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OIRPOSDRU REGIUNEA CENTRU
UNIVERSITATEA DE MEDICINĂ ŞI
FARMACIE "CAROL DAVILA"
BUCUREŞTI

AD-COR Program inovativ de formare in domeniul cardiologiei pediatrice POSDRU/179/3.2/S/152012

*Data:*14-09-2015

MODUL TEORETIC

PAEDIATRIC CARDIAC CRITICAL CARE

Imputernicit: Prof. Dr. Tammam Youssef

Activitate prestata de I.R.C.C.S. POLICLINICO SAN DONATO – MILANO, ITALIA in baza contractului nr. 18/22144/29.07.2015

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Acest material a fost documentat/ validat/ prezentat la sesiunile de formare în cadrul proiectului *„AD-COR Program inovativ de formare în domeniul cardiologiei pediatrice”* - POSDRU/179/3.2/S/152012, proiect cofinanțat din Fondul Social Operațional Sectorial Dezvoltarea Resurselor Umane 2007-2013.

Beneficiar: Universitatea de Medicină și Farmacie „Carol Davila” București

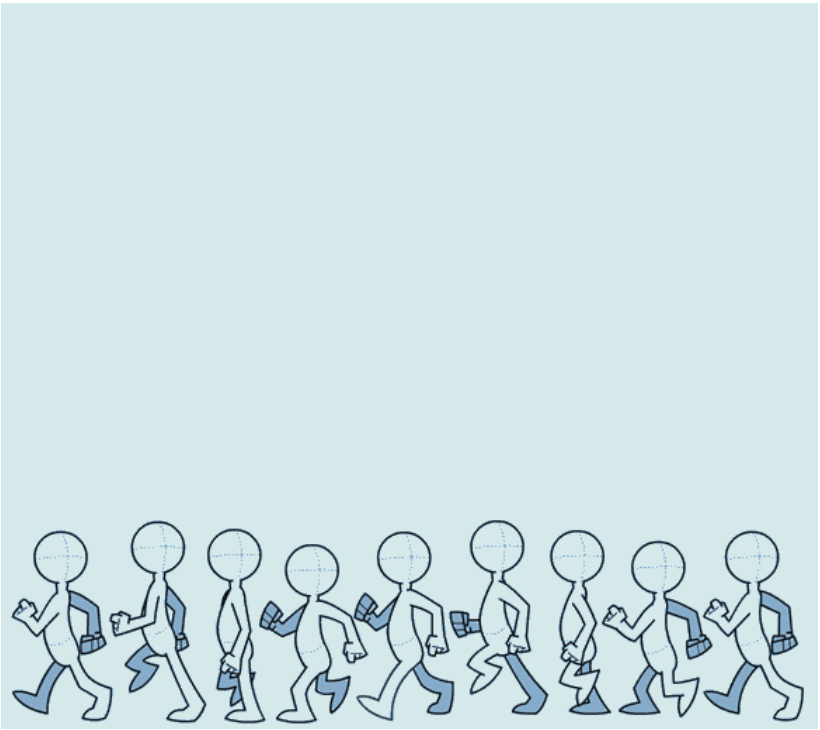
PAEDIATRIC CARDIAC CRITICAL CARE

Bucharest, September 14, 2015

Welcome

Matthias Angrés, MD, PhD
RobinAid Foundation
Hamburg

Let‘s start a common walk



14 lectures during the next months

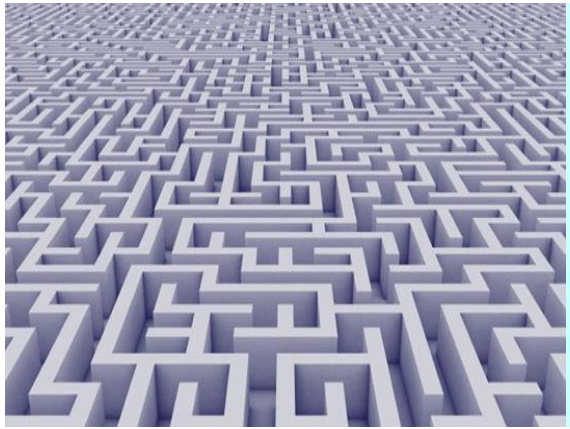
1. Inotropic agents in paediatric cardiac critical care
2. Human factors in paediatric cardiac critical care
3. Risk factors and outcome of pediatric cardiac surgery
4. The effects of cardiopulmonary bypass following pediatric cardiac surgery
5. Strategies in sedation and pain management
6. Respiratory assessment and management / respiratory complications
7. Cardiac arrhythmias: assessment and management / care of patients with temporary pacemaker

14 lectures during the next months

8. Medistinal bleeding and cardiac tamponade / blood transfusion, coagulation disorders, and postoperative anticoagulation
9. Post-cardiac surgery pulmonary hypertension: identification and management
10. Infections in the cardiac intensive care unit
11. Fast-track extubation in pediatric cardiac surgery
12. Basics of echocardiography in monitoring the postoperative pediatric cardiac surgery patient.
13. Mechanical circulatory support in pediatric cardiac surgery
14. One hundred useful references in pediatric cardiac intensive care

The most important message

The highly complex paediatric patients with congenital or acquired heart disease require interprofessional teamwork and collaboration to ensure high quality outcomes with low mortality and morbidity.



Paediatric Cardiac TEAM

- Pediatric Cardiac Intensivist
- Pediatric Cardiologist
- Neonatologist
- Pediatric Cardiac Anesthetist
- Congenital Heart Surgeon
- Nurses
- Technicians
- Respiratory therapy
- Infectious Disease
- Perfusionists
- Imaging

Benefit

To achieve more means to decrease the number of risks as well as complications and to increase the patients' safety.

How to reach the goal

Hard Skills ● Soft Skills = value to the patient

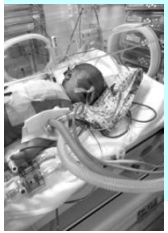
About me

- Training in anaesthesia and intensive care
- Specialization in cardiac anaesthesia and cardiac intensive care (adults as well as paediatrics)
- Deputy Head of Department of Anaesthesiology and Intensive Care at Bad Rothenfelde Cardiac Centre
- Medical Director and Head of Department of Anaesthesiology and Intensive Care at Cottbus Cardiac Centre
- Medical and Managing Director at Friedrichshafen Medikor WUND Group of Companies
- Medical Director and Chairman Department of Intensive and Emergency Care at Hamburg Albertinen Hospital

- Starting full-time humanitarian profession in 2008 and founding of Hamburg based RobinAid
- Regularly medical missions as paediatric cardiac intensivist in many different projects worldwide
- Extensive teaching activities on subjects of cardiac anaesthesia, intensive care, emergency care, hospital management and medical ethics

About RobinAid

RobinAid is an independent and non-profit humanitarian, medical organization.



Chaine de l'Espoir Europe
international medical network

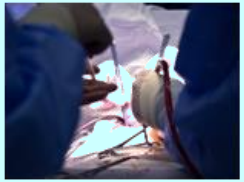
La chaîne de l'espoir ▪ France
De Keten van Hoop ▪ Belgium
Bambini Cardiopatici nel Mondo ▪ Italy
RobinAid Foundation ▪ Germany
Cadeia da Esperança ▪ Portugal

United as **Chaîne de l'Espoir Europe** we work as an international medical network in order to give disadvantage children around the world access to the best healthcare.

What we do

Paediatric Critical Care

Urgent Medical Care



Centres of Expertise

RobinAid stands for highly specialized medical care. We provide urgent medical assistance, support the set-up of local centres of expertise and accompany them as partners on their own way to autonomy.

We focus on the treatment of lifethreatening disorders by neonates, infants and elderly children, particularly congenital and acquired heart disease.

Paediatric Cardiac Critical Care

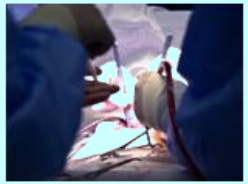
Paediatric General Critical Care

Paediatric Critical Care

How we work

We are always working in cooperation with local partners. By sending medical teams as well as equipment we assist them to take medical responsibility for their little patients.

- Qualified Medical Experts
- Medical Equipment
- Urgent Medical Care

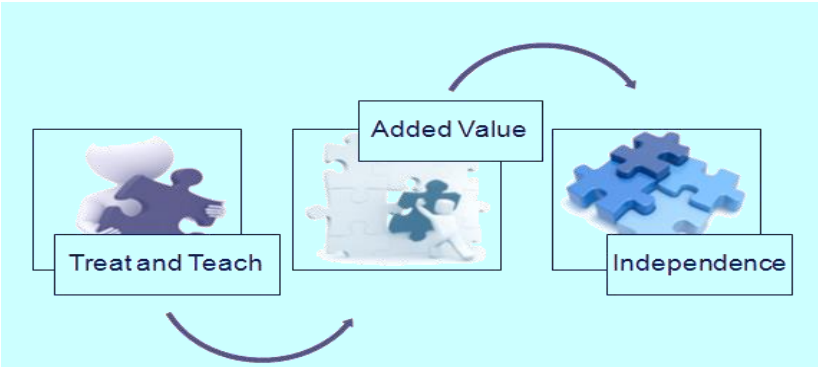


- Centres of Expertise

- Certified Training & Fellowship Programs
- Access to International Medical Networks

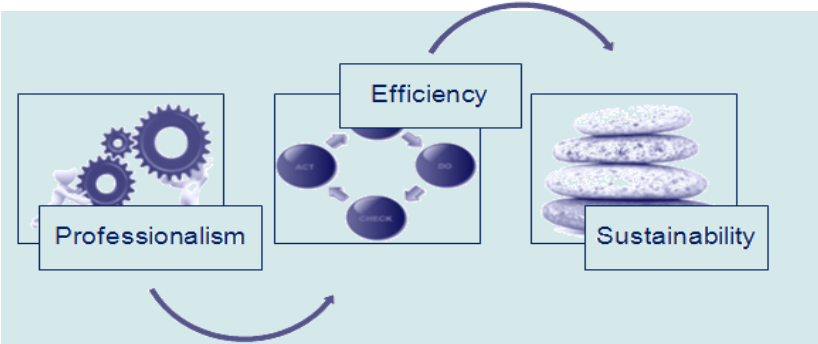
We share our knowledge with the local colleagues. Training and access to international medical networks are of primary importance to encourage them in their own abilities.

Our approach



Our investment of resources is always linked to the concept “treat and teach”. This strategy focuses in creating added values to enable our local partners to become independent as soon as possible.

High professional competence in accordance with international quality standards, well-structured working procedures and cross-linked thinking as well as teamwork are the essential key parameters of sustainable development.



Fellowship Programs

On the way to independence access to international knowledge and experience are of great importance.

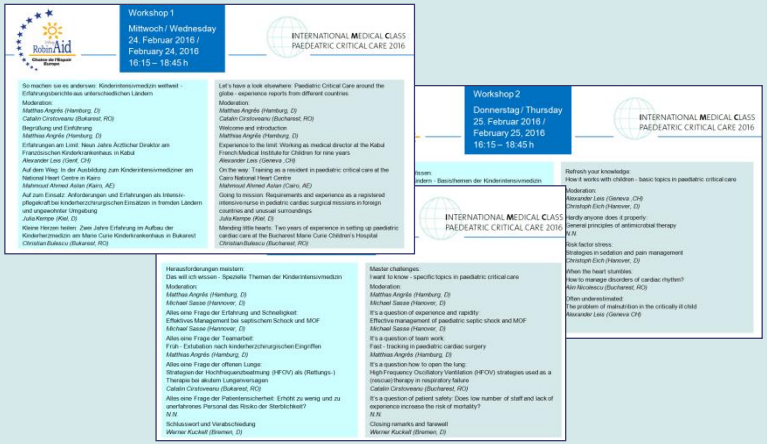
RobinAid performs the following fellowship programs:

Paediatric Cardiac Critical Care
Paediatric Cardiac Nursing
Paediatric Cardiac Anaesthesia

International Medical Class Bremen Symposium Intensive Care Medicine + Intensive care Nursing

The **IMC** Paediatric Critical Care is a joint - project between the Bremen Symposium Intensive Care Medicine + Intensive Care Nursing and RobinAid Foundation.

International fellows are coming to Bremen to learn and discuss with German and colleagues in interesting workshops.



Common projects with Bambini Cardiopatici nel Mondo

Dohuk Azadi Heart Centre

Cairo
Giza El Agouza Hospital

Dakar Paeditric Cardiac Centre
Fan University Hospital

Main project with La Chaine de l‘Espoir

French Medical Institute for Children
Kabul / Afghanistan

This children hospital was founded in 2006 by our French parent organization La Chaîne de l‘Espoir and is managed by the Aga Khan Development Network. The PICU is the only mechanical ventilation unit throughout Afghanistan. More than 1,200 children are treated and more than 250 paediatric cardiac surgeries are performed annually.

Paediatric Cardiac Surgery at Bucharest Marie Curie Children‘s Hospital

Because of the urgent need in 2011 the local NGO Inima Copiilor realized the construction of a brand new paediatric cardiac unit which was financed by a big fundraising campaign throughout Romania and the Ministry of Health.

The unit includes two operating theaters, 6 beds in the intensive care unit as well as a cath lab and is very well equipped. In September 2013 Bambini Cardiopatici nel Mondo started the first mission and in beginning of 2014 RobinAid joined the project.

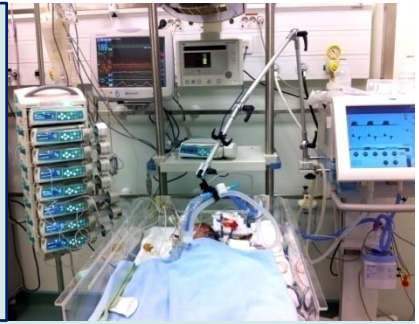
Involved partners

Bambini Cardiopatici nel Mondo:

Surgical teams

RobinAid Foundation:

ICU teams



Local Department of Paediatric Cardiology:

Preparation and follow up of the patients

Local Neonatal Intensive Care Unit:

Follow up by need of prolongued intensive care

Frequency of missions

	January	February	March	April	May	June	July	August	September	October	November	December
2013												
2014												
2015												

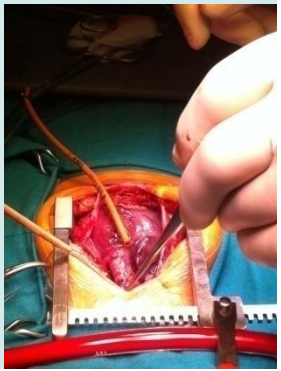
Procedures 9/13 - 6/15

DATE	DIAGNOSIS	INTERVENTION
23-Sep-13	ASD OS	ASD closure
23-Sep-13	ASD OS	ASD closure
24-Sep-13	ASD OS	ASD closure
24-Sep-13	ASD OS	ASD closure
25-Sep-13	ASD OS	ASD closure
2-Dec-13	ASD OS	ASD closure
3-Dec-13	ASD OS	ASD closure
4-Dec-13	PDA	PDA closure
4-Dec-13	ASD OS	ASD closure
9-Dec-13	Co Ao	Co Ao repair (Crafoord technique)
9-Dec-13	VSD	VSD closure
10-Dec-13	Co Ao	Co Ao repair (patch enlargement)
10-Dec-13	VSD	VSD closure
11-Dec-13	AVSD partial	AVSD repair
12-Dec-13	ASD + VSD	ASD + VSD closure
12-Dec-13	ASD OS	ASD closure

Data collected by Dr. Cristian Bulescu

DATE	DIAGNOSIS	INTERVENTION
3-Feb-14	Infundibular stenosis	Infundibular stenosis repair
3-Feb-14	VSD (Pezzi-Laubry)	VSD closure
4-Feb-14	TOF	TOF repair
4-Feb-14	ASD + VSD	ASD + VSD closure
5-Feb-14	VSD	VSD closure
5-Feb-14	VSD (Pezzi-Laubry)	VSD closure
6-Feb-14	VSD	VSD closure
6-Feb-14	Ao regurgitation S/P VSD repair	Ao valve replacement
7-Feb-14	ASD	ASD closure
7-Feb-14	VSD	VSD closure
7-Apr-14	VSD + mid-ventricular stenosis	VSD closure + resection
7-Apr-14	VSD	VSD closure
8-Apr-14	Co Ao	Co Ao repair (patch enlargement)
8-Apr-14	ASD + PAPVR	ASD closure + PAPVR repair
5-May-14	DORV type Fallot	Total repair
5-May-14	Subvalvular Ao stenosis	Subvalvular stenosis resection
6-May-14	TOF	TOF repair
6-May-14	Tricuspid atresia	Modified B-T shunt
7-May-14	AVSD partial	AVSD repair
7-May-14	VSD	VSD closure
8-May-14	ASD + PAPVR	ASD closure + PAPVR repair
8-May-14	Vascular ring	Vascular ring resection
9-May-14	ASD OS	ASD closure
9-May-14	ASD + PAPVR	ASD closure + PAPVR repair
8-Jul-14	PDA	PDA closure
8-Jul-14	ASD OS	ASD closure
9-Jul-14	PDA	PDA closure
9-Jul-14	PDA	PDA closure
9-Jul-14	PDA	PDA closure
25-Sep-14	PDA	PDA closure
25-Sep-14	DSA OS	ASD closure
26-Sep-14	PDA	PDA closure
26-Sep-14	ASD OS	ASD closure
26-Sep-14	VSD	VSD closure
29-Sep-14	TOF	TOF repair
29-Sep-14	VSD	VSD closure
30-Sep-14	DORV type Fallot	Total repair
1-Oct-14	TOF	TOF repair
1-Oct-14	ASD OS	ASD closure
2-Oct-14	VSD + infundibular stenosis	VSD closure + infundibular patch repair
2-Oct-14	TOF	Modified B-T shunt
3-Oct-14	ASD + VSD	ASD + VSD closure
13-Nov-14	Recurrent pericardial effusion	Pleuro-pericardial window
13-Nov-14	VSD	VSD closure
13-Nov-14	VSD	VSD closure
14-Nov-14	ASD OS	ASD closure
14-Nov-14	VSD	VSD closure
8-Dec-14	DORV type Fallot	Total repair
8-Dec-14	VSD	VSD closure
9-Dec-14	TOF	Total repair
9-Dec-14	VSD	VSD closure
10-Dec-14	TOF	Total repair
10-Dec-14	VSD	VSD closure
11-Dec-14	Co Ao	Co Ao repair (Crafoord technique)
11-Dec-14	Supravalvular pulmonary stenosis	Main pulmonary artery enlargement
12-Dec-14	ASD OS	ASD closure

DATE	DIAGNOSIS	INTERVENTION
12-Jan-15	VSD	VSD closure
12-Jan-15	TGA	Arterial switch operation
13-Jan-15	LCOS S/P ASO	Mediastinal inspection
14-Jan-15	Co Ao	Co Ao repair (patch enlargement)
14-Jan-15	VSD	VSD closure
15-Jan-15	S/P ASO	Delayed sternal closure
9-Feb-15	TOF	Total repair
9-Feb-15	VSD	VSD closure
10-Feb-15	VSD + mid-ventricular stenosis	VSD closure + resection
10-Feb-15	VSD + mid-ventricular stenosis	VSD closure + resection
11-Feb-15	TGA	Arterial switch operation
12-Feb-15	DORV type Fallot	Total repair
12-Feb-15	Subvalvular Ao stenosis + PDA	Ao valve repair + Ao valve replacement + PDA closure
13-Feb-15	Supravalvular aortic stenosis	Doty
23-Mar-15	TOF	Total repair
23-Mar-15	VSD	VSD closure
24-Mar-15	VSD + mid-ventricular stenosis	VSD closure + resection
24-Mar-15	VSD	VSD closure
25-Mar-15	VSD	VSD closure
25-Mar-15	PDA	PDA closure
26-Mar-15	Fibroadenoma of the right thigh with vascular involvement	Tumor resection
27-Mar-15	PDA	PDA closure
11-May-15	TOF + absent pulmonary valve	TOF repair
11-May-15	TOF	TOF repair
12-May-15	AVSD intermediate	AVSD repair
13-May-15	VSD + mid-ventricular stenosis	VSD closure + resection
13-May-15	DORV type Fallot	Total repair
14-May-15	ASD + VSD	ASD + VSD closure
15-Jun-15	AVSD complete	AVSD repair
16-Jun-15	AVSD complete	AVSD repair
16-Jun-15	TAPVR cardiac type	Total repair
17-Jun-15	Pulmonary pseudoatresia & intact septum	Pulmonary commissurotomy + infundibular patch
18-Jun-15	DORV type Fallot	Total repair
18-Jun-15	Pulmonary atresia & intact septum	Pulmonary commissurotomy
19-Jun-15	AVSD partial + pectus excavatum	AVSD repair + pectus repair
22-Jun-15	Pu veins stenosis + DORV + Pu stenosis + ASD S/P TAPVR (cardiac) repair	Pulmonary veins enlargement
23-Jun-15	PDA	PDA closure
24-Jun-15	End-stage kidney disease	Brachio-basilic fistula creation

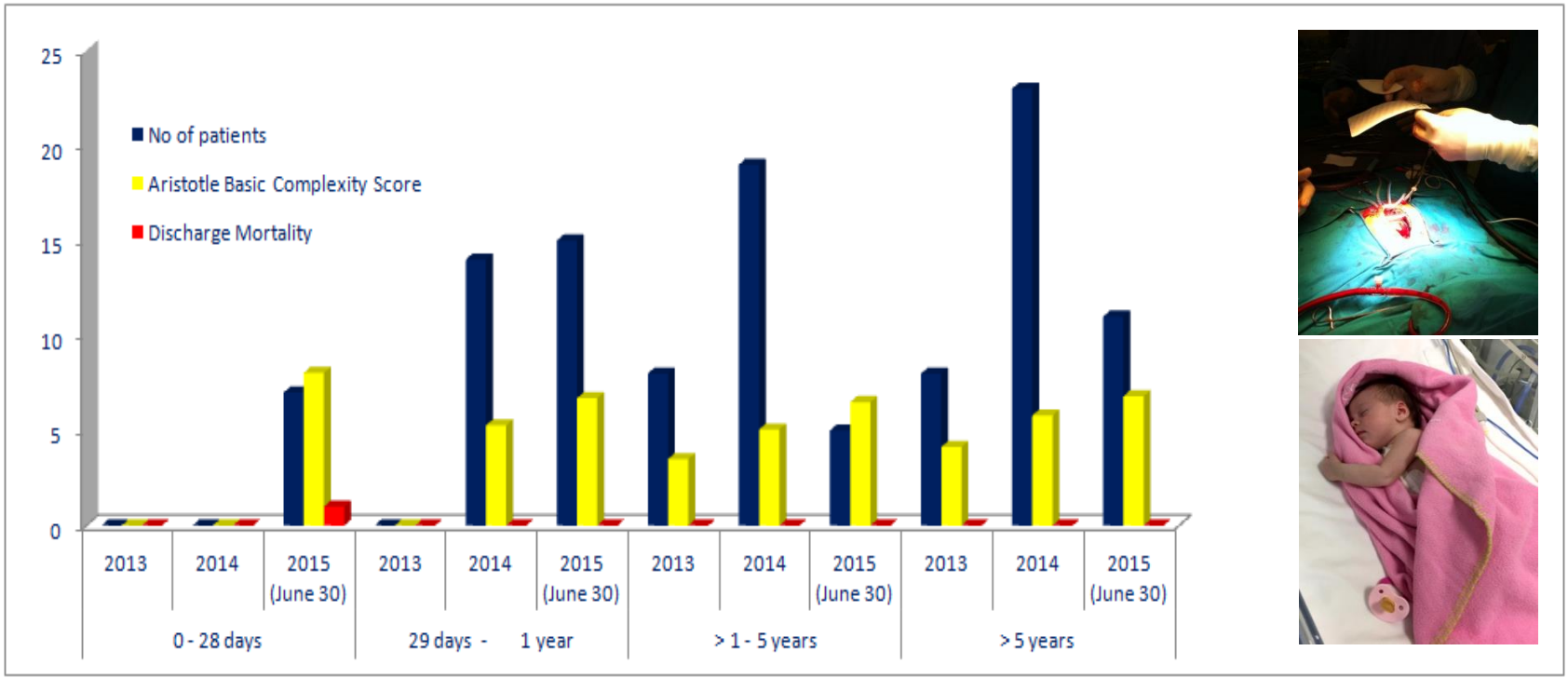


Results

Year	2013				2014				2015 (by June 30)				Total
Age	0 - 28 days	29 days - 1 year	> 1 - 5 years	> 5 years	0 - 28 days	29 days - 1 year	> 1 - 5 years	> 5 years	0 - 28 days	29 days - 1 year	> 1 - 5 years	> 5 years	
No of patients	0	0	8	8	0	14	19	23	7	15	5	11	110
Aristotle Basic Complexity Score	0	0	3,5	4,13	0	5,27	5,06	5,79	8,04	6,7	6,5	6,8	5,59
Discharge Mortality	0	0	0	0	0	0	0	0	1	0	0	0	1 (0,9%)

Data collected by Dr. Cristian Bulescu

Results



Data collected by Dr. Cristian Bulescu

Now let‘s start with the todays‘s topic

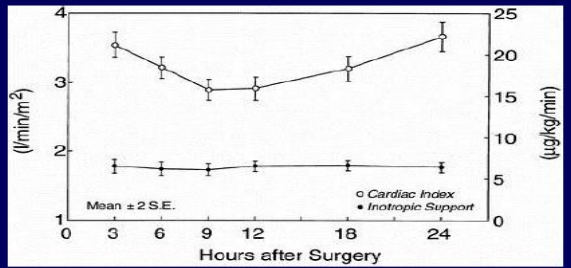
1. Inotropic agents in paediatric cardiac critical care

"Because of your age, I'm going to recommend doing nothing."

Heart failure / Low Cardiac Output

Low cardiac output syndrome (LCOS) is a clinical condition that is caused by a transient decrease in systemic perfusion secondary to myocardial dysfunction. The outcome is an imbalance between oxygen delivery and oxygen consumption at the cellular level which leads to metabolic acidosis.

- Wernovsky et al reported that 25% of neonate with DTGA who underwent ASO had a decline in CI to <2L/Min/M2



Wessel, DL. Crit Care Med 2001;29(10):S220-S230

Important

Low cardiac output syndrome (LCOS) is the most important cause of morbidity and mortality in the early postoperative phase.
It is an urgent indication for an immediate goal directed therapy.

Don’t lose time!

Heart failure / Low Cardiac Output

Etiology of Low Cardiac Output Syndrome following congenital heart surgery

- Inadequate myocardial protection
- Myocardial ischemia during aortic cross clamping and cardioplegia
- Reperfusion injuries
- Hypothermia
- Ventriculotomy
- Post - bypass inflammatory injury:
  systolic contractile dysfunction
  diastolic dysfunction (altered preload)
  altered vascular reactivity (altered afterload)

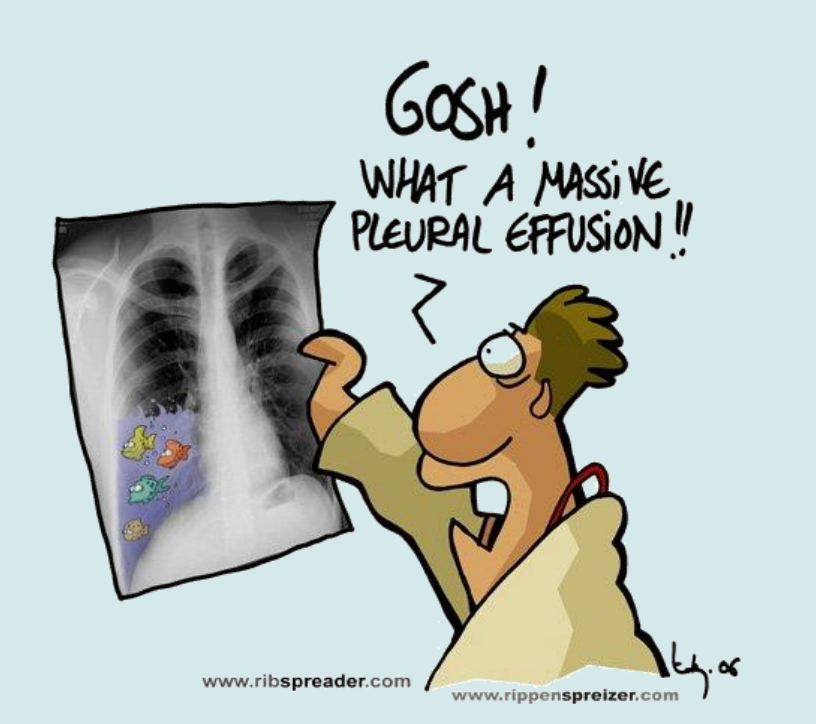
Heart failure / Low Cardiac Output

Etiology of Low Cardiac Output Syndrome following congenital heart surgery

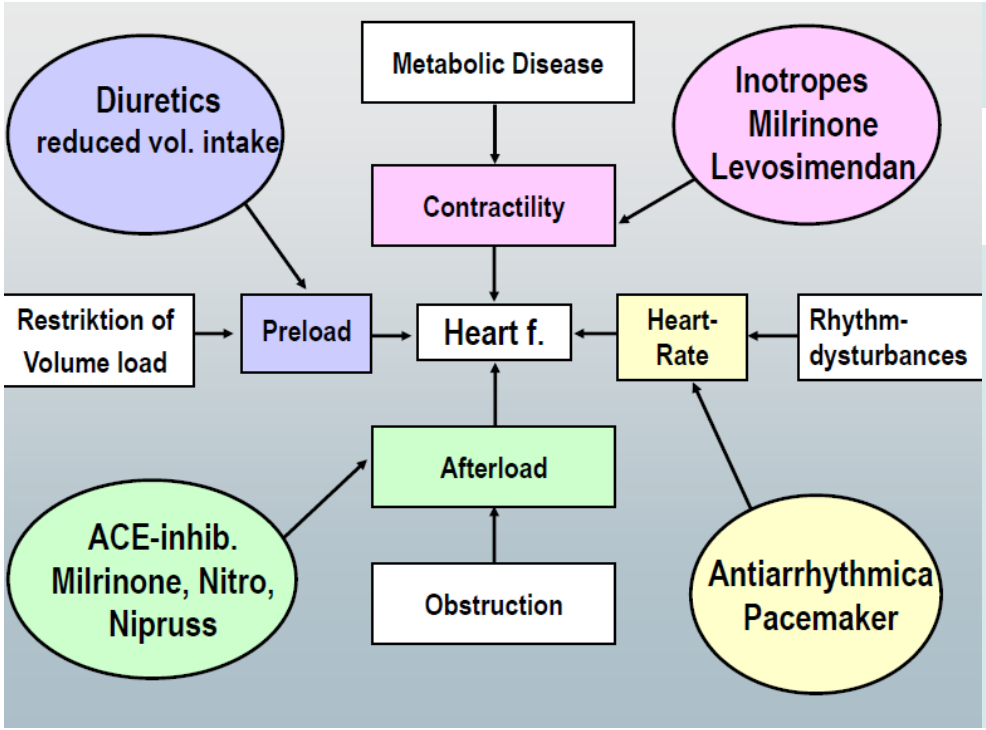
- Loss of AV synchrony
- Residual cardiac lesion
- Post-op. bleeding
- Pulmonary hypertension
- Endocrine derangement (Cortisol, Thyroid, Vasopressin)

Clinical presentation

- Tachycardia / Dysrhythmia
- Hypotonia, small amplitude of blood pressure
- Mottled skin and delayed capillary refill
- Centralization
- Low urine output
- Pulmonary edema
- Pericardial effusion
- Hepatomegaly
- Ascitis
- Generalized edema
- Multiorgan failure



Management



Heart failure treatment is more than inotropes!

Management

Catecholamine therapy

… is not a curative intervention, but a temporary support,

…effects and side effects have to be considered well,

…is only a part of medical treatment in LCOS,

…can be necessary to provide cellular oxygen supply + organ perfusion during / after CPB surgery.

Caution:

“perfusion is not the same as pressure!”

Management

First line :

Additional strategies

- Reduction of oxygen demand: sedation / analgesia / control fever / paralysis (?)
- Normalization of acidosis (NaHCO3)
- Optimizing of Oxygenation
  ventilation
  FiO2 high
  RBC - transfusion

Let‘s discuss

Case:

- 8 years, VSD, 24 kg, ICU for 20 min.
  RR 70/40 mmHg
  ECG: SR 155 bpm
  Lactate elevated
- What would you do ?
- Do you need more information ?
  Normal oxygenation and ventilation
  CVP 2 mmHg
  Mixed venous saturation: 55 %

Let‘s discuss

What is your therapy of choice?

?

- Adrenalin iv 0.25 mcg bolus
- Adrenalin infusion (0.1 mcg/kg/min)
- Crystalloide volume (300 ml in 30 min)
- Noradrenalin iv 0.4 mcg bolus
- Milrinone (0.6 mcg/kg/min)
- Levosimendan (0.2 mcg/kg/min)

The right answer

RR 72/40 mmHg	→	95/40 mmHg
ECG: SR 135 bpm	→	SR 95 bpm
Lactate elevated	→	normalized

Normal oxygenation and ventilation

CVP 2 mmHg	→	5 mmHg
Mixed venous saturation: 55 %	→	65 %

- Adrenalin iv 0.25 mcg bolus
- Adrenalin infusion (0.1 mcg/kg/min)
- Crystalloide volume (300 ml in 30 min)
- Noradrenalin iv 0.4 mcg bolus
- Milrinone (0.6 mcg/kg/min)
- Levosimendan (0.2 mcg/kg/min)

Before you use catecholamine therapy ...

- Perform haemodynamic measurements
- Check ventilation, x-ray…
- Treat metabolic acidosis
- Optimize fluid status
- Rule out arrhythmia

Monitoring

Invasive monitoring is necessary during catecholamine therapy!

- NIBP-measurements are often misleading (too high)
- Central venous pressure: RV function and fluid status
- Mixed venous saturation: cardiac output
- Arterial BP: perfusion pressure (area under curve)
- Arterial saturation: organ perfusion
- Lactate: organ perfusion

Catecholamine

What is the ideal catecholamine?

- It should increase the cardiac index + stabilize blood pressure

  WITHOUT

  increase in myocardial oxygen consumption

  disturbance of microcirculation due to vasoconstriction

  Inflammation, elevated cytokines (SIRS) + cardio toxicity

Let‘s discuss

- Dopamine
- Dobutamine
- Epinephrine / Adrenaline
- Norepinephrine / Noradrenaline
- Milrinone
- Levosimendan …..

What do you think …. is it

?

Dopamine

- Precursor of norepinephrine
- Releases norepinephrine in the heart
- Moderate α1, α2 and ß1- effect
- Direct effect on dopaminergic receptors (DA1, DA2)

- Effects are dose-dependent:
- **Low dose 1 - 5 mcg/kg/min:** increases renal and mesenteric blood flow (vasodilation)
- **Intermediate-dose 5 - 15 mcg/kg/min:** increases renal blood flow, heart rate, cardiac output (DA and ß1- effect)
- **High dose > 15 mcg/kg/min:** systemic and pulmonary vasoconstriction (α-effect)

Dopamine

BUT …. Severe adverse effects:

- **On heart rhythm:**
  tachycardia, induces VT´s
- ectopic beats
- AV-conduction abnormalities
- **pulmonary vasoconstriction**
- **Decrease of pituitary gland hormones:**
  prolactine (decrease of lymphocyte and macrophage activation)
  growth hormone (catabolism)
  Interaction with thyroid gland

Dopamine

There is no evidence-based data supporting the use of Dopamine as a renal protector in patients with heart failure !

We (and the most of the internantional centres all over the wolrd) **stopped giving Dopamine** in paediatric cardiac critical care.

Dobutamine

- Synthetic catecholamine with β1 inotropic effect (increases stroke volume) and β2 peripheral vasodilation (decreases afterload)
- Positive chronotropic effect (1β1, HR ↑)
- Some lusotropic effect
- No norepinephrine release

- Major metabolite is 3-O-methyldobutamine, a potent inhibitor of alpha-adrenoceptors
- Therefore, vasodilation is possible, secondary to this metabolite.
- Usual starting infusion rate is **5 mcg/kg/min**, with the dose being titrated to effect up **to 20 mcg/kg/min**.

Dobutamine

BUT …. Some adverse effects:

- **On heart rhythm:**
  tachycardia
  ectopic beats
- **Chest pain**
- **Contra indication:**
  LVOT obstruction in hypertrophic subaortic stenosis because increase of the outflow gradient

Norepinephrine

- Precursor of Epinephrine
- Acts primarily on α receptors
- **Increases Systemic vascular resistance** (SVR) without significantly increasing cardiac output (CO)
- Used in cases of low SVR and hypotension such as profound “warm shock” with a normal or high CO

- Dose:
  0,01 - 0,3 mcg/kg/min in LCOS
  0,4 - 2 mcg/kg/min in vasoplegia or under resuscitation by septic shock
- If effect **in vasoplegia** is not strong enough, think about Vasopressin

Norepinephrine

BUT …. Severe adverse effects:

- Tachycardia and tachyarrhythmias
- Increased myocardial oxygen requirements and **potential to cause ischemia**
- **Decreased splanchnic and hepatic circulation** (elevation of AST and ALT)
- Dermal necrosis
- Anti-Insulin effects: **lactic acidosis, hyperglycemia**

Epinephrine

- Adrenergic agonist with multiple actions on various organs
- potent α1-, ß1- and ß2- effect
- **Effects are dose-dependent:**

- **Low dose < 0.02 mcg/kg/min:**
  ß2 - effect, but β1 predominantly
  HR ↑**,** Duration of Systole ↓
  Myocardial contractility ↑
  Peripher arteriolar dilatation
  Renal BF ↑**/** ↓
  Renin secretion ↑
  Splanchnic BF ↑**/** ↓
  Glucose ↑
  Hypokalemia

Epinephrine

- Adrenergic agonist with multiple actions on various organs
- potent α1-, ß1- and ß2- effect
- **Effects are dose-dependent:**

- **Reasonable inotropic dose**
  0,02 - 0,5 mcg/kg/min
  β1- effect still present, but also α1- effect
  HR ↑, Duration of Systole ↓
  Myocardial contractility ↑/ ↓
  Renal BF ↓
  Renin secretion ↑
  Splanchnic BF ↓
  Glucose ↑
  Lactat ↑

Epinephrine

- Adrenergic agonist with multiple actions on various organs
- potent α1-, ß1- and ß2- effect
- **Effects are dose-dependent:**

- **High dose > 0,5 - 2,0 mcg/kg/min**

  α1 effect predominantly

  Vasoconstriction

  Renal BF ↓

  Splanchnic BF ↓

  Glucose ↑

  Lactat ↑ ↑ ↑

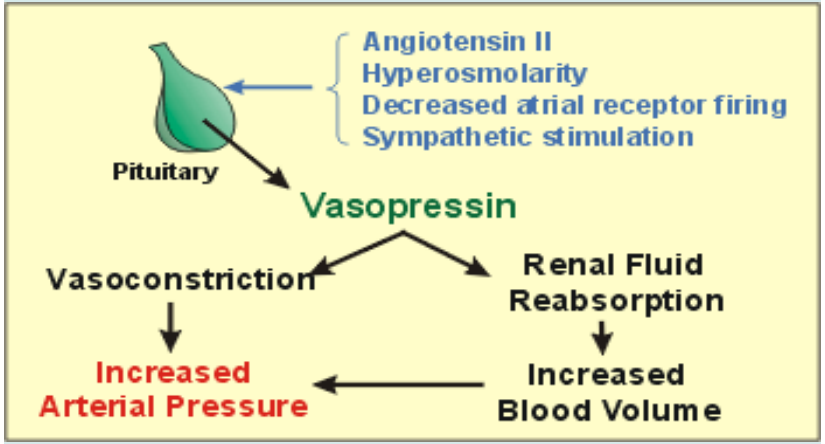
Epinephrine

BUT …. Severe adverse effects:

- Marked metabolic effect (hyperglycaemia, leucocytes↑)
  Tachycardia, ectopic beats,
  Decreased renal blood flow
  Ischemia, abdominal pain, bladder retention
  High doses can induce apoptosis of myocardial cells

(Vasopressin)

- *Peptide hormone, released by the posterior pituitary in response to rising plasma tonicity or falling blood pressure*
- *Possesses antidiuretic and vasopressor properties*
- *deficiency of this hormone results in diabetes insipidus*



(Vasopressin)

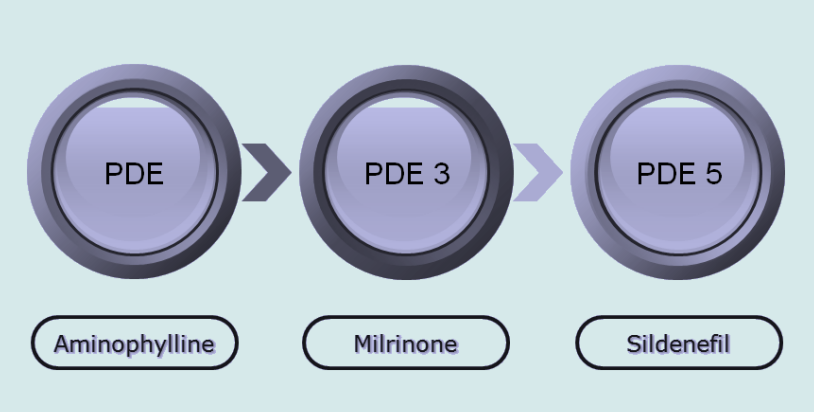
- *Administration by intravenous, intramuscular, or intranasal routes*
- *IV is route for vasopressor activity*
- *The half-life of circulating ADH is approximately 20 minutes, with renal and hepatic catabolism via reduction of the disulfide bond and peptide cleavage*

- *Interacts with two types of receptors*
  V1 receptors are found on vascular smooth muscle cells and mediate vasoconstriction
  V2 receptors are found on renal tubule cells and mediate antidiuresis through increased water permeability and water resorption in the collecting tubules
- ***Newer use in paediatric cardiac critical care !!!***
- *Maybe use in refractory septic shock with low SVR*

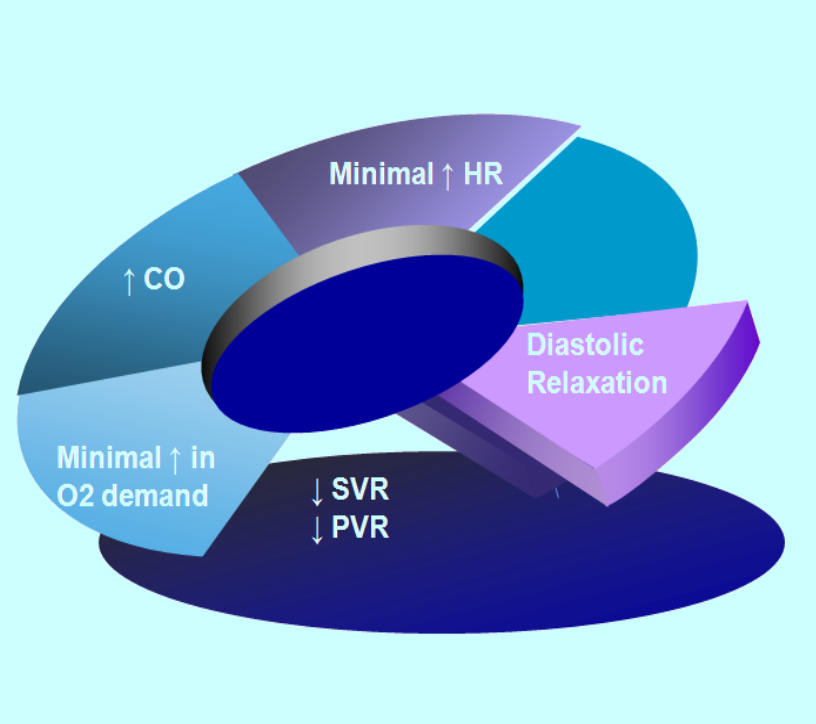
Milrinone

- Non-receptor mediated activity based on selective **inhibition of Phosphodiesterase Type III** enzyme resulting in cAMP accumulation in myocardium
- cAMP increases force of contraction and rate and extent of relaxation of myocardium
- **Inotropic, vasodilator and lusotropic effects**

- **Advantage over catecholamines:** Independent action from β - receptor activation, particularly when these receptors are down regulated (CHF and chronic catecholamine use)



Milrinone



- Increases CO by improving contractility
- Decreased SVR, PVR
- **Lusotropic effect**
- Decreased preload due to vasodilatation
- **Unique in beneficial effects on RV function**
- Half-life is 1-2 hours
- **Load with 50 mcg/kg** over 30 mins followed by **0.25 to 0.75 mcg/kg/min**
- No increase in myocardial O2 requirement

Milrinone

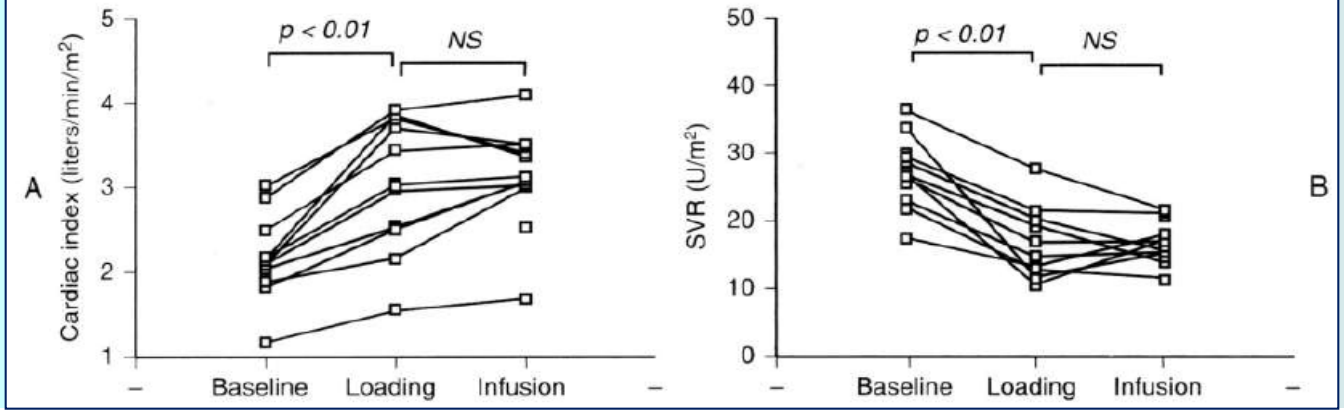
PRIMACORP study — Milrinone vs Placebo

Prophylactic iv Use of Milrinone after Cardiac Operation in Pediatrics (n=220)

Crit Care Med 1995:33:1907

46% reduced risk to develop LCOS after cardiac surgery

Cardiac Index improves — **Systemic resistant reduced**

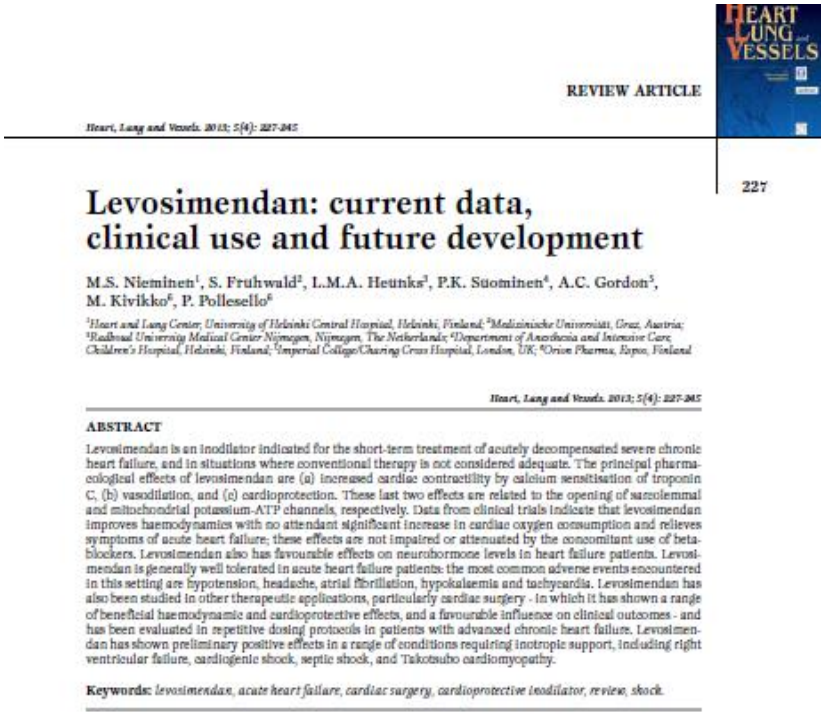


Levosimendan

- Levosimendan is a calcium sensitiser
- It exerts its **positive inotropic effect** by increasing calcium sensitivity of myocytes by binding to cardiac troponin C in a calcium-dependent manner
- It also has a **vasodilatory effect** by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle to cause smooth muscle relaxation.

- Data from clinical trials indicate that Levosimendan **improves haemodynamics with no attendant significant increase in cardiac oxygen consumption** and relieves symptoms of acute heart failure
- These effects are not impaired or attenuated by the concomitant use of beta-blockers.

Levosimendan



REVIEW ARTICLE

Heart, Lung and Vessels. 2013; 5(4): 227-245

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Levosimendan: current data, clinical use and future development

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[1]Heart and Lung Center, University of Helsinki Central Hospital, Helsinki, Finland; [2]Medizinische Universität, Graz, Austria; [3]Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands; [4]Department of Anesthesia and Intensive Care, Children's Hospital, Helsinki, Finland; [5]Imperial College/Charing Cross Hospital, London, UK; [6]Orion Pharma, Espoo, Finland

Heart, Lung and Vessels. 2013; 5(4): 227-245

ABSTRACT

Levosimendan is an inodilator indicated for the short-term treatment of acutely decompensated severe chronic heart failure, and in situations where conventional therapy is not considered adequate. The principal pharmacological effects of levosimendan are (a) increased cardiac contractility by calcium sensitisation of troponin C, (b) vasodilation, and (c) cardioprotection. These last two effects are related to the opening of sarcolemmal and mitochondrial potassium-ATP channels, respectively. Data from clinical trials indicate that levosimendan improves haemodynamics with no attendant significant increase in cardiac oxygen consumption and relieves symptoms of acute heart failure; these effects are not impaired or attenuated by the concomitant use of beta-blockers. Levosimendan also has favourable effects on neurohormone levels in heart failure patients. Levosimendan is generally well tolerated in acute heart failure patients: the most common adverse events encountered in this setting are hypotension, headache, atrial fibrillation, hypokalaemia and tachycardia. Levosimendan has also been studied in other therapeutic applications, particularly cardiac surgery - in which it has shown a range of beneficial haemodynamic and cardioprotective effects, and a favourable influence on clinical outcomes - and has been evaluated in repetitive dosing protocols in patients with advanced chronic heart failure. Levosimendan has shown preliminary positive effects in a range of conditions requiring inotropic support, including right ventricular failure, cardiogenic shock, septic shock, and Takotsubo cardiomyopathy.

Keywords: *levosimendan, acute heart failure, cardiac surgery, cardioprotective inodilator, review, shock.*

- Levosimendan is an inodilator **indicated** for the **short-term treatment** of acutely decompensated severe chronic heart failure, and **in situations where conventional therapy is not considered adequate**.
- Preferred Dose: Load with **12 mcg/kg bolus** over 30 mins followed by **infusion with rates up to 0.2 mcg /kg /min /24h**

Levosimendan in children

Pediatr Crit Care Med. 2006 Sep;7(5):445-8.

Early experience with Levosimendan in children with ventricular dysfunction.

Namachivayam P[1], Crossland DS, Butt WW, Shekerdemian LS.

Author information

Erratum in
Pediatr Crit Care Med. 2007 Mar;8(2):197.

Abstract

OBJECTIVE: To describe our preliminary experience with Levosimendan, a new calcium-sensitizing agent i severe heart failure.

DESIGN: Retrospective cohort analysis.

SETTING: Pediatric intensive care unit.

PATIENTS: Fifteen children aged 7 days to 18 yrs (median age 38 months) with severe myocardial dysfunc or acute heart failure, who were inotrope-dependent (requiring at least one catecholamine).

INTERVENTIONS: A single dose (bolus and intravenous infusion over 24-48 hrs) of Levosimendan was giv monitoring in our intensive care unit. Eleven children received a single dose, three children received two dos Echocardiographic assessments of ventricular function were made before and 3-5 days after Levosimendan

MEASUREMENTS AND MAIN RESULTS: Heart rate, systolic pressure, diastolic pressure, mean blood pre unchanged during and after Levosimendan. Levosimendan allowed for discontinuation of catecholamines in The dose of dobutamine was reduced from 6.4 microg/kg/min pre-Levosimendan to 1.8 microg/kg/min on da group as a whole improved from 29.8% to 40.5% (p = .015); this did not increase significantly in patients with end-stage heart failure but increased by 63% in the children with acute heart failure.

CONCLUSIONS: Levosimendan can be safely administered to infants and children with severe heart failure. Levosimendan allowed for substantial reduction in catecholamine infusions in children with end-stage or acute heart failure and also produced an objective improvement in myocardial performance in children with acute heart failure.

- Levosimendan can be safely administered to infants and children with severe heart failure
- Levosimendan allowed for substantial reduction in catecholamine infusions in children with end-stage or acute heart failure and also produced an objective improvement in myocardial performance in children with acute heart failure.

Inotropic agents

What is the ideal catecholamine?

- Dopamine
- Dobutamine
- Epinephrine / Adrenaline
- Norepinephrine / Noradrenaline
- **Milrinone**
- Levosimendan …..

- It increase the cardiac index + stabilize blood pressure

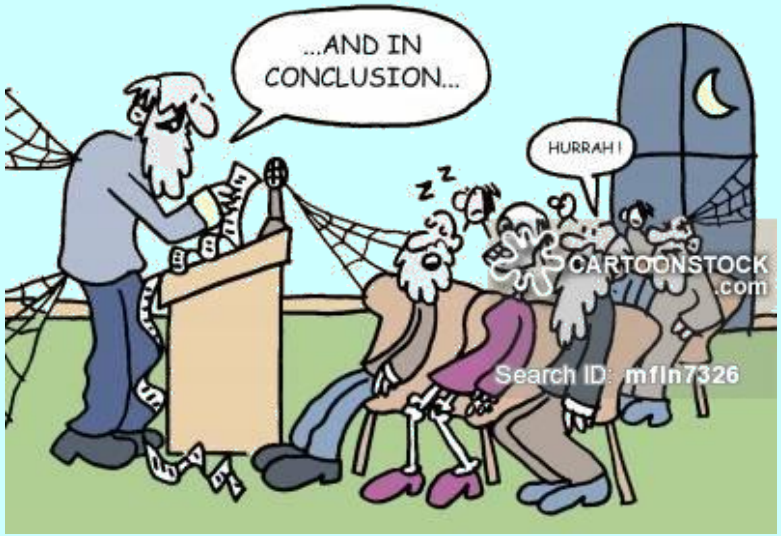
  WITHOUT

  increase in myocardial oxygen consumption

  disturbance of microcirculation due to vasoconstriction

  Inflammation, elevated cytokines (SIRS) + cardio toxicity

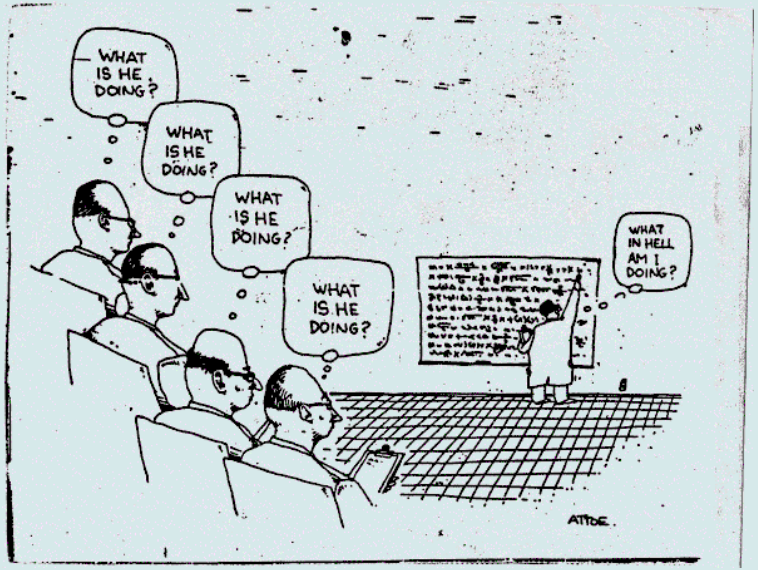
Conclusion



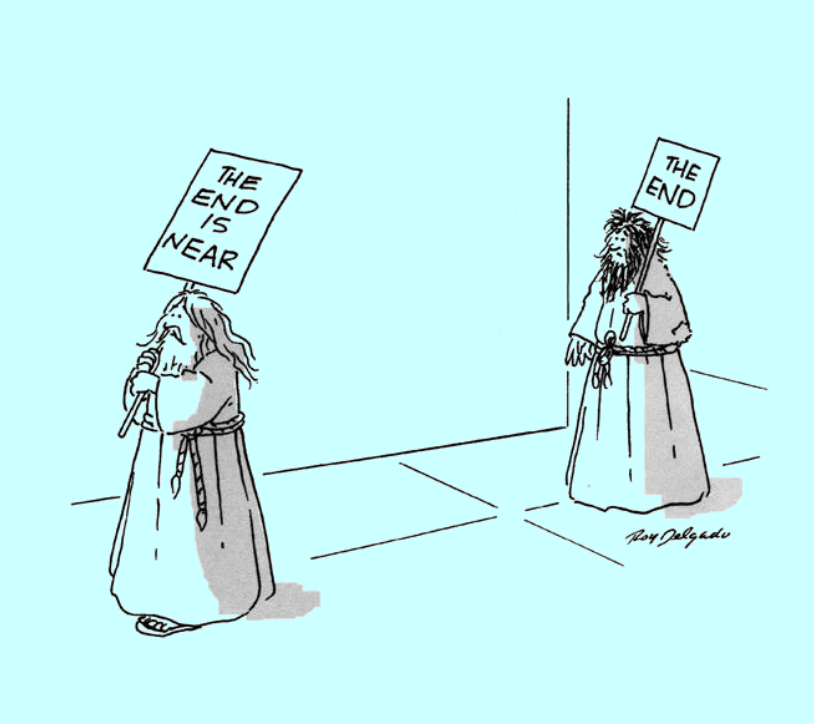
- Very poor evidence based data about inotropes in paediatric critical care
- Milrinone might be the drug of choice
- Dopamine can not be recommended for the first choice

Conclusion

- Dobutamine is recommended in low-output but often fails in LCOS
- A combination of dobutamine and norepinephrine is recommended only in adult LCOS



Conclusion

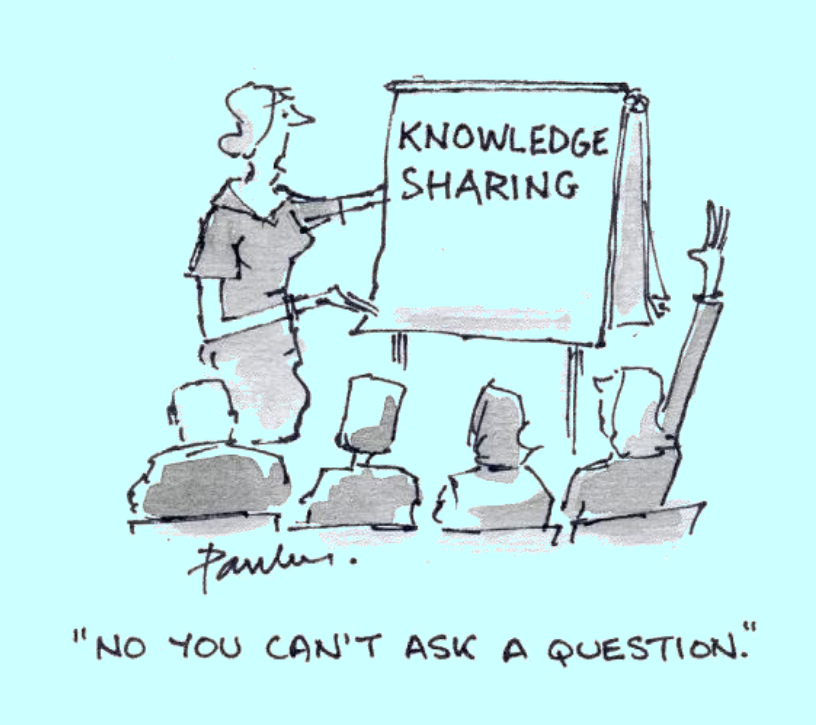


- Higher dosis Epinephrine has adverse effects and interferes with many organ systems
- Epinephrine can be used alone only in mild LCOS

Conclusion

- Epinephrine can be used together with Milrinone (or Levosimendan) in severe LCOS
- Milrinone can be used also for prevention of LCOS in paediatric cardiac surgery

Thank you for your attention



Yes, you can!