

Fluid management in critically ill patients

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Case presentation

A 60-year-man was admitted to an emergency room with pneumonia, sepsis and hypotension. There was a previous history of COPD and IHD. He received 2.5 liters of Ringer Lactate and broad spectrum antibiotics. Mechanical ventilation was started because of severe hypoxia and confusion. Several hours later, he was transferred to the ICU. The body weight was 75 kg. The ICU findings included the followings:

- T: 39° C, HR:110, BP: 80/50 mmHg
- Physical exam: 2+ peripheral edema
- CVP:14 mmHg
- Mechanical Ventilation Mode: SIMV (Intermittent spontaneous breathing)
- Tidal volume: 400 mL
- O₂ saturation: 97%
- ECG: Frequent PVC (No finding in favour of acute ischemia)
- Cardiac Ejection Fraction: 40%
- WBC: 20,000 /μL, BUN: 65 mg/dL, Cr: 1.1 mg/dL, Na: 138 mEq/L, K: 3.8 mEq/dl
- Lactate: 6.2 mmol/L



Should we give him more fluid?

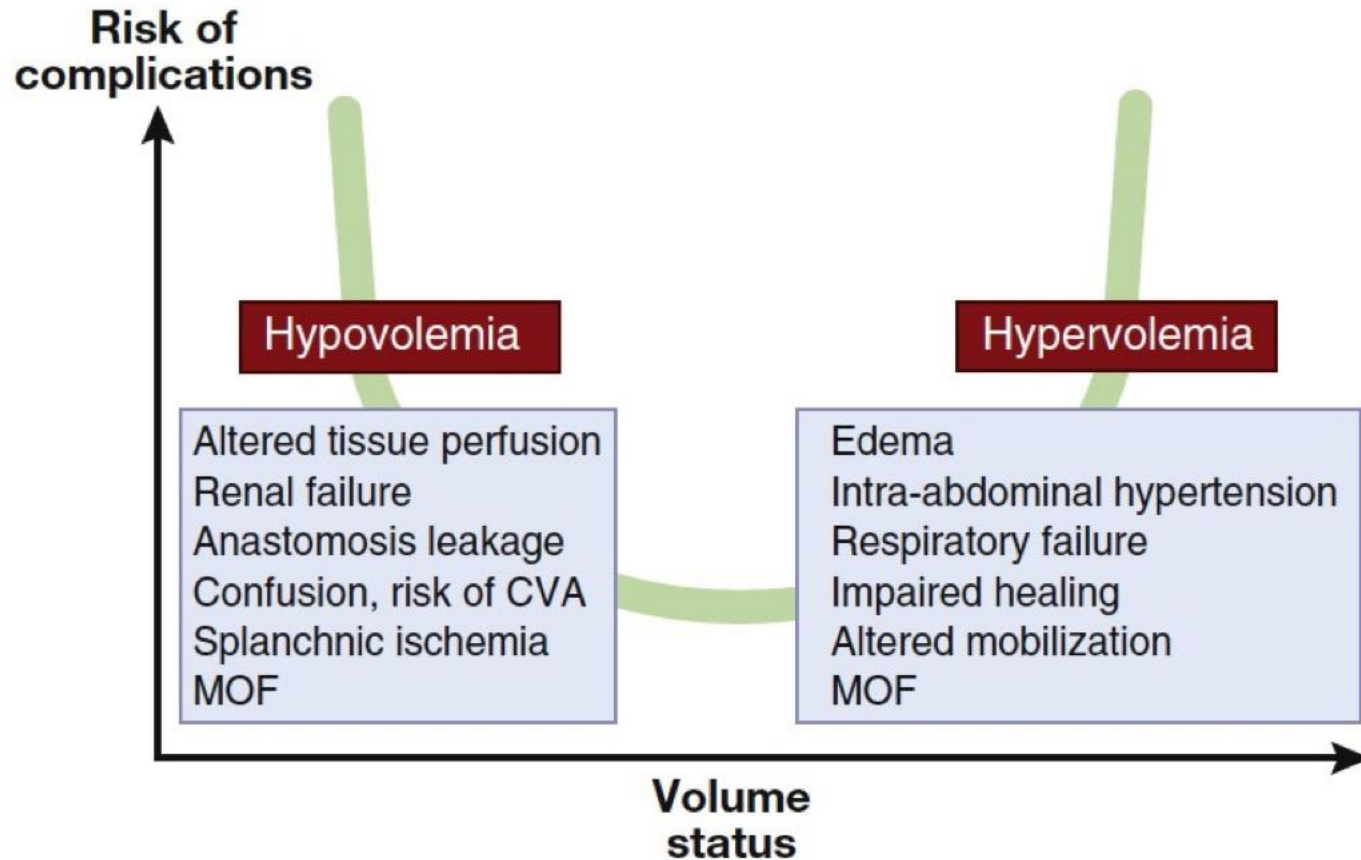
Findings indicating that volume administration may be helpful:

- The presence of sepsis
- Tachycardia
- Elevated lactate
- Hypotension
- High BUN to Cr ratio

Findings indicating that more fluid administration may be harmful:

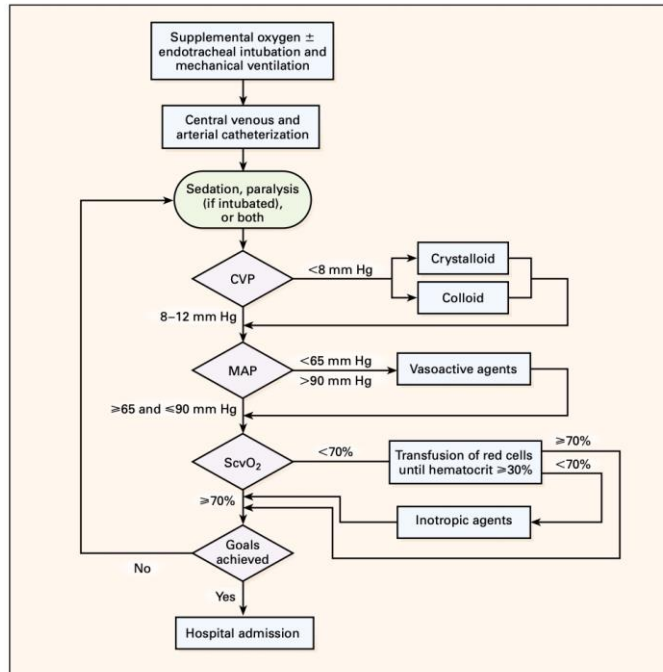
- Peripheral edema
- CVP:14 mmHg
- Already receiving 2.5 L of intravenous fluids
- Cardiac history





EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S.,
ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, Ph.D., AND MICHAEL TOMLANOVICH, M.D.,
FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*



vs. 65.3 ± 11.4 percent), a lower lactate concentration (3.0 ± 4.4 vs. 3.9 ± 4.4 mmol per liter), a lower base deficit (2.0 ± 6.6 vs. 5.1 ± 6.7 mmol per liter), and a higher

THE systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock.¹ Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock.² Administering fluids, vasopressors, and inotropics

Early goal directed therapy (EGDT) resulted in 16% absolute reduction in mortality

afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand.² End points used to confirm the achievement of such a balance (hereafter called resuscitation end points) include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH.⁸ Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy.⁹ In cases in which the insertion of a pulmonary-artery catheter is impractical, venous

Three large recent trials including; PROMISE, ARISE, and PROCESS did not show any survival benefit with EGDT compared to usual therapy in patients with sepsis. However, the patients of these three trials were less severely ill than those in the original EGDT Trial, and the volume of fluid was more similar between study arms.

Studies showing the effect of fluid accumulation on outcomes

First author	Patients	Population	Study design	Intervention	Significant results
Simmons, 1987	113	ARDS	prospective cohort	none	higher cumulative fluid balance and weight gain associated with increased mortality
Schuller, 1991	89	pulmonary edema	retrospective cohort	none	higher fluid balance associated with increased mortality, length of hospitalization and days on mechanical ventilation
Goldstein, 2001	21	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Brandstrup, 2003 [3]	172	elective colorectal surgery	randomized controlled trial	restrictive vs. standard perioperative fluid strategy	restrictive strategy reduced cardiopulmonary and tissue-healing complications
Foland, 2004	113	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Gillespie, 2004	77	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Michael, 2004	26	pediatric AKI	retrospective interventional	percentage of fluid overload <10%	100% of survivors vs. 40% of nonsurvivors had a percentage of fluid <10%
Goldstein, 2005	116	pediatric AKI	prospective cohort	none	higher fluid balance associated with mortality
Sakr, 2005	393	ALI/ARDS	prospective cohort	none	higher fluid balance associated with mortality
Uchino, 2006	331	critically ill	prospective	none	higher fluid balance associated with mortality
Wiedemann, 2006	1,000	ARDS	randomized controlled trial	conservative vs. liberal fluid strategy	conservative strategy improved lung function and shortened the duration of mechanical ventilation
Payen, 2008	1,120	critically ill	prospective cohort	none	higher fluid balance associated with mortality
Bouchard, 2009	618	AKI	prospective cohort	none	higher fluid balance associated with mortality and possibly reduced renal recovery



Fluid responsiveness and fluid overload in critically ill patients

- Hypotension in less than 50% of critically ill patients will respond to initial fluid administration.
- In patients with severe sepsis or septic shock, this proportion may be even lower.
- Continuing fluid administration to non-responders to the fluid administration may lead to the development of volume overload.
- Some studies have reported a prevalence of 62 to 64.8% for hypervolemia in critically ill patients.
- Volume overload is associated with an increased rate of mortality in these patients.



Phases of fluid resuscitation (The ROSE model)

Rescue

Optimization

Stabilization

De-escalation

Goals

Life-saving

Organ rescue

Organ Support

Organ Recovery

Phenotype

Severe Shock

Unstable

Stable

Recovering

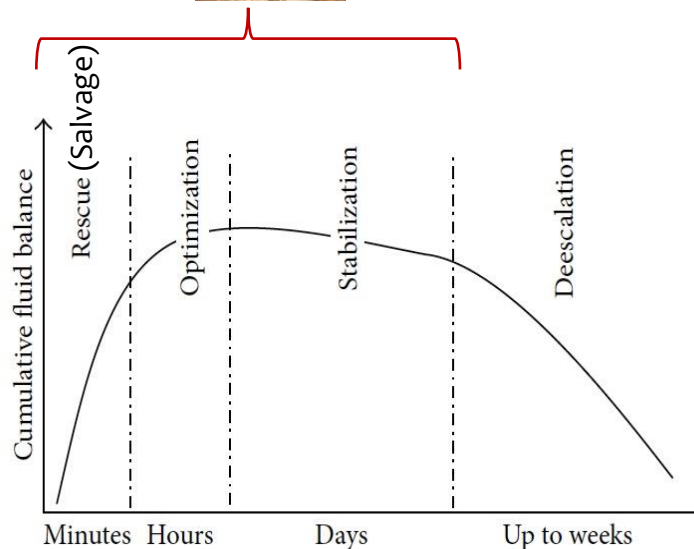
Fluid Therapy

Fluid Boluses

Fluid challenges

Neutral balance

Fluid removal



Surviving Sepsis Campaign (SSC): International Guidelines for Management of Sepsis and Septic Shock: 2016

A. INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS).
2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).
3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).



SPECIAL EDITORIAL



The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy^{1*}, Laura E. Evans² and Andrew Rhodes³

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate $\geq$ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq$ 65 mm Hg	Strong recommendation, moderate quality of evidence



Back to patient

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Volume overload?
volume depletion ?



What is the best blood pressure target in this patient?

- Our current data suggest that in the majority of patients a goal MAP of 65 mmHg is sufficient.
- In patients with baseline hypertension or severe atherosclerosis, a higher MAP goal of 80-85 mmHg may result in better renal outcomes.
- In younger patients or patients with cirrhosis, MAP goal can be lower than 65 mmHg.
- In this patient MAP is 60 mmHg.



What is the appropriate next step?

- In this patient, vasopressors/inotropes should be started immediately.
- Based on a retrospective cohort study, every one hour delay in the vasopressor initiation during the first 6 hours after the start of septic shock was associated with an increase of 5.3% in mortality.

Selection of the vasopressors:

- Norepinephrine is the vasopressor of choice in patients with septic shock.
- A second vasopressor typically is added when norepinephrine doses exceed 30-40µg/min.
- Epinephrine or low-dose vasopressin can be used as the second vasopressor.
- Epinephrine is a better choice because it is a combined vasopressor/inotrope.
- Dopamine is not recommended as initial therapy because of its association with arrhythmia.
- Dopamine may be recommended in patients with septic shock and bradycardia.



Do this patient need more fluids?

- The patient has already been resuscitated with more than 30cc/kg of intravenous fluids. But the mean arterial pressure is still 60 mmHg.
- Based on the time-dependent clinical phases of fluid treatment, this patient is in the optimization phase.
- In the optimization phase, patients with clear signs of volume depletion should immediately receive fluids. For other patients, fluid responsiveness should be evaluated before fluid administration.
- Tachycardia of this patient may result from fever or sepsis rather than a consequence of volume depletion.
- Edema and intravascular volume depletion can coexist in critically ill patients.
- In this patient, fluid responsiveness should be evaluated before administration of more fluids.

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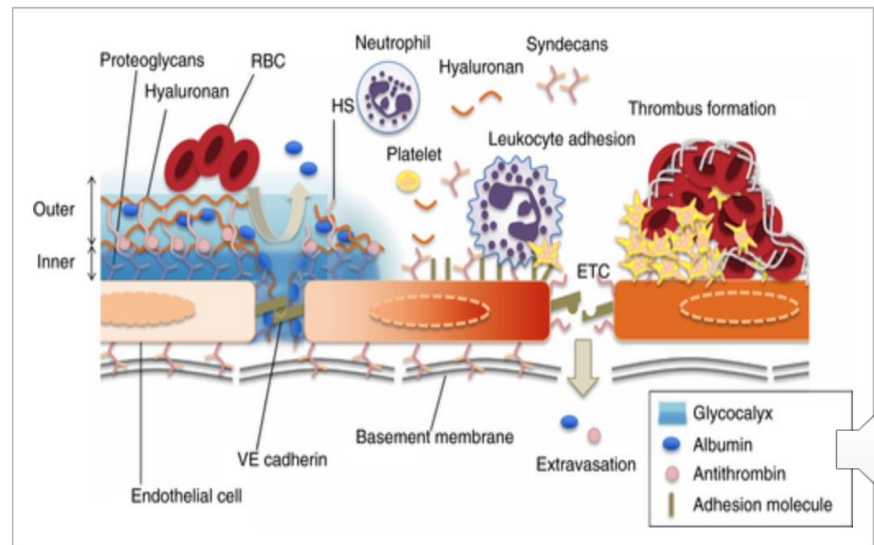
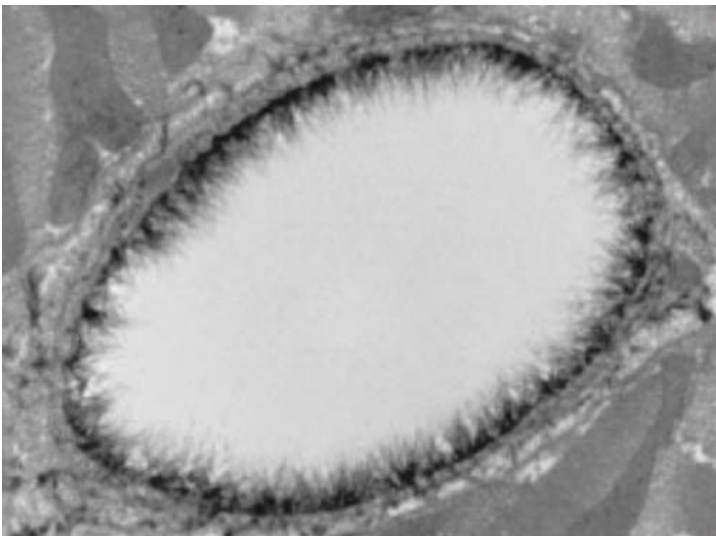
The reasons for peripheral edema in critically ill patients

- Right and left ventricular failure
- Impaired lymphatic drainage due to decreased muscular activity
- Decreased oncotic pressure resulted from receiving large volume of intravenous fluids
- Sodium retention by the kidneys due to hypo-perfusion
- Ventilator induced positive fluid balance
- Fluid leak as a result of endothelial dysfunction

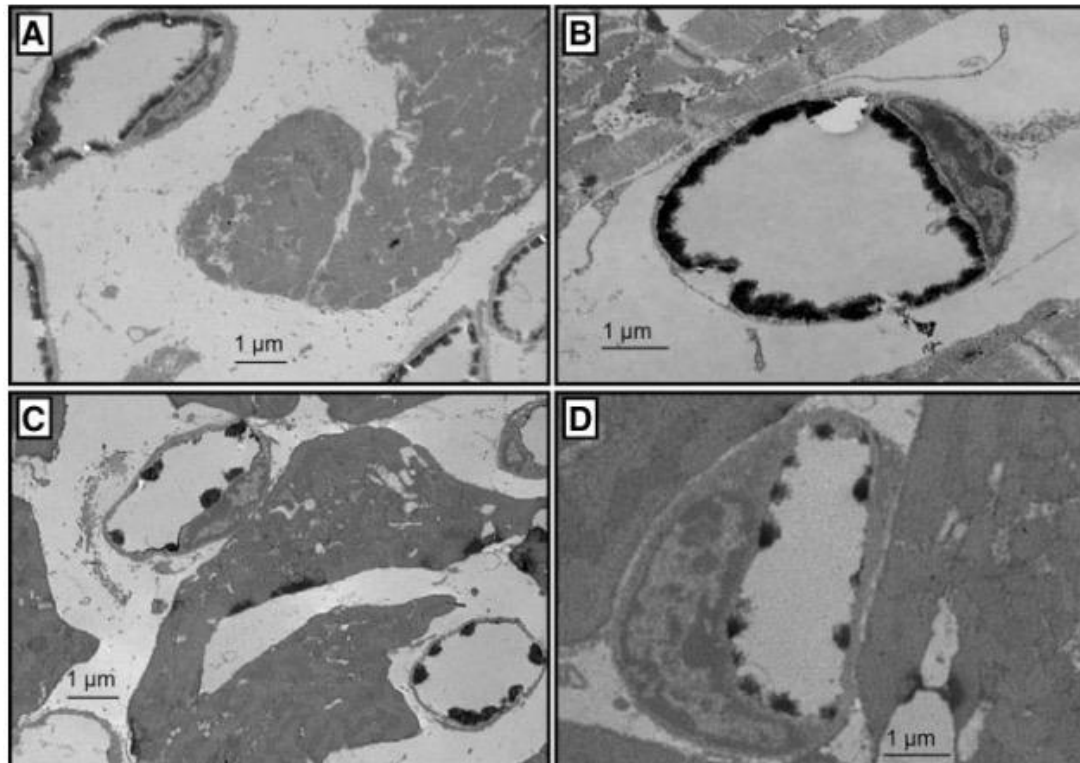


The protective role of endothelial glycocalyx

- The endothelial glycocalyx is a network of glycoproteins and proteoglycans covering endothelium.
- An intact glycocalyx is required for the vascular barrier to function properly.
- It prevent leukocyte activation and platelet aggregation and retain plasma proteins and fluids from moving across the endothelium.
- In sepsis and multi-organ failure glycocalyx shedding increases vascular permeability and contributes to fluid leak and activation of immune cascade.



Natriuretic peptides lead to the **shedding of glycocalyx** through the cleavage of the membrane-bound proteoglycans, mainly syndecan-1 and hyaluronic acid.



Electron microscopy of isolated Guinea pig hearts
A and B: infusion of HES (hydroxy ethyl starch)
C and D: infusion of HES and ANP



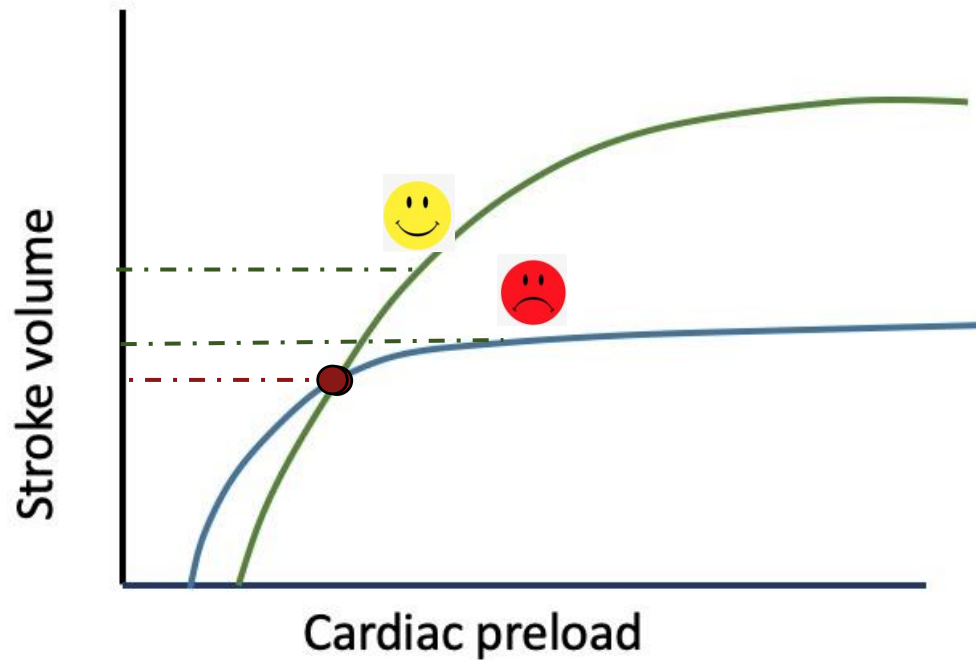
CVP can change with the following factors:

- **Intravascular volume**
- **Right ventricular compliance**
- **Isolated left sided heart disease**
- **Valvular heart diseases**
- **Pulmonary vascular disease**
- **Changes in intra-thoracic pressure**
- **Tense ascites**
- **Peripheral venous tones**

The result of a meta-analysis showed that only in 56% of critically ill patients, CVP can predict fluid responsiveness. Only extremely low values of filling pressure (<5 mmHg in CVP, and <7mmHg in PAOP) can predict fluid responsiveness.



Static tests vs. Dynamic tests in detection of fluid responsiveness



- **Static tests** like CVP can show only one point in Frank Starling curve, and had low sensitivity and specificity in evaluation of fluid responsibility.
- **Dynamic tests** are more accurate to detect fluid responsiveness. In these tests we use methods to increase preload and evaluate stroke volume variation to know the position of the patients in frank starling curve.

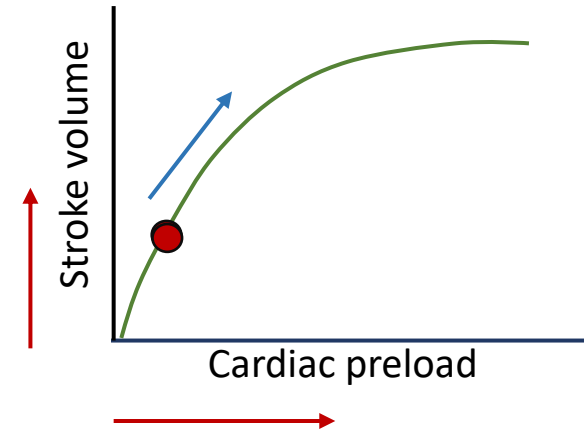
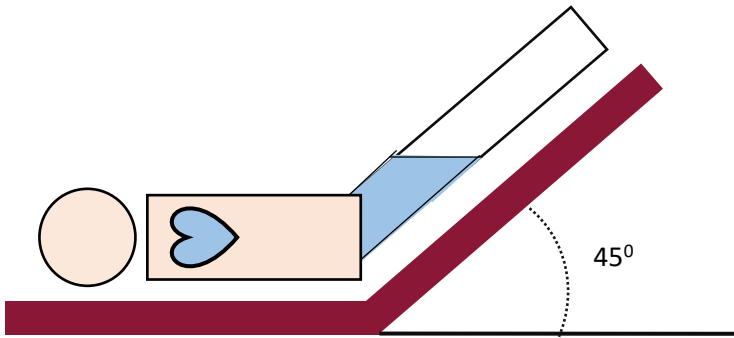
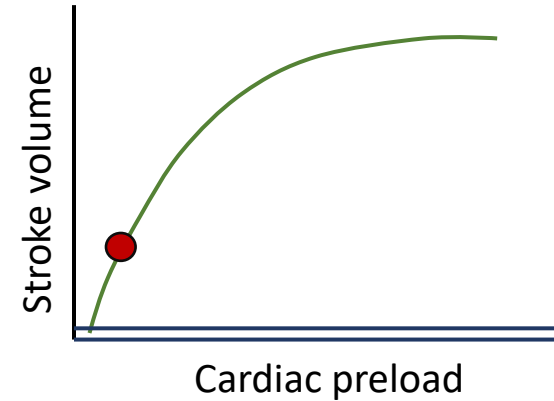
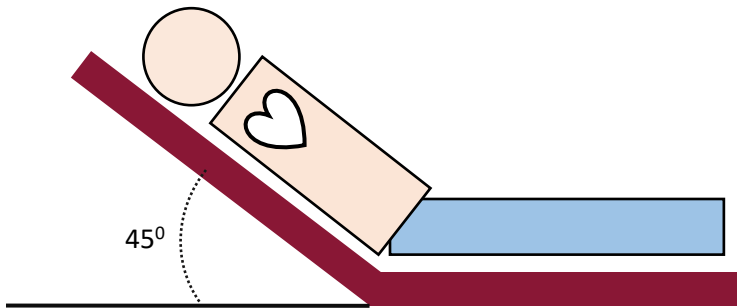


Fluid Bolus vs. Fluid Challenge

- **Fluid boluses:** The infusion of **20 cc/kg** (at least **250 to 500 mL**) of IV crystalloids, given as boluses **over a maximum of 15 minutes**.
- **Fluid challenge:** The infusion of **250 cc or 3mL/kg** of intravenous fluids **over 5 to 10 minutes**. A **10 to 15% increase** in cardiac output or **stroke volume 10 to 15 minutes** after the infusion is considered as a positive response.
- **Mini Fluid Challenge:** Administration of 100 cc over 1 minutes and evaluating for the response.



Passive leg raising test



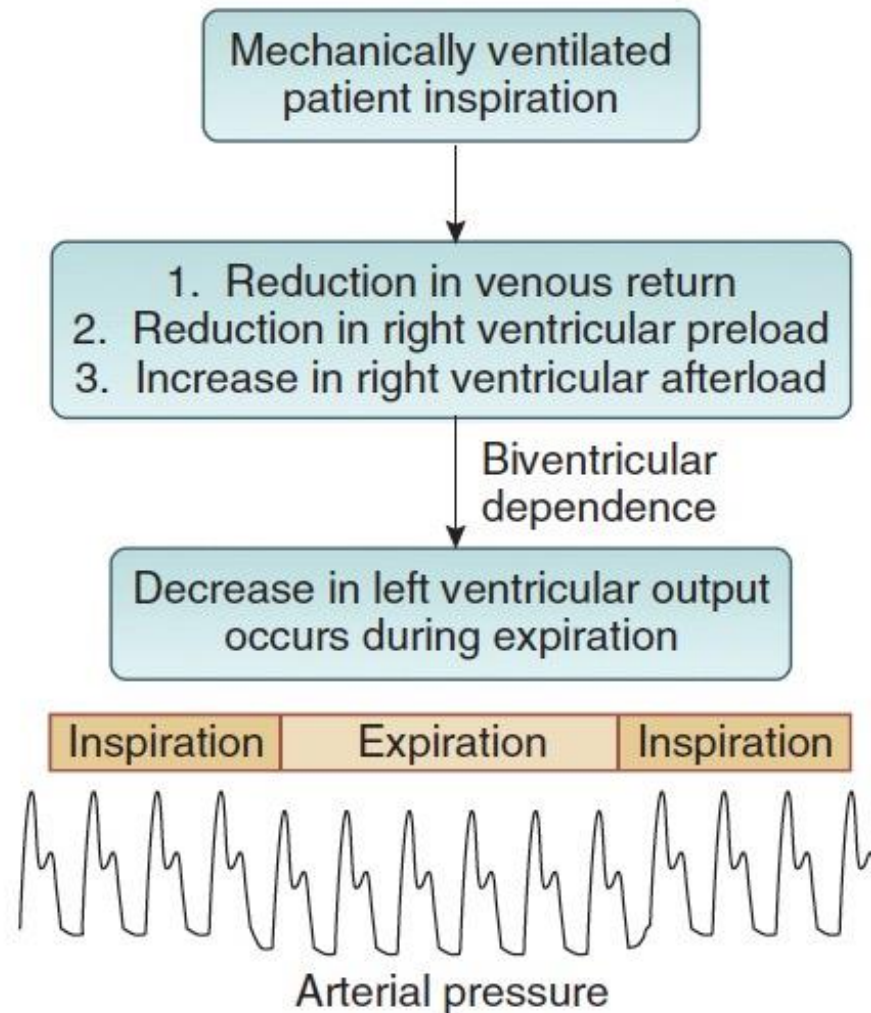
- The maneuver transfers about 300 cc of blood from the limbs and abdomen to the thorax.
- Stroke volume should be measured between 30 to 90 seconds after leg raising. Its maximal effects occur within 1 minute.
- Having an increase of 10% in stroke volume is considered as a positive response to fluid administration. (86% sensitive and 90% specific)



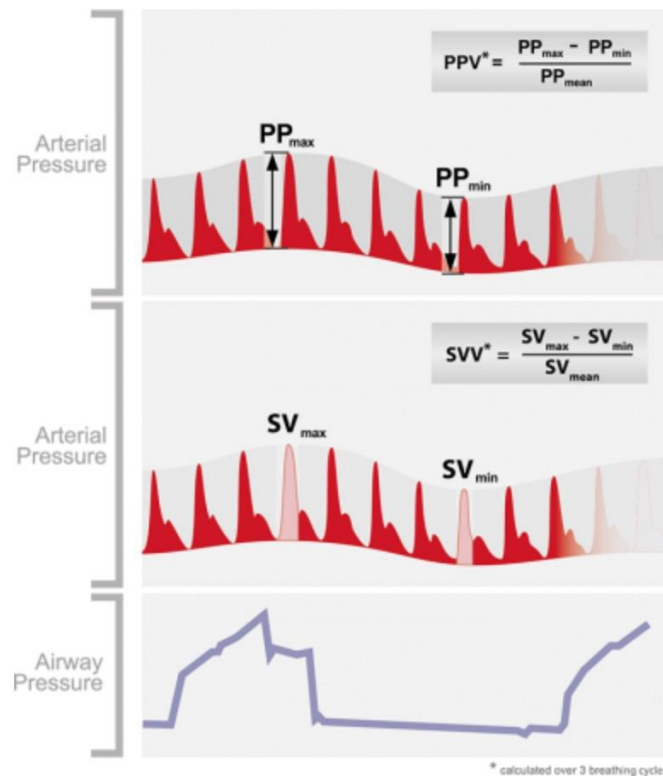
Passive leg raising test

- **Change of blood pressure is not a reliable sign of fluid responsiveness. (39% sensitivity for a rise of 17%)**
- **The test efficacy decreases in patients with extreme hypovolemia, cardiogenic shock or intraabdominal hypertension.**
- **It is contraindicated in patients with increased intracranial pressure.**





Pulse Pressure Variation (PPV) and Stroke Volume Variation (SVV)



Multiple studies has proven that $SVV > 10\%$ and $PPV > 13\%$ have high sensitivity and specificity in prediction of volume responsiveness.

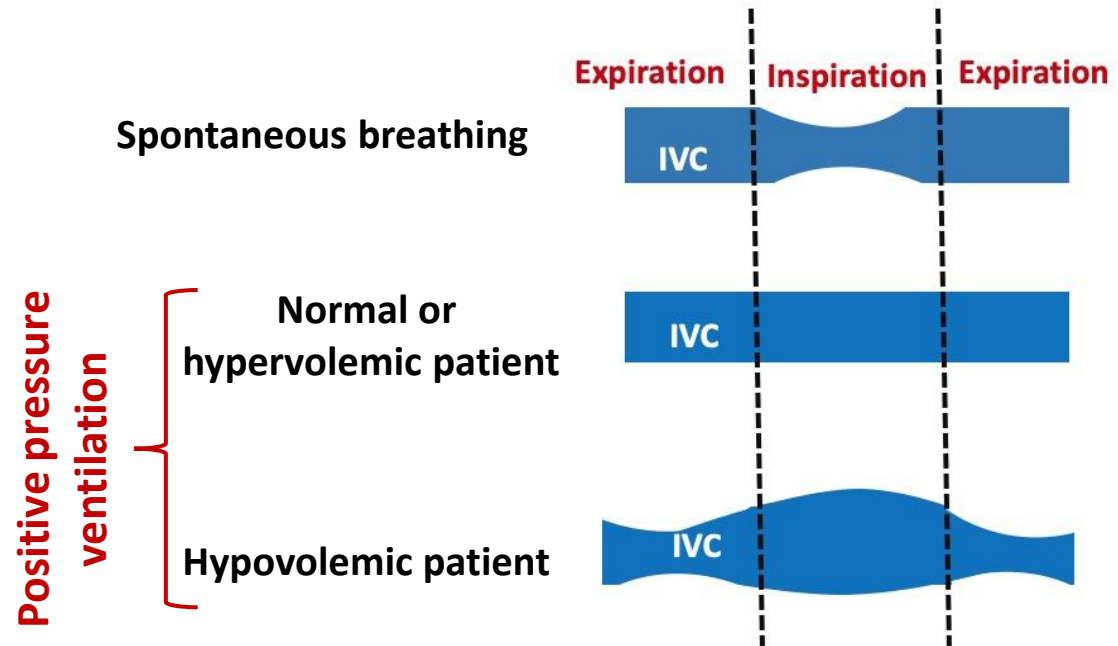
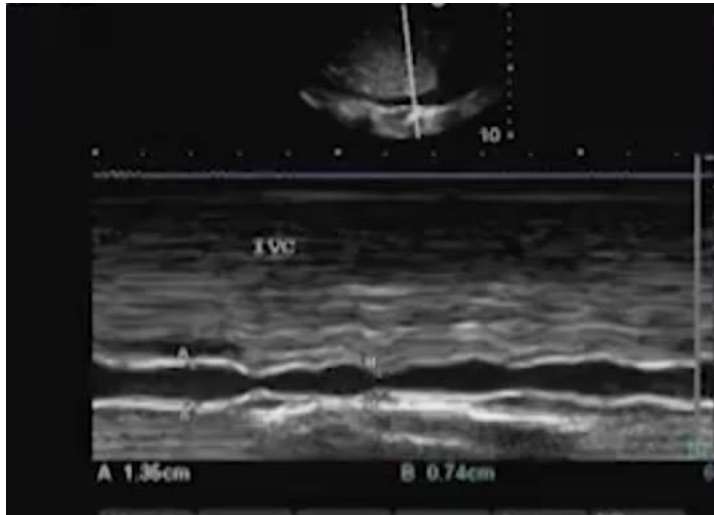


Requirements for use of pulse pressure variation stroke volume variation to assess fluid responsiveness

- Mechanical ventilation
 - Relatively large tidal volume
 - No spontaneous breathing activity
 - No major arrhythmia
 - No significant tachypnea
 - No right ventricular failure
 - No intra-abdominal hypertension
-



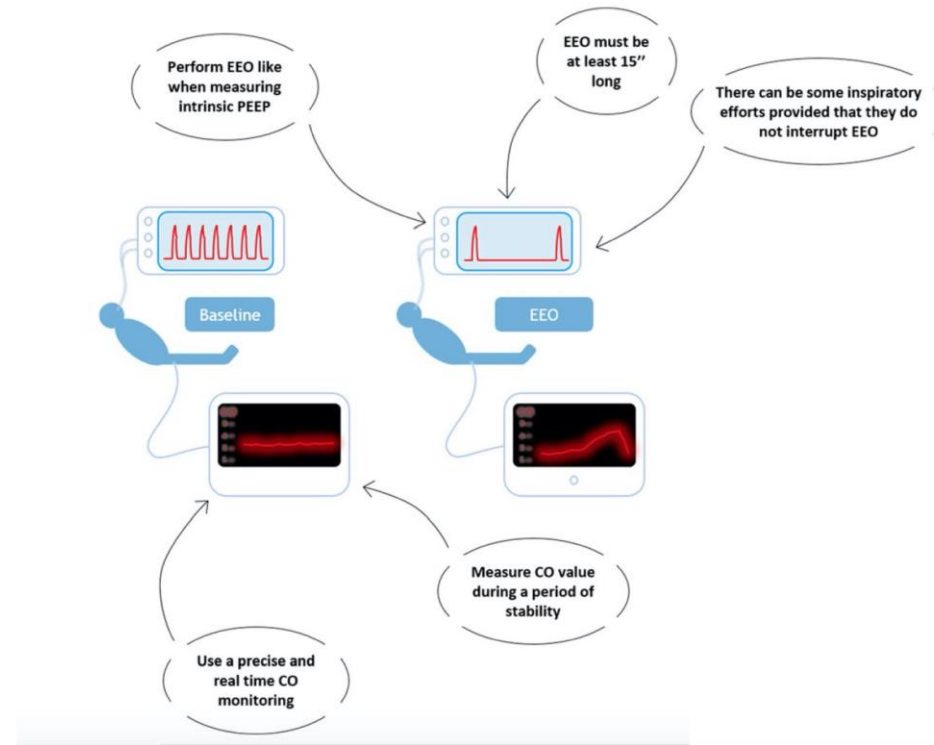
Respiratory changes of Inferior Vena Cava (IVC) diameter as an index of fluid responsiveness



A threshold of 18 % for the collapsibility index of the IVC can indicate fluid responsiveness with a sensitivity of 90% and specificity of 90%.



End Expiratory Occlusion (EEO)

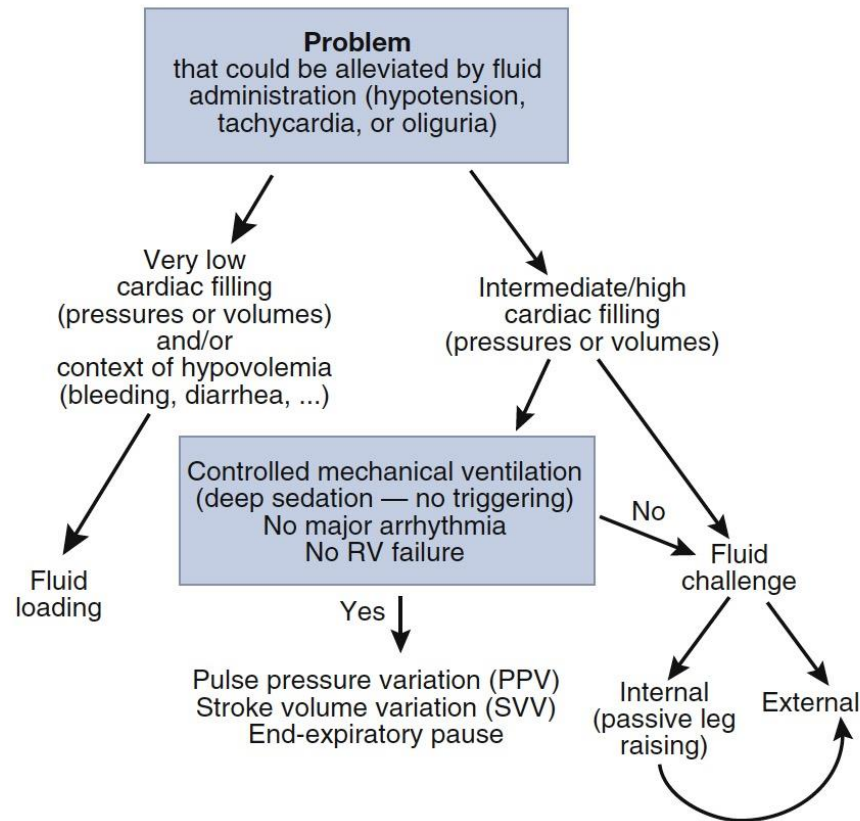


- An increase in intra-thoracic pressure during mechanical ventilation reduce venous return and SV. So, a short EEO may prevent the cyclic impediment in cardiac preload and increase venous return and SV.
- If cardiac output increases by more than 5% during a 15 second EEO test, volume responsiveness could be predicted with a good reliability.
- This test is reliable in patients with arrhythmia and spontaneous breathing.



a simple algorithm for fluid administration in critically ill patients

Optimization phase

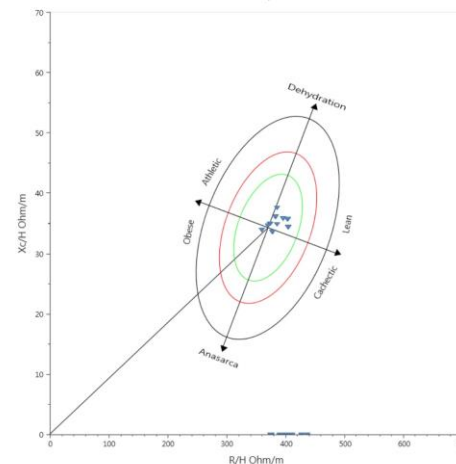
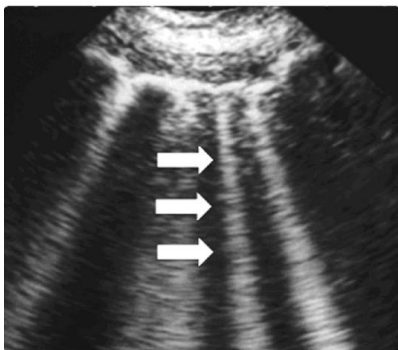


- As healthy persons are fluid responsive, a positive fluid responsive does not mean that the patient needs fluid.
- Whether using dynamic assessment for fluid responsiveness affects patients outcomes is unknown.



How to evaluate fluid overload in critically ill patients

- Fluid overload is defined by some studies as cumulative fluid balance (CFB) over initial body weight above 10% and has been associated with adverse outcome.
- It has been shown that body weights measured by electronic weighting beds and fluid balance using in-out chart are not accurate to detect fluid overload.
- The optimal approach to quantify fluid overload has not been determined.
- Recently, the modern bioelectrical impedance analysis (BIVA) methods and lung sonography has been suggested as more accurate methods in detection of fluid overload.



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Which tests are valuable in the prediction of fluid responsiveness in this patient?



Which tests are valuable in the prediction of fluid responsiveness in this patient?

- The use of mechanical ventilation makes the applying pulmonary lung interaction in the prediction of fluid responsiveness possible in this patient.
- However, the existence of spontaneous breathing, low tidal volume make the SVV , PPV and the respiratory variation of IVC inaccurate.
- SVV and PPV tests are not accurate in the presence of arrhythmia.
- Fluid challenge test and passive leg raising can be valuable for the prediction of fluid responsiveness in this patient.



In many ICU patients advanced fluid assessment techniques are not available. In these patients, the following approach for fluid challenge is applied:

- **About 250 cc of colloids or crystalloids is administered over 10 minutes with careful monitoring of efficacy and safety.**
- **Efficacy is monitored by improvement in heart rate, blood pressure, urine output and mental status.**
- **Safety is monitored by development of pulmonary edema.**
- **For patients who respond clinically, this process may be repeated.**

The results of an international study has shown that static measures are used in 36% and dynamic measures in 22% of patients.



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Balanced crystalloids

<i>Fluid Composition</i>	<i>Normal Saline</i>	<i>Ringer's Lactate</i>	<i>Plasmalyte</i>
Na (mEq/L	154	130	140
Cl (mEq/L	154	109	98
K (mEq/L	-	4	5
Ca (mEq/L	-	2.7	-
Mg (mEq/L	-	-	3
Buffer (mEq/L	-	Lactate 28	Gluconate 23 Acetate 27
PH	5	6.5	7.4
Osmolarity(mOsmol/L)	308	280	294
SID	0	28	50



The problems with high chloride content of isotonic saline in critically ill patients

- Hyperchloremic acidosis
- Renal afferent vasoconstriction
- Altered renal function
- Secretion of inflammatory cytokines
- GI dysfunction



ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Isotonic Solutions and Major Adverse Renal Events Trial (SMART trial)

Outcome	Balanced Crystalloids (N = 7942)	Saline (N = 7860)	Adjusted Odds Ratio (95% CI) [†]	P Value [‡]
Primary outcome				
Major adverse kidney event within 30 days — no. (%) [‡]	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%) [§]	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level $\geq 200\%$ of baseline — no./total no. (%) [§]	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		
Secondary outcomes				
In-hospital death — no. (%)				
Before ICU discharge	528 (6.6)	572 (7.3)	0.89 (0.78 to 1.02)	0.08
Before 60 days	928 (11.7)	975 (12.4)	0.92 (0.83 to 1.02)	0.13
ICU-free days [¶]				0.94
Median	25.3	25.3	1.00 (0.89 to 1.13)	
Interquartile range	22.1 to 26.6	22.2 to 26.6		
Mean	21.8 $\pm$ 8.3	21.7 $\pm$ 8.6		
Ventilator-free days [¶]			1.06 (0.97 to 1.16)	0.22
Median	28.0	28.0		
Interquartile range	26.0 to 28.0	26.0 to 28.0		
Mean	24.2 $\pm$ 8.6	23.9 $\pm$ 8.9		
Vasopressor-free days [¶]			1.05 (0.97 to 1.14)	0.26
Median	28.0	28.0		
Interquartile range	27.0 to 28.0	27.0 to 28.0		
Mean	24.7 $\pm$ 8.5	24.4 $\pm$ 8.8		
Renal-replacement therapy–free days [¶]			1.11 (1.02 to 1.20)	0.01
Median	28.0	28.0		
Interquartile range	28.0 to 28.0	28.0 to 28.0		
Mean	25.0 $\pm$ 8.6	24.8 $\pm$ 8.9		
Secondary renal outcomes[§]				
Stage 2 or higher AKI developing after enrollment — no./total no. (%)	807/7558 (10.7)	858/7458 (11.5)	0.91 (0.82 to 1.01)	0.09
Creatinine — mg/dl ^{**}				
Highest before discharge or day 30			1.01 (0.97 to 1.05)	0.58
Median	0.99	0.99		
Interquartile range	0.78 to 1.53	0.78 to 1.52		
Change from baseline to highest value			0.98 (0.94 to 1.02)	0.35
Median	0.04	0.04		
Interquartile range	–0.08 to 0.31	–0.08 to 0.32		



Is Ringer Lactate a suitable solution in this patient?

- As the availability and cost of saline and balanced crystalloids are not significantly different, saline should probably no longer be used for intravascular volume expansion especially in those who need large volumes.
- Ringer lactate will increase measured serum lactate, but this does not lead to a deleterious effect on the patient outcome. This lactate content in Ringer Lactate is sodium lactate rather than lactic acid.
- If the hemodynamic condition does not respond to crystalloids, colloids can be recommended.
- Albumin as a natural colloid solution with antioxidant and immunomodulatory function can be used in this patient as the second choice with a possible effect in decreasing mortality.
- Since 2013, the European Medicine Agency recommended that HES should not be used in critically ill patients due to the lack of supportive evidence and some safety concern, like the risk of kidney injury and death.



Future Directions

- In critically ill patients, hemodynamic stabilization is not always associated with improvement in microcirculatory parameters.
- Dark-field microscopy, is a new bedside technique that allows direct observation of sublingual microcirculatory perfusion in real time.
- The relationship between macro- and microcirculation in response to fluid challenge should be evaluated in future studies.



Summary

- Even though fluid management seems simple, it is a very complex and challenging issue. While it is a life-saving therapy, inappropriate fluid administration can be very harmful.
- About half of critically ill patients and even a lower proportion of septic patients will respond to fluid administration.
- Fluid therapy in critically ill patients is a dynamic process that should be guided by the frequent assessment of fluid status.
- As fluid overload is associated with worse outcomes, clinicians should target a neutral and then a negative fluid balance in the last phases of fluid administration.
- The type and the dosage of intravenous fluid should be individualized based on the underlying disease, hemodynamic situation and laboratory findings.
- The optimal type, volume, and endpoints of fluid therapy in critical illness remain unclear.



