The Myth of the Third Space

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Objectives

- Discuss the origins of IV fluid therapy in children
- Debate the existence of a third space
- Discuss IV fluid therapy and the risks of postoperative hyponatremia

Intravenous therapy – a historical perspective

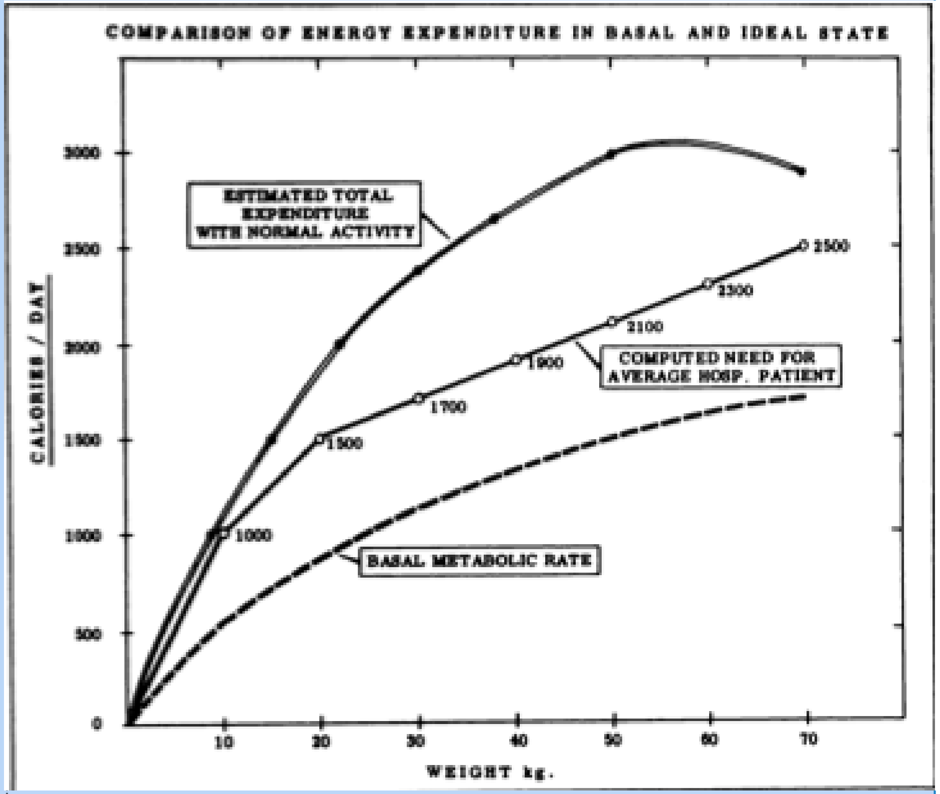
- 1613 Harvey described the circulatory system
- Mid 1600s Wren and Boyle designed the first "hypodermic" needle
- 1662 Major injected the first medicinal substance intravenously
- 1667 Lower performed the first blood transfusion with lamb blood

Intravenous therapy – a historical perspective

- 1818 Blundell performed first human to human blood transfusion
- 1831 O'Shaughnessy published landmark article in Lancet about fluid and solute deficits in cholera victims
- 1832 Latta reported that he had successfully resuscitated numerous moribund cholera patients with intravenous water and salts

Intravenous therapy – a historical perspective

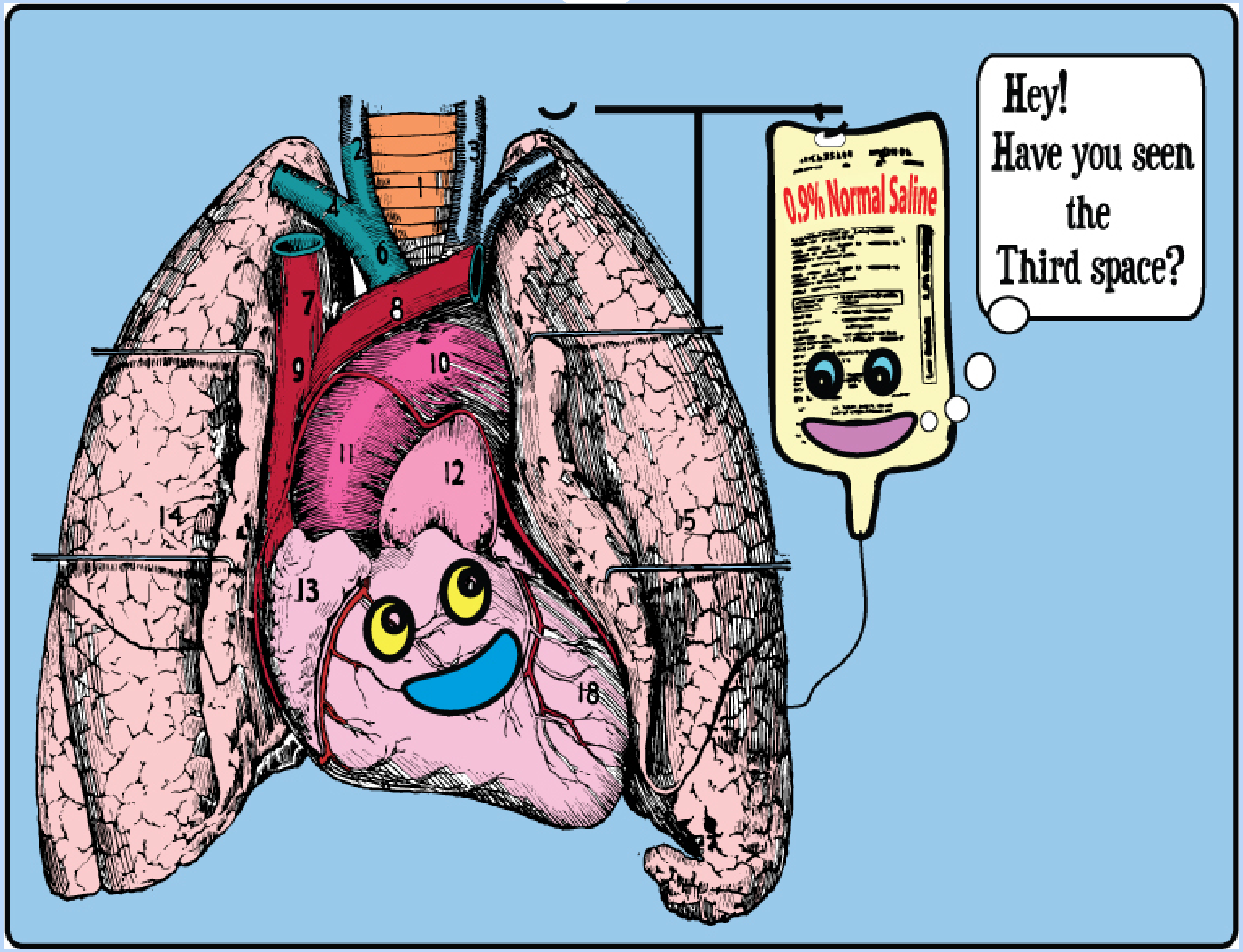
- 1918 Blackfan and Maxcy instilled 0.8% saline intraperitoneally to dehydrated infants
- 1931 Karelitz and Schick administered D5NS or D5LR intravenously via continuous infusion to dehydrated infants
- 1957 Holliday and Segar described the first practical method for the prescription of IV fluids



Intravenous therapy – perioperative practice

- The goals of perioperative intravenous fluid therapy
  - Replace preoperative deficits
  - Provide maintenance fluid therapy
  - Replace ongoing blood loss
  - Replace insensible losses
  - Replace third space losses

The third space – fact or fiction



The third space - defined

- Refers to sequestration of fluid in a non-functional extracellular space that is beyond osmotic equilibrium with the vascular space

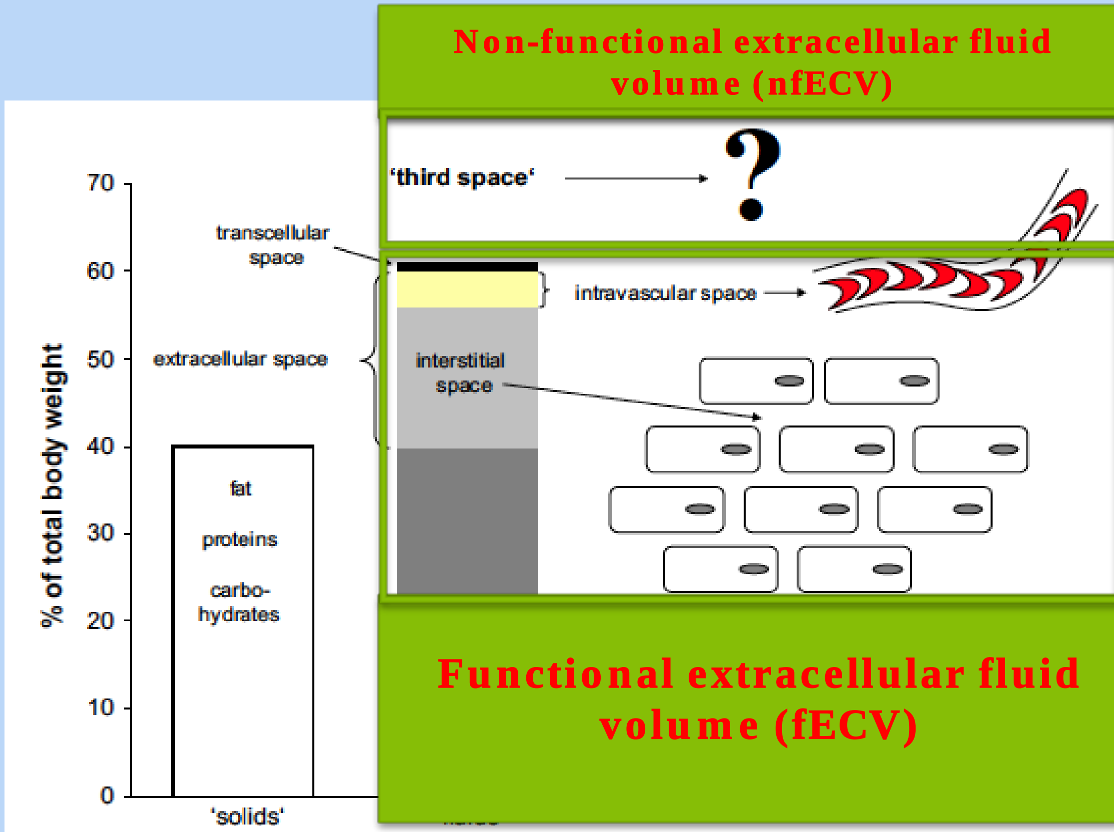


Fig. 1. Composition of the body compartments.

The third space – pediatric literature

Perioperative fluid therapy in pediatrics

Pediatric Anesthesia, 2008

- Third space losses
  - 1 ml/kg/hr for minor surgical procedures
  - 15-20 ml/kg/hr for major abdominal procedures
  - Up to 50 ml/kg/hr for surgery for necrotizing enterocolitis
- Children have a larger extracellular fluid volume
  - Neonates, ECV is 45 % of body weight
  - 1 year old, ECV is 30% of body weight
  - Adults, ECV is 20% of body weight

The third space – fact or fiction

Acute change in extracellular fluids associated with major surgical procedures

Annals of Surgery, 1961

- 13 adults, elective major surgical procedures
- Plasma volume, red blood cell mass, and extracellular fluid volume (ECV) measured preoperatively and after two hours of operative time
- Loss of ECV (up to 28%), presumed from internal redistribution to the third space
- Extracellular fluid volume loss correlated with amount of observed surgical trauma

The third space – fact or fiction

- Extracellular volume determination via tracer technique
  - Requires suitable tracer
  - Requires appropriate equilibration time
  - Requires multiple samples
  - Requires steady state conditions

The third space – fact or fiction

- Few subsequent trials reported a third space loss during surgery or hemorrhagic hypotension
  - Utilized the sulfate $^{35}SO_4$ tracer to estimate fECV
  - Calculated fECV from a single or very few blood samples
  - Calculated fECV after short equilibration times

The third space – fact or fiction

- Numerous trials report an unchanged or increased fECV after surgery
  - Utilized different tracers (i.e. Bromide)
  - Calculated fECV from multiple blood samples
  - Calculated fECV after longer equilibration times

The third space - FICTION

- The classic "third space" has never been localized
- The classic "third space" does not exist
- Fluid is shifted within the functional extracellular fluid compartment, from the intravascular space to the interstitial space

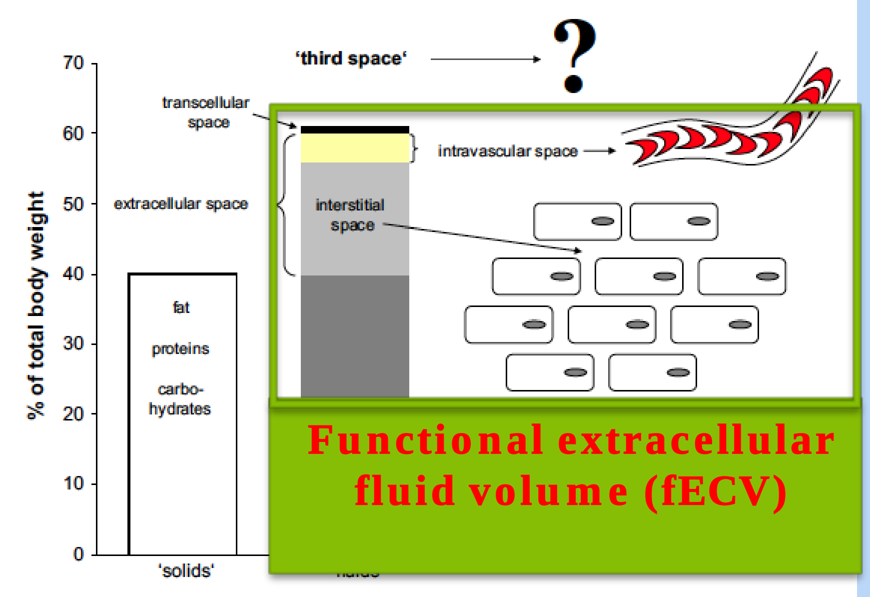


Fig. 1. Composition of the body compartments.

Perioperative fluid shift - implications

- Does surgery and trauma cause the fluid shift?
- Does aggressive perioperative fluid therapy make the fluid shift worse?
- Does aggressive perioperative fluid therapy impact patient outcomes?
- Should we reevaluate our practice?

Perioperative fluid shift - implications

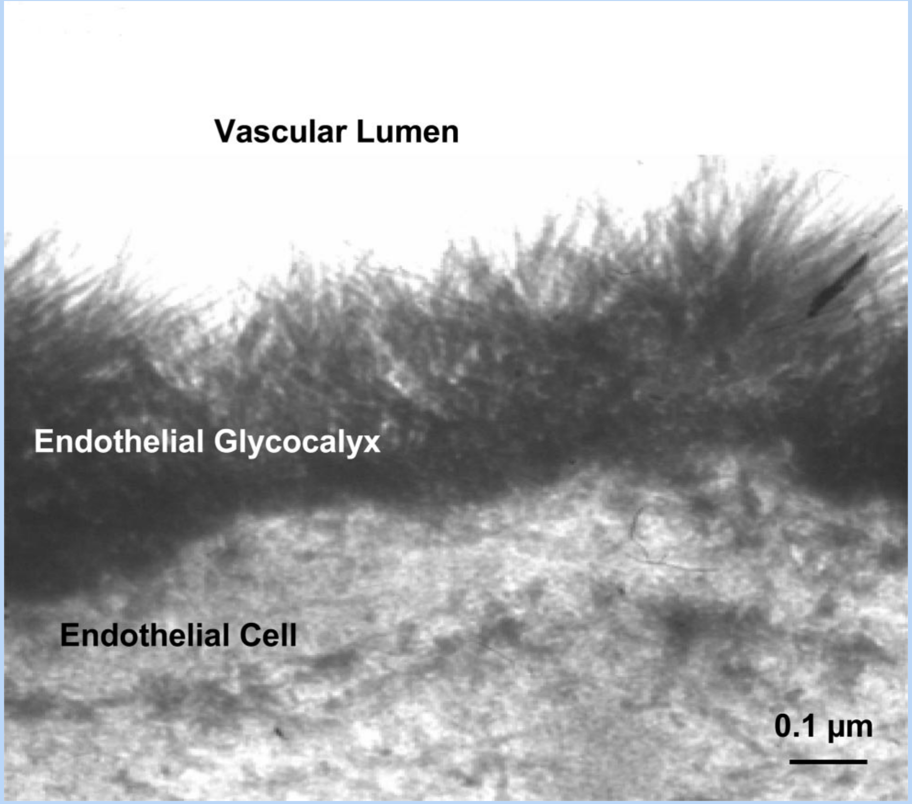
Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses

British Journal of Surgery, 1983

- Water content of enteral anastomosis measured in rabbits
- Group 1
  - Received no IV fluid therapy
  - Interstitial water load increased by 5-10%
- Group 2
  - Received 5 mL/kg/hr intraoperatively of crystalloid infusion
  - Interstitial water load double that of Group 1

Perioperative fluid shift - implications

- Surgical trauma increases the protein permeability of the vascular endothelium
  - Mechanical stress
  - Endotoxin exposure
  - Ischemia-reperfusion injury
  - Inflammation
- Acute hypervolemia from liberal fluid therapy alters the endothelial glycocalyx



Perioperative fluid shift - implications

Effects of intravenous fluid restriction on postoperative complications: Comparison of two perioperative fluid regimens
Annals of Surgery, 2003

- 141 adult patients, major colorectal surgery

	Restricted regimen	Standard regimen
Epidural	No preloading	500 ml HAES 6%
Loss to third space	No replacement	Replaced by NaCl 0.9% 7 ml/kg first hour 5 ml/kg hours 2 and 3 3 ml/kg following hours
Insensible losses during fast	500 ml glucose 5% - oral intake the previous 6 hours	500 ml NaCl 0.9%
Blood loss	Volume to volume with HES 6% Blood component therapy started at loss >1500 ml	$\leq$ 500 ml: 1000–1500 NaCl 0.9% > 500 ml: additional HES 6% Blood component therapy started at loss >1500 ml

Perioperative fluid shift - implications

Effects of intravenous fluid restriction on postoperative complications: Comparison of two perioperative fluid regimens

Annals of Surgery, 2003

- Restricted group: significant reduction in postoperative complications such as anastomotic leakage, pulmonary edema, pneumonia, and wound infection

Postoperative hyponatremia

- Case
  - 10 yo male trauma patient
  - Intubated for respiratory distress
  - Peri-intubation aspiration noted
  - To OR for left foot ORIF
  - 4 days mechanical ventilation for aspiration PNA
  - Surgical team prescribed D5 ½ NS post transfer to floor
  - Rapid response for acute mental status changes
  - Tonic-clonic seizure while in the CT scanner
  - Serum Na 116

Postoperative hyponatremia

- Children are at greater risk for cerebral edema
  - Difference in the ratio of intracranial capacity to brain size
  - CSF fluid volume relatively smaller
  - Brain intracellular concentration of sodium 27% higher

Postoperative hyponatremia

- What is the cause?
  - Retention of free water and excretion of hypertonic urine in the presence of increased ADH

Hemodynamic stimuli	Nonhemodynamic stimuli
Hypovolemia - vomiting, diarrhea, diuretics, renal salt wasting, hypoaldosteronism **Hypervolemia** - nephrosis, cirrhosis, congestive heart failure, hypoalbuminemia **Hypotension**	**CNS disturbances -** meningitis, encephalitis, stroke, brain abscess, head injury, hypoxic brain injury **Pulmonary diseases -** pneumonia, asthma, tuberculosis, empyema, COPD, bronchiolitis, ARF **Cancers -** lung, brain, CNS, head, neck, breast, GI tract, GU tract, leukemia, lymphoma, thymoma, and melanoma **Medications -** cyclophosphamide, vincristine, morphine, SSRIs, carbamazepime **Other -** nausea, emesis, pain, stress, postoperative state, cortisol deficiency

Postoperative hyponatremia

- What is the cause?
  - Administration of hypotonic fluids

Fluid	Na^+ mEq/L	Cl^- mEq/L	Tonicity
Lactated Ringers	130	109	Hypotonic (slightly)
Normal Saline (NS)	154	154	Isotonic
D5W	0	0	Hypotonic
D5 ¼ NS	34	34	Hypotonic
D5 ½ NS	77	77	Hypotonic

Postoperative hyponatremia

Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population

Critical Care Medicine, 1983

- 24 postoperative pediatric patients from spinal fusion
- 20 patients received hypotonic fluids postoperatively
  - Serum sodium dropped 6.2 +/- 2.9 mEq/L
  - 5 patients developed SIADH
- 4 patients received isotonic fluids postoperatively
  - Serum sodium dropped 3.0 +/- 0.8 mEq/L

Postoperative hyponatremia

Hospital-acquired hyponatremia in postoperative pediatric patients: Prospective observational study

Pediatric Critical Care Medicine, 2010

- 81 postoperative pediatric patients
- Prescribed hypotonic maintenance fluids (Na 40 mmol/L) per Holliday and Segar method
- Incidence of hyponatremia 21% at 12 hours and 31% at 24 hours

Postoperative hyponatremia

Prevention of hyponatremia during maintenance intravenous fluid administration: A prospective randomized study of fluid type versus fluid rate

The Journal of Pediatrics, 2010

- 124 postoperative pediatric patients
- 0.9% NS or 0.45% NS at 100% or 50% maintenance rates
- ADH concentration increased similarly across all groups
- Serum sodium decreased > 2 mmol/L in greater than 50% of the 0.45% groups versus 20% in the 0.9% groups
- The incidence of hyponatremia was not influenced by fluid rate
- No hypernatremia was observed in either group

Postoperative hyponatremia

National Patient Safety Agency

Patient safety alert 22: Reducing the risk of hyponatremia when administering IV infusions to children

- Safety alert called for the removal of all sodium chloride 0.18% with glucose 4% intravenous infusions from stock and general use in areas that treat children.
- The use of intravenous hypotonic solutions puts children at a greater risk of developing life-threatening hyponatremia than other types of fluid and should be prescribed with caution. All children are at risk. Wherever possible, carefully managed oral fluids are preferable to intravenous fluid therapy.
- Hyponatremia can develop within a short time frame. A robust fluid monitoring regime is essential.
- Intravenous fluids should be prescribed with the same rigor as other prescription medicines, particularly in respect of the volume given.
- Hyponatremic encephalopathy is a medical emergency and should be treated using hypertonic intravenous fluids under senior medical supervision.

Postoperative hyponatremia

Hospital-Acquired Hyponatremia: Why are there still deaths?

Commentary, Pediatrics, 20o4

- The current practice of prescribing hypotonic maintenance fluids in children is unsafe and should be abandoned.
- The administration of IV fluids should be considered an invasive procedure, and all hospitalized patients should be considered at risk for developing hyponatremia.
- Although no one parenteral fluid can be administered safely to all children, isotonic saline would seem to be the safest fluid for most children.

Conclusions

- The classic third space does not exist
- Intravenous fluid therapy should be goal directed
- Hypotonic intravenous therapy should be avoided in the postoperative pediatric patient
- Postoperative patients on maintenance intravenous therapy should have frequent electrolyte analysis

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