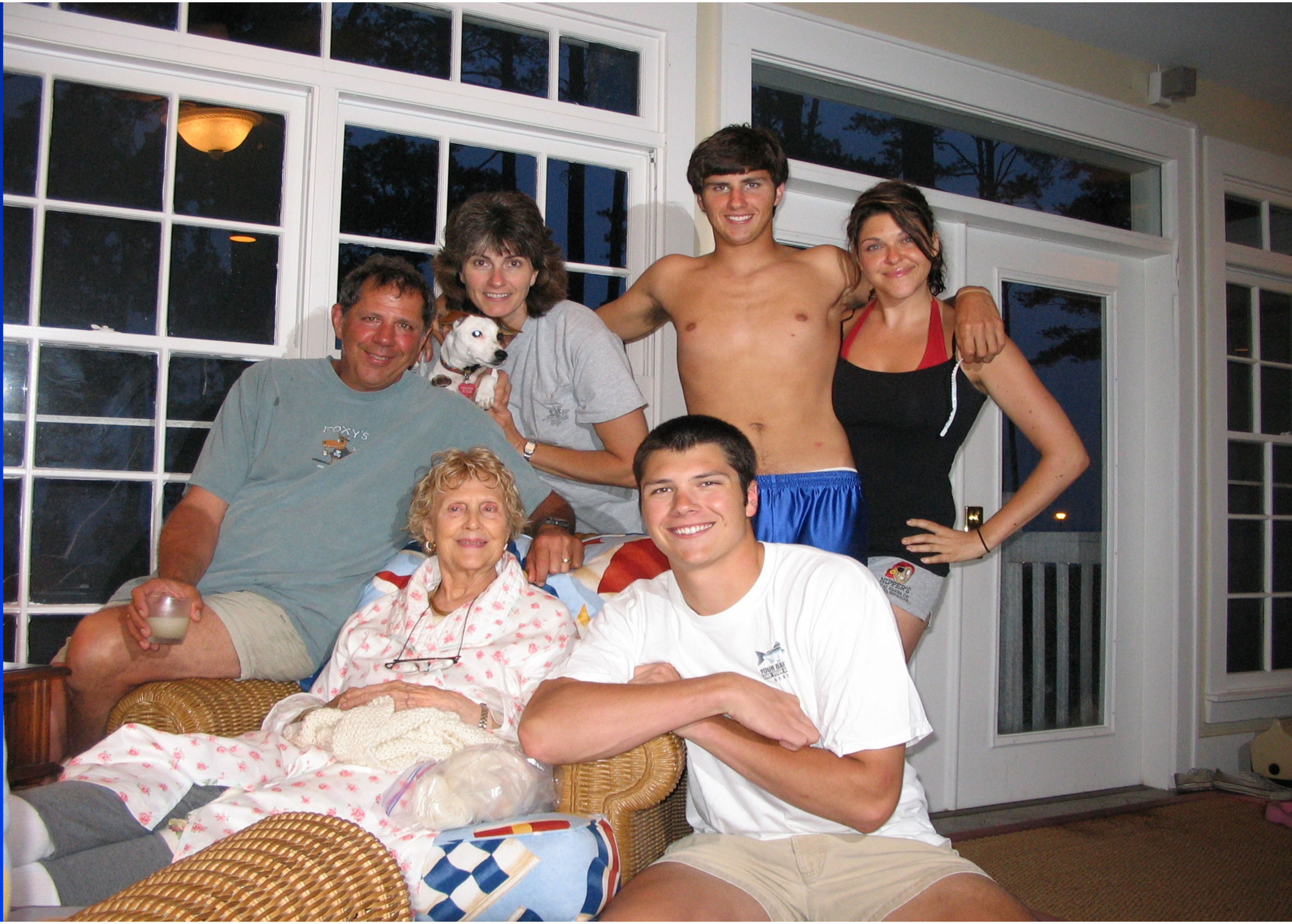

FOXY'S
NIPPER'S

WTA for ove

WTA Founders Basic Science Lecture

The Role of Hypertonic Saline in Modern Trauma Care

Steven R. Shackford MD FACS
Trauma Team Medical Group
Scripps Mercy
San Diego, CA

Out-of-hospital Hypertonic Resuscitation After Traumatic Hypovolemic Shock:

A Randomized, Placebo Controlled Trial

Eileen M. Bulger, MD[*], Susanne May, PhD[*], Jeffery D. Kerby, MD, PhD[†], Scott Emerson, MD, PhD[*], Ian G. Stiell, MD[‡], Martin A. Schreiber, MD[§], Karen J. Brasel, MD, MPH[‖], Samuel A. Tisherman, MD[¶], Raul Coimbra, MD, PhD[#], Sandro Rizoli, MD, PhD[**], Joseph P. Minei, MD[††], J. Steven Hata, MD[‡‡], George Sopko, MD, MPH[§§], David C. Evans, MD[‖‖], and David B. Hoyt, MD[¶¶] for the ROC investigators

Prehospital Hypertonic Saline Resuscitation of Patients With Hypotension and Severe Traumatic Brain Injury

A Randomized Controlled Trial

D. James Cooper, BMBS, MD

Paul S. Myles, MBBS, MD

Context Prehospital hypertonic saline (HTS) resuscitation of patients with traumatic brain injury (TBI) may increase survival but whether HTS improves neurological out-

Trauma care is like cross country travel

Pre-hospital intervention = getting on  *in San Diego*

Objectives

- ***Review the physiologic basis of hypertonic resuscitation***
- ***Using clinical and basic science research demonstrate that:***
    - ***hypertonic resuscitation is physiologic***
    - ***hypertonic solutions are safe and effective***
    - ***solute free water may be harmful***

Disclaimer

- *No financial interests*
- *No self-deception*
- *No immunology*

BASIC SCIENCE REFRESHER

TABLE 10.1

BODY FLUID COMPARTMENTS **70 kg male***

	Body weight (%)		Total body water (%)
Total	60	42 L	100
Intracellular	40	28 L	67
Extracellular	20	14 L	33
Intravascular	5	3.5 L	8
Interstitial	15	10.5	25
Transcellular	2		4

TABLE 10.2

ELECTROLYTE CONCENTRATIONS OF INTRACELLULAR AND EXTRACELLULAR FLUID COMPARTMENTS

	Extracellular fluid (mEq/L)		
	Plasma (0.8%)	Interstitial	Intracellular fluid (mEq/L)
Cations			
Na^+	140	146	12
K^+	4	4	150
Ca^{2+}	5	3	10^{-7}
Mg^{2+}	2	1	7
Anions			
Cl^-	103	114	3
HCO_3^-	24	27	10
SO_4^{2-}	1	1	—
HPO_4^{3-}	2	2	116
Protein	16	5	40
Organic anions	5	5	—

Definition of terms

- ***Osmolarity**: refers to the number of osmotically active particles dissolved in solvent (without reference to cell volume)*
  - *Physical property of a solution*

- ***Tonicity**: refers to the effect of dissolved osmotically active particles on CELL VOLUME*

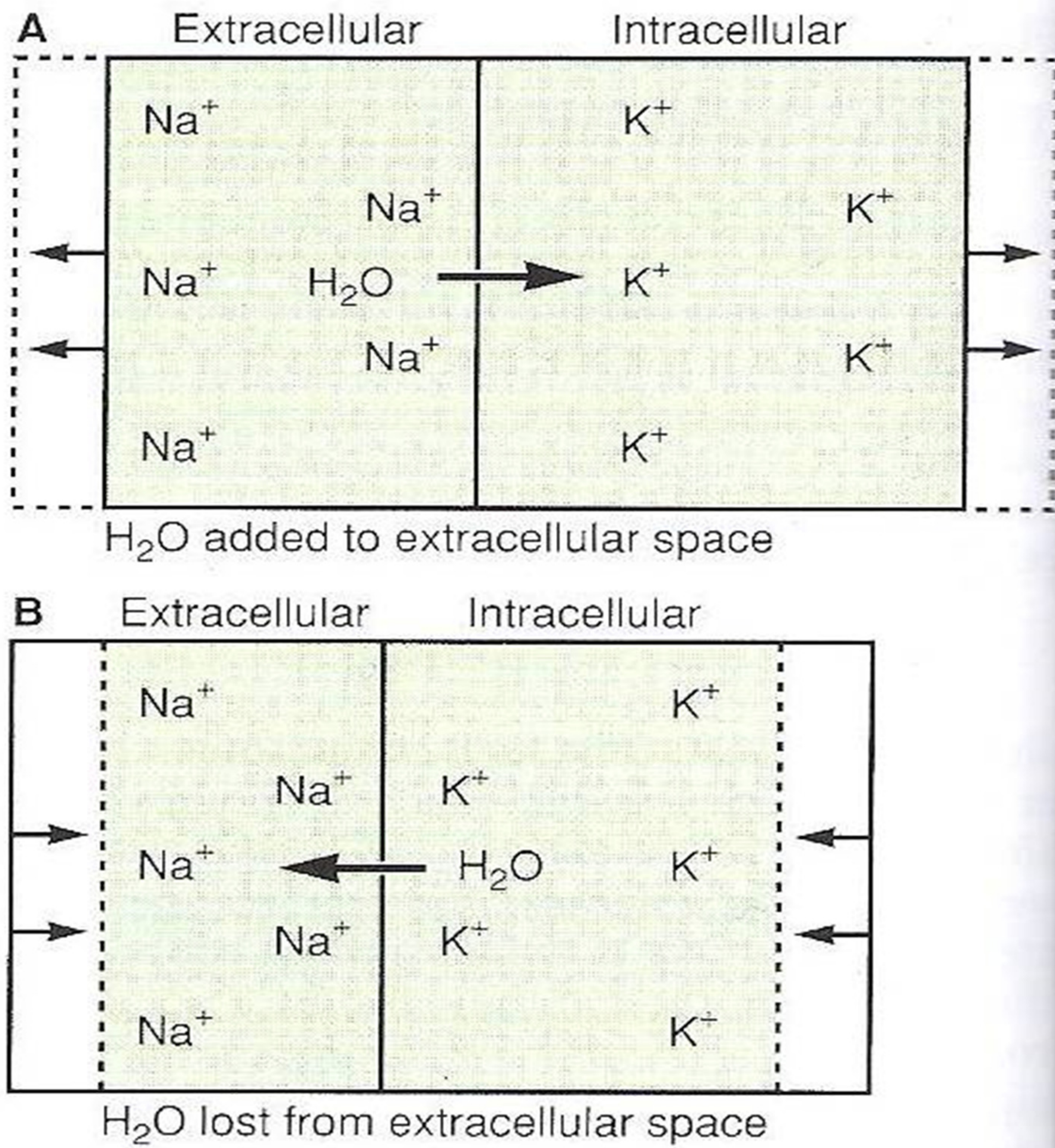

A
Extracellular
Intracellular
Na+
Na+
Na+
Na+
Na+
H2O
K+
K+
K+
K+
K+
H2O added to extracellular space
B
Extracellular
Intracellular
Na+
Na+
Na+
Na+
Na+
H2O
K+
K+
K+
K+
K+
H2O lost from extracellular space

TABLE 10.4

ELECTROLYTE CONTENT OF COMMONLY USED INTRAVENOUS CRYSTALLOID SOLUTIONS

0.8%Plasma **mOsm 280**

		Electrolyte (mEq/L)					
Solution	mOsm	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	HCO_3^-
0.9% NaCl	308	154	—	—	—	154	—
0.45% NaCl		77	—	—	—	77	—
0.33% NaCl		56	—	—	—	56	—
0.2% NaCl		34	—	—	—	34	—
Lactated Ringer's	274	130	4	4	—	109	28
3.0% NaCl		513	—	—	—	513	—
5.0% NaCl		855	—	—	—	855	—

Ocean water: 3.5% saline (1198 mOsm)

Anaesthesia, 1981, Volume 36, pages 1115–1121

HISTORY

Sydney Ringer (1834–1910) and Alexis Hartmann (1898–1964)

J. ALFRED LEE

Ringer's = Hartmann's

Hartmann added the lactate and the free water


Our origin?

DETERMINANTS OF INTRACRANIAL PRESSURE

Δ ICP = ^{V}Brain + ^{V}blood + ^{V}CSF + ^{V}ECF + ^{V}ICF + ^{V}**X**

Where: V = volume

CSF = cerebrospinal fluid

ECF = extracellular fluid

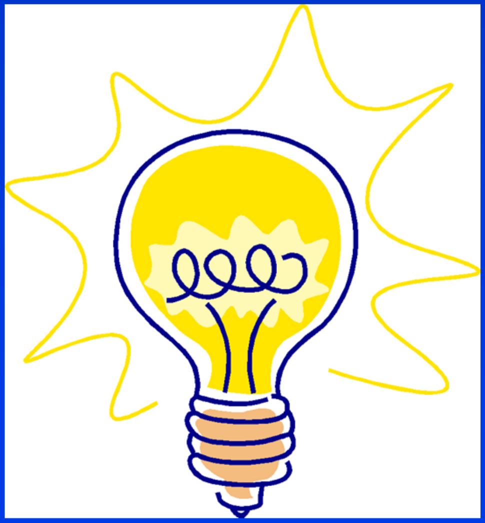
ICF = intracellular fluid

X = hematoma, edema, swelling, etc

In the beginning….

"Let there be…."

An idea…




Bacon

Ideal Asanguinous solution

- *Carry oxygen*
- *Rapidly effective in small volumes*
  - *Increase oxygen delivery*
  - *Preserve vital organ function*
- *Minimal side effects*
- *Long shelf life **
- *Inexpensive **

** Important attributes for the military*

Hypertonic Saline Solutions

Pulmonary changes due to hemorrhagic shock resuscitation with isotonic and hypertonic saline. Fulton RL, Fischer RP.Surgery. 1974; 75:881-91

The protective effect of hypertonic solutions in shock.

Messmer K, Mokry G, Jesch F. Br J Surg. 1969;56:626.

Hyperosmotic NaCl and severe hemorrhagic shock.

Velasco IT, Pontieri V, Rocha e Silva M Jr, Lopes OU. Am J Physiol. 1980 Nov;239(5):H664-73

The treatment of burn shock by the intravenous and oral administration of hypertonic lactated saline solution. Monafo WW. J Trauma 1970;10:575-86

Clinical Study of Hypertonic Solutions?

- ***Minimal clinical data in 1976***
  - ***Monafo in burned patients***
- ***Safe elective surgical patients?***
- ***Standard major operation***
- ***Homogeneous population***

Hypertonic sodium lactate versus lactated Ringer's solution for intravenous fluid therapy in operations on the abdominal aorta

Steven R. Shackford, CDR, MC, USN, Michael J. Sise, LCDR, MC, USN, Peggy H. Fridlund, R.N., William R. Rowley, CDR, MC, USN, Richard M. Peters, M.D., F.A.C.S., Richard W. Virgilio, M.D., F.A.C.S., *and* John E. Brimm, M.D., *San Diego, Calif.*

Surgery 1983; 94:41-51

- ***58 patients undergoing aortic reconstruction***
- ***PRCT: RL or HSL (1.8%)***
    - ***Keep PCWP ± 3 torr BL***
    - ***Postop for hypovolemia***
    - ***Maintenance fluids similar (0.25% saline)***

ONR contract (N-00014-76-C-0282)PHS grant (GM-24901)

Table I. Parameters studied and sequence of measurement/calculation

Parameter	Baseline	During operation: Every 15 min	During operation: After 1 hr	During operation: After 3 hr	Immediate postop.	Postop. period: A.M./P.M. day 1	Postop. period: A.M./P.M. day 2	Postop. period: A.M. day 3
Mean arterial pressure	x	x	x	x	x	x	x	x
Central venous pressure	x	x	x	x	x	x	x	x
Mean pulmonary artery pressure	x	x	x	x	x	x	x	x
Pulmonary artery pressure	x	x	x	x	x	x	x	x
Cardiac index	x	*	x	x	x	x	x	x
Functional residual capacity	x				x	x	x	x
Oxygen delivery	x		x	x	x	x	x	x
Intrapulmonary shunt	x		x	x	x	x	x	x
Colloid osmotic pressure	x		x	x	x	x	x	x
COP-PWP gradient	x		x	x	x	x	x	x
Serum electrolytes, glucose, BUN	x		x	x	x	x	x	x
Serum lactate	x				x	x	x	x
Serum creatinine	x		x	x	x	x	x	x
Serum osmolarity	x	x	x	x	x	x	x	x
Urine electrolytes								
Aliquot	x		x	x				
Spot					x	x	x	x
Urine osmolarity								
Aliquot	x		x	x				
Spot					x	x	x	x
Urine creatinine (2-hr)						A.M. only	A.M. only	x
Creatinine clearance						x	x	x
Free water clearance						x	x	x
Fractional excretion of sodium						x	x	x

*Measured every 30 minutes during the operation.

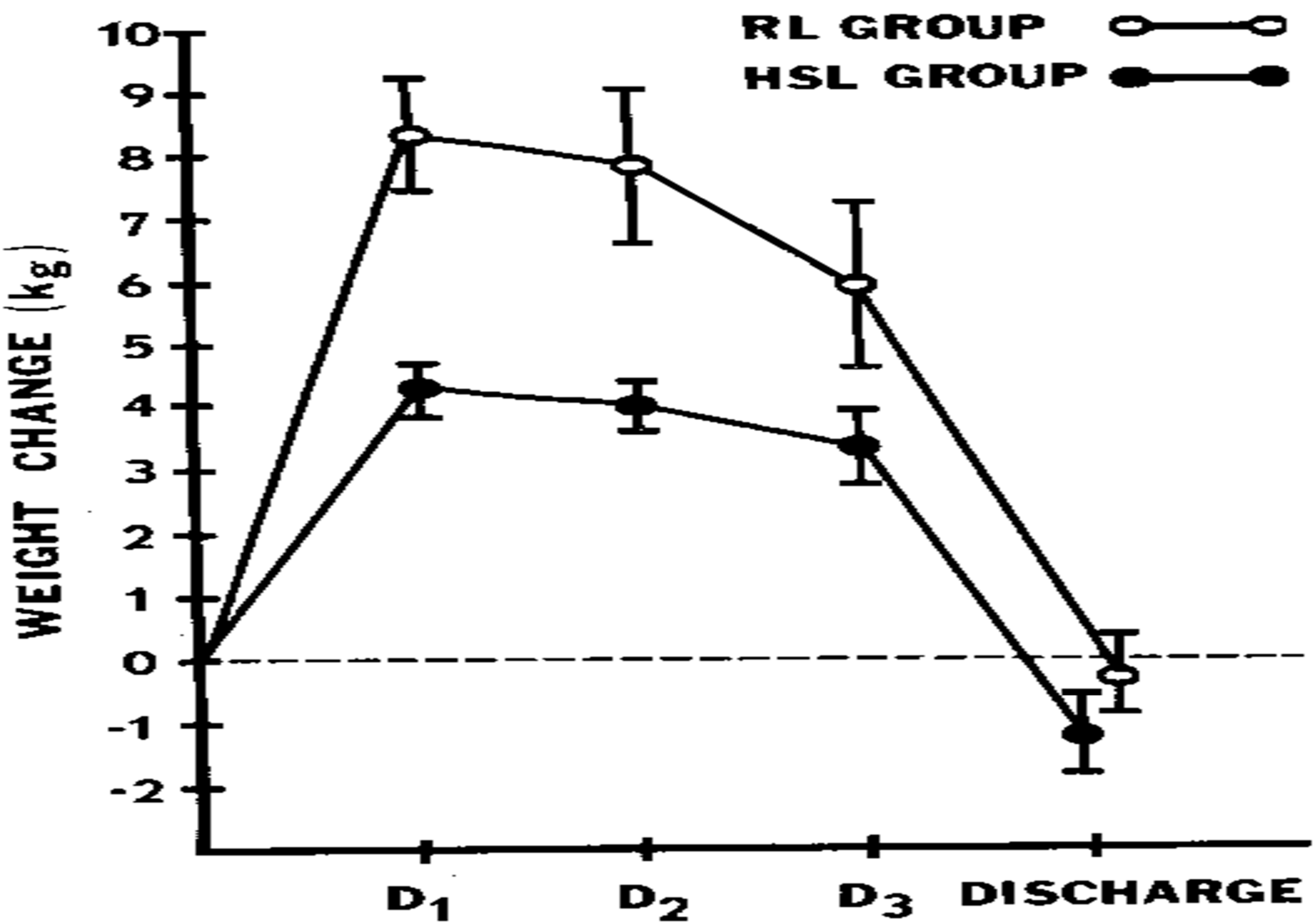
Table II. Patient data (mean ± SEM)

	HSL	*RL*
No. patients	30	28
Age (yr)	60.5 ± 1.5	61.7 ± 1.6
Weight (kg)	72.9 ± 1.5	77.5 ± 2.3
Body surface area (M^2)	1.88 ± 0.02	1.94 ± 0.03
Associated disease (no. patients)		
Hypertension	17	10
Congestive heart failure	0	1
Chronic arrhythmia	3	1
Cerebrovascular accident	2	3
Myocardial infarction	8	3
Chronic obstructive pulmonary diseas	1	2
Vascular procedure (no. patients) ***open surgery)***		
Abdominal aortic aneurysmectomy	12	13
Aortobifemoral bypass	18	15
Blood volume (70 ml/kg)	***5,110 ml***	***5,390 ml***

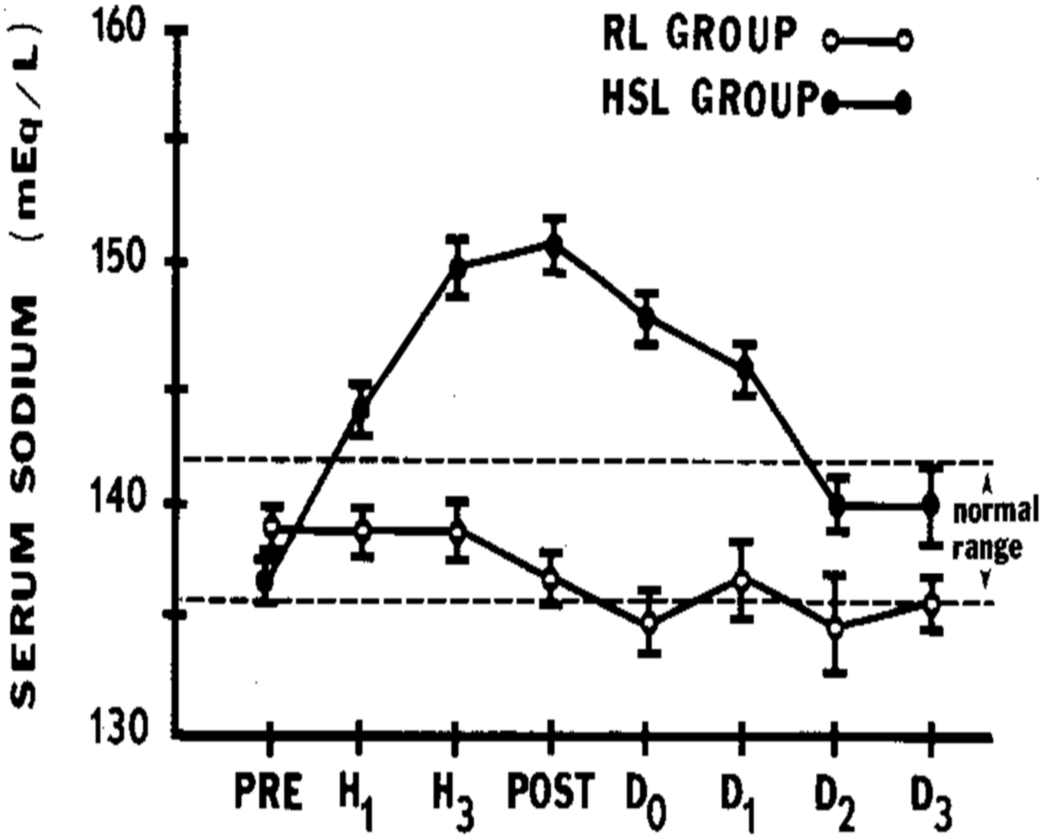
Table IV. Intraoperative measurements (mean ± SEM)

	HSL	*RL*
Duration of operation (hr)	4.8 ± 0.2	5.4 ± 0.3
Estimated blood loss (ml)	2416 ± 352	3027 ± 355
Transfusions (U)	3.7 ± 0.5	4.7 ± 0.5
PWP (torr)	10 ± 1	11 ± 1
CI (L/min/M^2)	3.1 ± 0.1	3.0 ± 0.1
Oxygen delivery (cc/min)	926 ± 37	866 ± 33
Q_s/Q_t (%)	16 ± 1	17 ± 1
Blood volume deficit	***47%***	***56%***

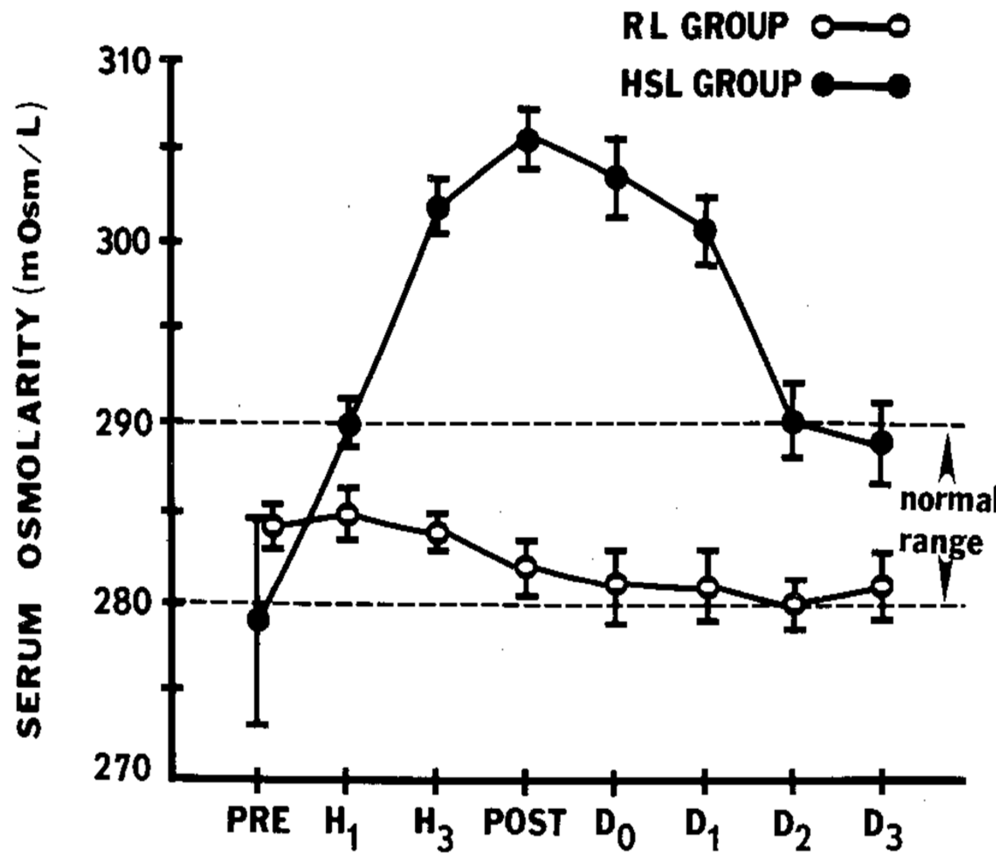
We were slow, BUT we lost a lot of blood



RL GROUP
HSL GROUP
WEIGHT CHANGE (kg)
10
9
8
7
6
5
4
3
2
1
0
-1
-2
D_1
D_2
D_3
DISCHARGE



SERUM SODIUM (mEq / L)
160
150
140
130
RL GROUP
HSL GROUP
normal range
PRE
H_1
H_3
POST
D_0
D_1
D_2
D_3



SERUM OSMOLARITY (m Osm / L)
310
300
290
280
270
RL GROUP
HSL GROUP
normal range
PRE
H_1
H_3
POST
D_0
D_1
D_2
D_3

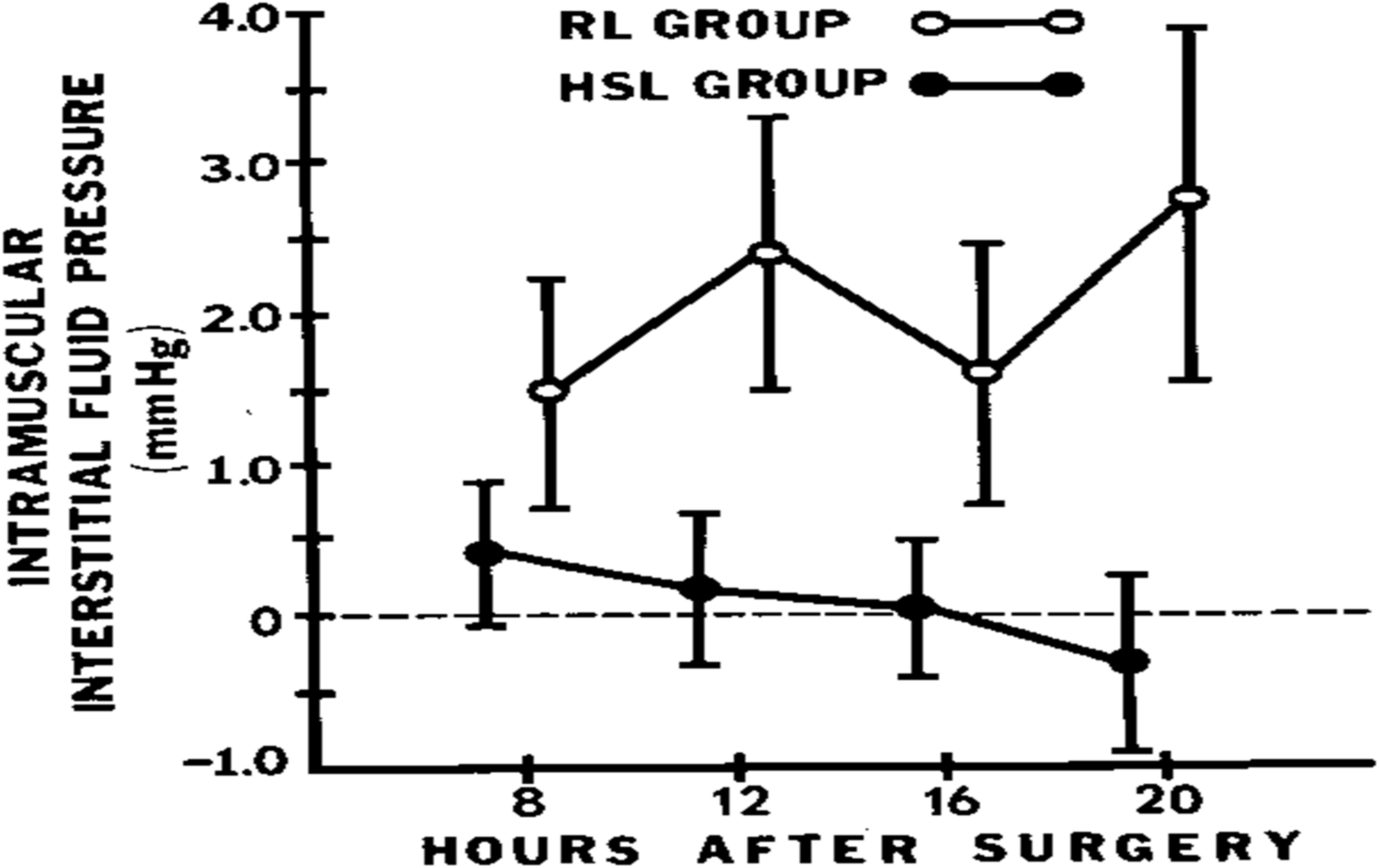


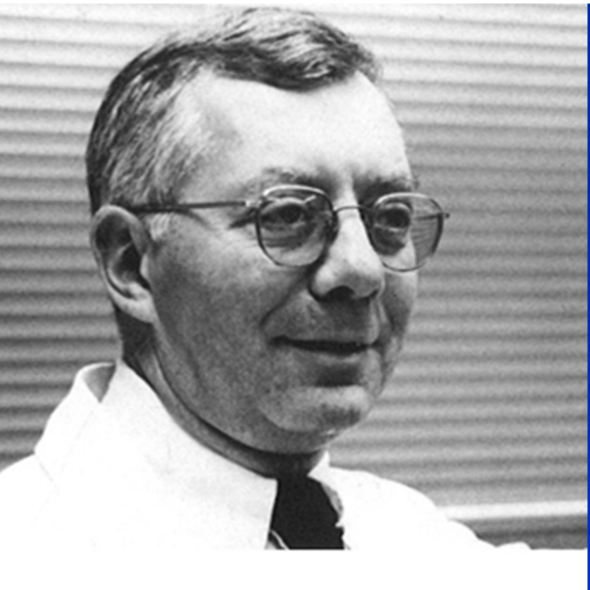
Fig. 5. Intramuscular interstitial fluid pressure. The inter-

Conclusions

- ***HSL is safe and effective for intraoperative resuscitation of major blood loss provided that S_{Na} and S_{osm} are monitored.***

Further Investigation

- ***What about hostile environments?***
  - ***Marines at the BAS/FOB***
- ***Is free water administration necessary to normalize the S_{Na} and the S_{osm} ? Is solute free water excreted to normalize them ?***



Background

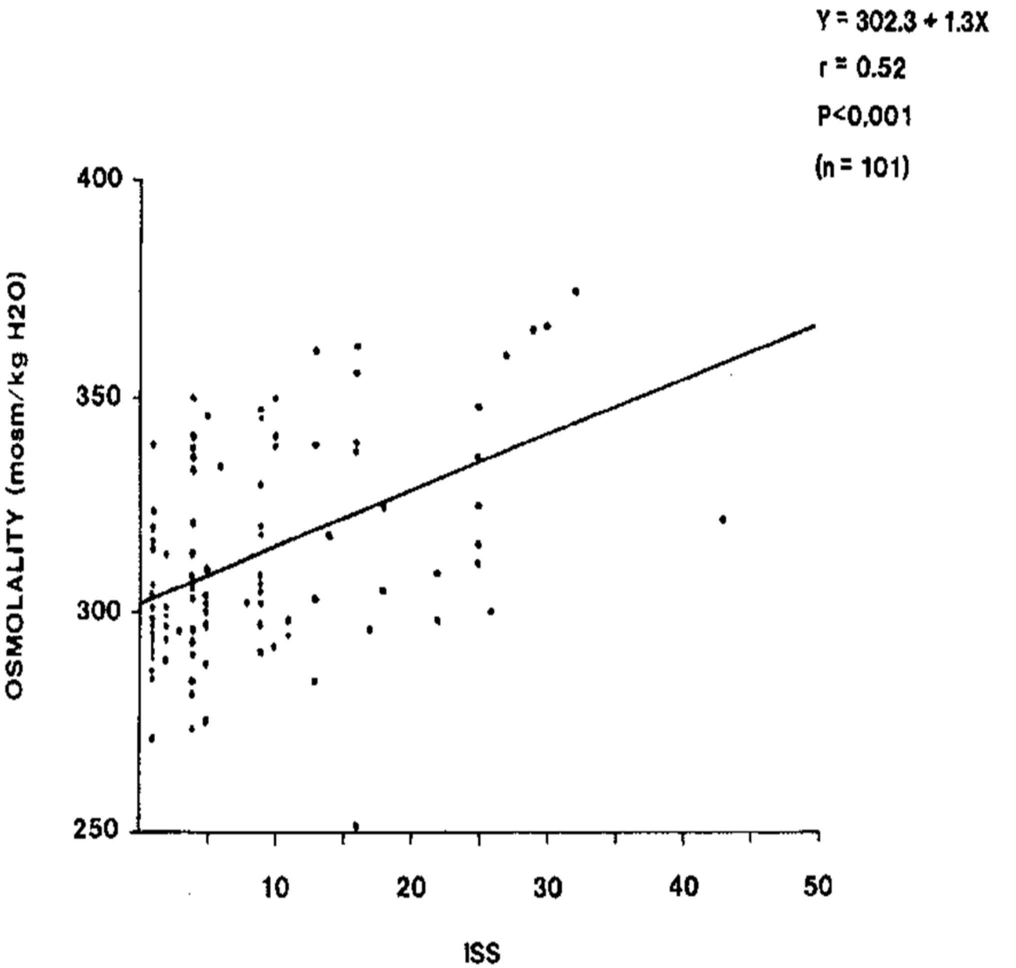
- ***Gann* and Drucker** had demonstrated that restitution of blood volume following hemorrhage required an increase in interstitial osmolarity and the extraction of water from cells***

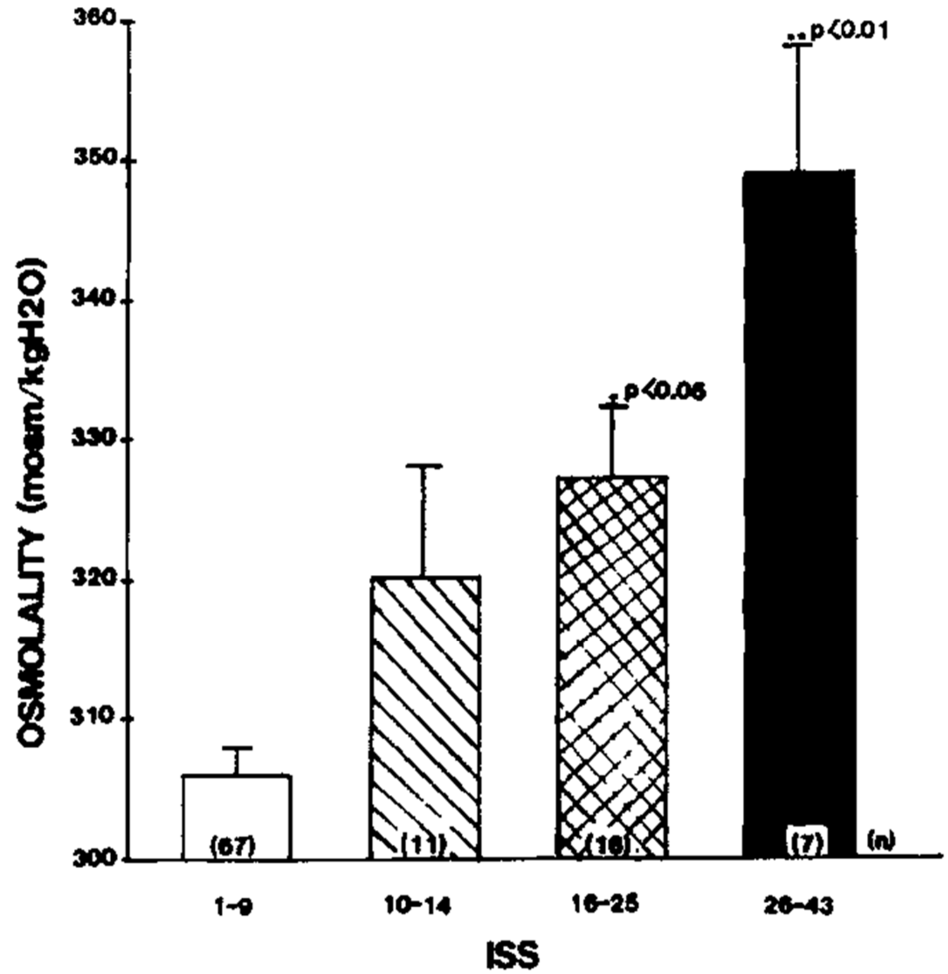
** *Transcapillary refill in hemorrhage and shock*
Drucker WR, Chadwick DJ, Gann DS
Arch Surg 1981; 116: 1344-1353

**Role of solute in the early restitution of blood volume after hemorrhage.*
Gann DS, Carlson DE, Byrnes GJ, Pirkle JC Jr, Allen-Rowlands CF.
Surgery. 1983 Sep;94(3):439-46.

Glucose and Osmolality as Predictors of Injury Severity

PARDON R. KENNEY, M.D., CATHERINE F. ALLEN-ROWLANDS, M.S., AND
DONALD S. GANN, M.D.






"Mother Nature", Rafal Tom


adidas
Marine Corps Marathon™
Rock 'n' Roll Marathon San Diego 2009

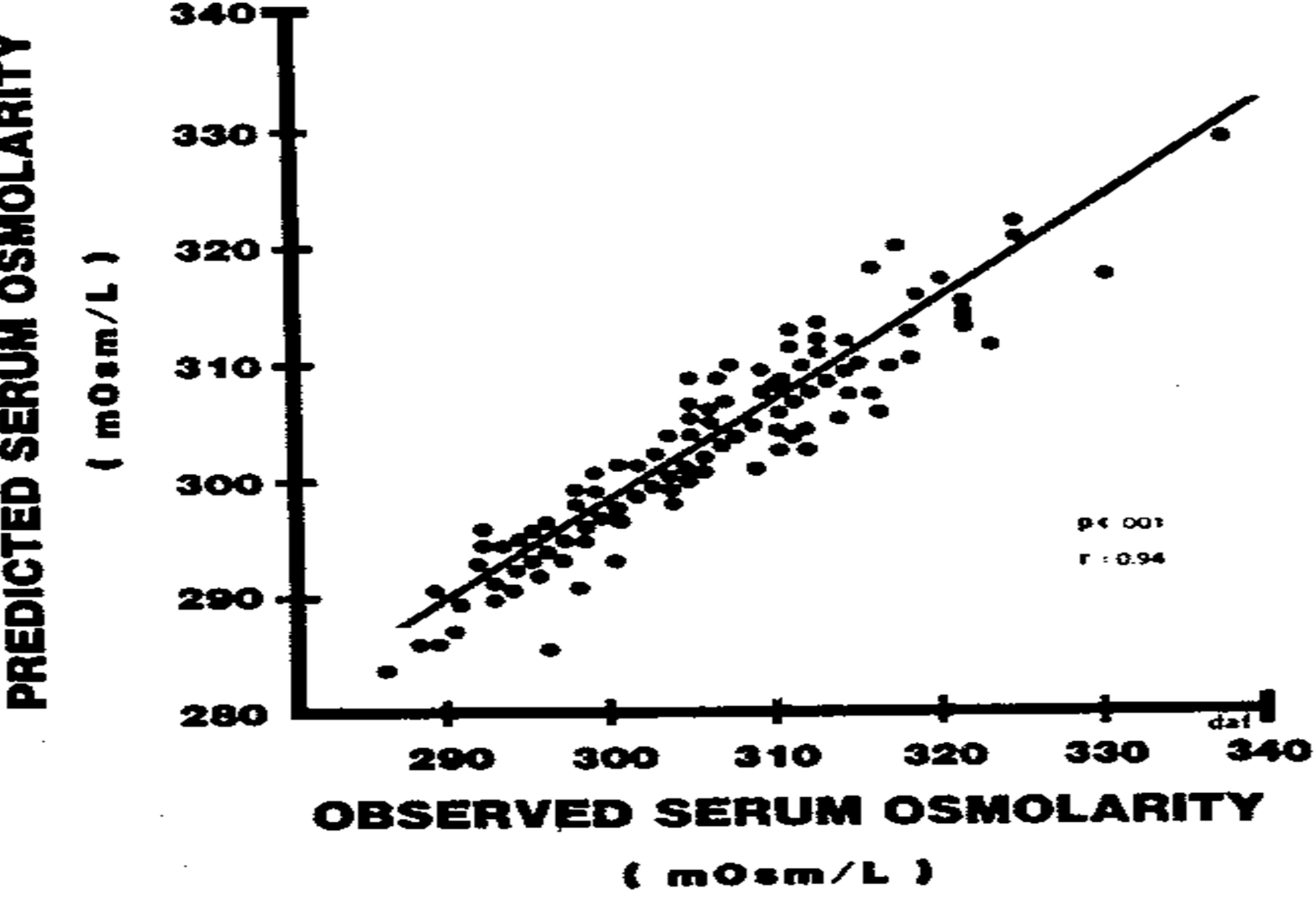
SERUM OSMOLAR AND ELECTROLYTE CHANGES ASSOCIATED WITH LARGE INFUSIONS OF HYPERTONIC SODIUM LACTATE FOR INTRAVASCULAR VOLUME EXPANSION OF PATIENTS UNDERGOING AORTIC RECONSTRUCTION

Steven R. Shackford, M.D., F.A.C.S., Dale A. Fortlage, B.A., Richard M. Peters, M.D., F.A.C.S., Peggy Hollingsworth-Fridlund, R.N., *and* Michael J. Sise, M.D., F.A.C.S., *San Diego, California*

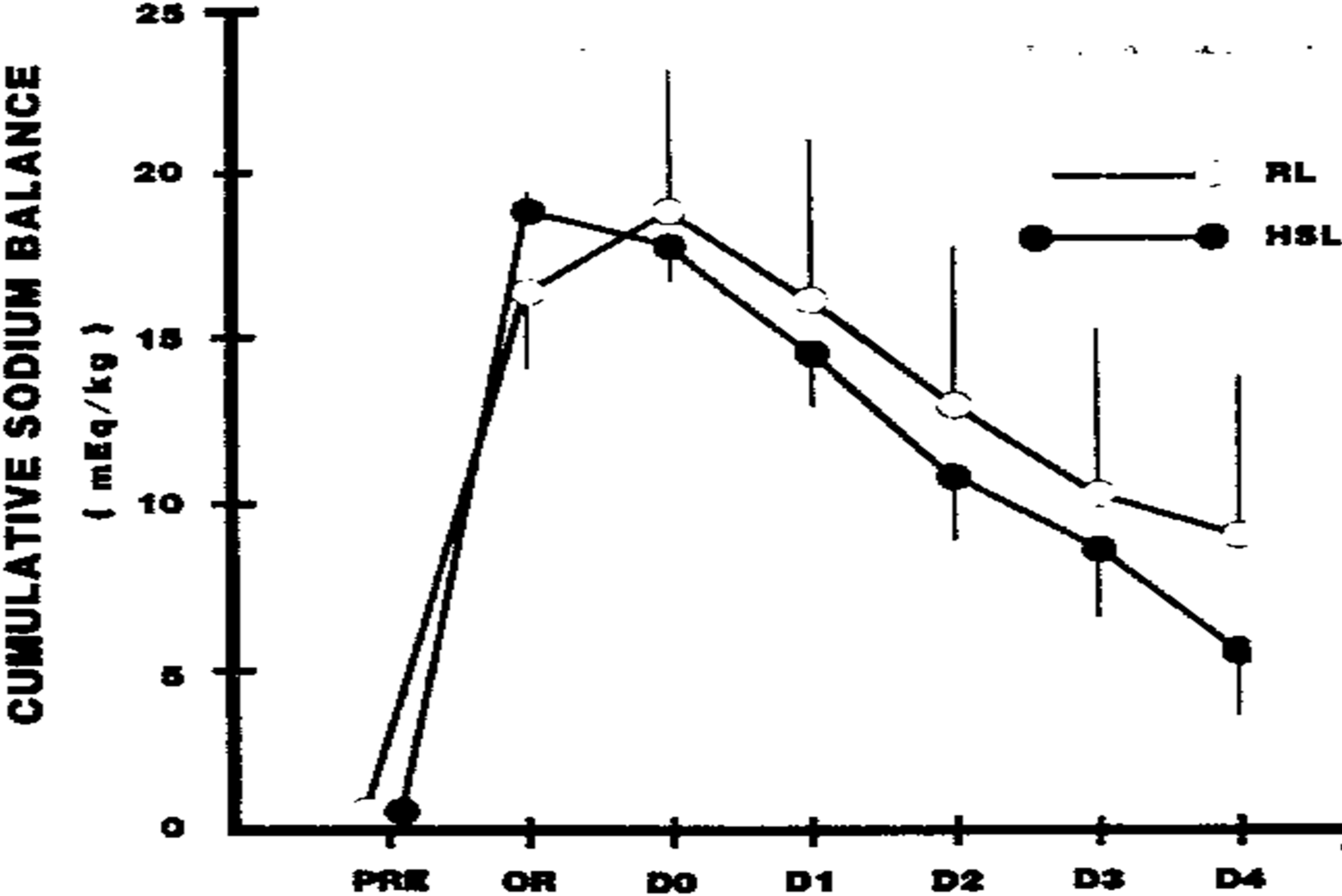
Surg Gynecol Obstet 1987; 164:127-136

- ***52 patients, major aortic reconstruction***
- ***PRCT, same methodology, same data collected***
- ***Same results: weight gain, physiology, etc***

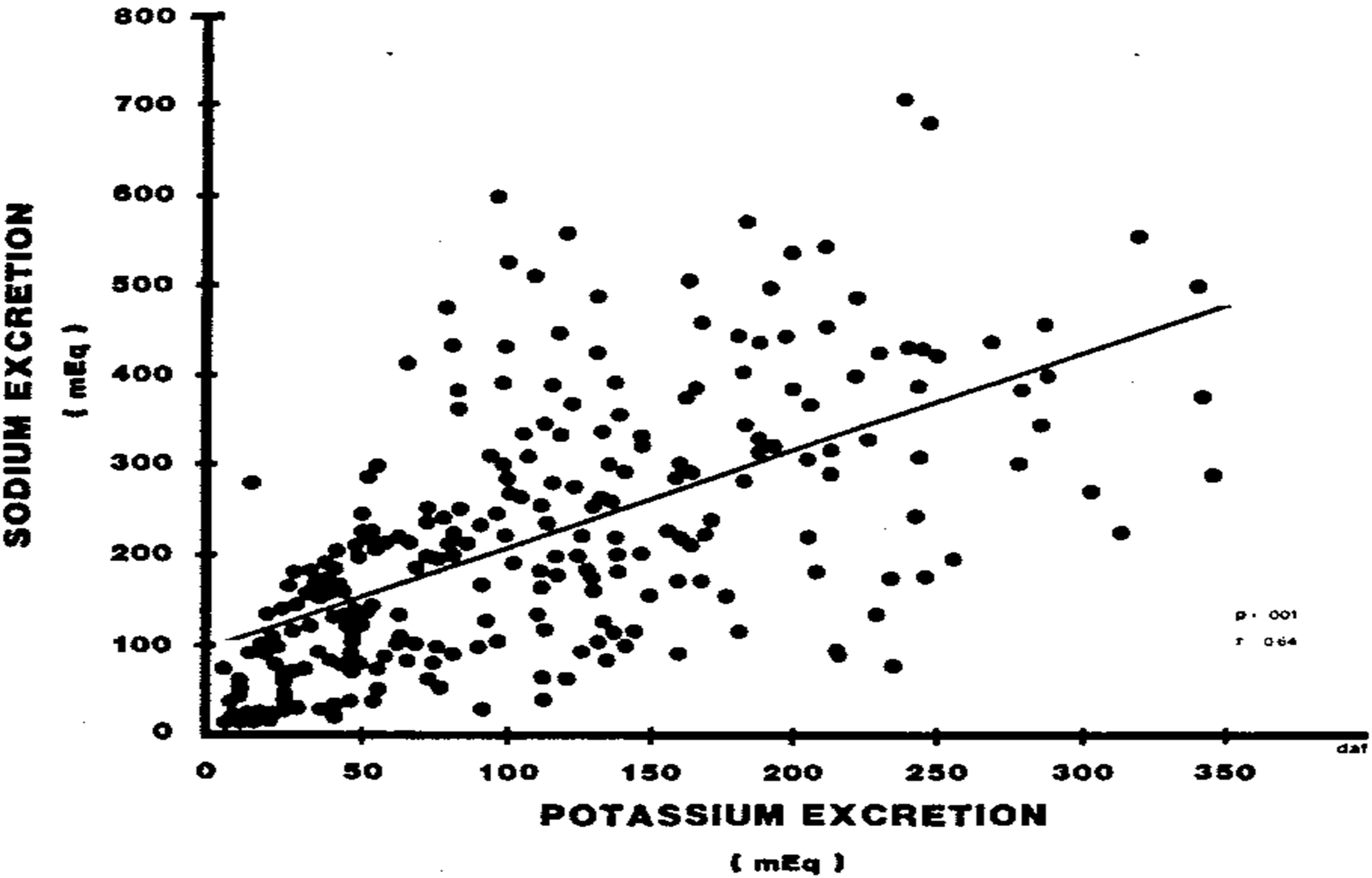
ONR contract (N-00014-76-C-0282)PHS grant (GM-24901)



PREDICTED SERUM OSMOLARITY
(mOsm/L)
340
330
320
310
300
290
280
290
300
310
320
330
340
OBSERVED SERUM OSMOLARITY
(mOsm/L)
p< .001
r : 0.94



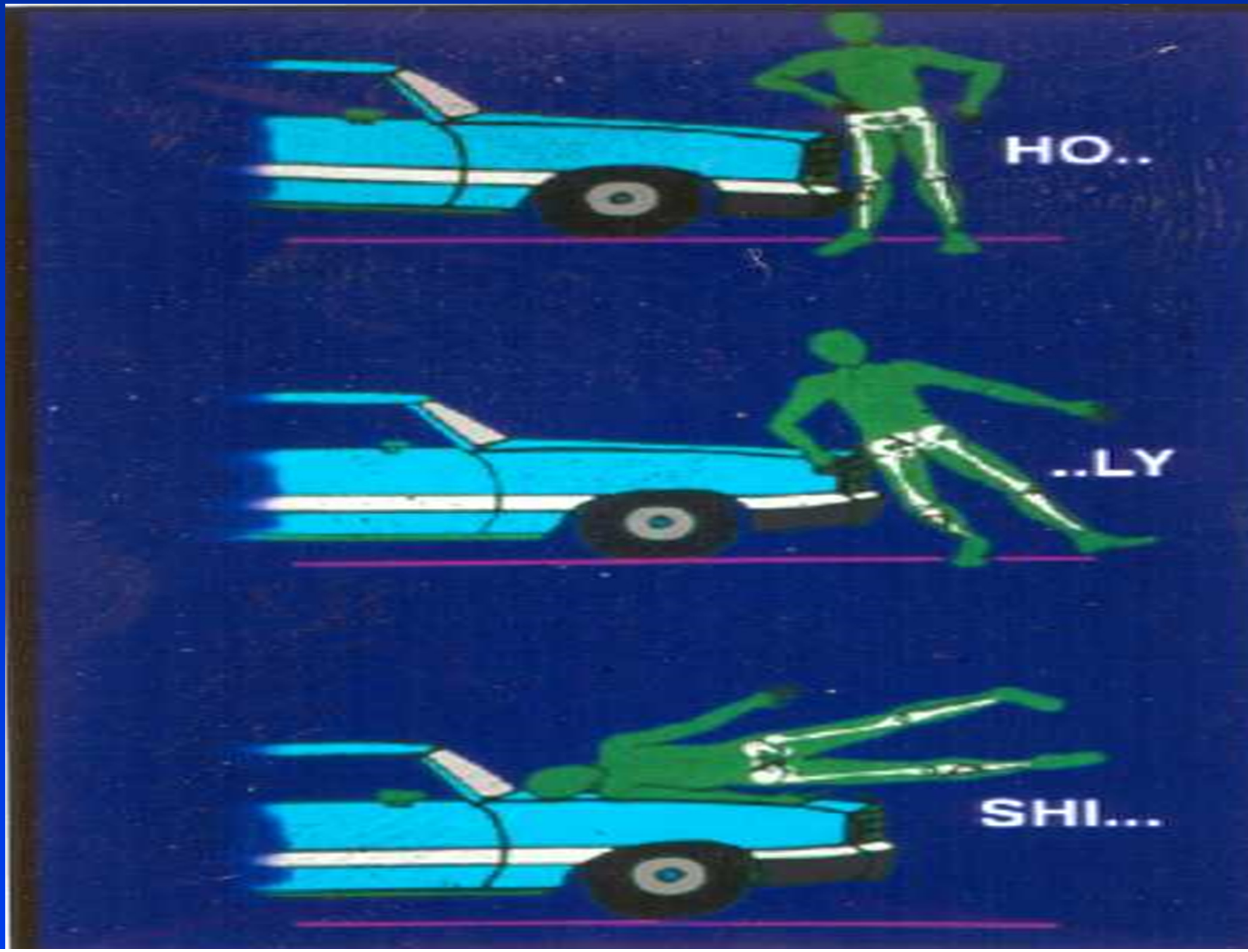
CUMULATIVE SODIUM BALANCE
(mEq/kg)
25
20
15
10
5
0
RL
HSL
PRE
OR
D0
D1
D2
D3
D4


800
700
600
500
400
300
200
100
0
SODIUM EXCRETION
(mEq)
p · 001
r 0.64
daf
0
50
100
150
200
250
300
350
POTASSIUM EXCRETION
(mEq)


UCSD


PATHOLOGIC PHYSIOLOGY
MEDICAL PHYSIOLOGY
MOSBY
CLINICAL
MAN
CPT
VASC TRM
LOCUS
DICTIONARY
ROGETS THESAURUS
S.R.Shackford M.D.
James W. Davis M.D
REGIONAL TRAUMA CENTE

Primary Brain Injury



Treatment of resistant intracranial hypertension with hypertonic saline. Report of two cases.

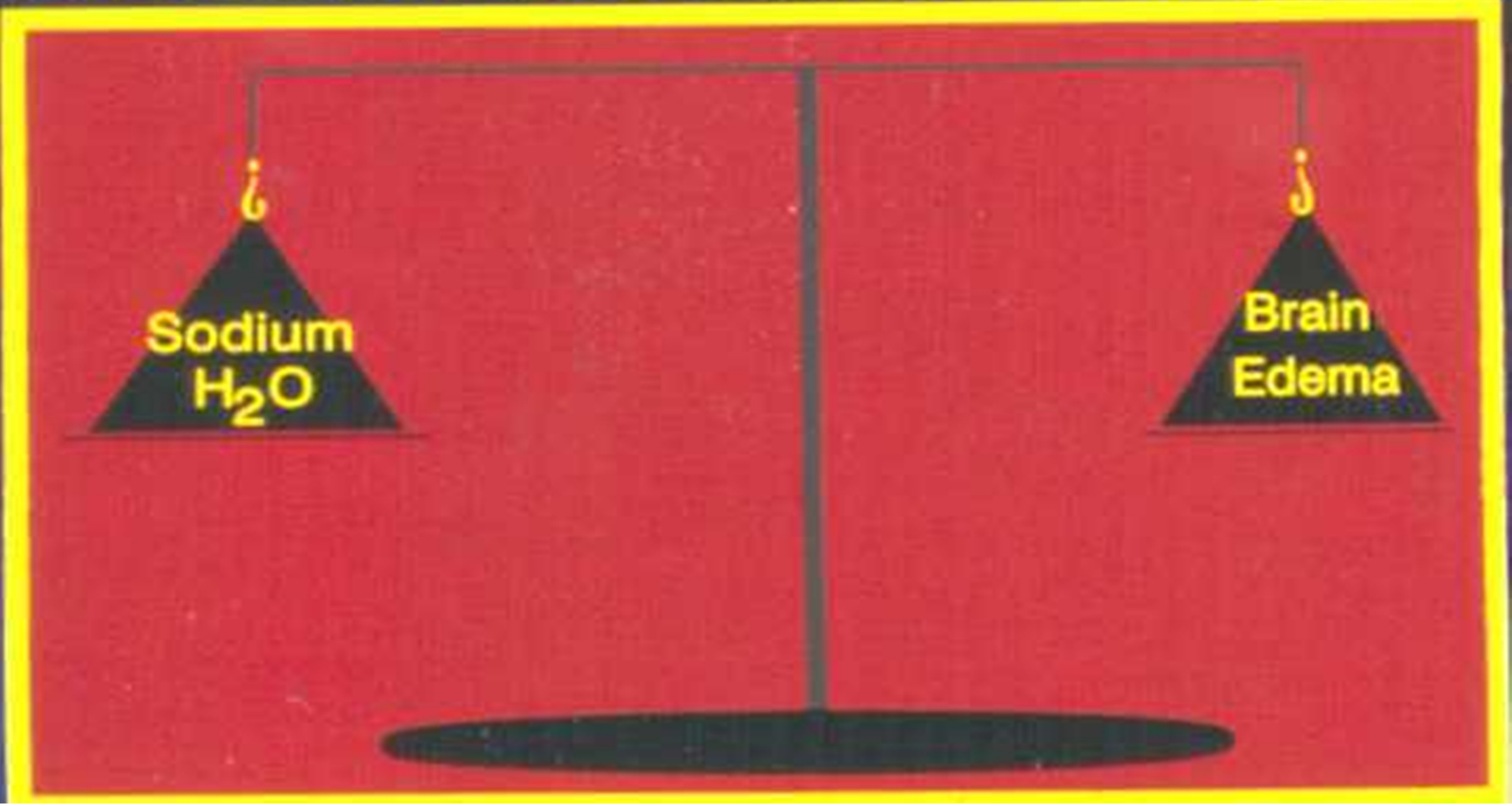
Worthley LI, Cooper DJ, Jones N.

Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital, South Australia.

***J Neurosurg* 1988; 68:478-481**

Abstract

FLUID RESUSCITATION IN THE HEAD INJURED PATIENT



Effect of a Hypertonic Lactated Ringer's Solution on Intracranial Pressure and Cerebral Water Content in a Model of Traumatic Brain Injury

MARK H. ZORNOW, M.D., MARK S. SCHELLER, M.D., AND STEVEN R. SHACKFORD, M.D.

J Trauma 1989; 29:484-488

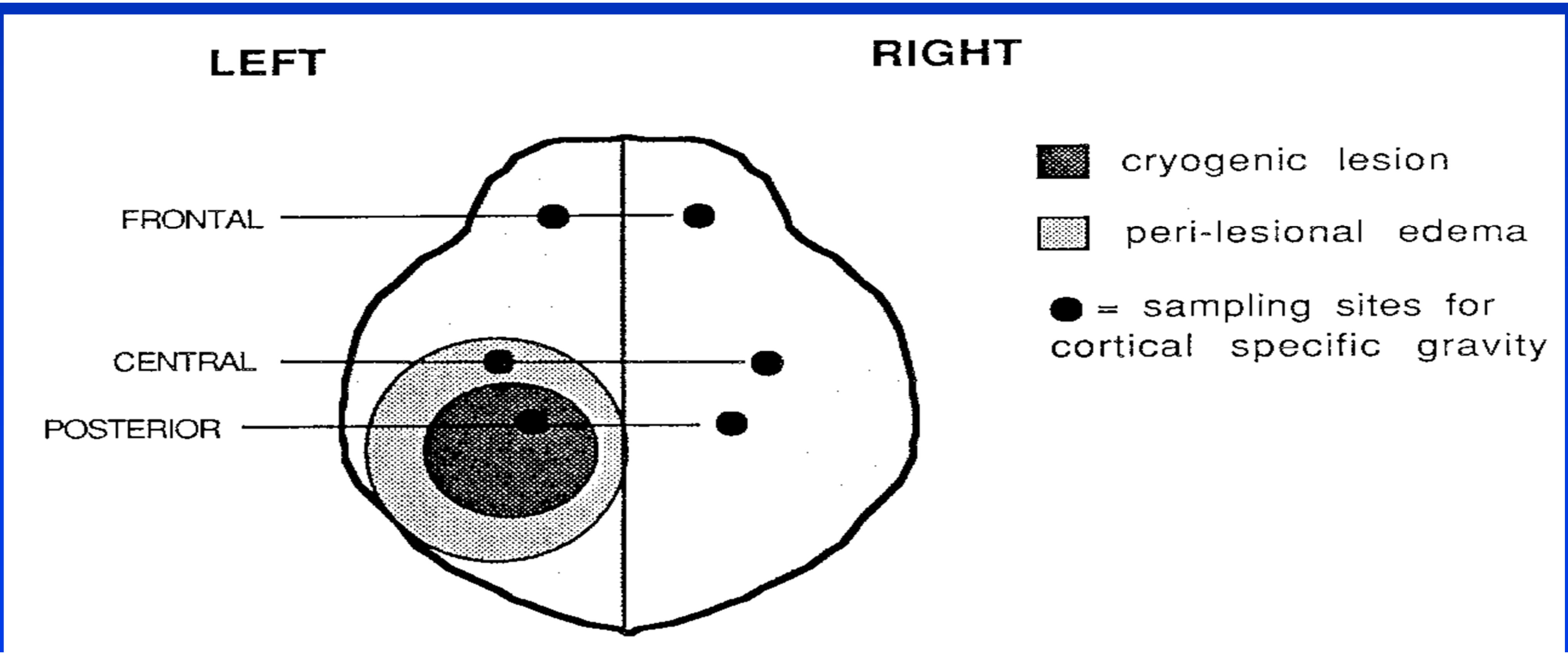
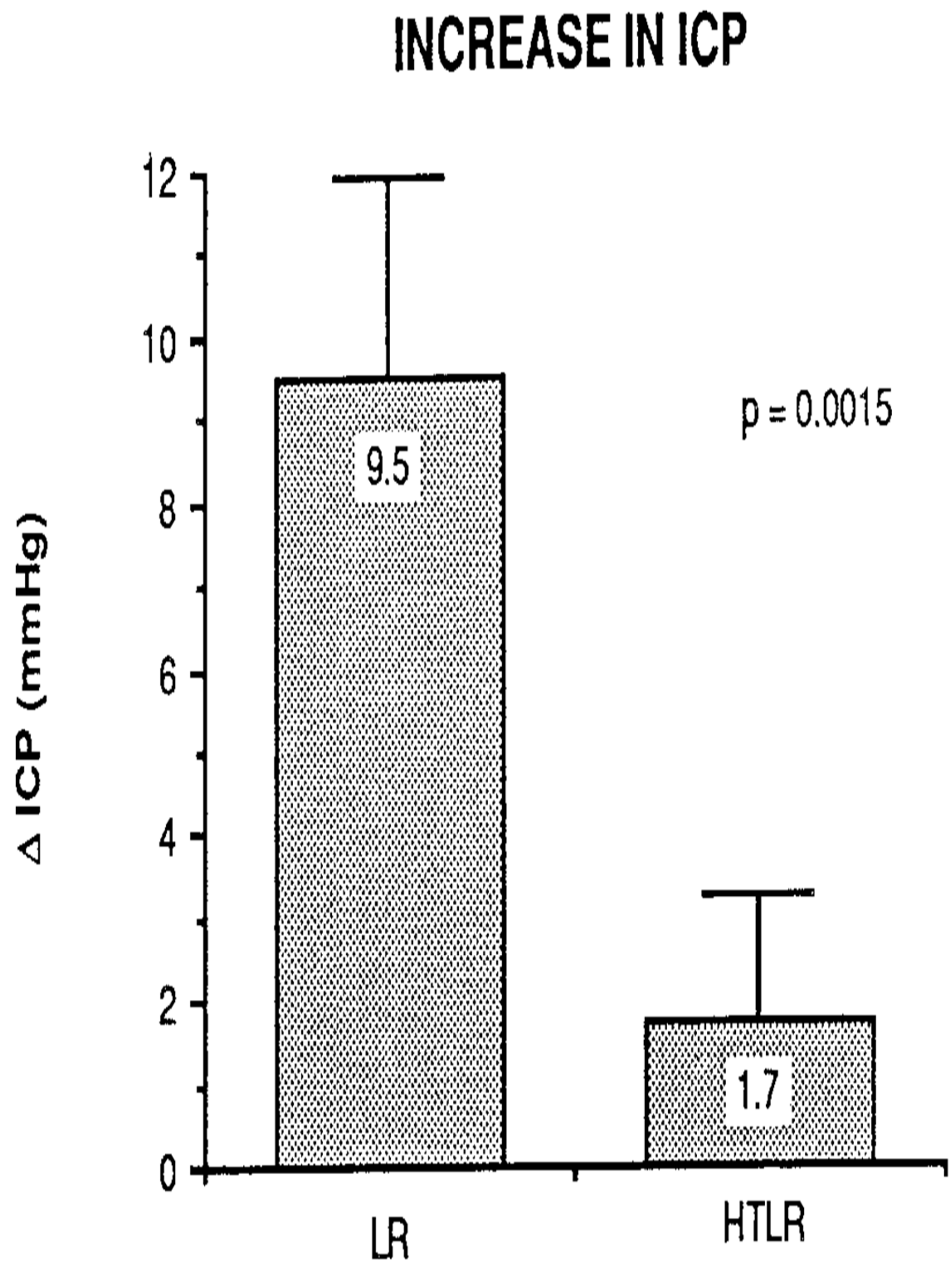
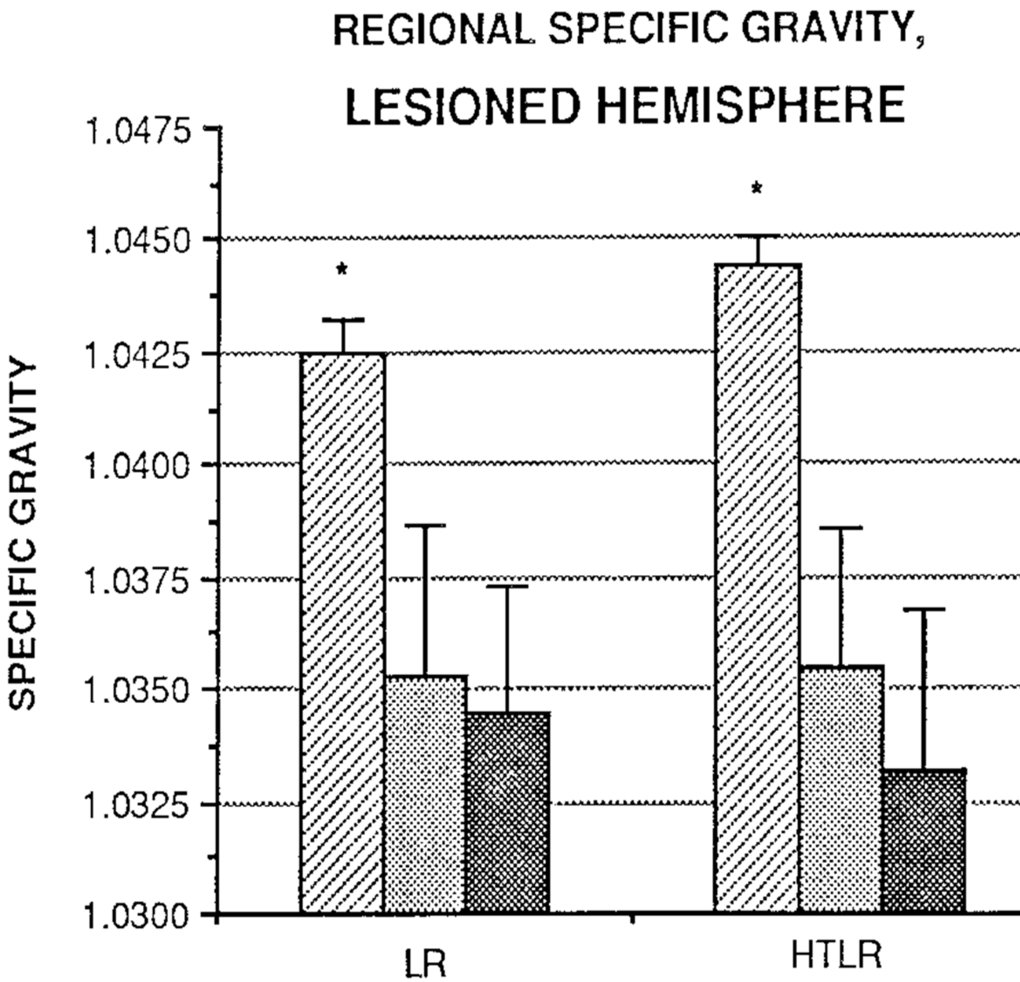


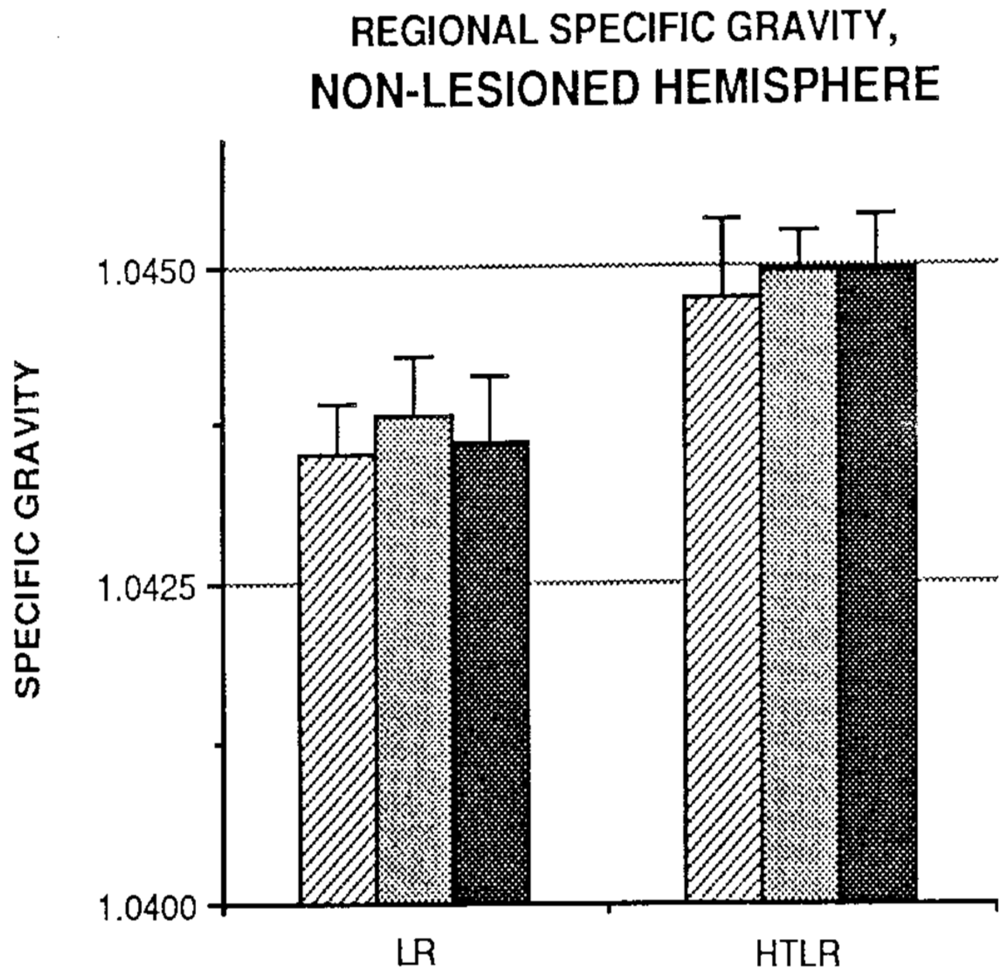
TABLE I
Post-hemodilution values

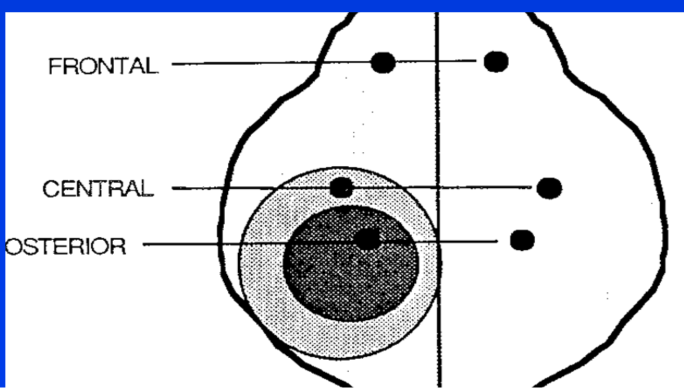
		LR	HTLR
MAP	(mm Hg)	87 ± 14	80 ± 8
CVP	(mm Hg)	3.5 ± 1.7	3.7 ± 1.7
Fluid in	(ml)	**245 ± 6**	**132 ± 20**
Blood out	(ml)	84 ± 3	82 ± 6
Serum Osm.	(mOsm/kg)	**293 ± 5**	**311 ± 5**
Na^+	(mEq/L)	**139 ± 4**	**155 ± 2**
HCT	(%)	23 ± 2	23 ± 2
COP	(mm Hg)	12 ± 1	11 ± 1
pH		7.33 ± 0.02	7.31 ± 0.03
$PaCO_2$	(mm Hg)	37 ± 2	38 ± 2
PaO_2	(mm Hg)	175 ± 14	170 ± 8

All values are Mean ± SD upon conclusion of hemodilution. Values in bold type denote a significant difference between the LR and HTLR groups ($p < 0.05$). COP = colloid oncotic pressure, Osm = osmolality.




REGIONAL SPECIFIC GRAVITY,
LESIONED HEMISPHERE
SPECIFIC GRAVITY
1.0475
1.0450
1.0425
1.0400
1.0375
1.0350
1.0325
1.0300
*
*
LR
HTLR


REGIONAL SPECIFIC GRAVITY,
NON-LESIONED HEMISPHERE
SPECIFIC GRAVITY
1.0450
1.0425
1.0400
LR
HTLR


FRONTAL
CENTRAL
OSTERIOR

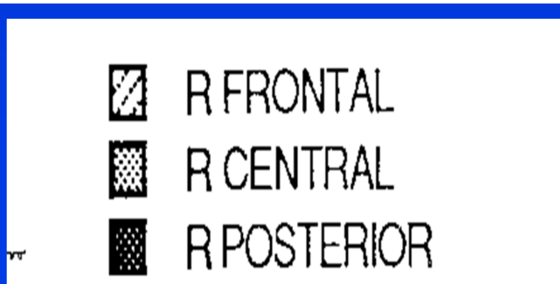

R FRONTAL
R CENTRAL
R POSTERIOR

Table 1. Prospective, Randomized Human Trials of Hypertonic Resuscitation Fluid

First author	Year	Population	n	Fluid	Outcomes
Holcroft[8]	1987	Prehospital trauma	49	7.5% NaCl/6% dextran-70	Improved SBP and overall survival
Holcroft[15]	1989	Hypotensive trauma	32	7.5% NaCl/6% dextran-70	No difference in survival
Vassar[9]	1991	Prehospital trauma patients, SBP < 100 mmHg	166	7.5% NaCl/6% dextran-70	Improved SBP and improved survival for TBI patients
Mattox[6]	1991	Prehospital trauma patients, SBP < 90 mmHg, 72% penetrating injury	359	7.5% NaCl/6% dextran-70	Improved SBP, trend toward improved survival, decrease in ARDS
Younes[16]	1992	Hypovolemic shock in ED, SBP < 80 mmHg	105	7.5% NaCl and 7.5% NaCl/6% dextran-70	Improved SBP, no difference in survival
Vassar[5]	1993	Prehospital trauma patients, SBP < 90 mmHg	258	7.5% NaCl and 7.5% NaCl/6% dextran-70	Improved survival versus predicted MTOS
Vassar[5]	1993	Prehospital trauma patients, SBP < 90 mmHg	194	7.5% NaCl and 7.5% NaCl/6% dextran-70	Improved survival versus predicted MTOS and for patients with TBI
Younes[10]	1997	Hypovolemic shock in ED	212	7.5% NaCl/6% dextran-70	Improved survival for patients with SBP < 70 mmHg
Cooper[11]	2004	Prehospital trauma patients with shock and TBI	229	7.5% NaCl/LR	No difference in 6 mo neurologic outcome, trend toward improved survival in hypertonic group
Bulger[12]	2006	Prehospital trauma patients with SBP < 90 mmHg	209	7.5% NaCl/6% dextran-70	Improved ARDS-free survival in patients receiving ≥ 10 U PRBCs

ED, emergency department; MTOS, Major Trauma Outcome Study; PRBCs, packed red blood cells; SBP, systolic blood pressure; TBI, traumatic brain injury.

The only hypertonic was given in the field

A Comparison of Hypertonic to Isotonic Fluid in the Resuscitation of Brain Injury and Hemorrhagic Shock[1]

JON C. WALSH, M.D.,* JING ZHUANG, M.D.,† AND STEVEN R. SHACKFORD, M.D., F.A.C.S.†

*†Department of Surgery, College of Medicine, University of Vermont, Burlington, Vermont 05405, and *Department of Surgery, College of Medicine, University of California, San Diego, La Jolla, California 92122*

J Surg Res 1991; 50:284-292

NINCDS 1-RO-1-NS 28637-01

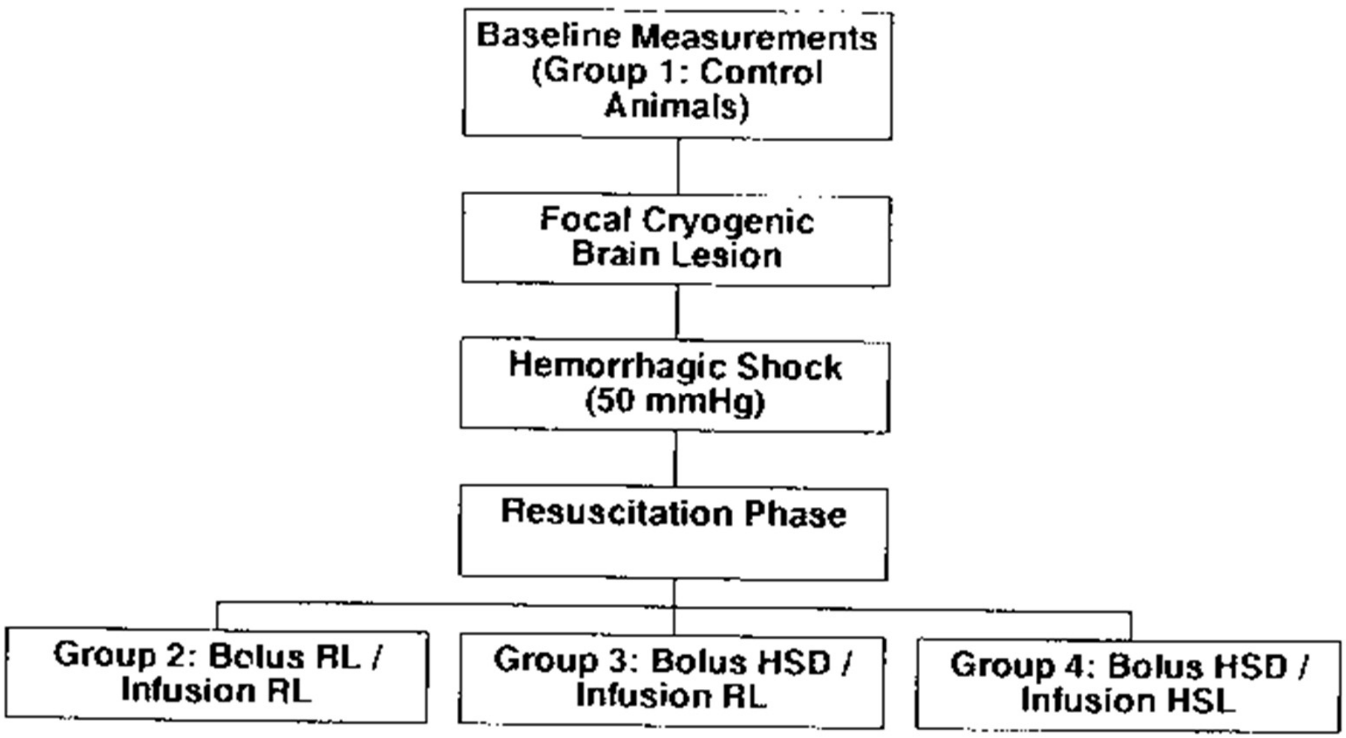
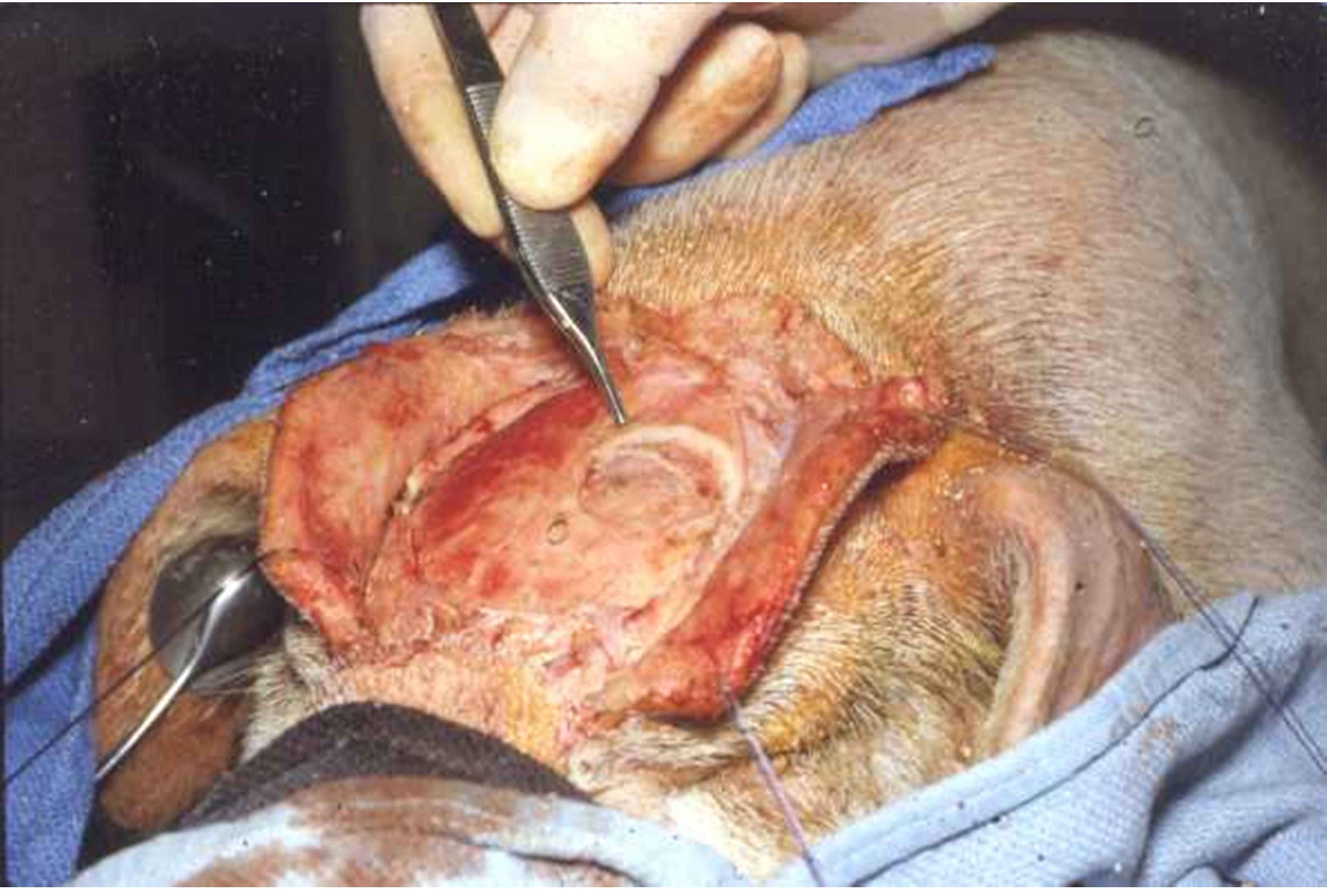
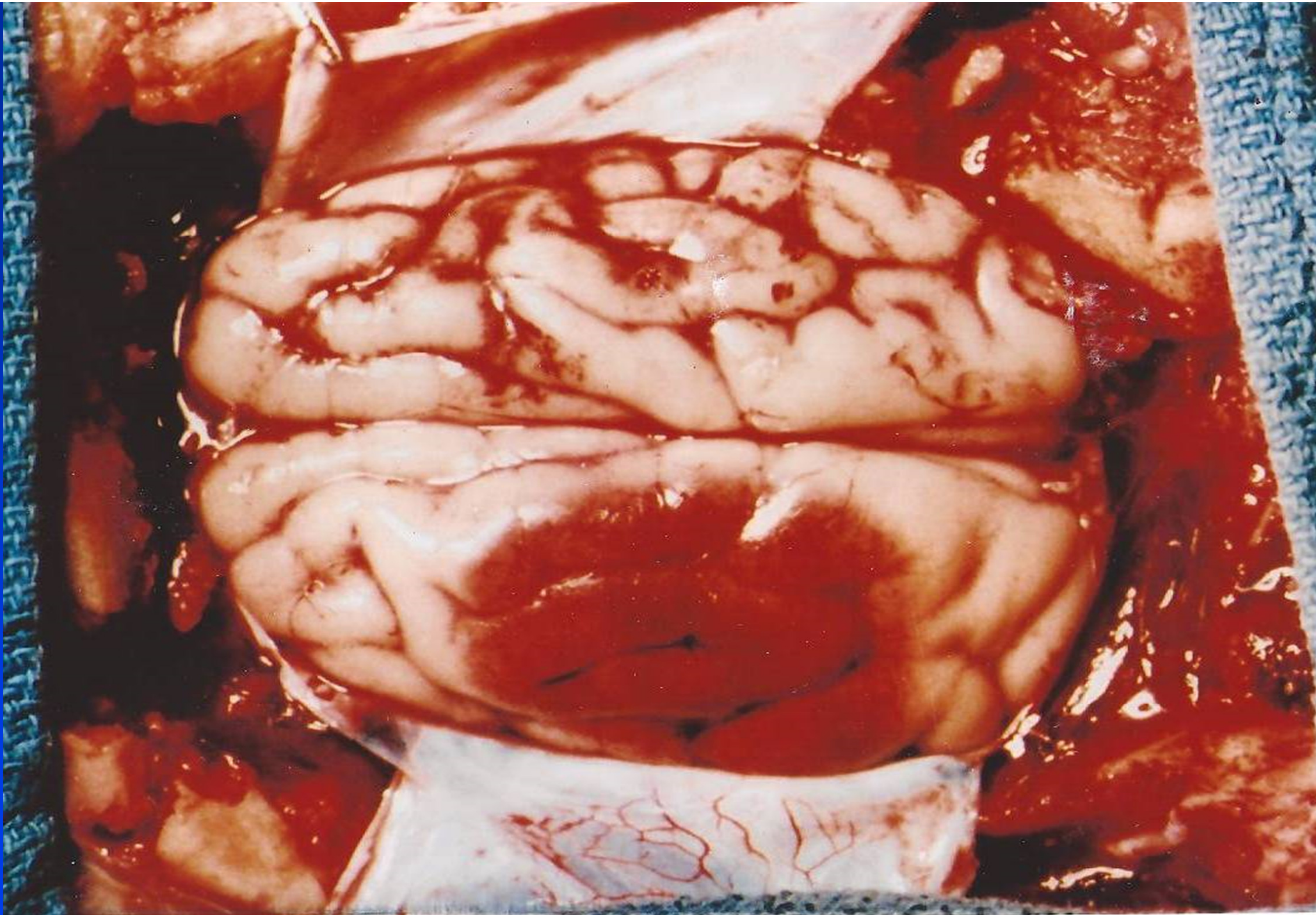
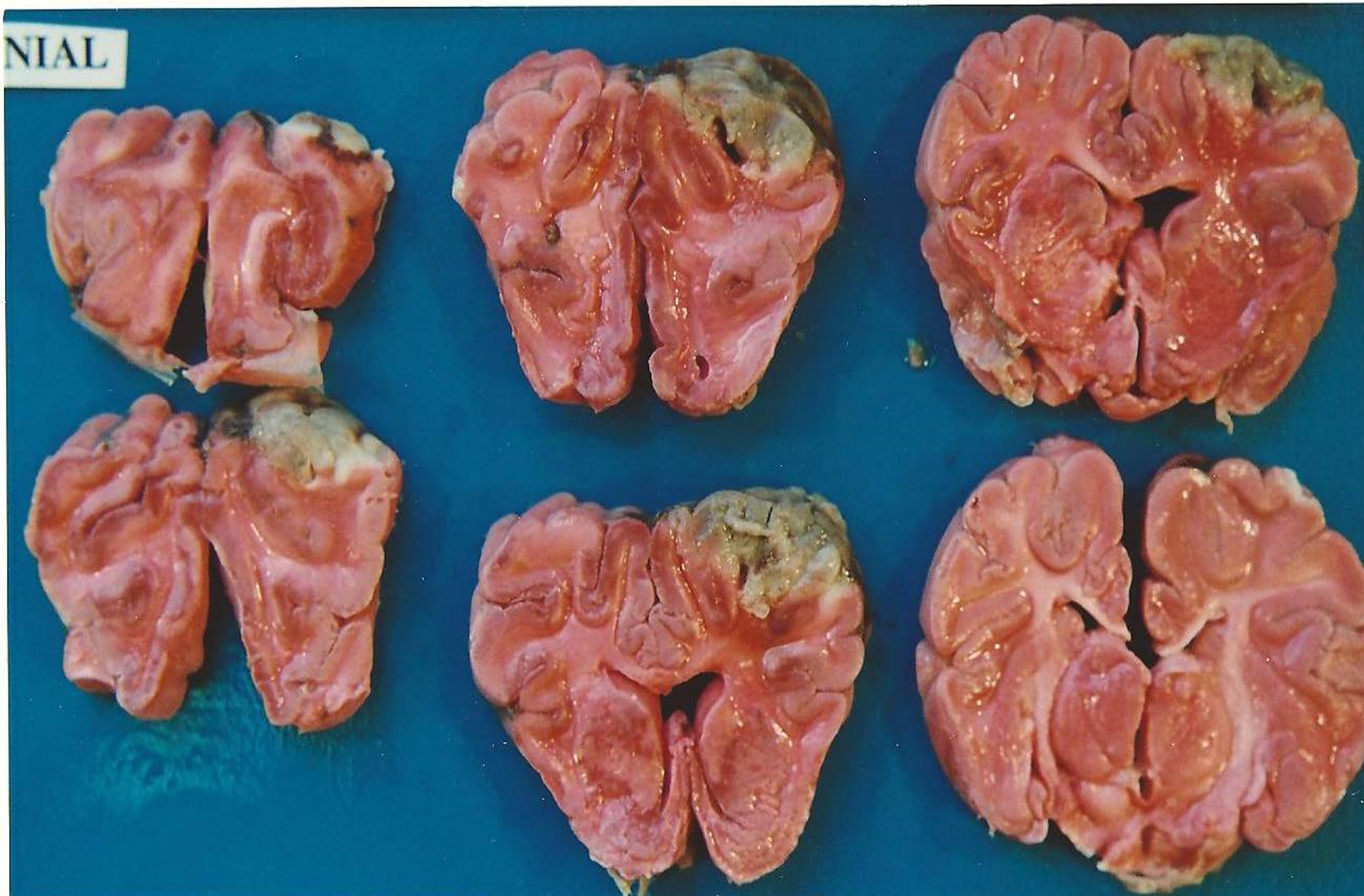
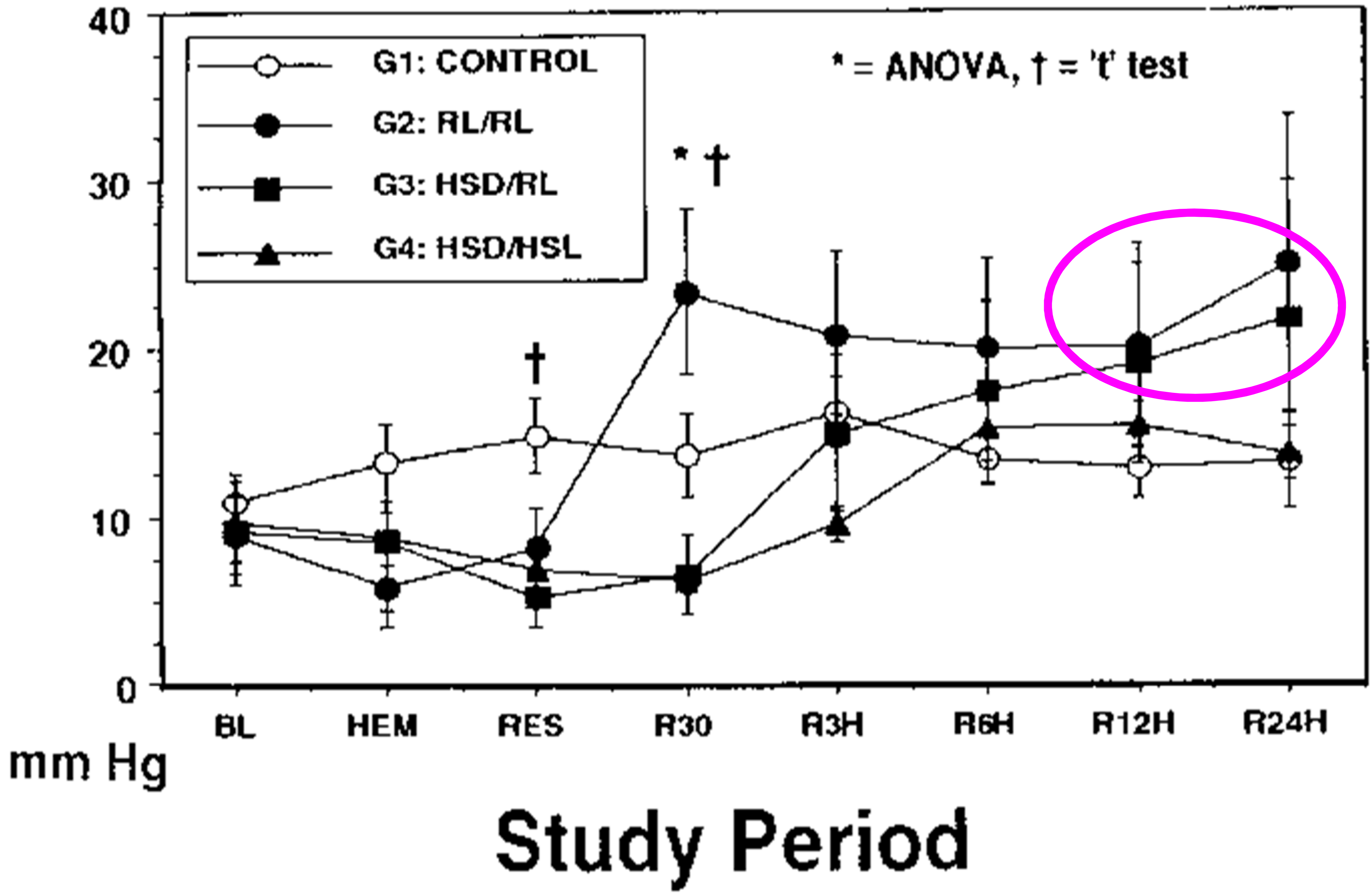


FIG. 2. A diagram of the experimental protocol. Control animals






NIAL



40
30
20
10
0
G1: CONTROL
G2: RL/RL
G3: HSD/RL
G4: HSD/HSL
* = ANOVA, † = 't' test
* †
†
BL
HEM
RES
R30
R3H
R6H
R12H
R24H
mm Hg
Study Period

Hypertonic Fluid Resuscitation Improves Cerebral Oxygen Delivery and Reduces Intracranial Pressure After Hemorrhagic

JOSEPH D. SCHMOKER, MD, ... ACKFORD, MD, FACS

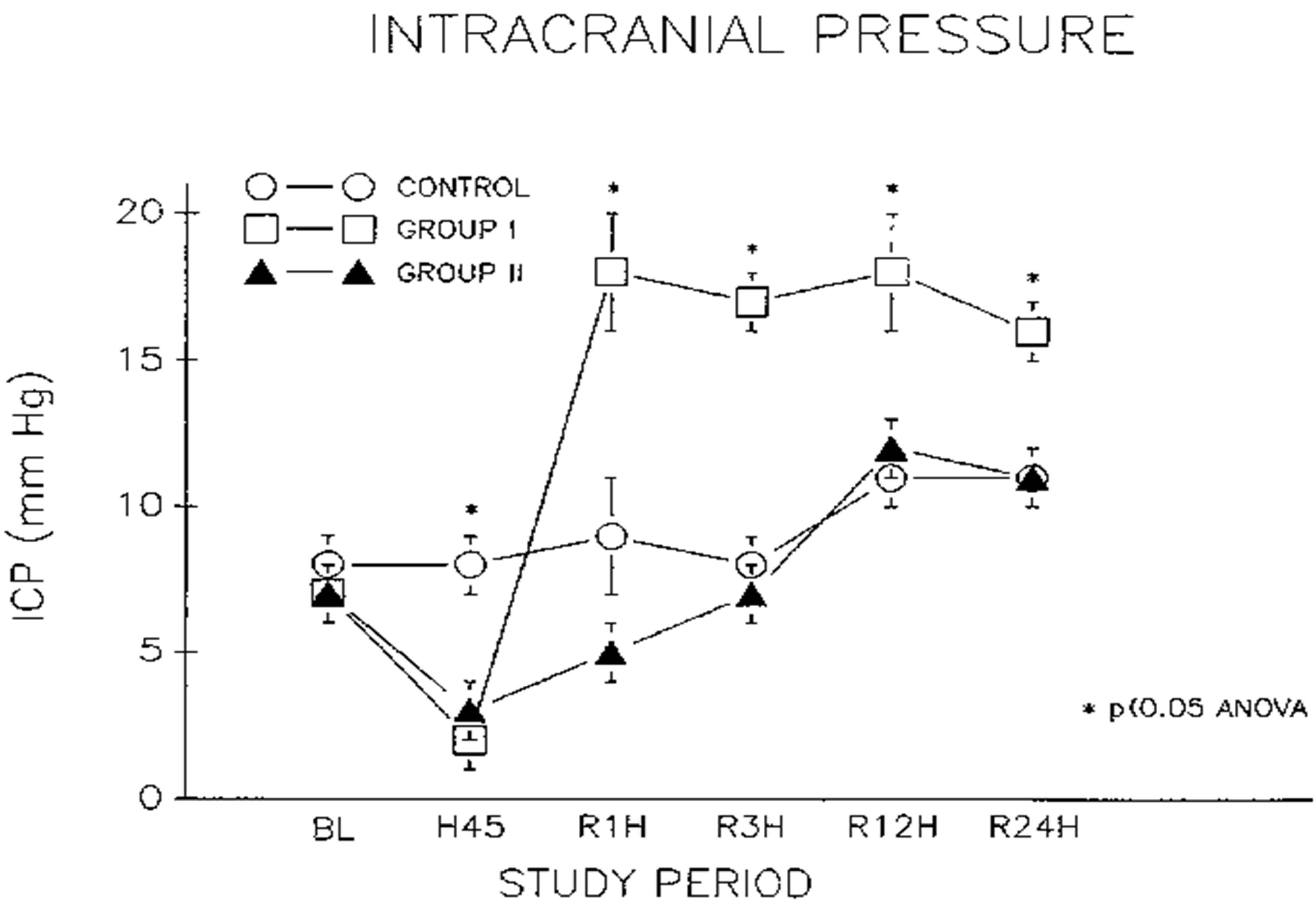
...991; 31:1607-1613

From the Departm... College of Medicine, Burlington...
Supported by a gr...
Presented at the ... n Trauma Association, Februar... oming.
Address for repri... artment of Surgery, The Fletche... f Vermont, Burlington, VT 0540...

Resident

Joseph Schmoker,

Joseph Schmoker,



INTRACRANIAL PRESSURE
CONTROL
GROUP I
GROUP II
ICP (mm Hg)
20
15
10
5
0
BL
H45
R1H
R3H
R12H
R24H
STUDY PERIOD
* p(0.05 ANOVA

The Effects of Hyperosmolarity on the Viability and Function of Endothelial Cells[1]

E. H. LUH, M.D., S. R. SHACKFORD, M.D., M. A. SHATOS, PH.D., AND J. A. PIETROPAOLI, M.D.

Department of Surgery, University of Vermont College of Medicine, Burlington, Vermont 05401

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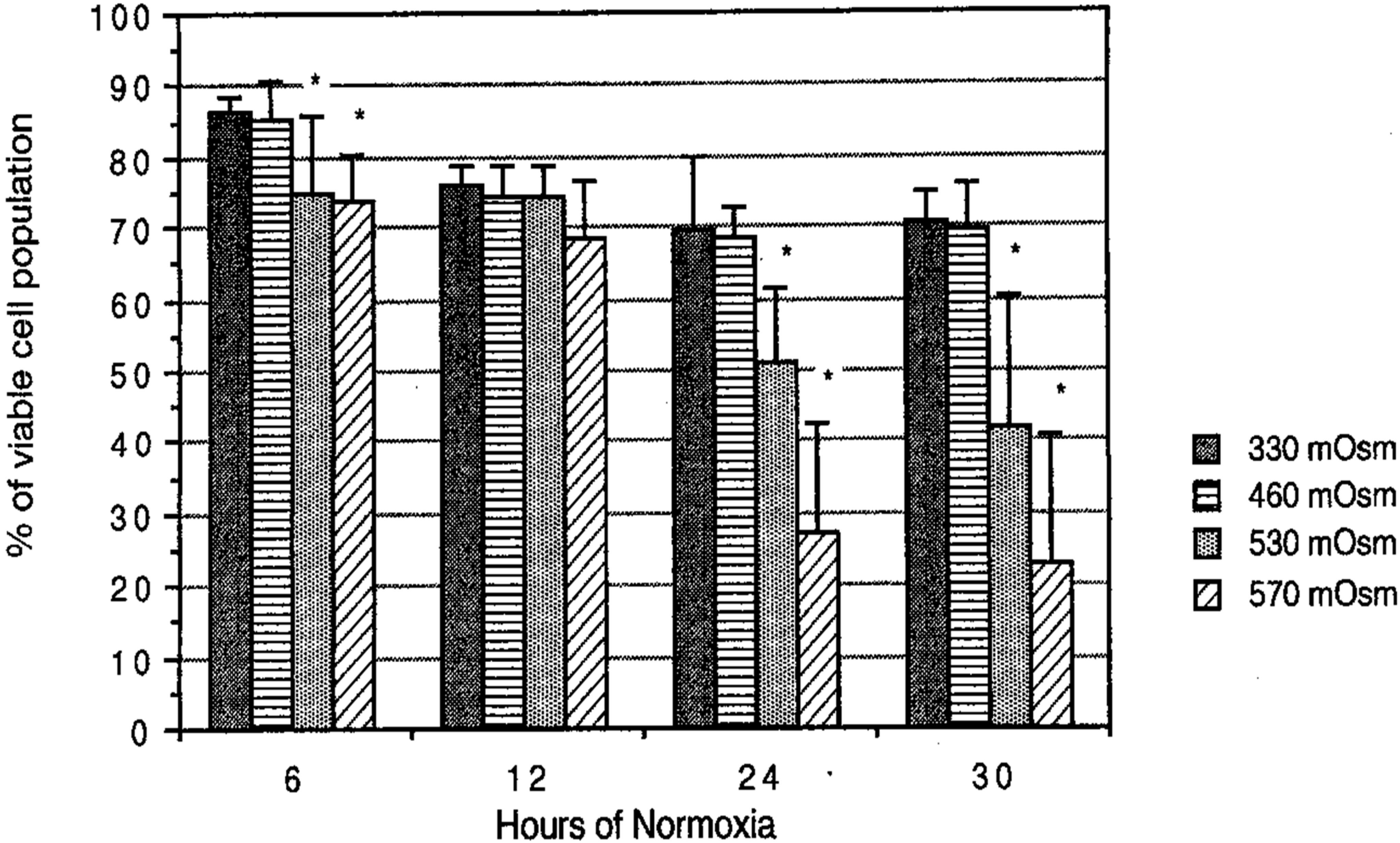
J Surg Res 1996; 60:122-126

- ***Tolerance of human cells unknown***
- ***Studied bovine AEC's in vitro:***
  - ***Normoxia***
  - ***Anoxia***
  - ***Anoxia and reperfusion***

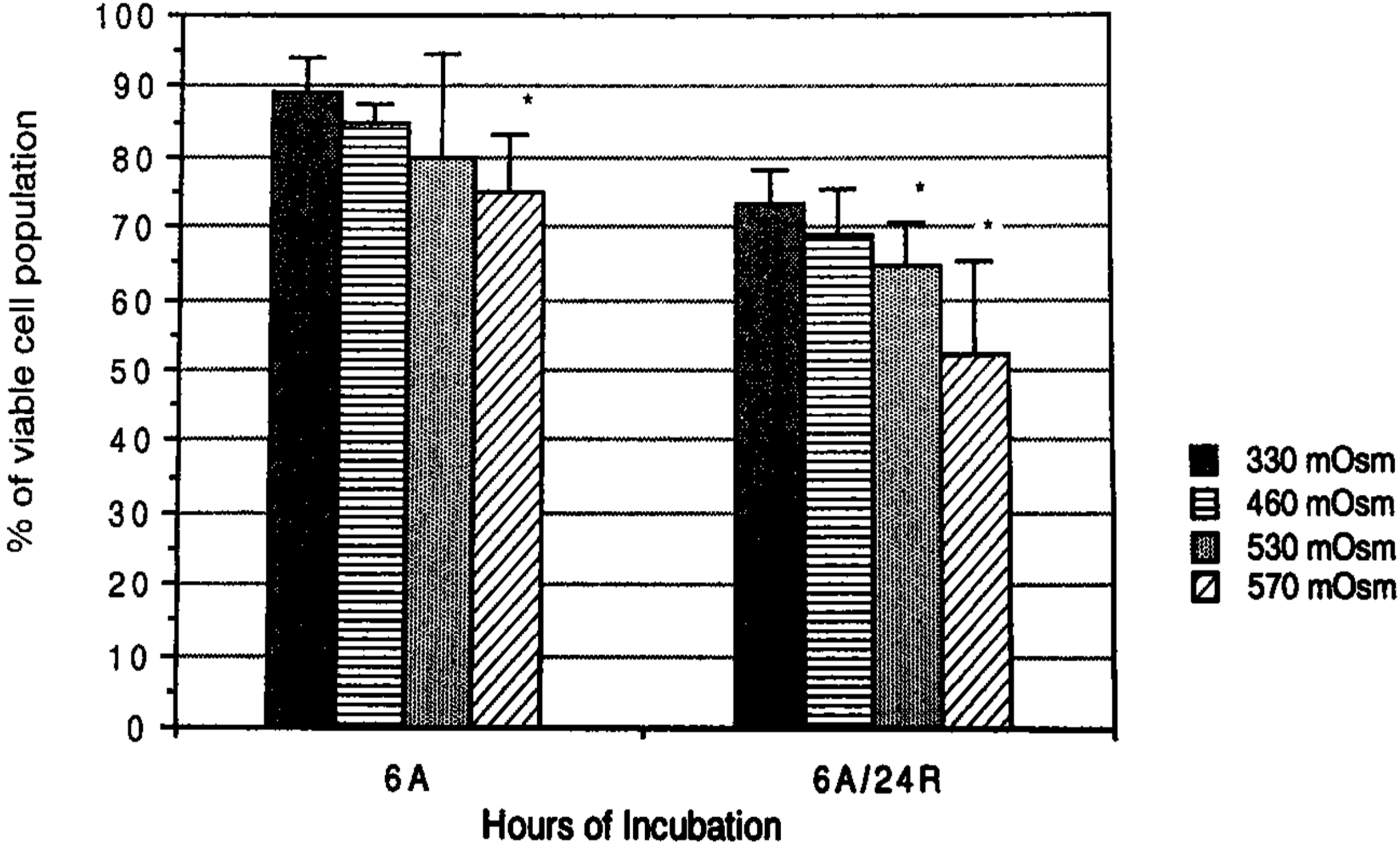
[1] Supported in part by Grant NINDS P20 NS30324-03 from the National Institutes of Health. Winner of the Association for Academic Surgery Student Research Award.

Methods

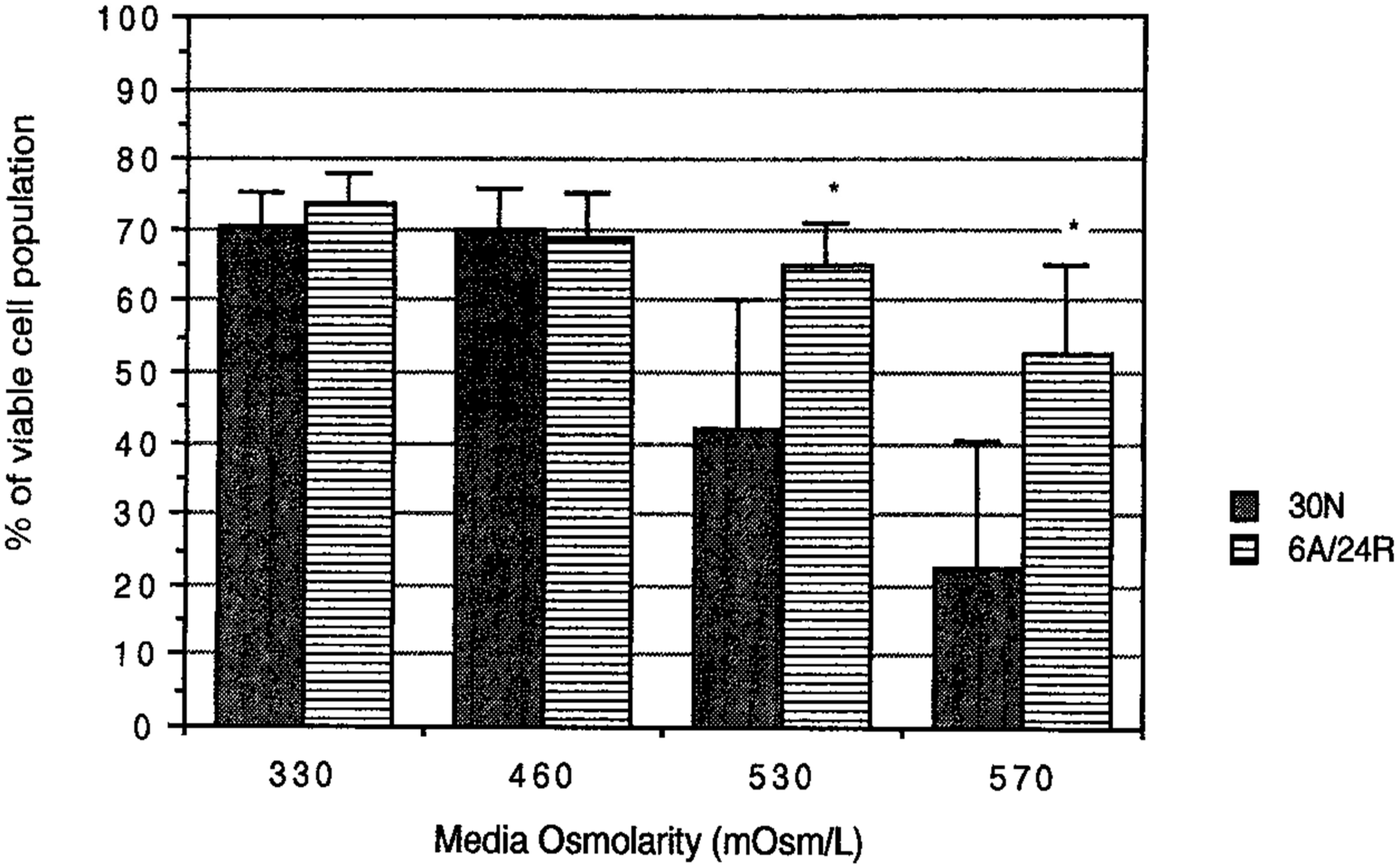
- *Compared mOsm: 330, 460, 530, 570*
- *Normoxia: 95% air, 5% CO_2 (30 h)*
- *Anoxia/reperfusion: 95% N_2, 5% CO_2 → normoxia (6 h/24 h)*
  - *Generates O_2 free radicals and lactate*
- *Viability and function determined*
  - *Trypan blue exclusion, replating efficiency*



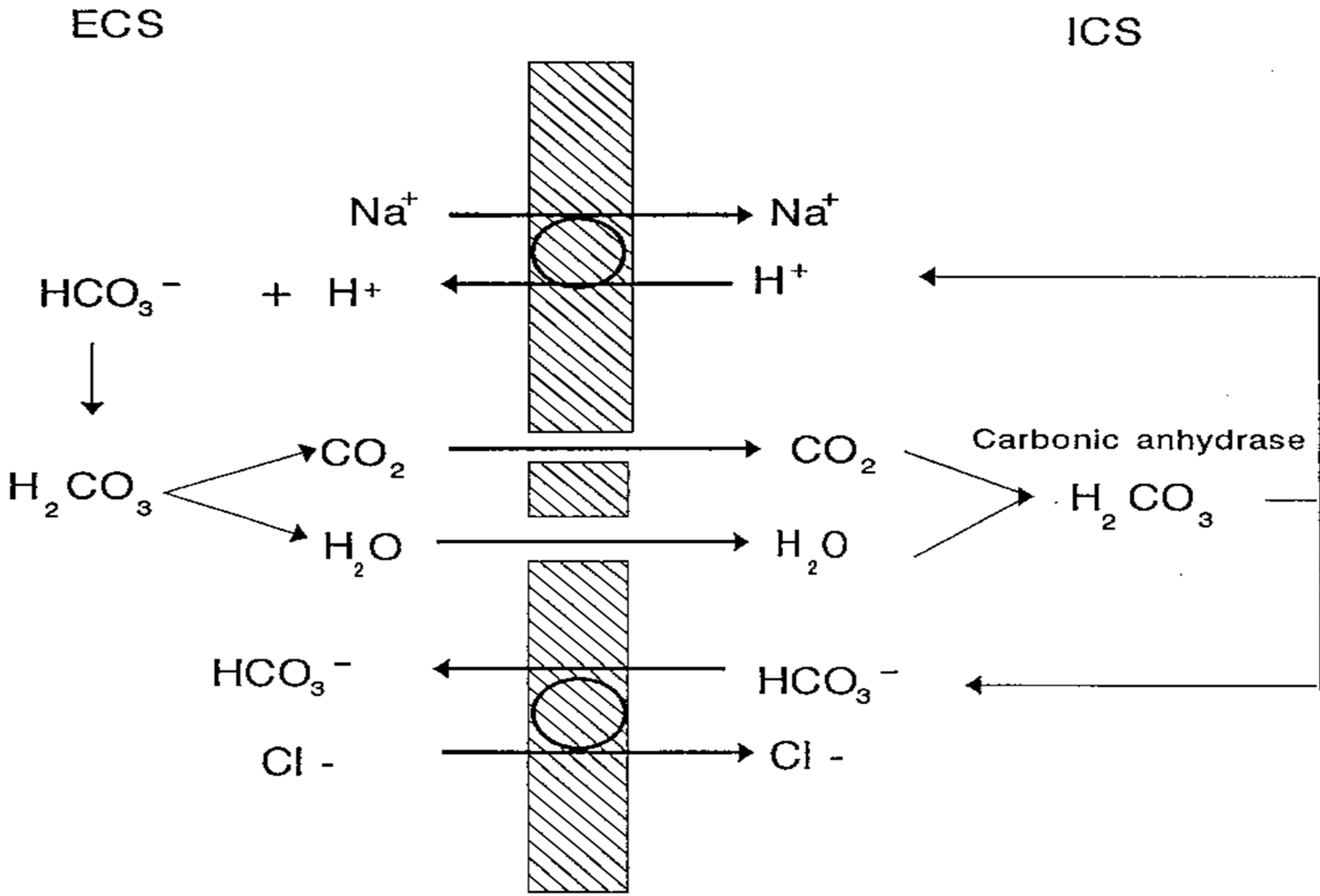
100
90
80
70
60
50
40
30
20
10
0
% of viable cell population
6
12
24
30
Hours of Normoxia
330 mOsm
460 mOsm
530 mOsm
570 mOsm



% of viable cell population
100
90
80
70
60
50
40
30
20
10
0
*
*
*
6A
6A/24R
Hours of Incubation
330 mOsm
460 mOsm
530 mOsm
570 mOsm



% of viable cell population
100
90
80
70
60
50
40
30
20
10
0
*
*
330
460
530
570
Media Osmolarity (mOsm/L)
30N
6A/24R


ECS
ICS
Na+
Na+
HCO3− + H+
H+
CO2
CO2
Carbonic anhydrase
H2CO3
H2CO3
H2O
H2O
HCO3−
HCO3−
Cl -
Cl -

Conclusions

- ***BAEC's are tolerant of an osmolarity of up to 430 mOsm/L***
- ***Viability/replating in hypertonic media unaffected by simulated shock and resuscitation***
- ***Hyperosmolar tolerance a consequence of evolution from a salt water envirnoment?***

Summary of literature

- *HSL improves cardiac function with less fluid requirement*
- *Improves CBF and cerebral O2 delivery while lowering ICP*
- *Lowers intramuscular compartment pressures*
- *Does not require free water administration*
- *Safe: not a single reported case of CPM*

Hypertonic Solutions in Modern Trauma Care

- *Brain injury to control ICP*
- *Brain injury associated with hypotension*
- *Adjuvant crystalloid for DCR*
  - *1:1 increases μ, hypertonic reduces μ*
  - *Improved capillary flow*
- *Earlier fascial closure*
- *Hemodynamic instability in the elderly*

Hypertonic Solutions in Modern Trauma Care (cont'd)

- *Patients at risk for leg compartment syndromes*
- *Whenever size matters…*
- *Hypertonic solutions:*
  - *3%, 5% FDA approved, but not in common use*


ROAD
CLOSED
AHEAD
2836
A