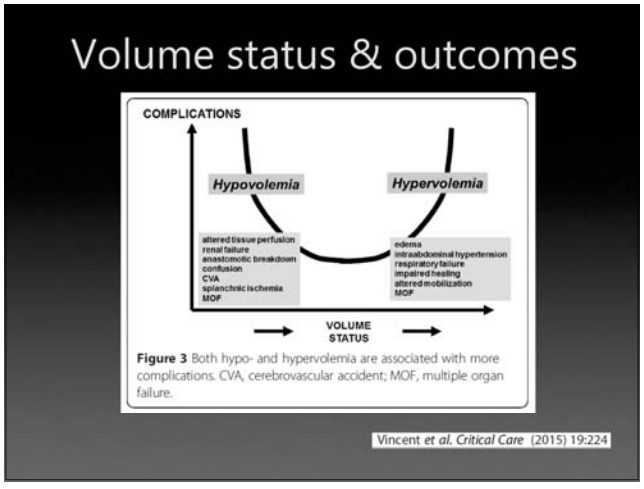
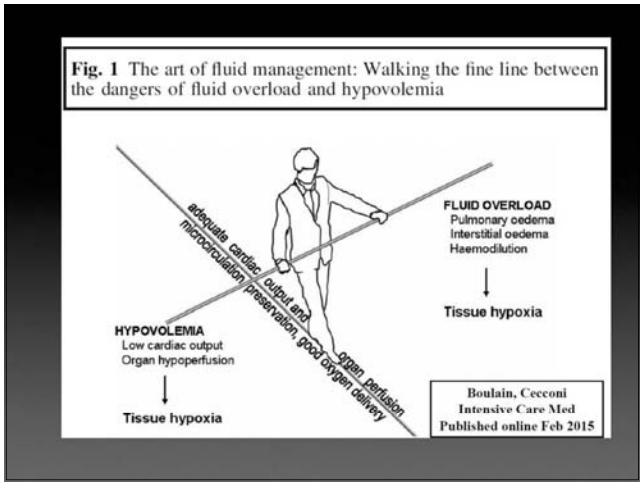
【2016년 중환자의학연구회 학술대회】

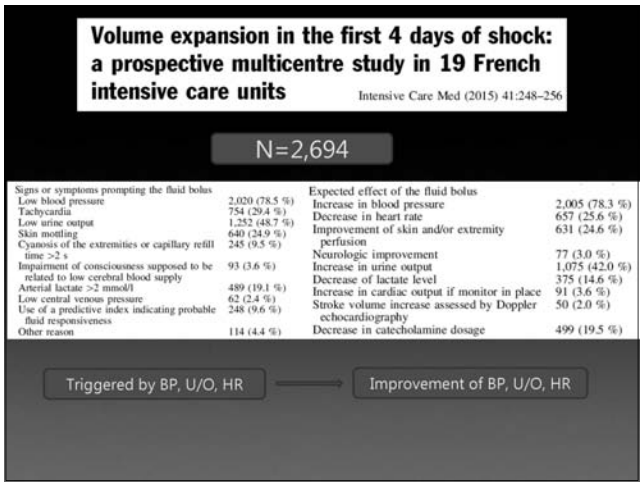
Volume Status & Preload Responsiveness Assessment

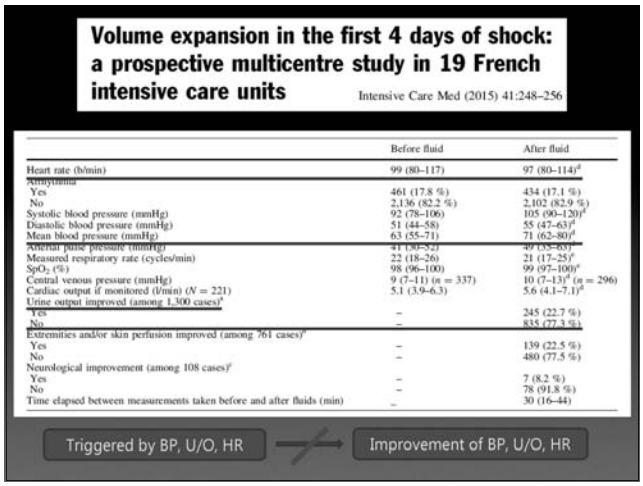
Emergency ICU, Regional Emergency Center

Jun Wan Lee, MD









Importance of intravenous fluid dose and composition in surgical ICU patients

Curr Opin Crit Care 2012, 18:350–357

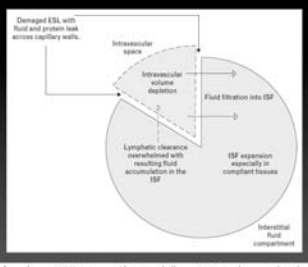


FIGURE 2. Endothelial surface layer (ESL) injury with critical illness. ESL is damaged with inflammation after surgery and with endothelial injury in critical illness. Crystalloids and colloids have equivalent volume effects during hypovolemia and with ESL damage as plasma proteins are lost to the interstitial compartment. Fluid accumulates in compliant tissues once capillary pressures rise to near normal. Less accumulation occurs in noncompliant tissues (such as encapsulated organs and/or rigid compartments).

McDermid RC *et al.* Controversies in fluid therapy

Table 3 Studies in critically ill patients describing the association with fluid overload and worse outcome

Study	Design	Population	Exposures	Outcomes
Pediatric Studies				
Goldstein *et al*[75]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Foland *et al*[66]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ organ dysfunction + mortality
Sutherland *et al*[71]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Arikan *et al*[58]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↓ lung function
Adult Studies				
Payen *et al*[61]	Post-hoc prospective	Adult critically ill septic patients	FB	↑ FB associated with ↑ mortality
Murphy *et al*[62]	Retrospective	Adult critically ill ALI patients	AIFR + CLFM	↑ Survival for ↑ AIFR + ↑ CLFM
Bouchard *et al*[57]	Post-hoc prospective	Adult critically ill AKI patients	% FO > 10%	↑ FB associated with ↑ mortality
Wiedemann *et al*[54]	RCT	Adult critically ill with ALI	Conservative vs liberal fluid management strategy	↑ MV-free days; ↑ ICU-free days with conservative strategy
Fulop *et al*[64]	Retrospective	Adult critically ill starting CRRT	VRWG	↑ VRWG associated with ↑ mortality
Boyd *et al*[55]	Post-hoc analysis from VASST	Adult critically ill septic patients	Quartiles of FB + CVP at 12 h and 4 d	↑ FB at 12 h and 4 d associated with ↑ mortality; CVP < 8 at 12 h ↓ mortality
Grams *et al*[56]	Post-hoc FACCT	Adult critically ill with ALI + AKI	FB + diuretics	↑ FB associated with ↑ mortality
Hwang *et al*[67]	Retrospective	Adult critically ill starting CRRT	% FO	↑ % FO associated with ↓ kidney recovery
Bellomo *et al*[68]	Post-hoc RENAL	Adult critically ill with AKI	FB	↑ FB associated with ↑ mortality

Adapted from Raghunathan *et al*[59]. ALI: Acute lung injury; AIFR: Adequate initial fluid resuscitation; CLFM: Conservative late fluid management; VRWG: Volume-related weight gain; AKI: Acute kidney injury; CVP: Central venous pressure; ICU: Intensive care unit; RCT: Randomized clinical trial.

Fluid overload ⇒ Mortality ⇧ MV duration ⇧ kidney recovery ⇩

Resuscitation Fluids

John A. Myburgh, M.B., B.Ch., Ph.D., and Michael G. Mythen, M.D., M.B., B.S.

N ENGL J MED 369;13 NEJM.ORG SEPTEMBER 26, 2013

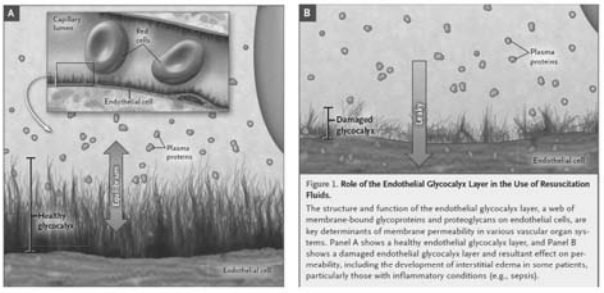


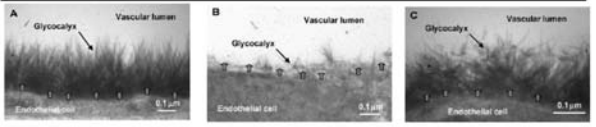
Figure 1. **Role of the Endothelial Glycocalyx Layer in the Use of Resuscitation Fluids.**
The structure and function of the endothelial glycocalyx layer, a web of membrane-bound glycoproteins and proteoglycans on endothelial cells, are key determinants of membrane permeability in various vascular organ systems. Panel A shows a healthy endothelial glycocalyx layer, and Panel B shows a damaged endothelial glycocalyx layer and resultant effect on permeability, including the development of interstitial edema in some patients, particularly those with inflammatory conditions (e.g., sepsis).

Cardiovascular Research (2010) 87, 300–310
doi:10.1093/cvr/cvq137

SPOTLIGHT REVIEW

Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential†

Bernhard F. Becker[1]*, Daniel Chappell[2], Dirk Bruegger[2], Thorsten Annecke[1,2], and Matthias Jacob[2]



- Maintain high concentration of plasma proteins
- Plasma albumin
- Hydrocortisone and mast cell
- Anti-thrombin III and protease inhibitors
- Avoidance - antioxidants, normo-volemia
- No preparations of syndecans, hyaluronan, chodndrotin sulfate for human use except Heparan sulfate

Not clinically tested....

STATIC AND DYNAMIC MEASURE OF PRELOAD AND THE DEVICES USED FOR MEASUREMENT

PRELOAD

STATIC		DYNAMIC
PRESSURE	VOLUME	
CVP PAOP	GEDV LVEDV	PPV SPV SVV IVC/ SVC 'collapsibility'
CVP= Central venous pressure Measurement device: Central venous catheter	GEDV= Global end-diastolic volume (transpulmonary thermodilution) Measurement device: PiCCO™, VolumeView™	PPV= pulse pressure variation Measurement device: PiCCO™, LiDCOplus™, Mostcare™
PAOP=Pulmonary artery occlusion pressure Measurement device: Pulmonary artery catheter	LVEDV= Left ventricular end- diastolic volume Measurement device: Echocardiography	SPV= systolic pressure variation Measurement device: PiCCO™, LiDCOplus™, Mostcare™
		SVV= stroke volume variation Measurement device: PiCCO™, LiDCOplus™, Flotrac/Vigileo™, Mostcare™, Volume clamp method (e.g. Finapres™, Nexfin™), Oesophageal Doppler, Echo-Doppler
		IVC= inferior vena cava SVC= superior vena cava

Does Central Venous Pressure Predict Fluid Responsiveness?*

A Systematic Review of the Literature and the Tale of Seven Mares

Paul E. Marik, MD, FCCP; Michael Baram, MD, FCCP; and Bobbak Vahid, MD

CHEST 2008; 134:172–178

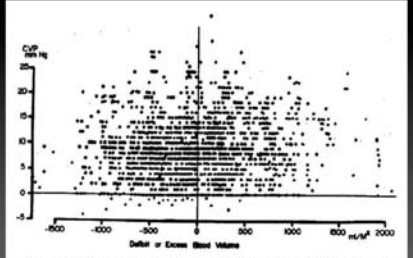
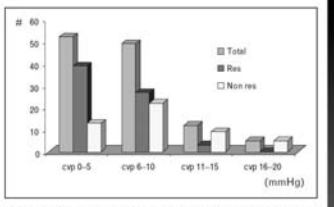


FIGURE 1. Fifteen hundred simultaneous measurements of blood volume and CVP in a heterogeneous cohort of 198 ICU patients demonstrating no association between these two variables ($r = 0.27$). The correlation between ΔCVP and change in blood volume was 0.1 ($r^2 = 0.01$). This study demonstrates that patients with a low CVP may have volume overload and likewise patients with a high CVP may be volume depleted. Reproduced with permission from Shippy *et al*.[11]

Fluid status and fluid responsiveness
Sheldon Magder

Current Opinion in Critical Care 2010,

Figure 2 Bar graph of number of patients responding to fluid challenge with different starting central venous pressure

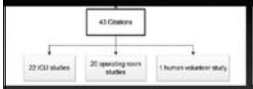


Data is obtained from a prospective series of 68 patients who received fluid challenges based on the decision of the treating team. In all cases the central venous pressure (CVP) increased by at least 2 mmHg. The first column at each quartile indicates the total patients in that group, the second shows those who responded (res) and the third who did not respond (non res). There were less boluses at higher CVP values based on the clinician's impressions. There were no responders in this series above 13 mmHg. Adapted from [16].

Does the Central Venous Pressure Predict Fluid Responsiveness? An Updated Meta-Analysis and a Plea for Some Common Sense*

Paul E. Marik, MD, FCCM[1]; Rodrigo Cavallazzi, MD[2]

www.ccmjournal.org
July 2013 • Volume 41 • Number 7



Data Synthesis: Overall 57% ± 13% of patients were fluid responders. The summary AUC was 0.56 (95% CI, 0.54–0.58) with no heterogenicity between studies. The summary AUC was 0.56 (95% CI, 0.52–0.60) for those studies done in the ICU and

In conclusion, there are no data to support the widespread practice of using CVP to guide fluid therapy. This approach to fluid resuscitation is without a scientific basis and should be abandoned.

REVIEW

Bench-to-bedside review: An approach to hemodynamic monitoring - Guyton at the bedside

Sheldon Magder*

Magder *Critical Care* 2012, 16:236

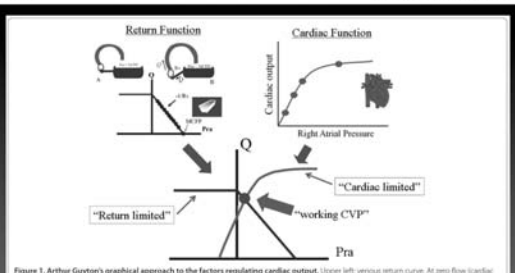


Figure 1. Arthur Guyton's graphical approach to the factors regulating cardiac output. Upper left: venous return curve. At zero flow (cardiac output (Q)), the right atrial pressure (Pra) is equal to the mean circulatory filling pressure. (MCFP) The lower Pra, the greater Q up to a maximum (flat line), in which case the flow is limited. Upper right: cardiac function curve (Starling curve). The greater Pra, the greater Q up to a plateau, in which case flow is limited by cardiac function. Lower: Since both graphs have the same axes, they can be put together with the working cardiac output and working Pra (or central venous pressure (CVP)) given by the intersection.

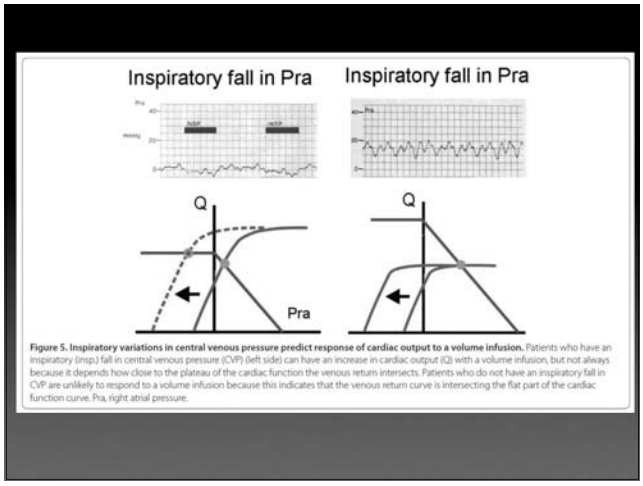
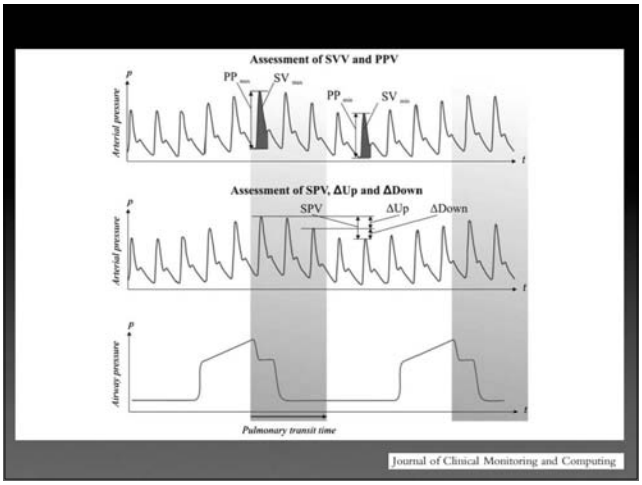


Figure 5. Inspiratory variations in central venous pressure predict response of cardiac output to a volume infusion. Patients who have an inspiratory (insp.) fall in central venous pressure (CVP) (left side) can have an increase in cardiac output (Q) with a volume infusion, but not always because it depends how close to the plateau of the cardiac function the venous return intersects. Patients who do not have an inspiratory fall in CVP are unlikely to respond to a volume infusion because this indicates that the venous return curve is intersecting the flat part of the cardiac function curve. Pra, right atrial pressure.



Journal of Clinical Monitoring and Computing

CURRENT OPINION

Functional haemodynamic monitoring

Michael R. Pinsky

Curr Opin Crit Care 2014, 20:288–293

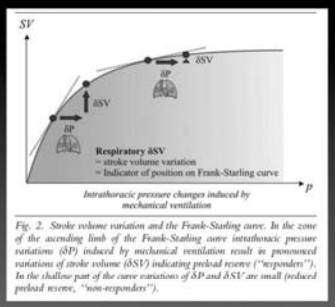
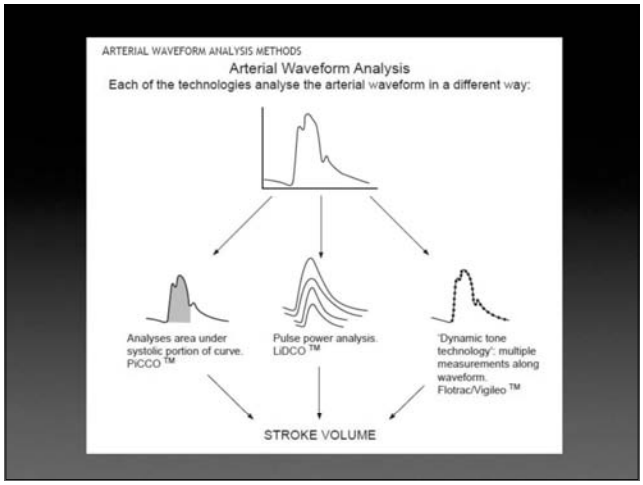
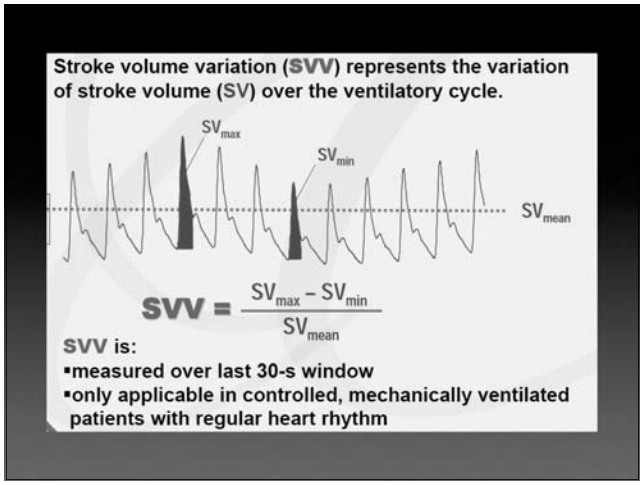
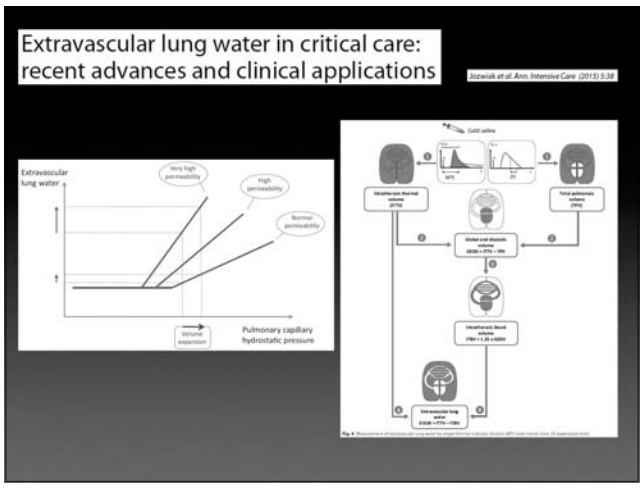
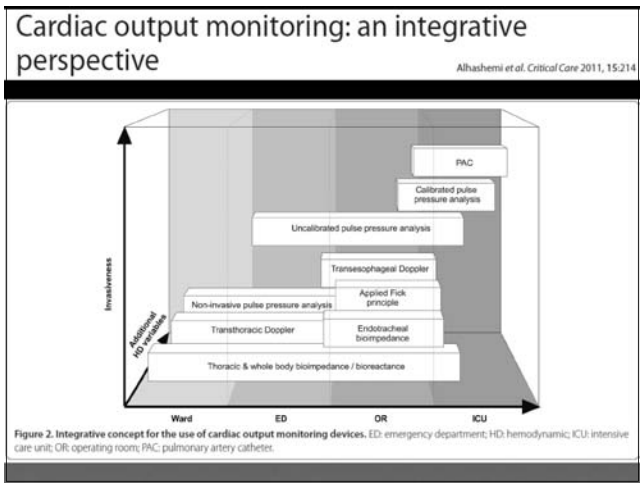


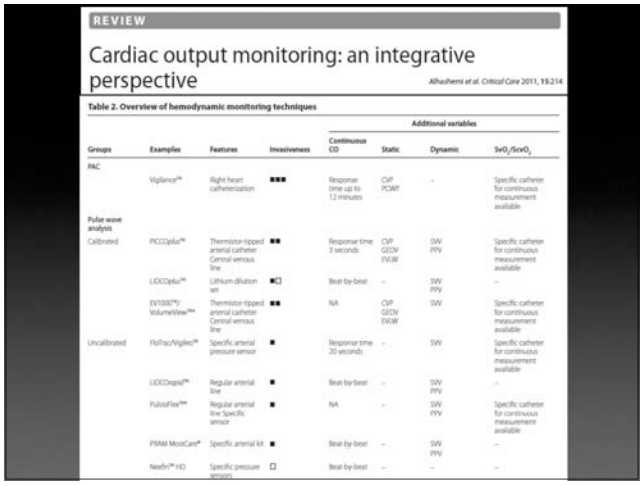
Fig. 2. Stroke volume variation and the Frank-Starling curve. In the zone of the ascending limb of the Frank-Starling curve intrathoracic pressure variations (δP) induced by mechanical ventilation result in pronounced variations of stroke volume (δSV) indicating preload reserve ("responders"). In the shallow part of the curve variations of δP and δSV are small (reduced preload reserve, "non-responders").

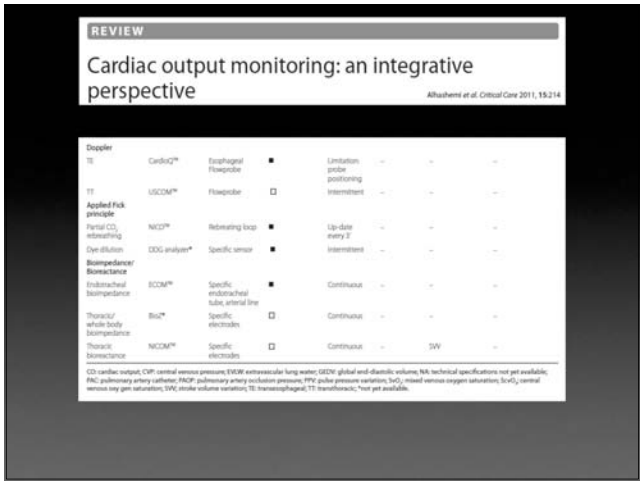

ARTERIAL WAVEFORM ANALYSIS METHODS
Arterial Waveform Analysis
Each of the technologies analyse the arterial waveform in a different way:
Analyses area under systolic portion of curve. PiCCO™
Pulse power analysis. LiDCO™
'Dynamic tone technology': multiple measurements along waveform. Flotrac/Vigileo™
STROKE VOLUME


Stroke volume variation (SVV) represents the variation of stroke volume (SV) over the ventilatory cycle.
SVmax
SVmin
SVmean
SVV = (SVmax – SVmin) / SVmean
SVV is:
▪measured over last 30-s window
▪only applicable in controlled, mechanically ventilated patients with regular heart rhythm


Extravascular lung water in critical care: recent advances and clinical applications
Jozwiak et al. Ann. Intensive Care (2015) 5:38
Extravascular lung water
Pulmonary capillary hydrostatic pressure
Cold saline


Cardiac output monitoring: an integrative perspective
Alhashemi et al. Critical Care 2011, 15:214
PAC
Calibrated pulse pressure analysis
Uncalibrated pulse pressure analysis
Transesophageal Doppler
Applied Fick principle
Non-invasive pulse pressure analysis
Transthoracic Doppler
Endotracheal bioimpedance
Thoracic & whole body bioimpedance / bioreactance
Invasiveness
Additional HD variables
Ward
ED
OR
ICU
Figure 2. Integrative concept for the use of cardiac output monitoring devices. ED: emergency department; HD: hemodynamic; ICU: intensive care unit; OR: operating room; PAC: pulmonary artery catheter.


REVIEW
Cardiac output monitoring: an integrative perspective
Alhashemi et al. Critical Care 2011, 15:214
Table 2. Overview of hemodynamic monitoring techniques
Groups
Examples
Features
Invasiveness
Additional variables
Continuous CO
Static
Dynamic
SvO2/ScvO2
PAC
Pulse wave analysis
Calibrated
Uncalibrated


REVIEW
Cardiac output monitoring: an integrative perspective
Alhashemi et al. Critical Care 2011, 15:214
Doppler
Applied Fick principle
Bioimpedance/ Bioreactance

British Journal of Anaesthesia 114 (4): 562–75 (2015)
Advance Access publication 16 January 2015 · doi:10.1093/bja/aeu447

BJA

Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine

Table 2 Heterogeneity of results and conclusions presented in validation studies of different noninvasive continuous cardiac output monitoring technologies. In this table, we present the results on accuracy and precision and the authors' conclusions of validation studies on different noninvasive continuous cardiac output monitoring technologies

Technology	Study/Reference	Studied device	Setting (patient population)	No. of patients	Criterion standard technology	Cardiac output (CO) or Cardiac index (CI)	Bias (standard deviation) (criterion standard – studied technology)	'Conclusion'
Thoracic electrical bioimpedance								
	Jegerman and colleagues[47]	BioZ	intensive care unit (postoperative cardiac surgery patients)	20	pulmonary artery thermodilution	CI	−0.07 (0.20) litre min^{-1} m^{-2}	'Thoracic electrical bioimpedance is **equivalent** to pulmonary artery thermodilution-derived cardiac index […]'
	Spiess and colleagues[48]	BioZ	operating theatre (cardiac surgery patients)	47	pulmonary artery thermodilution	CI	0.28 (0.67) litre min^{-1} m^{-2}	'Thoracic electrical bioimpedance reporting of cardiac index during coronary artery surgery **generally agreed** with pulmonary artery catheter thermodilution cardiac index […]'
	Engoren and colleagues[49]	BioZ	intensive care unit (mixed population of critically ill patients)	46	pulmonary artery thermodilution	CO	1.0 (1.3) litre min^{-1}	'Bioimpedance [and] thermodilution […] determinations of cardiac outputs are **not interchangeable** in a heterogeneous population of critically ill patients.'
Thoracic bioreactance								
	Squara and colleagues[50]	NICOM	intensive care unit (postoperative cardiac surgery patients)	130	pulmonary artery thermodilution	CO	−0.06 (0.71) litre min^{-1}	'Cardiac output measured by NICOM had **most often acceptable accuracy [and] precision** […] in a wide range of circulatory situations.'
	Raval and colleagues[51]	NICOM	cardiac care units, intensive care units, cardiac catheterization laboratories (mixed population)	111	pulmonary artery thermodilution	CO	intensive care units: −0.09 (1.22) litre min^{-1}; catheterization laboratories: −0.17 (1.04) litre min^{-1}	'On average, compared to thermodilution, bioreactance-based NICOM has **acceptable accuracy** in challenging clinical environments.'
	Raber and colleagues[52]	NICOM	operating theatre (surgical patient with ovarian cancer)	35	transpulmonary thermodilution	CI	−0.26 (0.85) litre min^{-1} m^{-2}	'Cardiac index assessment by bioreactance showed **acceptable accuracy** […]. However, its **precision was poor**.'
Vascular unloading technique								
	Bracht and colleagues[53]	Nexfin	operating theatre (cardiac surgery patients)	40	transpulmonary thermodilution	CI	pre-cardiopulmonary bypass: 0.06 (0.27) litre min^{-1} m^{-2}; post-cardiopulmonary bypass: 0.09 (0.37) litre min^{-1} m^{-2}	'We conclude that the Nexfin is a **reliable method** of measuring cardiac output during and after cardiac surgery.'

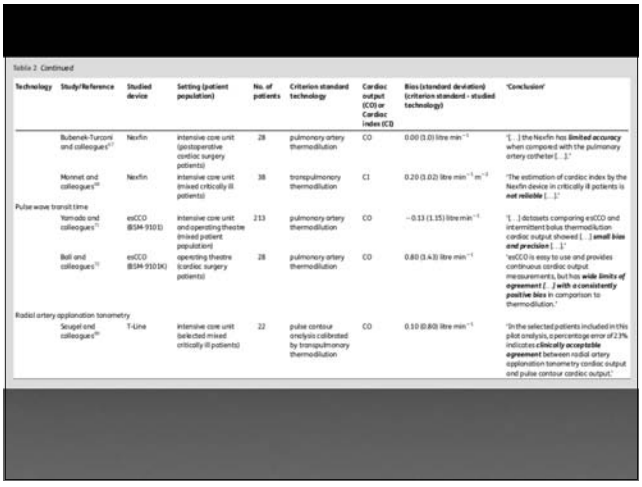
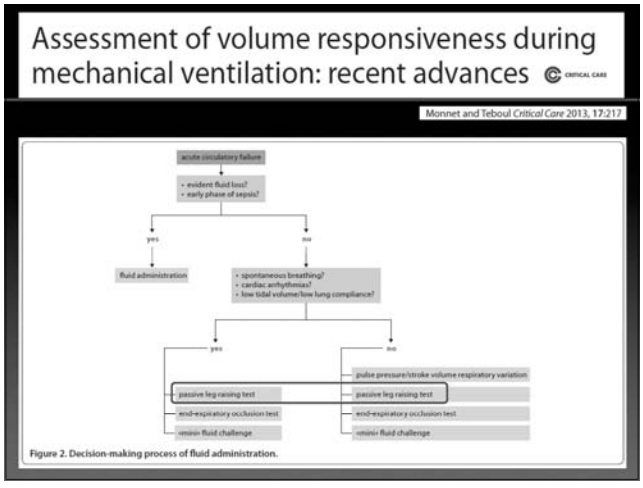


Table 2 Continued

Technology	Study/Reference	Studied device	Setting (patient population)	No. of patients	Criterion standard technology	Cardiac output (CO) or Cardiac index (CI)	Bias (standard deviation) (criterion standard – studied technology)	'Conclusion'
	Bubenek-Turconi and colleagues[47]	Nexfin	intensive care unit (postoperative cardiac surgery patients)	28	pulmonary artery thermodilution	CO	0.00 (1.0) litre min^{-1}	'[…] the Nexfin has **limited accuracy** when compared with the pulmonary artery catheter […].'
	Monnet and colleagues[48]	Nexfin	intensive care unit (mixed critically ill patients)	38	transpulmonary thermodilution	CI	0.20 (3.02) litre min^{-1} m^{-2}	'The estimation of cardiac index by the Nexfin device in critically ill patients is **not reliable** […].'
Pulse wave transit time								
	Yamada and colleagues[51]	esCCO (BSM-9101)	intensive care unit and operating theatre (mixed patient population)	213	pulmonary artery thermodilution	CO	−0.13 (1.15) litre min^{-1}	'[…] datasets comparing esCCO and intermittent bolus thermodilution cardiac output showed […] **small bias and precision** […].'
	Ball and colleagues[52]	esCCO (BSM-9101K)	operating theatre (cardiac surgery patients)	28	pulmonary artery thermodilution	CO	0.80 (3.43) litre min^{-1}	'esCCO is easy to use and provides continuous cardiac output measurements, but has **wide limits of agreement** […] **with a consistently positive bias** in comparison to thermodilution.'
Radial artery applanation tonometry								
	Seupel and colleagues[56]	T-Line	intensive care unit (selected mixed critically ill patients)	22	pulse contour oneiysis calibrated by transpulmonary thermodilution	CO	0.10 (0.80) litre min^{-1}	'In the selected patients included in this pilot analysis, a percentage error of 23% indicates **clinically acceptable agreement** between radial artery applanation tonometry cardiac output and pulse contour cardiac output.'

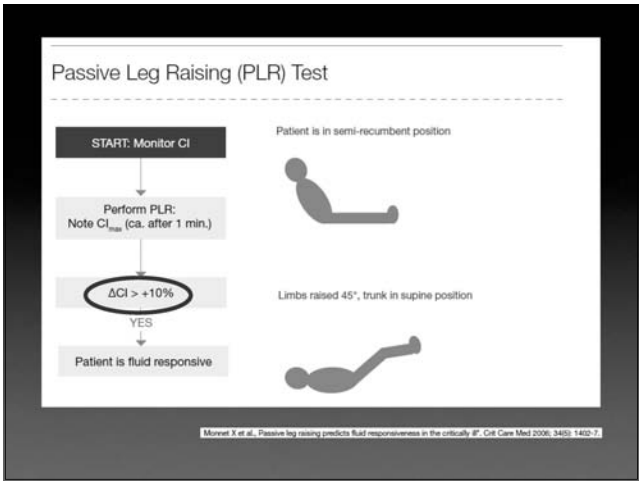


Assessment of volume responsiveness during mechanical ventilation: recent advances

CRITICAL CARE

Monnet and Teboul *Critical Care* 2013, 17:217

Figure 2. Decision-making process of fluid administration.



Passive Leg Raising (PLR) Test

START: Monitor CI

Perform PLR: Note CI_{max} (ca. after 1 min.)

$\Delta CI > +10\%$

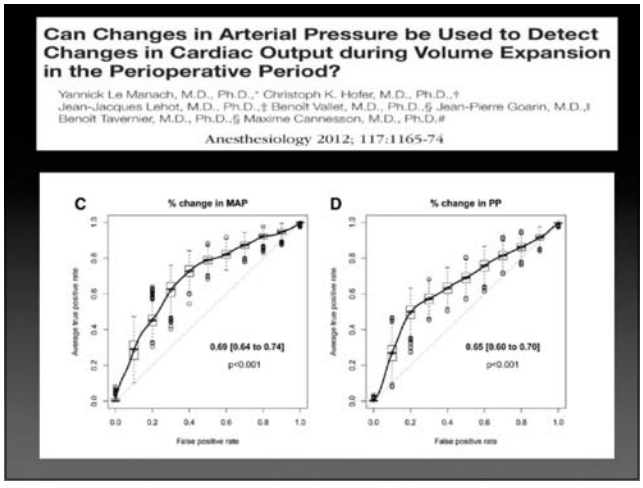
YES

Patient is fluid responsive

Patient is in semi-recumbent position

Limbs raised 45°, trunk in supine position

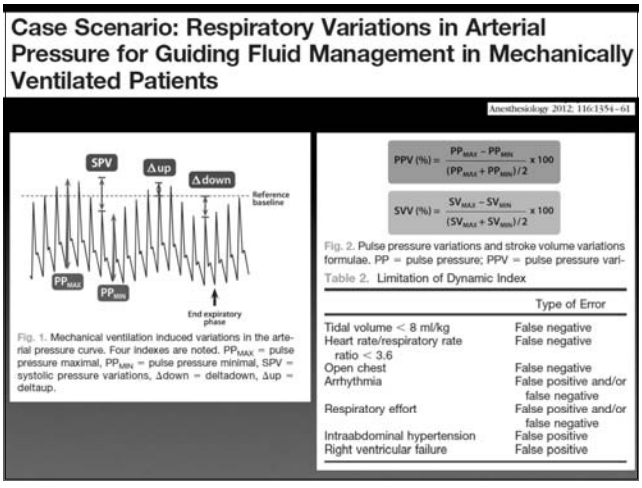
Monnet X et al., Passive leg raising predicts fluid responsiveness in the critically ill*. Crit Care Med 2006; 34(5): 1402-7.



Can Changes in Arterial Pressure be Used to Detect Changes in Cardiac Output during Volume Expansion in the Perioperative Period?

Yannick Le Manach, M.D., Ph.D.,* Christoph K. Hofer, M.D., Ph.D.,† Jean-Jacques Lehot, M.D., Ph.D.,‡ Benoît Vallet, M.D., Ph.D.,§ Jean-Pierre Goarin, M.D.,‖ Benoît Tavernier, M.D., Ph.D.,§ Maxime Cannesson, M.D., Ph.D.#

Anesthesiology 2012; 117:1165-74



Case Scenario: Respiratory Variations in Arterial Pressure for Guiding Fluid Management in Mechanically Ventilated Patients

Anesthesiology 2012; 116:1354–61

Fig. 1. Mechanical ventilation induced variations in the arterial pressure curve. Four indexes are noted. PP_{MAX} = pulse pressure maximal, PP_{MIN} = pulse pressure minimal, SPV = systolic pressure variations, Δdown = deltadown, Δup = deltaup.

$$PPV\,(\%) = \frac{PP_{MAX} - PP_{MIN}}{(PP_{MAX} + PP_{MIN})/2} \times 100$$

$$SVV\,(\%) = \frac{SV_{MAX} - SV_{MIN}}{(SV_{MAX} + SV_{MIN})/2} \times 100$$

Fig. 2. Pulse pressure variations and stroke volume variations formulae. PP = pulse pressure; PPV = pulse pressure vari-

Table 2. Limitation of Dynamic Index

	Type of Error
Tidal volume < 8 ml/kg	False negative
Heart rate/respiratory rate ratio < 3.6	False negative
Open chest	False negative
Arrhythmia	False positive and/or false negative
Respiratory effort	False positive and/or false negative
Intraabdominal hypertension	False positive
Right ventricular failure	False positive

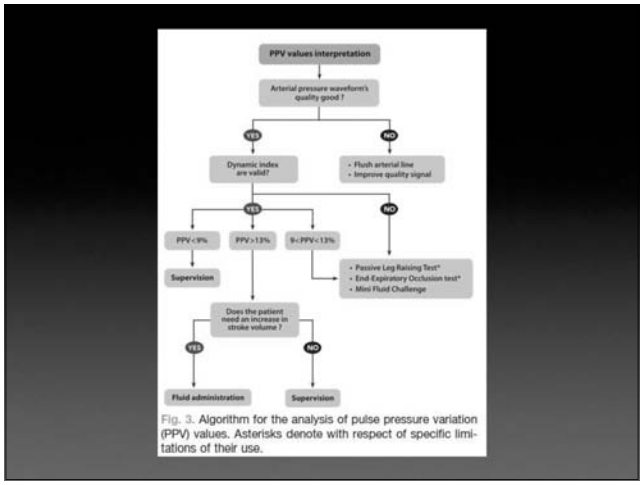
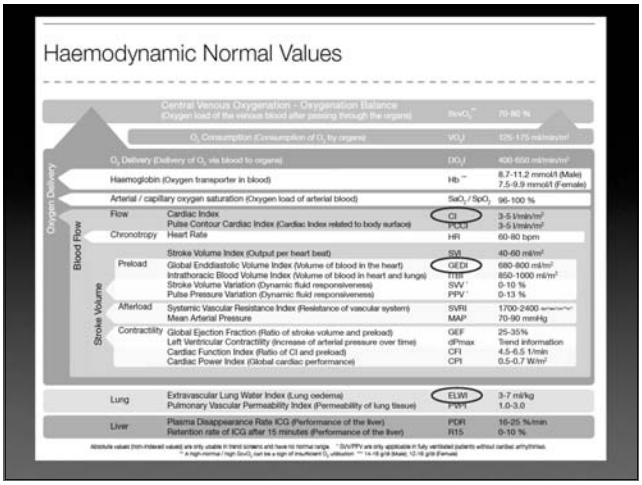
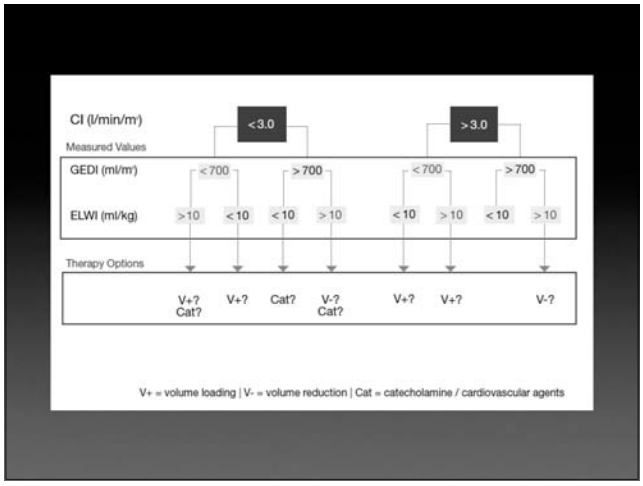


Fig. 3. Algorithm for the analysis of pulse pressure variation (PPV) values. Asterisks denote with respect of specific limitations of their use.





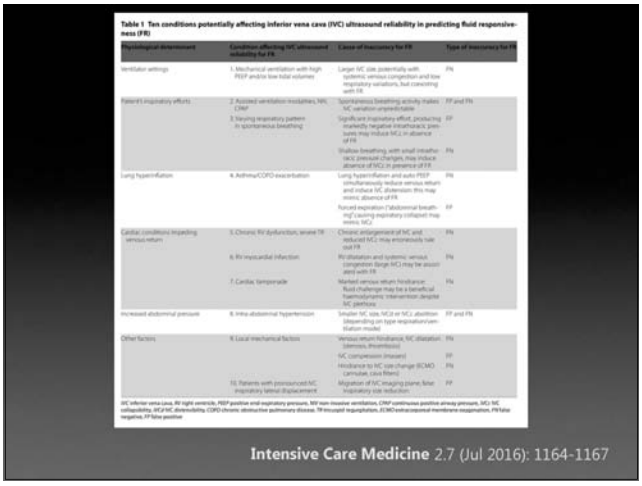


Table 1 Ten conditions potentially affecting inferior vena cava (IVC) ultrasound reliability in predicting fluid responsiveness (FR)

Physiological determinant	Condition affecting IVC ultrasound reliability for FR	Cause of inaccuracy for FR	Type of inaccuracy for FR
Ventilation settings	1. Mechanical ventilation with high PEEP and/or low tidal volumes	Larger IVC size, potentially with systemic venous congestion and low respiratory variations, fluid consisting with FR	FN
Patient's inspiratory efforts	2. Assisted ventilation modalities, NIV, CPAP	Spontaneous breathing activity makes IVC variation unpredictable	FP and FN
	3. Varying respiratory pattern in spontaneous breathing	Significant inspiratory effort, producing markedly negative intrathoracic pressures may induce IVCc in absence of FR	FP
		Shallow breathing, with small intrathoracic pressure changes, may induce absence of IVCc in presence of FR	FN
Lung hyperinflation	4. Asthma/COPD exacerbation	Lung hyperinflation and auto PEEP simultaneously reduce venous return and induce IVC distension: this may mimic absence of FR	FN
		Forced expiration ("abdominal breathing") causing expiratory collapse may mimic IVCc	FP
Cardiac conditions impeding venous return	5. Chronic RV dysfunction, severe TR	Chronic enlargement of IVC and reduced IVCc may erroneously rule out FR	FN
	6. RV myocardial infarction	RV dilatation and systemic venous congestion (large IVCc) may be associated with FR	FN
	7. Cardiac tamponade	Marked venous return hindrance: fluid challenge may be a beneficial haemodynamic intervention despite IVC plethora	FN
Increased abdominal pressure	8. Intra-abdominal hypertension	Smaller IVC size, IVCd or IVCc abolition (depending on type respiration/ventilation mode)	FP and FN
Other factors	9. Local mechanical factors	Venous return hindrance, IVC dilatation (stenosis, thrombosis)	FN
		IVC compression (masses)	FP
		Hindrance to IVC size change (ECMO cannulae, cava filters)	FN
	10. Patients with pronounced IVC inspiratory lateral displacement	Migration of IVC imaging plane, false inspiratory size reduction	FP

IVC inferior vena cava, RV right ventricle, PEEP positive end-expiratory pressure, NIV non-invasive ventilation, CPAP continuous positive airway pressure, IVCc IVC collapsibility, IVCd IVC distensibility, COPD chronic obstructive pulmonary disease, TR tricuspid regurgitation, ECMO extracorporeal membrane oxygenation, FN false negative, FP false positive

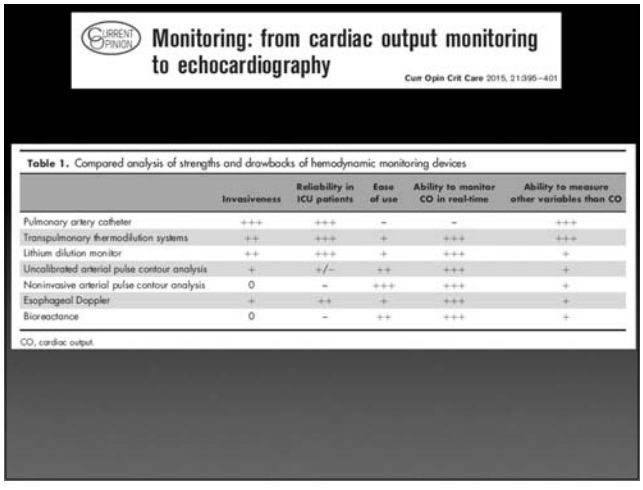


Table 1. Compared analysis of strengths and drawbacks of hemodynamic monitoring devices

	Invasiveness	Reliability in ICU patients	Ease of use	Ability to monitor CO in real-time	Ability to measure other variables than CO
Pulmonary artery catheter	+++	+++	–	–	+++
Transpulmonary thermodilution systems	++	+++	+	+++	+++
Lithium dilution monitor	++	+++	+	+++	+
Uncalibrated arterial pulse contour analysis	+	+/–	++	+++	+
Noninvasive arterial pulse contour analysis	0	–	+++	+++	+
Esophageal Doppler	+	++	+	+++	+
Bioreactance	0	–	++	+++	+

CO, cardiac output.

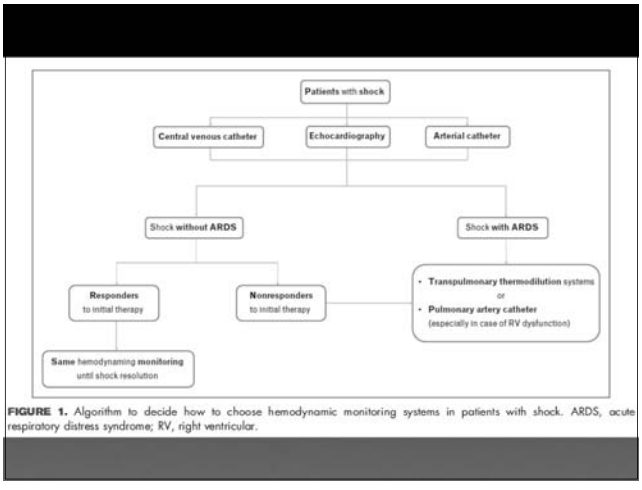
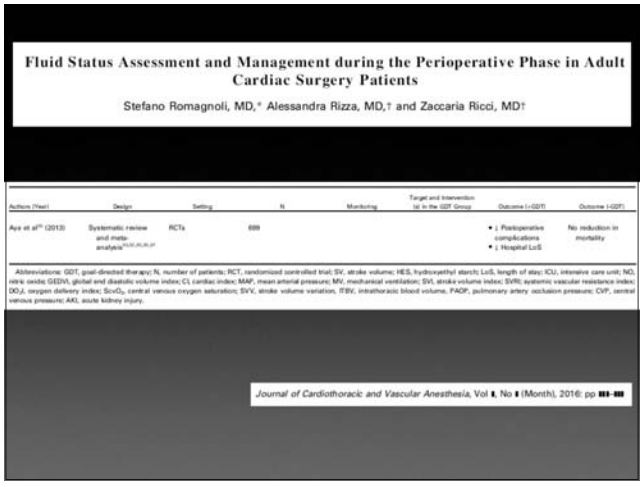


FIGURE 1. Algorithm to decide how to choose hemodynamic monitoring systems in patients with shock. ARDS, acute respiratory distress syndrome; RV, right ventricular.



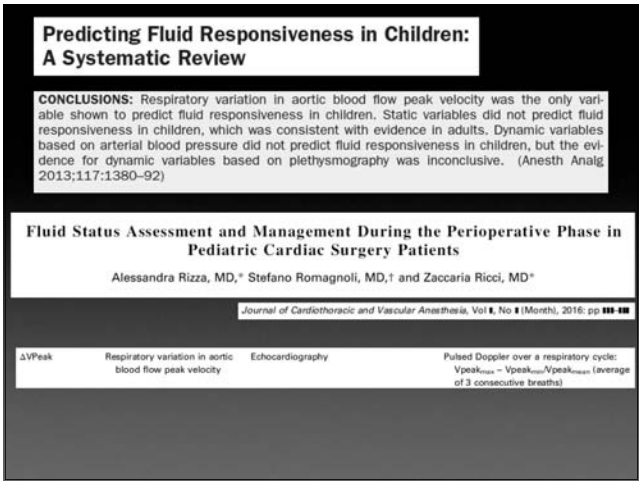
Fluid Status Assessment and Management during the Perioperative Phase in Adult Cardiac Surgery Patients

Stefano Romagnoli, MD,* Alessandra Rizza, MD,† and Zaccaria Ricci, MD†

Authors (Year)	Design	Setting	N	Monitoring	Target and Intervention (a) in the GDT Group	Outcome (+GDT)	Outcome (-GDT)
Aya et al[30] (2013)	Systematic review and meta-analysis[16,17,20,26,27]	RCTs	699			• ↓ Postoperative complications • ↓ Hospital LoS	No reduction in mortality

Abbreviations: GDT, goal-directed therapy; N, number of patients; RCT, randomized controlled trial; SV, stroke volume; HES, hydroxyethyl starch; LoS, length of stay; ICU, intensive care unit; NO, nitric oxide; GEDVI, global end diastolic volume index; CI, cardiac index; MAP, mean arterial pressure; MV, mechanical ventilation; SVI, stroke volume index; SVRI, systemic vascular resistance index; DO_2, oxygen delivery index; $ScvO_2$, central venous oxygen saturation; SVV, stroke volume variation, ITBV, intrathoracic blood volume, PADP, pulmonary artery occlusion pressure; CVP, central venous pressure; AKI, acute kidney injury.

Journal of Cardiothoracic and Vascular Anesthesia, Vol ▮, No ▮ (Month), 2016: pp ▮▮▮–▮▮▮



Predicting Fluid Responsiveness in Children: A Systematic Review

CONCLUSIONS: Respiratory variation in aortic blood flow peak velocity was the only variable shown to predict fluid responsiveness in children. Static variables did not predict fluid responsiveness in children, which was consistent with evidence in adults. Dynamic variables based on arterial blood pressure did not predict fluid responsiveness in children, but the evidence for dynamic variables based on plethysmography was inconclusive. (Anesth Analg 2013;117:1380–92)

Fluid Status Assessment and Management During the Perioperative Phase in Pediatric Cardiac Surgery Patients

Alessandra Rizza, MD,* Stefano Romagnoli, MD,† and Zaccaria Ricci, MD*

Journal of Cardiothoracic and Vascular Anesthesia, Vol ▮, No ▮ (Month), 2016: pp ▮▮▮–▮▮▮

ΔVPeak	Respiratory variation in aortic blood flow peak velocity	Echocardiography	Pulsed Doppler over a respiratory cycle: $Vpeak_{max} - Vpeak_{min}/Vpeak_{mean}$ (average of 3 consecutive breaths)

Fluid, Fluid, Fluid

Seoul National University Hospital, Seoul National University, College of Medicine

Hyun Joo Lee, MD, PhD

Fluid

- Hydration
- Nutrition
- Intravascular volume replacement, blood products

Contents

- Introduction
- Fluid disposition
- Fluid types : harm / benefit
- Evidences
- Summary

Terminology

- Osmolarity : solute / solvent + solute (mol/L)
  (osmoles of solute per liter of solution)
- Osmolality : solute / solvent (mol/kg)
  (osmoles of solute per kilogram of solvent)
- Tonicity : relative osmolality of one solution in reference to another
- Crystalloid : electrolytes, glucose (small solutes)
- Colloid : macromolecules suspended in electrolyte solutions
- Balanced : physiological pH/isotonic salt concent.

Terminology

- Fluid bolus: a rapid infusion to correct hypotensive shock.
  at least 500 ml over a maximum of 15 min
- Fluid challenge: 100–200 ml over 5–10 min
  with reassessment to optimize tissue perfusion
- Fluid infusion: continuous delivery of i.v. fluids
  to maintain homeostasis, replace losses, or prevent organ injury
  prehydration for contrast nephropathy
- Maintenance: fluid administration for the provision of fluids
  for patients who cannot meet their needs by oral route.
  no more than 1 –2 ml/ kg

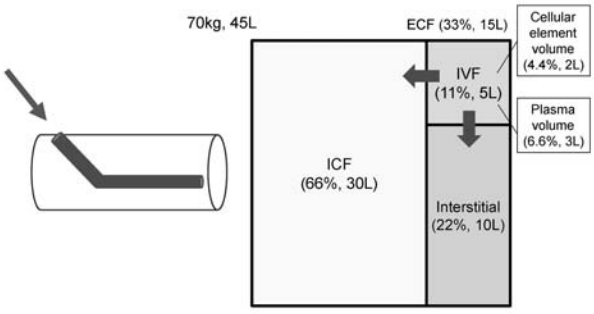
Fluids

Fluid	pH	Na	Cl	K	Ca	Mg	Buffer	Osmol	Acid-Base
Plasma	7.4	141	103	4-5	5	2	Bicarbonate	289	
Normal Saline	5.7	154	154					308	Acidosis
Lactated Ringer's (Hartmann)	6.4	130	109	4	3		Lactate 28mEq	273	No effect
Plasma Sol A	7.4	140	98	5		3	Acetate 27mEq / Gluconate 23mEq	295	Alkalosis

Fluid	분자량	삼투압	혈장용적증가배수	혈청반감기
5% albumin	69,000 Dalton	20 mmHg	0.7-1.3	16시간
6% Hetastarch	69,000 Dalton	30 mmHg	1.0-1.3	17일

중환자의학 제2판

Fluid Distribution



Starling Principle

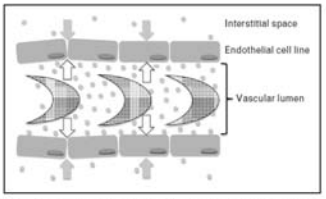


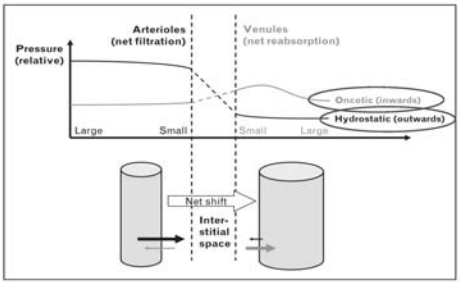
FIGURE 1. The vascular system is under (blood) pressure (white arrows), which is, according to the traditional view, opposed by the inward-directed oncotic gradient (grey arrows) generated across the vascular wall by a difference in the protein (grey circles) concentration.

$$F = \mathrm{HC} \times [(PV - PI) - (\pi V - \pi I)]$$

- *Hydrostatic Pressure*
- *Oncotic Pressure*
- *Net filtration of water and small molecules towards the interstitial space is determined by the two competing forces*

Curr Opin Crit Care 2013;19:282

Starling Principle



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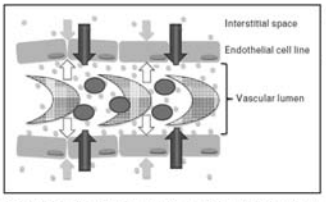


FIGURE 1. The vascular system is under (blood) pressure (white arrows), which is, according to the traditional view, opposed by the inward-directed oncotic gradient (grey arrows) generated across the vascular wall by a difference in the protein (grey circles) concentration.

$$Jv = Kf[(Pc - Pi) - \sigma(\pi c - \pi i)]$$

- Colloid -> 100% intravascular + α
- Isotonic solution -> 20% intravascular
- Dextrose -> 6% intravascular

⇒ *Resuscitation!!!*
Colloid > Hartmann / NS > D5W

Curr Opin Crit Care 2013;19:282

- 391 ICU across 25 countries

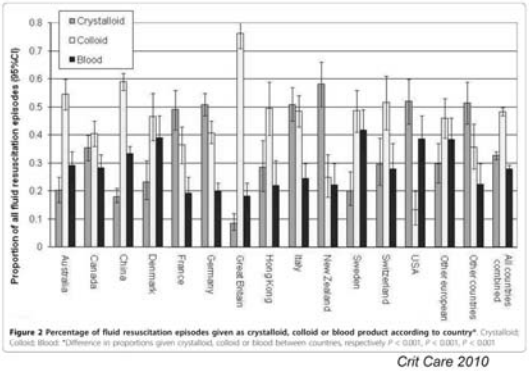
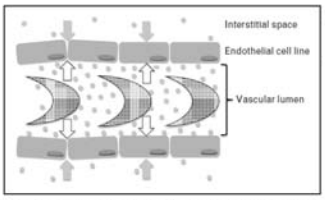


Figure 2 Percentage of fluid resuscitation episodes given as crystalloid, colloid or blood product according to country* Crystalloid, colloid, Blood. *Difference in proportions given crystalloid, colloid or blood between countries, respectively $P < 0.001$, $P < 0.001$, $P < 0.001$

Crit Care 2010

Starling Principle



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Curr Opin Crit Care 2013;19:282

Fluids

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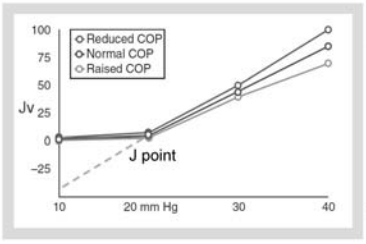
중환자의학 제2판

No Absorption Rule



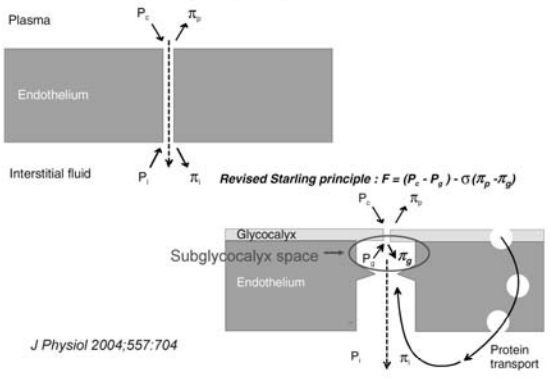
$$Jv = Kf[(Pc - Pi) - \sigma(\pi c - \pi i)]$$

- No absorption under a dominant COP gradient
- Much less effect of πi on transvascular fluid exchange

⇒ *Revised Starling Equation!!!*

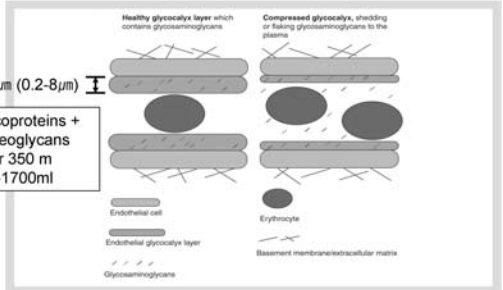
J Physiol 2004;557:889
Br J Anaesth 2012;108:384

Classic Starling principle : $F = (P_c - P_i) - \sigma(\pi_p - \pi_i)$



J Physiol 2004;557:704

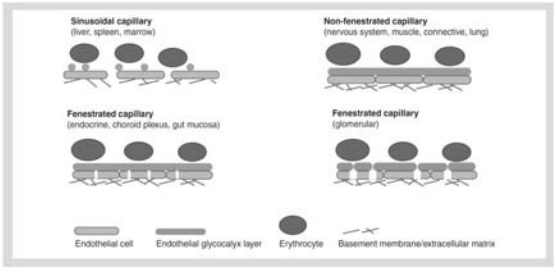
Endothelial Glycocalyx Layer (EGL)



- Glycoproteins + Proteoglycans
- Over 350 m
- 700-1700ml

Br J Anaesth 2012;108:384

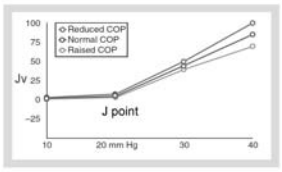
Endothelial Glycocalyx Layer



Revised Starling Principle

Original Starling Principle	Revised Starling Principle
Plasma + Cellular element	Glycocalyx + Plasma + RBC distribution volume
Plasma – high protein ISF – low protein Capillaries separate between both	Different types of capillaries Continuous capillaries exhibit 'no absortion'
Transendothelial filtration (Jv) depends on transendothelial pr difference and plasma-interstitial COP difference	Jv depends on transendothelial pr difference and plasma-subglycocalyx COP difference
Fluid is filtered from the arterial end and absorbed form the venous end Small portion returns as lymph	Jv is much less than predicted Major route for return is as lymph Autotransfusion is acute, transient, and limited to 500ml
Colloid – intravascular volume Isotonic sol – extracellular volume	Isotonic sol also remain intravascular space with subnormal capillary pr

No Absorption Rule



$$Jv = Kf[(Pc - Pi) - \sigma(\pi c - \pi i)]$$

Capillary pressure(Pc)	Colloid	Isotonic sol
Subnormal	Jv≈0, intravascular	Jv≈0, intravascular
Normal, Supranormal	Jv∞Pc, Reduce Jv with raised COP	Jv∞Pc, Increase Jv with reduced COP

Plasma Protein

- TCERA (Transcapillary Escape Rate of Albumin to the tissue) : index of vascular permeability
  - Index of vascular permeability
  - Normal 5%, during surgery 10%, septic shock 20%
- Albumin Therapy
  - Hypoalbuminemia : marker of disease severity, predictor of complications, but no clinical benefit with albumin therapy
  - ARDS : negative fluid balance > Albumin therapy

Fluid Issues

- Colloid vs Crystalloid
- Albumin
- HES
- Balanced vs non-balanced

Colloid vs Crystalloid

Trial	Full name	Comparator	Group	Design
SAFE (2004)	Saline versus Albumin Fluid Evaluation	4% Albumin / Saline	Australia, New Zealand, 16 ICU (6997)	blind
VISEP (2008)	Volume Substitution and Insulin Therapy in Severe Sepsis	HES 200/0.5(pentastarch)/ Ringer's lactate (intensive /conventional insulin therapy)	Germany 18 ICU (600)	open
6S (2012)	Scandinavian Starch for Severe Sepsis/Septic Shock	HES 130/0.42 in Ringer's acetate (Tetraspan) / Ringer's acetate	Scandinavian 26 ICU (804)	blind
CHEST (2012)	Crystalloid vs Hydroxyethyl Starch Trial	HES 130/0.4 in Saline (voluven)/ Saline	Australia, New Zealand 32 ICU (7000)	blind
CRISTAL (2013)	Colloids Versus Crystalloids for the Resuscitation of the Critically Ill	Colloid (gelatin, dextrans, HES, albumin) / Crystalloid (NS, HS, Ringer's lactate)	France, Belgium, North Africa, Canada 51 ICU (2857)	open
ALBIOS (2014)	Albumin Italian Outcome Sepsis	20% Albumin / Crystalloid	Italy 100 ICU (1818)	open

Study	Fluid	Patients	Results
SAFE (2004)	4% Albumin Saline	Critically ill patients (3497/3500)	28-day mortality (-) (20.8%/20.8%) organ failure (-) ICU stay, MV, HOS, RRT (-), 1: 1.4 Severe sepsis: albumin + trend, Traum (brain hemorrhagic injury): albumin -
VISEP (2008)	HES 200/0.5 (10% pentastarch) Ringer's lactate Intensive/conventional insulin	Septic shock or severe sepsis (300/300)	28-day mortality (-) (26.7%/24.1%) Organ failure (-), 1: 1.32 90-day mortality: HES↑ trend (41.0%/33.9%) HES: AKI & RRT high, PLT low, RBC transfusion high (correlation btw cumulative dose)
6S (2012)	HES 130/0.42 (Tetraspan) Ringer's acetate	Severe Sepsis within 24hr (389/400)	90-day mortality: HES↑(51%/43%), 1:1 RRT: HES↑, severe bleeding trend (10%/6%)
CHEST (2012)	HES 130/0.4 (voluven) Saline	Requiring fluid resuscitation (3315/3336)	90-day mortality (-) (18%/17%), less volume, more blood Renal injury: (-) Renal failure: HES↑ trend RRT: HES↑ Adverse : HES↑(pruritus, rash)
CRISTAL (2013)	Colloid (gelatin, dextrans, HES, albumin) Crystalloid (NS, HS, Ringer's lactate)	Clinically ill pt (sepsis, trauma, hypovolemic shock), 9yrs (1414/1443)	28-day mortality (-) (25.4%/27.0%), 2000:3000 90-day mortality : colloid↓(30.7%/34.2%) RRT (-) MV, vasopressor use free: colloid↑
ALBIOS (2014)	20% Albumin + Crystalloid Crystalloid	Severe Sepsis(within 24hr), 1818 pts	28-day mortality (-) (31.8%/32.0%) 90-day mortality (-) (41.1%/43.6%), (w shock) Albumin : net fluid balance low, HR low, MBP high, cardiovascular failure low

Surviving Sepsis Campaign

Hemodynamic Support and Adjunctive Therapy (Table 6)

G. Fluid Therapy of Severe Sepsis

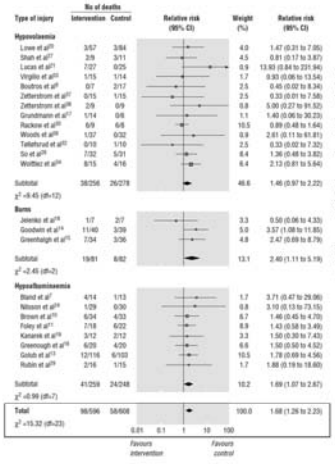
1. We recommend crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (grade 1B). (This recommendation is based on the results of the VISEP [128], CRYSTMAS [122], 6S [123], and CHEST [124] trials. The results of the recently completed CRYSTAL trial were not considered.)
3. We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).

TO BE CO
1) Measure
2) Obtain b
3) Administ
4) Administ

TO BE CO
5) Apply va
to maint
6) In the ev
shock) o
- Me
- Me
7) Remeas

*Targets fo
$ScvO_2$ of ≥70%, and normalization of lactate.

Dellinger RP
Crit Care Med 2013;41:580-637



Albumin / Plasma protein fraction vs crystalloid or non-albumin

Pooled relative risk of death with albumin was 1.68 (95% CI 1.26-2.23)

Pooled difference in the risk of death with albumin was 6% (95% CI 3-9%)

1 additional death / every 17 critically ill pts treated with albumin

Cochrane Group
BMJ 1998;317:235-40

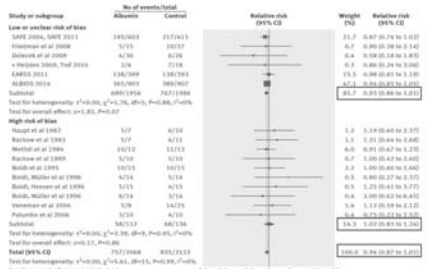
SAFE study

Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)

0.5 1.0 2.0
Albumin Better | Saline Better

SAFE Study Investigators
N Engl J Med 2004;350:2247-56

Meta-analysis (Albumin in sepsis)



No Harm,
No benefit to survival

Fig 3 Relative risk of all-cause mortality in patients exposed to human albumin solutions compared with exposure to control fluids in the 16 randomised clinical trials included in analysis. Studies are ordered chronologically within subgroups

Patel A. BMJ 2014;349:g4561

Balanced Salt Solution

2012	Matched –cohort observational study	927 pts for replacement of fluid losses on the day of surgery	0.9% Saline vs PlasmaLyte(Ca-free)	Use of balanced salt solution was associated with a significant decrease in the rate of major complications (OR 0.79, CI 0.66-0.97) Lower incidence of postop. Infection, RRT, blood transfusion, acidosis-associated inverstigations
2012	Single center, sequential, observational study	1533 pts adm in ICU	Cl-restrictive fluid (lactated/Ca-free balanced solution) vs Cl-rich fluid (0.9% saline, succinylated gelatin, 4% albumin)	Use of Cl-restrictive fluid strategy was significant decrease in the incidence of AKI, rate of RRT
- RCT (saline vs balanced salt solution) is warranted				

Cl-liberal vs Cl-restrictive

Table 2. Composition of Trial Fluids[a]

	0.9% Saline	Hartmann	4% Gelatin	Plasma-Lyte 148	Albumin 4%	Albumin 20%
Sodium	150	129	154	140	140	48-100
Potassium	0	5	0	5	0	0
Chloride	150	109	120	98	128	19
Calcium	0	2	0	0	0	0
Magnesium	0	0	0	1.5	0	0
Lactate	0	29	0	0	0	0
Acetate	0	0	0	27	0	0
Gluconate	0	0	0	23	0	0
Octanoate	0	0	0	0	6.4	32

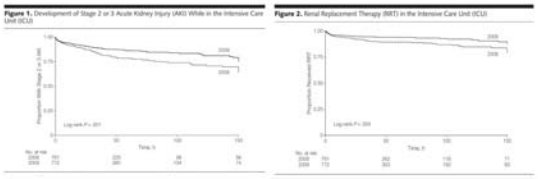
[a] All concentrations in mmol/L.

JAMA 2012;308:1566-72

Table 3. Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria

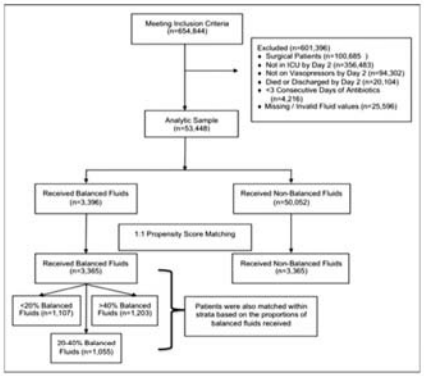
	No. (%) [95% CI] of Patients[a]		
	Control Period (n = 760)	Intervention Period (n = 773)	*P* Value
RIFLE class			
Risk	71 (9.0) [7.2-11.0]	57 (7.4) [5.5-9.0]	.16
Injury	48 (6.3) [4.5-8.1]	23 (3.0) [1.8-4.2]	.002
Failure	57 (7.5) [5.6-9.0]	42 (5.4) [3.8-7.1]	.10
Injury and failure	105 (14) [11-16]	65 (8.4) [6.4-10.0]	<.001

[a] The control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.



JAMA 2012;308:1566-72

Balanced vs non-balanced

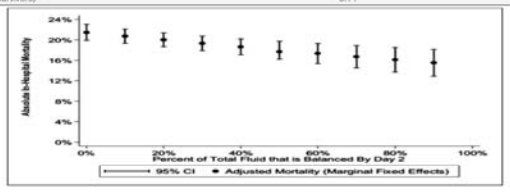


Raghunathan K Crit Care Med 2014;42:1585-91

Balanced vs non-balanced

TABLE 1. Association Between Resuscitation With Balanced Fluids and Primary and Secondary Outcomes in Propensity-Matched Cohorts

Outcome	Balanced Fluid–Matched Cohort	No-Balanced Fluid–Matched Cohort	Effect Estimate	95% CI
Absolute in-hospital mortality	19.6% (659 of 3,365)	22.8% (768 of 3,365)	Relative risk, 0.86	0.78, 0.94; $p = 0.001$
ARF with dialysis	4.52% (142 of 3,144)	4.74% (149 of 3,144)	Relative risk, 0.953	0.761, 1.194
ARF without dialysis	7.12% (159 of 2,655)	7.50% (199 of 2,655)	Relative risk, 0.950	0.784, 1.150
Hospital LOS in days (survivors)	11.26	11.37	Absolute difference, −0.11	−0.55, 0.34
ICU LOS in days (survivors)	5.39	5.50	Absolute difference, −0.11	−0.37, 0.15



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

Kathryn Maitland, M.B., B.S., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med., Robert O. Opoka, M.B., Ch.B., M.Med., Charles Engoru, M.B., Ch.B., M.Med., Peter Olupot-Olupot, M.B., Ch.B., Samuel O. Akech, M.B., Ch.B., Richard Nyeko, M.B., Ch.B., M.Med., George Mtove, M.D., Hugh Reyburn, M.B., B.S., Trudie Lang, Ph.D., Bernadette Brent, M.B., B.S., Jennifer A. Evans, M.B., B.S., James K. Tibenderana, M.B., Ch.B., Ph.D., Jane Crawley, M.B., B.S., M.D., Elizabeth C. Russell, M.Sc., Michael Levin, F.Med.Sci., Ph.D., Abdel G. Babiker, Ph.D., and Diana M. Gibb, M.B., Ch.B., M.D., for the FEAST Trial Group[a]

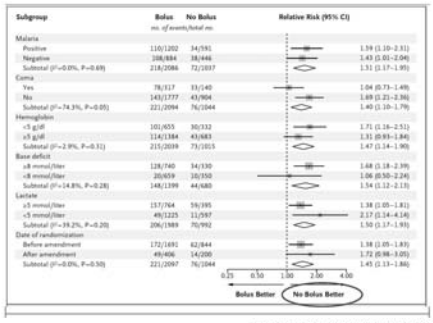
ABSTRACT

BACKGROUND
The role of fluid resuscitation in the treatment of children with shock and life-threatening infections who live in resource-limited settings is not established.

METHODS
We randomly assigned children with severe febrile illness and impaired perfusion to receive boluses of 20 to 40 ml of 5% albumin solution (albumin-bolus group) or 0.9% saline solution (saline-bolus group) per kilogram of body weight or no bolus (control group) at the time of admission to a hospital in Uganda, Kenya, or Tanzania (stratum A); children with severe hypotension were randomly assigned to one of the bolus groups only (stratum B). All children received appropriate antimicrobial treatment, intravenous maintenance fluids, and supportive care, according to guidelines. Children with malnutrition or gastroenteritis were excluded. The primary end point was 48-hour mortality; secondary end points included pulmonary edema, increased intracranial pressure, and mortality or neurologic sequelae at 4 weeks.

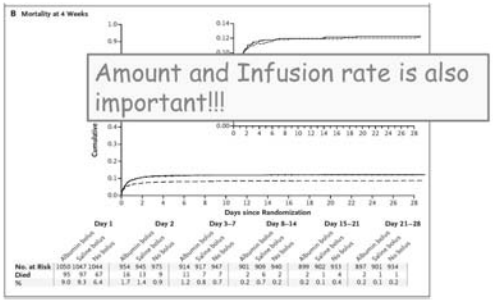
From Kilifi Clinical Trials Facility, Kenya Medical Research Institute (KEMRI)–Wellcome Trust Research Programme, Kilifi, Kenya (K.M., S.O.A., T.L., B.B.); Wellcome Trust Centre for Clinical Tropical Medicine, Department of Paediatrics, Faculty of Medicine, Imperial College (K.M., B.B., M.L.), and the Medical Research Council (MRC) Clinical Trials Unit (J.C., E.C.R., A.G.B., D.M.G.) — both in London; the Department of Paediatrics, Mulago Hospital, Makerere University, Kampala (S.K., R.O.O.), Soroti Regional Referral Hospital, Soroti (C.E.), Mbale Regional Referral Hospital, Mbale (P.O.-O.), and St. Mary's Hospital, Lacor (R.N.) — all in Uganda; the Joint Malaria Programme, Teule Hospital, Muheza, Tanza-

FEAST Trial



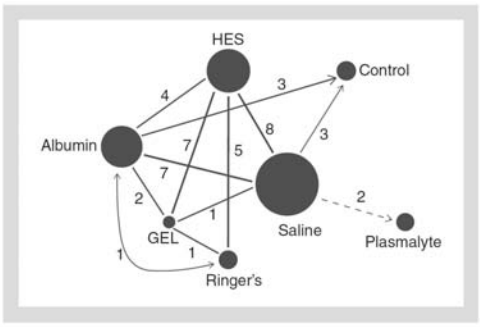
FEAST Study *N Engl J Med 2011;364:2483*

FEAST Trial



FEAST Study *N Engl J Med 2011;364:2483*

Network Meta-Analysis



Br J Anaesth 2014;113:772-83

Four Phases of iv Fluid Therapy

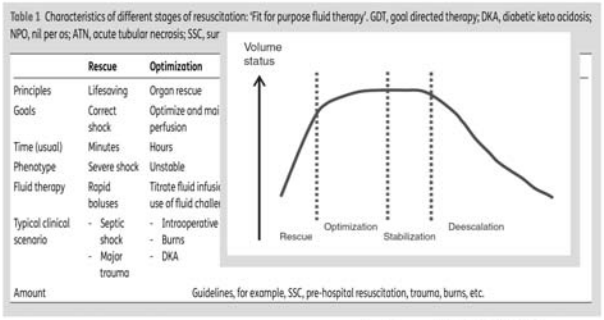


Table 1 Characteristics of different stages of resuscitation: 'Fit for purpose fluid therapy'. GDT, goal directed therapy; DKA, diabetic keto acidosis; NPO, nil per os; ATN, acute tubular necrosis; SSC, sur

	Rescue	Optimization
Principles	Lifesaving	Organ rescue
Goals	Correct shock	Optimize and mai perfusion
Time (usual)	Minutes	Hours
Phenotype	Severe shock	Unstable
Fluid therapy	Rapid boluses	Titrate fluid infusi use of fluid challe
Typical clinical scenario	- Septic shock - Major trauma	- Intraoperative - Burns - DKA

Amount

Guidelines, for example, SSC, pre-hospital resuscitation, trauma, burns, etc.

Br J Anaesth 2014;113:740-7

Acute Dialysis Quality Initiative

- Fluid therapy is also a drug therapy
- Little evidence of superiority for any iv fluid (esp. mortality)
- RRT, AKI : balanced sol > NS, albumin > HES
- Chloride content of iv fluid

Summary

- Fluid Type
- Amount and Infusion rate : Purpose
- Patient

Summary

- Colloid vs Crystalloid : controversial
  HR ↓ , mBP ↑ , CVP ↑ , volume ↓ , cardiovascular (+)
- Albumin : mortality (=)
  traumatic brain injury – harmful
  septic shock – benefit (?)
  deteriorated coagulation panel?
- HES : bleeding, AKI, pruritus, allergic reaction
  not recommended
- Balanced > non-balanced
- Cl-restrictive > Cl-rich

Transfusion: Strategies, Complication

계명대학교 동산병원 흉부외과/중환자의학과

김 재 범

1667년 루이 14세의 주치의였던 Jean Denis가 열병을 앓던 15세 소년에게 양의 피를 수혈하였으나 사망함.

1818년 12월 영국의 산부인과 의사인 James Blundell가 위암으로 죽어가던 환자에게 사람의 혈액 약 400cc를 수혈하는 데 성공 (인류 최초 사람의 혈액을 사용한 수혈)

수혈이 안전하다고?… 맹신은 금물

수혈의 배신/후나세 슌스케, 우츠미 사토루 지음/김영진 옮김/성안당/1만4000원

중환자를 수술할 때 수혈은 필수적인 과정이다. 특히 수혈 없이 암 환자 수술을 진행한다는 것은 불가능하다. 하지만 수혈에 따른 부작용이 훨씬 크다면 수혈을 마냥 고집할 수만은 없을 것이다. 일본의 의료전문 저널리스트와 현직 의사인 저자들은 '수혈의 배신'에서 인류는 수혈의 효과와 부작용을 공론화한 적이 거의 없다고 지적한다. 의료계도 피를 흘리니 피를 보충한다는 통념에서 그저 관행대로 수혈해왔다는 것이다. 저자들은 이런 수혈 맹신주의에 경종을 울리면서 수혈 없이도 중환자 수술이 가능한 의료 기술을 소개한다.

"수혈의 가장 큰 약점은 면역력 저하에 있으며 암환자에게 수혈은 거의 치명적일 수 있다. 다른 혈액이 몸에 들어오면 면역체계가 손상돼 암 증식이 가속화하기 때문이다. 그럼에도 수혈의 42%는 암환자에게 처방되고 있다. 수혈은 오히려 암을 유발하는 의료행위다."

Contents

- Transfusion complication
  - TRALI
  - others
- Transfusion strategy
- Transfusion guideline (2016)
  - RBC transfusion
  - FFP transfusion
  - PLT transfusion

Complication of transfusion

- Most common adverse side effects are usually mild and non-life-threatening.
- Two categories:
  1) Infectious complications
  2) Non-infectious complications

Infectious complications

- Human immunodeficiency virus risk: 1:2.3 million[1]
- Hepatitis C risk: 1:1.8 million[1]
- Hepatitis B: 78,000 new infections annually, United States [2]
  - Risk of transmission through transfusion of 1 unit of blood, 1:58,000-1:149,000 [3]
- Bacterial Contamination:
  More common with platelet transfusions.
  Risk is less in single donor apheresis derived units.

*In humans, confined to South and Central America and Mexico.
1. Busch MP, et al. Transfusion. 2005;45:254-264
2. Centers for Disease Control and Prevention. Available at: www.cdc.gov/vaccine/pubs/pinkbook/downloads/hepb.pdf. Accessed March
3, 2008; 3. Goodnough LT, et al. Lancet. 2003;361:161-169

Non-infectious Complications

- Acute (< 24hrs)
  1) Immunologic
  2) Non-immunologic
- Delayed (> 24hrs)
  1) Immunologic
  2) Non-immunologic

Acute (< 24hrs) Immunologic

- Hemolytic
- Fever/chills, non-hemolytic
- Urticarial / Allergic
- Anaphylactic

Hemolytic

- Etiology
  1) 1:38,000 to 1:70,000
  2) Clerical and other human error
  3) most common causes of ABO- incompatible transfusion
  4) CAP survey – 3601 institution 834 HTR over 5 year period w/ 50 (6%) fatality
  5) Mortality estimated to be 1:1,000,000 transfusion
- Can occur after infusion of as little as 10-15 mL ABO- incompatible blood Etiology
- Mortality is high when more than 200 ml has been transfused

Hemolytic

- Clinical feature
  1) Pain at the infusion site and along the vein
  2) Facial burning
  3) Chest and back pain
  4) Fever, rigor and vomiting
  5) Restlessness, breathlessness, flushing and hypotension
  6) Bleeding from vascular access sites and wound

Hemolytic

- Treatment/Prevention

1) Stop transfusion

2) Supportive care to maintain renal function

Adequate hydration and Forced diuresis

Goal of urine output 100 mL/hr. in adults for at least 18- 24 hours

3) Low dose dopamine

4) Treatment of DIC

5) Prevention of clerical/human errors

Non hemolytic Febrile Transfusion Reactions

- Result of alloimmunization to leucocyte and platelet antigens (HLA an tigens)
- Symptoms: Rigor followed by Fever usually within the start of 30-60 m in of transfusion
- Managed by cessation or slowing of the transfusion and administratio n of an antipyretic
- Pretreated with antipyretic in repeated transfusions and patient who h as history
- If above measure fail, leucocyte-depleted cell components are given.

Allergic reaction

- Symptoms: Urticarial rash and itch within minutes
- Treatment: Antihistamines and reduction of transfusion rate

Anaphylaxis

- Rare, fatal, caused by antibodies to IgA in patients wh o have extremely low levels of this immunoglobulin in plasma (Hereditary IgA Deficiency), who have been se nsitized to IgA in previous transfusions.
- Treatment: Termination of blood transfusion, IV crystall oids, Maintenance of airway, Oxygen, Adrenalin, IV ant ihistamine and salbutamol

Acute (< 24hrs) Non-Immunologic

- Hypotension associated with ACE inhibition
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated Circulatory overload (TACO)
- Nonimmune hemolysis
- Air embolus
- Hypocalcemia
- Hypothermia

Transfusion-related acute lung injury (TRALI)

- Between 2001 – 2003, FDA report on causes of transfusion related deaths

TRALI	16.3%
ABO/Hemolytic transfusion reaction	14.3%
Bacterial contamination	14.1%

- UK SHOT Data 7 years experience (from 1996)

Total 155 cases 32 Deaths

Transfusion-related acute lung injury (TRALI)

- UK SHOT Data 7 years experience (from 1996)

Reaction Type	1996/1997	1997/1998	1998/1999	1999/2000	2000/2001	2001/2002	2003
IBCT	81	110	144	201	213	256 (343)	358
ATR	27	28	34	34	37	38 (49)	44
DTR	27	24	31	28	40	33 (46)	32
PTP	11	11	10	5	3	3 (3)	1
TA-GVHD	4	4	4	0	1	0 (0)	0
TRALI	11 (6.5%)	16 (8.2%)	15 (6.3%)	19 (6.5%)	15 (4.8%)	26 (7.2%) (32) (6.7%)	37 (7.7%)
TTI	8	3	9	6	6	5 (5)	8
Unclassified	0	0	7	0	0	0	0
TOTAL	169	196	255	293	315	363 (478)	480

Transfusion-related acute lung injury (TRALI)

- Non cardiogenic edema after blood transfusion was first described by Banard (1951) & Brittingham (1957)
- Term " transfusion related acute lung injury" by Popovsky. (1983)
- A series of 36 TRALI patients is analyzed by Popovsky (1985)
  1) Acute respiratory distress & new bilateral lung infiltrate within 6 h of blood transfusion, absence of volume overload or cardiac dysfunction
  2) Leukocyte antibodies in the blood of 89% of implicated donors

Transfusion-related acute lung injury (TRALI)

- TRALI criteria
  a. ALI (acute lung injury): onset, P/F ratio, CXR,..
  b. No preexisting ALI before transfusion
  c. During or within 6 hr of transfusion
  d. No temporal relationship to an alternative risk factor for ALI
- Risk factor: Aspiration, multiple trauma, pneumonia, cardiopulmonary bypass, burn injury, toxic inhalation, lung contusion, pancreatitis, drug overdose, near drowning, shock, severe sepsis

Transfusion-related acute lung injury (TRALI)

- Incidence: ~8% of transfused pts.
- Pulmonary microvascular occlusion by platelets, leucocytes and fibrin
- Clinical feature
  1) Rapid onset of respiratory distress
     a. symptoms appear within the first 2–6 hrs from initiation of blood transfusion.
     b. some cases occur much later, even up to 48 hrs
  2) Common clinical presentation: rapid onset of severe hypoxemia, marked hypovolemia, hypotension
  3) Fever, Breathlessness, Non-productive cough, Hypoxia

Transfusion-related acute lung injury (TRALI)

- Clinical course
  1) Symptoms generally resolve in 48 to 96 hours
  2) Resolution of pulmonary infiltrates within 1-4 days with no long term sequelae (80%)
  3) Mortality rate : 5% to 10%
  4) However, higher mortality rate in a critically ill patients population(up to 67%)
- TRALI has been associated with all plasma-containing products (Whole blood, PRBCs, FFP, platelets, cryoprecipitate, IV IG)
- High plasma volume products (FFP and platelets, esp multiparous female donors) are the most implicated products.

Transfusion-related acute lung injury (TRALI)

- Treatment of TRALI
  1. Treatment is largely supportive.
  2. Monitor Oxygen saturation, Provide supplemental oxygen to maintain saturation above 92%
  3. Hypoxemia severe enough to require Endotracheal Intubation and PPV occurs in 70-75% of patients.
  4. No evidence supports the routine use of Corticosteroids.

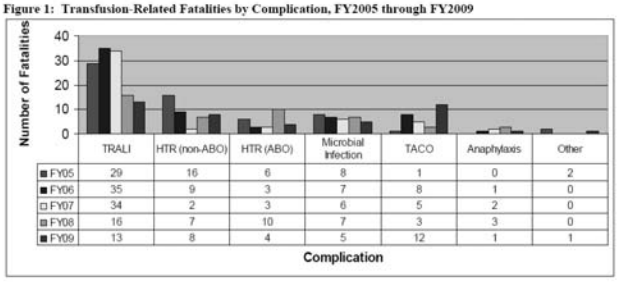
Transfusion-related acute lung injury (TRALI)

- Prevention of TRALI

1) Use plasma from male donor or female donor with negative leukocyte screening test
   - SHOT recommendation: obtain the all the FFP from male donors and HLA-pre-screening for female donors who are giving platelets
2) Leukocyte depleted blood
   - Reduce TRALI due to lekcocyte Ab in the recipient
3) Use fresh blood
   - Biologically active lipids accumulate with storage
   - RBC less than 14 days
   - Platelet less than 2 days

Transfusion-related acute lung injury (TRALI)

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY05	29	16	6	8	1	0	2
FY06	35	9	3	7	8	1	0
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1

Transfusion-associated Circulatory overload (TACO)

- Definition

1) no universally agreed-upon definition
2) Serious Hazards Of Transfusion (SHOT) definition: TACO includes any 4 of the following that occur within 6 hours of transfusion
   a. Acute respiratory distress
   b. Tachycardia
   c. Increased blood pressure
   d. Acute or worsening pulmonary edema
   e. Evidence of positive fluid balance

Transfusion-associated Circulatory overload (TACO)

- Incidence

1) One of the most common complications of transfusion
2) Young children and elderly at risk
3) Cardiac and pulmonary compromise
4) Chronic anemia with expanded plasma volume
5) Infusion of 25% albumin
   Shifts large volume of extravascular fluid into the vascular space

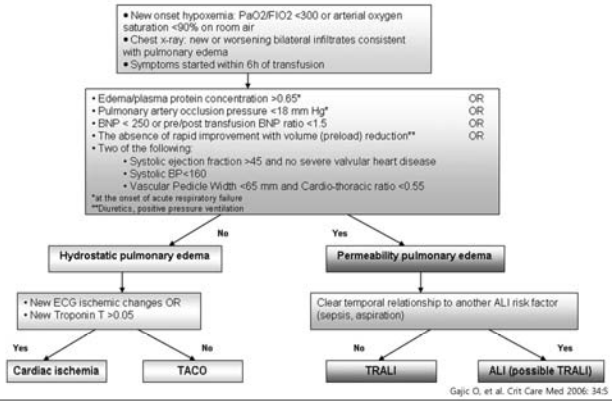
- Signs/Symptoms: Dyspnea, cyanosis, orthopnea, severe HA, HTN, CHF during or soon after transfusion

Transfusion-associated Circulatory overload (TACO)

- Treatment/Prevention

1) Stop transfusion
2) Supportive care
3) Phlebotomy
4) Diuretic
5) Slow transfusion
   a) Usually 4 hours, can be extended to 6 hours
   b) Other strategies

Transfusion-associated Circulatory overload (TACO)



Transfusion-associated Circulatory overload (TACO)

- TRALI: Differentiate with TACO

Metabolic complications

- In patients with massive blood transfusion(1 ml/kg/min or 1 unit of blood per 5 minutes).
- Metabolic consequences include
  1. Hypothermia (prevented by transfusing blood through blood warmer)
  2. Acidosis
  3. Increased affinity of oxyhaemoglobin for oxygen(due to transfusion of 2,3 DPG depleted blood)
  4. Citrate intoxication(causes temporary reductions in ionised calcium levels – If symptomatic treated by administering calcium gluconate)
  5. Hyperkalemia

Delayed (> 24hrs) Immunologic

- Allo-immunization
  1) RBC antigens
  2) HLA
- Hemolytic
- Graft-versus-host disease (GVHD)
- Post-transfusion purpura
- Immuno-modulation

Delayed Hemolytic Transfusion Reactions

1. Result of Anamnestic Response to Donor RBC antigen to which a recipient has been previously exposed.
2. Commonly involve antibodies against Kell, Kidd and Rhesus antigens.
3. Occur within first or second week following transfusion
4. Symptoms include low grade fever, increased indirect bilirubin or unexpected reduction in Hb concentrations.
5. It is typically mild and self limiting.
6. Treatment is supportive including Hb monitoring, hydration and provision of compatible blood if necessary.

Graft-versus-host disease

- Rare, but fatal complication
- Occurs mainly in immunodeficient patients
- Caused by the T-lymphocytes from donor blood get engrafted into the immunodeficient host's marrow and launch an immune response against the host.
- Starts 3-30 days after the transfusion
- Patient develops high fever, diffuse erythematous skin rash, desquamation, GI symptoms, severe hepatic dysfunction and pancytopenia
- Prevented by administering gamma-irradiated cellular components

Haemostatic complications

1. Dilutional Coagulopathy
   – Stored blood is deficient in platelets and labile clotting factor (factor V and VIII)
   – Massive transfusion induces dilution of Fibrinogen, Clotting factor– II, V and VIII in addition to moderate Thrombocytopenia.
   – Treated by administering FFP or platelets as decided on basis of laboratory evidence of coagulopathy or by clinical suspicion due to rapid ongoing blood loss

Haemostatic complications

2. Post Transfusion Purpura
   - Platelet-specific alloantibodies may cause post-transfusion purpura
   - It is initially treated with high dose corticosteroids and intravenous immunoglobulin
   - If platelets needed , have to be compatible with patient alloantibodies

Transfusion Related Immunomodulation

1. There are changes in immunity related processes such as T-lymphocyte Helper/Suppressor ratio, function of T-killer cells, Lymphocyte responsiveness and delayed hypersensitivity.
2. Adverse effects on immunocompetence such as accelerated reccurences of malignancy, increased rates of infection and more rapid progression of HIV/AIDS.
3. Cause Unknown.

Delayed (> 24hrs) Non-Immunologic

- Iron overload

Transfusion haemosiderosis

- Iron overload in monocyte-macrophage system
- Especially a problem in childhood anemias (e.g. thalassemia) and in patients with chronic refractory anemia
- Iron chelation therapy with desferrioxamine

Transfusion strategy

Transfusion Requirements After Cardiac Surgery

The TRACS Randomized Controlled Trial *JAMA. 2010;304(14):1559-1567*

Ludhmila A. Hajjar, MD, PhD
Jean-Louis Vincent, MD, PhD
Filomena R. B. G. Galas, MD, PhD

Context Perioperative red blood cell transfusion is commonly used to address anemia, an independent risk factor for morbidity and mortality after cardiac operations; however, evidence regarding optimal blood transfusion practice in patients undergoing cardiac surgery is lacking.

- liberal strategy of blood transfusion (to maintain a hematocrit 30%) or to a restrictive strategy (hematocrit 24%).(n=502)
- Among patients undergoing cardiac surgery, the use of a restrictive perioperative transfusion strategy compared with a more liberal strategy resulted in noninferior rates of the combined outcome of 30-day all-cause mortality and severe morbidity.

Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial

Jeffrey L Carson, Frederick Sieber, Donald Richard Cook, Donald B Hoover, Helaine Noveck, Bernard R Chaitman, Lee Fleisher, Lauren Beaupre, William Macaulay, George G Rhoads, Barbara Paris, Aleksandra Zagorin, David W Sanders, Khwaja J Zakriya, Jay Magaziner

Summary

Background **Blood transfusion might affect long-term mortality by changing immune function and thus potentially increasing the risk of subsequent infections and cancer recurrence. Compared with a restrictive transfusion strategy, a more liberal strategy could reduce cardiac complications by lowering myocardial damage, thereby reducing future deaths from cardiovascular disease. We aimed to establish the effect of a liberal transfusion strategy on long-term survival compared with a restrictive transfusion strategy.**

Lancet 2015; 385: 1183–89
Published Online December 9, 2014
http://dx.doi.org/10.1016/S0140-6736(14)62286-8

- no evidence to suggest that a liberal transfusion strategy has a moderate adverse effect on long-term mortality or affects cause of death.

OPEN ACCESS

Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/BMJ.h1354)
Cite this as: BMJ 2015;350:h1354

ABSTRACT

OBJECTIVE
To compare the benefit and harm of restrictive versus liberal transfusion strategies to guide red blood cell transfusions.

DESIGN
Systematic review with meta-analyses and trial sequential analyses of randomised clinical trials.

DATA SOURCES
Cochrane central register of controlled trials, SilverPlatter Medline (1950 to date), SilverPlatter Embase (1980 to date), and Science Citation Index Expanded (1900 to present). Reference lists of identified trials and other systematic reviews were assessed, and authors and experts in transfusion were

RESULTS
31 trials totalling 9813 randomised patients were included. The proportion of patients receiving red blood cells (relative risk 0.54, 95% confidence interval 0.47 to 0.63, 8923 patients, 24 trials) and the number of red blood cell units transfused (mean difference −1.43, 95% confidence interval −2.01 to −0.86) were lower with the restrictive compared with liberal transfusion strategies. Restrictive compared with liberal transfusion strategies were not associated with risk of death (0.86, 0.74 to 1.01, 5707 patients, nine lower risk of bias trials), overall morbidity (0.98, 0.85 to 1.12, 4517 patients, six lower risk of bias trials), or fatal or non-fatal myocardial infarction (1.28, 0.66 to 2.49, 4730 patients, seven lower risk of bias trials). Results were not affected by the inclusion of trials with

Compared with liberal strategies, restrictive transfusion strategies were associated with a reduction in the number of red blood cell units transfused and number of patients being transfused, but mortality, overall morbidity, and myocardial infarction seemed to be unaltered. Restrictive transfusion strategies are safe in most clinical settings.

Thresholds for red blood cell transfusion in adults

Condition	Hgb threshold for transfusion
Symptomatic patient (eg, myocardial ischemia, tachycardia)	10 g/dL*[1,2]
Hospitalized patient	
Preexisting coronary artery disease	8 g/dL*[2]
Acute coronary syndromes	8 to 10 g/dL¶[2,3]
Heart failure	7 to 8 g/dL¶
Intensive care unit (hemodynamically stable)	7 g/dL*[4,5]
Gastrointestinal bleeding (hemodynamically stable)	7 g/dL*[6]
Non-cardiac surgery	8 g/dL*[1]
Cardiac surgery	7 to 8 g/dL*[7]
Ambulatory outpatient	
Oncology patient in treatment	7 to 8 g/dL¶
Palliative care setting	As needed for symptoms; hospice benefits may vary

These thresholds are not a substitute for direct assessment of the patient and clinical judgment. Refer to UpToDate topics on red blood cell transfusion and specific clinical settings for further details.

Hgb: hemoglobin.
* Based on results from clinical trial(s).
¶ There are no large clinical trials yet performed in this setting. These recommendations are based on the authors' opinions.

References:
1. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453.
2. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013; 165:964.
3. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol 2011; 108:1108.
4. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group [see comments]. N Engl J Med 1999; 340:409.
5. Lacroix J, Hebert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007; 356:1609.
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7. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 2010; 304:1559.

UpToDate

Thresholds for red blood cell transfusion in adults

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2016년 수혈가이드라인 개정(안)

□ **배경 및 필요성**

○ 수혈가이드라인은 2002년 대한수혈학회에서 국내최초로 발간하고 2009년 대한수혈학회와 질병관리본부가 공동으로 제정한 이후 2011년, 2013년에 오류 수정과 일부 내용을 보완하는 부분개정을 한 바 있음

○ 수혈가이드라인이 각 의료기관에서 수혈에 대한 기본 지침으로 활용되고 있는 만큼 초판 발행 후 약 7년이 지난 현재 발전하는 수혈의학의 최신지견과 변화하는 의료현실을 반영한 수혈가이드라인이 필요함

○ 또한, 적정수혈 강화를 위해 최신경향이 반영된 수혈가이드라인 개정이 필요함

적혈구수혈

- 혈류역학적(hemodynamic)으로 안정된, 내과적 질환을 가진 중환자실(ICU) 환자에서는 적혈구 수혈의 제한적 지침(혈색소 7 g/dL에서 수혈, 수혈 후 목표치 7-9 g/dL)이 권장된다.
- 수술로 인한 출혈환자에서는 기본적으로 증상이 있거나 혈색소 수치가 8 g/dL 미만으로 떨어지면 적혈구 수혈을 실시한다.

적혈구수혈

- 관상동맥질환 환자 중 안정된 상태이고 증상이 없는 경우에는 혈색소 8 g/dL 미만에서 수혈을 고려한다. 하지만 급성관상동맥증후군(예를 들어 급성심근경색(acute myocardial infarction)이나, 불안정형협심증(unstable angina))환자, 폐기능 이상 혹은 뇌순환 이상이 있는 환자에서는 혈색소 수치가 8-10 g/dL이라도 수혈을 고려할 수 있으며 특히 심근허혈이 진행 중이거나 증상이 있는 경우에는 혈색소 10 g/dL을 유지하도록 권장한다.

신선동결혈장제제 수혈

- 비타민 K, 동결침전제제, 제8응고인자 농축액, 프로트롬빈 복합체 농축제제나 섬유소원 농축제제가 더 효과적인 경우는 신선동결혈장보다 우선적으로 사용할 것을 권장한다. 이와 같은 대안적인 치료가 가능하지 않은 경우에만 신선동결혈장제제의 적응증이 된다.

신선동결혈장제제 수혈

- 투여 전 PT, aPTT 를 측정하고, 대량출혈 시에는 섬유소원 수치도 측정한다.
- 응고인자 결핍이나 섬유소원 결핍 때 사용한다.

혈소판수혈

- 출혈이 없는 안정상태: 혈소판 수를 10,000/uL 이상으로 유지한다.
- 출혈은 없으나 불안정상태: 혈소판 수를 20,000~50,000/uL으로 유지한다.
- 활동성 출혈이 있거나 침습적인 처치를 시행하는 경우:
  혈소판 수를 50,000~ 100,000/uL으로 유지한다.
- 혈소판 기능에 이상이 있는 경우 수혈한다.

Stress Induced Cardiomyopathy

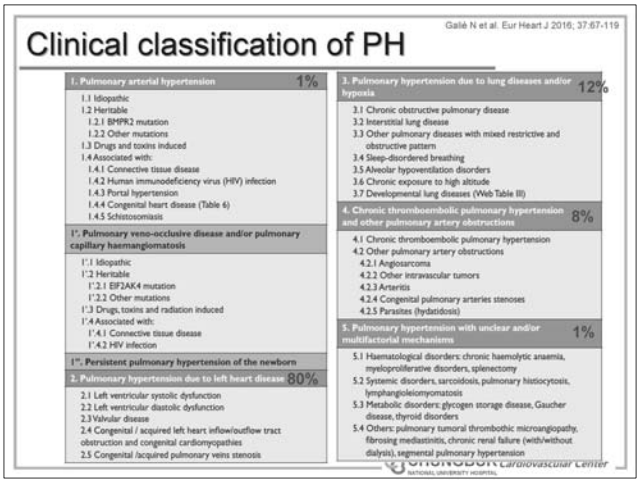
울산대학교 의과대학 서울아산병원 흉부외과학교실

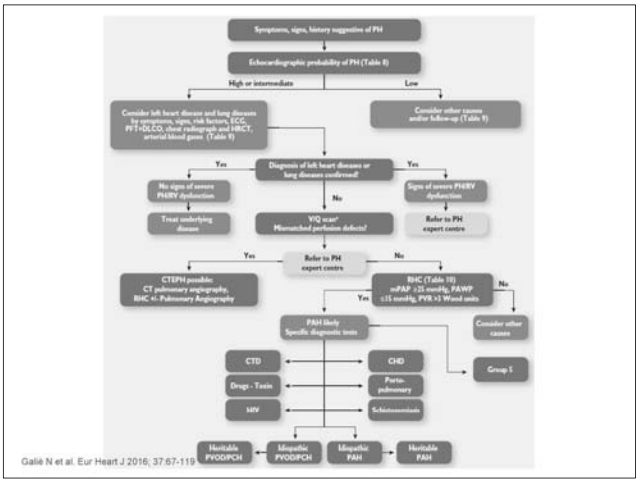
임 주 영

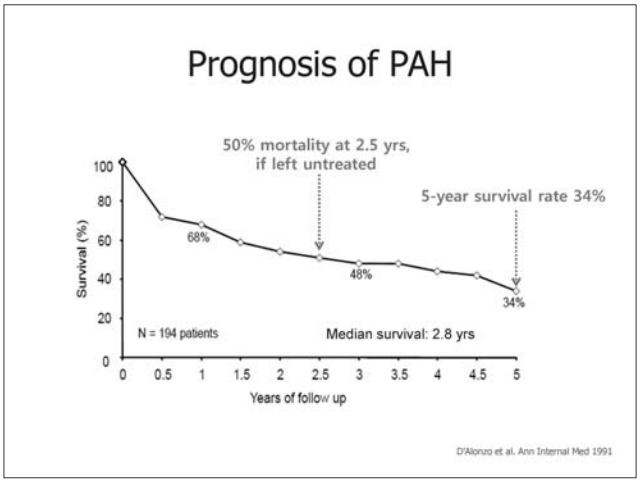
Various Causes of Cardiogenic Shock in the ICU: Pulmonary HTN and RHF

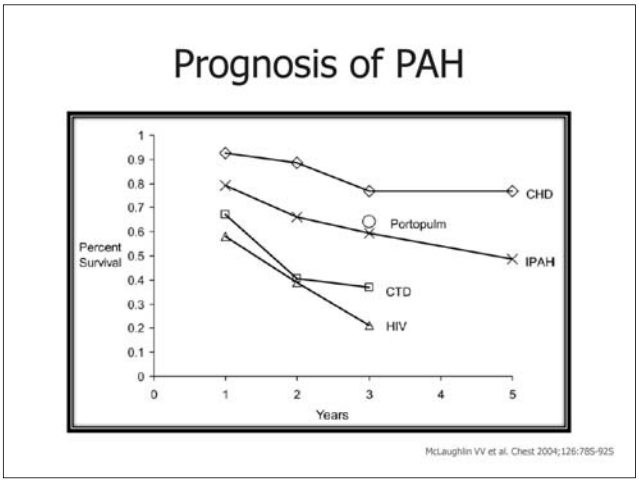
Department of Thoracic and Cardiovascular Surgery,
Chungbuk National University College of Medicine, Cheongju

Hong Ju Shin

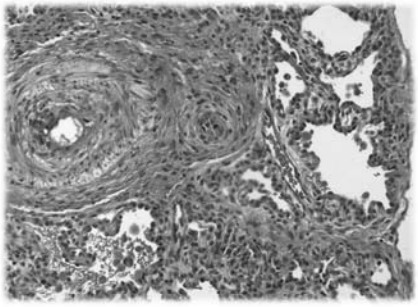








Historical perspectives

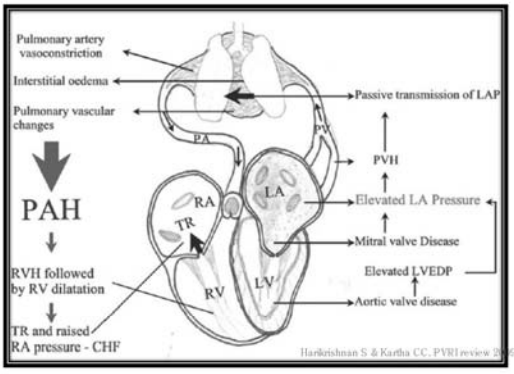


What is pulmonary hypertension ?

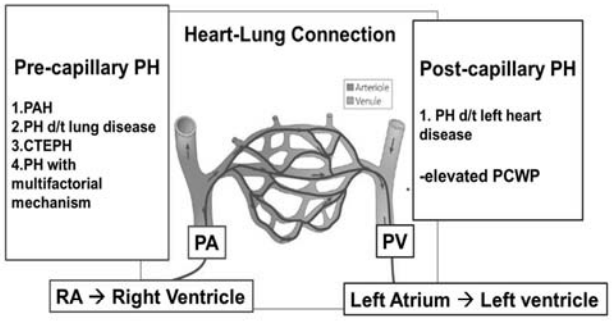
Pulmonary = Lung
Hypertension = High blood pressure

Pulmonary hypertension **is**
a disorder affecting the arteries in the lungs – the connection between the heart and the lung

Mechanism of pulmonary hypertension



Pulmonary hypertension: Define lesion

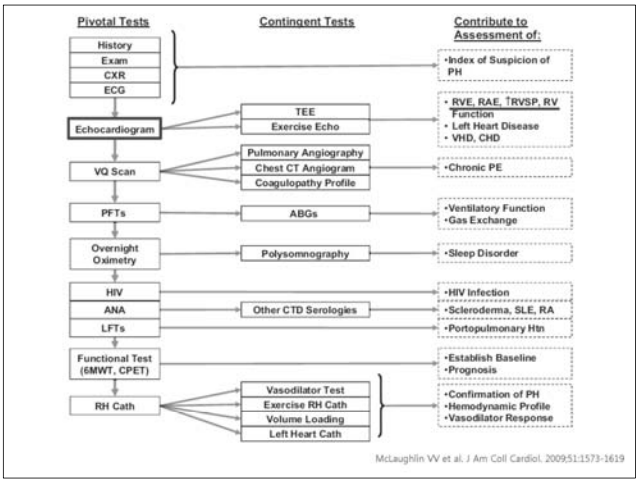


Hemodynamic definitions of PH

Confirm "PH"

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

Galiè N et al. Eur Heart J 2009; 30:2493-537
Galiè N et al. Eur Resp J 2009; 34:1219-63



McLaughlin VV et al. J Am Coll Cardiol. 2009;51:1573-1619

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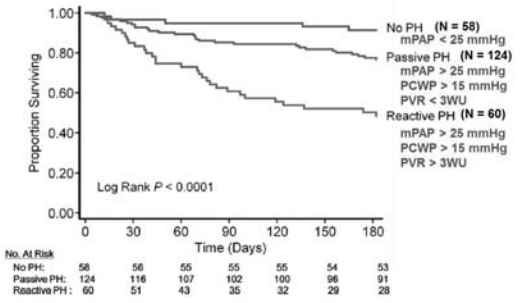
Galiè N et al. Eur Resp J 2009; 34:1219-63

Reactive PH: associated with adverse outcome

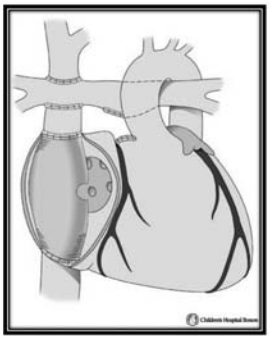
VMAC trail subgroup analysis: 242 patients with ADHF



Aronson et al. Circ Heart Fail. 2011;4:644-650.

Pulmonary hypertensive crisis

- Correction of Lt to Rt. Shunt lesion
  - VSD, ASD, Truncus…
- TAPVR repair
- Pulmonary vein stenosis
- Fontran with high PAP



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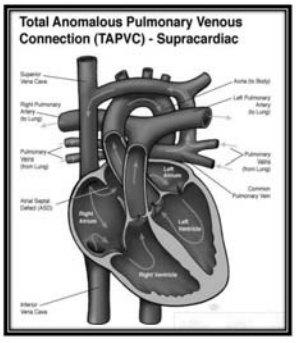

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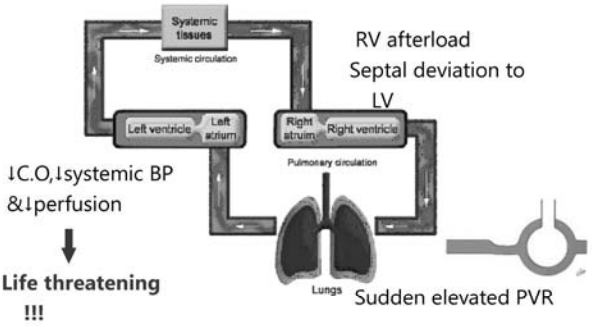
Pulmonary hypertensive crisis

- Immediate postoperative period
  - increased pulmonary vascular reactivity
  - most vulnerable to a sudden or sustained increase in PVR

Pulmonary hypertensive crisis

- Pts. with reactive pulmonary vascular beds
- May be triggered by stressful stimulus
  : Tracheal suction, pain, anxiety

Pulmonary hypertensive crisis



Postoperative Pulmonary hypertension

- Management
- Prevention is worthy goal of Tx.
  - Pain control esp. for stressful or invasive procedure
  - Avoid low alveolar PaO2
  - Alkalosis
  - Attention to lung volume
  - Nitric Oxide : most selective pulmonary vasodilator
  - Consider I.V vasodilators
    - nitroprusside, milrinone, Prostacyclin, tolazoline, isoproterenol

Pathophysiology

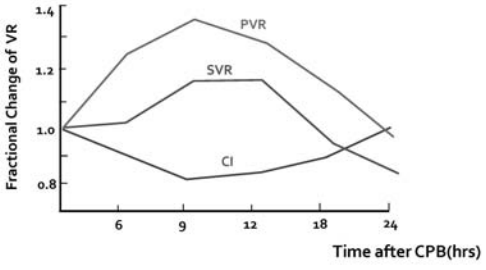
- Major deleterious effects of CPB on lungs
  - systemic inflammatory response syndrome
    - significant pul. vascular endothelial dysfx.→ reduced intrinsic NO production
    - Leukocyte sequestration inducing tissue impairment
    - Increased capillary permeability→ interstitial edema

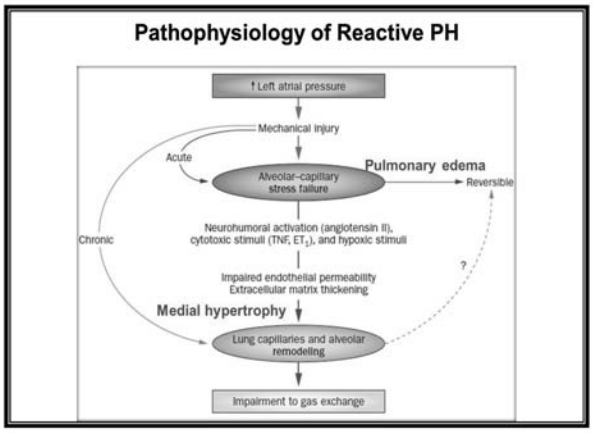
Postoperative high PVR

⇩

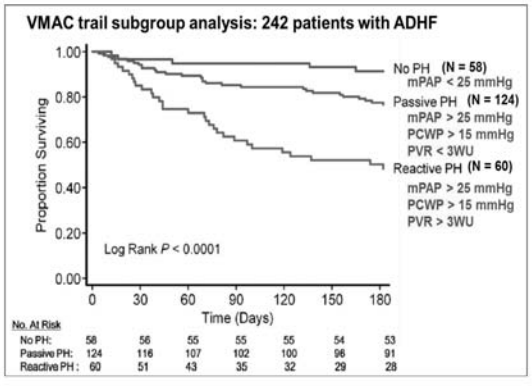
Postoperative pulmonary hypertension

CPB effect





Guazzi et al. Nat. Rev. Cardiol. 2010;7:648-659.



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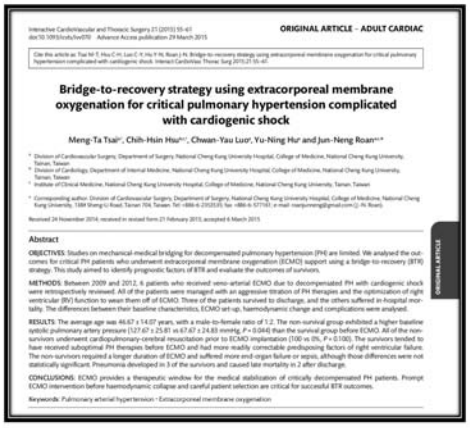


ORIGINAL ARTICLE - ADULT CARDIAC

Bridge-to-recovery strategy using extracorporeal membrane oxygenation for critical pulmonary hypertension complicated with cardiogenic shock

Meng-Ta Tsai[a], Chih-Hsin Hsu[a,c], Chwan-Yau Luo[a], Yu-Ning Hu[a] and Jun-Neng Roan[a,c,*]

Abstract

OBJECTIVES: Studies on mechanical-medical bridging for decompensated pulmonary hypertension (PH) are limited. We analysed the outcomes for critical PH patients who underwent extracorporeal membrane oxygenation (ECMO) support using a bridge-to-recovery (BTR) strategy. This study aimed to identify prognostic factors of BTR and evaluate the outcomes of survivors.

METHODS: Between 2009 and 2012, 6 patients who received veno-arterial ECMO due to decompensated PH with cardiogenic shock were retrospectively reviewed. All of the patients were managed with an aggressive titration of PH therapies and the optimization of right ventricular (RV) function to wean them off of ECMO. Three of the patients survived to discharge, and the others suffered in-hospital mortality. The differences between their baseline characteristics, ECMO set-up, haemodynamic change and complications were analysed.

RESULTS: The average age was 46.67 ± 14.07 years, with a male-to-female ratio of 1:2. The non-survival group exhibited a higher baseline systolic pulmonary artery pressure (127.67 ± 25.81 vs 67.67 ± 24.83 mmHg, $P = 0.044$) than the survival group before ECMO. All of the non-survivors underwent cardiopulmonary-cerebral resuscitation prior to ECMO implantation (100 vs 0%, $P = 0.100$). The survivors tended to have received suboptimal PH therapies before ECMO and had more readily correctable predisposing factors of right ventricular failure. The non-survivors required a longer duration of ECMO and suffered more end-organ failure or sepsis, although those differences were not statistically significant. Pneumonia developed in 3 of the survivors and caused late mortality in 2 after discharge.

CONCLUSIONS: ECMO provides a therapeutic window for the medical stabilization of critically decompensated PH patients. Prompt ECMO intervention before haemodynamic collapse and careful patient selection are critical for successful BTR outcomes.

Keywords: Pulmonary arterial hypertension · Extracorporeal membrane oxygenation

Table 1: Patient characteristics and peri-ECMO titration of PH therapies

Patient	Age	Gender	PH aetiology	Predisposing factor for RV failure	Transplant candidacy (contraindication)	sPAP baseline	PH therapy baseline	PH therapy before ECMO	PH therapy during ECMO	PH therapy post-ECMO explant	sPAP post-ECMO explant	ECMO days
Survivor 1	51	M	Pulmonary fibrosis	General anaesthesia[a]	Yes	60	Iloprost	Iloprost	iNO milrinone iloprost	iNO milrinone	70	2
Survivor 2	58	M	IPAH	Fluid overload	No (renal failure)[b]	X	Treatment-naive[c]	Milrinone iloprost	Milrinone iloprost sildenafil	Sildenafil	27	10
Survivor 3	49	F	Porto-pulmonary hypertension	Anaemia	No (cirrhosis)	X	Treatment-naive	Treatment-naive	iNO milrinone iloprost sildenafil	Sildenafil iloprost	50	11
Non-survivor 1	48	F	SLE CTEPH	SLE flare-up	Yes	97	Sildenafil iloprost	Sildenafil iloprost	iNO milrinone iloprost sildenafil	Milrinone iloprost sildenafil	73	30
Non-survivor 2	55	F	IPAH	Pneumonia	No (hypoxic encephalopathy)[b]	X	Treatment-naive	Bosentan	iNO milrinone bosentan	X	X	12
Non-survivor 3	19	F	SLE	SLE flare-up	No (sepsis/ leucopenia)[b]	83	Sildenafil	Sildenafil milrinone iloprost	iNO milrinone iloprost sildenafil	X	X	16

[a]For planned lung transplant the operation was cancelled due to malignancy in the donor.
[b]Complications after ECMO or CPCR.
[c]Considered inoperable.
[d]without any PH medication.
sPAP: systolic pulmonary artery pressure; IPAH: idiopathic pulmonary arterial hypertension; SLE: systemic lupus erythematosus; CTEPH: chronic thromboembolic pulmonary hypertension; M: male; F: female.

Table 2: Haemodynamic data before and after ECMO

	Survivor (n = 3)		Non-survivor (n = 3)	
	Before ECMO	Post-ECMO D1	Before ECMO	Post-ECMO D1
Inotrope equivalents (μg/kg/min)	83.77 ± 58.89	47.26 ± 19.29	118.89 ± 44.90	45.70 ± 36.96
CVP[a] (mmHg)	18.00 ± 11.31	11.00 ± 8.66	23.00 ± 8.49	13.50 ± 7.78
sPAP (mmHg)	67.67 ± 24.83*	39.67 ± 0.58	127.67 ± 25.81*	74.67 ± 33.50
MAP (mmHg)	54.00 ± 10.58	75.00 ± 23.30	44.33 ± 27.33	77.00 ± 5.57
PaO_2/FiO_2	112.33 ± 66.71	579.33 ± 337.55	85.55 ± 23.26	562.23 ± 105.81
$ScvO_2$ (%)	NA	92.00 ± 4.58	NA	90.00 ± 2.83
Lactate (mmol/l)	10.67 ± 7.61	3.87 ± 2.15	14.40 ± 1.04	4.40 ± 2.70

*P = 0.044, survivor vs non-survivor before ECMO.
[a]n = 2 for each group.
CVP: central venous pressure; sPAP: systolic pulmonary artery pressure; MAP: mean arterial pressure, $ScvO_2$: central venous pressure; NA: not available.

Table 3: Complications of ECMO and outcomes

	Survivor (n = 3)	Non-survivor (n = 3)
VT/VF	1/3 (33.3%)	2/3 (66.7%)
ECMO wound bleeding	1/3 (33.3%)	1/3 (33.3%)
Hypoxic encephalopathy	0/3 (0%)	1/3 (33.3%)
Infarcted stroke	1/3 (33.3%)	0/3 (0%)
Pneumonia	3/3 (100%)	1/3 (33.3%)
Sepsis	0/3 (0%)	2/3 (66.7%)
Gastrointestinal bleeding	2/3 (66.7%)	3/3 (100%)
Tracheostomy	1/3 (33.3%)	0/3 (0%)
Renal failure requiring dialysis	1/3 (33.3%)	2/3 (66.7%)
Hepatic failure after ECMO (Bil-T >2)	2/3 (66.7%)	2/3 (66.7%)
Hepatic failure after ECMO (Bil-T >10)	0/3 (0%)	1/3 (33.3%)
Duration of ECMO (days)	7.67 ± 4.93	19.33 ± 9.45
Weaning-off rate of ECMO	3/3 (100%)	1/3 (33.3%)

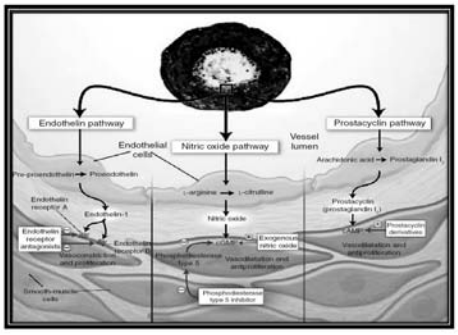
VT/VT: ventricular tachycardia/fibrillation; Bil-T: total bilirubin (mg/dl).

Table 4: Bridge-to-recovery (BTR) strategies of ECMO support for PH patients

Author/group	Age	Gender	PH classification	ECMO types	ECMO days	Non-intubation or extubation before weaning off ECMO	Follow-up period after discharge	Final outcome
Srivastava [3]	35	F	IPAH with PFO	VV	10	O	2 months	Subarachnoid haemorrhage during ECMO run
Javidfar [11]	41	F	ASD Eisenmenger	VV	23	×	4 months	Mortality after 4 m due to pneumonia
Belohlavek [6]	42	M	IPAH	VA	16	×	3 months	Mortality after 3 m due to sudden cardiac death
New York-Presbyterian [8, 9, 21]	57	F	HPAH	VA	13	×	NA	In-hospital mortality
	42	F	ASD Eisenmenger	VA	12	×	NA	In-hospital mortality
	20	F	VSD	VA*	15	O	NA	In-hospital mortality
	22	F	IPAH, TGA repaired, LPV stent	VA*	8	O	21 months	Survival
	48	F	IPAH	VA	6	×	2 months	Mortality due to pneumonia
	41	F	APAH-CHD	VV	23	×	3 months	Mortality due to pneumonia
	21	F	HPAH	VAV	10	×	NA	In-hospital mortality, ECMO withdrawn due to hypoxic brain injury

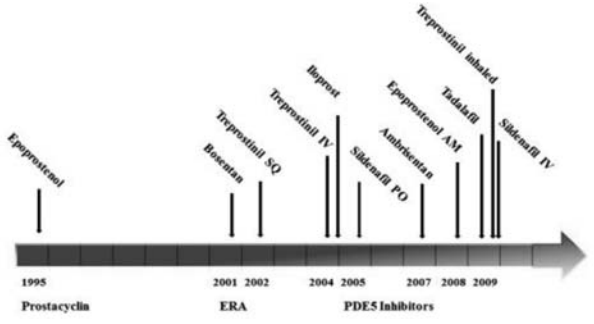
IPAH: idiopathic pulmonary arterial hypertension; PFO: patent foramen ovale; ASD: atrial septal defect; VSD: ventricular septal defect; HPAH: hereditary pulmonary arterial hypertension; TGA: transposition of great arteries; LPV: left pulmonary vein; APAH-CHD: associated pulmonary arterial hypertension with congenital heart disease; VAV: venoarterial-venous.
*Using an upper body configuration with subclavian artery cannulation; M: male; F: female.

Specific targets for PAH treatment



Humbert M et al. N Eng J Med. 2004;351:1425-1436

Timeline of drug approval



CE Ventetuolo, JR Klinger. Prog Cardiovasc Dis 2012;55:89-103

Available drugs in Korean market

(Sildenafil) Beraprost (Tadalafil) Bosentan Treprostini

1999 2000 2001 2002 2003 2004 2005 2006 2009 2010 2011

Iloprost Ambrisentan

Off-label Use of PDE5s

국내 발기부전 치료제 발매 현황

출시 연도	제조사	제품명
1999년	화이자	비아그라
2003년	릴리	시알리스
2003년	바이엘헬스케어	레비트라
2005년	동아제약	자이데나
2007년	종근당	아일라
2007년	SK케미칼	엠빅스
2010년	한국얀센	브라본토
2011년	바이엘헬스케어	레비트라ODT
2011년 (9월 예정)	JW중외제약	아바나필

Prostacyclin analogs

	Approval	Improve	Route	S/E
Epoprostenol	PAH with FC III/IV	Sx, FC, Ex cap, Hemody, surv in idiopathic PAH Ex cap, Hemody in scleroderma-PAH	Civ via CV cath Reconstitute and dilution, Refrigeration	Cath-related infection, fatal inadvertent discontinuation, headache, jaw pain, flushing, nausea, diarrhea, skin rash, musculoskeletal pain
Treprostinil	PAH with FC II-IV	Sx, Ex cap, Hemody	Civ or SC, inhaled	Iv ; similar to epo Sc ; injec-site pain Inhaled ; Cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, diarrhea
Inhaled iloprost	PAH with FC III/IV	Ex cap, FC, Hemody Long-term efficacy established	Inhaled 9/day	Flushing, cough, headache

Endothelin receptor antagonists

- Block the effects of ET-1 by targeting and inhibiting its receptors (endothelin receptor subtypes A and B, ETA, and ETB, respectively).

	Approval	Improve	Common S/E	S/E
Bosentan	PAH with FC II-IV Twice-daily oral	Ex cap, QOL, Hemody, Time to clinical worsening Long-term use -> 2-year surv rate 87~89% in idiopathic PAH	headache, flushing, peripheral edema, sinus congestion, mild anemia, and rare hypotension teratogenic	Hepatotoxicity 10%
Ambrisentan	PAH with FC II-III Once-daily oral	Sx, Ex cap, FC, QOL, Hemody, Time to clinical worsening Long-term use -> 2 year surv rate 88% in idiopathic PAH and associated PAH as initial Tx		Hepatoxicity 2%

PDE-5 inhibitors

- Target the nitric oxide pathway
- Effectively enhancing the effects of nitric oxide by inhibiting the breakdown of cGMP, the intracellular messenger of nitric oxide

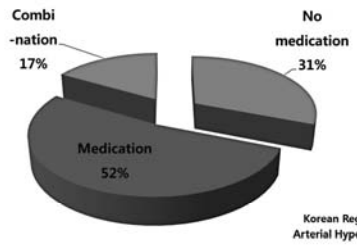
	Approval	Improve	Route	S/E
Sidenafil	PAH with FC II/III	Sx, Ex cap, Hemody No surv benefit	Orally 3/day	Epistaxis, flushing, headaches, GI disturbance
Tadalafil	PAH with FC II/III	Ex toler, Hemody, Delay clinical worsening	Once daily	Headache, myalgia, nausea, dyspepsia, flushing, resp tract infection

Combination therapy

- Basic rationale for combination Tx
  : pulmonary vascular remodeling in PAH occurs via 3 main pathways
- Several combinations of PAH-specific agents have been evaluated, and although initial results are promising, more controlled trials are needed to confirm the benefit and the combination of agents to use.
- Ex) Bosentan → +Sildenafil → + Iloprost → LT or iv iloprost
  : 6MWD > 380m, peak O2 uptake >10.4mL/min/kg, pSBP during exercise test > 120mmHg

Medication status in Korea

- **No PAH-specific treatment 30.9 %**
- **Combination treatment 16.5%**



Korean Registry of Pulmonary Arterial Hypertension (KORPAH)

Important parameters in PAH

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (>500 m)[a]	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption <12 mL/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE[b] >2.0 cm	Echocardiographic findings[b]	Pericardial effusion TAPSE[b] <1.5 cm
RAP <8 mmHg and CI ≥2.5 L/min/m²	Haemodynamics	RAP >15 mmHg or CI <2.0 L/min/m²

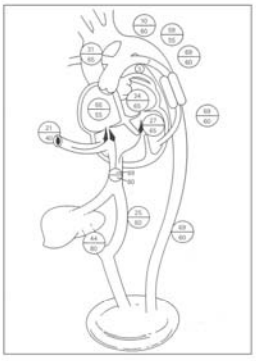
Galiè N et al. Eur Heart J 2009; 30:2493-537
Galiè N et al. Eur Resp J 2009; 34:1219-63

Fetal circulation

- Parallel circulation
- Preferential flow

1) SVC(40%)
   → MPA (50~55%)
   → DA (52%)
   → dAo (55~60%)
2) UV (80%)
   → FO→ LA (65%)
   → aAo (65%)

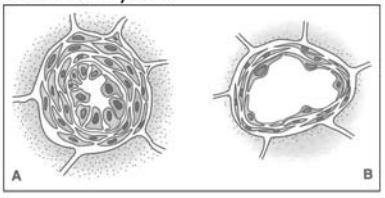
- High PVR (RVP=LVP)



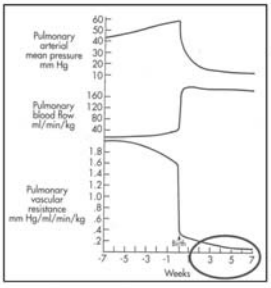
Pulmonary Vascular Resistance

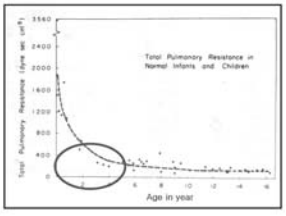
- Regression of pulmonary arteriole
→ Rapid reduction of PVR for 10~14 days
- By 6~8wks after birth, PVR reaches adult values
→ Thereafter slow reduction for 1 years
(20~25% of LVP)

A: Near term fetus
B: Within 24 hours after

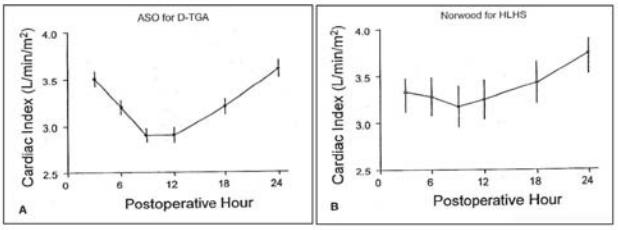


Pulmonary Resistance

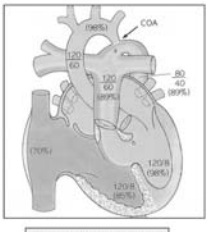




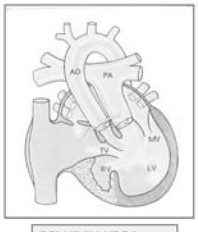
'Midnight sag'



Biventricle vs FSV

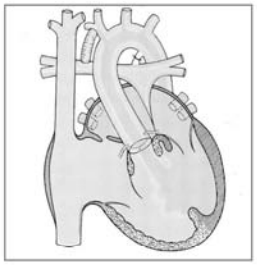


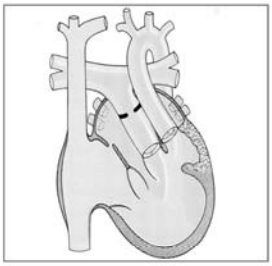
대동맥 축착(CoA) with VSD



FSV(DILV,TGA rudimentary RV)

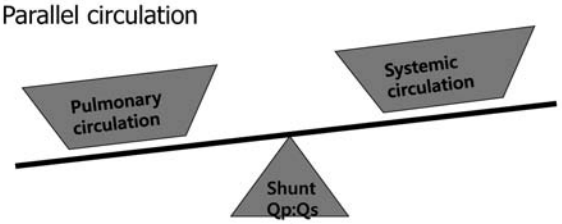
- Decreased pulmonary flow
  → Systemic to pulmonary artery shunt (RMBT)
- Increased pulmonary flow
  → Pulmonary artery banding (PAB)





FSV-shunt dependent circulation

Parallel circulation



Pulmonary overcirculation
Qp > Qs
SaO_2 > 90%
Systemic Hypoperfusion

Pulmonary undercirculation
Qp < Qs
SaO_2 < 70%
Hypoxia

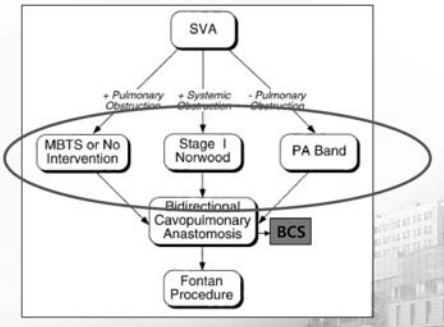
Physiologic Parallel Circulation

- Proportion of ventricular output : determined by the relative resistance to flow in the two circuit
- Assuming equal mixing, normal CO, full PV saturation
  - ✓ **SaO_2 80~85% & Qp/Qs = 1.0**
  - : **Optimal O_2 delivery in all physiology state & shunt size**

Factors influencing PVR

Increased PVR	Decreased PVR
Lower pH	Increased pH
High airway pr.	Low airway pr.
Atelectasis/pleural effusion	Normal functional residual
Sympathetic stimulation	Blunted sympathetic response
Alveolar hypoxia	Increased FiO_2
High Hct	Low Hct
Drug, humoral influence	Drug, humoral influence

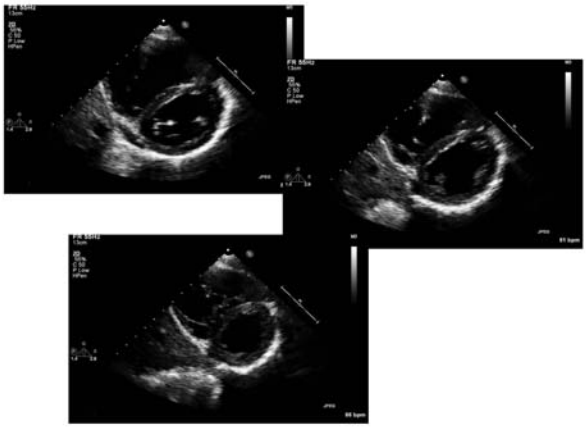
Treatment pathway for FSV

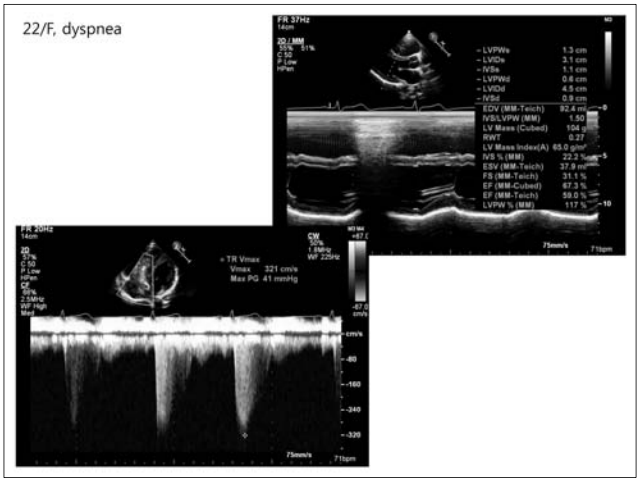


SEVERANCE

Case 1.

CHUNGBUK Cardiovascular Center
NATIONAL UNIVERSITY HOSPITAL





Case 2.

CHUNGBUK Cardiovascular Center
NATIONAL UNIVERSITY HOSPITAL

Patient's information

- F/38Y
- 147cm/43kg(BSA 1.33m2)
- C.C: DOE, peripheral edema
  - SaO2 : 72%
- NYHA class IV
- Dx: FSV, Hypoplastic RV, CAVSD(Rastelli C)

Past Hx

- 1st op : 13yr (1986. 06)
  - B-T shunt, Rt
- 2nd op : 36yr (2010. 12)
  - Bidirectional Glenn operation
  - Common AV repair and annuloplasty
  - Maze operation c RF

- 5th Cath : 38yr(2013. 04. 10)

	Saturation	Pressure
R-SVC	70	45/35(40)
L-SVC	66	45/35(40)
RA		40/30(35)
IVC	64	
RV		
CPA	71	45/35(40)
RPA		
LPA		
PV		
LA		
LV		
A Ao	81	125/75(90)
Ventricle	82	125/10/32

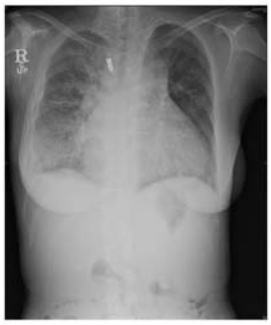
Qp	3.44
Qs	2.47
Qp/Qs	1.40
Qeff	2.47
Q(L->R)	0.98
Q(R->L)	0.00
Q net shunt	0.98
Rp	1.45
Rs	24.33
Rp/Rs	0.06

RPA(mm)	17.00	McGoon	1.65
LPA(mm)	16.00	Blackstone	0.49
DAO(mm)	20.00	Nakada	317
BSA(m2)	1.35		

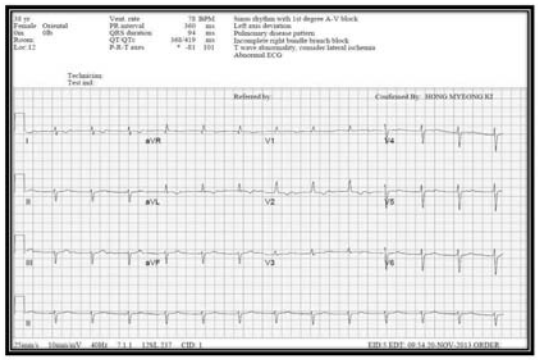
- PS(infund. & val.) /c PV thickening /c no flow
- Pulmonary arterial hypertension(mean BP=40mmHg)
- Rt subclavian artery interruption

Medication for PAH

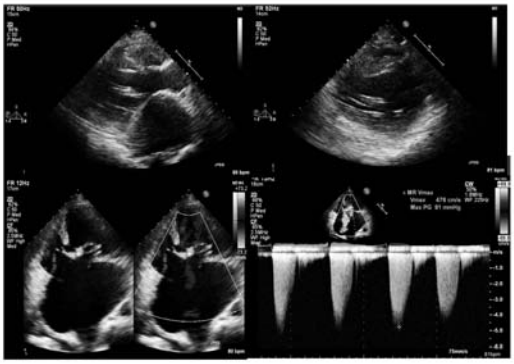
Preoperative Chest PA



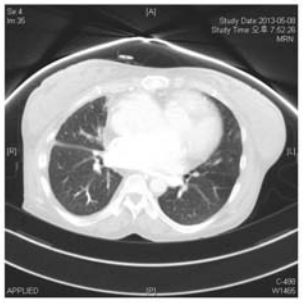
Preoperative EKG



Preoperative Echocardiogram

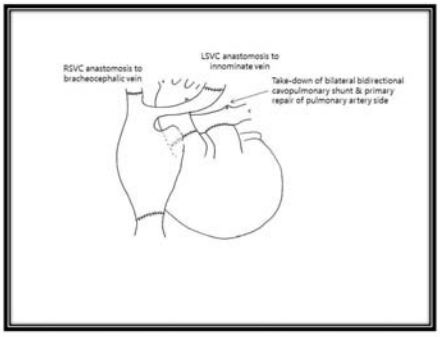


Preoperative Chest CT

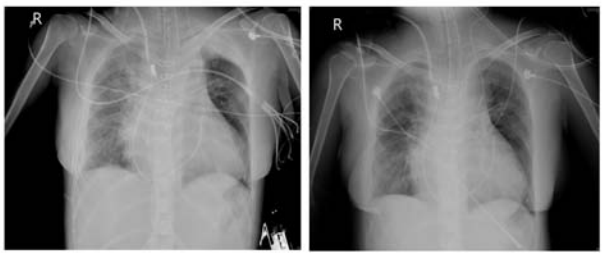


- Interlocular septal thickening in both lungs, suggesting pulmonary edema probably due to AV valve regurgitation

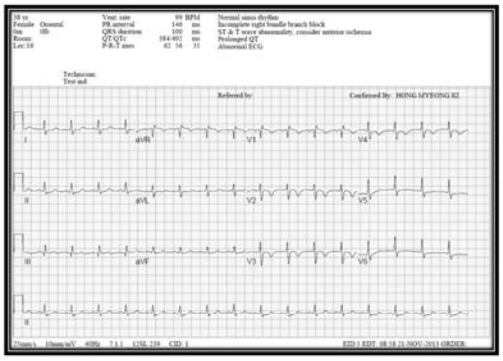
Heart transplantation



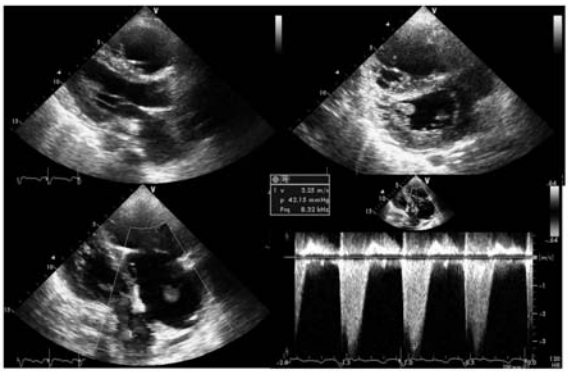
POD #0-1



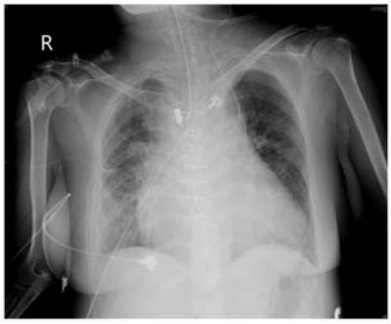
Postoperative EKG POD#1



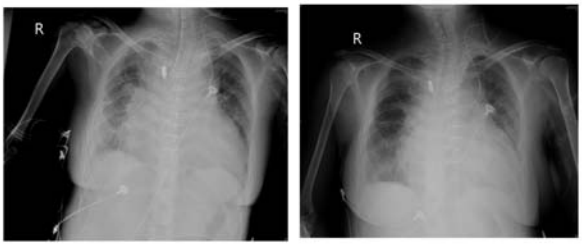
Postoperative Echo POD#1



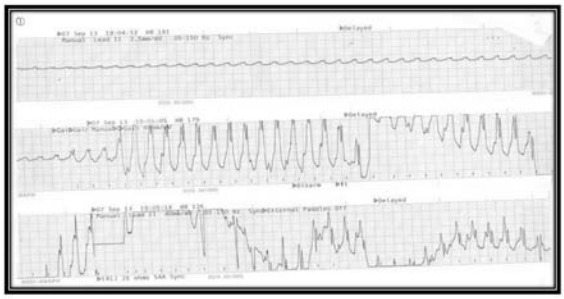
POD #10



POD # 11~12

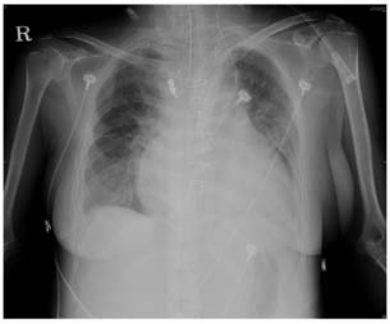


POD #12

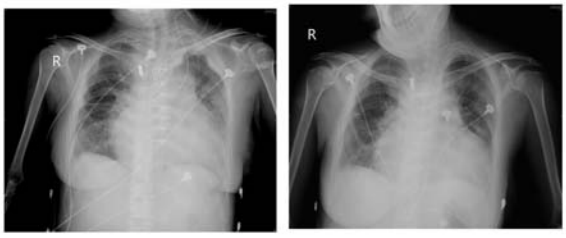


- 첫번째 extubation 이후 VT 발생하여 re-intubation 시행.
- LV apicoseptal origin으로 생각되며 QTc prolongation 및 hypoxia에 의해서 trigger 된 것으로 추정됨
- Lidocain infusion 후 호전

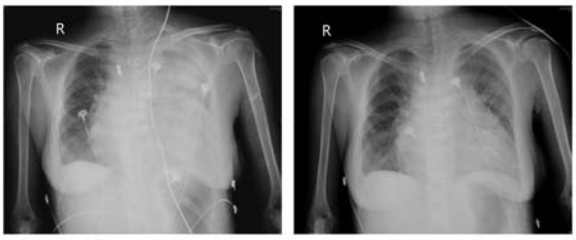
POD # 16



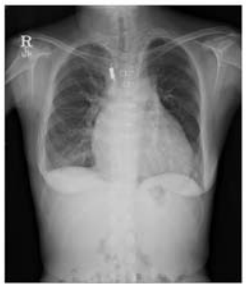
POD #21~22



POD #27~29

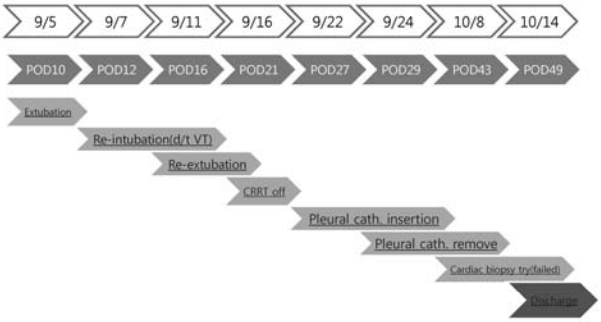


POD#49 - Discharge



V/S 110/70 - 94 – 20 – 36.8 – 98%

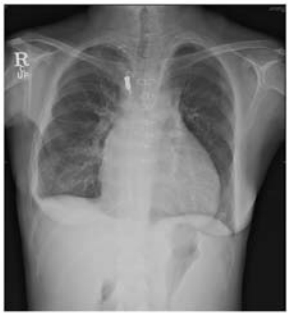
Progress



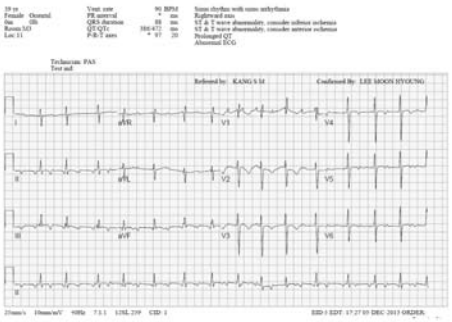
OPD F/U 1mo Later

- 특이 증상 없음
- V/S Stable
- Medication for pulmonary hypertension
  - Pahtension 20mg Tid, Tracleer 62.5mg Bid

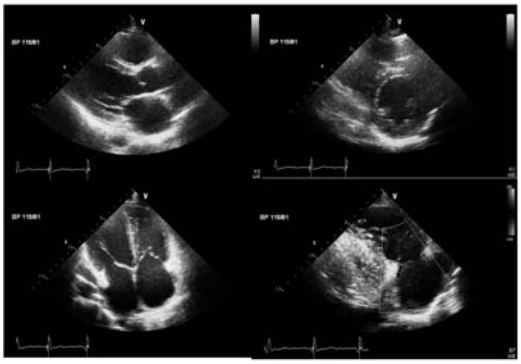
OPD F/U Chest PA



OPD F/U EKG(11/8)



OPD F/U Echocardiogram



FEATURED CASE REPORT

Pulmonary artery dissection: an emerging cardiovascular complication in surviving patients with chronic pulmonary hypertension

R S Khattar, D J Fox, J E Alty, A Arora

Heart 2005;91:142-145. doi: 10.1136/hrt.2004.045799

Pulmonary arterial dissection is an extremely rare and usually lethal complication of chronic pulmonary hypertension. The condition usually manifests as cardiogenic shock or sudden death and is therefore typically diagnosed at postmortem examination rather than during life. However, recent isolated reports have described pulmonary artery dissection in surviving patients. The first case of pulmonary artery dissection in a surviving patient with cor pulmonale caused by chronic obstructive pulmonary disease is presented. The aetiology, pathophysiology, and clinical presentation of pulmonary artery dissection are reviewed and factors that may aid diagnosis during life are discussed.

resulting in resolution of the cough, but the dyspnoea continued to worsen and was accompanied by the development of peripheral oedema. She was a longstanding heavy smoker; she did not have any pets, and there was no history of occupational dust exposure. Clinical examination showed a thin body habitus, respiratory rate of 22 breaths/min, resting tremor, peripheral cyanosis, palmar erythema, and mild kyphoscoliosis. She was afebrile, her heart rate was 100 beats/min, and her blood pressure was 145/92 mm Hg. The jugular venous pressure was raised and there was bilateral leg oedema to the knees. A right ventricular heave was palpable and auscultation found a loud pulmonary component of the second heart sound followed by an early diastolic murmur heard loudest over the left sternal edge radiating to the pulmonary area and apex. Chest expansion and breath sounds were greatly reduced bilaterally. A smooth

The Journal of Thoracic and Cardiovascular Surgery
Volume 121, Number 5

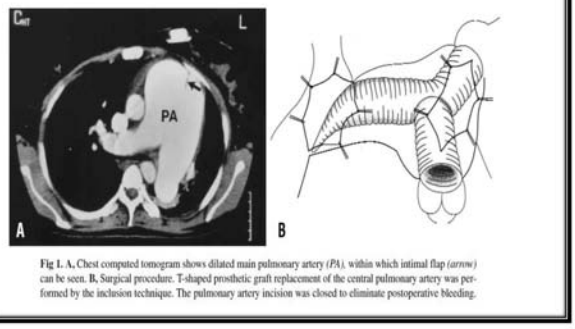


Fig 1. A, Chest computed tomogram shows dilated main pulmonary artery *(PA)*, within which intimal flap *(arrow)* can be seen. **B,** Surgical procedure. T-shaped prosthetic graft replacement of the central pulmonary artery was performed by the inclusion technique. The pulmonary artery incision was closed to eliminate postoperative bleeding.

JTCVS 2001

Case Report

Pulmonary hypertension and pulmonary artery dissection*,**

Dissecção da artéria pulmonar e hipertensão pulmonar

Ricardo de Amorim Corrêa, Luciana Cristina dos Santos Silva, Cláudia Juliana Rezende, Rodrigo Castro Bernardes, Tarciane Aline Prata, Henrique Lima Silva

Abstract

Pulmonary artery dissection is a fatal complication of long-standing pulmonary hypertension, manifesting as acute, stabbing chest pain, progressive dyspnea, cardiogenic shock, or sudden death. Its incidence has been underestimated, and therapeutic options are still scarce. In patients with pulmonary hypertension, new chest pain, acute chest pain, or cardiogenic shock should raise the suspicion of pulmonary artery dissection, which can result in sudden death.

Keywords: Hypertension, pulmonary; Chest pain; Pulmonary artery.

Resumo

A dissecção da artéria pulmonar é uma complicação fatal da hipertensão pulmonar de longa duração que se manifesta como dor torácica aguda e lancinante, dispneia progressiva, choque cardiogênico ou morte súbita. Sua incidência é subestimada, e as opções terapêuticas são ainda limitadas. O aparecimento de uma dor torácica aguda ou nova, choque cardiogênico ou morte súbita em pacientes portadores de hipertensão pulmonar deve alertar para o diagnóstico de dissecção da artéria pulmonar.

Descritores: Hipertensão pulmonar; Dor no peito; Artéria pulmonar.

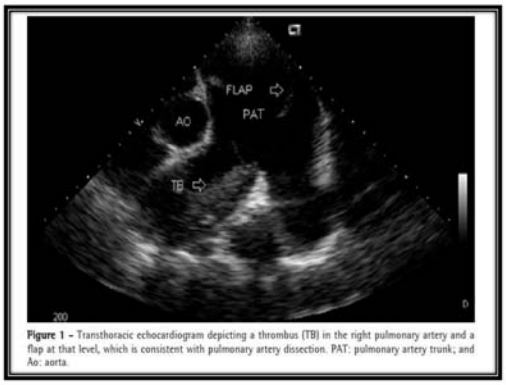


Figure 1 – Transthoracic echocardiogram depicting a thrombus (TB) in the right pulmonary artery and a flap at that level, which is consistent with pulmonary artery dissection. PAT: pulmonary artery trunk; and Ao: aorta.

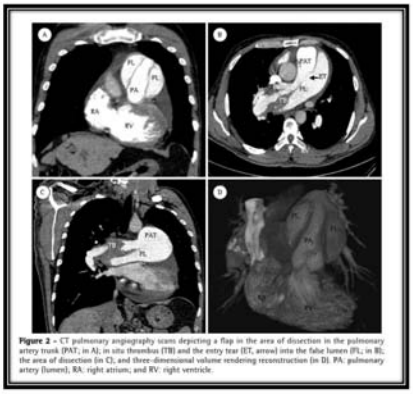
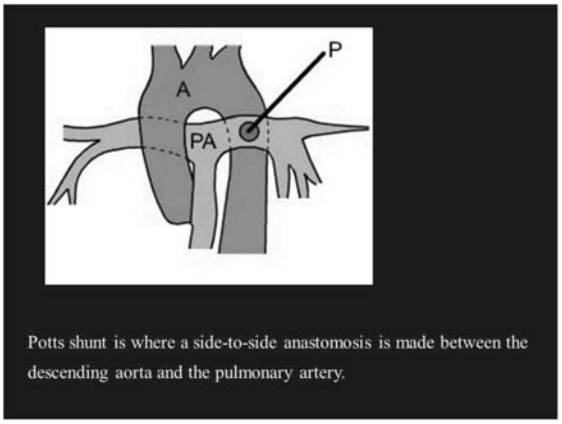


Figure 2 - CT pulmonary angiography scans depicting a flap in the area of dissection in the pulmonary artery trunk (PAT; in A); in situ thrombus (TB) and the entry tear (ET, arrow) into the false lumen (FL; in B); the area of dissection (in C), and three-dimensional volume rendering reconstruction (in D). PA: pulmonary artery (lumen), RA: right atrium; and RV: right ventricle.



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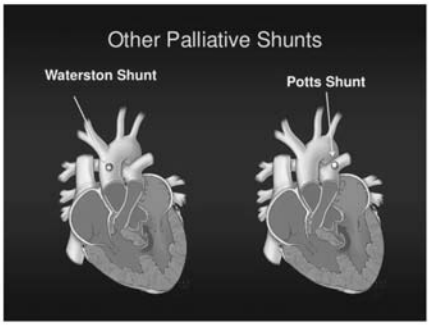

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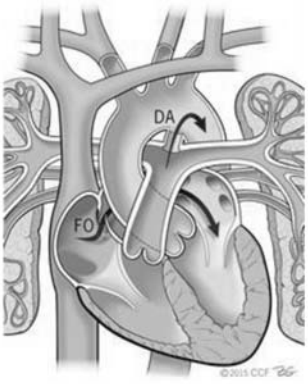
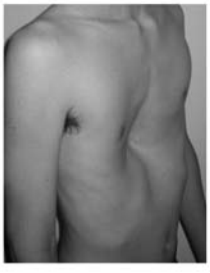
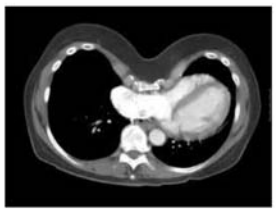


my.clevelandclinic.org



en.wikipedia.org

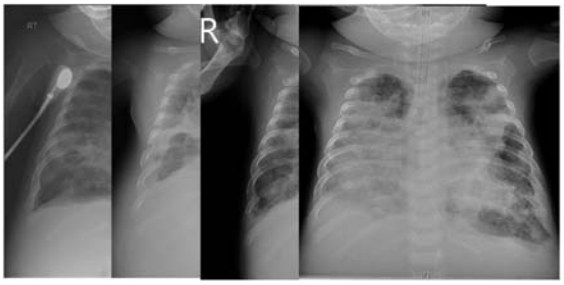


news.wgbh.org

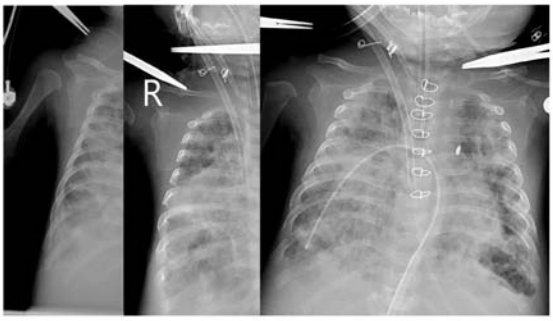
CHD, BPD, Endotracheal bleeding

- 5mo/M
- BW 5.5Kg
- Down syndrome (47, XY, +21)
- RDS
- BPD
- VSD multiple 3개이상(mid muscular, d=2.5mm)
- ASD 2' (d=6.4mm, L-R shunt)

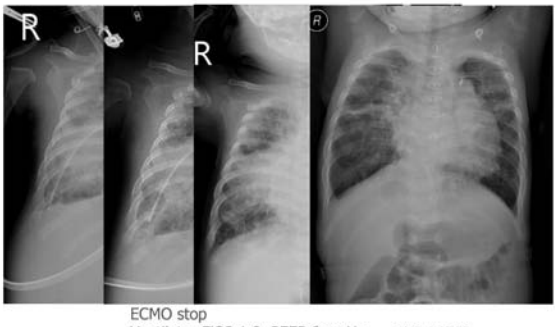
CHD, BPD, Endotracheal bleeding



CHD, BPD, Endotracheal bleeding



CHD, BPD, Endotracheal bleeding



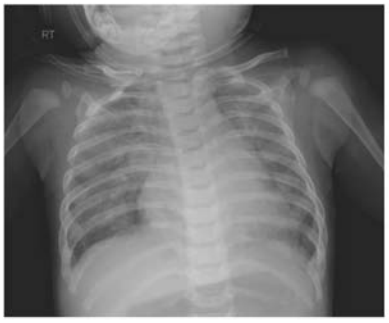
ECMO stop
Ventilator FiO2 1.0, PEEP 6mmHg 1YR LATER
Lt. hand saturation 80%, foot saturation 50%

DORV, Subaortic VSD

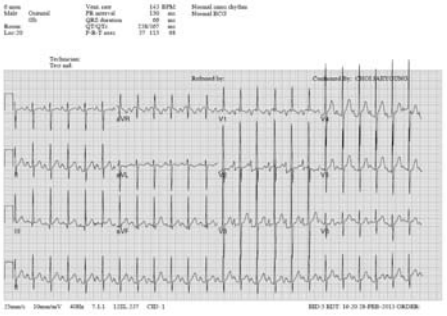
2013-2-23 Echo

- DORV {S, D, S} with subaortic VSD (d=14mm, bid. shunt, mainly Lt to Rt shunt)
- Bicuspid aortic valve (RCC & LCC fusion)
- No AS (flow pv=1.5m/sec), No AR
- mitral valve prolapse (inflow Vmax =2.4m/sec, mean dp=11mmHg)
- Severe pulmonary hypertension
- TR(G2/4, dp=80mmHg)
- LVEF 70%

2013-2-23



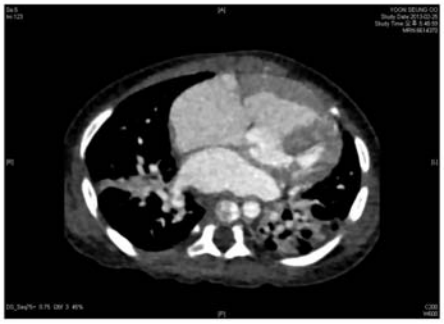
Preoperative EKG



2013-2-25 CT

- DORV with large subaortic VSD.
- RV and RA enlargement.
- Enlargement of main and both pulmonary artery.
- Aberrant right subclavian artery
- Patchy consolidations in both lungs with multifocal air-trapping.

2013-2-25 CT



2013-02-26 Cath

- RVpr. 80/0/10 mmHg
- LPApr. 75/72 mmHg
- LV 80/0/10 mmHg
- Ao 80/30/52 mmHg

Cath Conference

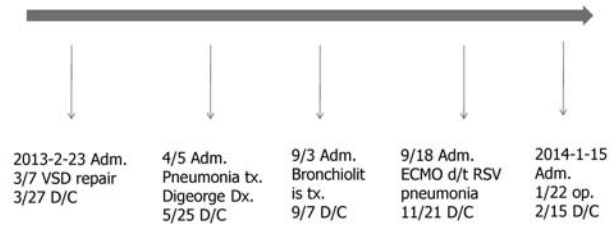
- SpO2 97%
- General condition 호전되는 일주일 뒤 fenestration VSD repair 진행할 것임

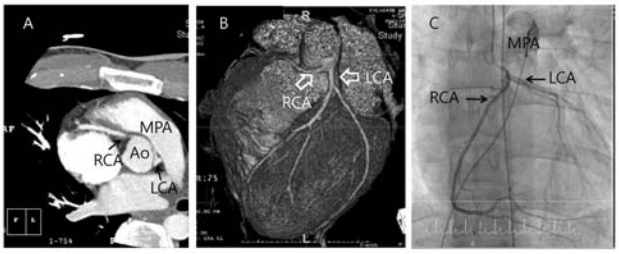
2013-03-05 f/u Echo

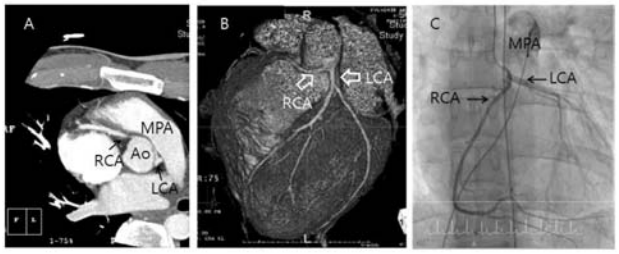
- DORV {S, D, S} with subaortic VSD (d=13mm, bid. shunt, mainly Lt to Rt shunt)
- PFO (very small)
- **MS (mitral inflow pv=2.5~2.7m/sec, peak dp=25~30mmHg / mean dp=15mmHg)**
- **- MV annulus: d=11mm (Z=-1.8), opening: d=6.2mm**
- **- papillary muscle 두 개이나 가까이 위치함.**
- **- MV:TV annulus=11:18mm**
- Severe pulmonary hypertension
- TR (G2/4, dp=90mmHg)
- PI (trivial, peak dp>44mmHg)
- MR (trivial)

2013-3-7 Op.

- Total correction
- Intraventricular baffling of ventricular septal defect with a fenestratration
- Primary closure of PFO
- Mitral papillary muscle splliting







Kyobu Geka. 2001 Feb;50(2):184-7.

[Left main coronary trunk compression by dilated main pulmonary artery in a patient with atrial septal defect].

Article in Japanese]

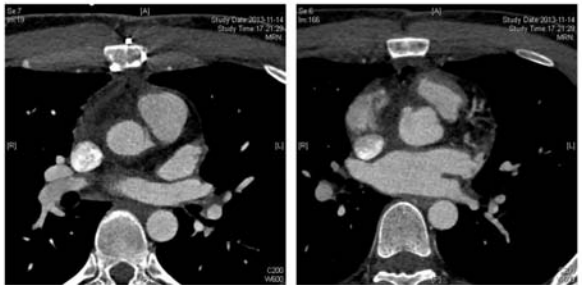
Ito K, Fujiwara Y, Kimura T, Shimada Y.

Author information

Abstract

A 12-year-old girl with atrial septal defect combined with pulmonary hypertension and 90% stenosis of the left main coronary artery caused by dilated pulmonary artery was scheduled for atrial septal closure and coronary artery bypass graft under general anesthesia. During the echocardiographic examination to evaluate the anatomical relationship between the pulmonary artery and left main coronary trunk, bradycardia and ST depression of ST-segment on electrocardiogram appeared suddenly when the operator compressed the pulmonary artery with a probe of echocardiography from the operative field. The circulatory collapse and ischemic change on electrocardiogram might have been caused by a further reduction of blood flow to the left main coronary trunk narrowed originally by dilated pulmonary artery. Although various etiologies, such as atherosclerosis, syphilis, and congenital abnormalities are widely known to cause stenosis of the left main coronary trunk, external compression by dilated pulmonary artery has not been widely known. Malignant arrhythmias from coronary artery compression with subsequent ischemia could contribute to an incidence of sudden death. Coronary angiography and magnetic resonance imaging are useful for the preoperative evaluation. Careful management is needed to protect such a patient from ischemic event in the perioperative period.

PMID: 11244776 [PubMed - indexed for MEDLINE]

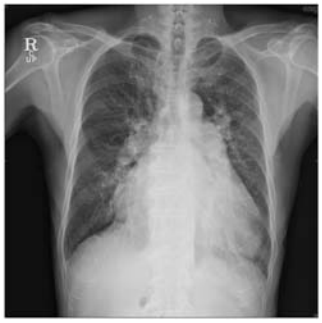


ASD in Old Age

Patient Profile

- **72/M**
- **Chief Complain**
  - dyspnea on exertion
- **Past History**
  - diagnosed with ASD and pulmonary hypertension on July, 2012
- **Medication**
  - Aspirin/ Herben/ Cozaar/ Dichlozid

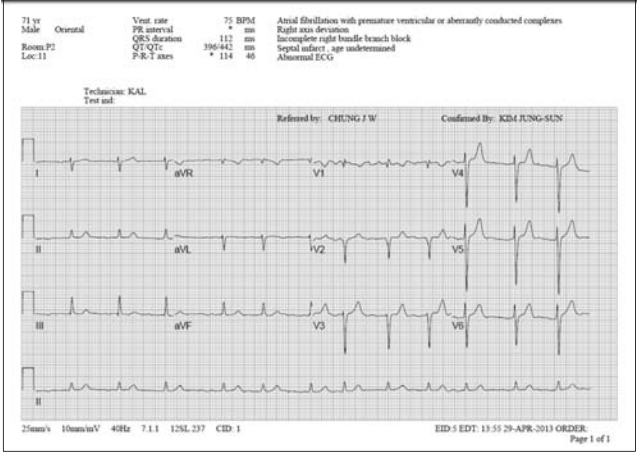
Initial Presentation (2013/04)



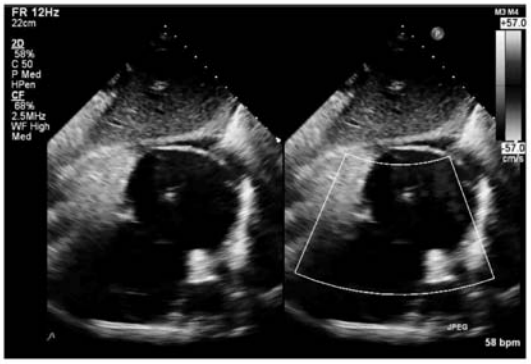
- Vital signs
  - BP 125/78 mmHg
  - HR 63 /min
  - SpO2 92%
- Laboratory findings

CBC	3940 (56%)/ 13.9/ 171K
BUN/ Cr (eGFR)	20.6/ 0.73 (>90)
PT/ aPTT	1.42/ 34.7
AST/ ALT	25 /20
CK/ CK-MB	75/ 1.5

EKG

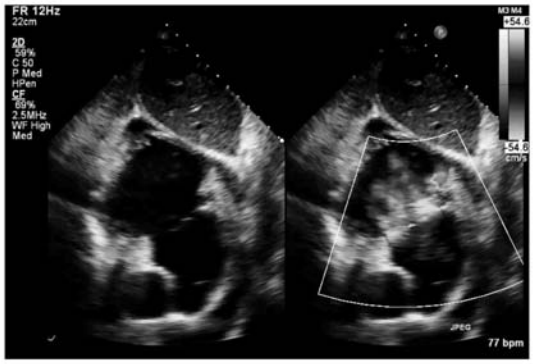


Echocardiography - Initial



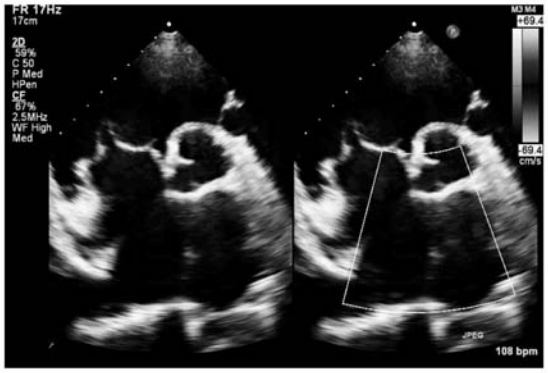
Multiple ASD 2' d= 16~25mm & 8mm & 7mm, total: d=40mm

Echocardiography - Initial



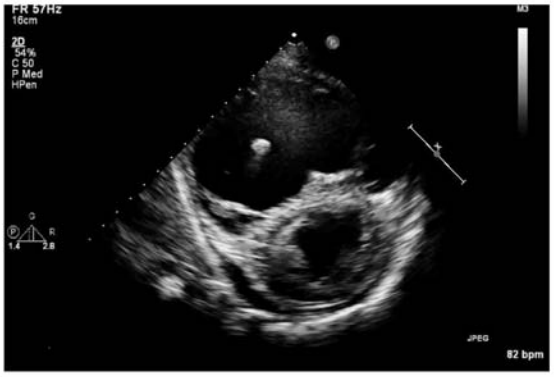
Multiple ASD 2' d= 16~25mm & 8mm & 7mm, total: d=40mm

Echocardiography - Initial



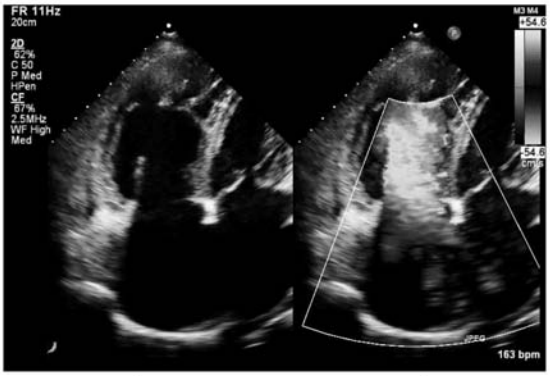
Multiple ASD 2' d= 16~25mm & 8mm & 7mm, total: d=40mm

Echocardiography - Initial



LVEF 76 % (by M-mode), RVP = 2~3/5 of LVP
Pericardial effusion (LV side 13 mm, RV side 9~15 mm, RA side 7 mm)

Echocardiography - Initial



TR G2~3/4 (dp = 54 mmHg)

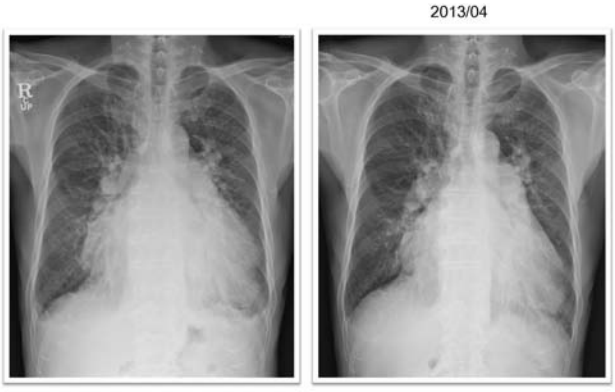
Diagnosis

- ASD, secundum
- Pulmonary hypertension, mild
- Atrial fibrillation, chronic, persistent
- Pericardial effusion

Medication

- Cozaar 50 mg #1
- Herben SR 90 mg #1
- Dichlozid 50 mg #2
- Pahtension 60 mg #3
- Aspirin protect 100 mg #1
- Warfarin 3.5 mg #1

Chest x-ray (2014/03)

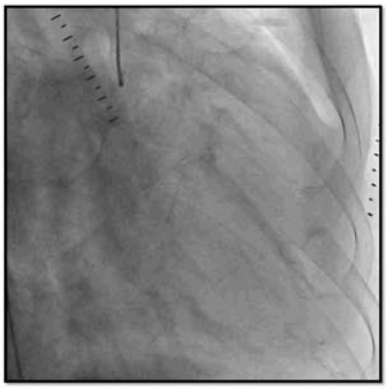


Cardiac Catheterization (2014/04)

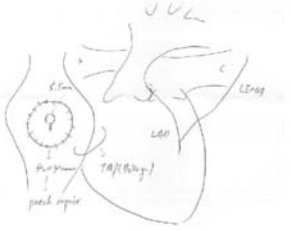
	Sat. (%)	Pr. (mmHg)
SVC	69	
RA	82	25/13 (19)
IVC	74	
RV		52/5 (19)
MPA		52/14 (30)
RPA		52/14 (30)
LPA	86	
LA		25/16 (19)
LV	91	140/2
Asc. Ao	90	140/60 (90)

Qp	11.11
Qs	3.37
Qp/Qs	3.29
Qeff	3.06
Q (L→R)	8.04
Q (R→L)	0.31
Q net shunt	7.73
Rp	1.62
Rs	21.04
Rp/Rs	0.08

Cardiac Catheterization (2014/04)



Operation (April 3 / 2014)

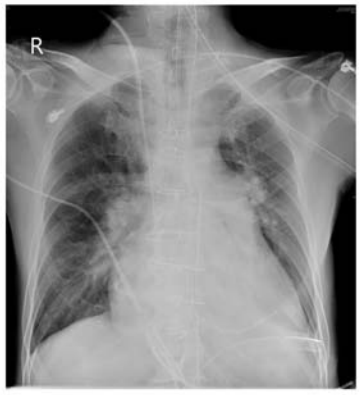


- Patch repair of ASD with a fenestration (5.5 mm)
- Tricuspid annuloplasty, DeVega technique
- Maze procedure, bi-atrial
- RA reductoplasty
- CABG, LIMA to LAD

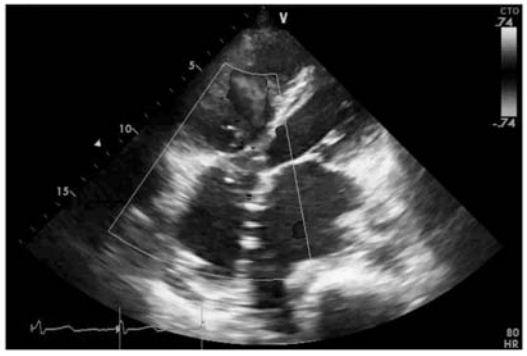
Operation

- **Post-repair hemodynamics**
  - PAP 50 (30) mmHg, systemic BP 100/70 mmHg
- **Post-repair EKG**
  - 1st degree AV block, HR 70 /min
- **Post-repair TEE**
  - TR G1/4, MR G1/4

Chest x-ray _ immediate post-op.

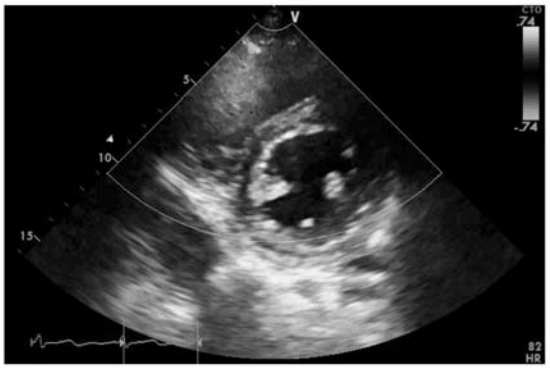


Echocardiography _ POD #1



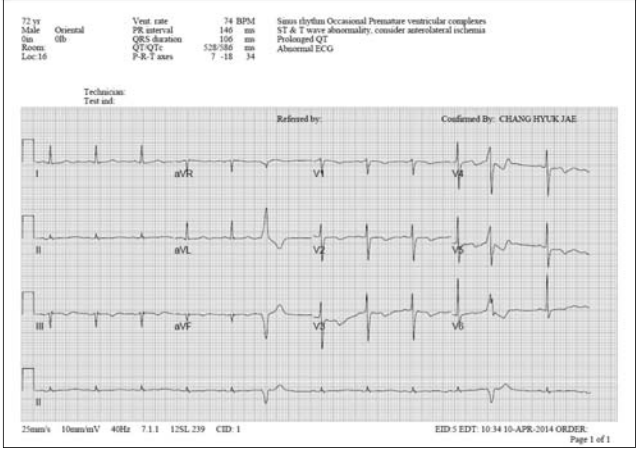
Patent fenestration (d= 5 mm), TR (trivial)

Echocardiography _ POD #1



LVEF = 70 % (by M-mode), RVP = 2/5 of LVP

EKG – POD#1



Progress

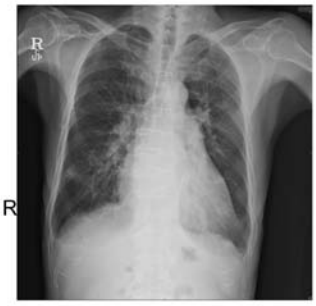
Op. day:
- PAP 22/3 mmHg
- Sinus tachycardia
- Codarone infusion

POD #1 :
- Extubation

POD #2 :
- Chest tube insertion, R

POD #3 :
- Transfer to GW

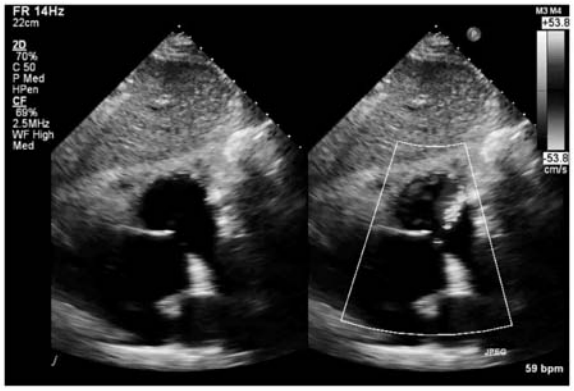
POD #30 :
- Discharge



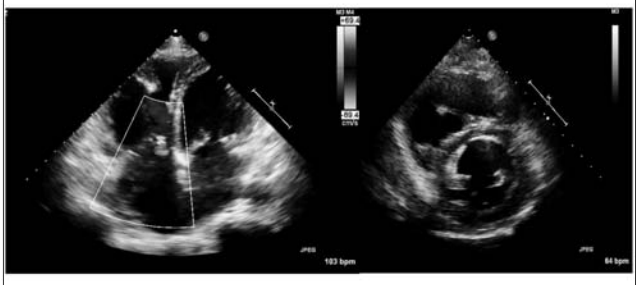
Medication_ on discharge

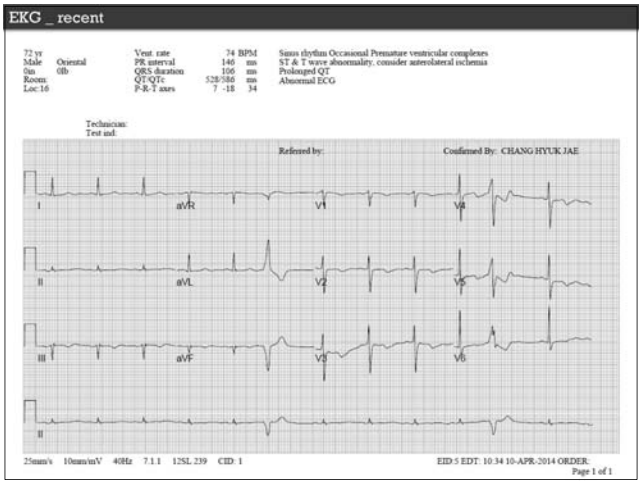
- Cozaar 25 mg #1
- Betaloc 50 mg #1
- Torsem 2.5 mg #1
- Pahtension 60 mg #3
- Aspirin protect 100 mg #1
- Coumadin 5 mg #1

Echocardiography _ recent

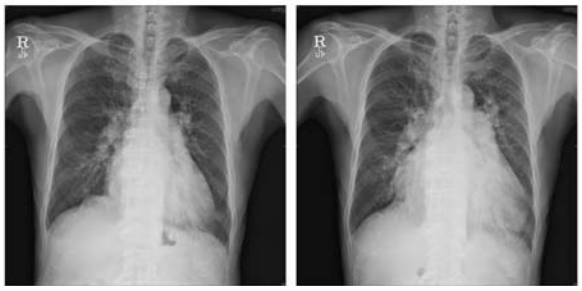


Echocardiography _ recent



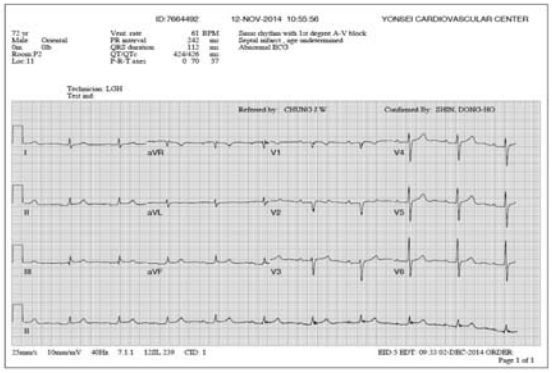


Chest X-ray



Postop. 7 months　　Preop.

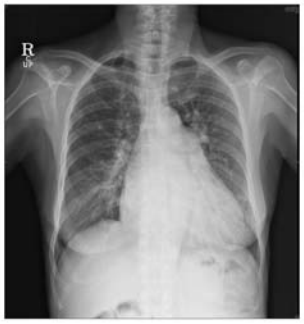
Postop. 7 months



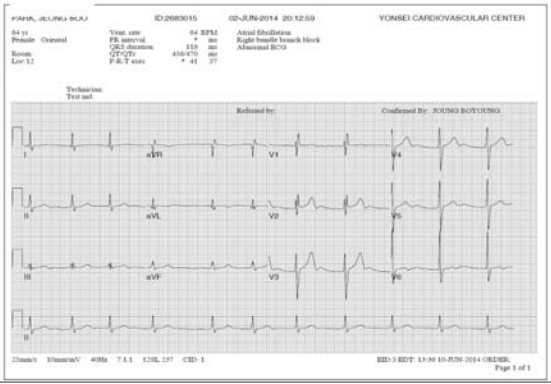
Patient Profile

- **64/F, 박O수, 2683015, 2014/6/5 OP.**
- **s/p ASD primary closure , Maze operation**
  RA reduction plasty (2014. 6. 5)
- **Last echo findings**
  TR (trivial~G1/4, dp=46mmHg)
  MR (trivial<G1/4) d/t mild MVP (AML)AR (trivial),
  PI (trivial)Ao : PA = 20 : 30mm
- **Medication**
  - Lasix/ Aldactone/ LipiLOU

Preop. Chest X-ray



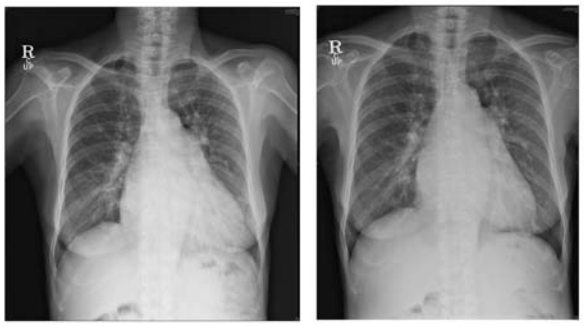
Preop. EKG



Progress

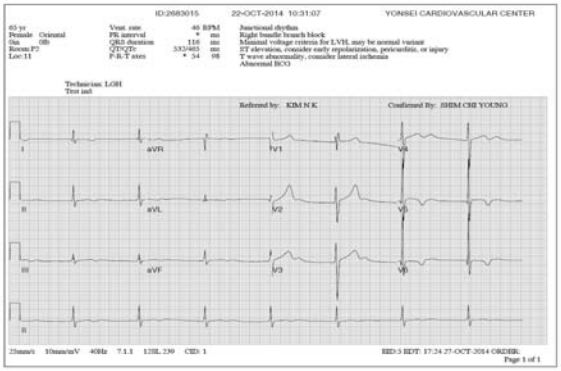
- POD #2 Extubation
- POD #5 Transfer to the GW
- POD #24 Discharge

Chest X-ray



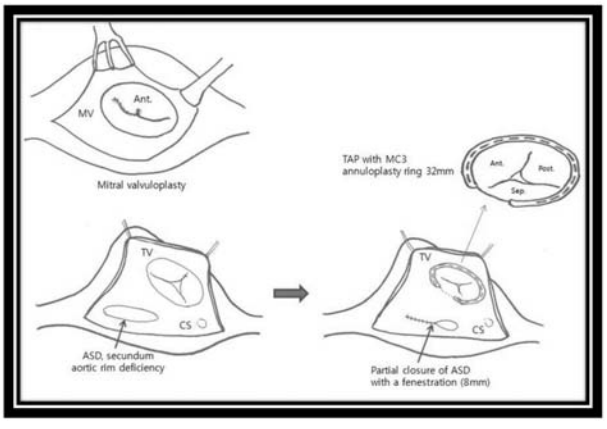
Preop. Postop. 4 months

Postop. EKG

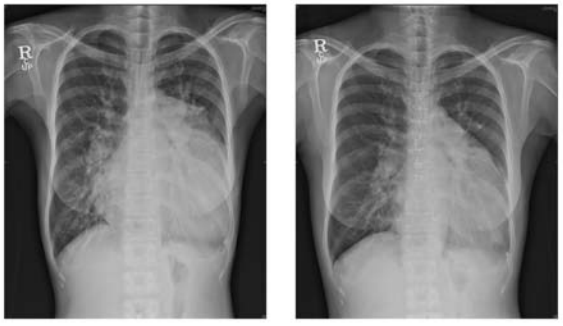


Patient Profile

- **61/F, 김O숙, 7863396, 2014/7/30 OP.**
- **s/p ASD direct closure with fenestration (7~10mm)**
  TAP (MC3 ring 32mm) / MV repair, PA reuction plasty (internal plication) d/t ASD secundum, TR, MR, A-fib, Dilated PA, Pul.HTN
- **Last echo findings**
  Patent ASD fenestratoin flow: d=5~6 <- 8mm (LR shunt)*Remained pul. HTN
  TR (G 1/4 - G2/4, dp=33
  PI (mild, dp=30(8)mmHg)
  MR (G1~2/4, dp=82mmHg) d/t MVP (AML)

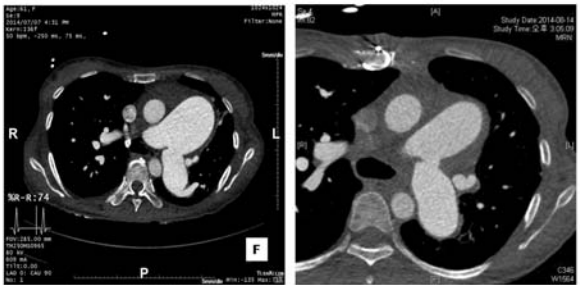


Chest X-ray



Preop. Postop. 4 months

Chest CT



Preop. Postop.

Patient Profile

- **60/F, 이O자, 7907084, 2014/8/13 OP.**
- **S/P ASD patch repair c fenestration, TAP(DeVega), Maze OP, RPA, LPA reduction plasty, RA reduction plasty**
- **Last echo findings**

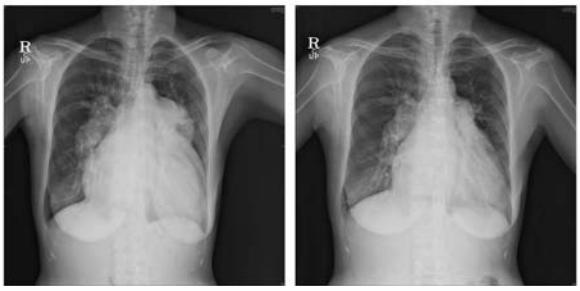
  Patent ASD fenestration (d=7mm & 3mm & small, Lt to Rt shunt)

  Remained pulmonary hypertension

  TR (trivial~G1/4, dp=35mmHg), PI (mild)

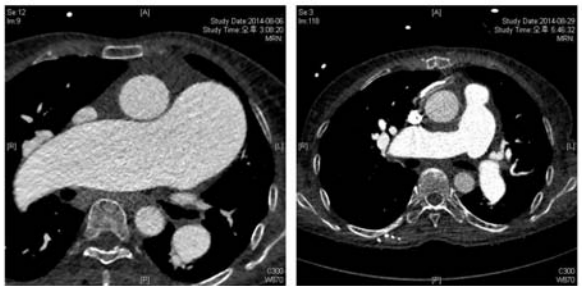
  MR (trivial~G1/4), AR (trivial)

Chest X-ray



Preop. Postop. 2months

Chest CT



Preop. Postop.

Outcome of Surgical Closure of ASD with PAH : Does Pulmonary Vascular Resistance Predict Long-term Outcome?

ASD closure in adult patients

- Pulmonary arterial hypertension
- Age
- The decision criteria for closure
- PVR (Rp 4 Wood units, 8 Wood units)

  -> Acute vasodilatory testing
- Looked "inoperable"
- Operability of Patients with PAH

ASD with severe PAH

Treatment and Repair

vs

Repair and Treatment

123 patients of isolated ASD at Mayo clinic
Between 1956 and 1960
27 to 32 years f/u
<Independent predictors of long-term survival>
1) Age at operation
2) Systolic MPA pressure
< Conclusion>
- Those operated on before the age of 25 have an excellent prognosis, but older patients require careful, regular supervision

JOHN W. KIRKLIN, M.D., AND GORDON K. DANIELSON, M.D.

Table 1. Significant Predictors of Long-Term Survival in Patients Undergoing Repair of Atrial Septal Defects, According to Univariate and Multivariate Analyses.

Variable*	Patients Evaluated	P Value†	Relative Risk‡ (95% Confidence Interval)
Univariate analysis			
Age at operation	123	<0.0001	
MPA systolic pressure	97	<0.0001	
Area of defect at operation	55	0.0001	
Use of Ivalon patch§	123	0.002	
Preoperative dyspnea	123	0.0006	
Preoperative cardiomegaly	123	0.0025	
Preoperative diuretic use	123	0.0001	
Preoperative syncope	123	0.0016	
Multivariate analysis			
Age at operation (10-yr increments)		<0.00001	2.22 (1.05–3.0)
MPA systolic pressure (25–mm Hg increments)		0.0027	1.82 (1.23–2.66)

Murphy JG et al, N Engl J Med 1990;323:1645-1650

Belgian Registry on Adult Congneital Heart Disease
Isolated ASD secundum / **295 patients**
PAH after ASD closure
-> related to mortality, atrial arrhythmia, RHF (<0.05)
Age at repair
-> the most important predictor for PAH
<Conclusions>
1) PAH in closed ASD is not uncommon
2) PAH ↑ when the defect was repaired above 55 years
3) **PAH may even develop despite normal mPAP**
4) New guidelines of PAH
-> Whether the cutoff value for mPAP before closure should be adjusted

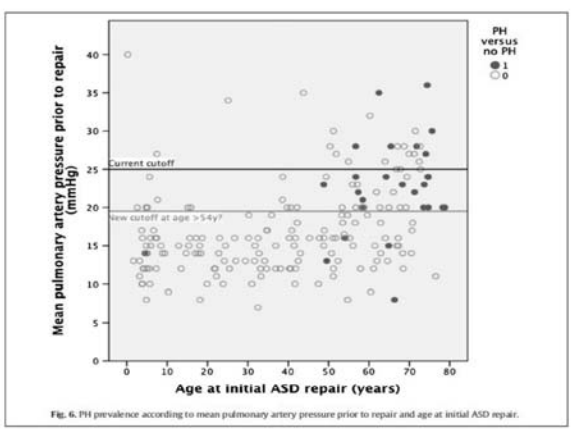


Fig. 6. PH prevalence according to mean pulmonary artery pressure prior to repair and age at initial ASD repair.

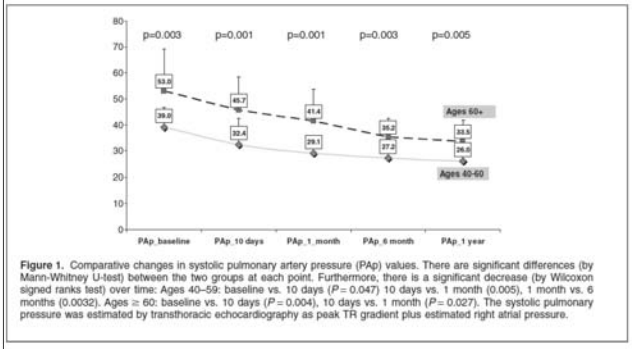


Figure 1. Comparative changes in systolic pulmonary artery pressure (PAp) values. There are significant differences (by Mann-Whitney U-test) between the two groups at each point. Furthermore, there is a significant decrease (by Wilcoxon signed ranks test) over time: Ages 40–59: baseline vs. 10 days ($P = 0.047$) 10 days vs. 1 month (0.005), 1 month vs. 6 months (0.0032). Ages ≥ 60: baseline vs. 10 days ($P = 0.004$), 10 days vs. 1 month ($P = 0.027$). The systolic pulmonary pressure was estimated by transthoracic echocardiography as peak TR gradient plus estimated right atrial pressure.

Yalonetsky S et al, Congenit Heart Dis 2009;4:17-20

PVR

- (Total) Rp = mean PAP / Qp
- Total R p = 200-250 dyne·sec·cm^{-5} or 4-5 unit·M^2
- Qp (ℓ/min/M2)

$$\frac{VO2}{O2\ content\ of\ P\ vein - O2\ content\ of\ PA}$$

- VO2 -> 산소소비량 -> 연령과 심박동수에 따라 산소소비량 정해진 표
- O2 content
  = Hb x 1.36 x 10 x SpO2 + 3 x PaO2 (100mmHg = 1)

Letter to the Editor

Successful shunt closure and improvement of hemodynamics in an ASD patient with severe pulmonary arterial hypertension and small shunt following a long-term use of bosentan

Nobuhiro Tahara [a,*], Minori Mizoguchi [a], Akihiro Honda [a], Atsuko Tahara [a], Yoshikazu Nitta [a], Norihiro Kodama [a], Hiroshi Koiwaya [a], Shigeaki Aoyagi [b], Tsutomu Imaizumi [a]

[a] Department of Medicine, Division of Cardio-Vascular Medicine, Kurume University School of Medicine, Kurume, Japan
[b] Department of Surgery, Kurume University School of Medicine, Kurume, Japan

Table 1
Serial hemodynamic data by cardiac catheterization and clinical data ASD, atrial septal defect; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; SvO_2, mixed vein oxygen saturation; Qp/Qs, pulmonary/systemic blood flow ratio; WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance.

	Before bosentan therapy		3 mo	1 y	2 y	1 mo	6 mo	2.5 y
	2004.11	2005.9	After bosentan therapy			After ASD closure		
			2006.1	2006.10	2007.7	2007.10	2008.3	2010.3
PAP, mm Hg	96/35	91/29	69/26	70/24	73/25	62/27	46/19	43/18
Mean PAP, mm Hg	58	53	42	42	43	42	32	33
PVR, Woods unit	15.1	17.4	11.5	9.4	11.0	6.0	4.1	2.5
SaO_2, %	95.3	95.5	94.5	95.4	96.7	94.5	97.3	97.3
SvO_2, %	67.7	67.4	69.0	67.8	70.8	73.4	79.7	81.8
Qp/Qs	1.54	1.71	1.69	1.94	2.19	1.00	1.00	1.00
WHO-FC	III	III	II	II	II	II	I	I
Deviation index	1.5	1.5	1.4	1.4	1.4	1.4	1.2	1.2
R,S ratio in V1	2.2	5.9	4.5	4.4	6.1	3.5	1.2	0.7

Table 1. Case Studies of Patients with PAH Who Have Undergone Surgical Correction for Congenital Heart Defects Following Treatment with PAH-specific Therapies

Age and Sex	Defect	Drug Treatment	Hemodynamics Pre-drug Treatment	Hemodynamics Post-drug Treatment	Operation	Outcome at Last Follow-up	Reference
31-year-old female	ASD	Intravenous epoprostenol for 5 years prior to operation	Mean PAP: 58 mm Hg Qp:Qs: 1.5 PVR: 824 dyn·s·cm^5 (10.3 Wood units)	Mean PAP: 51 mm Hg Qp:Qs: 2.0 PVR: 471 dyn·s·cm^5 (5.9 Wood units)	Transcatheter ASD closure with continued epoprostenol	1 year postoperation Mean PAP: 39 mm Hg Qp:Qs: 1.0 PVR: 256 dyn·s·cm^5 (3.2 Wood units)	33
71-year-old female	ASD (Large type 9 [15 × 36 mm]) with bidirectional shunt	Bosentan 125 mg/day increased to 250 mg/day after 1 month for 10 months prior to operation	Mean LAP: 17 mm Hg Mean PAP: 16 mm Hg Mean PAP: 54 mm Hg Qp:Qs: 2.7 PVR: 480 dyn·s·cm^5 (3.9 Wood units)	Mean LAP: 11 mm Hg Mean PAP: 10 mm Hg Mean PAP: 30 mm Hg Qp:Qs: 2.2 PVR: 325 dyn·s·cm^5 (2.6 Wood units)	Closure with Dacron patch and continued bosentan therapy	6 months postoperation Mean LAP: 13 mm Hg Mean PAP: 7 mm Hg Mean PAP: 36 mm Hg Qp:Qs: 1 PVR: 536 dyn·s·cm^5 (4.2 Wood units)	34
39-year-old female	PDA	Bosentan 125 mg/day for 2.5 years prior to operation	Systolic PAP: 112 mm Hg Mean PAP: 75 mm Hg Qp:Qs: 2.0 PVR: 9.3 Wood units PVR:SVR: 0.31	Systolic PAP: 106 mm Hg Mean PAP: 76 mm Hg Qp:Qs: 4.3 PVR: 6.1 Wood units PVR:SVR: 0.15	Closure using a 18F Frey catheter and Gore-tex patch under circulatory arrest Bosentan therapy was continued	9-months post-operation Systolic PAP: 42 mm Hg Mean PAP: 29 mm Hg Qp:Qs: 1 PVR: 3.3 Wood units PVR:SVR: 0.14	35
63-year-old male	PDA	Bosentan, 62.5 mg/twice daily for 30 days then 125 mg/twice daily for 3 month prior to operation	Mean RAP: 8 mm Hg Mean PAP: 65 mm Hg	Mean RAP: 10 mm Hg Mean PAP: 55 mm Hg	Percutaneous closure with amplatzer duct occluder. Bosentan therapy continued	3-months post-operation Mean RAP: 7 mm Hg Mean PAP: 35 mm Hg	36
36-year-old female	ASD (large 20 mm)	Intravenous epoprostenol for 2.5 years prior to operation	Mean SAP: 92 mm Hg RAP: 3 mm Hg Mean PAP: 53 mm Hg Qp:Qs: 0.88 PVR: 8.8 Wood units (reducing to 4.2 Wood units with vasodilation response)	Systolic PAP: 65–80 mm Hg RAP: 3 mm Hg Mean PAP: 32 mm Hg PVR: 2.8 Wood units	Percutaneous shunt closure with continued epoprostenol therapy for 1 year and 7 months and then bosentan therapy	3 months postoperation Systolic PAP: 55–56 mm Hg	37
29-year-old female	ASD	Intravenous epoprostenol for 4 years prior to operation	PAP: 105/40 mm Hg RAP: 12 mm Hg LVP: 99/10 mm Hg CO: 6 L/min	PAP: 40–50 mm Hg Qp:Qs: 2	Closure of ASD, receiving amlodipine and warfarin since cessation of epoprostenol	6 years postoperation PAP: 45 mm Hg CO: 3.7 L/min	38
41-year-old female	ASD	Sildenafil, 25 mg/twice daily for 9 months increasing to 50 mg/twice daily for 2 years prior to operation	PAP: 87/20 mm Hg Mean PAP: 1 mm Hg Mean PAP: 55 mm Hg Qp:Qs: 0.87 PVR index: 25 Wood units × m^2 (23.7 Wood units × m^2 with vasodilation response)	PAP: 128/32 mm Hg Mean PAP: 10 mm Hg Mean PAP: 76 mm Hg Qp:Qs: 1.73 PVR index: 12.63 Wood units × m^2 (12.1 Wood units × m^2 with vasodilation response)	Partial temporary occlusion of defect with 34 mm diameter test balloon with subsequent surgical repair of the ASD. Sildenafil therapy was continued for 3 years	6 months after repair echocardiography showed mild tricuspid regurgitation with peak velocity 3.8 m/s	39
31-year-old female	Sinus venosus ASD with partial anomalous pulmonary venous drainage (PAPVD)	Bosentan 125 mg/twice daily for approximately 1 year prior to surgery	Mean PAP: 42 mm Hg PCWP: 5 mm Hg PVR: 4.06 Woodunits Pulmonary artery oxygen saturation 84% Mean PAP and PVR decreased on adenosine challenge but pulmonary artery oxygen saturation did not.	Mean PAP: 47 mm Hg (decreasing to 44 mm Hg on vasoreactivity challenge) RAP: 13 mm Hg LAP: 14 mm Hg RVP: 16 mm Hg LVP: 12 mm Hg Qp:Qs: 1.9 CO: 5.0 L/min	ASD closed and the PAPVD redirected to the left atrium with a superior vena cava baffle, with the patient foramen ovale left open as an escape route. Bosentan therapy was maintained	1 year after surgery mean PAP was 25 mm Hg	40

ASD, atrial septal defect; CO, cardiac output; LAP, left atrial pressure; LVP, left ventricular pressure; PAP, pulmonary arterial pressure; PAPVD, partial anomalous pulmonary venous drainage; PVR, pulmonary vascular resistance; PVR:SVR, pulmonary vascular resistance : systemic vascular resistance; Qp:Qs, pulmonary-to-systemic blood flow ratio.

Beghetti M et al, Congenit Heart Dis 2012;7:3-11

Surgical Treatment of an Adult Patient with Ventricular Septal Defect with Pulmonary Hypertension

Cardiac Catheterization

	Saturation		Pressure	
	Pre	Post (O2 5L/ Ventavis)	Pre	Post (O2 5L/ Ventavis)
SVC	66	67		
RA	64	72	12/6 (8)	
IVC	68	74		
RV	81	87	95/0/13	
MPA			95/35 (55)	92/33 (54)
LPA	81	89	95/30 (55)	
LV	88		95/0/14	
Ao		90	95/65 (75)	92/62 (74)
PCW			16/13 (14)	

	Pre	Post
Qp	5.49	9.87
Qs	2.81	2.32
Qp/Qs	1.95	4.25
Qeff	2.37	1.95
Q(L → R)	3.12	7.92
Q(R → L)	0.44	0.37
Q net shunt	2.68	7.55
Rp	7.46	4.05
Rs	23.84	28.42
Rp/Rs	0.31	0.14

Cardiopulmonary Function Test

- VO2 peak: 23.86 ml/kg/min (6.81 METs)
- VE/VCO2 slope: 49.3
- Age predicted aerobic capacity: 54%
- peak RER: 1.02
- 운동중단사유: dyspnea
- 운동중 & 회복기 PVC
- no ST change

Diagnosis

- VSD, perimembranous
- Tricuspid regurgitation, GIII/IV
- severe pulmonary hypertension

Operation

- Patch repair of VSD with a fenestration (8 mm)
- PFO enlargement (6 mm)
- Tricuspid annuloplasty (DeVega method)

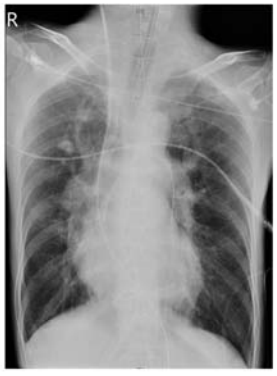
Operation

Perioperative Hemodynamics

Pressure (mmHg)	Post-induction	Post-CPB weaning	In the HICU
Systemic BP	102/64 (75)	95/46 (61)	115/63 (79)
PAP	85/39 (55)	49/28 (37)	50/30 (40)
CVP	12	7	5

Progress

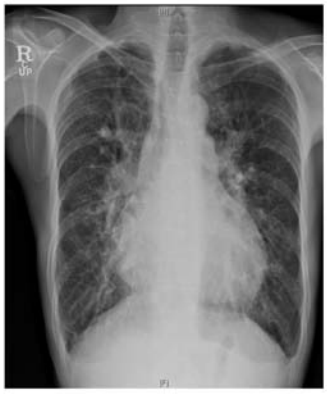
POD #1 : Extubation
POD #2 : Cardioversion due to atrial fibrillation
POD #4 : Transfer to GW
POD #20 : Discharge



Current Medication

- Digoxin 0.25 mg
- Aspirin 100 mg
- Sildenafil 10 mg *3
- Bosentan 125 mg *2
- Bisoprolol 1.25 mg *2
- Warfarin 3 mg

Last Assessment (POD #30)



- SpO2 96% in room air
- Functional class
  - NYHA II

PERIOPERATIVE MANAGEMENT

Repair of Ventricular Septal Defect with Eisenmenger Syndrome After Bosentan Treatment

Lei Hu, M.D., Lin-hua Tan, M.D., Ph.D., and Jing Ye, M.D.

Department of Surgical Intensive Care Unit, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

ABSTRACT We report a patient with ventricular septal defect (VSD) and Eisenmenger syndrome. The patient was treated with bosentan for 12 weeks, with a decrease in pulmonary vascular resistance index (PRVI) from 18.84 to 9.63 Wood unit (WU) m^2, and underwent successful corrective repair of the VSD after 12 weeks of bosentan therapy. doi: 10.1111/jocs.12325 *(J Card Surg 2014;29:401–402)*

- 10-year old female
- VSD (PM)
- NYHA class III
- SpO2 85%.
- VSD with a bidirectional shunt
- TR with peak velocity of 4.8 m/s, with an estimated systolic right ventricular pressure of 98.5 mmHg

- Discharged on diuretics and bosentan (Patheon, Inc., Toronto, Canada) 3 mg/kg, twice daily
- After 12 weeks of bosentan treatment
- She underwent surgical repair of the VSD (20X25mm) without significant perioperative problems
- Closed using a Gortex sheet with mattress sutures

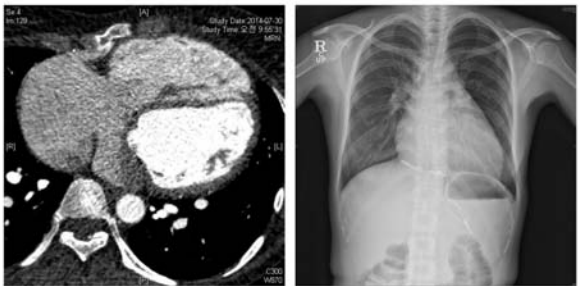
- The patient was weaned from cardiopulmonary bypass without difficulty
- PAP decreasedto 53/22 (36) mmHg while systemic arterial pressure (SAP) was 83/56(67) mmHg
- Bosentan was discontinued one month following surgery
- At one year postoperation,t he patient was in NYHA functional class I,

TABLE 1
Clinical and Hemodynamic Parameters before Operation

	Pre-Bosentan		Post-Bosentan	
	Baseline	O_2 (10 L/min)	Baseline	O_2 (10 L/min)
mPAP (mmHg)	55	53	63	51
mSAP (mmHg)	52	52	69	65
Pp/Ps ratio	1.06	1.02	0.91	0.78
Qp (L/min/m^2)	2.92	2.97	6.54	6.95
Qs (L/min/m^2)	3.65	3.70	4.61	4.58
Qp/Qs ratio	0.80	0.80	1.42	1.52
PVRi (WU·m^2)	18.84	18.83	9.63	6.34
SVRi (WU·m^2)	14.30	14.33	14.21	14.20
PVRi/SVRi ratio	1.32	1.31	0.67	0.45
SaO_2 (%)	84.9	87.5	93.7	98.8
NYHA class	III	—	II	—
6MWT	233	—	350	—

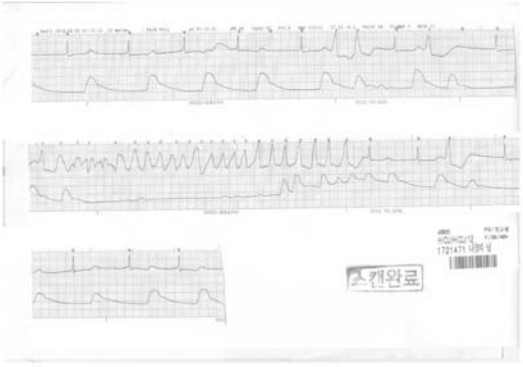
mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; Ps, systemic arterial pressure; Pp, pulmonoary arterial pressure; Qp, body surface area indexed pulmonary blood flow; Qs, body surface area indexed systemic blood flow (cardiac index); PVRi, body surface area indexed pulmonary vascular resistance; SVRi, body surface area indexed systemic vascular resistance; WU, Wood unit; SaO_2, arterial oxygen saturation; NYHA class, New York Heart Association functional class; 6MWT, 6-minute walk test.

s/p TOF repair



- 86.01.30 s/p TOF total correction / VSD patch repair/infundibulectomy / RVOT
- patch enlargement
- ASD patch repair, permanant pacemaker lead onto RV

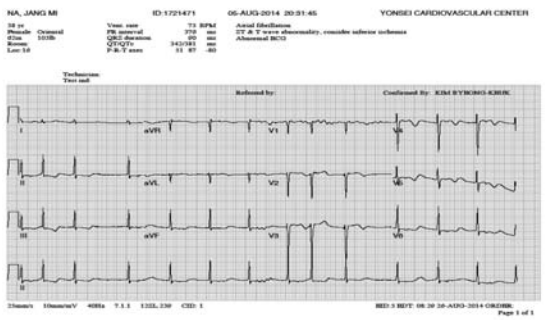
Preoperative EKG



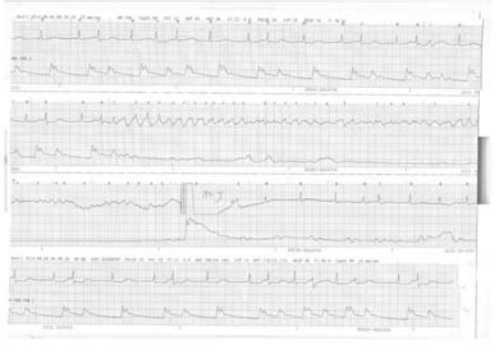
Operation

- PR, TR, LPA stenosis, Ventricular arrhythmia (ventricular tachycardia, PVC), s/p TOF total correction (1986년), bilateral SVC
- Pulmonary valve replacement (On-X 25mm), LPA angioplasty with bovine pericardium, TAP (DeVega), RVOT cryoablation

POD #O EKG



Postop. ICU EKG



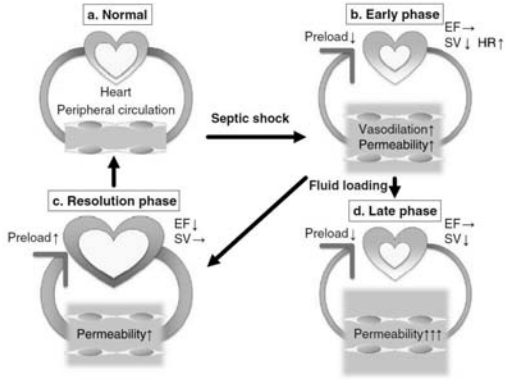
Sepsis-Induced Cardiac Dysfunction

Team Director, CNUH ECMO Team,
Department of Thoracic and Cardiovascular Surgery,
Chonnam National University Hospital

In-Seok Jeong, MD, PhD

Definition

- **General Characteristics**
  - left ventricular (LV) dilatation
  - depressed ejection fraction (EF)
  - recovery in 7–10 days



Yasuyuki Kakihana et al. *J Intensive Care 2016;4:22*

Prevalence

ORIGINAL ARTICLE

MAYO CLINIC

Clinical Spectrum, Frequency, and Significance of Myocardial Dysfunction in Severe Sepsis and Septic Shock

Juan N. Pulido, MD; Bekele Afessa, MD; Mitsuru Masaki, MD, PhD; Toshinori Yuasa, MD, PhD; Shane Gillespie, DO; Vitaly Herasevich, MD, PhD; Daniel R. Brown, MD, PhD; and Jae K. Oh, MD

Abstract

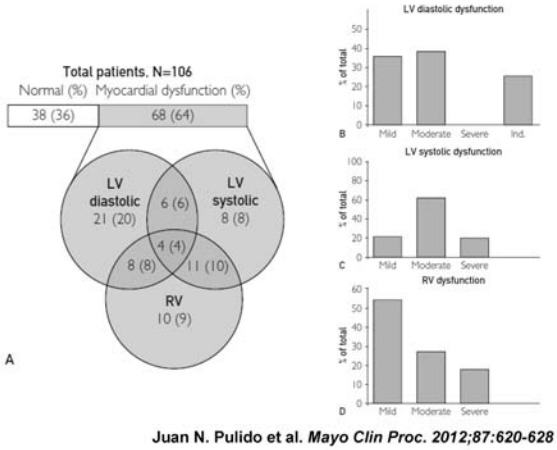
Objective. To determine the frequency and spectrum of myocardial dysfunction in patients with severe sepsis and septic shock using transthoracic echocardiography and to evaluate the impact of the myocardial dysfunction types on mortality.

Patients and Methods. A prospective study of 106 patients with severe sepsis or septic shock was conducted from August 1, 2007, to January 31, 2008. All patients underwent transthoracic echocardiography within 24 hours of admission to the intensive care unit. Myocardial dysfunction was classified as left ventricular (LV) diastolic, LV systolic, and right ventricular (RV) dysfunction. Frequency of myocardial dysfunction was calculated, and demographic, hemodynamic, and physiologic variables and mortality were compared between the myocardial dysfunction types and patients without cardiac dysfunction.

Results. The frequency of myocardial dysfunction in patients with severe sepsis or septic shock was 64% (n=68). Left ventricular diastolic dysfunction was present in 39 patients (37%), LV systolic dysfunction in 29 (27%), and RV dysfunction in 33 (31%). There was significant overlap. The 30-day and 1-year mortality rates were 36% and 57%, respectively. There was no difference in mortality between patients with normal myocardial function and those with left, right, or any ventricular dysfunction.

Conclusion. Myocardial dysfunction is frequent in patients with severe sepsis or septic shock and has a wide spectrum, including LV diastolic, LV systolic, and RV dysfunction types. Although evaluation for the presence and type of myocardial dysfunction is important for tailoring specific therapy, its presence in patients with severe sepsis and septic shock was not associated with increased 30-day or 1-year mortality.

 Mayo Clin Proc. 2012;87(7):620-628



Juan N. Pulido et al. *Mayo Clin Proc. 2012;87:620-628*

- Follow-up Echocardiogram
  - 70% : complete normalization
  - 26% : improved
  - 4% : no change

Juan N. Pulido et al. *Mayo Clin Proc. 2012;87:620-628*

Pathogenesis

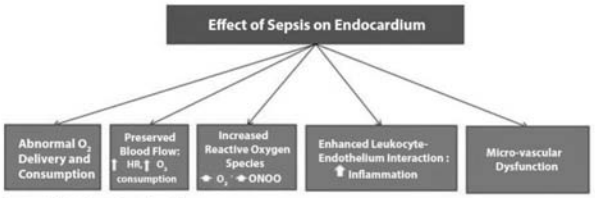


Figure 2 Effects of sepsis on endocardium.
Cardiac dysfunction in the setting of sepsis is associated with abnormal oxygen delivery and consumption, initially preserved blood flow by increasing heart rate (HR), increased formation of reactive oxygen species, altered leukocyte-endothelium interactions, and microcirculatory dysfunction. HR, Heart Rate; O2•, Superoxide; ONOO, Peroxynitrite.

Brittany A Potz, et al. *J of Intensive and Crit Care 2016;2:1*

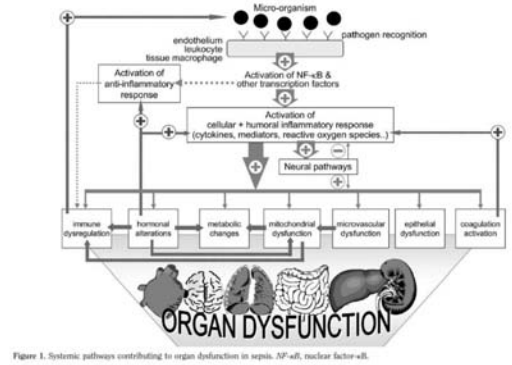
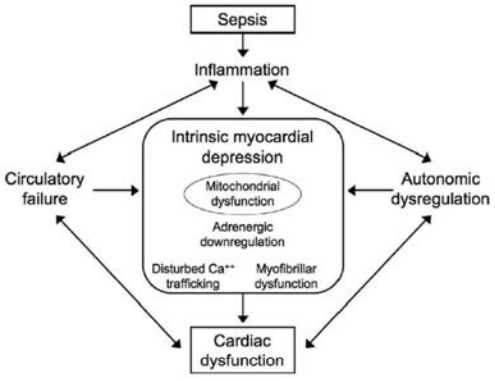


Figure 1. Systemic pathways contributing to organ dysfunction in sepsis. NF-κB, nuclear factor-κB.

Edward Abraham et al. *Crit Care Med 2007;35:2408-2416*



Alain Rudiger et al. *Crit Care Med 2007;35:1599-1608*

Novel Consideration of Septic Shock

- Recently recognized pathophysiological mechanisms
  1) Ventricular Elastance (Ees)
  2) Myocardial Depression
  3) Arterial Elastance (Ea)
  4) Ventricular-Arterial (V-A) Coupling

2016 Annual Update in Intensive Care and Emergency Medicine ; 2016: 165-172

- **V-A coupling** plays a key role in determining the altered hemodynamic state in septic shock.
- Most septic shock patients present **V-A decoupling because of alterations of Ea, Ees or both**.
- The normalization of systemic arterial pressure is one of the first targets of early-goal therapy in septic shock, but **exaggerated peripheral vasoconstriction can result in an increase of Ea and V-A decoupling in human septic shock**.

2016 Annual Update in Intensive Care and Emergency Medicine ; 2016: 165-172

Treatment

No Specific Treatment of

Septic Induced Myocardial Dysfunction

Surviving Sepsis Campaign

International Guidelines for Management of Severe Sepsis and Septic Shock: 2012
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1. Optimization of hemodynamic parameter
   - Early aggressive fluid resuscitation
   - Vasopressors and inotropic based therapy
2. Infection control
   - Broad spectrum antibiotics
   - Control of infection focus

Dellinger RP et al. *Crit Care Med 2013;41:580-637*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

CONCLUSIONS

In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days. (Funded by the Italian Medicines Agency; ALBIOS ClinicalTrials.gov number, NCT00707122.)

Research

Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE For patients in septic shock, open-label use of esmolol vs standard care was associated with reductions in heart rates to achieve target levels, without increased adverse events. The observed improvement in mortality and other secondary clinical outcomes warrants further investigation.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01231698

JAMA. 2013;310(16):1683-1691. doi:10.1001/jama.2013.278477
Published online October 9, 2013.

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Corresponding Author: Andrea Morelli, MD, Department of Anesthesiology and Intensive Care, University of Rome, "La Sapienza," Viale del Policlinico 155, Rome 00161, Italy (andrea.morelli@uniroma1.it).

DESIGN, SETTING, AND PATIENTS Open-label, randomized phase 2 study, conducted in a university hospital intensive care unit (ICU) between November 2010 and July 2012, involving patients in septic shock with a heart rate of 95/min or higher requiring high-dose norepinephrine to maintain a mean arterial pressure of 65 mm Hg or higher.

INTERVENTIONS We randomly assigned 77 patients to receive a continuous infusion of esmolol titrated to maintain heart rate between 80/min and 94/min for their ICU stay and 77 patients to standard treatment.

Ince *Critical Care* (2015) 19:339
DOI 10.1186/s13054-015-1059-6

CRITICAL CARE

COMMENTARY Open Access

To beta block or not to beta block; that is the question

Can Ince

See related research by Jacquet-Lagrèze et al., http://www.ccforum.com/content/19/1/241

Abstract

The fast-acting β-1 blocker esmolol has been the center of attention since the landmark article by Morrelli and colleagues suggesting that, in patients with sepsis, reducing heart rate by administering esmolol can result in a survival benefit. However, the use of esmolol for the treatment of sepsis and the underlying mechanism responsible for this benefit remain controversial. This commentary discusses the study by Jacquet-Lagrèze and colleagues, who in a pig model of sepsis tested the hypothesis that administration of esmolol to reduce heart rate may correct sepsis-induced sublingual and gut microcirculatory alterations which are known to be associated with adverse outcome.

why experimental investigations in animal models, which provide a deeper insight into underlying mechanisms, are helpful. If novel monitoring techniques which can be translationally applied to patients are also used, such studies are especially relevant for the introduction of new treatment modalities.

In such a study, Jacquet-Lagrèze and colleagues investigated the possible beneficial effect of the fast-acting β-1 blocker, esmolol, in improving sublingual and gut microcirculation in a porcine model of sepsis [1]. The study is opportune because, even though there is a theoretical benefit for administering a β-blocker to reduce heart rate (HR) and control the adverse effects of an adrenergic storm associated with sepsis, there is uncertainty about which precise mechanism affected by β-blockers causes a potential therapeutic benefit. Fuelled by the improved survival study in patients with sepsis by

THE LANCET Infectious Diseases

For sepsis, the drugs don't work

www.thelancet.com/infection Vol 12 February 2012

- HA-1A; Centoxin; monoclonal antibody; withdrawn 1993
- Drotrecogin alfa; Xigris; activated protein C; withdrawn 2011
- AZD9773; CytoFab; TNF-antibody; withdrawn 2012 (F IIb)
- ASEPSIS Trial; atorvastatin 40 mg; sepsis progression↓? 2012

- EUPHRATES Trial; polimyxinB HP endotoxine elim. 2013
- OASIS Trial; talactoferrin alfa; immunmodulant protein 2014

Pediatric Extracorporeal Life Support in Specialized Situations

V. Ben Sivarajan, MD, MS[1,2]; Mel C. Almodovar, MD[3,4]; Mark D. Rodefeld, MD[5]; Peter C. Laussen, MD[1,2]

TABLE 4. Summary of Extracorporeal Life Support Series for Septic Shock

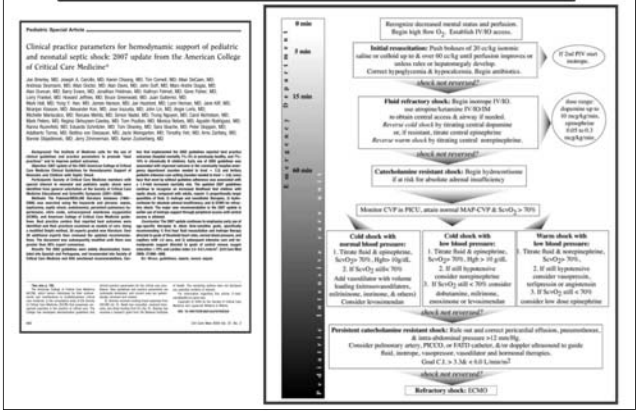
Study	Center	Years	*n*	Type(s)	Survival
Beca et al (59)[A]	Melbourne, Australia	1989–1991	9	Cx F/N VAE	5 (56%)
Goldman et al (55)[A]	Multicenter	1989–1996	12	NR	8 (67%)[a]
Hocker et al (56)	Louisville, KY	1986–1989	15	NR	13 (87%)[a]
Horton et al (60)[A]	Melbourne, Australia	1988–2007	47	Cx F/N/C VAE	22 (47%)
McCune et al (58)	Washington, DC	1984–1986	15	? N VAE	14 (93%)[a]
MacLaren et al (62)[A]	Melbourne, Australia	1988–2006	45	Cx F/N/C VAE	21 (47%)
MacLaren et al (61)[A]	Melbourne, Australia	2000–2009	23	Cx C VAE	17 (74%)

Recommendations and quality of evidence for VA ECMO in septic shock: Class IIa, Level C.

Sivarajan VB et al. *Pediatr Crit Care Med 2013;14;s51-s61*

Pediatric and Neonatal Sepsis Update

Joe Brierly et al. *Crit Care Med 2009;37:666-688.*



Surviving Sepsis Campaign

International Guidelines for Management of Severe Sepsis and Septic Shock: 2012
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Steven Webb
Richard J. Beale
Jean-Louis Vincent
Rui Moreno
The Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup*

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

E. Extracorporeal Membrane Oxygenation

1. We suggest ECMO in children with refractory septic shock or with refractory respiratory failure associated with sepsis (grade 2C).

Conclusion (1)

- The mortality rate of patients with sepsis induced cardiac dysfunction.
- The Surviving Sepsis Campaign guidelines recommend early-goal directed therapy with fluid administration, vasopressors and inotropes to resuscitate these patients with severe hypotension and metabolic disturbances due to organ hypoperfusion.

Conclusion (2)

- Understanding of the complex mechanism lead to potential novel therapeutic targets.
- V-A decoupling is one of the most important features of the hemodynamic impairment in human septic shock and sepsis induced cardiac dysfunction.
- Novel drugs and mechanical circulatory support still have not brought break through.

Thanks

Please send your feedback to:

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