Title: SURVIVAL AFTER SEVERE HEMORRHAGIC SHOCK IN MONKEYS: CNS, PULMONARY, HEPATIC AND RENAL OUTCOME

Authors: G. Bar-Joseph, M.D., P. Safar, M.D., S.W. Stezoski, H. Alexander
(With the assistance of K. Swint, B.S. and D. Gross)

Affiliation: Resuscitation Research Center and Department of Anesthesiology/CCM, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Introduction. Pressure controlled hemorrhagic shock (HS) models (Wiggers) in dogs do not resemble the clinical picture as seen in humans. Renal and pulmonary failure do not occur in dogs who succumb to intestinal necrosis. However, an ARDS-like picture was reported in monkeys surviving HS (1). We developed a volume controlled HS model in monkeys, where withdrawal of 40% of measured blood volume without resuscitation resulted in cardiac arrest at 142±42 minutes (2). In this study we attempted to define in this model a "point of irreversibility", beyond which "standard" therapy will fail to result in long-term survival and complete recovery of vital organs.

Methods. Male cynomolgous monkeys were anesthetized with halothane 0.5-1%, N_2O/O_2=75/25%. Catheters were inserted under sterile conditions. Halothane was discontinued 15 min before bleeding, and anesthesia maintained with N_2O/O_2=75/25% and spontaneous breathing via endotracheal tube. Animals were bled 21ml/kg (n=4) or 27ml/kg (n=8) at a constant rate over 20 min (Time 0) with no further intervention. Resuscitation therapy (RT) was initiated at increasing time intervals after Time 0. RT included Ringers/5% dextrose X2 of shed blood volume over 30 min followed by blood re-infusion over 30 min; then maintenance fluids at 5ml/kg/hr with additions to maintain MAP >70 torr. Also IPPV for 24 hrs with N_2O/O_2=75/25%, rate adjusted to maintain $PaCO_2$=30±5 torr, and $NaHCO_3$ given for base deficit >4mEq/L. Full monitoring in animal ICU until RT+48 hrs, and observation until RT+7 days, when final evaluation, sacrifice and autopsy were performed. Continuous monitoring included EKG, arterial and pulm. artery pressures, EEG, and end-tidal CO_2

Results. (I). Survival, CNS, cardiovascular and pulmonary functions: in 8 animals bled 27ml/kg, RT was initiated at 0+30 min (n=1), 0+45 min (n=2), 0+75 min, 0+90 min, 0+2 hrs, 0+3 hrs and 0+5 hrs (1 each). After Time 0 BP spontaneously increased ("self-resuscitation"), but animals remained hypotensive, anuric and stuporous, with severe lactic acidosis and marked EEG depression. All responded immediately to RT with increased cardiac output and MAP, restoration of urine output, improved alertness and normalization of EEG. 1 animal died at RT+8 hrs, with sudden EEG depression noted before hypotension. 7/8 animals survived 7 days with no neurobehavioral deficit. (Table 1)

	MAP	Card. Output	BE	Lactate
Control	104±15	0.95±0.14	-1±2	2.6±1.3
Time 0	21± 4*	0.44±0.05*	-7±5*	7.3±1.8*
0+1 hr	40±11*	0.43±0.02*	-12±6*	8.8±4.4*
RT+1 hr	99±16	0.94±0.17	-11±4*	6.3±3.1*
RT+24 hrs	109±14	0.66±0.08*	-4±2	1.6±0.9
RT+48 hrs	107±10	1.10±0.12	-1±4	2.4±1.1

mean±SD. *p<0.01 compared to control (t-test)

Pulmonary functions as evaluated by PaO_2 (FIO_2=0.25), % Q_S/Q_T and respiratory index ($RI=A\text{-}aDO_2/PaO_2$) showed no signs of pulm. dysfunction up to RT±48 hrs. On autopsy all lungs looked macroscopically normal. (Table 2)

	PaO_2	% Q_S/Q_T	RI
Control	122±13	1.3±0.9	0.1±0.1
0+1 hr	122±23	1.3±0.9	0.2±0.2
RT+1 hr	123±11	1.7±1	0.2±0.1
RT+24 hrs	119±10	1.2±0.4	0.2±0.0
RT+48 hrs	92±10*	2.1±1.1	0.3±0.1

*FIO_2=0.21.

(II): Renal and liver functions. 11 animals were divided into 2 groups according to severity of insult: Gr. 1-moderate insult (n=7): 21ml/kg bleeding with RT at 0+60 and 0+90 min, or 27ml/kg bleeding with RT before 0+2 hrs. Gr. 2-severe insult (n=4): 27ml/kg bleeding with RT at 0+3 and 0+5 hrs, or at 0+45 min but with MAP ≤30 torr for the entire period. RT restored urine output in all animals. Gr. 2 had sign. higher BUN, creatinine and SGPT at RT+24 and RT+48 hrs than Gr. 1. In both groups SGPT was sign. elevated at 24 and 48 hrs after RT. No abnormalities in serum Na and K, and their fractional excretion ratios were noted. (Table 3)

		BUN	Creat.	SGPT
Control	Gr.1	16±3	0.9±0.2	11± 4
	Gr.2	18±4	1.2±0.2	23±13
RT+24 hrs	Gr.1	10±2*	1.0±0.2*	35±11*#
	Gr.2	22±3	1.8±0.6#	172±82#
RT+48 hrs	Gr.1	10±4*	0.9±0.1*	59±16*#
	Gr.2	22±3	1.7±0.6	304±136#

mean±SD, #p<0.05 compared to Control. (t-test)
*p<0.01 Gr. 1 compared to Gr. 2.

Discussion and conclusions. This HS model is more physiologic than the Wiggers model, since it retains the natural response to severe blood loss. Standard fluid therapy and intensive care, even when started after 5 hrs of shock, led to survival without neurologic deficit. None of our animals developed ARDS, as reported by Rutherford (2), possibly because we avoided fluid overload. Prolonged, severe hypotension alone is not sufficient to cause ARDS. Additional trauma, endotoxins or fluid overload may be necessary to produce pulm. damage. However, prolonged liver and renal damage occurred in the more severely insulted animals. It may be possible to use these parameters as "markers" in therapy experiments with this model.

Supported by the A. Laerdal Company and the Pennsylvania Department of Health.

References.

1. Rutherford RB, Arora S, Fleming PW, et al: Delayed-onset pulmonary insufficiency in primates resuscitated from hemorrhagic shock. J. Trauma 19:422-431, 1979.

2. Bar-Joseph G, Safar P, Stezoski WS: A realistic hemorrhagic shock model in the monkey. (Abstract) Circulatory Shock, 8:206, 1981.