OBJECTIVES

- Understand current theory of the pathophysiology in sepsis
- Understand the significance of EARLY treatment of severe sepsis and septic shock
- Know the components of early goal directed therapy and what they are meant to accomplish in the resuscitation of septic patients
- Understand the limitations of CVP
- Understand the alternatives to CVP in the treatment of sepsis and their limitations/barriers to implementation in your hospital
**BASIC SEPSIS PATHOPHYSIOLOGY**

- **Sepsis** is when an organism invades the body and the body responds with an inflammatory response
  - Traditionally, the inflammatory response was defined by having at least 2 of 4 systemic inflammatory response syndrome (SIRS) criteria
    - HR > 90
    - RR > 20 or PaCO2 < 32 mmHg
    - Temperature > 38 or < 36
    - WBC > 12, < 4, or > 10% bands
  - Other criteria are often used as well to define a systemic inflammatory response

- Sepsis with organ dysfunction is defined as “**severe sepsis**”
- Sepsis with serum lactate > 4 or hypotension after adequate fluid resuscitation is defined as “**septic shock**”
BASIC SEPSIS PATHOPHYSIOLOGY

- It is important to understand that sepsis is a dynamic disease that exists along a continuum of severity.
- Definitions such as severe sepsis and septic shock are arbitrary.
- Sepsis may progress or resolve over time, and it is often difficult to predict which way a patient is heading.
  - Patients therefore must be closely followed once they have been found to be septic.
What happens in sepsis?

- An organism invades the body
- The body recognizes the organism as a threat and initiates an inflammatory reaction to clear the infection
  - Inflammation also damages the body’s tissues
  - Inflammation is intricately tied to coagulation cascades
  - Inflammation has effects on cardiac function and vascular function
- The inflammatory reaction is counter balanced by an anti-inflammatory reaction
  - Anti-inflammatory reactions leave the body susceptible to new or worsening infections
What happens in sepsis?

- The septic state increases the body’s metabolic demands (oxygen consumption).
- The septic state can increase or decrease the cardiovascular system’s ability to pump blood and deliver oxygen to the tissues.
- When tissue becomes hypoxic:
  - Inflammation is activated (and also a reactive anti-inflammation reaction).
  - Coagulation is activated (and anti-coagulation reactions are activated).
  - Mitochondria lose the ability to utilize oxygen.
- Hypoxic tissue eventually dies.
  - Multi-organ dysfunction (MODS).
- Eventually an irreversible spiral ensues and death is the result.
BASIC SEPSIS PATHOPHYSIOLOGY

How do we treat sepsis?

1) Eradicate the infectious organism
   - Simple: Give the right antibiotic (broad spectrum to get it right the first time)

2) Treat the dysfunctional pro-inflammatory/anti-inflammatory system
   - Difficult: We don’t really know how
   - Multiple drugs and therapies have failed to improve outcomes in sepsis
   - Efforts to optimize perfusion have often failed when studied (“goal directed therapies”)
   - In fact, LATE correction of cardiac function and perfusion has been proven NOT to improve outcomes
     - Hayes, 1994
     -Gattinoni, 1995
   - To date, the most effective therapy for the second part in the treatment of sepsis is to optimize cardiac function and perfusion to the tissues as EARLY as possible (in the first 6 hours)
EARLY GOAL DIRECTED THERAPY

- The components for cardiac/tissue perfusion optimization (in order) consist of:
  - Preload optimization (CVP)
  - Blood pressure (MAP) optimization
  - Central venous oxygen saturation (ScvO2) optimization
  - Maintenance of adequate U.O.
    - Rivers, 2001
In order to get the heart to pump at its maximal potential, the optimum amount of “stretch” should be put on the muscle fibers.

Too little stretch or too much stretch will negatively effect contractility.

“Stretch” on the muscle fibers is called preload.

The idea is to do everything you can to make the heart pump well on its own, before giving drugs to make it work harder.
CVP: THE THEORY
CVP: THE THEORY

- CVP is a pressure measurement
- Preload is a measure of how full (and thus stretched) the ventricle is before it contracts
- Pressure is NOT Preload
  - CVP is used to give us an idea of what the preload is
  - It is assumed that measuring pressure near the right atrium will give us an idea of how much preload there is on the left ventricle before it contracts
  - When we use CVP to estimate preload we are making multiple assumptions
The Assumptions:

1) Pressures correlates with preload
   - Importantly, given a certain pressure range, we can predict optimum preload
2) Pressures near the right atrium can give us an idea of what the pressures are in the right ventricle and/or the pulmonary circulation
3) Pressures in the right ventricle/pulmonary circulation can give us an idea about pressures in the left ventricle
   - Once again, we are assuming that certain pressure ranges predict optimum preload
4) Sepsis does not “stiffen” or “relax” the heart muscle/pulmonary circulation to any significant degree that would affect our pressure measurements’ ability to predict preload
5) Our patient does not have any other condition that can affect our pressure measurements’ ability to predict preload
CVP: THE THEORY

The Reality:

- Pressures near the right atrium DO correlate with pressures in the right ventricle and pulmonary circulation
- Pressures near the right atrium don’t reliably correlate with pressures in the left ventricle
- Pressures near the right atrium don’t correlate with preload in either the right ventricle or left ventricle (except at very low pressures)
- Sepsis often affects how stiff (and resistant to stretch) the ventricle is
- Patients often have medical conditions that affect ventricular stiffness
How useful is CVP in sepsis then?

- CVP was used in River’s EGDT bundle, which showed a significant benefit to sepsis patients
- Placing a CVP line will give you the ability to measure ScvO2, which was also part of Rivers’ bundle
  - Non-invasive strategy without ScvO2?
- Why did CVP measurement improve outcomes (or did it)?
RIVERS’ EGDT STUDY (FLUIDS GIVEN)

Treatment group
- Hours 0-6 ml fluids
  - 4,981 +/- 2,984
- Hours 7-72 ml fluids
  - 8,625 +/- 5,162
- Hours 0-72 ml fluids
  - 13,443 +/- 6,390

Standard Therapy group
- Hours 0-6 ml fluids
  - 3,488 +/- 2,438
    - P=<0.001
- Hours 7-72 ml fluids
  - 10,602 +/- 6,216
    - P=<0.01
- Hours 0-72 ml fluids
  - 13,358 +/- 7,729
    - P=0.73
CVP TO PREDICT OPTIMAL PRELOAD?

- Osman, 2007
  - 150 volume challenges given to septic patients with pulmonary artery catheters
  - CVP and PAOP measured and patients were checked for an increase in CI of 15%
  - CVP of <8 or PAOP of <12 predicted fluid responsiveness only 47% and 54%, respectively
  - ROC AUC for CVP and PAOP were 0.58 and 0.63 respectively
- Marik (2013)
  - Meta-analysis of 43 studies in which CVP and fluid responsiveness were investigated
  - ROC AUC for CVP to predict fluid responsiveness was 0.58
    - AUC range was 0.27-0.68
NON-INVASIVE STRATEGY?

▶ Jones 2010

▶ 300 patients (150 each group) assigned to get traditional EGDT (CVP, MAP, ScvO2) vs. Group that received Lactate clearance >10% along with CVP and MAP optimization

▶ Mortality was 23% in the ScvO2 group vs. 17% in the Lactate Clearance group (non significant difference)

▶ Rivers’ study did appear to have sicker patients on average than Jones’ patients
So CVP doesn’t predict how much fluid we need to give patients, but when used in a bundle, outcomes improve.

Lactate clearance is non-inferior to ScvO2 (unless, at least, the patients are no sicker than Jones’ patients).

What alternatives do we have to CVP measurement?

Are there tools we can use that give us an idea of what preload actually is?

Are the tools easy to use?

Do the tools require a lot of training?

Are the tools more expensive than CVP monitoring?

Are the tools as safe as CVP?
THE TOOLS

- Ultrasound for CVP
- Ultrasound of the IVC and IVC collapse
- Stroke volume monitoring
  - Stroke volume variability and fluid challenge
- Aortic or brachial artery peak flow measurement
  - Stroke volume variability and fluid challenge
- Bioreactance cardiac output monitoring
ULTRASOUND FOR CVP IN THE NECK

FIGURE 1. Transverse view of the right side of the neck in the supine position showing the internal jugular vein (V), the common carotid artery (A), the overlying sternocleidomastoid muscle (SCM), and the more medial thyroid gland (T).

FIGURE 3. Longitudinal view of the neck showing the tapering portion of the internal jugular vein (V). This is where jugular pulsations are present in real-time.
IVC ULTRASOUND

- Can be used as a surrogate for CVP or as its own estimate of optimal preload
- IVC collapse may have additional use in that it gives respiratory/hemodynamic information related to fluid status
- IVC can be interpreted in two clinical scenarios
  1) Evaluation of low fluid status
  2) Reassurance that the patient has not reached maximal fluid tolerance
- IVC potentially can be used in intubated patients or patients with spontaneous respirations
IVC U/S AS SURROGATE FOR CVP

- Nagdev 2010
  - Investigators looked at IVC collapse with inspiration compared with expiration and found that 50% collapse of the IVC was consistent with CVP of 8 (91% sensitive and 94% specificity)
IVC FOR INTUBATED PATIENTS

- There are lots of papers in different settings on this.
- Here are a few references suggested by the EMCrit blog, but there are a lot more:
  - Intensive Care Med. 2004 Sep;30(9):1740
  - Intensive Care Med. 2004 Sep;30(9):1834
  - J Trauma 2007;63:495
- Bottom line is that if the IVC collapses >20% the patient will most likely respond to more fluids.
- Patients will need to be on at least 8-10cc/kg tidal volume.
- If the IVC collapse is <20%, the patient may still be fluid responsive.
IVC FOR SPONTANEOUSLY BREATHING PATIENTS

- Muller, 2012
  - Subaortic velocity time index compared to IVC collapse percentage
  - 40% collapse was the best cut off to predict fluid responsiveness
  - ROC AUC was 0.77
CARDIAC OUTPUT OR SV MONITORING

- Multiple methods are available to detect changes in SV or CO to either fluid challenges or ventilator breaths
  - Lithium Dilution & Pulse Contour Analysis (LiDCO)
  - Transpulmonary Thermodilution and Pulse Contour Analysis (PiCOO)
  - Pressure recording analytic Method (PRAM)
  - Flotrac
  - Others as well
    - (Marik, 2013)

- Many methods are too invasive/complicated to make them practical for use in the ED

- Many require special training and can be user dependent, thus limiting usefulness
FLOTRAC

- Requires a radial artery line or a femoral artery line
- Samples arterial pressure waveform every 20 seconds at 1,000 Hz
- Gives SVV, SV, CO, SVI, and CI values
- If slaved to a CVP line, can give you SVR and SVRI as well
- Can be used to assess optimal fluid status in 2 ways:
  - Intubated patients with Stroke Volume Variation
  - Non-intubated patients with SV response to fluid challenge
STROKE VOLUME VARIATION
HOW TO USE FLOTRAC IN NON-IN TUBATED PATIENTS

1) Fluid challenge:
   - Look at the Stroke volume (SV) on the screen
   - Give 250cc fluids as fast as it will go in
   - If the stroke volume increases by >10%, give more fluids
   - Must repeat multiple times to find out when you’ve given enough fluids

2) Passive leg raise:
   - Sit the patient up
   - Rapidly lay the patient down an raise the legs 45 degrees
   - Wait about 30-90 seconds
   - Again, assess for stroke volume increase >10%

   Patient cannot have a dysrhythmia for the system to work
HOW TO USE FLOTRAC IN INTUBATED PATIENTS

- Three requirements must be met:
  1) Patient must be control-ventilated
  2) Patient must receive at least 8cc/kg with each breath
  3) Patient cannot have a dysrhythmia

- Look at the stroke volume variation number on the monitor (SVV)
  - >13% give fluids
  - <13% don’t give fluids
HOW ACCURATE IS FLOTRAC?

- FloTrac appears to predict fluid responsiveness accurately in patients whose SVR is normal.
- When SVR is low (as in advanced sepsis) FloTrac has had problems with reliability to predict fluid responsiveness.
- 3rd generation software has attempted to address this issue.
- De Backer, 2011
  - Compared thermodilution techniques of CO monitoring (gold standard) to 2nd and 3rd generation FloTrac software in patients with septic shock and low SVR.
  - 2nd generation FloTrac failed to accurately predict fluid responsiveness.
  - 3rd generation had significant, but weak differences in accuracy to predict fluid responsiveness if the radial artery was used but not if the femoral artery was used.
Patients were intubated and had no dysrhythmia.

Brachial artery evaluated 5-10 cm above the antecubital fossa.

Probe is angled < 60 degrees to artery.

Velocity waveform measured from center of the artery.

Peak velocity variation was equal to:

\[ 100 \times \frac{(V_{\text{peak max}} - V_{\text{peak min}})}{(V_{\text{peak max}} + V_{\text{peak min}})/2} \]

Peak velocity variation > 10% predicted fluid responsiveness.

(Garcia, 2009)
COMPARISONS IN GARCIA STUDY

ROC Curves (AUC)

- Radial a. pressure variation:
  - 0.97
- FloTrac SVV >11%:
  - 0.89
- Brachial a. peak velocity variation:
  - 0.88
- CVP:
  - 0.64
SUMMARY

- Sepsis is a dynamic process that requires close monitoring to avert an irreversible progression that leads to death.
- Early and aggressive treatment of sepsis is the only proven method to improve mortality.
- EGDT components are CVP, MAP, ScvO2 and O.U., however CVP has been proven not to be helpful to guide fluid management.
- Alternative methods to guide fluid management exist, but each have their limitations. A complete and vigilant assessment of the patient and aggressive early interventions remain the best course of action in the treatment of septic shock.
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