Cardiopulmonary bypass in small baby

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Histories in CPB

In 1950 Bigelow :

the first application of hypothermia in cardiac surgery

In 1952 Lewis & Taufic :

the first application of hypothermia and inflow occlusion for repair of ASD in humans

In 1953 Gibbon :

establish the feasibility of artificially supported circulation during temporary occlusion of he pulmonary artery

successfully used extracorporeal circulation in a young woman

Histories in CPB

In 1954 Lillehei et al :

technique of controlled cross-circulation

In 1954 Cooley :

the application of heat exchangers

In 1960s :

emphasized the use of bubble oxygenators

In 1970s :

switching to membrane oxygenators

Next advances

miniaturization of elements of the CPB circuits

modulation of the systemic inflammatory response and injury from CPB

CPB for infants *vs* adults

- Immature organ systems
- Smaller circulation blood volumes
- Higher oxygen consumption rate
- Reactive pulmonary vascular bed
- Presence of intracardiac and extracardiac shunting
- Impaired temperature control
- Poor tolerance to microemboli

Immature organ systems

Liver :

decreased clotting factors

Lung :

fragile, potential for pulmonary edema & pulmonary hypertension

Kidney :

sodium reabsorption & excretion, concentration & diluting mechanism are limited

Immune system :

complement generation is low

neonatal mononuclear cells are dysfunctional

Brain in neonates & infants

Low cerebral oxygen consumption rate :

- low cerebral blood flow
- low energy requirements (small number of active synapses)
- high activity of glycolytic enzyme

Cerebral response to hypoxia :

- circulatory adaptation
- rapid induction of electrical silence
- blood glucose tend to rise (by catecholamine release)
- in adult : intracellular acidosis ↑, neural injury ↑
- in neonate : neuroprotective (mechanism is unclear)

Smaller circulating blood volume

Circuit capacity cannot be reduced proportionate to patient size

Significant hemodilution

→ ↓ clotting factors, plasma proteins → dilutional coagulopathy

→ ↓ colloid osmotic pressure → interstitial edema

→ electrolyte imbalance

→ ↑release of stress hormones

→ activation of complement, WBC, platelets

In neonate : as much as 200~300% of patient's blood volume

In adults : about 25~33% of patient's blood volume

Higher oxygen consumption rate

Higher flow rates per BSA to meet metabolic demands
(maintained both cooling & rewarming phase of CPB)

< 3 kg	150 ~ 200 ml/kg/min
3 ~ 10kg	125 ~ 175 ml/kg/min
10 ~ 15kg	120 ~ 150 ml/kg/min
15 ~ 30kg	100 ~ 120 ml/kg/min
30 ~ 50kg	75 ~ 100 ml/kg/min
> 50kg	50 ~ 75 ml/kg/min

Switch from a relatively anaerobic metabolism in a immature heart to more aerobic metabolism.

Difference between adult and immature myocardium

- Denser structure with a higher water & protein content per gram
- Less compliant, less preload reserve, narrower range of function closer to the peak of the Frank-Starling curve
- Lower rate of maximum tension development
- Reduced inotropic reserve
- Operate under maximal adrenergic stimulation

Difference between adult and immature myocardium

- Abundant endogenous glycogen store

  : more depend on glucose metabolism from glycogenolysis

- Lower sarcoplasmic reticular calcium adenosine triphosphatase activity with less calcium sequestration

  : calcium-channel blockade → depress neonatal myocardial function more than adult heart

- Improved high-energy phosphate homeostasis

  : due to a relative deficiency of 5' nucleotidase

	Pediatric	Adult	Potential Impact on Ischemia Tolerance in the Pediatric Heart
Preferred substrate for adenosine triphosphate production	Glucose	Fatty acids	Increase
Glycogen content	High	Low	Increase
Insulin sensitivity	Impaired	Normal	?
Calcium handling (intracellular)	Impaired	Normal	?
Calcium sensitivity	Increased	Normal	Decrease?
Antioxidant defense	Low	High	Decrease
5′ nucleotidase	Low	High	Increase
Catecholamine sensitivity	Low	Normal	?
Ischemic preconditioning	Absent	Present	?

? = potential effect unknown.

Ischemic tolerance of the immature heart

- Immature heart has a greater tolerance to **hypoxia and ischemia** than the adult

: greater glycogen stores

: improved anaerobic metabolism

: better maintenance of ischemic calcium exchange

: higher levels of adenosine triphosphate

: increased amino acid substrate utilization

Tolerance of the immature heart to hypoxia or ischemia

- Better tolerable

  : increased glycolytic capacity

  : better preservation intracellular, high-energy phosphates

  : increased ability to utilize amino acid as substrate during hypothermic ischemia

- Lower tolerable

  : greater intracellular accumulation of lactic acid as a result of anaerobic metabolism

  : myocardial ischemic times (>85min) were associated with a significant mortality risk in infants, despite the use of cardioplegia

Ischemic tolerance of the immature heart

- Although laboratory models suggest an improved tolerance to ischemia, most research has been conducted in the normal heart
- Adverse preoperative conditions such as acidosis, cyanosis, and hypertrophy may seriously compromise myocardial protection in the immature heart

Special situations affecting myocardial protection in neonates with CHD

- Severe hypoxia
- Chronic cyanosis
- Children with decreased pulmonary blood flow have increased bronchial collateral flow to the left heart that can markedly compromise intraoperative myocardial protection

→ noncoronary collateral flow

: wash out cardioplegia, rewarms the heart,

causes resumption of contractile activity

Principle of myocardial protection

- Reduction of metabolic activity by hypothermia
- Arrest of contractile apparatus and electrical activity of the myocyte by administering cardioplegic solution
- Others
  - : buffering the cardioplegic solution,
  - : increasing osmolarity,
  - : decreasing calcium content,
  - : adding substrate to enhance recovery,
  - : incorporate leukocyte filters in the CPB circuit

Causes of post-op Low CO

- Residual volume or pressure load – most important
- Ventricular distention
- Retraction / stretch injury to the myocardium
- Coronary artery injury
- Ventriculotomy
- Edema – inappropriate degree of hemodilution of red cells or colloid oncotic pressure
- Reperfusion condition, e.g. pressure, calcium, oxygen, additives such as adenosine and free radical scavengers
- Other perfusion factors, e.g. pH strategy

Strategies of CO_2 management : Alpha stat *vs* pH stat

Alpha stat : maintains pH 7.40 (temperature uncorrected)

intracellular pH, enzymatic activity and

perfusion-pressure autoregulation is preserved

maintains cellular enzyme function

Strategies of CO_2 management : Alpha stat *vs* pH stat

pH stat : lowers intracellular pH (temperature corrected)

suppressing cellular function

→ increase cerebral tissue oxygenation

oxygen dissociation curve is displaced to the Rt.

→liberating more oxygen to the tissues

cerebral vasodilation, increase cerebral blood flow

→decease local edema,

improve cerebral cooling

Alpha stat *vs* pH stat

Table 1 Blood gases, hematocrit, mean arterial pressure, and pump flow

Variable Group	37 °C CPB	31 °C CPB	25 °C CPB	19 °C CPB	15 °C CPB
PH					
Alpha-stat	7.42±0.01	7.35±0.01	7.35±0.02	7.41±0.01	7.45±0.01
PH-stat	7.39±0.02	7.31±0.02	7.28±0.02	7.26±0.03*	7.13±0.04*
Pa_{CO_2} (mmHg)					
Alpha-stat	42.3±1.68	47.2±1.35	45.8±1.49	38.5±1.78	34.0±1.45
PH-stat	46.3±2.15	49.9±2.29	46.6±2.28	63.1±5.20*	84.1±8.21*
Pa_{O_2} (mmHg)					
Alpha-stat	396±24	411±26	416±25	421±27	428±30
PH-stat	394±22	408±24	411±25	419±26	422±28
Hematocrit (%)					
Alpha-stat	24.1±1.00	22.9±0.94	21.1±0.74	19.5±0.64	19.4±0.62
PH-stat	23.9±1.12	22.7±1.10	20.9±0.85	19.4±0.73	19.2±0.78
Mean BP (mmHg)					
Alpha-stat	63.6±2.14	58.7±2.11	59.1±1.86	61.2±1.78	64.5±1.82
PH-stat	62.6±1.50	60.0±1.39	59.1±0.68	60.6±1.05	60.2±0.17
Pump flow [ml/(kg·min)]					
Alpha-stat	68.9±3.07	68.1±2.97	69.3±2.63	68.1±2.79	67.3±2.68
PH-stat	70.2±3.45	69.5±3.26	70.8±3.47	68.9±3.12	67.8±2.98

Values are mean±*SEM*. *P<0.05 vs alpha-stat; CPB=cardiopulmonary bypass; Alpha-stat=alpha-stat group; pH-stat=pH-stat group

Alpha stat *vs* pH stat

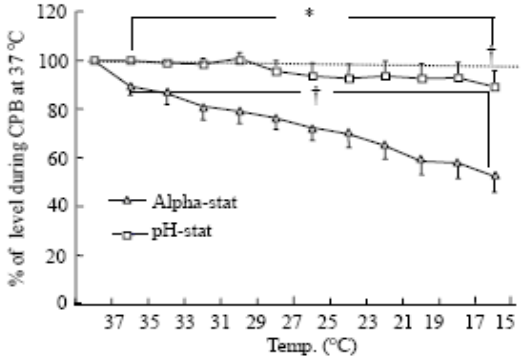


Fig.1 Change in brain tissue blood flow determined by laser flowmetry during hypothermia in both the alpha-stat and pH-stat. Levels obtained during initial cardiopulmonary bypass (CPB) at 37 °C were used as baseline
*P<0.05 vs alpha-stat; †P<0.05 vs baseline within the group

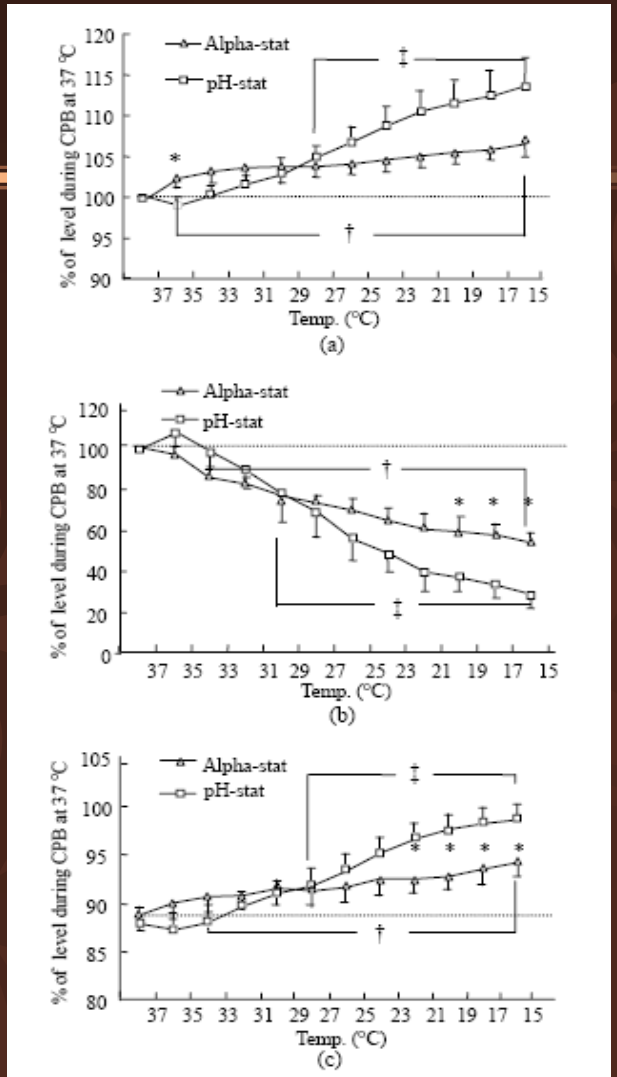
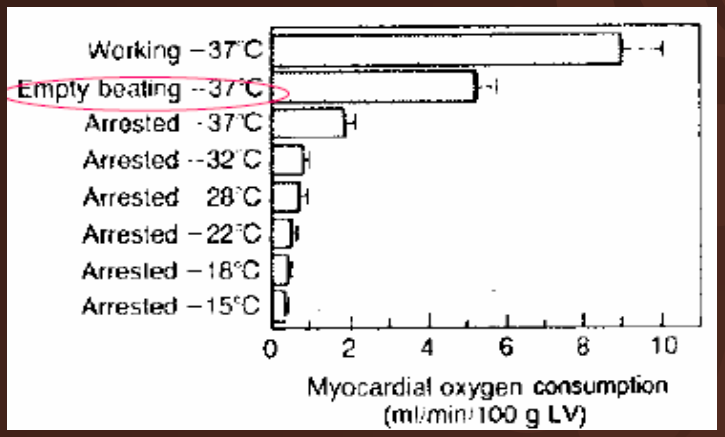
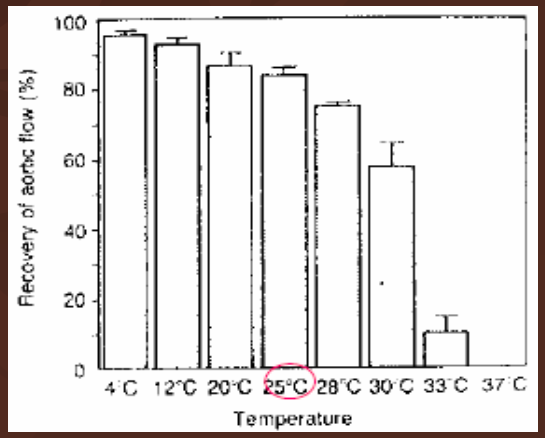


Fig.2 Changes in brain tissue oxyhemoglobin (a) and deoxyhemoglobin (b), as well as brain tissue oxygen saturation (c) determined by NIR spectroscopy during deep hypothermic CPB in both the alpha-stat and pH-stat. In (a) and (b), the levels obtained during initial CPB at 37 °C were used as baselines. The plus and double plus sign indicate P<0.05 vs levels obtained at 37 °C CPB within the group. *P<0.05 vs pH-stat

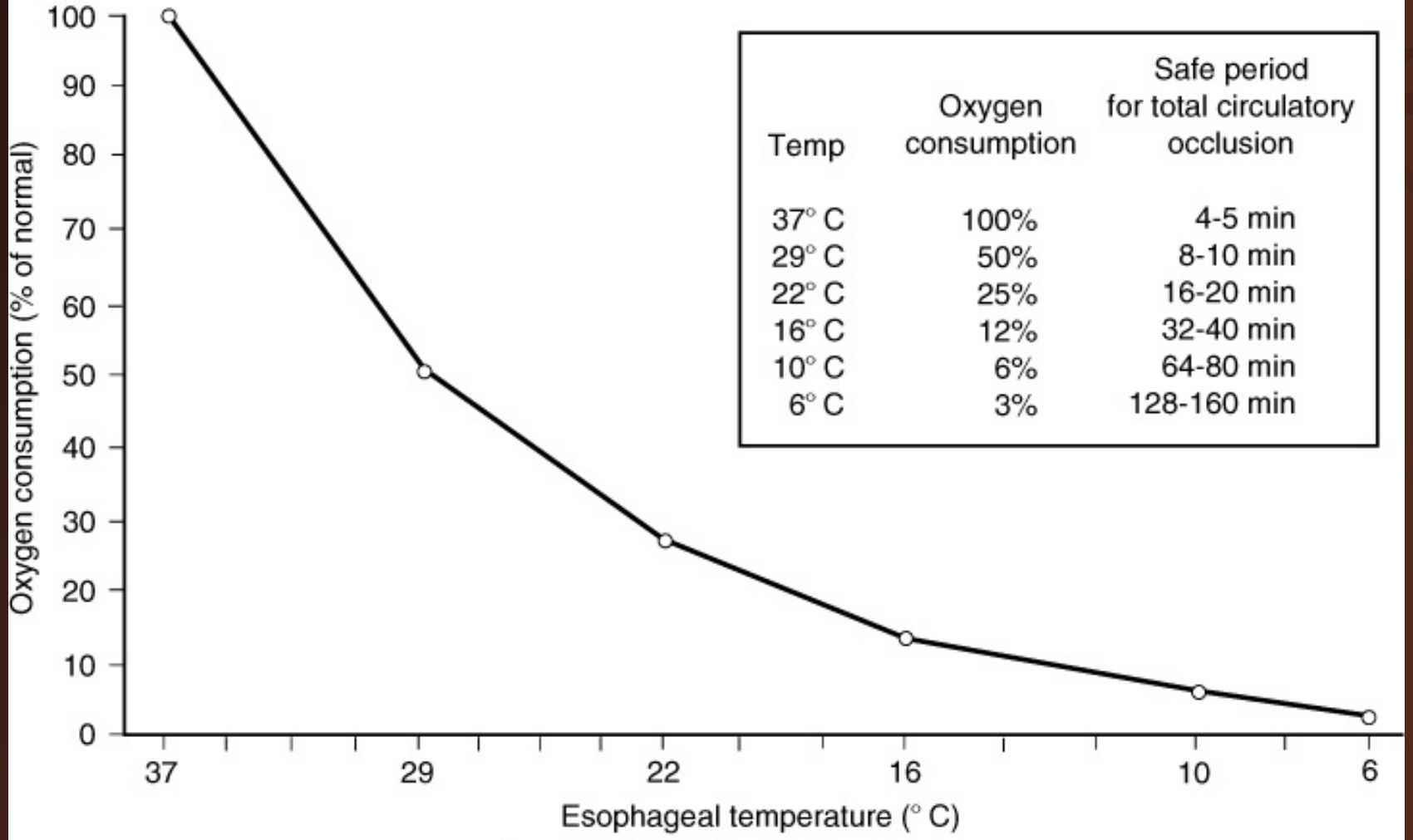
Hypothermia

- Reducing Oxygen requirements
  - flow rates can be reduced
- Reducing the temperature difference between the heart and body
  - enhances the safe duration of cardiac ischemia.
- Adds safety to the perfusion, since more time is available for repairs if perfusion must be interrupted because of accidents in the surgical field or failure of the perfusion apparatus.





RELATIONSHIP BETWEEN BODY TEMPERATURE AND OXYGEN CONSUMPTION
(MEAN VALUE FOR 10 DOGS)



Temp	Oxygen consumption	Safe period for total circulatory occlusion
37° C	100%	4-5 min
29° C	50%	8-10 min
22° C	25%	16-20 min
16° C	12%	32-40 min
10° C	6%	64-80 min
6° C	3%	128-160 min

Neurologic injury

- 10-25% of incidence
- preexisting risk (associated structural anomalies with the brain)

  : esp. in Down sydnrome, CATCH 22
- injury induced by CPB

  : microembolic event, esp. air embolism

    low cerebral flow

The systemic inflammatory response

Stimuli
Blood contact
with CPB surfaces
Abnormal shear stress
Surgical trauma
Endotoxemia
Ischemia

Mediators
Contact system
Complement system
Cytokines
Oxygen free radicals

Effects
Leukocyte extravasation
Lipid peroxidation
Edema
Cell death

Organ damages
Myocardial dysfunction
Respiratory failure
Renal, neurologic
and liver dysfunction
neurologic dysfunction
Bleeding disorders

Basic consideration of CPB

- Circulation
- Oxygenation & CO_2 removal
- Temperature regulation
- Surgical exposure
- Provide the surgeon with a quiet, bloodless field for the procedure

- Adequate flow
- Adequate drainage
- Perfusion and drainage of all organs
- Unobstructed field

The pediatric CPB circuits

- Cannulation
- Perfusion pump
- Oxygenators
- Prime
- Initiation of cardiopulmonary bypass
- Delivery system of cardioplegic solution
- Weaning from cardiopulmonary bypass
- Ultrafiltration
- Anticoagulation

Current strategies for optimizing use of CPB in neonates & infants

1. Prebypass
2. Bypass
    - CPB circuit
    - hemostasis & anticoagulation
    - deep hypothermic circulatory arrest
    - ultrafiltration
    - anticoagulation
3. Postbypass

Prebypass

One of potential complications as a result of exposure to CPB is a systemic inflammatory response (leukocytes are partly response)

→ capillary leakage, soft tissue edema, end-organ dysfunction

=> 1. using leukocyte filter

2. high dose steroid before CPB

Prebypass

High dose steroid before CPB :

(IV methylprednisolone at 10mg/kg 8hr & 2hr before CPB)

decrease in post-CPB fluid gain

less postoperative edema

improvement in pulmonary compliance

& pulmonary vascular resistance

Bypass

1. Steroid is added to circuit prime
2. Aprotinin : protease inhibitor

   reduce the inflammatory response

   (by inhibit kallikrein and contact activation)

   reduce the postoperative bleeding

   (240 mg/m² bolus infusion at beginning and same dose in circuit prime,

   continuous infusion of 56 mg/m²/h throughout the procedure)

Aprotinin

Table 2 Perioperative Parameters

	Aprotinin group (n=40)	*Control group (n=40)*	*p value*
Cross-clamp time (min)	*53.0±4.6*	*52.7±6.9*	*NS*
CPB time (min)	*72.2±13.8*	*75.0±7.3*	*NS*
Time to extubation (min)	*285.0±17.4*	*285.5±27.9*	*NS*
No. of grafts			
Anesthesia time (min)			
Postoperative bleeding			
Length of ICU stay (d			
Length of hospital stay			

Table 3 CK-MB Levels

CK-MB (IU/L)	*Aprotinin group (n=40)*	*Control group (n=40)*	*p value*
CK0	*20.4±5.5*	*20.3±4.3*	*NS*
CK1	*47.8±5.5*	*52.3±7.2*	*<0.01*
CK2	*42.0±12.3*	*46.9±8.6*	*<0.05*
CK3	*41.5±13.5*		
CK4	*32.6±10.2*		

CK, creatine kinase; CK0, before surge CK2, at postoperative 6th h; CK3, at post tive 24th h.

Table 4 Cardiac Troponin I Levels

Troponin I (ng/ml)	*Aprotinin group (n=40)*	*Control group (n=40)*	*p value*
TN0	*0.08±0.02*	*0.07±0.02*	*NS*
TN1	*2.49±0.42*	*2.59±0.28*	*NS*
TN2	*2.87±0.47*	*3.11±0.46*	*<0.05*
TN3	*2.10±0.51*	*2.39±0.53*	*<0.05*
TN4	*1.38±0.39*	*1.60±0.36*	*<0.05*
TN5	*0.68±0.20*	*0.78±0.26*	*NS*

TN0, before surgery; TN1, immediately after surgery; TN2, at postoperative 6th h; TN3, at postoperative 12th h; TN4, at postoperative 24th h; TN5, on postoperative 5th day.

Aprotinin

Table 5 CI, SvO_2 and LDH Measurements

	Aprotinin group (n=40)	*Control group (n=40)*	*p value*
SvO_20	*48.82±3.20*	*49.77±3.58*	*NS*
SvO_21	*48.32±2.53*	*48.02±2.86*	*NS*
SvO_22	*54.42±4.55*	*51.75±4.75*	*<0.05*
SvO_23	*56.27±5.63*	*52.65±6.09*	*<0.01*
SvO_24	*57.92±5.04*	*55.80±5.04*	*NS*
CI0	*2.70±0.29*	*2.74±0.30*	*NS*
CI1	*2.64±0.23*	*2.58±0.26*	*NS*
CI2	*2.73±0.28*	*2.60±0.26*	*<0.05*
CI3	*2.82±0.29*	*2.69±0.25*	*<0.05*
CI4	*2.83±0.30*	*2.78±0.29*	*NS*
LDH0	*214.05±13.58*	*211.22±18.95*	*NS*
LDH1	*221.87±18.71*	*235.12±26.84*	*<0.05*
LDH2	*298.97±27.70*	*313.80±36.99*	*<0.05*

CI, cardiac index (L/min); SvO_2, mixed venous oxygen saturation (%); LDH, lactate dehydrogenase (IU/ml); SvO_20, SvO_2 levels before surgery; SvO_21, SvO_2 levels immediately after surgery; SvO_22, SvO_2 levels at postoperative 6^{th} h; SvO_23, SvO_2 levels at postoperative 12^{th} h; SvO_24, SvO_2 levels at postoperative 2^{th} h; CI0, CI levels before surgery; CI1, CI levels immediately after surgery; CI2, CI levels at postoperative 6^{th} h; CI3, CI levels at postoperative 12^{th} h; CI4, CI levels at postoperative 24^{th} h; LDH0, LDH levels before surgery; LDH1, LDH levels immediately after surgery; LDH2, LDH levels at postoperative 1^{st} day.

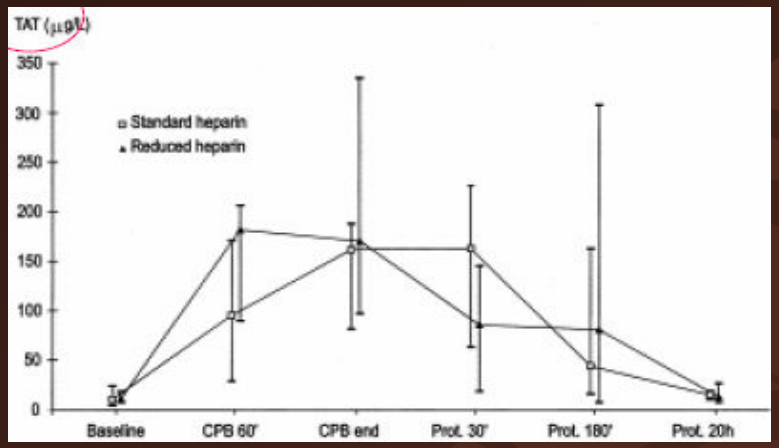
Bypass

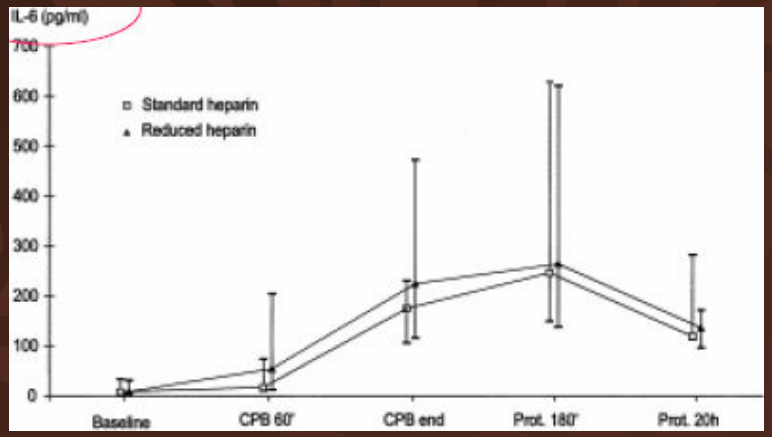
3. CPB circuitry

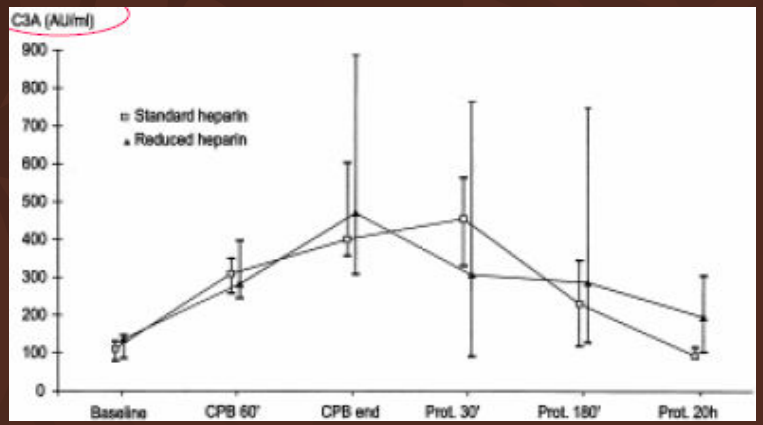
- Miniaturization of the CPB
- Using biocompatible-coated circuits (heparin-coated circuit) :

  reduce the direct contact of blood cell with foreign materials
- Using vacuum-assisted venous drainage (VAVD)

Heparin-coated curcuit







Bypass

4. Deep hypothermic circulatory arrest and low flow CPB

continuous hypothermic low flow CPB :

- more soft tissue edema
- diminished pulmonary function
- substantial cerebral edema
- damage to neural golgi apparatus

There is some acute neurologic metabolic injury after prolonged exposure to continuous hypothermic low flow CPB that is not apparent if brain is exposed to short duration of DHCA

Bypass

4. Deep hypothermic circulatory arrest and low flow CPB

Modified DHCA :

1)prebypass with steroid & aprotinin

2)hyperoxygenation before the initiation of DHCA

3)adequate cooling duration(≥20 min)

4)maintenance of higher Hct during the cooling phase

5)using pH stat during cooling phase

6)limiting duration of DHCA

(by intermittent cerebral perfusion for 1-2 min at 15-20 min interval)

7)use of MUF

8)attension to postoperative cerebral energetics

-much cerebral injury can occur

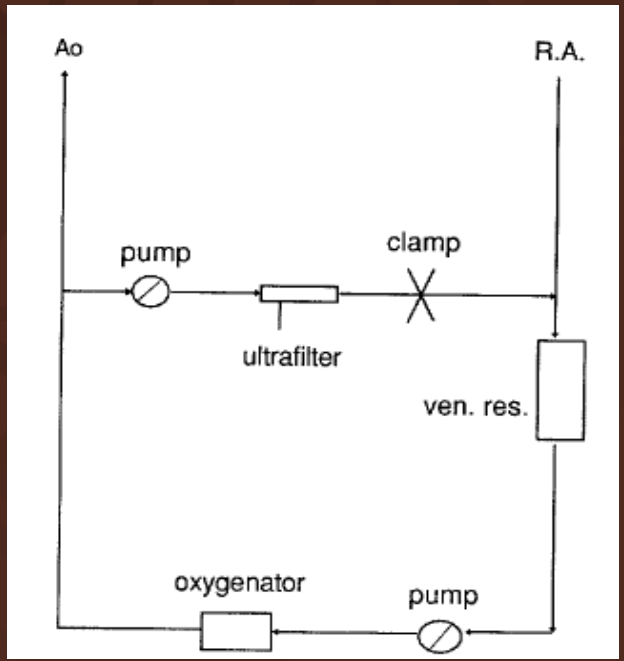
Bypass

5. Ultrafiltration

reduce postoperative edema, reduce postoperative blood loss, decrease time to extubation, remove a tissue necrosis factors

- Conventional ultrafiltration (CUF) :

during CPB (rewarming phase)
isovolemic exchange of fluid
removal of fluid & activated inflammatory mediators



Bypass

5. Ultrafiltration
   - Modified ultrafiltration (MUF) :
     more effective in hemoconcentration &
     improving ventricular functional recovery
     after the completion of CPB
     remove the patient 500 to 700ml of fluid

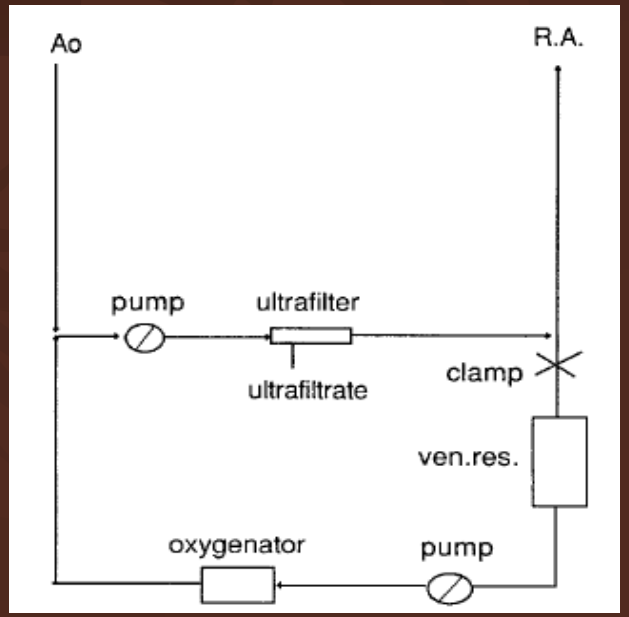


TABLE 4. Studies comparing MUF and conventional CUF in children undergoing cardiac surgery

First author	Group	Age* (mo)	n	Ultrafiltrate (mL/kg)	Hct† (%)	Clinical outcome
Wang[18]	MUF	62	24	—‡	18	No difference in inotrope use, diuresis, duration of ventilation, ICU stay
	CUF	44	26	—‡	18	
Thompson[16]	MUF	13	43	95	28-30	No difference in blood product transfusions, hemodynamics, left ventricle shortening, duration of ventilation, ICU stay
	CUF	9	67	68	28-30	
Maluf[19]	MUF + CUF	9	20	39	25	No difference in inotrope use, transfusions, duration of ventilation, ICU stay, hospital stay
	CUF	15	21	20	25	
Sever[20]	MUF + CUF	9	13	—‡	>20	MUF + CUF: better hemodynamics, less bleeding and transfusions, shorter duration of ventilation, shorter ICU stay
	CUF	13	14	—‡	>20	
Bando[5]	MUF + DCUF	17	50	155	14-18	MUF + DCUF: high-risk patients§ had less transfusions, better oxygenation, shorter duration of ventilation, shorter ICU stay
	CUF	30	50	29	14-18	
Journois[8]	MUF + DCUF	13	10	>200	—‡	MUF + DCUF: less blood loss, better alveolar-arterial oxygen gradient, shorter duration of ventilation
	MUF	6	10	30	—‡	
Hiramatsu[21]	MUF + DCUF	67	11	186	18-28	MUF + DCUF: lower pulmonary vascular resistance (Fontan procedure)
	CUF	74	11	25	18-28	

MUF, modified ultrafiltration; *CUF*, conventional ultrafiltration; *ICU*, intensive care unit; *DCUF*, dilutional ultrafiltration. *Mean or median age of patients. †Target hematocrit during cardiopulmonary bypass. ‡Value not published. §High risk factors were neonatal age, pulmonary hypertension, and CBP duration longer than 120 minutes.

Ann Thorac Surg. 1997 Dec;64(6):1787–9. Friesen RH

Table 1. Changes in Fibrinogen Concentration, Plasma Protein Concentration, Hematocrit, and Platelet Count During Modified Ultrafiltration After Cardiopulmonary Bypass in 20 Infants[a]

Variable	Before CPB	Before MUF	After MUF
Fibrinogen (mg/dL)	220 ± 70	65 ± 29[b]	101 ± 45[c]
Proteins (g/dL)	7.0 ± 0.7	2.7 ± 0.3[b]	4.9 ± 0.7[c]
Hematocrit (%)	35 ± 7	19 ± 6[b]	
Platelets (1,000/μL)	362 ± 91	111 ± 4	

[a] Data are expressed as mean ± standard deviati
less than the value before CPB ($p < 0.001$). [c] Sign
the value before MUF ($p < 0.001$).

CPB = cardiopulmonary bypass; MUF = modifi

Table 3. Red Blood Cell Transfusion[a]

Transfusion	No UF	MUF	p Value[b]
Mean RBC volume transfused during CPB (mL)	173 ± 10.41	157 ± 10.52	0.26
Mean RBC volume transfused after CPB (mL)	147 ± 13.43	109 ± 9.17	<0.05
Mean total RBC volume transfused (mL)	318 ± 16.78	267 ± 11.89	<0.05

[a] Data are presented as mean ± SEM. [b] Student's *t* test.

CPB = cardiopulmonary bypass; MUF = modified ultrafiltration; RBC = red blood cell; UF = ultrafiltration.

Table 4. Hemoglobin and Hematocrit Values During and After the Operation[a]

Measurement	No UF	MUF	*p* Value[b]
Mean hemoglobin during CPB (mmol/L)	5.2 ± 0.09	4.9 ± 0.06	<0.05
Mean hematocrit during CPB (%)	25 ± 5	24 ± 3	<0.05
Mean hemoglobin after CPB/MUF (mmol/L)[c]	5.2 ± 0.09	6.7 ± 0.10	<0.001
Mean hematocrit after CPB/MUF (%)[c]	25 ± 5	33 ± 5	<0.001
Mean hemoglobin 4 h after arrival at ICU (mmol/L)	6.8 ± 0.12	6.6 ± 0.09	0.24
Mean hematocrit 4 h after arrival at ICU (%)	33 ± 6	32 ± 5	0.20

[a] Data are presented as mean ± SEM. [b] Student's *t* test. [c] In the group with no ultrafiltration, values were measured after discontinuation of CPB; in the group with MUF, values were measured after MUF.

CPB = cardiopulmonary bypass; ICU = intensive care unit; MUF = modified ultrafiltration; UF = ultrafiltration.

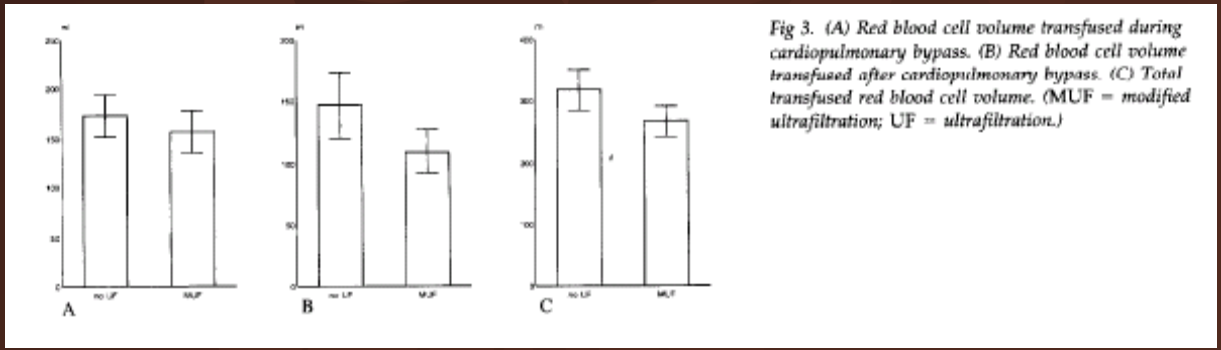


Fig 3. (A) Red blood cell volume transfused during cardiopulmonary bypass. (B) Red blood cell volume transfused after cardiopulmonary bypass. (C) Total transfused red blood cell volume. (MUF = modified ultrafiltration; UF = ultrafiltration.)

Bypass

6. Anticoagulation

The amount of heparin to be delivered based on the patient's weight

(Dosage : adult 2 mg/kg, child 3 mg/kg)

do not based on the patient's blood volume

←effects of hypothermia, hemodilution, pre-existing heparin therapy

children require high doses of heparin to maintain ACT of 350-450 sec

> 200 sec : insertion cannula

> 400 sec : CPB start

> 480 sec : during CPB

> 750 sec : aprotinin is added

Bypass

6. Anticoagulation

after injection of initial heparin : ACT check q 30min

< 400 sec : 1mg/kg heparin

400-480 sec : 0.5mg/kg heparin

after CPB stop

Protamine dosage: 1.0 -1.5 mg for 100 unit (or mg) of heparin

> 480 sec : protamine 130% of initial doses of heparin

130-150 sec : 1/10 of initial doses of protamine

120-200 sec : 1/5 of initial doses of protamine

Postbypass

Once separated from CPB, the patient may continue to capillary leakage and accumulate excessive soft tissue fluid for 24 to 36hr

- Leaving a foramen defect open
- Use of inotropic agents
- Leaving the sternum open
- Placement of peritoneal dialysis catheters
- Short period of ECMO

Thank you for your attention!