Prim. Doz. Dr. Johann Knotzer, MSc
Anästhesiologie und Intensivmedizin
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Hämodynamik - wann Gas, wann Bremse?

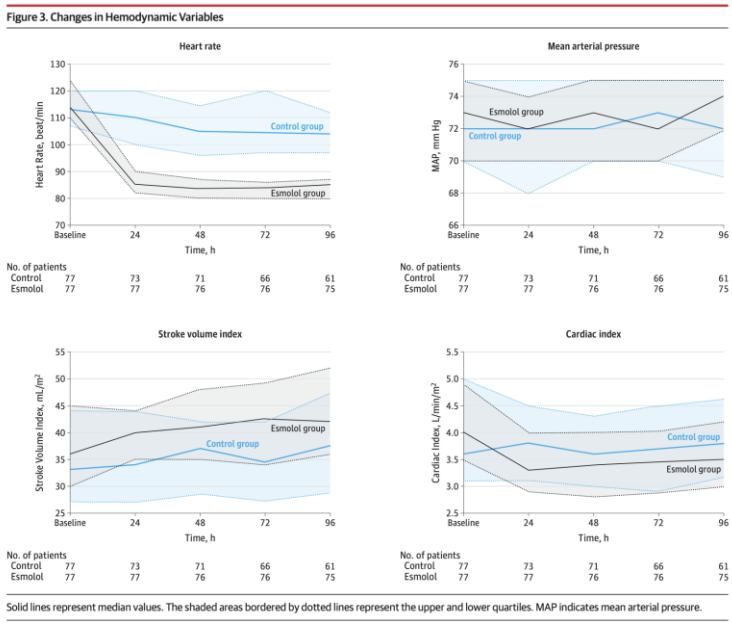
Declaration of Interest

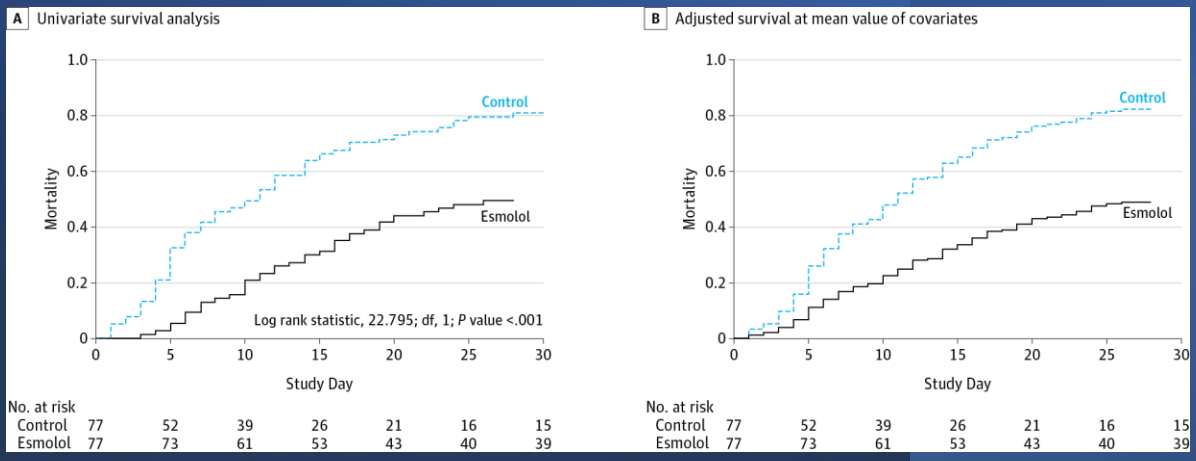
- Honoraria from AOP Health und Astropharma


"A cat killer? Is that the face of a cat killer? Cat chaser maybe. But hey—who isn't?"

Morelli, JAMA, 2013

Esmolol in Septic Shock





Morelli, JAMA, 2013

Rehberg S, Intensive Care Medicine 2024

Landiolol in Septic Shock

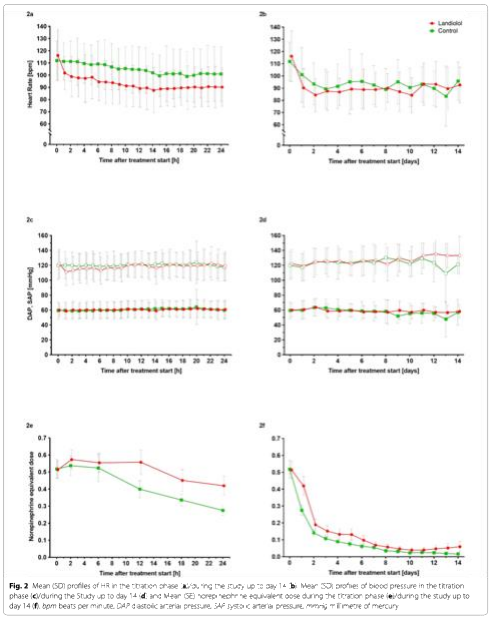


Fig. 2 Mean (SD) profiles of HR in the titration phase (**a**) during the study up to day 14 (**b**). Mean (SD) profiles of blood pressure in the titration phase (**c**) during the study up to day 14 (**d**) and Mean (SD) norepinephrine equivalent dose during the titration phase (**e**) during the study up to day 14 (**f**). bpm beats per minute, DAP diastolic arterial pressure, SAP systolic arterial pressure, mmHg millimetre of mercury

Table 3 Secondary efficacy analyses

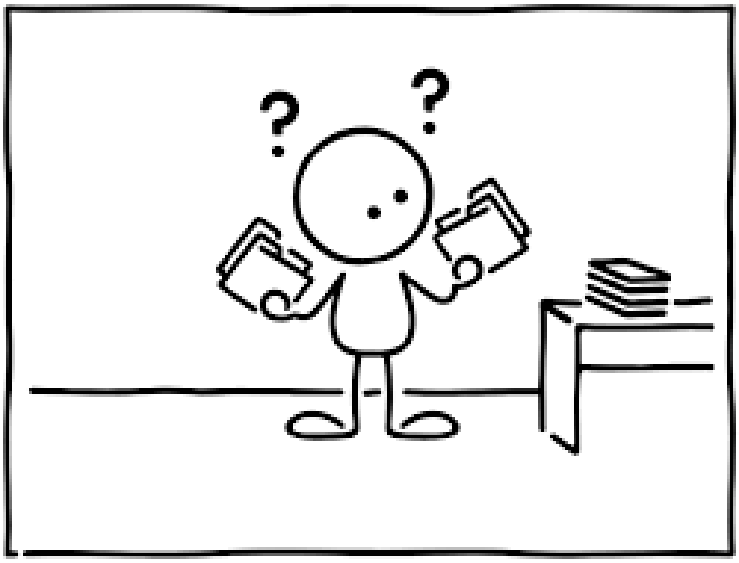
Response	Landiolol group ($n = 98$)	Control group ($n = 98$)	Overall	Effect estimate (95% CI)	*P* value
28-day mortality, n (%)[a]	43 (43.9)	39 (40.2)	82 (42.1)	MD, 3.8% (− 9.9 to 17.3%)	0.60
ICU mortality, n (%)[b]	43 (43.9)	33 (34)	76 (39)	MD, 9.9% (− 3.8 to 23%)	0.16
Duration of ICU stay for patients alive on day 28, median (95% CI), days	14 (10.2–15.3)	13.9 (10.2–20.4)	–	HR, 1.17 (0.70–1.94)	0.55
Duration of hospital stay for patients alive on day 28	–	–	–	HR, 0.80 (0.41–1.54)	0.50

CI confidence interval, *HR* hazard ratio, *ICU* intensive care unit, *MD* mean difference, *SD* standard deviation

[a] *N* (Landiolol group) = 98, *N* (Control group) = 97

Rehberg S, Intensive Care Medicine 2024

Wo liegt der Unterschied?



Faktor Zeit

Rivers E. NEJM 2001

Rivers Studie – Early Goal Directed Therapy

TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

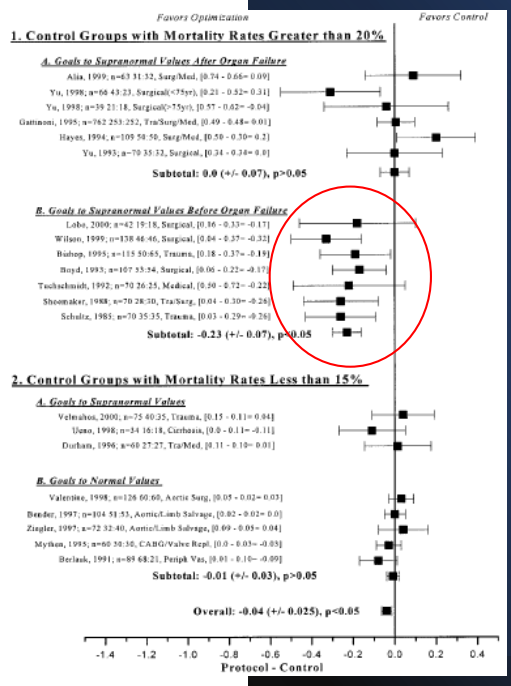
*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

Fluss und Zeit

- **Supranormal:**
- CI > 4.5 L/min/m2
- DO2I > 600 ml/min/m2
- VO2I > 170 ml/min/m2



Knotzer H. Anesth Analg 2006

Zeitpunkt des MODS

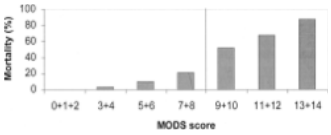


Figure 1. Mortality and multiple organ dysfunction syndrome (MODS) score. Figure 1 presents data on intensive care unit (ICU) mortality of 2783 patients admitted to the Division of General and Surgical Intensive Care Medicine between 1999 and 2002. Patients with a MODS score ≤8 had a highly significant mortality rate when compared to patients with a MODS score >8 (3.81% [94 of 2469] versus 61.78% [194 of 314]; $P < 0.005$).

regional variables of microvascular function, such a comparison would have merely changed the fact that once MODS is established, regional variables of microvascular function and vascular reactivity do not reflect severity of organ dysfunction.

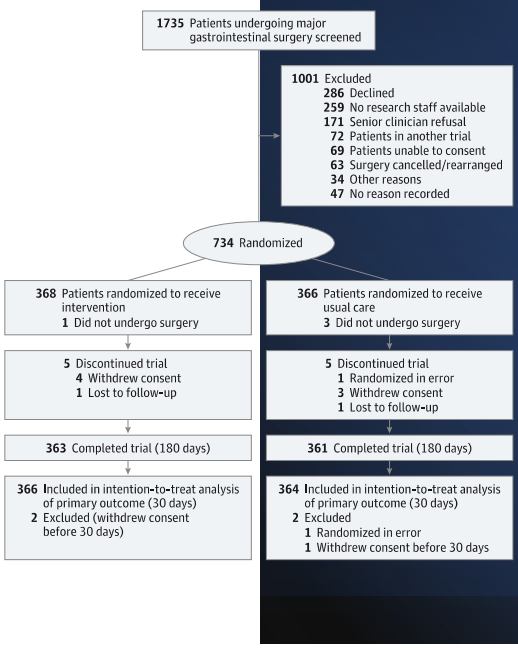
Table 3. Microcirculatory Measurements in Patients with Moderate and Severe Multiple Organ Dysfunction Syndrome

	Moderate MODS	Severe MODS	*P*-values
Reactive hyperemia			
Tc Po_2/Pco_2			
B-Ptco2 (mm Hg)	7.07 ± 5.23	8.87 ± 6.74	0.539
B-$Ptcco_2$ (mm Hg)	52.53 ± 10.55	56.67 ± 8.61	0.421
PIP-$Ptco_2$ (mm Hg)	17.00 ± 7.58	16.53 ± 9.82	0.885
PIP–B-$Ptco_2$ (mm Hg)	9.93 ± 6.79	7.67 ± 6.40	0.177
$ERCO_2$ (mm Hg/min)	0.38 ± 0.26	0.54 ± 0.33	0.172
LDF			
B-PU (PU)	14.91 ± 9.81	16.14 ± 7.22	0.418
PIP-PU (PU)	69.09 ± 41.67	58.15 ± 42.35	0.479
PIP – B PU (PU)	54.18 ± 36.42	42.02 ± 37.96	0.206
VCP			
Kf (mL · min $^{-1}$ · 100mL $^{-1}$ · mm $Hg^{-1} \times 10^{-3}$)	4.02 ± 1.48	5.33 ± 2.04	0.062
Pv_i (mm Hg)	15.34 ± 5.94	18.56 ± 4.63	0.122
Gastric tonometry			
pHi	7.37 ± 0.12	7.34 ± 0.14	0.501
Pco_2gap (mm Hg)	7.33 ± 1.72	9.69 ± 3.68	0.089

Values are given as mean ± SD. Tc Po_2/Pco_2 = transcutaneous Po_2/Pco_2 electrode; B-$Ptco_2$ = baseline cutaneous Po_2; B-$Ptcco_2$ = baseline cutaneous Pco_2; PIP-$Ptco_2$ = postischemic peak of $Ptco_2$; PIP-$Ptcco_2$ = postischemic peak of $Ptcco_2$;PIP–B-$Ptco_2$ = magnitude of reactive hyperemia (transcutaneous); $ERCO_2$ = elimination rate of carbon dioxide; LDF = laser Doppler flowmetry; B-PU = baseline perfusion units; PIP-PU = postischemic peak PU; PIP–B-PU = magnitude of reactive hyperemia (laser Doppler flowmetry); VCP = venous congestion plethysmography; K_f = filtration coefficient; Pv_i = isovolumetric venous pressure; pHi = intramucosal pH; Pco_2 gap = arterial carbon dioxide level minus regional intramucosal carbon dioxide level.

Gas geben!? HZV

- **Optimise** – Studie
- 734 hoch Risiko Patienten
- Cardiac output guided (LIDCO)
- Volumen (250 mL Colloid) u/o
- Dopexamin 0.5 µg/kg/min



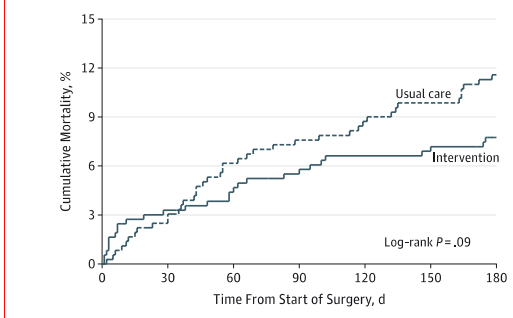
Pearse RM. JAMA 2014; 311:2181-2190

Optimise Studie

Outcomes	Cardiac Output–Guided Hemodynamic Therapy Algorithm	Usual Care	Relative Risk (95% CI)	*P* Value
POMS-defined morbidity at 7 d following surgery, No./total (%)[b]	182/275 (66.2)	195/287 (67.9)	0.97 (0.87-1.09)	.72
Infectious complications at 30 d following surgery, No./total (%)	87/366 (23.8)	108/364 (29.7)	0.80 (0.63-1.02)	.08
Critical care–free days at 30 d following surgery, median (IQR)	27 (26-29)	28 (25-29)		.98
All-cause mortality at 30 d following surgery, No./total (%)[c]	12/366 (3.3)	11/364 (3.0)	1.08 (0.48-2.43)	>.99
All-cause mortality at 180 d following surgery, No./total (%)[d]	28/363 (7.7)	42/361 (11.6)	0.66 (0.42-1.05)	.08
Duration of postoperative hospital stay, median (IQR), d	10 (7-14)	11 (7-17)		.05
Survivors	10 (7-14)	11 (7-17)		
Nonsurvivors	7 (3-33)	16 (9-36)		

Pearse RM. JAMA 2014; 311:2181-2190

Figure 2. Cumulative Incidence of Mortality Up to 180 Days After Surgery Using a Cardiac Output–Guided Hemodynamic Therapy Algorithm Intervention vs Usual Care



No. at risk

Intervention	368	350	344	339	334	333	306
Usual care	365	348	331	325	321	317	286

Catecholamines and Outcome

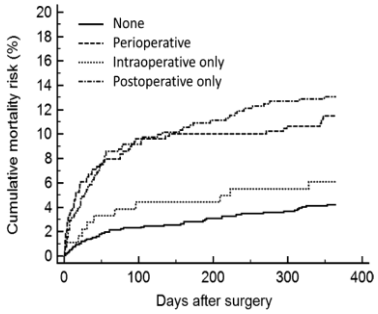


Fig. 4. Cumulative 1-yr mortality risk stratified by timing of inotropic therapy. Log-rank *P* value <0.0001.

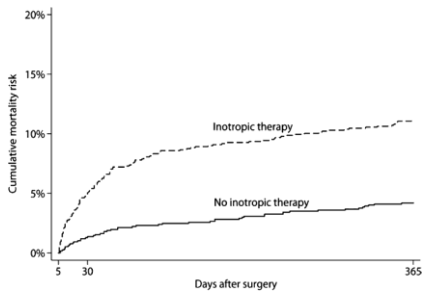


Fig. 3. Cumulative 1-yr mortality risk by treatment status. Log-rank *P* value <0.00001.

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

Results of a Propensity Score–matched Analysis

Dorthe Viemose Nielsen, M.D., Malene Kærslund Hansen, M.B.B.S., Søren Paaske Johnsen, M.D., Ph.D., Mads Hansen, M.D., Karsten Hindsholm, M.D., H.D., Carl-Johan Jakobsen, M.D.

Nielsen DV et al. Anesthesiology 2014; 120: 1098-1108.

Katecholamin-Toxicity

	Levosimendan	Dobutamin	Milrinon
Anstieg cAMP?	**Nein**	Ja	Ja
Zunahme O_2-Verbrauch?	**Nein**	Ja	Ja
Interaktion mit β-Blocker?	**Nein**	Ja	Nein
Zunahme Arrhythmien?	**Nein**	Ja	Ja
Tachyphylaxie?	**Nein**	Ja	Nein

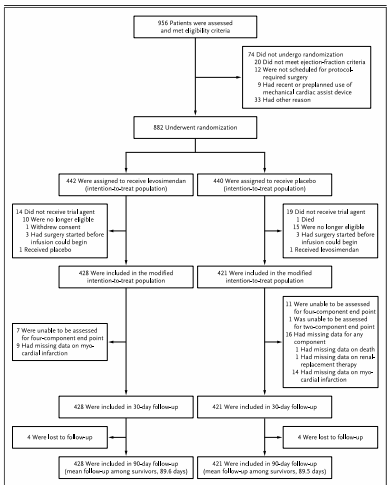
Buerke M, Symposium bei der gemeinsamen Jahrestagung der ÖGAIN und DGIN, 13. 6. 2014 (Abb. adaptiert)

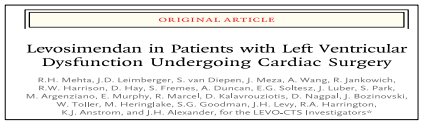
Überladung mit Ca intrazellulär führt zur Apoptose und Nekrose

Extremfall beim Gesunden „Tako-Tsubo-Kardiomyopathie“

Catecholamine Toxicity

LEVO-CTS




ORIGINAL ARTICLE

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

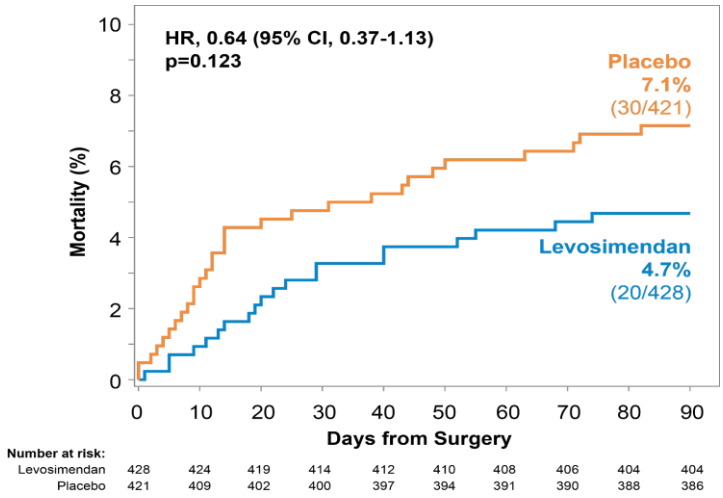
849 Patienten
EF < 35% herzchirurgisch mit HLM
0.2 µ/kg über 1 h dann
0.1 µ/kg über 23 h

LEVO-CTS. NEJM 2017;376:2032-42

Inotropie für jeden?

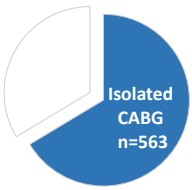
LEVO-CTS 90-Day Mortality

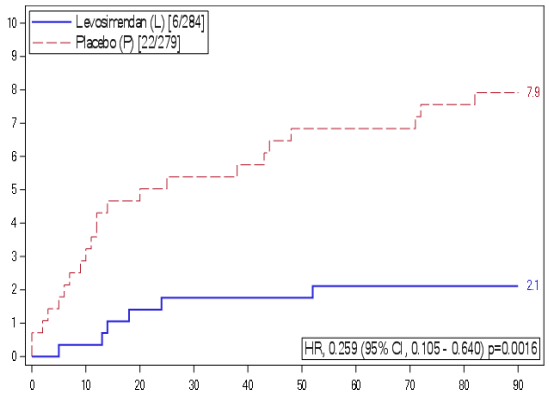
N=849 As Treated Population



Abhängig vom Eingriff?

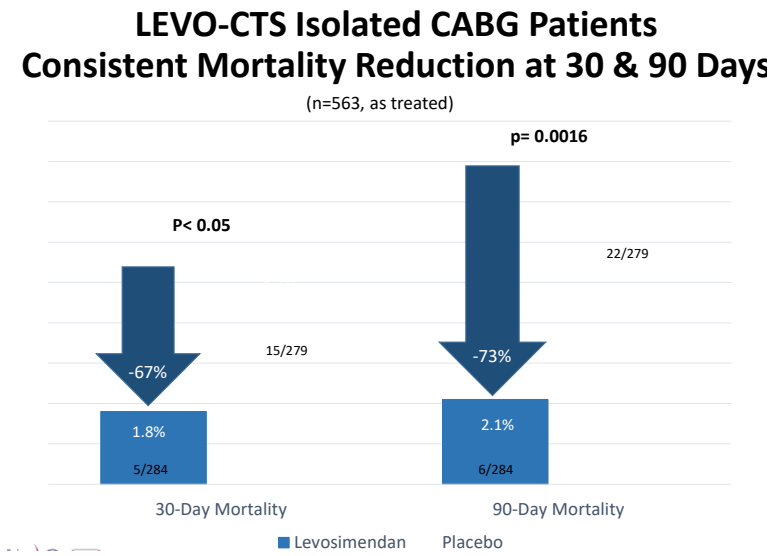
LEVO-CTS
90-Day Mortality in Isolated CABG Patients



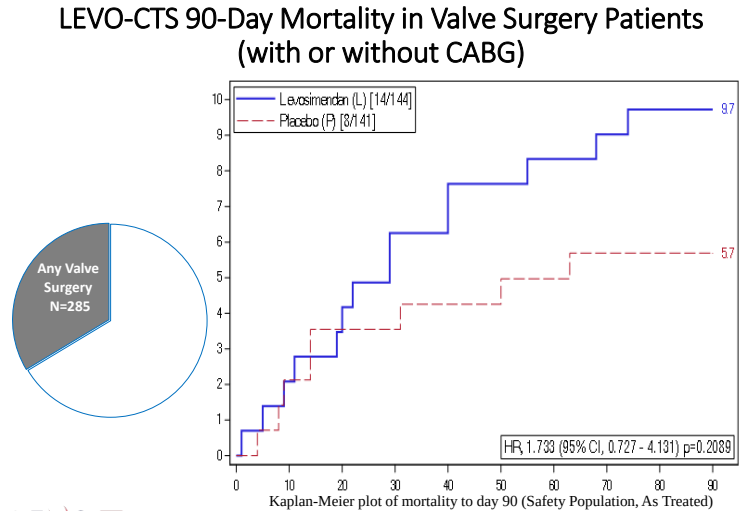


Kaplan-Meier plot of mortality to day 90 (Safety Population, As Treated)

Individuelle Therapie?



Bsp.: Klappen und Inotropie



CHEETAH und LICORN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

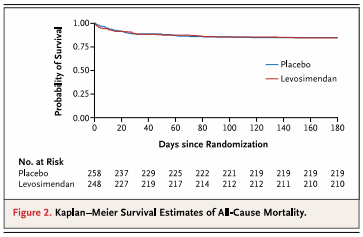


Figure 2. Kaplan–Meier Survival Estimates of All-Cause Mortality.

dan treatment. Fourth, we did not systematically collect cardiac-output data, which could have helped us understand and interpret the results of the trial. Owing to the fact that our enrollment

JAMA | Original Investigation

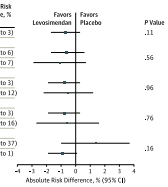
Effect of Levosimendan on Low Cardiac Output Syndrome in Patients With Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting With Cardiopulmonary Bypass

The LICORN Randomized Clinical Trial

Bernard Chollet, MD, PhD; Thibaut Caruba, PharmD, PhD; Sandrine Grosjean, MD; Julien Amour, MD, PhD; Alexandre Ouattara, MD, PhD; Judith Villacorta, MD; Bertrand Miguet, MD; Patrick Guinet, MD; François Lévy, MD; Pierre Squara, MD; Nora Ait Hamou, MD; Aude Carillon, MD; Julie Boyer, MD; Marie-Fazia Boughenou, MD; Sebastien Rosier, MD; Emmanuel Robin, MD; Mihail Radutoiu, MD; Michel Durand, MD; Catherine Guidon, MD, PhD; Olivier Desebbe, MD; Anais Charles-Nelson, MSc; Philippe Menaschè, MD, PhD; Bertrand Rozec, MD, PhD; Claude Girard, MD, PhD; Jean-Luc Fellahi, MD, PhD; Romain Pirracchio, MD, PhD; Gilles Chatellier, MD, PhD

Figure 3. Forest Plot of the Absolute Risk Difference in the Primary End Point According to Predefined Subgroups

Subgroup	No. of Events/Total No. (%) Levosimendan	Placebo	Absolute Risk Difference, % (95% CI)	P Value
Combined primary end point	87/167 (52)	101/168 (61)	−7 (−17 to 3)	.11
LVEF, %				
30-40	68/134 (51)	73/127 (57)	−6 (−17 to 6)	.56
<30	19/33 (58)	28/39 (72)	−11 (−29 to 7)	
Preoperative β-blocker therapy				
Yes	69/134 (51)	82/136 (60)	−8 (−19 to 3)	.96
No	18/33 (55)	19/30 (63)	−5 (−22 to 12)	
Type of surgery				
CABG only	58/123 (47)	70/123 (57)	−8 (−19 to 3)	.76
CABG combined with other cardiac repair	29/44 (66)	31/43 (72)	−6 (−27 to 16)	
Preoperative inotrope treatment and/or mechanical assistance				
Yes	8/9 (89)	6/8 (75)	14 (−10 to 37)	.16
No	79/158 (50)	95/158 (60)	−9 (−19 to 1)	

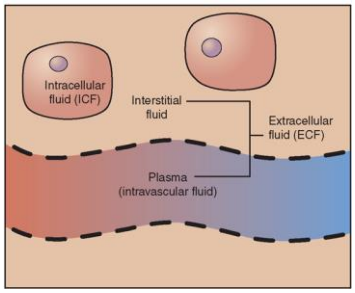


this figure to 50%, but the observed prevalence was 52% in the intention-to-treat population (51% in the per-protocol population). Because the study was powered according to a 15% absolute risk reduction and the point estimate favored levosimendan (by 7%) but included a reduction of 17%, it is possible that the study was underpowered to definitely rule out a clinically important benefit for the drug for the primary composite outcome.

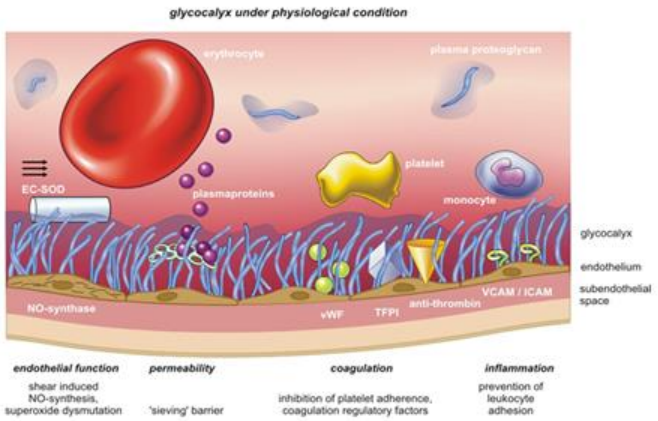
Flüssigkeit – Wann, Was, Wieviel

Escape-rate from Intravascular to Extravascular

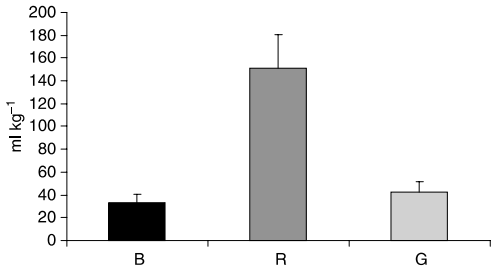
Lactated Ringer´s Solution
68%
4% Succinylated Gelatine
21%
6% Hydroxyethyl Starch
16%



Glycocalyx under physiological condition



Volume effect in hemorrhagic shock = Glycocalyx primär intakt



50% Verlust Blutvolumen =
35 mL/kg Blutverlust

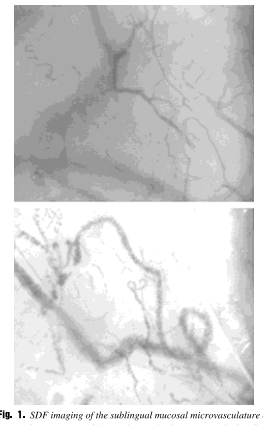
151 mL/kg RL
43 mL/kg Gelo
33 mL/kg Blut

➔ Baseline PCWP 12 mmHg

Kristalloid zu Blut 4-5 : 1
Kolloid zu Blut 1,2 : 1

Knotzer H. BJA 2006; 97: 509-516

After resuscitation – Ischemia/Reperfusion



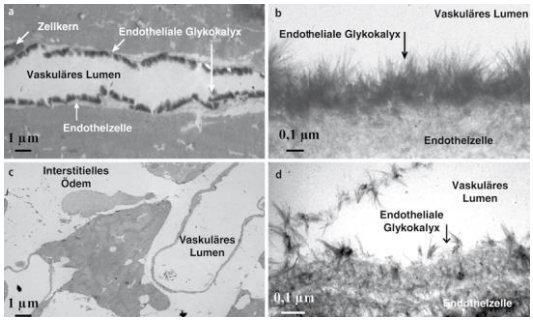
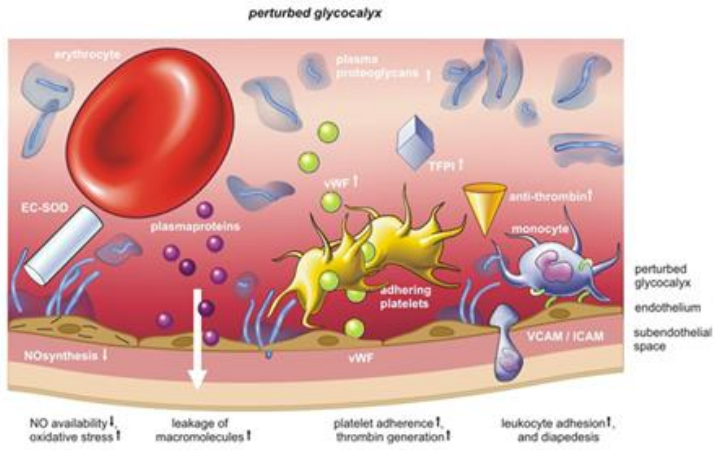


Fig. 1. *SDF imaging of the sublingual mucosal microvasculature of a pig after initiation of hemorrhagic shock* (upper) *and after fluid resuscitation* (below).

Maier S. J Trauma 2009; 66: 337-345
Chappell D. Anästhesist 2008; 57: 959-969

Glycocalyx unter pathophysiologischen Bedingungen



Volume effect during inflammation

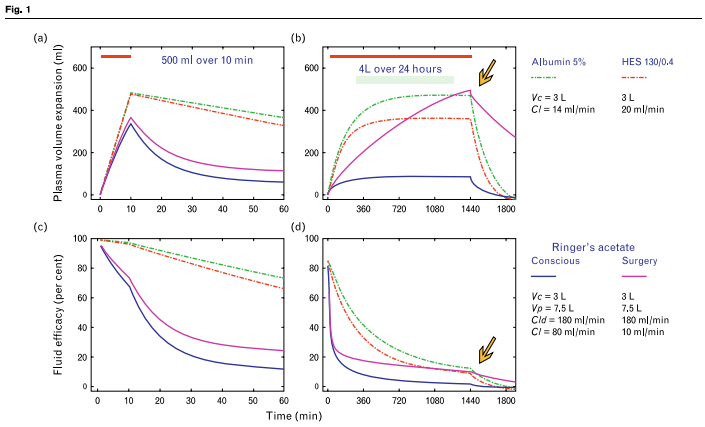
		Albumin		NACL	
Net positive fluid balance (ml)					
Day 1	3363	1543.6±1619.7	3382	1990.5±2061.7	<0.001
Day 2	3044	1015.3±1826.9	3052	1505.1±2215.9	<0.001
Day 3	2190	422.1±1633.3	2182	553.0±1732.3	0.007
Day 4	1671	137.2±1491.0	1649	155.7±1650.6	0.70

did patients in the HES group. The ratio of total fluid in the Ringer's lactate group to that in the HES group was 1.32 for the entire study period (1.58 on day 1 and 1.44 on days 1 to 4). Patients in the HES group received a median cumulative dose of 70.4 ml per kilogram of body weight (interquartile range, 33.4 to 144.2). The median central venous pressure was 11.8 mm Hg (interquartile range, 9.5 to 14.2) in the HES group and 10.7 mm Hg (interquartile range, 8.6 to 12.7) in the Ringer's lactate group (P<0.001); the median

Kristalloid zu Kolloid = 1,5 : 1

Finfer S. N Engl J Med 2004; 350: 2247-2256
Brunkhorst FM. N Engl J Med 2008; 358: 125-139

Fluid Shift auf der Intensivstation

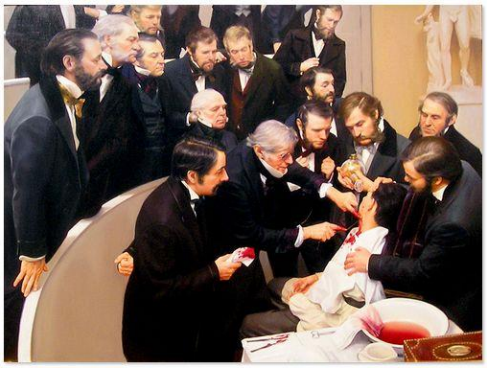


Hahn RG. European J Anaesth 2013; 30: 515-518

Zusammenfassung

- ß-Blocker in der Sepsis – JA, aber in der Early Phase
- DO_2-Erhöhung in der Sepsis – JA, aber nur in der Early Phase
- Inotropika? Nicht nur Zeitpunkt, sondern auch richtiger Patient
- Flüssigkeit in der Sepsis – Ja, nur in der Early Phase

Discussion



'Ether Day' von W.Prosperi, 1846

"Gentlemen, this is no Humbug"

John C. Warren, 1846

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