Blood Artificial Surface Interaction

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Summary of Red Book 4th Edition, Chapter 5
(Blood Biomaterial Surface Interaction During ECLS)

1. Introduction

Significant advancements in the materials, components, and techniques of ECLS have been realized over the past 50 years. However, the inability to completely control the interaction between blood and the biomaterials of the extracorporeal circuitry and the subsequent inflammatory and coagulation reactions results in these same challenges to the use of ECLS today and going forward. In order to regain the loss of hemostatic balance and prevent thrombosis, administration of antithrombotic therapy is necessary.

2. Normal Hemostasis

Normal Physiologic hemostasis is dependent upon maintaining a fine balance between thrombosis and hemorrhage. Coagulation and fibrinolysis are the two pathways responsible for hemostasis. These pathways are comprised of a number of protein components which when activated by a stimulus, interact with red blood cells and platelets and result in thrombus formation (coagulation) and/or thrombus degradation (fibrinolysis).

1) Activation of the Coagulation Pathway

The classic 'coagulation cascade' model of hemostasis described a series of reactions extrinsic and intrinsic pathways. The cell based model of hemostasis replaces the classic 'coagulation cascade' model, and proposes that cells play very active roles in controlling coagulation. Cell based coagulation takes place on different cell surfaces in three overlapping steps: initiation, amplification, and propagation (Figure 5-1)

2) Activation of the Fibrinolytic Pathway

The above cell-mediated coagulation is regulated continuously by the fibrinolytic pathway. The fibrinolytic pathway (constituent proteins: tissue plasminogen activator and plasminogen) is activated when thrombin is generated. This regulation occurs in three phases as well: termination, elimination, and stabilization (Figure 5-2).

3) Developmental Hemostasis

These normal physiologic differences in hemostasis are termed "developmental in hemostasis." Epidemiologic studies have demonstrated that infants and children have decreased venous thrombosis compared to adults which is a result of unique protective mechanisms (increased α2 macroglobulin, decreased thrombin generation, and altered vessel wall properties). However, there are high risk cohorts of children with an increased incidence of thrombosis, including children who undergo ECLS.

3. Initiation of ECLS: Coagulation Pathway Activation and Inflammatory Response

When blood is exposed to the nonbiologic surfaces of an extracorporeal circuit, a complex inflammatory response is initiated involving both the coagulation pathway and the inflammatory response pathway (Figure 5-3). This complex response leads to capillary leak which can cause temporary dysfunction of every organ.

1) Pathophysiology of the blood surfaces interaction

Contact with synthetic, non-endothelial cell surfaces, shear stresses, turbulence, cavitation, and osmotic forces directly injure blood. Plasma proteins and lipoproteins are progressively denatured during ECLS. Protein denaturation increases plasma viscosity, produces macromolecules, decreases protein solubility, and increases protein reactive side groups.

Multiple blood cells and plasma protein systems are activated as part of a series of cellular and enzymatic reactions that occur during response involves the contact and complement systems, along with the activation of coagulation, fibrinolysis, and most cell lines including platelets, neurtrophils, monocytes, lymphcytes, lymphocytes, and endothelial cells.

2) Platelets

Platelets are the mainstay for hemostasis and preservation of vascular wall integrity. Platelets respond to minimal stimulation and become activated when they encounter a thrombogenic stimulus such as injured endothelium, subendothelium, or artificial surfaces. Normal platelets participate in the balance of hemostasis through the following activties: activation, adhesion, secretion of active substances, and aggregation.

It is known that during ECLS platelet adhesion and aggregate formation reduce the circulating platelet count; however, it should be noted that high consumption and formation of microemboli, rather than occlusive thrombi, can occur even in the event of minimal adhesion to the circuitry surface. As ECLS continues, adhesion platelets detach, leaving fragments of platelet membrane

behind; these will also detach and circulate. Bleeding times increase in the presence of structurally normal appearing platelets, and as ECLS continues beyond 24 hours, platelet consumption continues.

3) Leukocytes

Neutophils, monocytes, and lymphocytes are the main groups of cells involved in the inflammatory responses during ECLS. Exposure of patient blood to the extracorporeal circuit results in activation of innate immunity. Circulating leukocytes, including peripheral blood mononuclear cells (PBMCs) are activated in part by tissue factor activation releases numerous circulating proinflammatory cytokines (e.g,. TNF-α, IL-Iβ) that activated circulating neutrophils facilitating their adhesion to the vascular surfaces of numerous organs. This accumulation is associated with increased capillary permeability, interstitial edema, and large alveolar arterial oxygen differences during and after perfusion.

Extracorporeal perfusion decreases the total number of lymphocytes and specific subsets of lymphocytes particularly B lymphocytes, natural killer cells, helper T-cells, and T-suppressor lymphocytes. Lymphocyte counts usually recover within five days of weaning from ECLS; shower recovery is associated with a poor prognosis.

A compensatory antiinflammatory response syndrome (CARS) also exists that is aimed at countering the proinflammation. While CARS is a necessary response, an exaggerated or dysregulated CARS response can impair immunity thus rendering a host susceptible to infection and infectious complication such as sepsis and multiple organ dysfunction syndrome (MODS).

4) Endothelial cells

Endothelial cells maintain the fluidity of blood and the integrity of the vascular system. Endothelial cells produce prostacyclin, heparin sulfate, tPA, and TFPI, which help regulate the coagulation pathway.

5) Complement

The alternative complement pathway, as opposed to the classic complement pathway, is primarily activated by ECLS as part of this procoagulant activation and inflammation. The alternative pathway does not require antibody or immune complexes for activation. It is activated by foreign surfaces including microbial organisms or elements, particles, or biomaterial surfaces.

4. Activation of the Coagulation System during ECLS

Within seconds of blood contact with the non-biologic surface of the extracorporeal circuit, plasma proteins are adsorbed onto that surface to form a monolayer of blood proteins. The physical and chemical composition of the polymer determines which proteins are most likely to adhere to that surface, which may not be the proteins of greatest concentration within the plasma. The contact system consists of four primary plasma proteins: FXII, prekallikrein, high molecular weigh kininogen (HMWK) and C-1 inhibitor.

Activation of coagulation occurs through TF expression on activated cells (monocytes, macrophages, neutrophils, activated endothelial cells, smooth muscle cells, apoptotic cells), or cellular components (platelet microparticles or circulating vesicles). Platelet activation and consumption occurs upon initiation of ECLS such that platelet number and function decrease within the first hour of ECLS. This platelet activation and consumption continues throughout the course of ECLS often requiring regular transfusions of platelets, and with the platelet activation neutrophils also become activated producing cytokines and further contributing to the inflammatory response to extracorporeal circulation. The cleavage reaction to form plasmin produces D-dimers, which have been shown to be elevated during the course of neonatal ECLS as a marker of ongoing fibrinolysis.

5. Activation of the Innate Immune System and Resultant Immune Dysregulation

Activation of the coagulation system and thrombin generation does not occur in isolation but in conjunction with the activation of the innate immune system. The initial activation of the components of the innate immune system by the ECLS circuit cumulatively contributes to the SIRS response that can clinically manifest as hemodynamic instability and capillary leak. Thus, depending on the degree of the innate immune response, a slight increase in hemodynamic support may be necessary following the first few hours after initiation of ECLS. The initial SIRS response is counterbalanced by a compensatory antiinflammatory response (CARS) meant to reestablish homeostasis and reset the innate immune system. However, a prolonged CARS response may lead to an acquired immunosuppressed state placing the patient at risk for nosocomial infections. Increased attention is being placed on understanding the immunology of this CARS phase. A key feature of this biologic response is the presence of "deactivated" monocyte.

This deactivated state is also associated with a decrease in the cell surface MHC-II molecule, HLA-DR. In time, the term "immunoparalysis" was coined to refer to the combination of decreased ex vivo LPS responsiveness and HLA-DR expression (less than 30% normal).

The one study investigating the impact of immunoparalysis following CPB in children examined HLA-DR expression in 82 children and showed that HLA-DR expression less than 60% 72 hours after CPB was predictive of the development of sepsis with an odds ratio of nearly 13.

Although the incidence of immunoparalysis while on ECLS is unknown, the potential for an acquired immunosuppressed state must be acknowledged and attention to proper antibiotic usage, adequate nutrition, and practices for the prevention of nosocomial infections are warranted.

Understanding the normal function of the coagulation system and normal inflammatory response, and pairing this with the pathophysiology of the blood biomaterial interface are crucial to maintaining stability in these patients while being supported on ECLS.

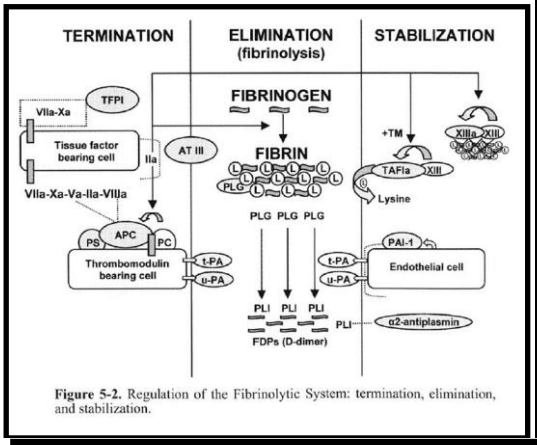


Figure 5-2. Regulation of the Fibrinolytic System: termination, elimination, and stabilization.

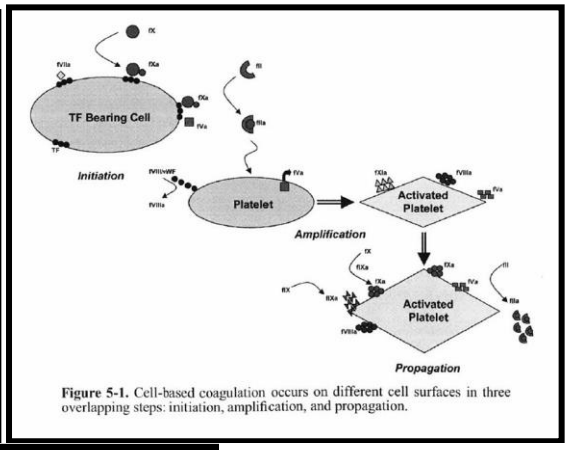


Figure 5-1. Cell-based coagulation occurs on different cell surfaces in three overlapping steps: initiation, amplification, and propagation.

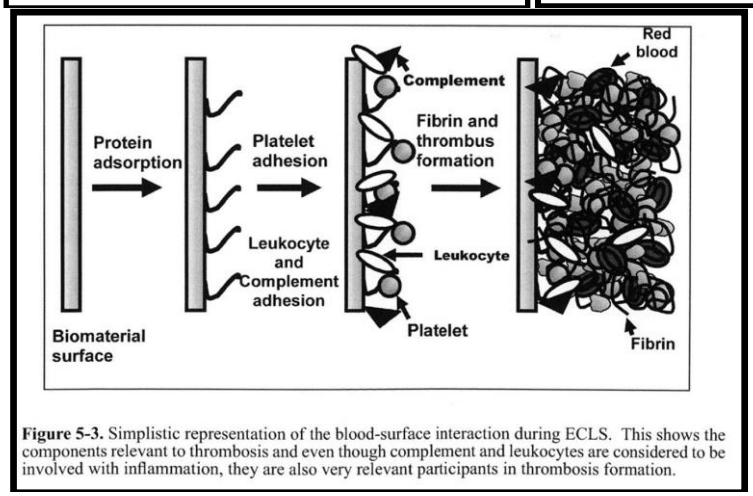
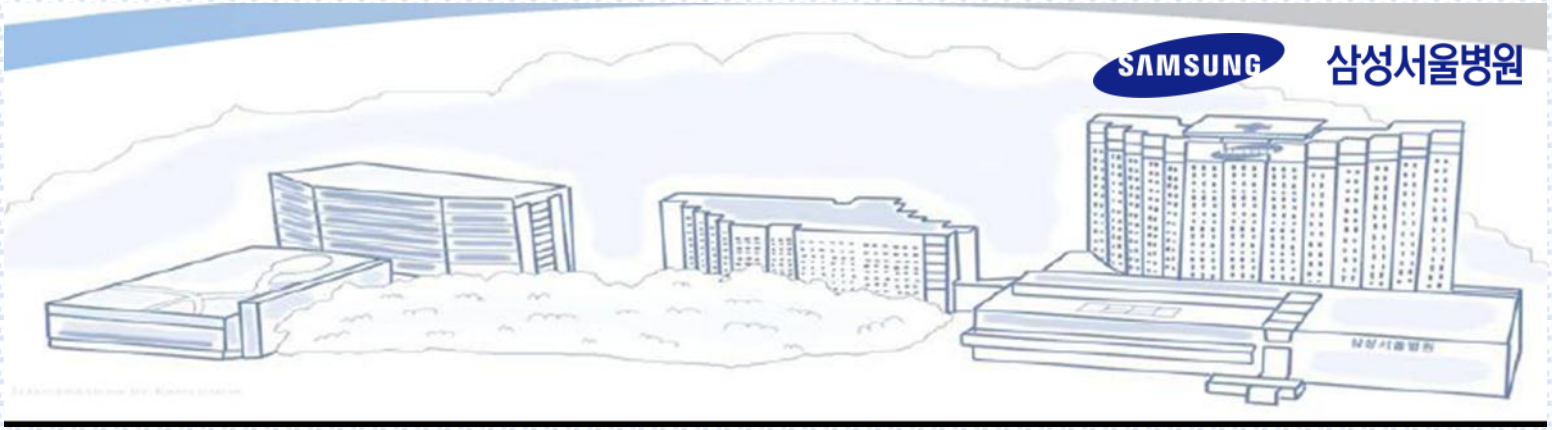


Figure 5-3. Simplistic representation of the blood-surface interaction during ECLS. This shows the components relevant to thrombosis and even though complement and leukocytes are considered to be involved with inflammation, they are also very relevant participants in thrombosis formation.

Circuits and components of ECMO

- Current Status of ECMO at SMC -



Su Hyun Cho, Perfusionist

Samsung Medical Center

Traditional ECMO Circuit

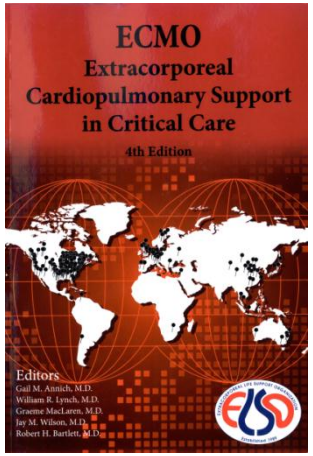
- **Three primary components**

  (1) Servo regulated blood pump

  (2) Gas exchange device

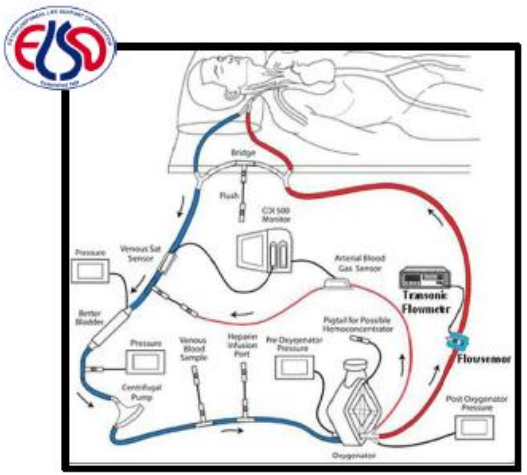
  (3) Heat exchanger

" The Circuit " Chapter 8. 107 page...

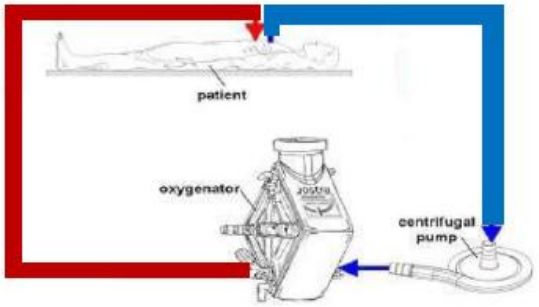


Components of ECMO

- **Pump - Centrifugal or Roller**
- **Membrane Oxygenator**
- ***Vascular access – Cannulas***
- ***Tubings***



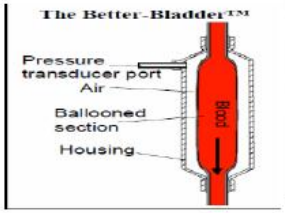
Traditional circuit components

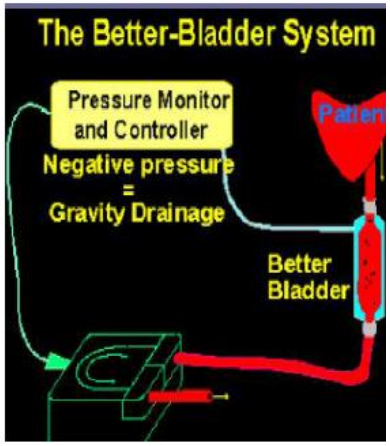


Simplified circuit components

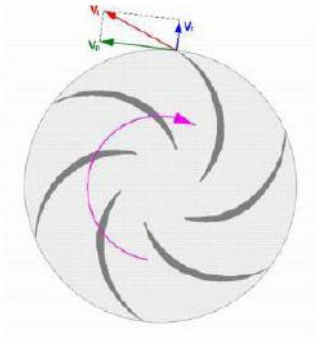
Blood Pump

Positive displacement pump
- Roller pump -



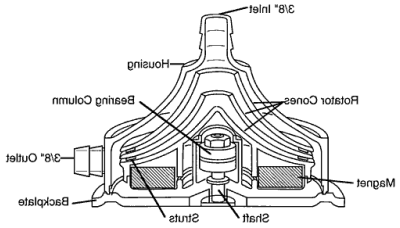


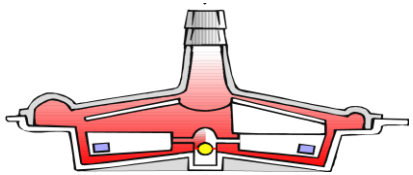
Hydrodynamic pump
- Centrifugal pump -

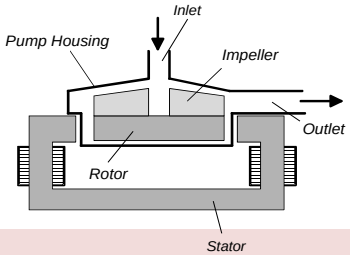


- Non-occlusive pump
- Centrifugal action creates pressure differential between center and periphery of pump

Centrifugal pump Innovation







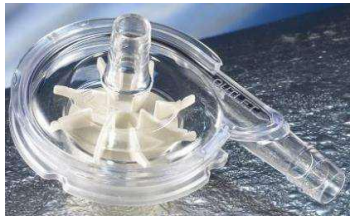
1st Generation

- Bearing
- Shaft
- Seal

2st Generation

- One point pivot bearing
- Low friction bearing
- Seal-less bearing

3st Generation

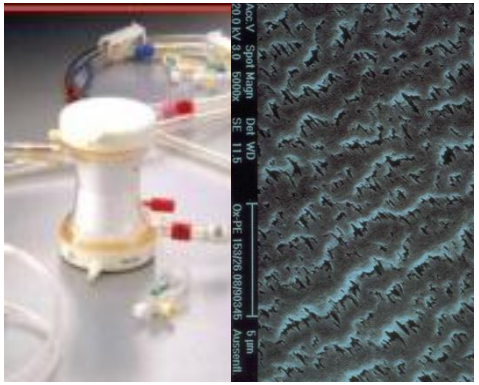


- No bearing
- No shaft
- No seal

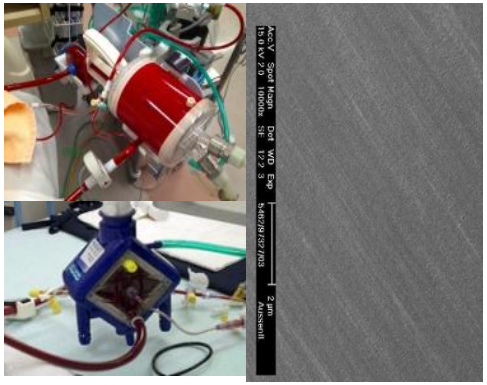
Oxygenator

- **Bubble type : Too much hemolysis**
- **Membrane type**
  - **Silicone**
  - **Polypropylene (PP) : Plasma leakage**
  - **Polymethylpentene (PMP)**

  : Skinned asymmetric microporous fiber



(Polypropylene)



(Polymethypentene)

Tubings

PVC (1/4 inch, 3/8 inch)

- **Heparin coating and its modifications**
- **Biocompatible surface coatings**

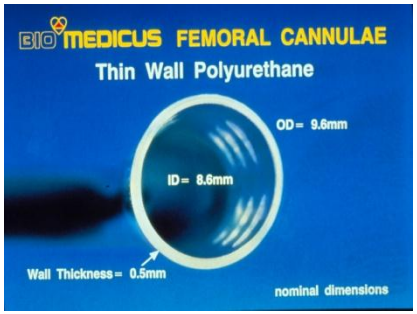
TERUMO
X Coating™ FOR TERUMO® PERFUSION PRODUCTS
An amphiphilic, biopassive polymer coating to reduce protein denaturation and platelet adhesion.

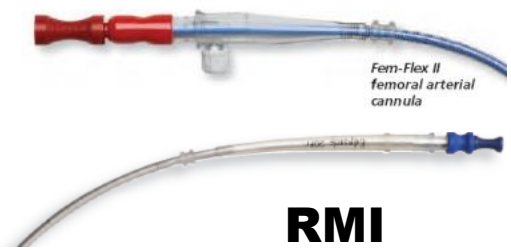
P.h.i.s.i.o **coating (Phosphorylcholine)**
SORIN GROUP
AT THE HEART OF MEDICAL TECHNOLOGY

MAQUET
GETINGE GROUP
BIOLINE Coating

Cannulae

- **Blood-compatible and tissue-friendly**
- **Polyurethane. Stainless steel reinforced**
- **Arterial has no side hole**
- **Venous has multiple side holes**
- **Marker rings**
- **Radiopaque maker at tip**



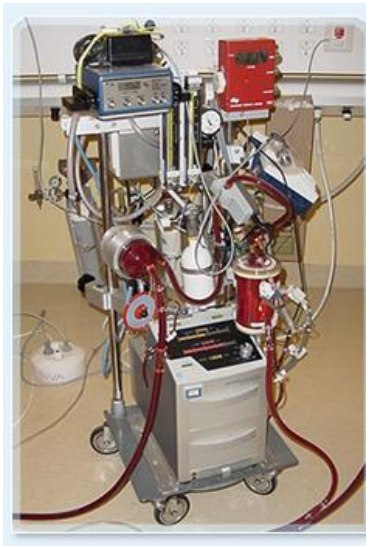


RMI

DLP

Bio-medicus

Modern ECMO system



Bio-medicus PBS

Portable
Bypass
System

EBS

Emergecy
Bypass
System

SCP

Sorin
Centrifugal pump
System

PLS

Permanent
Life
Support

Six hours VS two weeks

Max. time of use

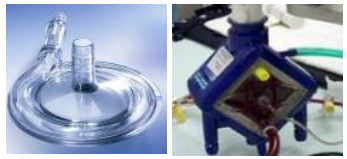
6 hours — 1 week — 2 weeks

- Medtronic Bio-Pump BPX 80
- Terumo CAPIOX SP pump
- SORIN Revolution

- Terumo EBS(PMP)
- SORIN Lilliput 2

5 days validation

- MAQUET
  Rota Flow 32
  QUADROX

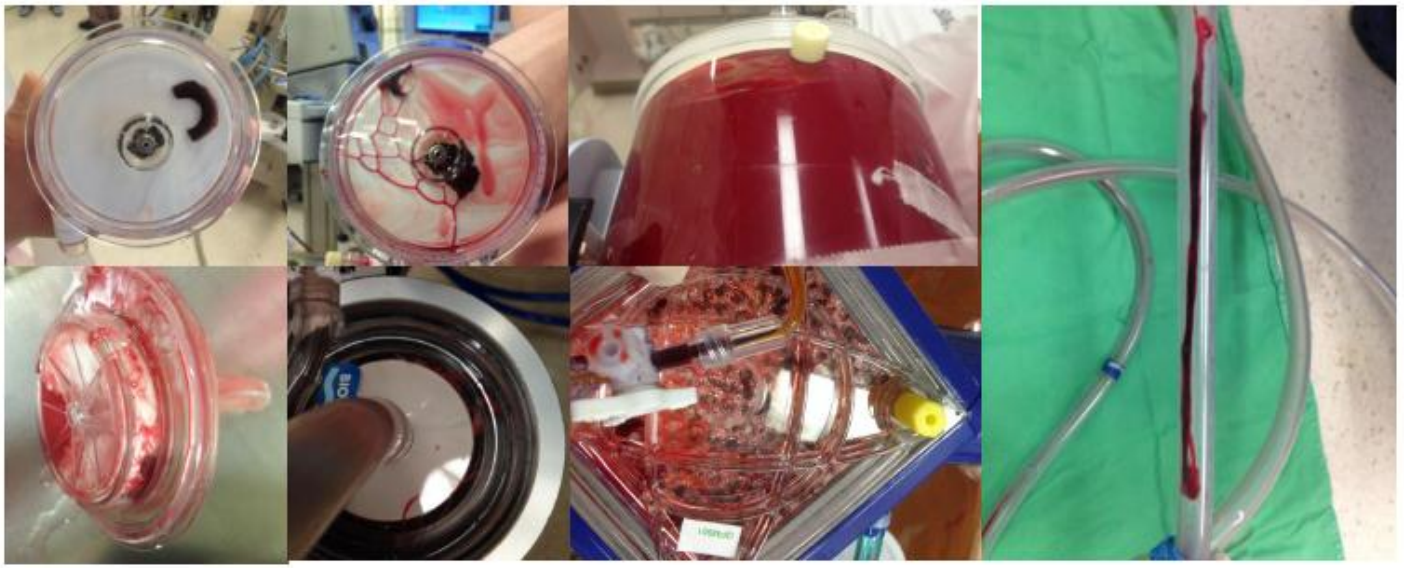


CPB : Intra OP

ECMO : ICU. ER. Cath Lab…
Anywhere and Anytime !!!

Mechanical Related Complications

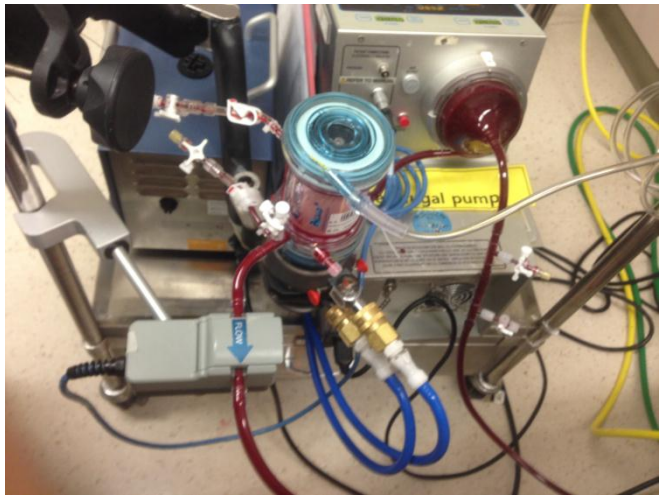
- Hemolysis
- Thrombosis (Clot)
- Raceway rupture (component crack)

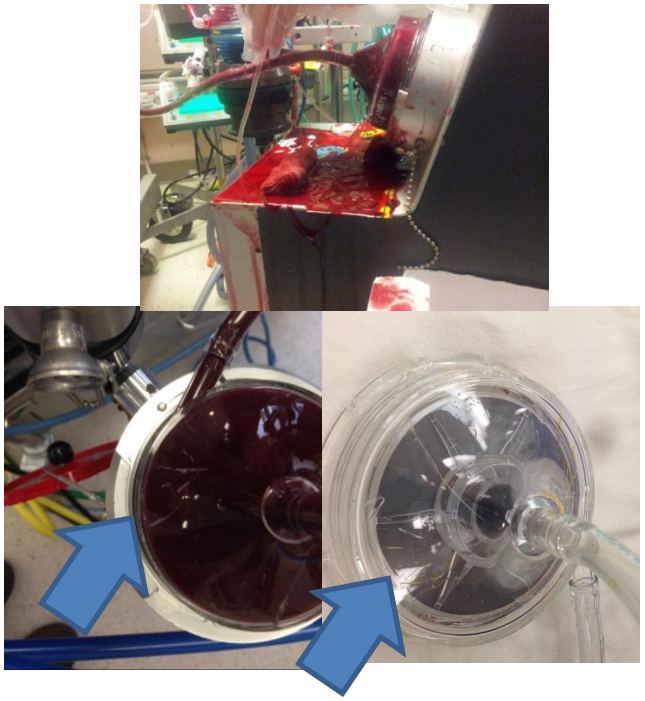


ECMO at SMC

- **Neonate : Bio pump ⇒ PLS Rota Flow**

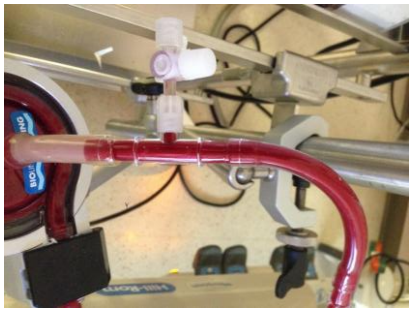
  SORIN Lilliput 2

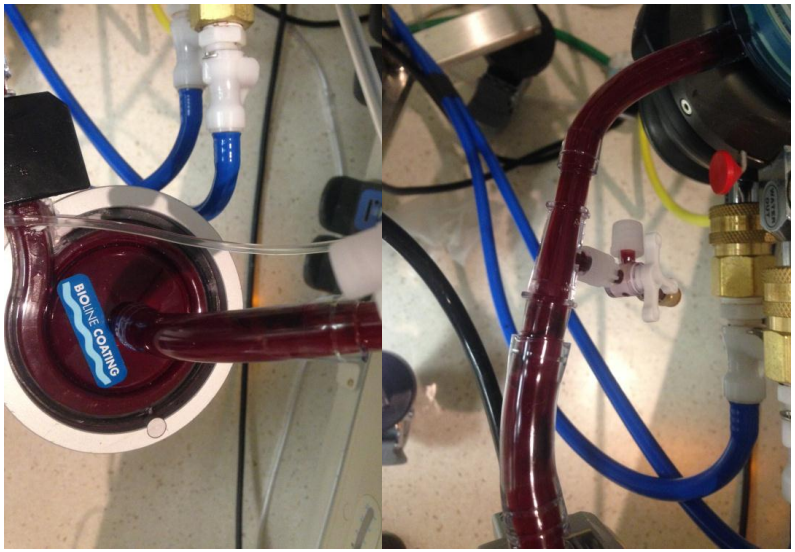




ECMO at SMC

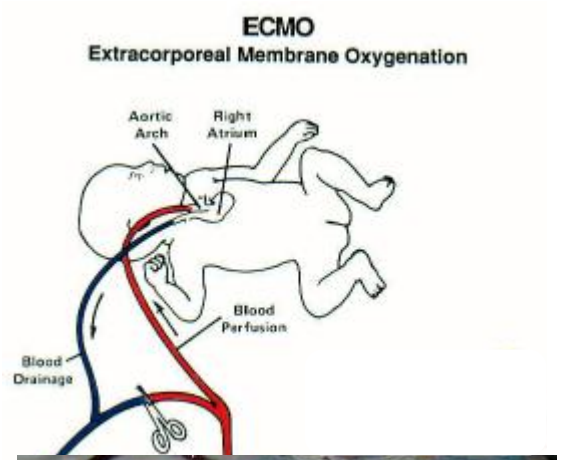
- **Neonate : Circuit modification**

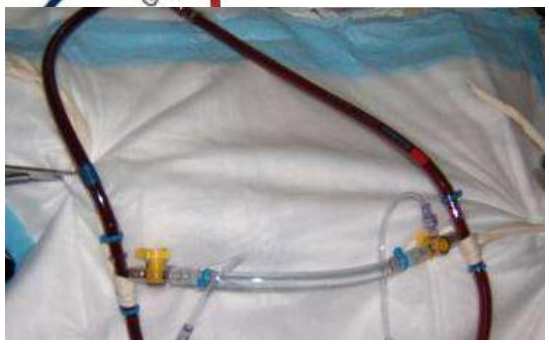




ECMO at SMC

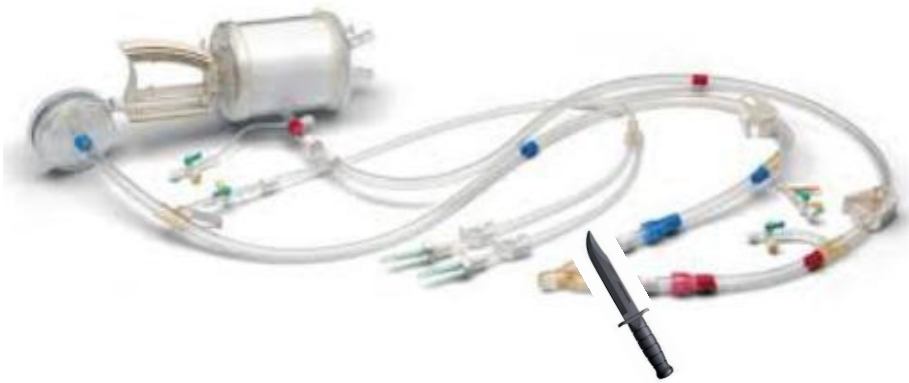
- **Neonate – Bridge (1/4 inch tubing)**





ECMO at SMC

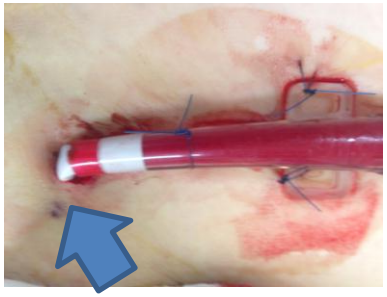
- **Adult : PLS or EBS**



Pre-M : Post-Membrane

- **Blood gas analysis : P/F ratio**
- **Pressure gradiant**

- **Hemofiltration**



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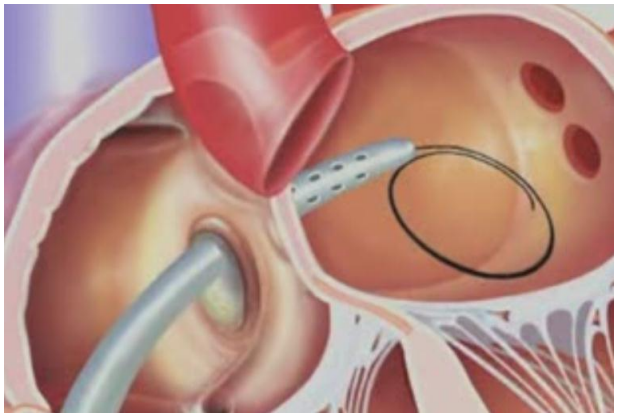
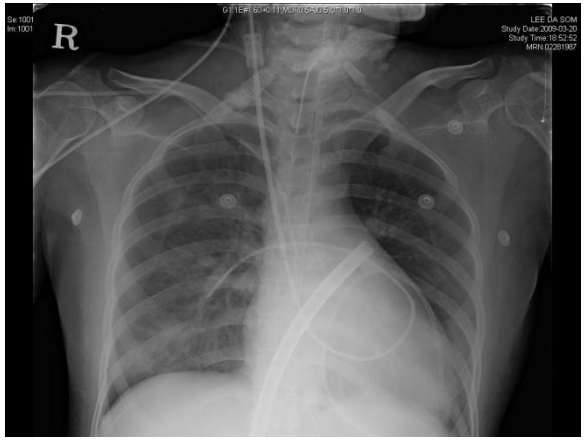
Left heart vent at SMC

- Intervention
  - Inter-atrial septostomy
- Surgical
  - LV apex via left anterior thoracotomy
  - RUPV via sternotomy
  - RUPV via right anterior thoracotomy

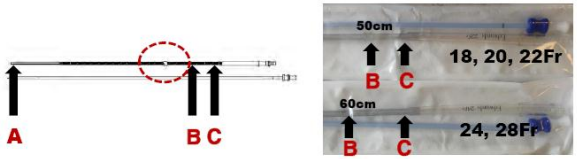
Left heart vent : Intervention

- **Using septostomy : 24Fr F.V cannula (RMI)**



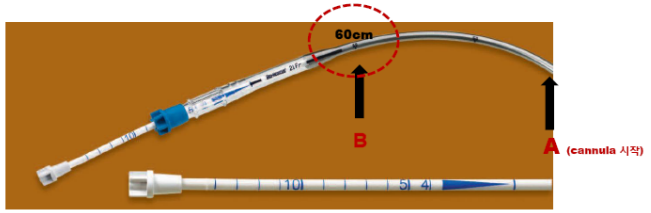


F.V Cannula RMI (VFEM)



회사명	상품명	Size (Fr)	*Length* (cm) A에서 B까지의 길이	최대사용가능길이 (cm) A에서 C까지의 길이
Edwards Lifesciences	Fem-Flex II (RMI)	18	50	55
		20	50	55
		22	50	55
		24	60	68
		28	60	68

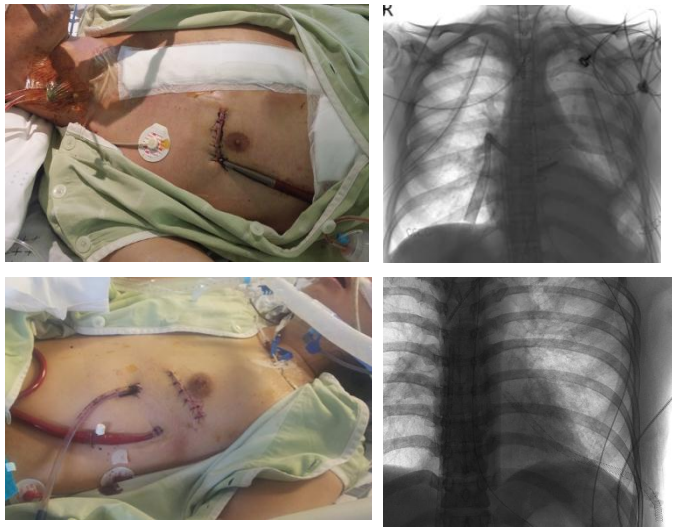
F.V Cannula Bio-Medicus



회사명	상품명	Size (Fr)	*Length* (cm) A에서 B까지의 길이	최대 사용 가능 길이 (cm)
Medtronic Medtronic, Inc.	Bio-Medicus multi-stage (96880)	17	60	60
		21	60	60
		25	60	60

Left heart vent : Surgical

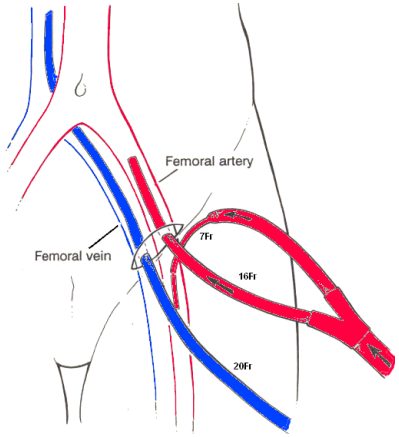
- LV apex via left anterior thoracotomy
- RUPV via sternotomy
- RUPV via right anterior thoracotomy



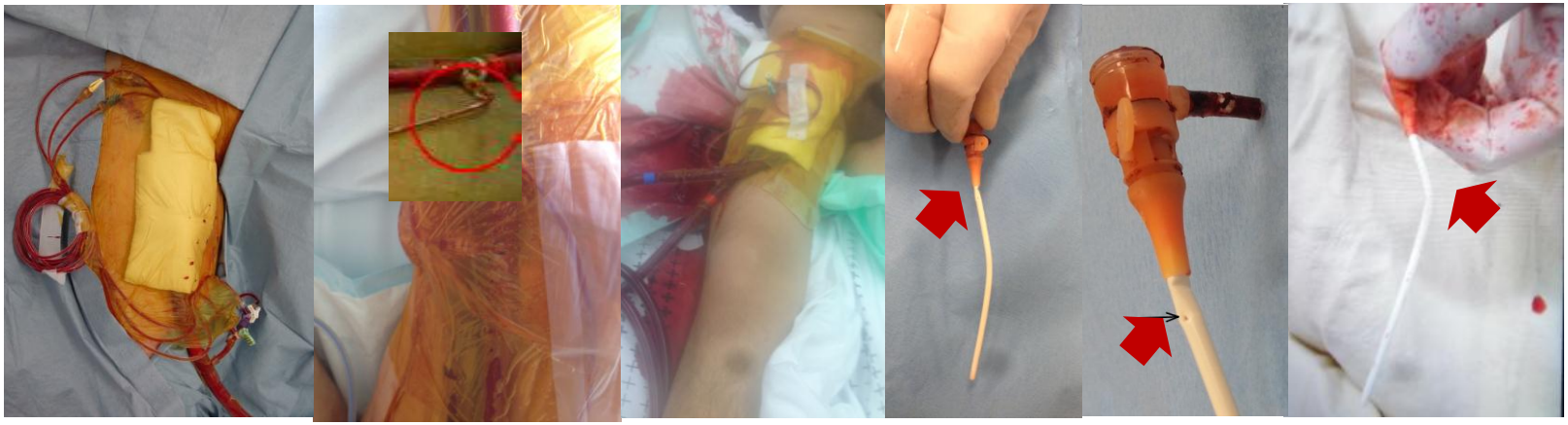
Femoral Artery Cannulae

회사명	상품명	Size (Fr)	Length (cm)	최대사용가능길이 (cm)
Edwards Lifesciences	Fem-Flex II (RMI)	16	15	15
		18	15	15
		20	15	15
Medtronic, Inc.	DLP	14	15	17.8 (17.2)
		17	15	17.8 (17.2)
		21	15	17.8 (17.2)
	Bio-Medicus (96530)	15	18	18
		17	18	18
		19	18	18
		21	18	18

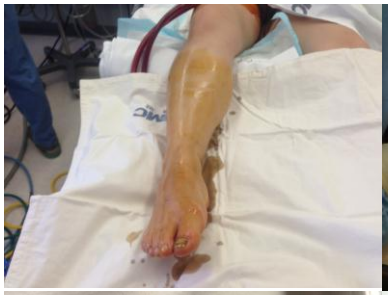
Distal perfusion at SMC

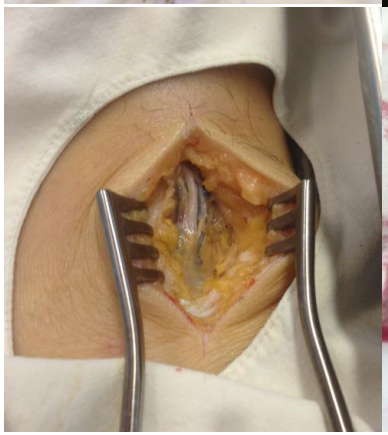


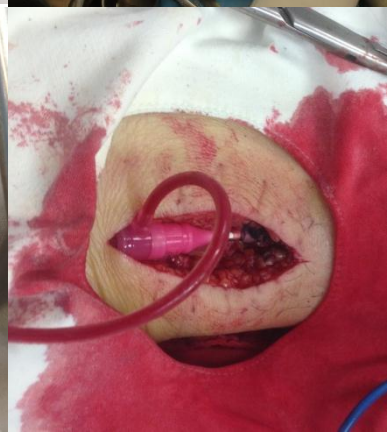
- **Sheath 7Fr**
- **Central catheter**

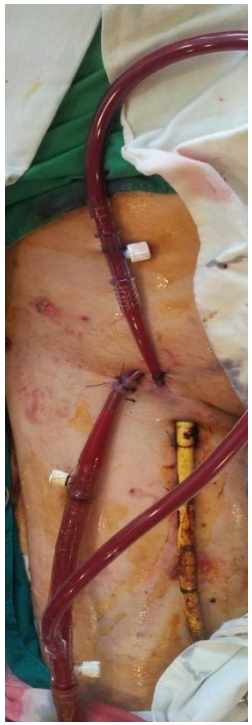


Distal perfusion : modification

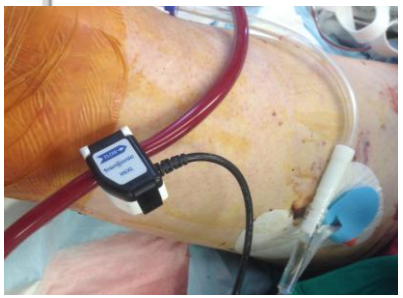








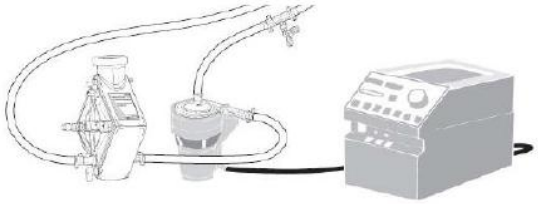
- FEM. A cannula (RMI)



- Sheath 7Fr : PTA
- 8Fr cannula + ¼ Tubing
- Blood Flow monitoring

Circuit Management

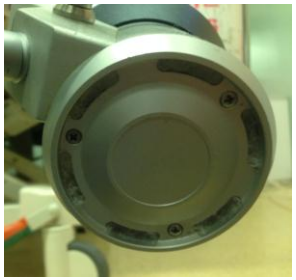
Complete visual circuit inspectio
with flashlight

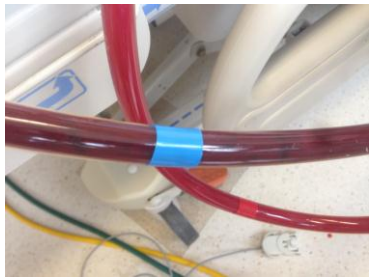


SMC

Visualization of the Clots

① 3-dimensional approach
② pump head, oxygenator membrance, tubing line, connector, connection site.
☐ No
☐ Normal : ECMO circuits normal clots - location와 size record
☐ Abnormal - Circuits change





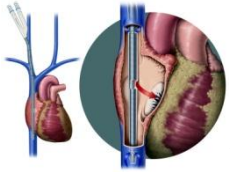
We are here now.....

- Low hemolysis
- Heat generation
- Stagnant areas
- No leakage possible

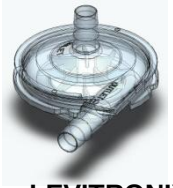
In 2015

- Durability
- Blood-compatible and tissue-friendly

Electronic Gas Blender



Double Lumen Catheter



LEVITRONIX

CentriMag : bearingless

- **Rehabilitation in ECMO**
- **In Hospital ECMO Transport**
- **Inter - Hospital ECMO Transport**

Thank You for Listening

Multidisciplinary ECMO Team

한림대학교 성심병원 김형수

Ireland 내에 인증 받은 ECMO program을 가진 의료기관이 없어 ECMO 대상이 되는 환자들은 주위 유럽의 ECMO 센터로 환자가 이송되어 치료를 받아야 했다. 2007년도에 Mater Misericordiae 병원에서 ECMO program을 시작하기로 결정한 후 위원회를 만들어 ECMO program이 운영되기 위한 장비와 인력구성을 하고, ECMO medical director를 정하면서 성공적으로 운영하고 있다.

국내의 경우 EBS 또는 PLS 장비만 있으면 ECMO를 누구나 비교적 쉽게 시작할 수 있다. 그러나 불행히도 국내에서는 ECMO program의 책임자 없이 여러 과에서 독립적으로 시행하고 있는 것이 현실이다.

적절한 ECMO team을 만들기 위해서는 1년 24시간 항시 연락이 가능한 의료진과 더불어 중환자실 간호사와 체외순환사, 코디네이터 등 필수 인원이 필요하다. ECMO에 관계된 주된 의료진들은 각각 ECMO 운영 분야에 따라서 중환자의학 전문의, 중재시술을 위한 전문의, 외과의 등이 기본적인 팀을 이루고, 환자의 상태에 따라서 해당 분야의 타과 전문의와도 협진 체계가 원활하여야 한다. 간호관리 분야에서는 적절한 환자 대 간호사 비율을 유지하는 것이 기본적으로 매우 중요하다. 참고로 Karolinka ECMO 센터의 경우 ECMO 환자 1 인당 1명의 ECMO specialist(간호인력), 2 명의 환자당 1명의 간호보조

인력, 그리고 ECMO 환자만을 치료하는 1명 내지 2명의 의료진으로 구성되어 있다. 이와 더불어 ECMO 팀의 정규적인 교육과정을 통해 환자 중심적으로 유기적이고 만족스럽게 전문적인 환자관리를 하고 있다.

국내의 경우 중환자실의 의료수익이 투자 대비 손실이 많은 상황에서, 외국의 ECMO 센터와 같이 장비와 전문적인 인력을 만족스럽게 투입하는 것은 현실적으로 불가능하다. 그러나 각 병원의 현실에 맞게 병원 내 의료 자원을 효율적으로 배분하고 타과와의 원활한 협진과 ECMO 관리 인력에 대한 교육을 통하여 질 관리를 적극적으로 시행한다면, 국내에서도 외국의 유수한 ECMO 센터와 같은 성과를 이룰 수 있을 것으로 생각된다.

Vascular access & complication management

부산대학교병원 송승환

Cannulation techniques vary depending on
1. The type of support
2. Patient age and size
3. Clinical situation

1) Patient management pre-ECLS
Where – ICU, operation room, emergency department
Adequate monitoring and nursing care
Ability of transport
Required equipment (cannula, surgical instrument, circuit, and component)
Personnel

Blood product, anesthesia, heparinization

2) Type of support
Veno-venous: respiratory support
Veno-arterail: both cardiac and respiratory support

Venous cannulation site: IJ, FV, RA
Arterial cannulation site: RCCA, Ax, fem, Ao

3) Selection of technique
Cutdown(open technique)
Semi-open technique
Seldinger technique

Placement of the cannula is aided by
Fluoroscopy or Echocardiography
Check with chest and abdominal x-ray

4) Transthoracic cannulation
If the peripheral cannulation is not possible or failed
Similar to cardiopulmonary bypass
Pursestring sutures, snares
Suturing the cannula to the chest wall
Closing wound

5) Cannulation complication
Cannula site bleeding
No flow after catheter placement – check kinking, reposition or replacement
Intrathoracic perforation – immediate median sternotomy
Distal ischemia due to arterial cannula
Leg ischemia
additional distal perfusion catheter
fasciotomy, amputation
Amputation can be delayed by applying a completely occlusiove tourniquet above the infracted area and packing the dead limb in ice