The use of vasoactive drugs in the ICU

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Use of vasoactive drugs

Next 25 minutes

• General remarks
• “Old” vasoactive drugs
• Focus on norepinephrine
• Focus on brain injured patient
• “New” vasoactive drugs
  – Levosimendan
  – AVP
  – Terlipressin
• Conclusions
Hemodynamics

• Goals of hemodynamic therapy
  – maintain sufficient FLOW
    • (oxygen rich blood)
  – maintain sufficient PERFUSION PRESSURE

• Continuous measurements
• Instantaneous action whenever necessary
Hemodynamics
In the ICU

• Assessment of preload
• Assess circulatory sufficiency
  – not “high”, not “low” but “sufficient”
• Target for “optimal preload”
  – Def*: further increase of preload will not increase SV
• Use of vasoactive drugs

* Girbes ARJ, Groeneveld ABJ. Clinical Intensive Care. 2000; 11:77-88
Hemodynamics

- Physiological cardiac reserve

Stroke volume vs. LV End Diast Volume
Hemodynamics

Indication for fluid administration

Effect fluid administration
Hemodynamics

- Indices of "fluid responsiveness"
  - In mechanically ventilated patients
  - Fluid administration
    - Favorable in steep part
    - Unfavorable in flat part

![Graph showing hemodynamics](image)
Hemodynamics
Hypovolemia

• **Suspicion of hypovolemia**
  – NOT one single parameter
    • BP, HR, circulatory indices – diuresis / physical exam
    • CVP (curve), [PAOP, CO / SV]
    • Arterial curve
  – Signs of poor peripheral perfusion: lactate, SvO₂

• **Effect of fluid administration**
  • BP, HR, etc
  • CVP (curve), [PAOP, CO / SV]
  • Arterial curve
  – Signs of peripheral perfusion, lactate, SvO₂
Hemodynamics
Vigilance armée & permanente

- Properties of heart change continuously
  - Compliance (→ Starling curve)
  - Contractility
- Changing vascular bed
- Effects of mechanical ventilation
- Effects of changing body temperature
- Fluid loss
  - Diuresis – transpiration/ perspiration
  - Ascites – pleural fluid
  - Capillary leakage
Hemodynamics

• Measure response on therapy
  (fluid challenge)
  – Bedside!!!!
  – Important role physician & ICU nurse
Hemodynamics
Vigilance armée & permanente

- Target: CVP 18 mm Hg

WRONG
Hemodynamics

Simple predictors of fluid responsiveness bedside

- Leg tilt - effect on RR / HR / CVP / CO / SV
- Systolic pressure variation
- Pulse pressure variation
Hemodynamics

Pulse Pressure variation

Michard et al. AJRCCM, 2000
Fluid resuscitation policy

- **Pulsepressure variation**
  - n=40 circulatory failure (in sepsis)
  - Response on 500 cc colloid

  - Distinguish
    - Responder = increase CI > 15%
    - Non-responder

Michard et al. AJRCCM, 2000
Hemodynamics

• **Pulse-pressure variation (delta-PP)**
  
  – Delta-PP (PPV) = PP max – PP min / PP mean
  
  → in %

  – PPV ≥ 13% distinguishes (non-) responders
    
    • Sensitivity 94%
    
    • Specificity 96%

Michard et al. AJRCCM, 2000
Hemodynamics

- What if fluids are not enough?
  - Problem brain
  - Problem heart
    - post resuscitation
    - post coronary intervention
    - post cardiac surgery
  - Problem kidney perfusion
  - other? e.g. vasoplegia / sepsis / SIRS/ etc.

Hemodynamics

• The organs need
  – flow
  – perfusion pressure
Relation pressure-perfusion

The relationship between perfusion pressure and organ flow for the kidney and heart under the pathophysiologic conditions of hypertrophy or renovascular disease. Coronary perfusion pressure = diastolic arterial pressure - left ventricular end diastolic pressure. Renal perfusion pressure = mean arterial pressure - tissue pressure.

Spaan JAE, 1990
## Hemodynamics

### Use of inotropes

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Hemodynamics

- **Use of inotropes**
  - Make the appropriate (hemodynamic) diagnosis
  - Use what you need
    - NB previous betablocker use! PDE
  - And good is good enough
    - If good is good, more is not necessarily better
    - “Supra-normal goals” - obsolete
Hemodynamics
Vaso-active drugs

- My personal experience:
  *Norepinephrine allergic syndrome*
  
  - specific effects of norepinephrine in the ICU
    - substantial increase in heart rate + BP
    - rise in temperature
    - aggressive behavior
    - rare cases: fighting behavior
    - strangely: not in patients
Metabolic effects
Vaso-active drugs

• Norepinephrine allergic syndrome
  – Epidemiology by experience
    • Dutch (cardiothoracic-) surgeons
    • Dutch Cardiologists

  ➢ case of norepinephrino-phobia

  ➢ But: decreasing incidence
The injured brain & Hemodynamics

Norepinephrine

- **Norepinephrine is bad for the heart**
  - Deleterious effects on aerobic metabolism
    - Increases BP
    - Increases Systemic Vascular Resistance
    - Induces vasoconstriction
    - Induces coronary vasoconstriction
    - Induces ischemia
  - Is it this simple?
The injured brain & Hemodynamics

Norepinephrine

- Norepinephrine
  - potent peripheral vasoconstrictor
  - widely used in the ICU
    - vasoplegic shock
    - during cardiac shock
  - restores perfusion pressure
- e.g. can improve brain perfusion, renal function
Hemodynamics
Norepinephrine and the Heart

- **Norepinephrine – cardiac effects**
  - induces coronary vasodilation
  - improves coronary circulation
  - improves oxygen delivery
  - improves endocardial oxygen delivery
  - reduces infarct size

Sun et al. July 2002, Circulation
Hoffman & Spaan, 1990
Coronary Circulation and Noradrenaline

- Effect of noradrenaline on human coronary arterioles
  Sun et al., Circulation, July 2002

![Graph showing the effect of noradrenaline on coronary arterioles]
In addition to metabolism, the coronary circulation possesses unique pharmacologic characteristics. Prominent among these is its reactivity to adrenergic stimulation. The majority of circulation in the body constrict to norepinephrine, a sympathetic neurotransmitter the body uses to increases blood pressure. In the coronary circulation, norepinephrine elicits vasodilation, due to the predominance of beta-adrenergic receptors in the coronary circulation. Agonists of alpha-receptors, such as phenylephrine, elicit very little constriction in the coronary circulation.
Pro-Contra

- Textbook: Goodman & Gilman
Norepinephrine
Effects on coronary blood flow

α-Adrenergic vasoconstriction reduces systolic retrograde coronary blood flow

KOICHI MORITA, HIDEZO MORI, KATSUHIKO TSUJIOKA, AKIHIRO KIMURA, YASUO OGASAWARA, MASAMI GOTO, OSAMU HIRAMATSU, FUMIHIKO KAJIYA, AND ERIC O. FEIGL
Department of Biomedical Engineering and Systems Cardiology, Kawasaki Medical School, Kurashiki City, Okayama 701-01, Japan

Koichi Morita, Hidezo Mori, Katsuhiko Tsujioka, Akihiro Kimura, Yasuo Ogasawara, Masami Goto, Osamu Hiramatsu, Fumihiko Kajiya, and Eric O. Feigl. α-Adrenergic vasoconstriction reduces systolic retrograde coronary blood flow. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2746–H2755, 1997.—There is a paradoxical α-adreno-
Vasoactive drugs

• Any news?

My selection
– Levosimendan
– AVP
– Terlipressin
Levosimendan

• Hits: n=365
  – Reviews: 92
  – Human: 250
  – RCT: 41
  – RCT + IC 2
Inotropes

• Background
  – All positive inotropic drugs
    → detrimental effect long-term treatment
  – PDE III inhibitors
    → high incidence of treatment related complications
    in short-term treatment (AF, hypotension)
Inotropes

• **Side effects**
  ↩ all drugs increase cAMP
  ↠ increase intracellular cytosol Ca++
    < sarcoplasmic reticulum

• **New developments**
  – New approach to positive inotropic therapy
Inotropes

- **New class – new promises**
  - Calcium sensitizer
    - Sensitises troponin C to Ca$^{++}$ ➔ increases effects of Ca$^{++}$
    - Increase cardiac contractility
    - No increase in mvO$_2$
    - No proarrhythmic effects
Levosimendan

- **Favourable properties**
  - Improves hemodynamics
    - Improves cardiac performance
      - SV increases, PAOP decreases
      - Not associated with increased myocardial Oxygen consumption
      - Not dysrythmogenic
      - Does not impair diastolic function (relaxation)
    - Induces vasodilation
      - Coronary, pulmonary, renal, splanchnic, cerebral, systemic arteries
      - Portal vein, systemic veins
Acute Hemodynamic and Clinical Effects of Levosimendan in Patients With Severe Heart Failure
Circulation 2000;102:2222-2227
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231-4352
Copyright © 2000 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539
Levosimendan

- RCT – double blind, placebo controlled
- CHF NYHA III-IV
  - PCWP > 15 mm Hg
  - CI < 2.5 L/min/m²
- N=146
- Levosimendan infusion (0.1-0.4 mcg/kg/min)
  - Titrated in 4 hour infusion

*Circulation. 2000;102:2222-2227*
Levosimendan

levosimendan (●) and placebo (○)

VU medisch centrum
Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression

Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study*

Andrea Morelli, MD; Jean-Louis Teboul, MD, PhD; Salvatore Maurizio Maggiore, MD, PhD; Antoine Vieillard-Baron, MD; Monica Rocco, MD; Giorgio Conti, MD; Andrea De Gaetano, MD, PhD; Umberto Picchini, Dr in statistics; Alessandra Orecchioni, MD; Iacopo Carbone, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Martin Westphal, MD

(Crit Care Med 2006; 34:2287–2293)
Levosimendan
Intensive Care

- **Sepsis study**
  - Levosimendan vs dobutamine (5 mcg/kg/min) – 24 hr infusion
  - Patients with sepsis related LVD n=28
  - Endpoints:
    - Hemodynamics
    - Echocardiography
    - Gastric tonometry
    - Lactate
Levosimendan
Intensive Care

- Results

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<tr>
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<th>Dobutamine</th>
<th>Levosimendan</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62.4±7.3</td>
<td>61.5±7.0</td>
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<tr>
<td>Sex: M/F</td>
<td>10/3</td>
<td>11/4</td>
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<tr>
<td>APACHE II</td>
<td>23.7±2.1</td>
<td>24.4±1.6</td>
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<tr>
<td>Gram-positive cultures (%)</td>
<td>59.3</td>
<td>62.5</td>
</tr>
<tr>
<td>Gram-negative cultures (%)</td>
<td>40.7</td>
<td>37.5</td>
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<tr>
<td>ICU mortality (%)</td>
<td>44.1</td>
<td>38.1</td>
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<tr>
<td>Hospital mortality (%)</td>
<td>54.3</td>
<td>47.2</td>
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<tr>
<td>30-day mortality (%)</td>
<td>51.7</td>
<td>47.8</td>
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<table>
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<tr>
<td>HR (bpm)</td>
<td>114±8.3</td>
<td>115±10.5</td>
<td>115±7.3</td>
<td>116±5.8</td>
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<tr>
<td>MAP (mmHg)</td>
<td>76.2±2.8</td>
<td>75.0±3.3</td>
<td>74.7±2.4</td>
<td>73.9±1.7</td>
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<tr>
<td>MPAP (mmHg)</td>
<td>26.2±2.4</td>
<td>23.1±2.4***</td>
<td>26.7±1.0</td>
<td>26.6±1.1</td>
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<tr>
<td>RAP (mmHg)</td>
<td>13.5±1.4</td>
<td>12.3±1.5*</td>
<td>12.8±0.7</td>
<td>13.0±0.7</td>
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<td>PAOP (mmHg)</td>
<td>16.8±1.2**</td>
<td>12.0±0.6***</td>
<td>13.9±0.6</td>
<td>14.4±0.7*</td>
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<tr>
<td>SI (ml m⁻²)</td>
<td>36.6±2.9</td>
<td>30.1±1.1*</td>
<td>37.1±3.7</td>
<td>36.4±2.7</td>
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<tr>
<td>CI (l min⁻¹ m⁻²)</td>
<td>4.1±0.2</td>
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<td>SVRI (dyne s⁻¹ cm⁻⁵ m⁻²)</td>
<td>1238±100</td>
<td>1181±114</td>
<td>1160±99</td>
<td>1143±71</td>
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<tr>
<td>PVR (dyne s⁻¹ cm⁻⁵ m⁻²)</td>
<td>226±56</td>
<td>202±45</td>
<td>233±55</td>
<td>231±47</td>
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<tr>
<td>DO₂I (ml min⁻¹ m⁻²)</td>
<td>715±58</td>
<td>746±59*</td>
<td>721±59</td>
<td>718±44</td>
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<tr>
<td>VO₂I (ml min⁻¹ m⁻²)</td>
<td>223±36</td>
<td>239±32*</td>
<td>225±23</td>
<td>227±24</td>
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<tr>
<td>LVSWI (g m⁻¹ m⁻²)</td>
<td>29.6±2.8</td>
<td>33.9±3.7***</td>
<td>28.5±1.4</td>
<td>27.9±1.0</td>
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</table>

* p<0.05 baseline vs. 24 h, ** p<0.05 levosimendan vs. dobutamine at baseline, *** p<0.05 levosimendan vs. dobutamine after 24 h
<table>
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<tbody>
<tr>
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<td>Baseline</td>
<td>24 h</td>
</tr>
<tr>
<td>EDVI (ml m⁻¹)</td>
<td>75.8±23.8</td>
<td>66.2±24.6*</td>
</tr>
<tr>
<td>ESVI (ml m⁻¹)</td>
<td>46.7±21.9</td>
<td>36.9±19.4*</td>
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<tr>
<td>LVEF (%)</td>
<td>37.1±3.0</td>
<td>45.4±8.4*</td>
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*p<0.05 baseline vs. 24 h, **p<0.05 levosimendan vs. dobutamine after 24 h

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<tr>
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<td>Baseline</td>
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<tr>
<td>Troponin cTnI (ng/ml)</td>
<td>0.14±0.07</td>
<td>0.13±0.06***</td>
</tr>
<tr>
<td>GMP (%)</td>
<td>–</td>
<td>+55.3±20.1***</td>
</tr>
<tr>
<td>ΔP_{a,CO₂} (mmHg)</td>
<td>15.3±1.1**</td>
<td>11.9±1.3***</td>
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<tr>
<td>Arterial lactate (mmol l⁻¹)</td>
<td>4.9±1.2</td>
<td>3.7±0.7***</td>
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<td>Creatinine clearance (ml min⁻¹)</td>
<td>43.9±12.8</td>
<td>72.1±16.2***</td>
</tr>
<tr>
<td>Urinary output (ml 24 h⁻¹)</td>
<td>–</td>
<td>2028±461***</td>
</tr>
<tr>
<td>Fluid perfused (ml 24 h⁻¹)</td>
<td>–</td>
<td>5907±330***</td>
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<tr>
<td>Norepinephrine rate (µg kg⁻¹ min⁻¹)</td>
<td>0.22±0.07</td>
<td>0.22±0.06</td>
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</table>

*p<0.05 baseline vs. 24 h, **p<0.05 levosimendan vs. dobutamine at baseline, ***p<0.05 levosimendan vs. dobutamine after 24 h

VU medisch centrum
Conclusions

These findings show that levosimendan improves systemic hemodynamics and regional perfusion in patients with septic cardiac dysfunction under conditions where administration of 5 µg/kg dobutamine per minute is no longer efficacious. Accordingly, our results suggest that levosimendan can be an alternative to the strategy of increasing the dose of dobutamine under such conditions.
Levosimendan
Intensive Care

• ARDS study
  – Levosimendan vs placebo (0.2 mcg/kg/min)
  – Patients with sepsis related ARDS (n=35)
  – Endpoints
    • Hemodynamics
  
  – Results
    • Improvement of RV performance
Levosimendan
Intensive Care

![Graphs showing changes in MPAP, CI, PVRI, and RVEF for Placebo and Levosimendan at baseline and 24 hours.](image)
**Levosimendan**

- **Conclusions & expectations**
  - New class of drugs
  - May improve hemodynamics
    - Promised (lack of) effect on HR not proven
  - Additional value unclear
    - Studies on low dose dobutamine
    - No studies comparing PDI
    - Patients who benefit not defined
  - Not registrated in most countries outside Scandinavian countries
  - In AHF: effect on mortality unknown
  - New trials underway
Vasopressin

- Potent endogenous vasopressor hormone
  - Most studies in ICU patients – all categories
    - Decrease need for NE
    - HR ↓ MAP ↑ SV ↑ CO ↓

Additional value: unclear

Ref: Dünser 2003 Circulation/2002 ICM; Luchner CCM 2005; Lauzier ICM 2006
Effects of AVP

SS=Septic Shock (n=103); PS=Postcardiotomy Shock (n=135); SIRS (n=78)
Effects of Terlipressin

- Synthetic AVP analogue
- Vasoconstrictive effects
  - Lowers HR
  - Decreases CO
  - Decrease need for NE
- Concern: effect on intestinal (mucosal) perfusion
- Additional value: unclear
Hemodynamics

• Final word on the injured brain
  – Trauma
  – Posthypoxic
  – Post SAB
The injured brain & Hemodynamics

- **Normal brain**
  - Well developed autoregulation
    - Maintenance of constant flow at different levels of perfusion pressure

- **Injured brain**
  - More or less disturbed autoregulation
The injured brain & Hemodynamics

• The brain
  – Does not forgive !! (like other organs)
  – The mean or median does not count!!
    • If you do 10 weeks perfectly, but 5 minutes not, only the 5 minutes will count
    • Only a winner when you win all & always!!
Use of vasoactive drugs

- **Conclusions**
  - Make a hemodynamic diagnosis
  - Maintain perfusion pressure AND flow
  - Sufficient is enough. “Better is the enemy of good”
  - Very very close observation of hemodynamics
  - Optimal preload
    - PPV and other indices
  - Vaso-actives based on hemodynamic profile
    - norepinephrine is not bad for the heart
Thank you!

Presentation available at:

www.ArmandGirbes.com

(after the congress)