MODEL OF HEMORRHAGIC SHOCK

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**ABSTRACT**—This study was designed as a prospective laboratory experiment to evaluate the effects of the ATP-sensitive potassium-channel inhibitor glibenclamide on hemodynamics and end-organ function in an ovine model of hemorrhagic shock. Twenty-four adult sheep were anesthetized and surgically prepared to measure hemodynamics of the systemic and pulmonary circulation. The anterior surface of the abdominal aorta was exposed at a location 6 cm superior to the iliac bifurcation. After a 60-min period of stabilization, this location was punctured with a 14-G needle. To induce a hemorrhagic hypotension (mean arterial pressure [MAP] less than 50 mmHg) via bleeding, the needle was left in place for 15 s to insure good blood flow. Thereafter, it was removed, and the abdomen closed. The animals were then randomized to receive either glibenclamide (4 mg/kg over 15 min) or an equal volume of the vehicle, started 1 h postinjury. Hemodynamic variables were measured every 30 min. Compared with the control group, MAP and systemic vascular resistance index (SVRI) were significantly higher in the intervention group throughout the entire 6-h study period. Ileal pH and urine output were higher in treated than in control animals (4 h, ileal pH  $7.29 \pm 0.31$  vs.  $7.17 \pm 0.6$ ; 6 h, urine output  $36 \pm 9$  vs.  $7.5 \pm 2$  mL; *P* value less than 0.05 each). Because glibenclamide improved both hemodynamics and organ function, it may be a beneficial component in the acute treatment of hemorrhagic shock.

**KEYWORDS**—Glibenclamide, hemodynamic, hemorrhage, shock, resuscitation, sheep, survival, trauma

### INTRODUCTION

Hemorrhagic shock (HS) following accidental injuries is a common cause of death in the industrialized world (1). Untreated hemorrhagic shock with acute blood loss leads to hypotension, which, in turn, contributes to organ dysfunction and failure. Clinical conditions that arise after acute blood loss include acute respiratory distress syndrome (ARDS), lung injury, systemic inflammatory response syndrome (SIRS), severe sepsis, multiple organ dysfunction syndrome (MODS), and death (1–3).

Although blood pressure may be aggressively treated and partially restored, such a correction may aggravate blood loss and thus result in a poor outcome (4, 5). Rapid crystalloid resuscitation with normal saline (NaCl 0.9%) or lactated Ringer's solution or colloids, plasma expanders, and surgical control of bleeding are essential for the treatment of HS. In rural areas or battlefield trauma, these interventions may be impractical or impossible, and medical attention and patient transport may be delayed (6). In these situations, where a large volume of fluid is needed to treat hemorrhagic shock and is not available, pharmacological support may be beneficial (7). However, the progressive loss of vascular response to vasoconstrictors seen in hemorrhagic shock has to be taken into account.

Several studies in small animal models have recently shown that glibenclamide, an adenosinetriphosphate (ATP)-sensitive potassium ( $K^+$ )-channel inhibitor, increased arterial pressure and improved survival of hemorrhagic shock and endotoxemia (8–14). It has also been reported that glibenclamide acts as a vasorelaxant by stimulating the release of nitric oxide (NO) from the endothelium (13–16). Glibenclamide's ability to maintain adequate splanchnic blood supply by dilating resistance vessels while constricting capacitance vessels may prove to be beneficial (17).

The present study is designed as a prospective, randomized laboratory experiment to investigate the impact of glibenclamide on hemodynamics, ileal intramucosal pH, renal function, and survival in a clinically relevant ovine model of hemorrhagic shock.

### MATERIALS AND METHODS

The experimental procedures reported in this manuscript were approved by the Animal Care and Use Committee of The University of Texas Medical Branch. All animals were handled according to the guidelines for ethical animal research established by the American Physiological Society and the National Institutes of Health.

#### Animal model

Twenty-four adult female Merino sheep, weighing  $37 \pm 1$  kg, were anesthetized with isoflurane (Vedco Inc., St. Joseph, MO), using an inhalation mixture of 1–2 Vol% in oxygen and endotracheally intubated. The sheep were ventilated with a mixture of room air and  $O_2$  ( $FiO_2 = 60\%$ ) at a frequency of 12–15  $min^{-1}$ . Under aseptic conditions, the animals were operatively prepared for hemodynamic monitoring. The right femoral artery was cannulated, and a polyvinylchloride catheter (Intracath™, 16-G, 24-inch, Becton Dickinson Vascular Access, Sandy, UT) was positioned in the descending aorta. Via the right jugular vein a 7-F Swan-Ganz™ thermolulution catheter (model 93A-131-7F, Edwards Critical Care Division, Irvine, CA) was advanced into the pulmonary artery. In addition, a 12-F urinary retention catheter (C. R. Bard, Inc. Covington, GA) was inserted into the urinary bladder via the urethra for urine collection.

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Through a midline laparotomy, a gastrointestinal tonometer (Trip Sigmoid Catheter, Tonometrics Division, Instrumentarium Corporation, Helsinki, Finland) was placed into the distal ileum for determination of regional  $PCO_2$  and intramucosal pH. Pancuronium bromide (Astra, Westborough, MA) was administered in 2-mg boli to maintain muscle relaxation. Heart rate (HR) and MAP were monitored on a moment-to-moment basis during surgery to ensure adequate anesthesia. Throughout surgery, there was no indication of increased stress. The gastric tonometer was filled according to the manufacturer's instructions, and the animals were allowed to stabilize for 60 min. The retroperitoneal fascia was incised to expose the anterior surface of the abdominal aorta. Thereafter, the abdomen was closed and an intravenous solution of 5% dextrose and 0.9% sodium chloride was started at a rate of  $3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  to guarantee constant hydration throughout the study. A body temperature of  $38\text{--}39^\circ\text{C}$  was maintained using a Bair Hugger® Patient Warming System (Model 500/OR, Augustine Medical, Eden Prairie, MN).

### Measurements

Systemic and pulmonary pressures were measured with pressure transducers (Model PX3X3, Baxter Edwards Critical Care Division, Irvine, CA) and recorded on a monitor with graphic and digital displays for electronically calculated mean pressures (model 7830A, Hewlett Packard, Santa Clara, CA). Cardiac output (CO) was determined with the thermal dilution technique and displayed on a cardiac output computer (COM-1, Baxter Edwards Critical Care Division, Irvine, CA). Core body temperature was measured with the thermistor of the Swan Ganz™ catheter. Ten milliliters of 5% dextrose solution at  $1^\circ\text{C}$  served as the thermal indicator. Arterial blood gas samples were analyzed at  $37^\circ\text{C}$  on freshly drawn heparinized blood using a conventional blood gas analyzer (Synthesis 15, Instrumentation Laboratories, Lexington, MA) and were corrected for core body temperature. Oxyhemoglobin saturation was measured using a CO-Oximeter (model IL482, Instrumentation Laboratory, Lexington, MA). Cardiac index (CI), systemic vascular resistance index (SVRI), oxygen delivery index ( $Do_2I$ ), oxygen consumption index ( $Vo_2I$ ) and pulmonary shunt fraction ( $Qs/Qt$ ) were calculated using standard equations. Blood glucose was measured with a glucometer (One Touch II, Lifescan, Johnson & Johnson, Milpitas, CA). Ileal intramucosal pH was calculated using the method advised by the tonometer manufacturer. Briefly,  $PCO_2$  of the tonometer saline is measured along with the bicarbonate ( $HCO_3^-$ ) of arterial blood. The saline  $PCO_2$  is then multiplied by an equilibration factor given in the instruction manual, following the regional  $PCO_2$ . Regional  $PCO_2$  and arterial  $HCO_3^-$  are then inserted into the Henderson-Hasselbalch equation to determine the ileal pH.

### Experimental procedure

Following a baseline measurement, the anterior surface of the abdominal aorta was exposed at a location 6 cm superior to the iliac bifurcation. After a 60-min period of stabilization, this location was punctured with a 14-G needle. To induce a hemorrhagic hypotension, the needle was left in position for 15 s. Thereafter, the needle was removed, and the abdomen closed. Pilot experiments demonstrated that this approach results in systemic hypotension with a MAP of  $40 \pm 5 \text{ mmHg}$  within 30 min.

The animals were then randomized to receive either an infusion of glibenclamide (4 mg/kg over 15 min) or an equal volume of the vehicle, started 1 h postinjury. Hemodynamic variables and blood gas variables were measured every 30 min. As compared with the control group, mean arterial blood pressure and systemic vascular resistance index were significantly higher in the intervention group through the entire study.

After completion of the experiment, the animals were anesthetized by an injection of ketamine (15 mg/kg, Vedco Inc., St. Joseph, MO) and xylazine-HCl (3 mg/kg, Vedco Inc., St. Joseph, MO) and euthanized by a lethal intravenous injection of 60 mL of saturated potassium chloride (P-4504, Sigma-Aldrich Co., St. Louis, MO). After sacrifice, the abdomen was reopened, to determine the amount of blood in the abdominal cavity.

### Statistical analysis

For statistical analysis, Sigma Stat 2.03 software (SPSS Inc., Chicago, IL) was used. After confirming normal distribution (Kolmogorov-Smirnov test), a two-way analysis of variance (ANOVA) for repeated measurements with appropriate Student-Newman-Keuls *post hoc* comparisons was used to detect differences within and between groups. Significance was assumed when  $P$  was less than 0.05. Data are presented as means  $\pm$  the standard error of the mean (S.E.M.).

## RESULTS

There were no differences in physiologic data between groups at baseline.

### Blood loss

As confirmed by autopsy, there was no difference in hemorrhage volume between the two groups. The control group had

a blood loss of  $773 \pm 75 \text{ mL}$ , whereas the glibenclamide group had an estimated blood loss of  $717 \pm 70 \text{ mL}$ , which is about 30% of the total blood volume of a sheep.

### Hemodynamic variables

Infusion of glibenclamide resulted in a significant increase in MAP within 30 min ( $40 \pm 5$  vs.  $85 \pm 5 \text{ mmHg}$ ,  $P < 0.05$  versus baseline and versus control; Fig. 1). This elevation persisted for the remainder of the experiment. Similarly, SVRI was significantly higher in treated versus untreated animals (Fig. 2). No significant differences were seen in mean pulmonary artery pressure (MPAP), HR, cardiac index (CI), or pulmonary capillary wedge pressure (PCWP) between groups (Table 1). Compared with controls, left ventricular stroke work index (LVSWI), an index of myocardial contractility, was significantly higher in the interventional group (Fig. 3).

### Blood gases

Glibenclamide infusion contributed to a decreased systemic pH over time. However, there were no significant differences in pH between groups (Table 1).  $Vo_2I$ ,  $Do_2I$ , and  $Qs/Qt$  were similar between groups.

### Blood glucose

After hemorrhage, blood glucose increased significantly in both groups as compared with baseline. Following glibenclamide infusion, there was no significant decrease in blood glucose in the two groups (Table 1).

### Ileal pH

Following hemorrhage, ileal intramucosal pH dropped significantly in both groups (Fig. 4). However, the ileal pH in the treatment group was higher than that in the control group.

### Urine output

A significant difference was seen in the total urine volume between groups. In the course of the study period, sheep in the glibenclamide group produced 0.92 mL/kg urine, while the

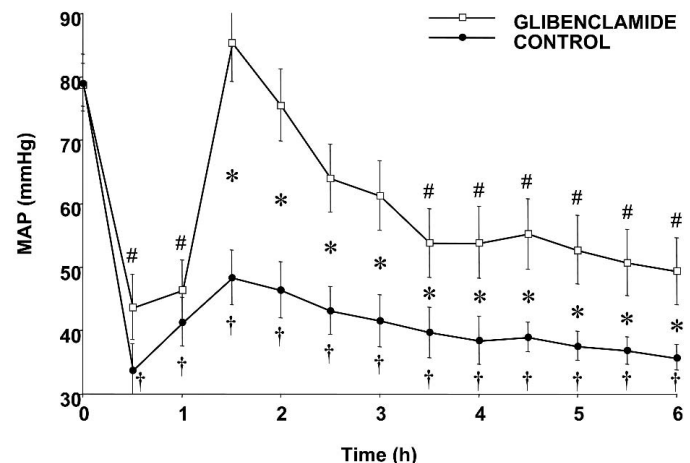


Fig. 1. Changes in mean arterial pressure (MAP) in adult sheep ( $n = 12$ ). Data are expressed as mean  $\pm$  SE of mean (S.E.M.). \* $P < 0.05$  between groups; # $P < 0.05$  glibenclamide versus baseline (BL = 0 h); and † $P < 0.05$  control versus BL.

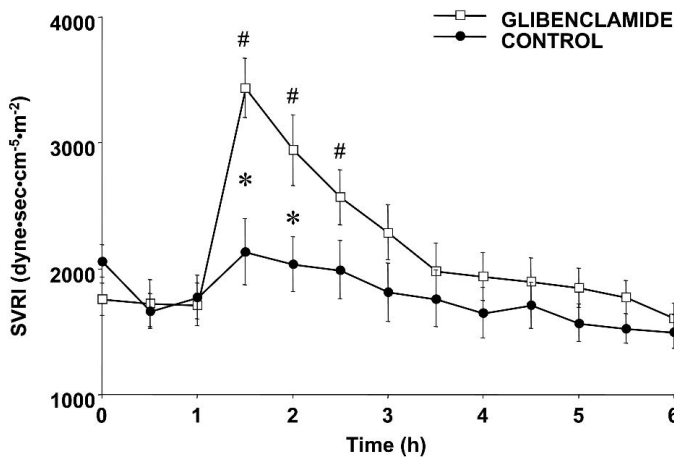


FIG. 2. Changes in systemic vascular resistance index (SVRI). Values are expressed as mean  $\pm$  SEM. \* $P < 0.05$  between groups; # $P < 0.05$  glibenclamide versus BL.

control group (hemorrhaged untreated) produced only 0.17 mL/kg (Fig. 5).

### Survival

All animals in the glibenclamide-treated group survived the 6-h study period. Two animals in the control group died within 30 and 240 minutes, respectively, after the hemorrhage.

## DISCUSSION

In the present study, a large-animal model of hemorrhagic shock was used to examine the role of pharmacologic intervention in supporting hemodynamic function under conditions such as rural or battlefield trauma, where fluid resuscitation cannot be implemented rapidly and where patient transport may be delayed. The major finding was that administration of glibenclamide, a potent  $K_{ATP}$ -channel blocker, sustained hemodynamics and improved renal function.

At first glance, it appears that glibenclamide improved not only hemodynamics and renal function but also survival. However, it has to be taken into account that MAP in the treatment group also declined over time. In addition, one of the two animals (of the control group) died 30 minutes after induction of hemorrhagic shock. At this time, neither infusion of glibenclamide nor of the vehicle had been started. The fact that only one sheep of the control died 240 min postinjury renders the question whether glibenclamide improved survival elusive. Future studies are, therefore, needed to address this very interesting issue.

The function of  $K_{ATP}$ -channels is modulated by the metabolic state of the cells. It is especially important that opening occurs in response to a decrease in intracellular ATP levels and tissue acidosis (9, 18). Opening of these channels characteristically results in potassium efflux, cellular hyperpolarization, reduction of the entry of extracellular calcium via voltage-dependent calcium channels, and ultimately, vascular smooth muscle relaxation (9, 18). Notably, opening of  $K_{ATP}$ -channels in the plasma membrane of vascular smooth muscle cells represents one of the major vasodilator mechanisms in response to vasoactive agents. It has also been shown that opening of these

channels is involved in the vasodilatation of blood vessels in response to calcitonin gene-related peptide and vasoactive intestinal peptide (9, 18) as well as to adenosine (19). In addition, the free radical nitric oxide (NO) has also been shown to open  $K_{ATP}$ -channels (20).

However, a variety of pharmacological agents that can be used *in vitro* and *in vivo* can modulate  $K_{ATP}$ -channels. Evgenov et al. reported that glipizide sodium salt, a  $K_{ATP}$ -channel inhibitor, attenuated vascular and endorgan dysfunction and prolonged short-term survival associated with severe hemorrhagic shock in rats (21). Also the antidiabetic sulfonylurea drug glibenclamide prevents the opening of these channels. In fact, the antidiabetic (insulin-releasing) properties of this drug are related to closing of the  $K_{ATP}$ -channels in the pancreatic islet  $\beta$  cells (and subsequent depolarization of the cell membrane followed by elevation of intracellular calcium and, eventually, insulin release) (22).

Szabó and associates have demonstrated that glibenclamide improves hemodynamics in rats subjected to hemorrhagic shock (9). Similar to these findings, we observed a significant improvement in cardiovascular function in the sheep treated with glibenclamide. A 4 mg/kg bolus infusion reversed the fall in MAP. Notably, MAP remained within 75% of baseline for 2 h. This was a result of an increase in SVRI and an increase in LVSWI.

There is clinical evidence that intestinal hypoperfusion and decreased microcirculation in regional tissue beds are major factors in progressive organ failure following shock states (23, 24). Vasoconstriction is an immediate physiologic response to hypovolemic shock. Because the splanchnic circulation is particularly susceptible to ischemia, a decreased mesenteric perfusion may result in net ischemia and subsequently tissue injury (24). In addition, mesenteric organ injury from ischemia related to any form of shock can lead to translocation of bacteria and endotoxin, triggering systemic inflammatory response syndrome (24).

In the present study, we noted a glibenclamide-associated decrease in systemic pH, which may have been caused by anaerobic glycolysis and lactate production in skeletal muscles. However, the local intestinal pH of the control group of this sheep model showed that ileal pH markedly decreased versus baseline. Ileal pH in the glibenclamide group was initially decreased but was markedly higher for the entire study period. The fact that glibenclamide stimulates endothelial NO production in the gut may have accounted for the improved intestinal microcirculation (25). However, future studies are needed to investigate the impact of glibenclamide in intestinal blood flow in greater detail.

Hypotensive shock situations can lead to acute renal failure followed by acute tubular necrosis and depressed glomerular filtration rate (26). In this study, glibenclamide maintained organ blood flow in the kidney, as indexed by quantitatively more urine production in the treatment group. This finding is in full agreement with the study by Ramsey and colleagues (27). Using a canine model, the authors have shown a close correlation between urine output and renal function. In addition, it has been demonstrated in a canine model of hemorrhagic shock

TABLE 1. Effects of acute ovine hemorrhage on hemodynamic variables, glucose, and arterial pH

Variable	Group	Time (h)							
		0	1	2	3	4	5	6	
CI (L · min <sup>-1</sup> )	G	4.6 ± 0.3	2.2 ± 0.3*	2.1 ± 0.3*	2.1 ± 0.2*	2.2 ± 0.3*	2.3 ± 0.3*	2.4 ± 0.3*	
	C	41. ± 0.2	1.8 ± 0.2*	1.8 ± 0.2*	1.8 ± 0.2*	1.9 ± 0.2*	1.8 ± 0.3*	1.8 ± 0.3*	
PCWP (mmHg)	G	5 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1	3 ± 1	3 ± 1	
	C	6 ± 1	5 ± 1	5 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1	
HR (beat · min <sup>-1</sup> )	G	98 ± 6	153 ± 9*	129 ± 9*	139 ± 6*	136 ± 6*	135 ± 5*	140 ± 5*	
	C	95 ± 7	157 ± 12*	143 ± 10*	142 ± 10*	138 ± 9*	122 ± 7*	127 ± 8*	
Glucose (mg · dL <sup>-1</sup> )	G	119 ± 28	314 ± 22*	262 ± 27*	265 ± 27*	236 ± 21*	251 ± 28*	241 ± 26*	
	C	110 ± 23	316 ± 30*	259 ± 27*	234 ± 30*	224 ± 27*	232 ± 32*	238 ± 31*	
Arterial pH (-log <sub>10</sub> H <sup>+</sup> )	G	7.39 ± 0.01	7.33 ± 0.02*	7.33 ± 0.02*	7.33 ± 0.02*	7.34 ± 0.02*	7.35 ± 0.02*	7.33 ± 0.02*	
	C	7.41 ± 0.01	7.36 ± 0.02*	7.37 ± 0.02	7.38 ± 0.02	7.38 ± 0.02	7.39 ± 0.02	7.37 ± 0.02	

G, treated with glibenclamide; C, control group; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; HR, heart rate. Data are presented as mean ± SEM of 12 animals per group. \*P < 0.05 glibenclamide versus baseline (BL = 0 h).

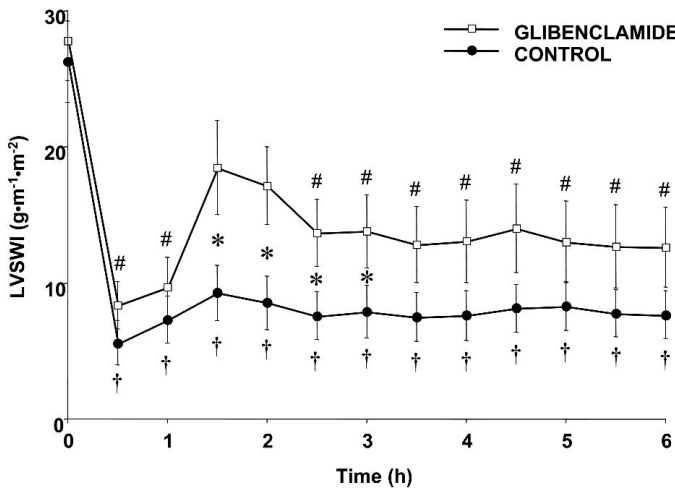


FIG. 3. Left ventricular stroke work index (LVSWI), an index of myocardial contractility compared with controls. Data are mean ± SEM. \*P < 0.05 between groups; #P < 0.05 glibenclamide versus BL; †P < 0.05 control versus BL.

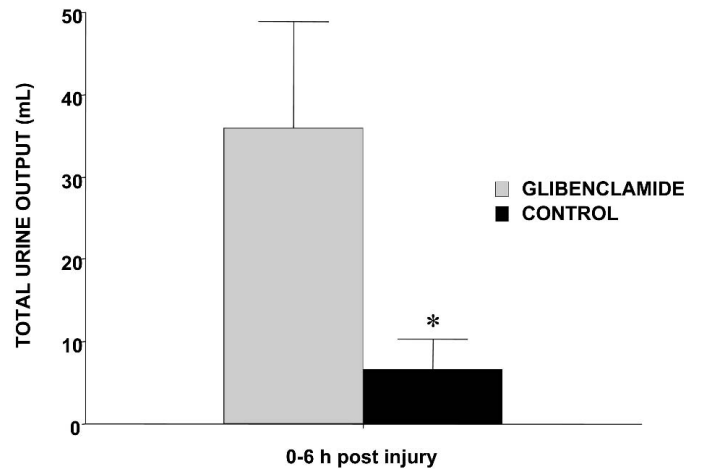


FIG. 5. Comparison of total urine output in glibenclamide-treated versus control sheep. The values are mean ± SEM. \*P < 0.05 between groups.

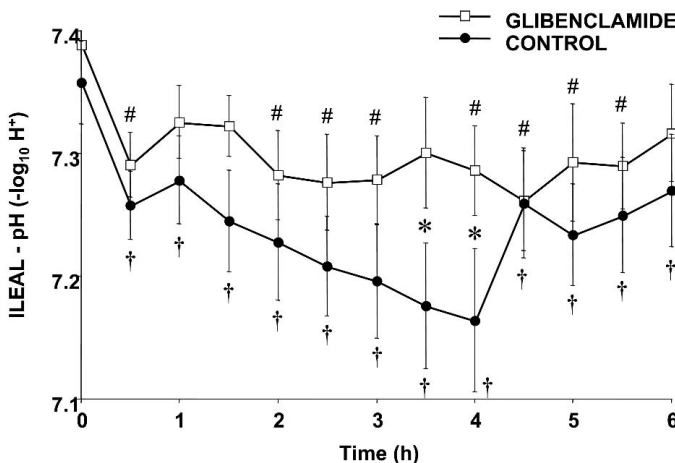


FIG. 4. Impact of glibenclamide on ileal pH in a sheep model. The values are expressed as mean ± SEM. \*P < 0.05 between groups; #P < 0.05 glibenclamide versus BL; †P < 0.05 control versus BL.

that the presence of urine output is correlated with a lower mortality rate (28).

A recent study by Tamion et al. (29) has shown that hemorrhage produces an inflammatory response by the overproduction of proinflammatory cytokines and that this response can be

attenuated by the administration of antioxidants. Because glibenclamide has been shown to possess antioxidant properties (30), it may also protect tissue against reperfusion injuries. In this regard, Bouskela and colleagues (31) have shown in a hamster model that glibenclamide improves tissue perfusion via a better microcirculatory blood flow. The potential reperfusion injury has obviously been ablated by the antioxidant properties of this pharmacologic agent.

Because of current use of glibenclamide as an antidiabetic drug, there was some concern that its use in this study might cause unwanted hypoglycemia. By infusing glucose simultaneously, we were able to prevent the anticipated impairment in glucose homeostasis. After manifestation of hemorrhagic shock, glucose plasma levels were even in supranormal ranges, most likely because of an initial hyperbolic stress response, which has also been shown by Korth et al. (32) in a shock model in pigs. However, no differences in glucose concentrations were seen between groups, suggesting that the investigated glibenclamide dose did not impair glucose metabolism.

A limitation of our study is that we did not investigate ATP tissue levels. In addition, it remains undetermined whether lactate production was affected by glibenclamide infusion.

In summary, the present study provides evidence that treatment with the K<sub>ATP</sub>-channel inhibitor glibenclamide improves

hemodynamics and organ function in a clinically relevant large-animal model of hemorrhagic shock. Therefore, glibenclamide is providing a window of opportunity for patient transport and subsequent fluid resuscitation. This clearly impacts on its direct clinical relevance and may be transferred to other shock situations. Future studies are warranted to investigate whether glibenclamide is also beneficial in human hemorrhagic shock, especially when rapid surgical intervention or fluid resuscitation is not feasible.

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