Postgraduate evening Leuven, 08.05.2017

Levosimendan – Pharmacological background and clinical evidence

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Conflicts of interest – financial disclosures

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Affiliation</th>
<th>Unlabeled Product Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orion Pharma, Orion Corporation</td>
<td>Speaker's fees</td>
<td>None</td>
</tr>
</tbody>
</table>

Orion Pharma, Orion Corporation
Speaker's fees
None
Inotropes
Can you imagine to work without?

Levosimendan

Inotropes
Which?

Dobutamine
Adrenaline
Levosimendan
Noradrenaline
PDE-III-Inhibitors
Dopamine
Inotropes
Which?

I. Catecholamines (α/β adrenergic)

II. Glycosides
- Narrow therapeutic index
- Modest inotropic support
- Arrhythmias

III. PDEI-III
- Ca**-mobilizers

IV. Levosimendan
- Ca**-sensitizer

Pharmacology
Inotropes: Four classes
Levosimendan

“Traditional” inotropes (Ca++ - mobilizers)
Side effects - Heart

- Cardiotoxicity
  - Ca++-overload
  - Ischemia-reperfusion injury
  - Stunning
  - Pro-apoptotic effects in myocardial, vascular smooth muscle and skeletal muscle myocytes
  - Intramyocardial release of pro-inflammatory cytokines

- Arrhythmogenesis (intracellular Ca++-content 🤔)

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Circulation

American Heart Association

EDITORIAL REVIEW

Catecholamine Cardiotoxicity

Neurohormonal Stimulation: Angiogenesis in Adult Rat Ventricular Myocytes by Activation of the β-Adrenergic Pathway
Catherine Cummard, Siobhan O’Reilly, Harry W. Spearritt, and William S. Colucci.

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“Traditional” inotropes
Side effects - Heart

Cardiotoxicity

- Myocardial oxygen demand
  - Contractility 🤩
  - Heart rate 🤩
  - Inopressors: Afterload 🤩
Inotropes: Do these side effects matter?

Mebazaa A. et al.
Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods.
The dilemma

**Inotropes: Do these side effects matter?**

De Backer D et al.
Comparison of Dopamine and Norepinephrine in the Treatment of Shock
The dilemma

Inotropes: Do these side effects matter?

Health Outcomes with and without Use of Inotropic Therapy in Cardiac Surgery

Results of a Propensity Score–matched Analysis

Dorte Vinggaard Nielsen, M.D., Malene Karslund Hansen, M.B.B.S., Simon Praxl Johnson, M.D., Ph.D., Mads Hansen, M.D., Karsten Hindsholm, M.D., H.D., Czsf-Johan Jacobsen, M.D.

Anesthesiology 2014; 120:1096-106

N= 6,005
Propensity matching on pre- and intraoperative variables
N = 1,170 receiving inotropic therapy versus
N = 1,170 comparable nonreceivers

Levosimendan – Triple mechanism of action

Farmakis D, ... Rex S, et al.

Need for new inotropes
Levosimendan – Triple mechanism of action

- Binding to cTnC
- cTnC binds to cTnI
  - De-inhibition of cTnI
- Translocation of cTnI-tropomyosin-complex away from myosin binding site
- Actin-myosin-interaction → Powerstroke → Contraction

Ca++

1) Ca++-Sensitization

- Binding to Ca++-saturated cTnC
  - Stabilization of cTnC-Ca++-complex
  - Improved disinhibition of cTnI
  - Dissociation of troponin-tropomyosin-complex from actin filaments

- Enhanced myosin-actin-interaction (positive inotropy) without changes in intracellular Ca++-concentration

- No increase in myosin-ATPase activity
  - No ATP-increase → NO INCREASED MVO₂

- No impairment of diastolic relaxation (binding to cTnC is dependent upon Ca++-concentration)

- Also effective during β-blockade
Need for new inotropes
Levosimendan – Triple mechanism of action

1) Inotropy
2) Opening of vascular $K_{ATP}$-channels
   - $K^+$-efflux
   - Cellular hyperpolarisation
   - Vasodilation
     - Systemic vessels (A + V)
     - Coronary arteries
     - Renal vessels
     - Capacitance vessels
     - Pulmonary vessels (A + V)

Pharmacology: Levosimendan
Inodilation: LV

- ↑ Inotropy
- ↓ Filling

Figure 3. Mean Change From Baseline in B-Type Natriuretic Peptide Levels at 1, 3, and 5 Days by Treatment Group

Mebazaa A. et al. Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure. The SURVIVE Randomized Trial. JAMA. 2007;297:1883-1891

Levosimendan

Pharmacology: Levosimendan

Inodilation: RV

Ventriculo-arterial coupling

RV-Contractility

RV-Coupling

RV-Afterload

RV Diastolic Function

Pharmacology: Levosimendan

Vasodilation: Caveats

REVIVE study

Figure 4 Hazard Ratio for All-Cause Mortality

Hazard ratio for all-cause mortality (levosimendan/placebo) at 14 days as a function of the systolic blood pressure at randomization.

Levosimendan

Carlo Moscati, MD; Steffen Rex, MD; Patrick Segers, PhD; Patrick F. Wouters, MD, PhD

Levosimendan improves right ventricular vascular coupling in a porcine model of right ventricular dysfunction

Crit Care Med 2007; 35:707–715
Need for new inotropes
Levosimendan – Triple mechanism of action

3) Opening of mitochondrial $K_{ATP}$-channels
- Inhibition of mPTP-opening
- Cardioprotection in ischemia-reperfusion-injury

Pharmacology: Levosimendan
Clinical cardioprotection

Preconditioning
10min before start of CPB
(Bolus 24 μg/kg)

Pretreatment
24h prior to cardiac surgery
(Bolus 10μg/kg; 0.1 μg/kg/min)

Postoperative complications within 48 h in the levosimendan versus control groups

<table>
<thead>
<tr>
<th>Complication</th>
<th>Levosimendan</th>
<th>Control</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>9 (5.6)</td>
<td>18 (12.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Congestive vasodilatation</td>
<td>8 (2.6)</td>
<td>17 (8.6)</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>Low cardiac output syndrome</td>
<td>9 (7.1)</td>
<td>26 (20.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Non-cardiac failure</td>
<td>7 (5.8)</td>
<td>18 (14.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diuresis</td>
<td>3 (2.4)</td>
<td>8 (6.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Prolonged stay on ventilator</td>
<td>7 (5.5)</td>
<td>21 (18.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Postoperative myocardial infarcion</td>
<td>1 (0.3)</td>
<td>3 (4.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stenocardic syndrome</td>
<td>4 (2.4)</td>
<td>12 (9.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>18 (14.2)</td>
<td>40 (32.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>9 (6.5)</td>
<td>19 (15.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systemic inflammatory syndrome</td>
<td>4 (3.1)</td>
<td>19 (12.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Septic</td>
<td>2 (1.0)</td>
<td>10 (8.0)</td>
<td>&lt;0.05</td>
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<tr>
<td>Transitory ischemic attack</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiovascular accident</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Levin R et al.
Preoperative levosimendan decreases mortality and the development of low cardiac output in high-risk patients with severe left ventricular dysfunction undergoing coronary artery bypass grafting with cardiopulmonary bypass.
Exp Clin Cardiol 2012;17(3):125-130

Tritapepe L. et al.
Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery.
British Journal of Anaesthesia 102 (2): 190-204 (2009)
Pharmacology: **Levosimendan**

**Clinical cardioprotection**

Levosimendan Reduces Cardiac Troponin Release After Cardiac Surgery: A Meta-analysis of Randomized Controlled Studies

Alberto Zangrillo, MD,* Giuseppe Biondi-Zoccai, MD,† Anna Mizi, MD,* Giovanna Bruno, MD,* Elena Bignami, MD,* Chiara Gerli, MD,* Vincenzo De Santis, MD,t Luigi Titapepe, MD,t and Giovanni Landoni, MD*


<table>
<thead>
<tr>
<th>Comparison</th>
<th>Levosimendan in cardiac surgery</th>
<th>Control</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or subcategory</td>
<td>Levosimendan Mean (SD)</td>
<td>Levosimendan Mean (SD)</td>
<td>Control Mean (SD)</td>
</tr>
<tr>
<td>Batin</td>
<td>22</td>
<td>3.90 (0.75)</td>
<td>20</td>
</tr>
<tr>
<td>Mazzezrno</td>
<td>12</td>
<td>2.90 (0.38)</td>
<td>12</td>
</tr>
<tr>
<td>Al-Shaaf</td>
<td>14</td>
<td>3.80 (1.40)</td>
<td>14</td>
</tr>
<tr>
<td>Tritapepe</td>
<td>12</td>
<td>2.40 (0.96)</td>
<td>12</td>
</tr>
<tr>
<td>De Hart</td>
<td>15</td>
<td>3.60 (0.25)</td>
<td>15</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14</td>
<td>65</td>
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</table>

[Expression of adhesion molecules in HHMEC]

**Pharmacology: Levosimendan**

**Anti-inflammatory actions**

Levosimendan exerts anti-inflammatory effects on cardiac myocytes and endothelial cells in vitro

Konstantina A. Kryuchkova,† Lukas Maticha,‡ Christoph Kraner,‡ Elisabeth Buhlberger,‡ Beatrice Hofer-Machacek,‡ Sulëna Doemenies,‡ Julia Pfeif,†† Sarolta Rovati,‡ Sabine Hauschild,‡ Markus Gütgemer,‡ Arne Althoff,‡ Andreas Dreller,‡ Gerald Maier,†† Rainer de Martin,†† Kurt Huber,‡‡ Johann Nepp,‡‡ Walter L. Spoel,‡‡"
**Summary of pharmacology**

**Levosimendan – Triple mechanism of action**

- **INOTROPY**
  - Troponin C sensitization
  - RV/LV contractility without increased myocardial oxygen consumption
  - Mortality
  - Preconditioning and anti-stunning effects

- **VASODILATION**
  - Smooth muscle ATP-sensitive K⁺ channel activation
  - RV afterload
  - Coronary perfusion
  - LV afterload

- **CARDIOPROTECTION**
  - Mitochondrial ATP-sensitive K⁺ channel activation
  - Systemic hypotension

Levosimendan

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**Pharmacokinetics: Levosimendan**

**Long duration of action**

- **Levosimendan**
- **Aktiver Metabolit OR-1896**

Lillevang J et al.
Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure.
European Journal of Heart Failure 9 (2007) 75 – 82

Levosimendan

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Inotropes - Levosimendan
Evidence?

Levosimendan

Pisano A et al.
Levosimendan: new indications and evidence for reduction in perioperative mortality?
Curr Opin Anesth 2016, 29:454–461

Levosimendan

Inotropes – Levosimendan
Mortality

Pollesello P. et al.
Levosimendan meta-analyses: Is there a pattern in the effect on mortality?
International Journal of Cardiology 209 (2016) 77–83

Meta-analysis of regulatory trials

- All meta-analyses published so far
- n=25, n > 6000 patients
- All show benefit on mortality
  (22/25 significant)
- Irrespective of clinical setting/comparator
- 10 in cardiac surgery, with 8 analysing mortality (all show significant effect)
Inotropes – Levosimendan
Mortality post cardiac surgery

Effect of Levosimendan on Survival and Adverse Events After Cardiac Surgery: A Meta-analysis

Robert W. Harrison, MD,⁎ Vic Hasselblad, PhD,⁎ Rajendra H. Mehta, MD, MS,⁎ Ricardo Levin, MD,†
Robert A. Harrington, MD,⁎ and John H. Alexander, MD, MHS⁎

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Difference</th>
<th>Meta-Difference</th>
<th>p-Value</th>
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<tr>
<td>Meta-Analysis</td>
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<tr>
<td>Levosimendan</td>
<td>130</td>
<td>105</td>
<td>1.00</td>
<td>-0.21</td>
<td>-0.21</td>
<td>0.12</td>
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<tr>
<td>Control</td>
<td>130</td>
<td>105</td>
<td>1.00</td>
<td>0.21</td>
<td>0.21</td>
<td>0.12</td>
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<td>Meta-Regression</td>
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<td>130</td>
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<td>130</td>
<td>105</td>
<td>1.00</td>
<td>0.21</td>
<td>0.21</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Levosimendan within 24 h after initiation of ECMO (on top of standard therapy vs. standard therapy alone)

N = 240

Levosimendan

Inotropes – Levosimendan
Mortality post cardiac surgery

Beneficial effects of levosimendan on survival in patients undergoing extracorporeal membrane oxygenation after cardiovascular surgery


<table>
<thead>
<tr>
<th>Survival</th>
<th>Levosimendan</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.04</td>
<td></td>
<td></td>
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</tbody>
</table>

Crude HR (95% CI) | P-value
ECMO weaning failure | 0.54 (0.31-0.93) | 0.03
30-day mortality | 0.61 (0.38-0.96) | 0.03
Long-term mortality | 0.77 (0.54-1.09) | 0.14

Adjusted HR (95% CI) | P-value
ECMO weaning failure | 0.64 (0.32-0.85) | 0.008
30-day mortality | 0.53 (0.32-0.89) | 0.016
Long-term mortality | 0.64 (0.42-0.93) | 0.04
Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

N = 882, USA + Canada
EF < 35%
CABG, CABG plus aortic-valve surgery, isolated mitral-valve surgery, or any combination of these procedures (CPB).
Prophylactic levosimendan after induction of anesthesia (0.2 µg/kg/min for the first hour, 0.1 µg/kg/min for the following 23h)
Time from infusion to surgery: 0.3h

Levosimendan for Hemodynamic Support after Cardiac Surgery

N = 506, 14 centers in Italy, Russia, Brazil
Preop. LVEF < 25%, preop. IABP, or the need for IABP-support or high-dose inotropic support (defined as a vasoactive–inotropic score of ≥ 10 in order to be weaned from CPB or at any time within the first 24 hours after surgery).
Levosimendan (0.07 µg/kg/min) vs. placebo on top of standard therapy
No difference in 30d mortality
**Summary**

**Inotropes**

- Marked improvement of cardiac performance
- (Inappropriate) use of traditional inotropes is associated with an **excess in mortality**
- **Restrictive use!**
- Should only be used as a **bridge** (to recovery, definitive therapy, MCS)
- „Traditional“ inotropes: cardiotoxic

- **Levosimendan:**
  - Triple mechanism of action:
    - Inotropy, vasodilation, cardioprotection
  - Majority of studies shows an improvement in outcome
  - Greatest benefit in patients with severely reduced LV function
  - **PREOPERATIVE** administration!

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**Thank you for your attention**
Clinical practice: Recommended use of levosimendan in cardiac surgery


Levosimendan

Type of patient:
- Low preoperative LVEF (eg, <35%)
- High-risk patients (eg, emergency operation, decompenated heart failure)
- Weaning failure from CPB

Scheduling for mechanical assist device (IABP/LVAD)

Postoperative LOS

Periureictic for optimal effect and safety
- Volume and/or electrolyte optimization
- Crystalloids/collodene as needed to reach euoxemia
- Tight blood pressure monitoring
- Especially during the first hours
- Administer antiplatelet, if SBP <90 mmHg at euoxemia

Optimization of diuretics
- Reduce dose or step and then readapt
- β-blocker use
- Continuous whenever possible

Mode of administration
- Usually without a bolus
- Routinely start with continuous infusion
- Start with 0.1 μg/kg/minute
- Time for first effects usually 2 h
- Adjust to 2-3 h (0.1-0.2 μg/kg/minute)

Bolus might be considered if
- Immediate effect is necessary (extrahepatically)
- Patient has high blood pressure
- Patient is volume overloaded

Inotropes – Levosimendan

Hospital length of stay

- N= 6480
- Setting:
  - Cardiology/ Cardiac surgery
- Control:
  - Dobutamine
  - Milrinone
  - Enoximone
  - PGE1
  - Placebo


Levosimendan
Inotropes – Levosimendan
Hospital length of stay

- N= 5480
- Setting:
  - Cardiology/ Cardiac surgery
- Control:
  - Dobutamine
  - Milrinone
  - Enoximone
  - PGE1
  - Placebo


Inotropes – Levosimendan
Mortality


A Bayesian network meta-analysis on the effect of inodilatory agents on mortality

T. Greco¹, M. G. Calabrò², R. D. Covello³, M. Greco¹, L. Pasin¹, A. Morelli², G. Landoni¹ and A. Zangrillo¹

- N= 46 trials
- Published between 1995 and 2014
- N = 2647 patients
- Setting:
  - Cardiac surgery
- Intervention:
  - Levosimendan
  - Dobutamine
  - Enoximone, or
  - Milrinone
- Control:
  - One of above, or
  - Placebo