# Patient Blood Management in Adult Cardiac Surgery

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## Abstract

Blood has been known as the most precious and human substance in the world. Current issue in cardiac surgery are moving from transfusing allogeneic blood products towards saving and preserving the patient's autologous blood. Patient's own whole blood offers the best natural healing abilities and homeostasis. No substitute, whether it is human or artificial, will ever work as well with fluid shifts, hemostasis and homeostasis. Someone reports commonly feature severe blood shortages and research documenting recognized transfusion risks such as how older stored blood can put heart surgery patients at increased risk and others that point to the morbidity and mortality with its use. Therefore the medical effort is moving towards more effective blood utilization by minimizing the exposure to donated blood. The techniques are saving of the patient's own blood as much as possible that might otherwise be mismanaged or lost during surgery. Techniques such as ultrafiltration, that quickly concentrate and reinfuse whole blood back to the patient are the best choice. From admission to discharge hemovigilance requires a concerted multidisciplinary team effort with multimodal tools available in the coagulation armamentarium to effectively avoid this form of organ transplant. Improving outcomes and reducing morbidity and mortality in cardiac surgery takes place at the microcirculatory capillary level and with control of hemostasis. Cardiac teams need to effectively communicate and minimize blood loss and hemodilution and reverse it for blood management in Cardiac surgery.

Key word: Patient Blood Management, Cardiac Surgery

## 서론

혈액은 인체에 있어서 가장 소중한 요소로 여겨지며 최근에는 개심술에 있어 타인의 혈액을 수혈 받는 것 보다 환자 본인의 혈액을 보존하고 절약하는 쪽으로 관심이 이동하고 있다[1] 자연 치유력과 항상성에 있어 타인의 혈액을 포함해서 인공적인 수액 어느 것도 환자 본인의 전혈을 대치할 수 있는 것은 현재까지 없으며 이러한 이유로 모든 동종의 수혈 제제들은 환자 본인의 전혈보다 좋지 않다.

## 본론

1980년대와 1990년대에는 후천성 면역 결핍증 및 C형 간염과 같은 질환을 선별할 수 있는 검사기술이 발달함에 따라 수혈 건수가 이전에 비해 급격히 증가하였다. 최근에는 혈액제제가 부족한 상태이며 또한 채혈 후 시간이 경과하여 오래 보관된 혈액은 개심술 환자에게 있어 수술 위험도와 합병증을 증가시킨다는 보고가 있다[2,3]. 이로 인해 채혈된 혈액을 외부와 접촉을 최소화하여 보관하는 방법을 연구하던 당시 보다는 최근에는 수술 중 버려지는 환자 자신의 혈액을 다시 주입하는 방법에 중점을 두고 있다. 자가 수혈을 시행하게 되면 환자의 임상 결과를 향상 시키고,치료비 감소,면역 억제 감소, 수혈관련 세균 및 바이러스 감염과 부적합 혈액 수혈로 인한 수혈 부작용 방지,수혈 관련 면역 체계 변화와 암세포의 혈행성 전이 방지 및 환자의 종교적 신념을 존중할 수 있는 장점들이 있다[4].

혈액 보존, 무수혈 수술 및 혈액 관리 등은 모두 같의 의미로서 현재 개심술에서의 이러한 추세를 나타내는 말들이다. 최근에는 종교적인 신념 때문만이 아니라 환자들이 무수혈 수술을 선호하며 임상의사들도 환자의 임상 경과를 호전시키는 목적으로 동종 수혈을 회피하고 있다. 특히 개심술의 경우 환자의 수술 결과는 다른 수술과 달리 확연히 드러나게 되고 미국의 경우 심혈관 질환의 이환률과 사망률이 여전히 높아 통계적 지표로서 유용하게 사용될 수 있기 때문에 다른 수술에 비해 특히 관심이 높아지고 있다. 미국의 경우 일년에 325000명의 환자가 개심술을 시행 받고 있으며, 이 숫자는 매해 5%씩 증가하고 있다.  혈액을 수합하는 것은 개심술에서 보편적으로 사용되며, 거의 대부분의 나라에서 수혈 비중이 가장 높은 수술 중에 하나로 여겨지고 있다. 개심술을 시행 받는 환자들 중 반 이상이 적어도 한 개 이상의 수혈을 받고 있으며, 개심술 환자가 수혈 받는 비율은 전체 혈액중 15-20%에 이를 정도로 높다[5]. 이러한 추세는 개심술을 시행하는 의료진이 수혈을 줄이는 데 관심을 가지지 않는다면 악화될 것 이다.

여러 가지 전략과 방법에 따르면 인공 심폐기를 가동하여 수술하는 개심술 모두 동종 혈액을 사용하지 않고 시행할 수 있으며 모든 환자들을 체표면적이 작고 수혈을 거부하는 여호와의 증인이라고 가정하여 치료하는 것이 보편적인 가정이다. 이러한 치료 전략은 다학제 및 다양한 방법을 이용하여 접근해야 하며 치료 목적은 환자 자신의 혈액을 효과적으로 보존하고 낭비되는 것을 방지하고 결과적으로 동종 수혈을 피하는데 주력해야 한다[6,7]. 이러한 유기적인 다학제적 접근이 개심술에 있어 혈액 보존을 성공시킬 수 있으며 이러한 치료 전략은 수술 당시 뿐 아니라 입원 전 수주간을 포함하여 수술 전 및 퇴원 시까지 환자의 모든 치료 기간을 포함해야 한다. 많은 병원들은 무수혈 수술을 시행함에 있어 긴급하지 않은 수술은 최대한 수개월까지 연기하고 입원 전 환자의 적혈구 용적을 최대화하여 의학적으로 최적의 상태를 만드는 것에서부터 이러한 치료를 시작한다.

체외순환 뿐만 아니라 개심술 전반에 걸친 모든 술기들은 환자의 혈희석을 야기하고 결과적으로 수술 후 환자의 혈액 응고장애를 유발할 수 있기 때문에 이러한 문제들의 책임을 단순히 체외 순환사에게로 돌리는 것은 옳지 않다[8]. 수술 중 지혈을 세심하게 하고 환자의 혈액을 희석하지 않아 혈희석으로 인한 빈혈과 응고장애를 예방한다면 혈액은 보다 효과적으로 보존될 수 있다. 인공 심폐기 충진액을 줄이면 적혈구 용적률과 혈관 내 삼투압을 증가시켜 수술 경과를 호전시키고 수혈을 피할 수 있는 장점이 있다고 보고하였다. 그러나, 안전하게 체외순환 회로의 길이를 단축시켜 충진액의 양을 줄이는 것은 쉬운 일이 아니다[9]. 단순히 체외순환 회로를 단축시켜면 체외순환중 환자의 안전을 확보하지 못하며 이는 매우 위험하다. 체외순환 충진액을 줄이는데 있어 체외순환은 단순하게 구성되어야 하며 전신 공기 색전증을 예방해야 한다는 중요한 원칙을 잊어서는 안 된다[10]. 통상적으로 체외순환이 혈희석의 가장 중요한 원인으로 여겨졌다. 이로 인해 체외순환사는 환자의 좋은 임상 결과 위해 체외순환 회로를 최대한 줄이려고 노력해왔다. 체외순환 회로를 최대한 압축하여 충진액을 1100에서 1500ml까지 안전하게 줄이고 마취과 의사와 외과의사의 도움으로 자가 충진을 시행하면 환자의 적혈구 용적율을 수술전과 거의 유사하게 맞출 수 있다. 혈희석을 방지하는 것은 단지 체외 순환 하나의 분야에서만 이루어지는 것이 아니며 이러한 책임을 체외순환에게만 돌리는 것은 옳지 않다. 혈액 관리는 효과적인 상호 소통간에 다학제적으로 접근하여야 성공적으로 시행 될 수 있다[8,11]. 마취과 의사와 중환자실 의료진은 환자 혈희석에 중요한 역할을 하므로 주의를 기울여야 한다[12]. 혈액 검사시 환자의 채혈량을 최소한으로 하고 심박출량을 모니터링하여 보다 수액을 공급하기 보다는 약물로써 안전하게 혈관 저항을 증가시켜 환자의 적혈구 양을 최대한으로 해야 한다[7].우선 수술시 실혈양을 최소로 해야 하며 혈희석을 예방하여 환자가 수혈 받는 것을 피해야 한다.

수혈 기준도 재정립 되어야 한다. 여러 문헌에서 개심술시 체외순환 최저 적혈구 용적율은 22%이상이면 안전하며 제한 없이 수혈한 경우 (혈색소치 10g/dL이하)와 비교하여 수혈을 제한한 경우 (혈색소치 8g/dL이하)가 수술 후 합병증과 사망을 예방하여 임상 경과를 좋게 하는데 효과적이라고 제시하였다[13-15]. 또한 살아있는 혈장세포와 단백질 성분들을 셀세이버를 거쳐 세척하여 버리는 것을 하지 않는 것이 중요하다. 혈소판과 혈액 응고 인자들이 충분하지 않으면 환자의 출혈양은 많아지고 적혈구를 포함한 고가의 혈액 제제를 수혈 받아야 한다. 본연의 기능을 보존한 혈소판과 혈장 단백질이 세척되어 버려지는 것은 반드시 다시 확인해야 하며 이러한 혈액 성분을 보존하는 것은 개심술에서 뿐만 아니라 혈액 보존적인 측면에서 모든 수술에서 보편적으로 고려되어야만 한다.

이러한 낭비와 혈액 공급의 안정성 측면에 따라 전혈을 초미세여과시키는 방법에 관심이 모아지고 있다. 이러한 과정을 거침으로써 적혈구 뿐만 다니라 셀세이버를 사용하여 세척되면 버려지는 혈소판, 혈액 응고인자, 주요 혈장 단백등의 혈액 성분들을 보존하고, 농축 시켜 환자에게 다시 주입할 수 있다. 이렇게 함으로써 개심술 환자의 상태를 안정적으로 유지하고 출혈을 방지 할 수 있다. 최근 문헌에 따르면 수술 중 인공심폐기를 가동한 환자 심장혈액을 순환하고 관리하는 체외순환사들이 환자 자신의 혈액을 다시 주입하는 용도로 개심술 중 사용되는 셀세이버로 얼마나 많은 양의 혈액 성분들이 버려지고 이것들의 가치가 얼마나 되는지 계산할 수 있는 방법을 제시하였다[16]. 수술 시 환자의 혈액을 보존하기 위해 만들어진 이러한 장비들로 인해 발생하는 이러한 낭비는 동종 수혈 건수와 병원비를 증가시키고 환자 상태를 악화 시킬 수 있다.

## 결론

개심술의 술기는 아직 큰 변화는 없지만, 환자 자신의 혈액을 얼마나 효율적으로 보존하고 동종 수혈 없이 안전하게 수술을 시행하는데 초점을 맞추고 있다. 대부분의 수술 시 필요하다면 환자 자신의 신선한 전혈만큼 좋은 것은 없다는 것을 주지해야 한다[17].

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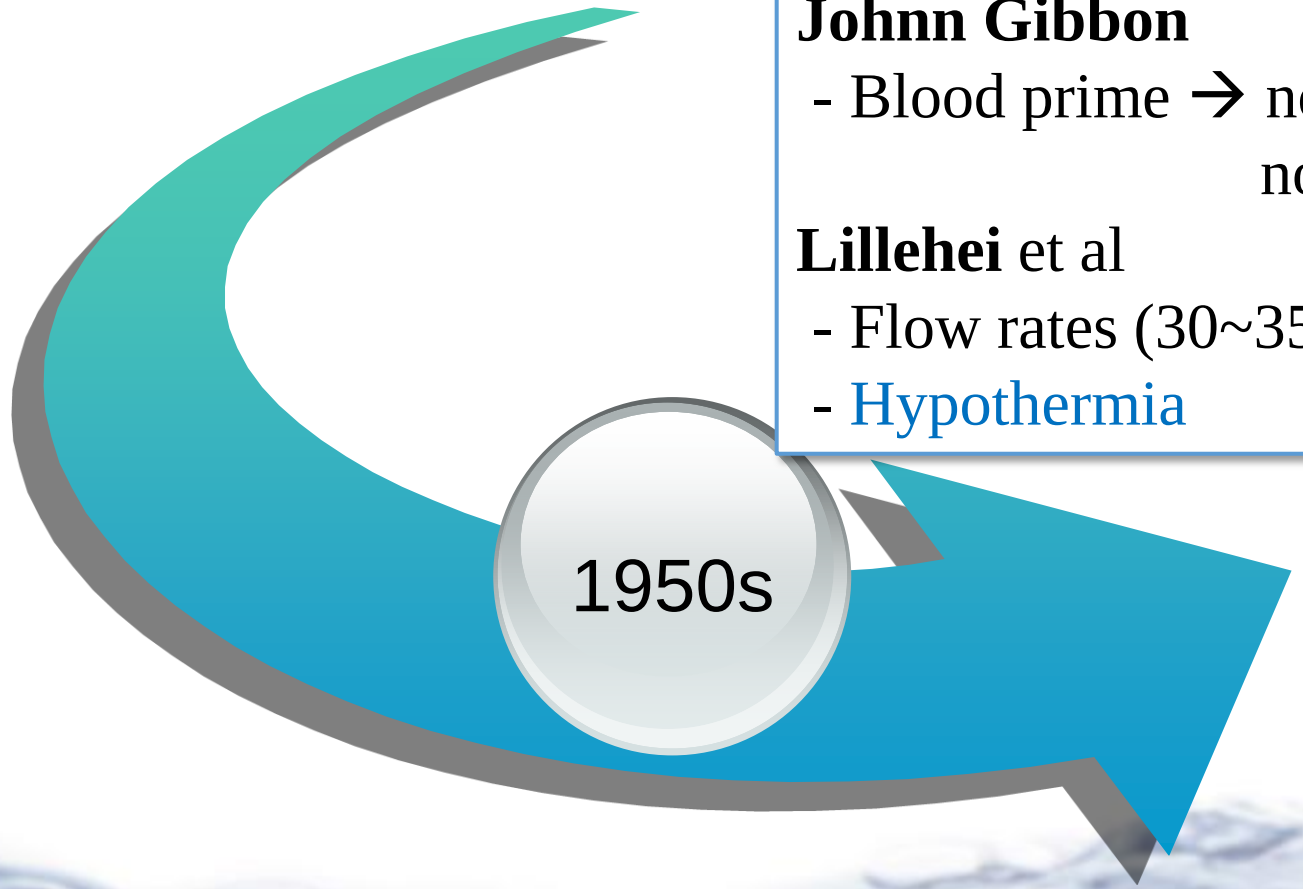
# Primimg and Hemodilution in Neonatal and Pediatric Cardiac Surgery

서울대학교어린이병원 흉부심장혈관외과

김 웅 한

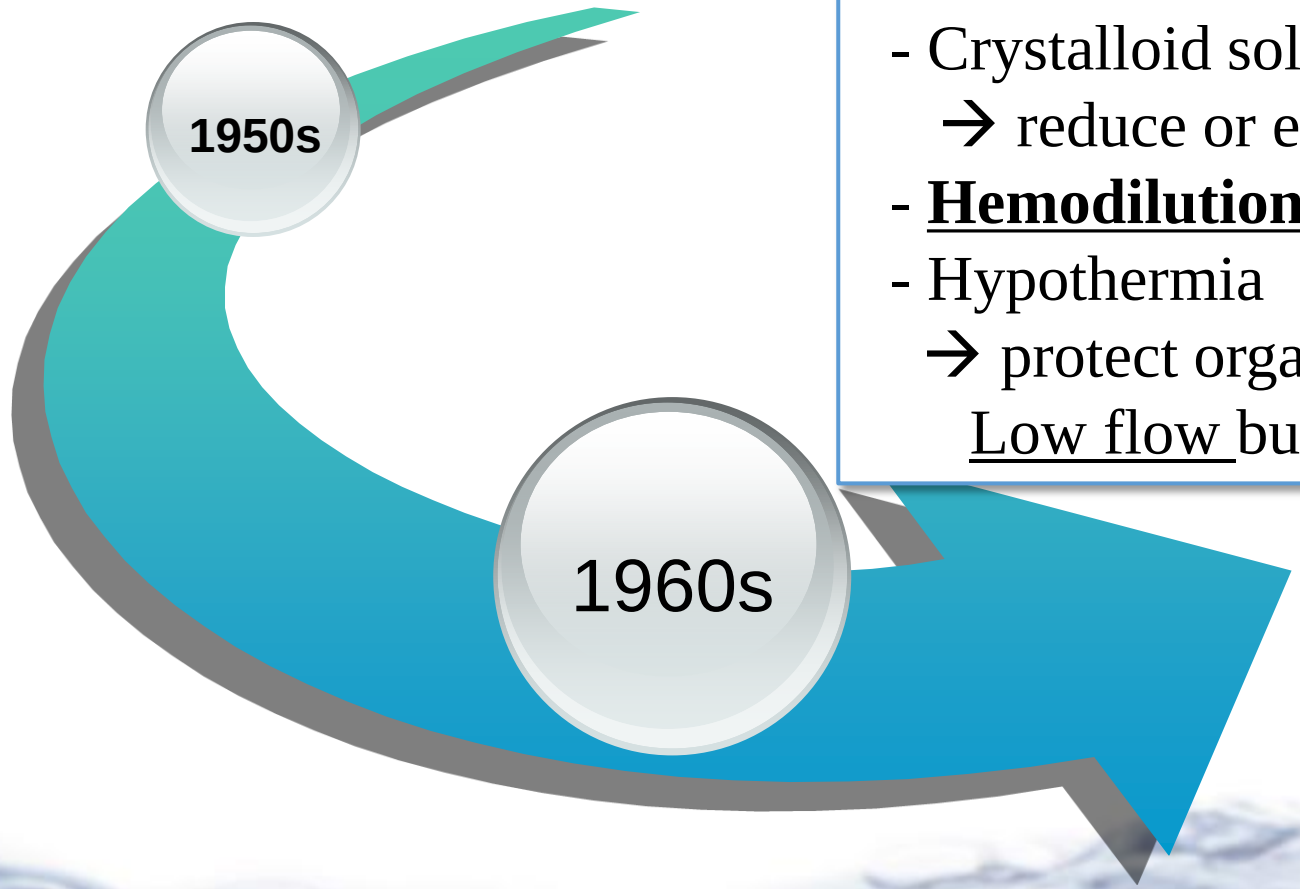
# Historical perspective




**Johnn Gibbon**
- Blood prime → normal flow rates (70~80ml/kg/min)
  normal blood pressure

**Lillehei** et al
- Flow rates (30~35 ml/kg/min)
- Hypothermia

# Historical perspective

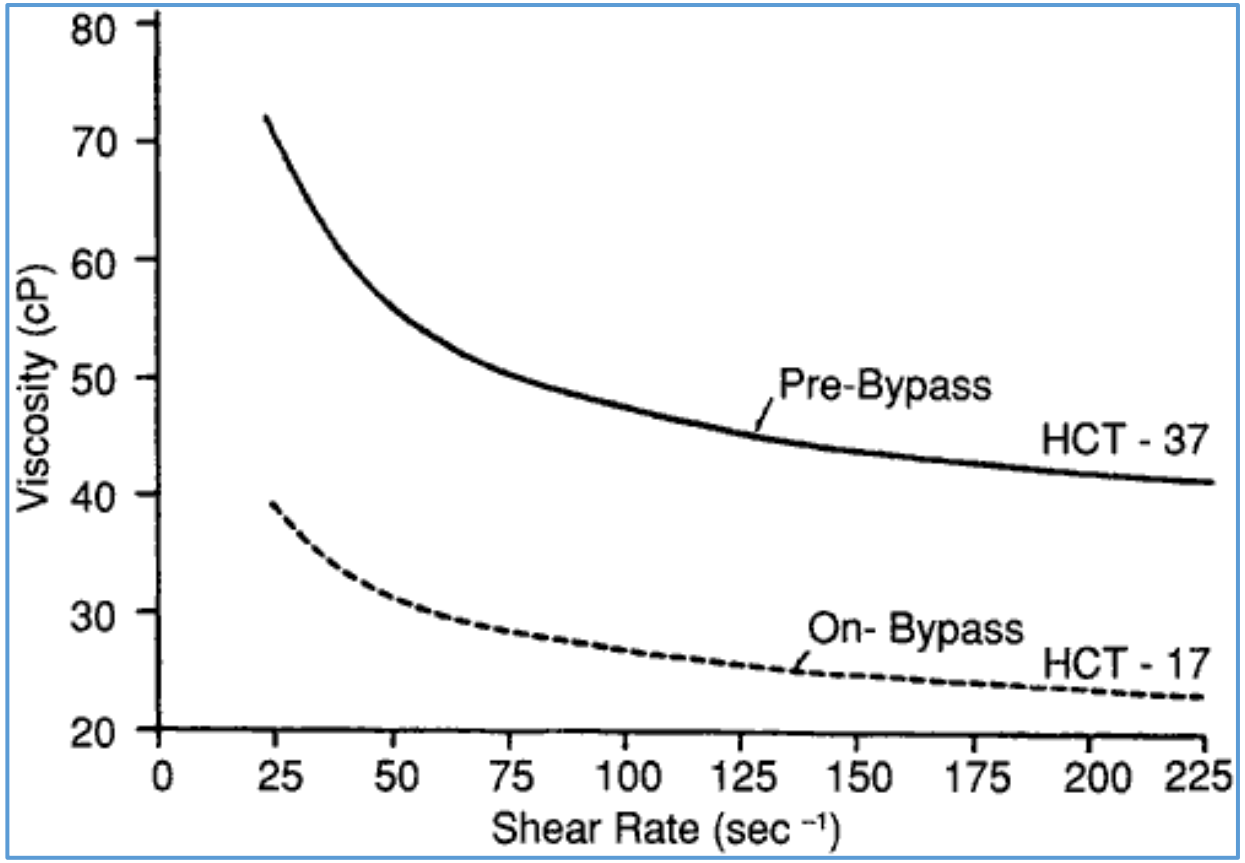



Panico et al.

- Crystalloid solutions or plasma-expanding colloids
  → reduce or eliminate blood from the prime
- **Hemodilution** : popularity and universally
- Hypothermia
  → protect organs from the adverse effects of not only Low flow but also Hemodilution

# Benefits of Hemodilution

- Decreased blood viscosity
- Improved regional blood flow
- Improved oxygen delivery to tissues
- Decreased exposure to blood products
- Improved blood flow at lower perfusion pressure (lower shear stress)




Viscosity change against shear rate : hematocrit fell from 37% to 17% after hemodilution

*J Thorac Cardiovasc Surg* 1975;69:552–561

# CPB for infants vs adults

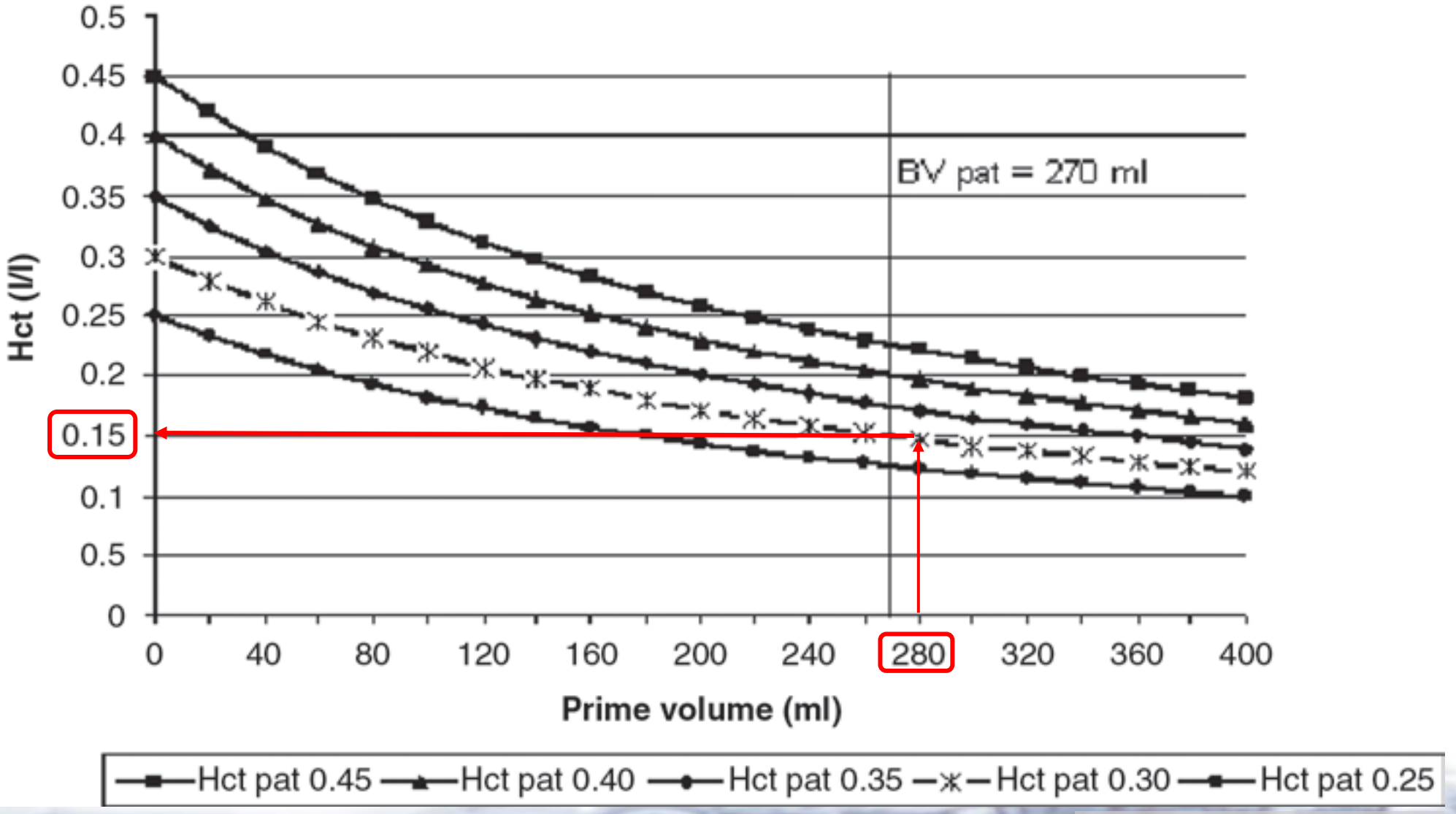
- **Immature organ systems**
- **Smaller circulation blood volumes**
- **Higher oxygen consumption rate**
- **Reactive pulmonary vascular bed**
- **Presence of intracardiac and extracardiac shunting**
- **Impaired temperature control**
- **Poor tolerance to microemboli**

# Hemodilution

$$P_{HCT} = \frac{Pt_{BV} \times Pt_{HCT}}{Pt_{BV} + Prime_{BV}}$$

PHCT= Predicted Pump HCT
PT. BV = Patient Calculated Blood Volume
PT.HCT = Patient HCT
PRIME BV = Total Priming Volume

# In 3kg-baby




Perfusion 25(4) 237–243

# Significant Hemodilution

↓ Clotting factors, plasma protein → dilution coagulopathy

↓ Colloid osmotic pressure → interstitial edema

Electrolyte imbalance

↑ Release of stress hormones

↑ Activation of complement, WBC, platelets

# Immature organ systems in neonate

## Liver

↓ Gluconeogenesis
Hepatic perfusion
Clotting factor

## Lung

↑ Potential for pulmonary edema
Pulmonary hypertension

## Kidney

↓ sodium reabsorption &excretion
concentration &diluting function

## Immune system

↓ Complement generation
Neonatal mononuclear cells

Prominent in Hemodilution

# Immature heart during CPB

Less compliant and less preload reserve

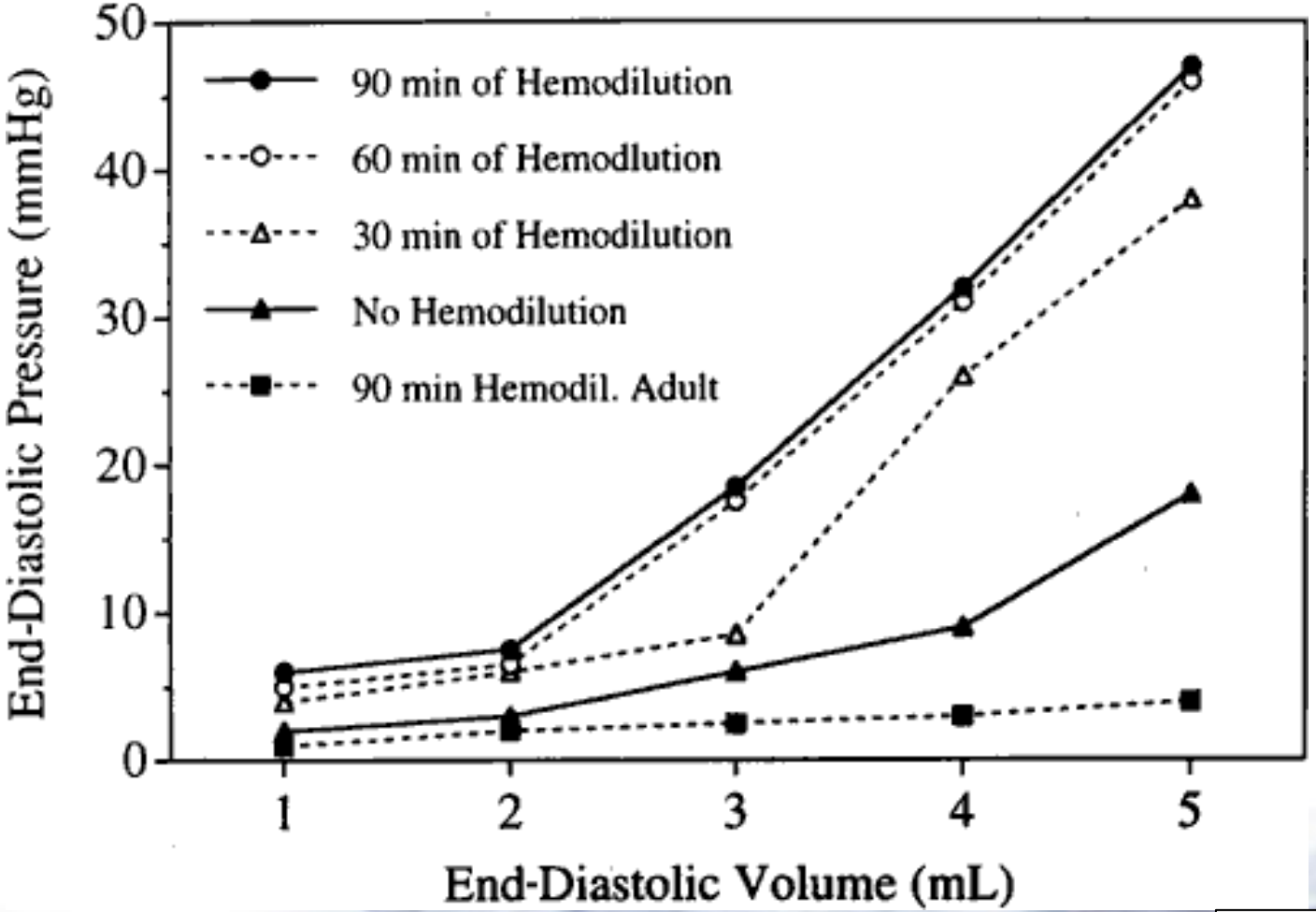
- very limited range on the Starling curve.

Inflammatory response to CPB

- microvascular leak → capillary leak syndrome
- when the heart becomes edematous → less compliant
- Higher filling pressures are required

Prominent in Hemodilution

# Duration of hemodilution related to LVEDV & LVEDP in Neonates




*Circulation* 1978;58:155–159

# Adverse effects and Potential risk of transfusion

- Infectious transmission
- Transfusion related acute lung injury
- Inflammatory response
- Immunologic compromise
- Graft vs host disease
- Volume overload

**Table 2** Transfusion reactions

| Immune-mediated | Nonimmune-mediated |
|---|---|
| Alloimmunization to: red blood cell antigens and HLA antigens | Infectious |
| Hemolytic transfusion reactions: acute and delayed | Volume overload |
| Febrile nonhemolytic transfusion reactions | Massive transfusion: metabolic, hypothermia, dilution and pulmonary microembolization |
| Allergic transfusion reactions | Miscellaneous: transfusion hemosiderosis, plasticizers |
| Posttransfusion purpura | |
| Transfusion-related acute lung injury | |
| Transfusion-associated graft versus host disease | |
| Transfusion-related immunomodulation | |

→ **Inflammatory response generated by CPB** ↑

Pediatric Anesthesia 21 (2011) 504–511

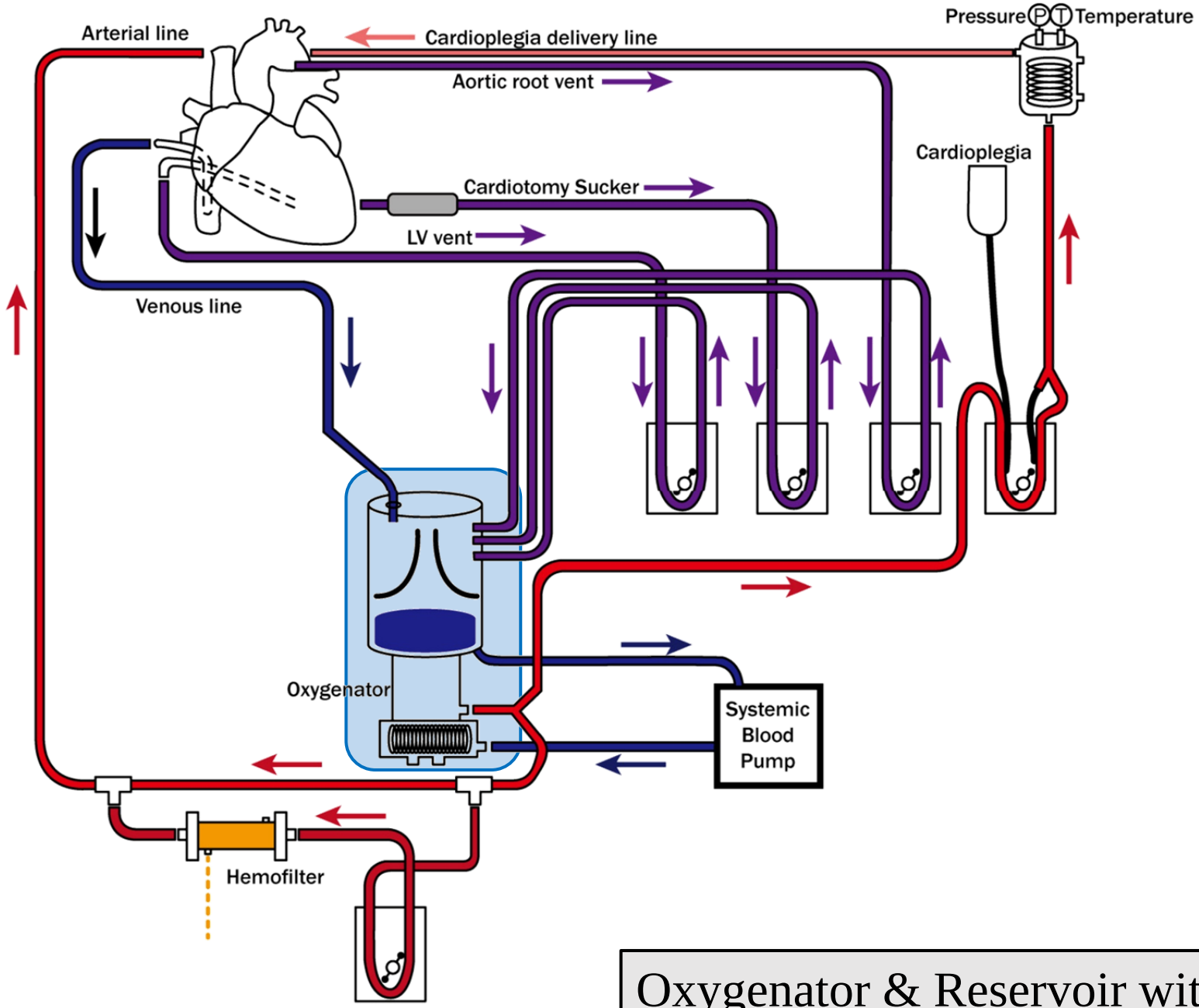
# Benefits of minimized prime volume

- Dilution of hemoglobin, platelets & coagulation factors
- Reduction priming volume – ameliorate inflammatory response independent from blood transfusion
- Reduced need for blood transfusion while maintain tissue oxygenation and patient safety

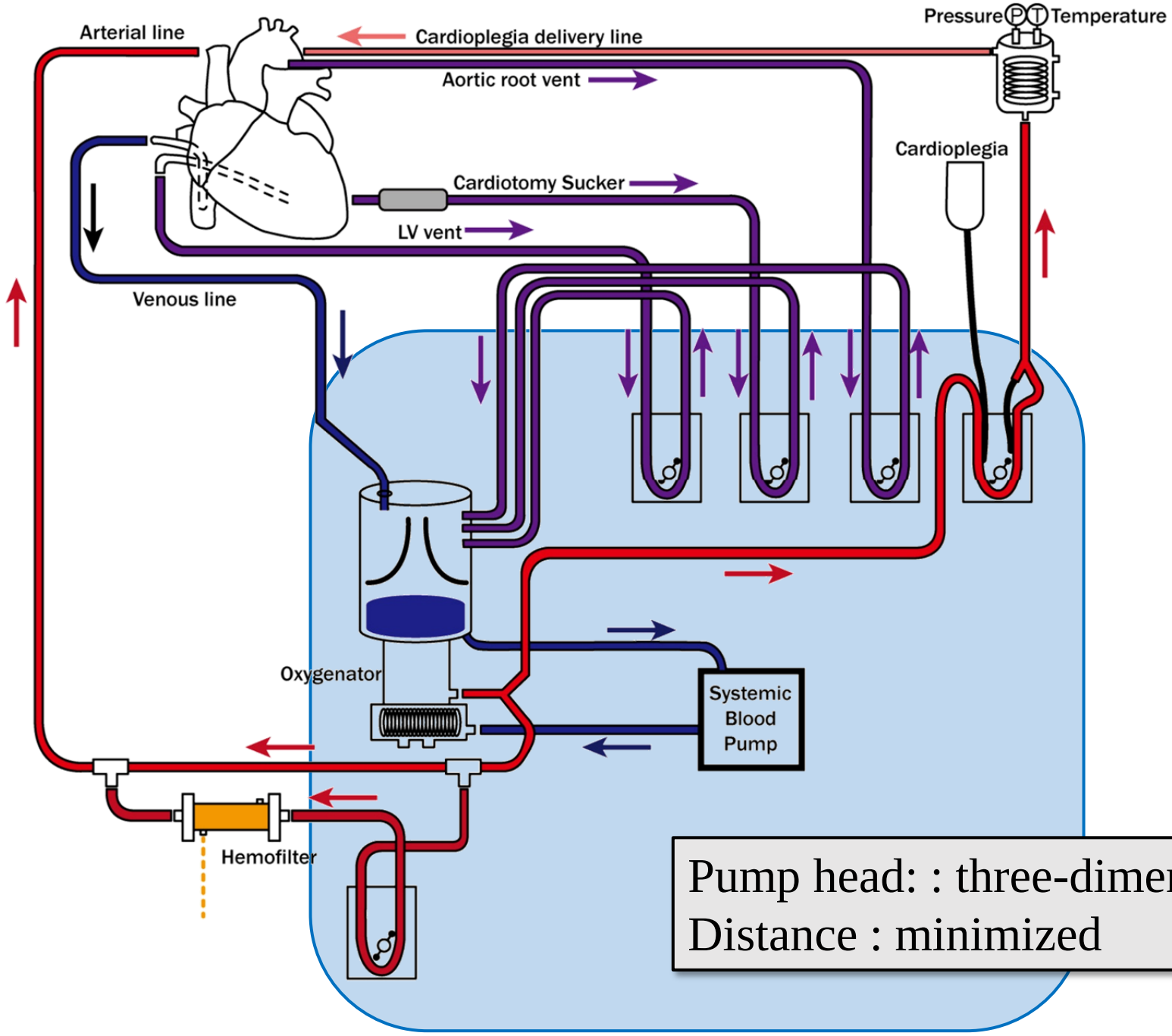
# Experience in SNUH

# Key points of mininmizing priming volume

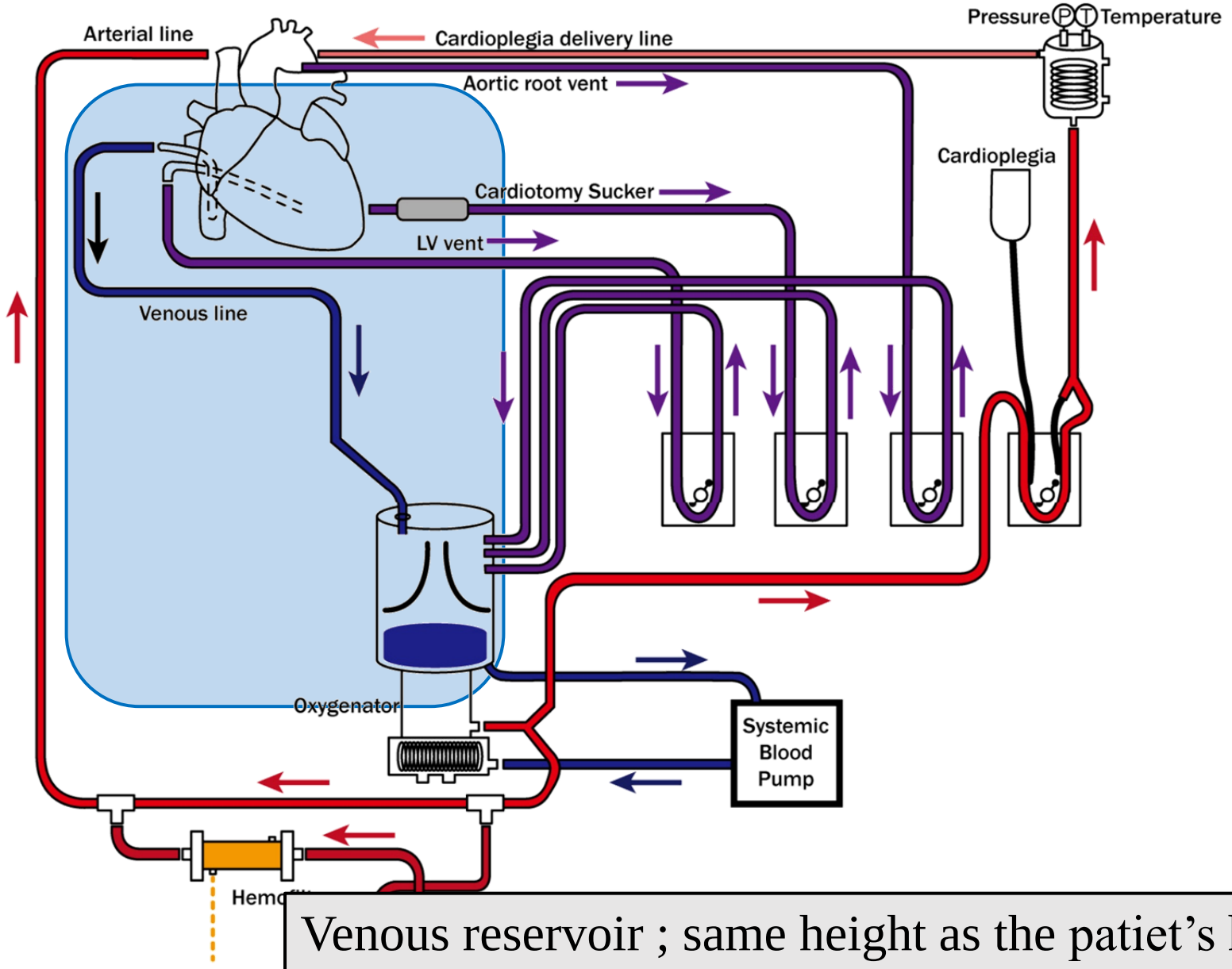
1. Oxygenators and hemofilters with small priming volumes
2. Small diameter circuit tubing (3/16 inch = 4.76 mm)
3. Length reduction
   - Heart-lung machines were positioned near the operator field
   - Aline + venous line = 170cm (30cc, 1.78mL/10cm)
   - Vent sucker head – venous reservoir : within 50cm
   - Minimizing the distance ; Arterial pump ~ Oxygenator
4. Venous reservoir ; same height as the patiet's heart
5. Draining venous blood with Vacuum assistance
6. Arterial line filter ; excluded
7. Minimum reservoir volume ; 15~25mL
8. Vigorous ultrafiltration



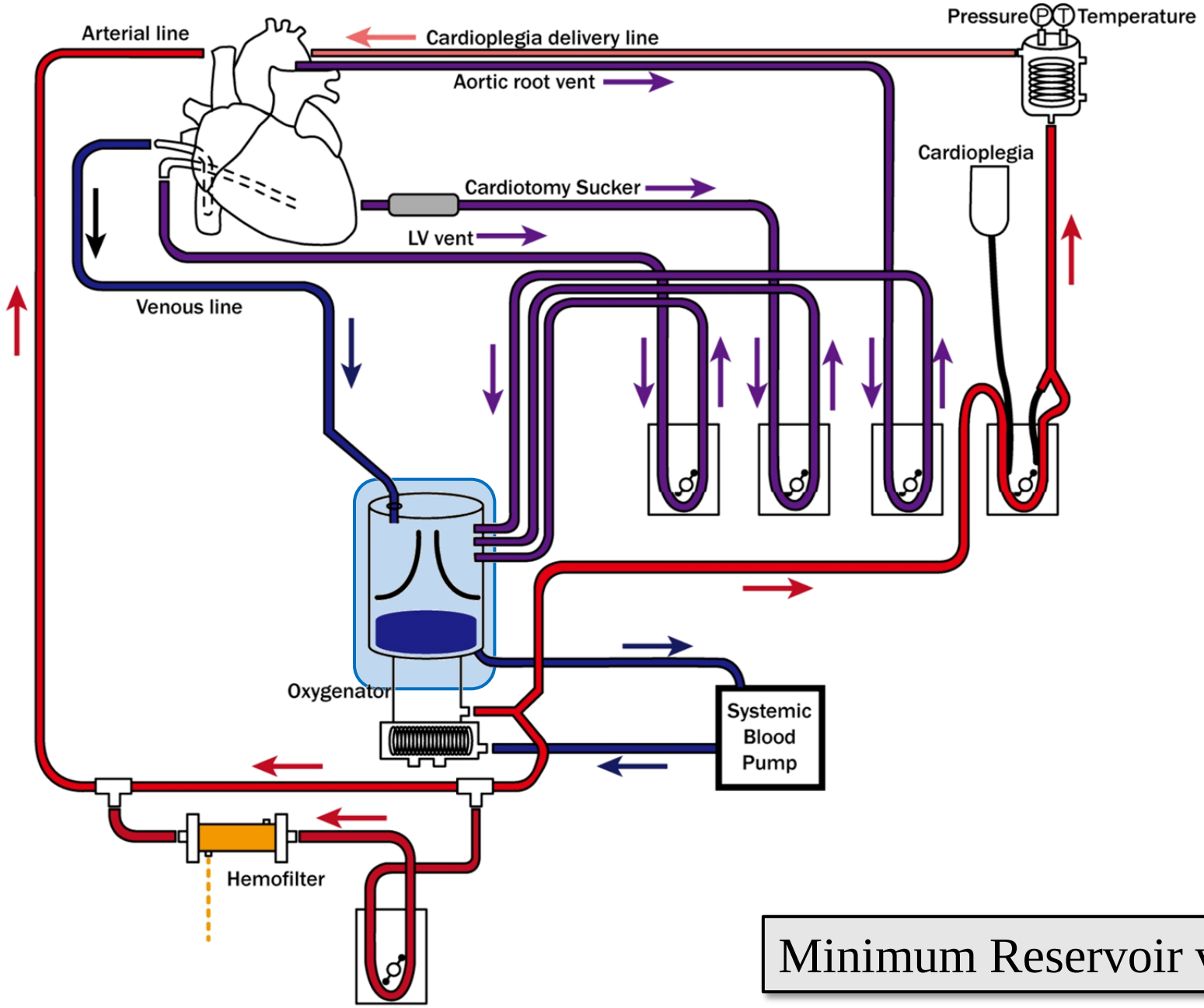

Oxygenator & Reservoir with small volume




Pump head: : three-dimension alignment
Distance : minimized




Venous reservoir ; same height as the patiet's heart
Draining Venous blood with Vacuum assistance




Minimum Reservoir volume

# Five-Year Experience With Mini-Volume Priming in Infants ≤5 kg: Safety of Significantly Smaller Transfusion Volumes

*Hyoung Woo Chang, *Jinhae Nam, *†Jae-Hee Cho,*Jeong-Ryul Lee, *Yong-Jin Kim, and *Woong-Han Kim

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2007 ~ 2012, 480 neonates and infants < 5kg

Mini-volume priming (MP) vs Conventional priming (CP)

Mean age : 48 ± 41 days

Mean body weight : 3.8 ± 0.8 Kg

Smallest Prime volume : 110 mL

*Artif Organs, Vol. 38, No. 1, 2014*

**TABLE 2.** *Composition of cardiopulmonary bypass system*

| | | Mini-volume priming methods ($n = 331$) | Conventional priming methods ($n = 149$) |
|---|---|---|---|
| Heart–lung machine | | Jostra HL30 | Sorin COBE Stroker HLM/Jostra HL30 |
| Oxygenator | | D-901 17 (5.1%)<br>Minimax Plus 1 (0.3%)<br>SAFE-micro 13 (3.9%)<br>SAFE-mini 1 (0.3%)<br>RX-05 298 (90.0%)<br>Quadrox neonate 1 (0.3%) | D-901 77 (51.7%)<br>D-902 1 (0.7%)<br>SAFE-micro 63 (42.3%)<br>SAFE-mini 1 (0.7%)<br>RX-05 7 (4.7%) |
| Height of reservoir | | Same as heart level | 80 cm below heart level |
| Hemofilter | | DHF-02 61 (18.4%)<br>FH22H 102 (30.8%)<br>Junior 14 (4.2%)<br>HPH400 3 (0.9%)<br>D150 151 (45.6%) | DHF-02 51 (34.2%)<br>FH22H 59 (39.6%)<br>Junior 1 (0.7%)<br>HPH400 1 (0.7%)<br>D150 37 (24.8%) |
| Vacuum drain | | Vacuum drainage only (−20 to −40 mm Hg) | Gravity drainage |
| Circuit tubing size | Arterial line | 3/16″ | 3/16″ |
| | Venous line | Mainly 3/16″ and 1/4″ | 1/4″ |
| | Cardiotomy | 3/16″ | 3/16″ |
| Arterial line filter | | Not used | |
| Bubble detector | | Not used | |
| Cardioplegic solution | | Basically crystalloid, mixed with small amount (<20 mL) of whole blood | |
| Ultrafiltration | | Applied | |
| Modified ultrafiltration | | Applied | |
| Content of priming solution | | Plasma solution<br>Voluven<br>20% albumin<br>$NaHCO_3$<br>Packed red blood cells | |

*Artif Organs, Vol. 38, No. 1, 2014*

**TABLE 4.** *Cardiopulmonary bypass parameters and postoperative outcomes*

| | Mini-volume priming group ($n = 331$) | Conventional priming group ($n = 149$) | $P$ value |
|---|---|---|---|
| CPB data | | | |
| CPB time (min) | 151 ± 60 | 133 ± 68 | 0.003 |
| ACC time (min) | 77 ± 45 | 71 ± 41 | 0.181 |
| TCA applied cases | 2 (0.6%) | 9 (6.0%) | 0.001 |
| TCA time (min) | 29 ± 27 | 37 ± 17 | 0.600* |
| Regional perfusion cases | 51 (15.4%) | 5 (3.4%) | <0.001 |
| Regional perfusion time (min) | 27 ± 12 | 26 ± 12 | 0.579* |
| Lowest rectal temperature (°C) | 26.1 ± 2.8 | 26.5 ± 3.6 | 0.976 |
| Hematocrit at CPB termination (%) | 26 ± 3 | 26 ± 4 | 0.878 |
| Total urine output during CPB (mL) | 106 ± 144 | 108 ± 149 | 0.901 |
| Hemofiltration during CPB (mL) | 429 ± 231 | 407 ± 189 | 0.263 |
| Modified ultrafiltration (mL) | 168 ± 96 | 174 ± 111 | 0.524 |
| CPB priming | | | |
| Plasma solution (mL) | 30.6 ± 18.1 | 78.1 ± 39.1 | <0.001 |
| Voluven (mL) | 28.2 ± 27.4 | 57.0 ± 36.8 | <0.001 |
| 20% Albumin (mL) | 48.8 ± 24.8 | 62.4 ± 24.6 | <0.001 |
| pRBC (mL) | 33.6 ± 17.2 | 94.6 ± 42.3 | <0.001 |
| Total priming volume (mL) | 141.3 ± 23.8 | 292.1 ± 49.5 | <0.001 |
| pRBC added during CPB (mL) | 48.2 ± 33.6 | 69.2 ± 63.3 | <0.001 |
| Lowest hematocrit during CPB (%) | 21.9 ± 3.1 | 21.8 ± 3.0 | 0.724 |
| Total transfusions via CPB (mL) | 81.6 ± 39.6 | 162.3 ± 82.3 | <0.001 |
| Postoperative neurological complications | 6 (1.8%) | 4 (2.7%) | 0.509 |
| Operative mortality (≤30 days) | 21 (6.3%) | 2 (1.3%) | 0.019 |

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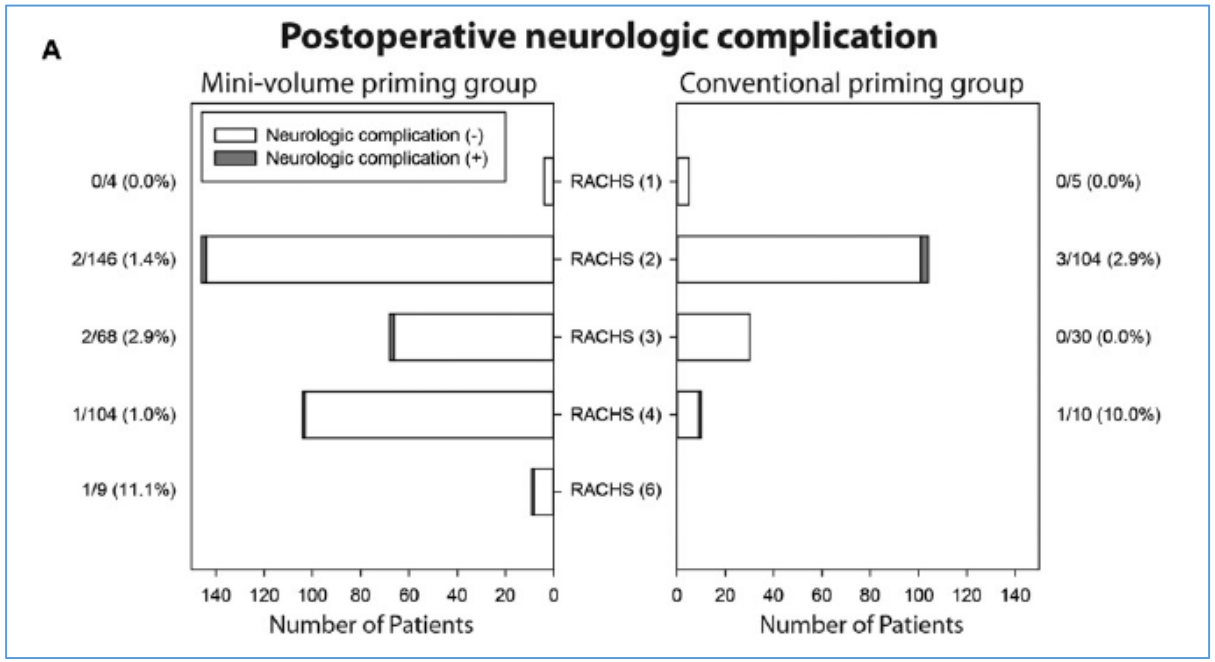


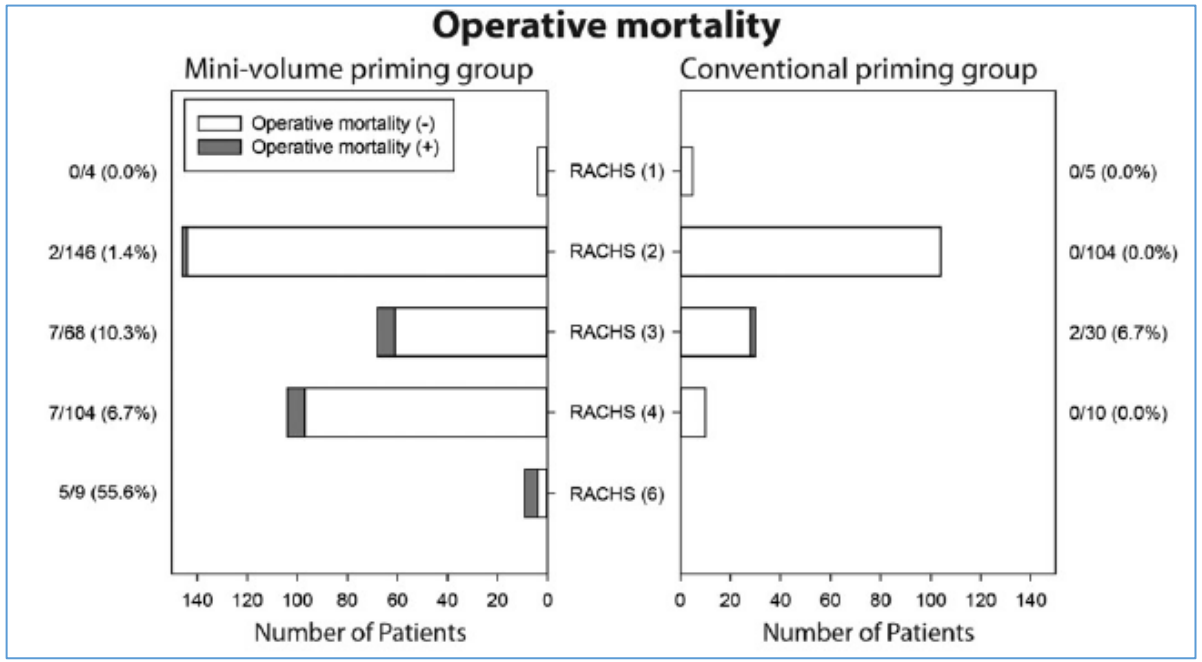


Risk factor of Postop neurologic complications : Age, BSA
Risk factor of Mortality : RACHS category

MP method : not a significant Risk factor

*Artif Organs, Vol. 38, No. 1, 2014*

# Future Direction

# Debate continues – Optimal Perfusion

- Further investigation is required to assess the

  "critical HCT as well as other perfusion variables"

  as a trigger for transfusion (with current practice)

- Follow-up studies are needed

  Does reduced transfusion result in better long-term outcomes?

# Superior neurologic outcome in children after exposure to higher Hct

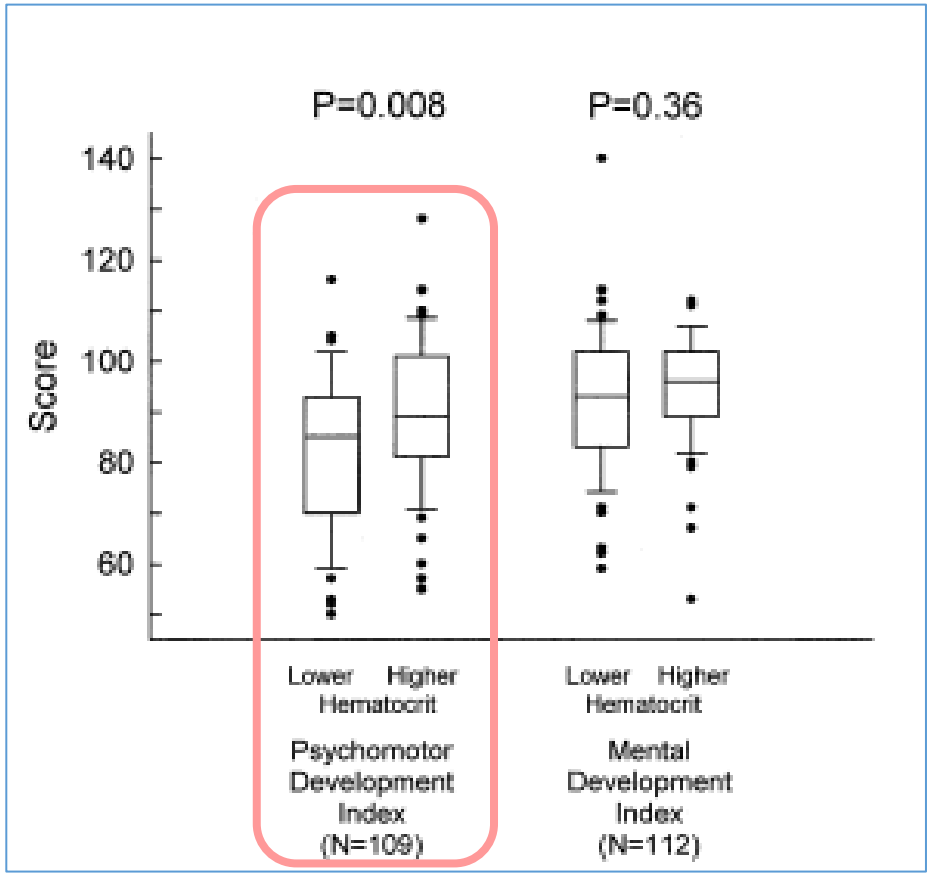


**TABLE 3. Scores on developmental tests according to treatment group**

| Test | Lower hematocrit level (n = 59), mean ± SD | Higher hematocrit level (n = 53), mean ± SD | *P* value* |
|---|---|---|---|
| Psychomotor Development Index | 81.9 ± 15.7 | 89.7 ± 14.7 | .008 |
| Mental Development Index | 92.1 ± 14.5 | 94.4 ± 11.0 | .36 |
| Psychomotor Development Index, no. with low score/total no. (%) | | | |
| ≤85 | 30/56 (54) | 22/53 (42) | .18 |
| ≤70 | 16/56 (29) | 5/53 (9) | .01 |
| Mental Development Index, no. with low score/total no. (%) | | | |
| ≤85 | 18/59 (31) | 6/53 (11) | .02 |
| ≤70 | 4/59 (7) | 2/53 (4) | .68 |

J Thorac Cardiovasc Surg 2003;126:1765-74

# The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: Results from the combined Boston hematocrit trials

David Wypij, PhD,[a,d,h] Richard A. Jonas, MD,[b,e,*] David C. Bellinger, PhD, MSc,[c,f] Pedro J. Del Nido, MD,[b,e] John E. Mayer, Jr., MD,[b,e] Emile A. Bacha, MD,[b,e] Joseph M. Forbess, MD,[b,e,†] Frank Pigula, MD,[b,e] Peter C. Laussen, MD,[a,g] and Jane W. Newburger, MD, MPH[a,d]

**TABLE 2. Perioperative and 1-year outcomes of 271 patients undergoing hypothermic CPB in infant heart surgery**

| Variable | n | Mean ± SD |
|---|---|---|
| Perioperative outcomes | | |
| Intraoperative fluid balance (mL) | 244 | 401 ± 259 |
| Intraoperative blood products (mL), median (range) | 270 | 208 (25–1383) |
| Serum lactate at 60 min after CPB (mmol/L) | 239 | 2.9 ± 1.6 |
| Nadir of cardiac index ($L \cdot min^{-1} \cdot m^{-2}$) | 102 | 3.1 ± 1.1 |
| Postoperative blood products (mL), median (range) | 271 | 111 (0–3551) |
| One-year outcomes | | |
| PDI | 215 | 86.2 ± 15.7 |
| MDI | 216 | 93.9 ± 12.4 |

*CPB*, Cardiopulmonary bypass; *SD*, standard deviation; *PDI*, Psychomotor Development Index; *MDI*, Mental Development Index.

Randomized trial of hematocrit strategy during CPB

271 infants, biventricular repair

- Psychomotor Developmental Index
- Mental Developmental Index

at age 1 year

J Thorac Cardiovasc Surg 2008;135:355-60

# We should challenge ourselves

- Encourage technology development and innovation
- Mini bypass circuitry
- Reduce transfusion
- Asanguinous CPB

# Transfusion Strategy in ECMO Support

고려대학교 안암병원 김태식

수혈(transfusion)을 받은 것에 대해 아무런 거부감이 없는 사람은 없을 것이다. 심지어 특정 종교의 신념에 의거해, 생명을 담보로 수혈 받기를 거부하는 경우도 있다. 그러나, 대개는 의학적으로 필요하다고 판단되면 별 무리 없이 우리 주변에서 수혈이 진행된다. 더욱이 생과 사의 기로에 직면해 있는 상황에서는 보다 빈번에 수혈이 이루어지는 경향이 있는 것 같다.

ECMO(extracorporeal membrane oxygenation) support를 받는 환자는 기본적으로 anticoagulation의 문제를 가지고 있기 때문에, transfusion에 관한 한 단순히 정리되게 어려운 점이 있어 보인다. 그럼에도 불구하고, Extracorporeal Life Support Organization(ELSO)는 수치화된 guideline을 제시하고 있다. 약 30 ~ 40% 이상의 정상 hematocrit을 유지하기 위해 pack RBC replacement를 권장한다. 검사 수치상 PT INR이 1.5 ~ 2.0 이상이거나 의미있는 bleeding이 진행중이라면 10ml/kg volume의 FFP를 수혈하는 것이 좋다. 또한, fibrinogen 수치가 100 ~ 150 mg/dl 이하이면 cryoprecipitate를 줄 수 있을 것이다. 신생아일 경우, 혈액검사 소견에서 platelet count가 100,000 cells/$mm^3$ 이상을 유지하도록 10 ml/kg volume의 platelet transfusion이 권고된다. 그러나, 성인에서는 platelet count threshold를 조금 낮게 정해도 될 것이다.

권위 있는 기관의 위와 같은 guideline은 정량화된 수치를 제시하고 있기 때문에, 실제 환자 옆에 서 있는 우리의 고민거리를 줄여 주는 것 같다. 그러나, 높은 수준의 명백한 근거에 기초한 protocol이라기 보다는 다소 낮은 수준의 문헌들이나 권위자의 임상적 경험들에 의거하고 있다는 것을 간과해서는 안 될 것이다. 또한, 다른 분야와 비교하여 높은 수준의 연구를 진행하기 어렵다는 ECMO가 지닌 본래의 특성뿐만 아니라, 비교적 new technology라는 한계점을 인정해야 한다. 그러므로, 기존 개별 연구의 design을 충분히 이해하고 각각의 주장이나 결론을 통합적으로 분석하는 일련의 노력들을 통해 보다 진일보하고 보다 적절한 strategy를 모색해 볼 수 있을 것이다.

# 한국, 미국, 일본 중환자 진정/진통/섬망 가이드라인 비교

계명대학교 동산병원
흉부외과/중환자의학과
김 재범

# 비교한 가이드라인

1) 한국: 2010 성인중환자실에서 진정, 진통의 임상진료지침
2) 미국: 2013 PAD guideline
3) 일본: 2014 Japanese guidelines for the management of Pain, Agitation and Delirium in intensive care unit (J-PAD)

# Japanese guidelines for the management of Pain, Agitation and Delirium in intensive care unit (J-PAD)

# 배경

1) 2009년 일본집중치료학회 보고서에 의한 진료지침 개정 필요성 대두

2) 2013년 미국 중환자의학회의 진료지침 개정

3) 일본 내 진료 및 시설 수준을 감안한 진료지침 필요

4) 개정된 미국 중환자의학회의 진료지침의 보완 필요

(자발호흡중인 환자의 관리 및 신체 억제 등에 관한 문제)

# 작성방법

1) 임상 현장에서 직면하는 의문(clinical question, CQ)
   에 대한 답변 형식으로 작성

2) 참고 문헌에 대한 검색 및 평가는 2013 PAD
   guideline의 방법과 동일

3) 참고문헌의 대상 시기

   - 영어문헌: 2014년 2월까지 공표된 문헌
   - 일본어 문헌: 1996년~2013년 2월 중 공표된 문헌

# 문헌평가

| 문헌수준 | 연구등급 | 연구유형 | |
|---|---|---|---|
| A | 상(高) | RCT(well designed) | 예상되는 결과가 이후 연구에 의해 변동되지 않을 것으로 판단되는 경우 |
| B | 중(中等度) | RCT or Observational Study(well designed) | 향후 연구에 의해 영향을 받을 가능성이 있는 경우 |
| C | 하(低) | Observational Study | 향후 연구에 의해 영향을 받을 가능성이 높을 경우 |

# 권장 정도

| | |
|---|---|
| 강한 권장(1) | 기대되는 효과가 예상되는 부정적 반응을 상쇄한다. |
| 약한 권장(2) | 기대되는 효과가 예상되는 부정적 반응을 상회할 것으로 예상되지만,<br>충분한 근거가 부족하거나 불명확하다. |

# Pain (한국)

1) 통증의 평가와 통증치료에 대한 반응은 적합한 방법에 의해 규칙적으로 평가하고 체계적으로 기록하여야 한다(Grade of recommendation C).

2) 환자에 의하여 보고되는 통증의 정도는 통증 및 이의 치료에 대한 반응 평가의 표준치로 고려되어야 한다. 통증의 평가 수단으로는 NRS의 사용이 추천된다(Grade of recommendation B).

3) 의사 표현을 할 수 없는 환자들은 통증 관련 행동(움직임, 표정, 자세)과 생리적 지표(심박수, 혈압, 호흡수) 및 이들의 통증 완화 치료에 따르는 변화를 관찰함으로써 평가하여야 한다(Grade of recommendation B).

# Pain

## SCCM

- Pain assessments be routinely performed in all adult ICU patients (+1B)
- Behavioral Pain Scale (BPS) and Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain scales for monitoring pain in medical, postoperative, or trauma (excepts for brain injury) adult ICU patients who are unable to self-report, and in whom motor function in intact and behaviors are observable. (B)

## JSICM

⇨ 통증을 평가하는 타이밍으로 바이탈 사인을 이용해도 좋다고 제안할 수 있다(+2C).

⇨ 환자가 통증을 스스로 말할 수 있는 경우에는 Numeric Rating Scale(NRS)이나 Visual Analogue Scale(VAS)가, 스스로 말할 수 없는 경우에는 Behavioral Pain Scale(BPS), Critical-Care Pain Observation Too(lCPOT)를 권장한다(B)

⇨ NRS < 3, 혹은 VAS < 3, 혹은, BPS < 5 혹은 CPOT < 2 를 통증대책 목표 점수로 조치할 것을 권장한다(B).

# Pain (한국)

4) 치료 계획 및 진통의 목표가 각 환자에서 정해져야 하고 이는 일관성 있는 진통 요법을 위하여 모든 치료자들이 공유하여야 한다(Grade of recommendation C).

5) 만약 마약성 진통제의 정주가 필요하다면 fentanyl, hydromorphone, 그리고 morphine 등이 추천되는 약제들이다(Grade of recommendation C).

# Pain (한국)

6) NSAIDs 혹은 acetaminophen은 선택된 환자에서 마약성 진통제의 보조제로 사용할 수 있다(Grade of recommendation B).
7) 다른 NSAIDs는 적절한 환자들에서 경구용으로 투여할 수 있다(Grade of recommendation B).
8) Ketamine을 투여함으로써 진통제의 진통효과를 증가시킬 수 있다.

# Pain (한국)

9) 일관성 있는 진통작용을 얻기 위해서는 일정한 시간 간격으로 계획된 약물 투여나 지속 정주하는 방법이 '필요 시 투여' 하는 방법보다 더 유용하다(Grade of recommendation B).

10) 만일 환자가 이해하고 장치를 작동할 수 있다면 마약성 진통제의 투여 시 PCA 장치를 사용하는 것이 도움이 된다 (Grade of recommendation B).

# Pain (한국)

11) 급성 상태의 환자에서는 빠른 진통작용을 원한다면 fentanyl을 사용하는 것이 좋다(Grade of recommendation C).

12) 혈역학적으로 불안정한 환자나 신부전 환자에서는 fentanyl이나 hydromorphone을 사용하는 것이 좋다(Grade of recommendation C).

13) 간헐적 투여가 불가피할 경우에는 작용시간이 긴 morphine과 hydromorphone을 사용한다(Grade of recommendation C).

# Pain

## SCCM

- Preemeptive analgesia and/or non-pharmacologic interventions (e.g., relaxation) should be administered to alleviate pain in adult ICU patients before chest tube removal. (+1C)
- For other types of invasive and potentially painful procedures in adult ICU patients, preemptive analgesic therapy and/or non-pharmacologic interventions may also be administered to alleviate pain. (+2C)

## JSICM

⇨ 흉강 드레인(Drain)의 제거나 상처 처치와 같은 통증을 동반하는 처치 전에는 진통에 대해 고려해야 한다(B).

⇨ 성인 ICU 환자에서 흉강 드레인 제거 시 이외의 침습적 처치나 통증을 동반할 가능성이 있는 처치에서도, 통증을 경감시키기 위해 선행성 진통이나 비약리적 조치를 시행할 것을 제안한다(+2C)

⇨ 진통 처치 전후에 통증 정도를 평가하는 게 중요하다(B).

# Pain

## SCCM

- Intravenous opioids should be considered as the first ling drug class of choice to treat non-neuopathic pain in critically ill patients. (+1C)
- All available intravenous opioids, when titrated to similar pain intensity endpoints, are effective. (C)
- Dexmedetomidine reduce need for opioids.

## JSICM

- ICU 환자의 통증을 치료하기 위해서는 정맥주사 오피오이드를 제 1 선택약으로 삼을 것을 장려한다(+1C).

# Pain

## SCCM

## JSICM

- ⇨ 의사, 간호사, 임상공학기사, 약제사, 이학요법사 등 환자 관리에 관한 모든 직종이 공통된 통증평가 척도를 사용하여 주기적, 계속적으로 평가하도록 제안한다(+2C).
- ⇨ 진통제 투여 방법으로는 환자의 자기 조절 진통법(patient controlled analgesia, PCA) 기능이 있는 펌프를 사용한다면 환자의 판단으로 추가 투여가 가능해진다. ICU에서도 수술/시술 후 진통에 사용했을 때, 조기이상(早期離床)에 좋은 영향을 미칠 가능성이 있다(C).
- ⇨ 의식이 또렷한 환자는 PCEA (patient controlled epidural analgesia, PCEA) 를 간호사가 관리하기보다 환자 스스로 관리하는 편이 통증을 제어하는 게 양호했다.

# Sedation (한국)

1) SAS, MAAS, VICS 같은 진정 평가 척도의 사용이 권장된다 (Grade of recommendation B).
2) BIS와 같은 객관적인 체계는 아직까지는 완전한 평가가 되어있지 않아 중환자실에서의 유용성이 확립되지 않았다 (Grade of recommendation C).

# Sedation (한국)

3) Acute agitation (급성격앙) 환자에서 신속한 진정을 위해서는 midazolam을 사용한다(Grade of recommendation C).

4) Propofol은 신경학적 평가나 기관내관 제거 등을 위해 신속한 각성이 필요한 경우에 유용하다(Grade of recommendation B).

5) Midazolam을 48–72시간 이상 사용하면 각성의 회복이나 기관내관 제거 시간의 예측이 어려워지므로 단기간 사용하는 것이 권장된다(Grade of recommendation A).

# Sedation (한국)

6) Lorazepam은 72시간 이상의 진전이 필요한 대부분의 환자에서 선호되는 진정제이다(Grade of recommendation B).

7) 불필요한 장기 간 진정을 피하기 위해 용량 자체의 체계적인 감량 또는 매일 설정된 진정 목표에 대한 용량을 재조정하여야 한다(Grade of recommendation A).

8) 해당 중환자실의 적절한 진정제 투여지침이나 치료흐름도 또는 프로토콜을 만들어 사용하는 것이 권장된다(Grade of recommendation B).

# Sedation (한국)

9) Propofol 정주 2일 후부터는 중성지방 농도를 감시해야 하고 유탁액 내 지방 열량을 총 열량에 포함시켜야 한다(Grade of recommendation B).

10) Benzodiazepine 및 propofol 금단 증상은 고용량 치료 시와 일주일 이상 지속 정주한 경우 발생할 가능성이 높다. 이러한 약물은 금단 증상을 예방하기 위해 체계적으로 감량해야 한다(Grade of recommendation B).

# Sedation

## SCCM

- Maintaining light levels of sedation in adults ICU patients is associated with improved clinical outcomes (e.g., shorter duration of MV and a shorter ICU length od stay). (B)
- Maintaining light levels of sedation increases the physiologic stress response, but is not associated with an increased incidence of myocardial ischemia. (B)
- Sedative medications should be titrated to maintain a light rather than a deep level of sedation in adult ICU patients. (+1B)

## JSICM

⇨ 얕은 진정심도를 유지함으로써 환자 스트레스 반응을 증가시킬 수도 있으나(C), 심근허혈 빈도가 증가하지는 않는다(B). 금기가 아니라면 깊은 진정심도보다 얕은 진정심도로 관리하는 것을 장려한다(+1B)

.

⇨ 목표 진정심도를 RASS=- 2 ~ 0 , SAS= 3 ~ 4 로 삼고 있다.

⇨ 과잉 진정인 경우, 진정제 투여를 중단하고, 목표 진정심도에 도달하면 중단 전 50% 용량으로 재개한다.

# Sedation

## SCCM

- Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients. (B)
- Objective measures of brain function (e.g., AEP, BIS, NI, PSI, and SE) be used as an adjunct to subjective sedation assessments in adult ICU patients who are either comatose or who are receiving neuromuscular blocking agents. (+2B)
- EEG monitoring be used to monitor non-convulsive seizure activity, and to titrate electrosuppressive medication to obtain burst suppression in adult ICU patients with either known or suspected seizures. (+1A)

## JSICM

인공호흡 중인 성인 환자에서는 진통을 우선적으로 시행하는 진정법 (analgesia-first sedation)을 시행할 것을 제안한다(+2B).

일본내 설문조사 결과에서 미다졸람, 프로포폴과 더불어 덱스메데토미딘이 ICU 환자 진정에 이용되는 일반적인 약제가 되었고, 로라제팜 사용은 감소하였으며, 바르비투르산계 약, 디아제팜, 케타민 빈도는 거의 없어졌다.

# Sedation

**SCCM**

- Sedation strategies using non-benzodiazepine sedatives may be preferred over sedation with benzodiazepines to improve clinical outcomes in mechanically ventilated adult ICU patients. (+2B)

**JSICM**

인공호흡 관리 중에는 '매일 진정을 중단한다' 혹은 '얕은 진정심도를 목표로 한다'는 프로토콜 중 어느 한 쪽을 루틴으로 사용할 것을 장려한다(+1B).

인공호흡 중인 성인 환자에게 진정제를 투여할 경우에는 벤조디아제핀계 진정제보다도 비벤조디아제핀계 진정제를 우선적으로 사용할 것을 제안한다(+2C).

# Delirium (한국)

1) 중환자실에 입실한 환자에서 섬망에 대한 평가가 필요하며 CAM-ICU를 이용하여 평가하며 NEECHAM이나 ICDSC을 평가 방법으로 사용할 수도 있다.
2) 섬망 시 치료제는 haloperidol를 사용할 수 있으며 사용 시에 부작용에 대한 감시가 필요하며 특히 심전도에 대한 감시를 요한다.
3) Haloperidol을 사용할 수 없을 때에 Olanzapine, Risperidone과 같은 약제를 고려할 수 있다.

# Delirium

## SCCM

- Delirium is strongly associated with increased mortality in adult ICU patients. (A)
- Delirium is strongly associated with prolonged length of stay in adult ICU patients. (A)
- Delirium is moderately associated with the development of post-ICU cognitive impairment in adult ICU patients. (B)

## JSICM

# Delirium

## SCCM

- Routine monitoring for delirium in adult ICU patients (+1B)
- The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools in adults ICU patients. (A)
- Routine monitoring of delirium in adult ICU patients is feasible in clinical practice. (B)

## JSICM

# Delirium

## SCCM

- Four baseline risk factors are significantly associated with the development of delirium in the ICU: pre-existing dementia; history of hypotension; history of alcoholism; and admission severity of illness. (B)
- There are conflicting data surrounding the relationship between the use of opioids and the development of delirium in adult ICU patients. (B)
- Benzodiazepines may be a risk factor for the development of delirium in adult ICU patients. (B)

## JSICM

⇨ 연령, 중증도, 감염(패혈증), 기존의 인지기능장애

⇨ 벤조디아제핀계 진정제와 오피오이드는 성인 ICU 환자의 섬망 발증에 관련된 ICU 치료 관련 인자이다(B).

⇨ 인공호흡 중인 성인 환자에게 진정제를 투여할 경우에는 벤조디아제핀계 진정제보다도 비벤조디아제핀계 진정제를 우선적으로 사용할 것을 제안한다(+2C).

# Delirium

## SCCM

- Coma is an independent risk factor for the development of delirium in ICU patients. Establishing a definitive relationship between various subtypes of coma (i.e., medication-related, structural, neurological, medical) and delirium in ICU patients will require further study. (B)

## JSICM

⇨ 모든 혼수가 ICU 환자의 섬망 발증의 위험 인자라고는 할 수 없다(B).

# Delirium

**SCCM**

- In mechanically ventilated adult ICU patients who are at risk for developing delirium, dexmedetomidine administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepines administered for sedation. (B)

**JSICM**

# Delirium

## SCCM

- Early mobilization of adult patients be performed whenever feasible to reduce the incidence and duration of delirium. (+1B)
- No recommendation for the use of a pharmacological (including DEX) or combined non-pharmacological & pharmacological delirium prevention protocol in adult ICU patients (0, C)

## JSICM

⇨ 비정형적 항정신병약 예방 투여는 시행하지 않도록 제안한다(-2C).

# Delirium

## SCCM

- Neither haloperidol nor atypical antipsychotics be administered to prevent delirium in adult ICU patients. (-2C)
- No specific recommendation on delirium treatment

## JSICM

⇨ 할로페리돌 투여가 ICU 환자의 섬망 발증을 예방한다고 하기 어렵다(0, C).

- 일본에서 승인된 투여량으로 덱스메데토미딘을 ICU 환자의 섬망 예방을 목적으로 사용할 것인지에 대해서는 불분명하다 (0, C).

# Delirium

## SCCM

- Recommend either daily sedation interruption or light target level of sedation be routinely used in mechanically ventilated adult ICU patients. (+1B)
- Suggest analgesia-first sedation be used in adult ICU patients who are mechanically ventilated. (+2B)

## JSICM

⇨ 인공호흡 관리 중에는 '매일 진정 중단(daily awakening)' 혹은 '얕은 진정심도 유지(light sedation)' 프로토콜 중 어느 한 쪽을 루틴으로 사용할 것을 장려한다(+1B). 현 시점에서는 '매일 진정 중단(daily awakening)'과, 환자가 늘 각성해 있어 협력적이고 편안한 '얕은 진정심도 유지(light sedation)', 둘 중 어느 쪽이 더 나은지는 분명하지 않다.

# 수면 (한국)

1) 중환자실에 입실한 환자에서 수면에 대한 평가가 필요하다.

2) 비 약물적 치료를 이용하여 적절한 수면을 유지시키는 노력이 필요하다.

# 수 면

## SCCM

- Recommend that sleep should be promoted in adult ICU patients by optimizing patients' environments in order to protect patients' sleep cycle. (+1C)
- Recommend that a multidisciplinary ICU team approach that includes provider education, preprinted and/or computerized protocols and order forms, and a quality ICU rounds checklist be used to facilitate pain, agitation, and delirium management guidelines or protocols in adult ICUs. (+1B)

## JSICM

- 진정제 필요량과 환자의 불안을 줄이기 위해, 가능한 경우에는 언제든 음악을 사용한 조치를 시행할 것을 제안한다(+2C).
- 조명이나 소리를 조절하고, 적극적으로 케어를 낮 동안에 집중시키는 등, 야간 수면 환경을 갖추는 다각적인 대처법을 장려한다(+1C).

# Others

## SCCM

## JSICM

- ⇨ 신체억제는 환자를 위험에 빠뜨리지 않고 이용할 수 있는 대안이 없는 경우에만 시행해야 하며, 일상적으로 사용해서는 안 된다(-1C).

- ⇨ 통증을 느끼는 비삽관 환자(NPPV 포함)는 통증 레벨을 평가하여 적절한 대책을 시행할 것을 장려한다(+1B). 다만, 비삽관 환자에 대한 진통, 진정제의 일상적 사용을 장려할 근거는 없다(0, No Evidence).

# Take home message

- Pain control
- Light sedation
- Delirium control
- Enough good sleep
- Early mobilization

# Post Intensive Care Syndrome (PICS)

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Yonsei University College of Medicine
Department of Anesthesiology & Pain Medicine

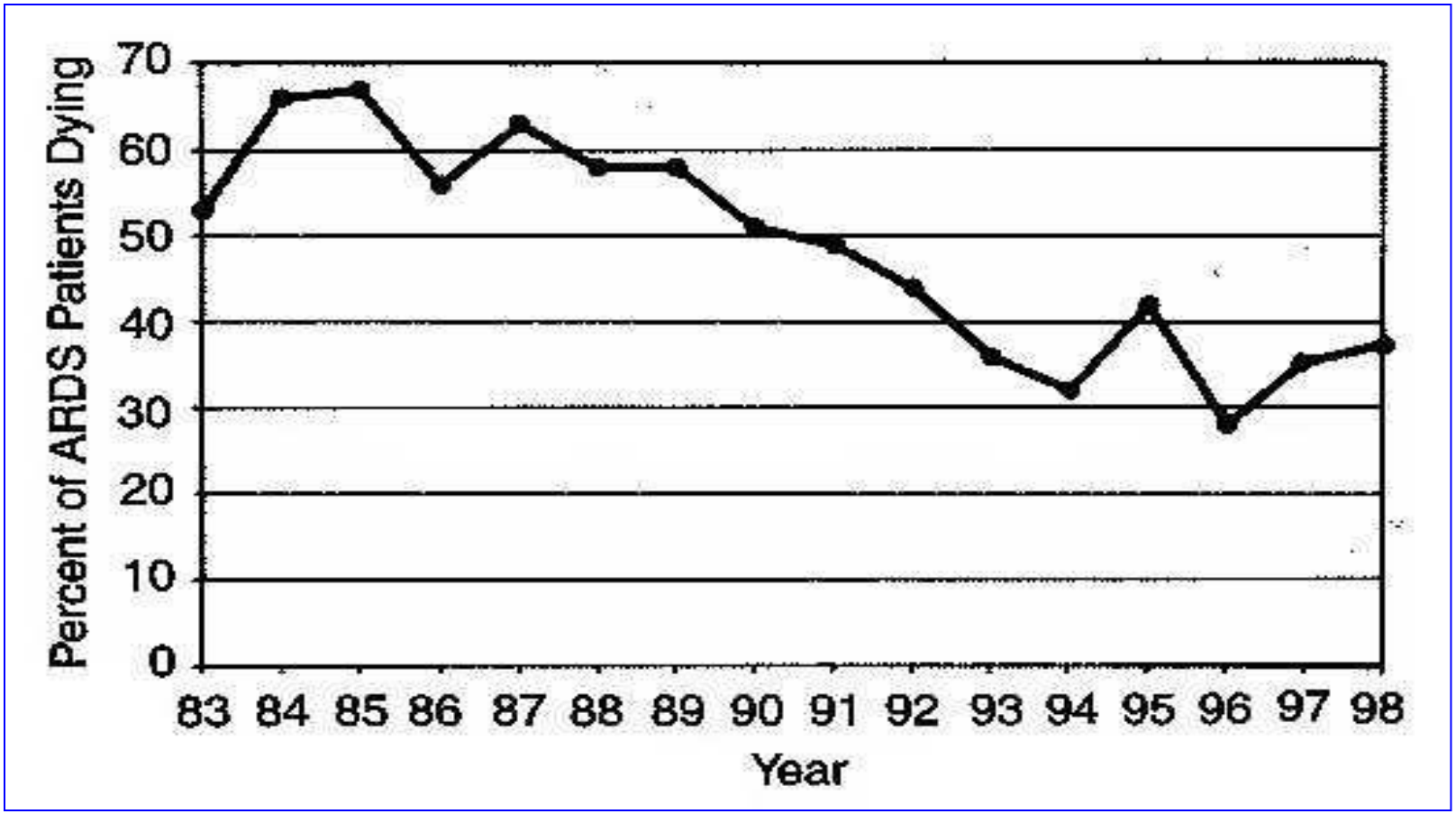
# PICS

- Introduction
- Definition
- 3 categories
  - Mental health: anxiety, PTSD, depression
  - Cognitive impairment: memory, attention,
  - Physical impairment: pulmonary, neuromuscular

# PICS

- Epidemiology
- Risk Factors
- Clinical Manifestations
- Dx
- Prevention & Treatment

# ARDS mortality



The NEW ENGLAND JOURNAL of MEDICINE

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# One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Angela M. Cheung, M.D., Ph.D., Catherine M. Tansey, M.Sc., Andrea Matte-Martyn, B.Sc., Natalia Diaz-Granados, B.Sc., Fatma Al-Saidi, M.D., Andrew B. Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Aiala Barr, Ph.D., Deborah Cook, M.D., and Arthur S. Slutsky, M.D., for the Canadian Critical Care Trials Group

# **109** ARDS survivors
# 3, 6, & 12 months after discharge from ICU
# Interview, P/E, PFT, 6 min-walk test & QOL

## 71% restored BW in 1 y

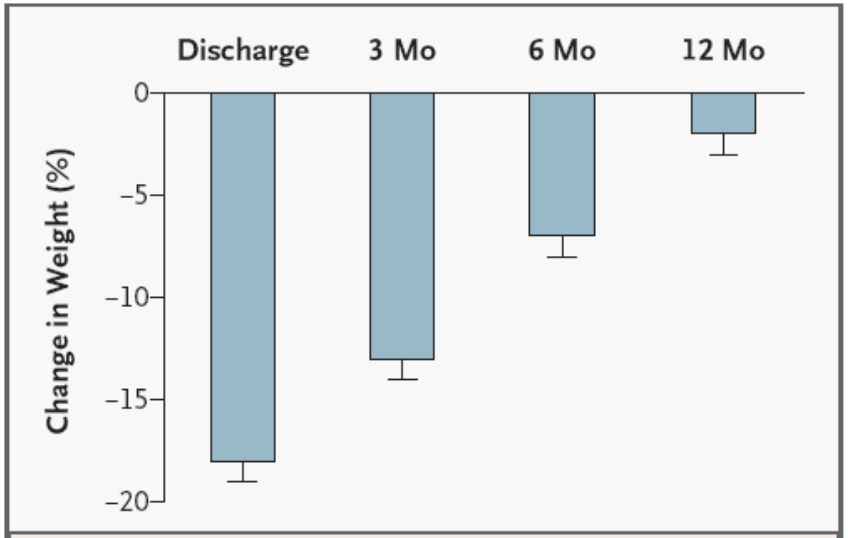
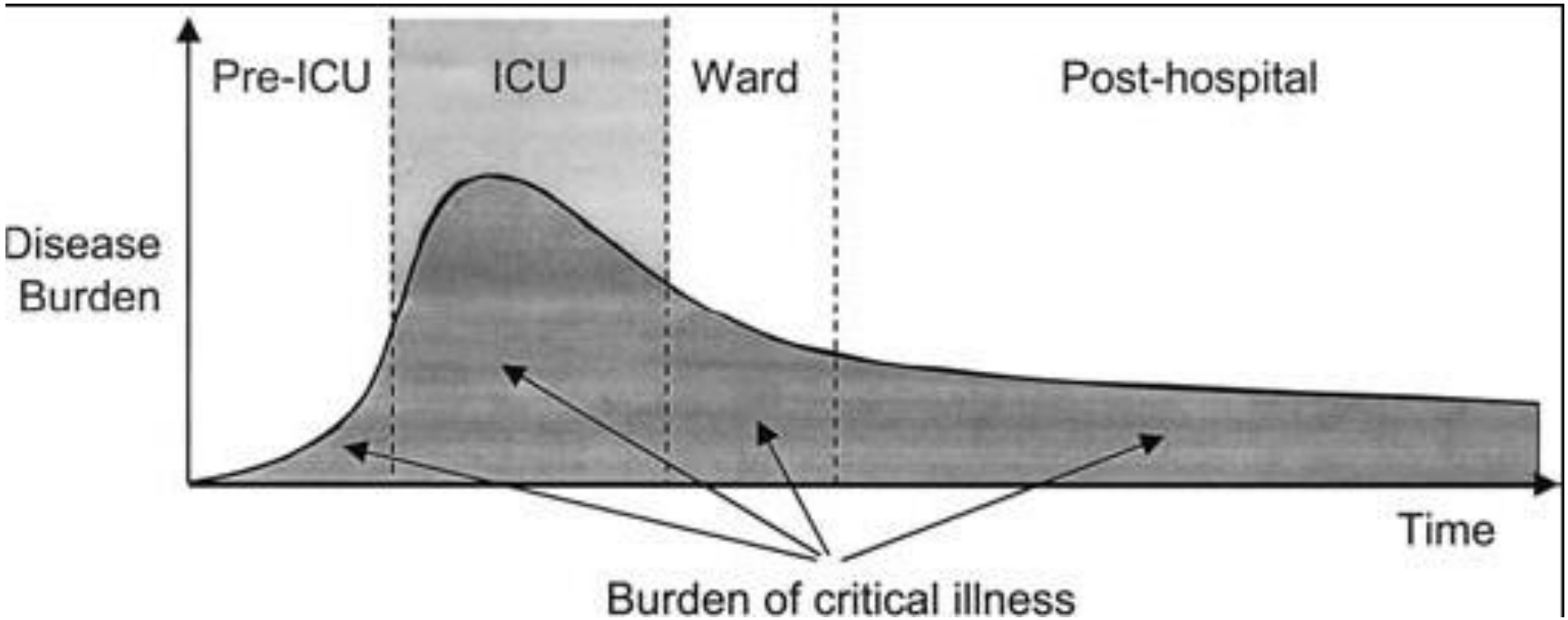



**Figure 2.** Mean (+SE) Change in Weight from Base Line among Patients with the Acute Respiratory Distress Syndrome at the Time of Discharge from the ICU and at 3, 6, and 12 Months.

## PFT

**Table 2.** Recovery of Pulmonary Function among Patients with the Acute Respiratory Distress Syndrome during the First 12 Months after Discharge from the ICU.

| Variable | 3 Mo (N=71)* | 6 Mo (N=77)† | 12 Mo (N=80)‡ |
|---|---|---|---|
| | *median (interquartile range)* | | |
| Forced vital capacity (% of predicted) | 72 (57–86) | 80 (68–94) | 85 (71–98) |
| Forced expiratory volume in one second (% of predicted) | 75 (58–92) | 85 (69–98) | 86 (74–100) |
| Total lung capacity (% of predicted)§ | 92 (77–97) | 92 (83–101) | 95 (81–103) |
| Residual volume (% of predicted)§ | 107 (87–121) | 97 (82–117) | 105 (90–116) |
| Carbon monoxide diffusion capacity (% of predicted)§¶ | 63 (54–77) | 70 (58–82) | 72 (61–86) |


Pre-ICU
ICU
Ward
Post-hospital
Disease Burden
Time
Burden of critical illness

# Survival -> Survival + QOL

Paradigm Shift

# Definition of PICS

- new or worsening function in one or more of the following domains after critical illness.
  - **Cognitive function**
  - **Psychiatric function**
  - **Physical function**
- **PICS-family**: effects of critical illness on acute/chronic psychological morbidity among patients' family members

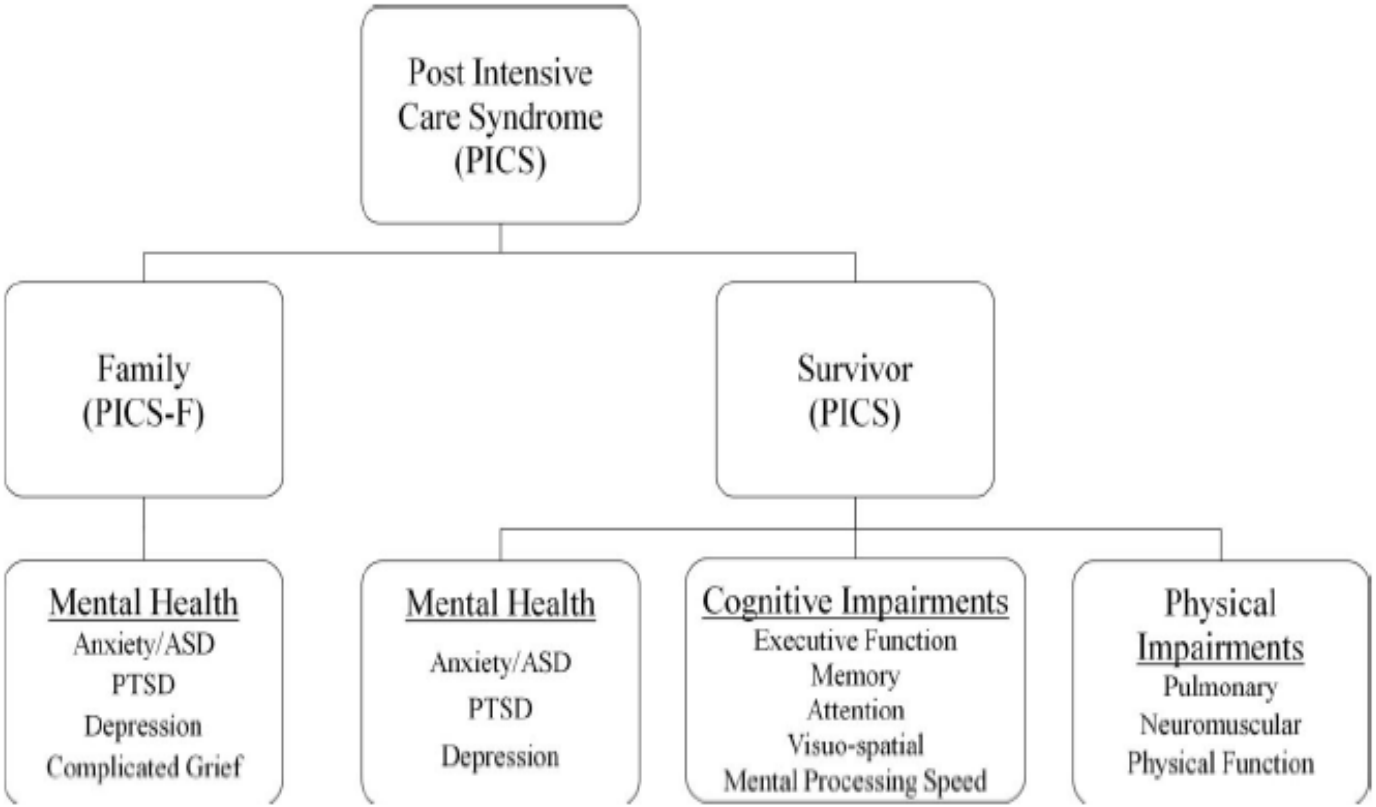


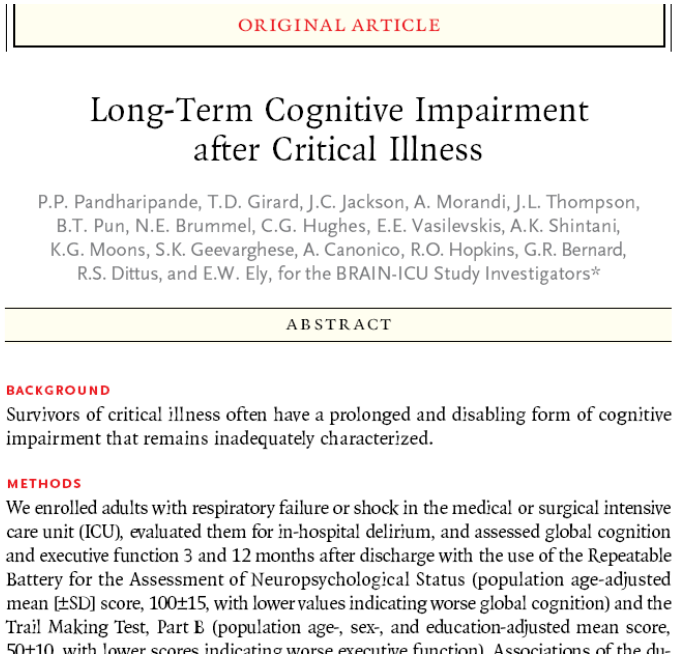

**Figure 1. Postintensive care syndrome (PICS) conceptual diagram.** *ASD*, acute stress disorder; *PTSD*, posttraumatic stress disorder.

# Epidemiology

- Poorly studied.
- 미국의 경우 매년 5700만명이 중환자실에 입실하며 이 중 4800만명이 생존한다.
- 이 중 1/4 - 1/2의 환자들이 세가지 PICS 카테고리 중 한가지 이상을 경험한다.

An exploration of social & economic outcome & associated health-related QOL after critical illness in general ICU survivors: a 12-month follow-up study. **Crit Care. 2013**
Physical & cognitive performance of patients with ALI 1 year after initial trophic vs full enteral feeding. EDEN trial follow-up. **Am J Respir Crit Care Med. 2013**
Long-term cognitive impairment after critical illness. **N Engl J Med. 2013**

# Cognitive impairment: 25-78% in ICU survivors



ORIGINAL ARTICLE

## Long-Term Cognitive Impairment after Critical Illness

P.P. Pandharipande, T.D. Girard, J.C. Jackson, A. Morandi, J.L. Thompson, B.T. Pun, N.E. Brummel, C.G. Hughes, E.E. Vasilevskis, A.K. Shintani, K.G. Moons, S.K. Geevarghese, A. Canonico, R.O. Hopkins, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the BRAIN-ICU Study Investigators*

ABSTRACT

**BACKGROUND**

Survivors of critical illness often have a prolonged and disabling form of cognitive impairment that remains inadequately characterized.

**METHODS**

We enrolled adults with respiratory failure or shock in the medical or surgical intensive care unit (ICU), evaluated them for in-hospital delirium, and assessed global cognition and executive function 3 and 12 months after discharge with the use of the Repeatable Battery for the Assessment of Neuropsychological Status (population age-adjusted mean [±SD] score, 100±15, with lower values indicating worse global cognition) and the Trail Making Test, Part B (population age-, sex-, and education-adjusted mean score, 50±10, with lower scores indicating worse executive function). Associations of the du-

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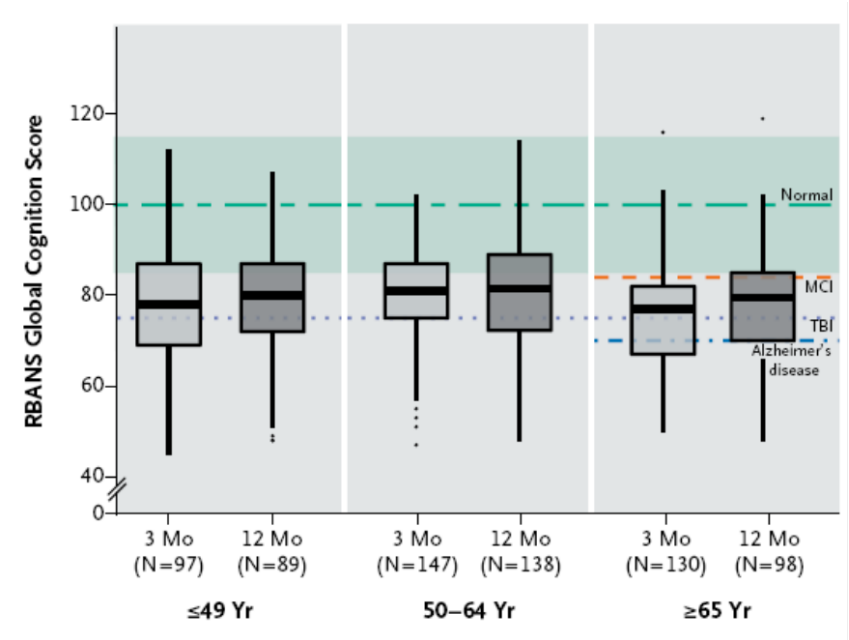
*The Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study Investigators are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2013;369:1306-16.

**BRAIN-ICU study**

- Prospective study
- 821 ICU survivors from MV.
- cognitive impairment: 6% @ baseline -> 40% @ 3 mo
- Delirium: 74% during the hospital stay.

# Median global cognition scores at 3 & 12 months: 79 (70-86) & 80 (71-87)
# Durations of delirium correlates worse global cognitive fx



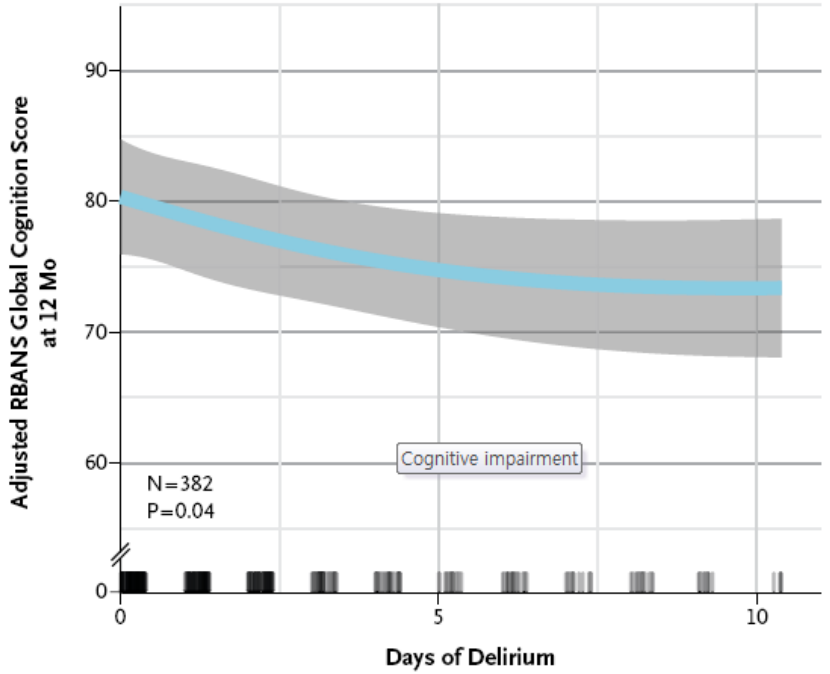
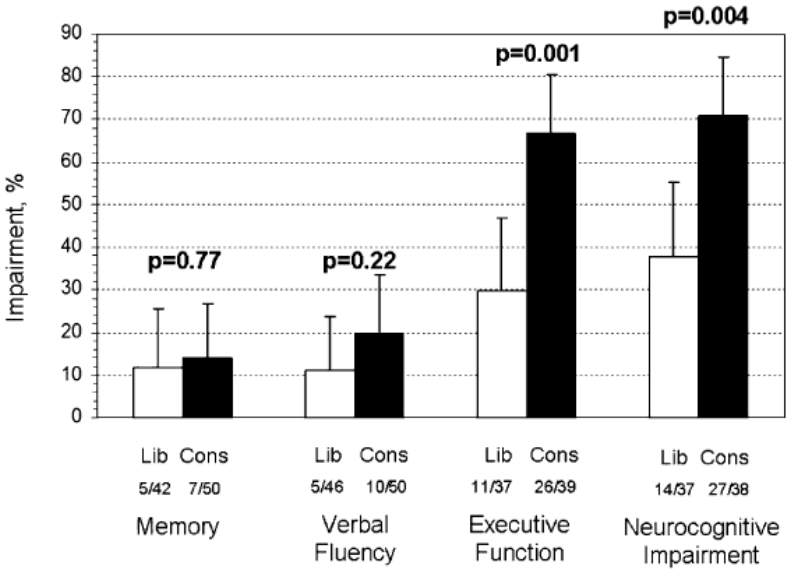




Figure 2. Duration of Delirium and Global Cognition Score at 12 Months.

# Long-term neuropsychological function in survivors of ALI. *Am J Respir Crit Care Med* 2012

- Adjunct study of FACTT trial
- f/u 102 ARDS survivors @ 2 & 12 months
  - Memory i. 13%
  - Verbal fluency i. 16%
  - Executive fx i. 49%



# Psychiatric illness

- Common (~62%) among ICU survivors (ARDS)
  - Depression
  - Anxiety
  - PTSD

Depressive symptoms & impaired physical function after ALI: a 2-year longitudinal study. **Am J Respir Crit Care Med.** 2012
Posttraumatic stress disorder in survivors of ALI. **Chest.** 2013
The ARDS cognitive outcomes study: long-term neuropsychological function in survivors of ALI. **Am J Respir Crit Care Med.** 2012
Psychiatric diagnoses & psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation**. JAMA.** 2014
Long-term complications of critical care. **Crit Care Med.** 2011

# Psychiatric dx & psychoactive meds among patients c MV. *JAMA* 2014

- 24,000 survivors of MV
- Psychiatric dx rate: 5.4% vs 2.4% (general population)
- 9912 ICU survivors s prev. psychiatric dis: new psychiatrist-diagnosed psychologic disorder 1% vs 19% received one or more prescriptions for psychoactive medications.

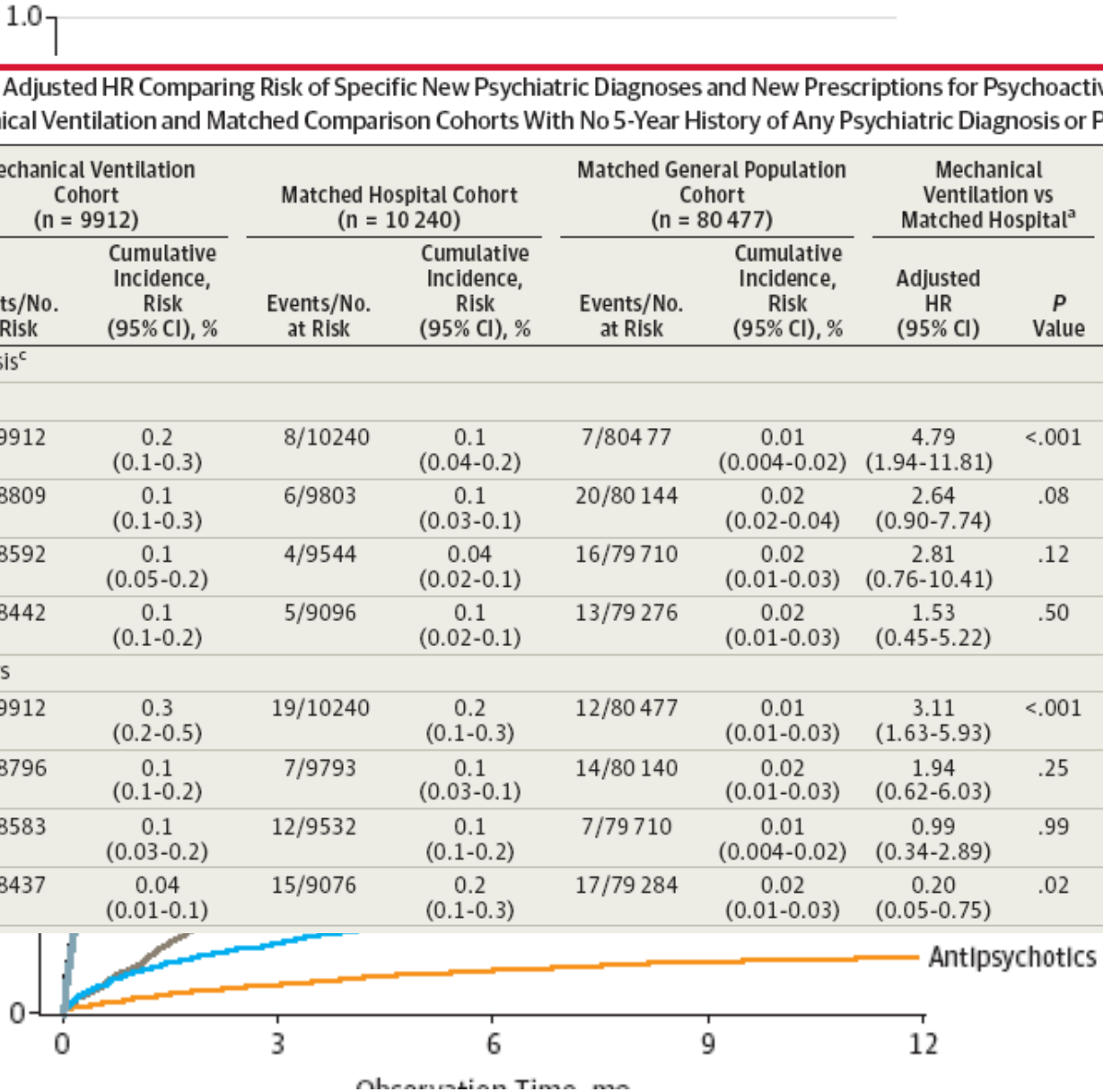



Table 4. Quarterly Adjusted HR Comparing Risk of Specific New Psychiatric Diagnoses and New Prescriptions for Psychoactive Medication in Patients Receiving Mechanical Ventilation and Matched Comparison Cohorts With No 5-Year History of Any Psychiatric Diagnosis or Prescription

| Months Since Discharge | Mechanical Ventilation Cohort (n = 9912) | | Matched Hospital Cohort (n = 10 240) | | Matched General Population Cohort (n = 80 477) | | Mechanical Ventilation vs Matched Hospital[a] | | Mechanical Ventilation vs Matched General Population[b] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Events/No. at Risk | Cumulative Incidence, Risk (95% CI), % | Events/No. at Risk | Cumulative Incidence, Risk (95% CI), % | Events/No. at Risk | Cumulative Incidence, Risk (95% CI), % | Adjusted HR (95% CI) | *P* Value | Adjusted HR (95% CI) | *P* Value |
| Psychiatric diagnosis[c] | | | | | | | | | | |
| Mood disorders | | | | | | | | | | |
| 0-3 | 20/9912 | 0.2 (0.1-0.3) | 8/10240 | 0.1 (0.04-0.2) | 7/804 77 | 0.01 (0.004-0.02) | 4.79 (1.94-11.81) | <.001 | | |
| >3-6 | 13/8809 | 0.1 (0.1-0.3) | 6/9803 | 0.1 (0.03-0.1) | 20/80 144 | 0.02 (0.02-0.04) | 2.64 (0.90-7.74) | .08 | 6.74 (2.20-20.59) | <.001 |
| >6-9 | 8/8592 | 0.1 (0.05-0.2) | 4/9544 | 0.04 (0.02-0.1) | 16/79 710 | 0.02 (0.01-0.03) | 2.81 (0.76-10.41) | .12 | 4.77 (0.75-30.40) | .10 |
| >9-12 | 9/8442 | 0.1 (0.1-0.2) | 5/9096 | 0.1 (0.02-0.1) | 13/79 276 | 0.02 (0.01-0.03) | 1.53 (0.45-5.22) | .50 | 4.68 (1.15-19.13) | .03 |
| Anxiety disorders | | | | | | | | | | |
| 0-3 | 32/9912 | 0.3 (0.2-0.5) | 19/10240 | 0.2 (0.1-0.3) | 12/80 477 | 0.01 (0.01-0.03) | 3.11 (1.63-5.93) | <.001 | 35.59 (10.43-121.40) | <.001 |
| >3-6 | 9/8796 | 0.1 (0.1-0.2) | 7/9793 | 0.1 (0.03-0.1) | 14/80 140 | 0.02 (0.01-0.03) | 1.94 (0.62-6.03) | .25 | 8.92 (1.31-60.61) | .03 |
| >6-9 | 6/8583 | 0.1 (0.03-0.2) | 12/9532 | 0.1 (0.1-0.2) | 7/79 710 | 0.01 (0.004-0.02) | 0.99 (0.34-2.89) | .99 | | |
| >9-12 | 3/8437 | 0.04 (0.01-0.1) | 15/9076 | 0.2 (0.1-0.3) | 17/79 284 | 0.02 (0.01-0.03) | 0.20 (0.05-0.75) | .02 | | |

# "Depressive sx & impaired physical fx after ALI: a 2-year longitudinal study." *Am J Respir Crit Care Med* 2012

- prospective, longitudinal cohort study
- follow-up 3, 6, 12, and 24 months after ALI.
- cumulative incidences of depressive symptoms and impaired physical function were 40 and 66%, respectively.

- Risk factors for incident depressive symptoms
  - education 12 years or less
  - baseline disability
  - unemployment
  - higher baseline medical comorbidity
  - lower blood glucose in the ICU.
- Risk factors for incident impaired physical function
  - longer ICU stay
  - prior depressive symptoms.

Systematic review reported higher incidence of depressive and PTSD symptoms in critical illness survivors as 28 and 22 %, respectively.

# Physical impairment

- ICU-acquired weakness is the most common form of physical impairment occurring in 25% or more of ICU survivors.

BRAIN-ICU study

- 32% were disabled in their ADL @ 3 mo.
- 26% were disabled in instrumental ADL

- 73% reported moderate/severe pain.

Griffiths et al. Critical Care 2013, 17:R100
http://ccforum.com/content/17/3/R100

CRITICAL CARE

RESEARCH Open Access

# An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study

John Griffiths[1,2], Robert A Hatch[1], Judith Bishop[1], Kayleigh Morgan[1], Crispin Jenkinson[3], Brian H Cuthbertson[4] and Stephen J Brett[5*]

**Abstract**

**Introduction:** The socio-economic impact of critical illnesses on patients and their families in Europe has yet to be determined. The aim of this exploratory study was to estimate changes in family circumstances, social and economic stability, care requirements and access to health services for patients during their first 12 months after ICU discharge.

**Methods:** Multi-center questionnaire-based study of survivors of critical illness at 6 and 12 months after ICU discharge.

**Results:** Data for 293 consenting patients who spent greater than 48 hours in one of 22 UK ICUs were obtained at 6 and 12 months post-ICU discharge. There was little evidence of a change in accommodation or relationship status between pre-admission and 12 months following discharge from an ICU. A negative impact on family

# "Social & economic outcome associated health-related QOL after critical illness : a 12-month follow-up study." *Crit Care* 2013

- 293 ICU surivors
- 25% needed care for >50 h/week, the major provic memb
- negat family
- 50% r emplo

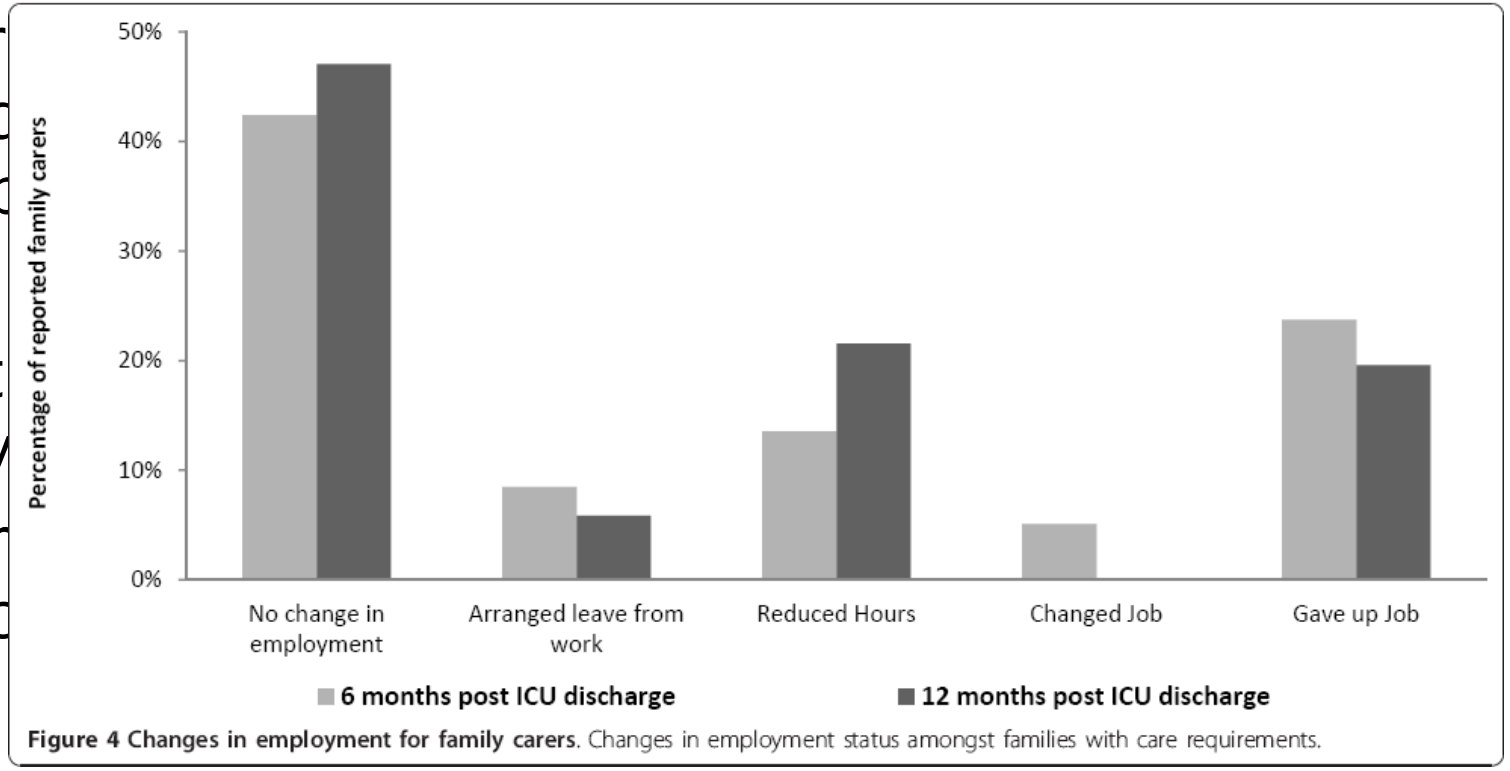



**Figure 4 Changes in employment for family carers.** Changes in employment status amongst families with care requirements.

# Risk factors of PICS

**Pre-existing**

- neuromuscular disorders
- Dementia
- psychiatric illness
- comorbid conditions

**ICU-specific**

- mechanical ventilation
- acute delirium
- Sepsis
- acute respiratory distress syndrome

# Risk Factors for Cognitive Impairment

- Delirium: independent risk factor for cognitive i. in BRAIN-ICU study
- Prior cognitive deficit: old age, ApoE
- Sepsis: OR 3.34 (sepsis survivors vs nonsepsis survivors) JAMA
- ARDS: ~73%
- Others: hypoxemia, alcoholism, hypotension, glucose dysregulation etc

# Risk Factors for Psychiatric Illness

- Sepsis
- ARDS
- Trauma
- Hypoglycemia
- hypoxemia

- Pre-existing anxiety and depression
- Female gender
- Age <50 years
- Lower education level
- Preexisting disability & unemployment
- Alcohol abuse
- ICU sedative & analgesia

# Glucocorticoids associated c a reduced risk for PTSD

- Reduced levels of cortisol play a role in the development of PTSD.

Schelling CCM 1999

- retrospective case-controlled analysis, septic shock
- stress doses of hydrocortisone (100 mg bolus, followed by 0.18 mg/kg/hr)
- lower incidence of PTSD in hydrocortisone group (5 of 27 vs. 16 of 27; p = .01)
- higher scores in QOL questionaire (68 vs. 44 points; p = .009).

# Risk Factors for Physical impairment

- Sepsis
- MOF
- Prolonged MV (> 7d)
- Prolonged bed rest
- ARDS
- SIRS
- glc dysregulation
- Vasoactive agents
- Corticosteroids
- NMB?

# CLINICAL MENIFESTATIONS OF PICS

Cognitive, psychiatric, and physical signs and symptoms which are **newly-recognized or worsened** after a critical illness.

**Weakness**
**poor mobility**
**Poor concentration**
**Fatigue**
**Anxiety**
**Depressed mood**

# Cognitive impairment

- Attention/concentration
- Memory
- Mental processing speed
- Executive function

# Psychiatric impairment

- Anxiety
- Depression
- PTSD

# Physical impairment

- Poor mobility
- Multiple falls
- Disability of ADL/instrumental A0|
- Contracture of joint
- Reduced lung function
- Malnutrition

# Diagnosis of PICS

- Cognition
  - Modified MMSE, Mini-Cog
  - Montreal Cognitive Assessment
- Mental health
  - Beck Anxiety/Depression Inventory, Post-traumatic stress syndrome 10-questions inventory
- Physical
  - Neurologist, physical/occupational therapist
  - EMG, nerve conduction study, spirometry

# Short PHQ & PHQ-9 patient health questionnaire

| Name: | Date: | | | |
|---|---|---|---|---|
| **Over the last two weeks, how often have you been bothered by any of the following problems?** | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
| Little interest or pleasure in doing things | | | | |
| Feeling down, depressed, or hopeless | | | | |
| Trouble falling or staying asleep, or sleeping too much | | | | |
| Feeling tired or having little energy | | | | |
| Poor appetite or overeating | | | | |
| Feeling bad about yourself, or that you are a failure, or have let yourself or your family down | | | | |
| Trouble concentrating on things, such as reading the newspaper or watching television | | | | |
| Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual. | | | | |
| Thoughts that you would be better off dead or of hurting yourself in some way | | | | |
| **Total ___ =** | | | | |
| **PHQ-9 Score ≥10: Likely major depression.** | | | | |
| **Depression score ranges:** | | | | |
| 5 to 9: mild | | | | |
| 10 to 14: moderate | | | | |
| 15 to 19: moderately severe | | | | |
| ≥20: severe | | | | |

| Over the past two weeks, how often have you been bothered by any of the following problems? | |
|---|---|
| Little interest or pleasure in doing things? | 0 = Not at all<br>1 = Several days<br>2 = More than half the days<br>3 = Nearly every day |
| Feeling down, depressed, or hopeless | 0 = Not at all<br>1 = Several days<br>2 = More than half the days<br>3 = Nearly every day |
| Total point score: | |

Score interpretation[1]:

| PHQ-2 score | Probability of major depressive disorder (percent) | Probability of any depressive disorder (percent) |
|---|---|---|
| 1 | 15.4 | 36.9 |
| 2 | 21.1 | 48.3 |
| 3 | 38.4 | 75.0 |
| 4 | 45.5 | 81.2 |
| 5 | 56.4 | 84.6 |
| 6 | 78.6 | 92.9 |

# PTSD checklist – military/civilian

**Patient's name:** _____

**Instruction to patient:** Below is a list of problems and complaints that veterans sometimes have in response to stressful military experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem in the last month.

| No. | Response: | Not at all (1) | A little bit (2) | Moderately (3) | Quite a bit (4) | Extremely (5) |
|---|---|---|---|---|---|---|
| 1. | Repeated, disturbing memories, thoughts, or images of a stressful military experience? | | | | | |
| 2. | Repeated, disturbing dreams of a stressful military experience? | | | | | |
| 3. | Suddenly acting or feeling as if a stressful military experience were happening again (as if you were reliving it)? | | | | | |
| 4. | Feeling very upset when something reminded you of a stressful military experience? | | | | | |
| 5. | Having physical reactions (eg, heart pounding, trouble breathing, or sweating) when something reminded you of a stressful military experience? | | | | | |
| 6. | Avoid thinking about or talking about a stressful military experience or avoid having feelings related to it? | | | | | |
| 7. | Avoid activities or situations because they remind you of a stressful military experience? | | | | | |
| 8. | Trouble remembering important parts of a stressful military experience? | | | | | |
| 9. | Loss of interest in things that you used to enjoy? | | | | | |
| 10. | Feeling distant or cut off from other people? | | | | | |
| 11. | Feeling emotionally numb or being unable to have loving feelings for those close to you? | | | | | |
| 12. | Feeling as if your future will somehow be cut short? | | | | | |
| 13. | Trouble falling or staying asleep? | | | | | |
| 14. | Feeling irritable or having angry outbursts? | | | | | |
| 15. | Having difficulty concentrating? | | | | | |
| 16. | Being "super alert" or watchful on guard? | | | | | |
| 17. | Feeling jumpy or easily startled? | | | | | |

**Total score:** ☐

**Patient's name:** _____

**Instruction to patient:** Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem in the last month.

| No. | Response: | Not at all (1) | A little bit (2) | Moderately (3) | Quite a bit (4) | Extremely (5) |
|---|---|---|---|---|---|---|
| 1. | Repeated, disturbing memories, thoughts, or images of a stressful experience from the past? | | | | | |
| 2. | Repeated, disturbing dreams of a stressful experience from the past? | | | | | |
| 3. | Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)? | | | | | |
| 4. | Feeling very upset when something reminded you of a stressful experience from the past? | | | | | |
| 5. | Having physical reactions (eg, heart pounding, trouble breathing, or sweating) when something reminded you of a stressful experience from the past? | | | | | |
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| 12. | Feeling as if your future will somehow be cut short? | | | | | |
| 13. | Trouble falling or staying asleep? | | | | | |
| 14. | Feeling irritable or having angry outbursts? | | | | | |
| 15. | Having difficulty concentrating? | | | | | |
| 16. | Being "super alert" or watchful on guard? | | | | | |
| 17. | Feeling jumpy or easily startled? | | | | | |

**Total score:** ☐

# *MRC Scale for Muscle Exam*

Upper extremity**: wrist** flexion, **forearm** flexion, **shoulder** abduction
Lower extremity: **ankle** dorsiflexion, **knee** extension, **hip** flexion

- 0–No visible contraction
- 1–Visible muscle contraction, but no limb movement
- 2–Active movement, but not against gravity
- 3–Active movement against gravity
- 4–Active movement against gravity and resistance
- 5–Active movement against full resistance

Maximum score: 60 (four limbs, maximum of 15 points per limb)
CRITERIA of weakness = **48**

# Prevention

**minimizes sedation & early rehabilitation**

- **A**wakening & **B**reathing **C**oordination c daily sedative interruption & ventilator liberation
- **D**elirium monitoring and management
- **E**arly ambulation in the ICU

# Treatment

- Treating underlying illness
- Timely referral to appropriate healthcare providers
- combination of nonpharmacologic and pharmacologic interventions

# ICU diary

- RCT of 352 ICU patients.
- ICU diary by family members/healthcare providers ↓PTSD 5 vs 13%.
- One systematic review of five RCTs, four studies showed positive effects of diaries on reducing the incidence of PTSD at three months.

Mehlhorn, J., A. Freytag, et al. (2014). "Rehabilitation interventions for postintensive care syndrome: a systematic review." Crit Care Med **42: 1263-1271.**

# Cognitive therapy

Intensive Care Med (2014) 40:370–379
DOI 10.1007/s00134-013-3136-0

ORIGINAL ARTICLE

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## Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial

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Published online: 21 November 2013


**Take-home message:** Cognitive therapy is feasible during the earliest stages of critical illness, yet long-term effects of this intervention remain inconclusive. Future work is needed to establish the optimal patient population, intensity of early

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# PICS-family

Family members of critically ill patients can be affected physically & psychologically during ICU stay, persisting after discharge.

- Sleep deprivation
- Anxiety
- Depression
- Grief
- PTSD

# Summary

- PICS is defined as new or worsening cognitive, psychiatric, or physical function after a critical illness.

- Prevalence of PICS among critical illness survivors is estimated that 1/4-1/2 or more will suffer from some component of PICS (cognitive, psychiatric, physical).

# Summary

- Risk factors are preexisting illnesses (neuromuscular disorders, dementia, psychiatric illness) as well as ICU-specific factors (MV, delirium, sepsis, and ARDS).
- Common features of PICS include muscle weakness, poor mobility, poor concentration, poor memory, fatigue, anxiety, and depressed mood.
- Although recovery is possible, many of the signs and symptoms of PICS last for months to years.

# Summary

- PICS may be prevented by a strategy that promotes light sedation and early physical rehabilitation during the intensive care unit stay.
- The signs and symptoms of PICS improve over the first 6 to 12 months following discharge from the intensive care unit. However, in many patients, deficits persist for years.
- PICS is frequently associated with the inability to return to work and decreased quality of life as well as an increased risk of death over the subsequent few years.

# Summary

- Clinical manifestations of PICS-Family include sleep deprivation, anxiety, depression, and post traumatic stress disorder.
- The psychological effects may persist for prolonged periods after discharge of the loved one from the intensive care unit.
- We advocate for **good communication** strategies between staff and family members of survivors of critical illness.