ß Blocker in der Sepsis

Gottfried Heinz
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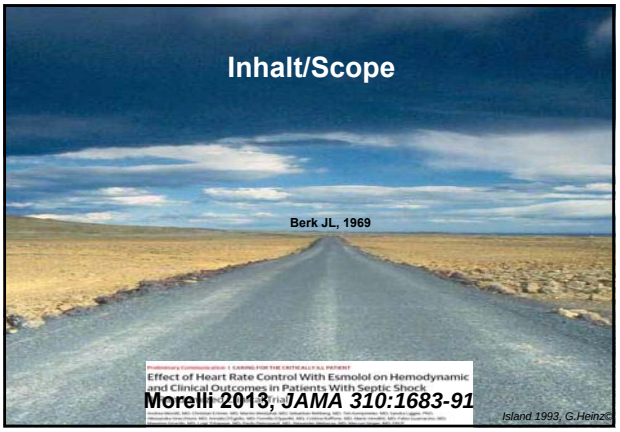
Wien

PGC 2018



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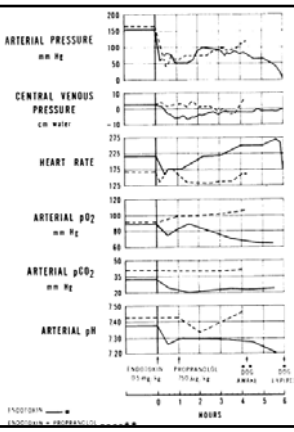
…bereits 1969

The Treatment of Endotoxin Shock by Beta Adrenergic Blockade

JAMES L. BERK,* M.D., J. F. HAGEN,** B.A., W. H. BEYER,*** PH.D., M. J. GERBER,† M.A., G. R. DOCHAT,†† M.D.

From the Surgical Research Laboratories of the Akron General Hospital, Akron, Ohio

Ann Surg 1969;169:74-81



90 Hunde, Endotoxin

3 Gruppen

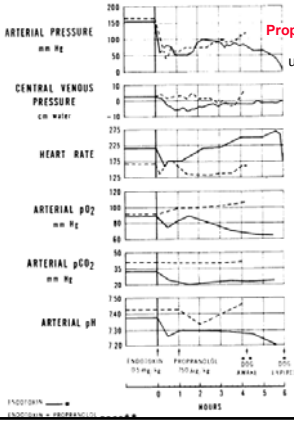
- **Propranolol (n=32)**
  - **2.5µg/kg über 120min oder**
  - **150-1500µg über 3min**
- **Fluid resuscitation (n=22)**
- **Untreated (n=36)**

Ann Surg 1969;169:74-81

TABLE 1. *Comparison of Propranolol Dose, Infusion Period, Time Given after Endotoxin Versus Survival*

Dose Propranolol (mcg./Kg.)	Infusion Period (minutes)	Time Given After Endotoxin (minutes)	No. Dogs	No. Lived	
300	120	5	6	5	Infusionsgruppe
150	3	5	3	3	
150	3	60	3	2	
200	3	15	1	1	
250	3	60	6	4	
500	3	60	1	1	
750	3	60	2	2	
1,000	3	15	2	1	Bolusgruppe
1,000	3	60	1	1	
1,500	3	15	2	1	
1,500	3	30	1	1	
1,500	3	45	1	1	
1,500	3	60	3	2	

Ann Surg 1969;169:74-81



Propranolol

unbehandelt

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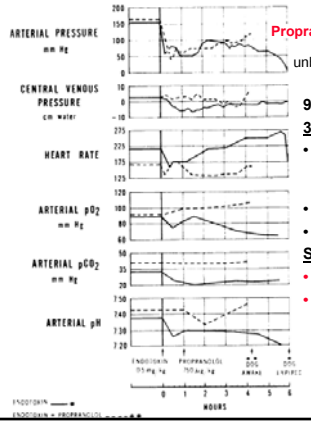
Survival (5h?)

- **25/32 Propranolol vs**
- **7/36 untreated or 6/22 fluid resuscitation**

Ann Surg 1969;169:74-81

death. The dogs that were given endotoxin and then treated with propranolol showed hemodynamic patterns that were quite different from those given endotoxin alone. These dogs had the early hypotensive phase but the second phase was absent (Fig. 1).

Ann Surg 1969;169:74-81



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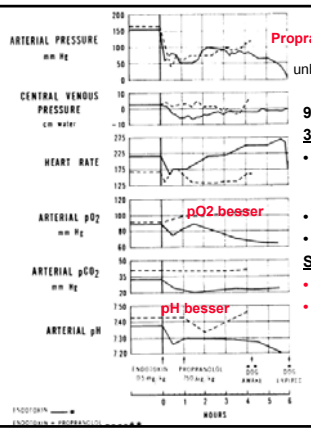

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pO2 besser

pH besser

Ann Surg 1969;169:74-81

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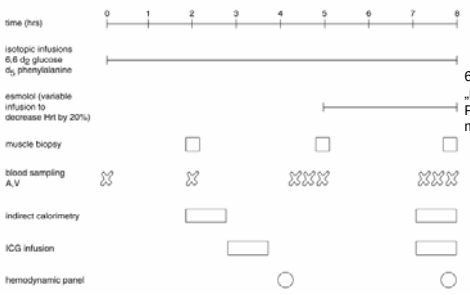
Hemodynamic and metabolic effects of selective β_1 adrenergic blockade during sepsis



6 pts
„moderat septisch“
Pneumonie
mechanisch beatmet

(Surgery 2006;139:686-94.

Hemodynamic and metabolic effects of selective β_1 adrenergic blockade during sepsis

Table II. Hemodynamics

	Basal	*Esmolol*
Cardiac index (L/minute × m^2)		
Normal range (2.5-4.0)	4.89 ± 1.00	3.88 ± 0.88*
Heart rate (beats/minute)		
Normal range (60-100)	114 ± 15	91 ± 12*
Blood pressure (mm Hg)		
Normal range (90-140)	108 ± 14	100 ± 12
Normal range (50-90)	62 ± 6	64 ± 7
Pulmonary artery wedge pressure (mm Hg)		
Normal range (4-12)	14 ± 4	13 ± 6
Systemic vascular resistance index (dyne/sec/cm^{-5}/m^2)		
Normal range (1,300-2,800)	1,366 ± 539	1,360 ± 521
Pulmonary vascular resistance index (dyne/sec/cm^{-5}/m^2)		
Normal range (100-240)	179 ± 94	208 ± 160
Stroke volume index (ml/bt × m^2)		
Normal range (33-47)	43 ± 6	43 ± 11
Leg blood flow (ml/min × 100 ml leg volume)	4.84 ± 1.91	5.07 ± 1.28
Hepatic clearance (ml/min × kg)	2.73 ± 1.32	3.13 ± 1.35

(Surgery 2006;139:686-94.

Hemodynamic and metabolic effects of selective β_1 adrenergic blockade during sepsis

comparable decrease in cardiac output. Esmolol administration failed to affect systemic or pulmonary vascular resistance, oxygen consumption, hepatic or leg blood flow, energy expenditure, or ATP availability/energy charge within muscle. Esmolol infuse did incite a shift in fuel oxidation toward an increase in palmitate oxidation and with a decrease in the oxidation of glucose. There was no demonstrable influence β_1 adrenergic blockade on muscle protein kinetics.

(Surgery 2006;139:686-94.

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Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression

Christian A Schmittinger[1], Martin W Dünser[1], Maria Haller[2], Hanno Ulmer[3], Günter Luckner[1], Christian Torgersen[1], Stefan Jochberger[1] and Walter R Hasibeder[2]

[1]Department of Anaesthesiology and Critical Care Medicine, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria
[2]Department of Anaesthesiology and Critical Care Medicine, Krankenhaus der Barmherzigen Schwestern, Schlossberg 1, 4910 Ried im Innkreis, Austria
[3]Department of Medical Biostatistics, Innsbruck Medical University, Schöpfstrasse 41/1, 6020 Innsbruck, Austria

Critical Care 2008, **12**:R99 (doi:10.1186/cc6976)

Hemodynamic variables at shock onset and during the observation period

	ICU admission[a]	Baseline	6 hours	12 hours	24 hours	48 hours	72 hours	96 hours	*P* value
Patients, number	40	40	40	39	37	37	35	33	
Heart rate, bpm	110 ± 19	101 ± 18	84 ± 17[b]	84 ± 14[b]	84 ± 13[b]	83 ± 13[b]	79 ± 13[b]	78 ± 14[b]	<0.001[c]
MAP, mm Hg	59 ± 19	85 ± 23	82 ± 15	85 ± 18	87 ± 15	90 ± 20	91 ± 20	90 ± 21	0.16
CVP, mm Hg	14 ± 4	12 ± 3	12 ± 4	12 ± 3	11 ± 3	11 ± 3[b]	10 ± 3[b]	9 ± 3[b]	<0.001[c]
Cardiac index, L/minute per m^2	1.9 ± 0.6	3.1 ± 1.1	3.2 ± 1.0	3.3 ± 0.9	3.4 ± 0.9	3.4 ± 1.0	3.5 ± 1.0	3.5. ± 0.8	0.56
SVI, mL/beat per m^2	18 ± 7	32 ± 12	40 ± 14	40 ± 12	42 ± 12[b]	42 ± 13[b]	42 ± 10[b]	44 ± 9[b]	0.002[b]
CPI, W/m^2	0.24 ± 0.14	0.61 ± 0.32	0.57 ± 0.22	0.60 ± 0.17	0.65 ± 0.18	0.68 ± 0.30	0.71 ± 0.25	0.68 ± 0.23	0.27
$ScvO_2$, percentage	64 ± 12	71 ± 10	72 ± 6	72 ± 11	74 ± 9	77 ± 8	73 ± 11	72 ± 11	0.35
SVRI, dyne-second/cm^5 per m^2	2,041 ± 1,181	2,114 ± 825	1,918 ± 897	1,913 ± 777	1,895 ± 647	2,014 ± 800	2,060 ± 852	1,824 ± 569	0.78
NE, μg/kg per minute	0.12 ± 0.25 (n = 18)	0.17 ± 0.11	0.18 ± 0.11	0.18 ± 0.11	0.17 ± 0.13	0.13 ± 0.13	0.09 ± 0.08[b]	0.06 ± 0.07[b]	<0.001[c]
AVP dosage, IU/hour	NA	2.0 ± 1.6	2.2 ± 1.3	2.1 ± 1.3	2.1 ± 1.2	1.9 ± 1.3	1.3 ± 1.3	0.8 ± 1.1[b]	<0.001[c]
MI, μg/kg per minute	0.24 ± 0.19 (n = 6)	0.31 ± 0.16	0.34 ± 0.17	0.33 ± 0.16	0.30 ± 0.17	0.24 ± 0.18	0.21 ± 0.19	0.12 ± 0.13[b]	<0.001[c]
Meto, mg	NA	47 ± 19	NA	NA	47 ± 41	52 ± 42	51 ± 42	54 ± 37	NA

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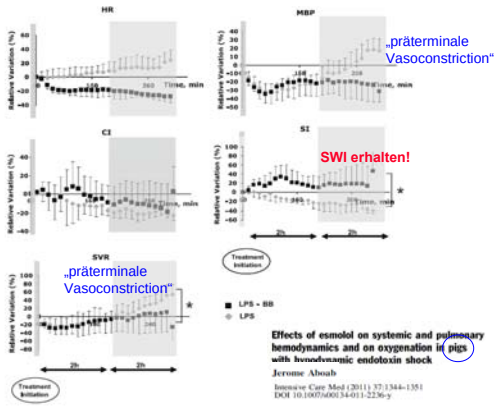

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Table 1. Esmolol and norepinephrine infusion rates, haemodynamic and calculated parameters, blood draws results and echocardiographic parameters at subsequent time (T) intervals (baseline before esmolol infusion (T0), following esmolol infusion, at 2 (T2), 6 (T6), 12 (T12), 24 h (T24) and 6 h after infusion ceasing (T30)

Time point	T0	T2	T6	T12	T24	T30	*p* value
Infusion							
Esmolol (mg/h)	0	213 ± 64	245 ± 82	255 ± 117	273 ± 90	0	NS
Nor (μg/kg/min)	0.13 ± 0.16	0.14 ± 0.17	0.15 ± 0.14	0.15 ± 0.15	0.17 ± 0.19	0.12 ± 0.12	NS
Hemodynamics, arterial lactate and calculated parameters							
HR (beats/min)	142 ± 11	127 ± 12	120 ± 11	113 ± 7	112 ± 9	116 ± 11	<0.001
MAP (mmHg)	91 ± 11	89 ± 9	87 ± 11	86 ± 8	84 ± 9	89 ± 8	NS
PAMP (mmHg)	29 ± 4	30 ± 5	29 ± 3	28 ± 3	30 ± 4	28 ± 4	NS
PAWP (mmHg)	16 ± 3	15 ± 2	15 ± 2	15 ± 3	15 ± 2	14 ± 2	NS
CO (l/min)	9.2 ± 1.9	8.8 ± 2.0	8.8 ± 2.1	8.2 ± 1.6	8.2 ± 1.7	8.7 ± 1.6	NS
CI (l/min/m²)	4.9 ± 0.8	4.7 ± 0.9	4.7 ± 1.0	4.3 ± 0.7	4.4 ± 0.7	4.7 ± 0.7	NS
SV (ml)	67 ± 16	69 ± 14	73 ± 14	72 ± 12	73 ± 15	77 ± 13	NS
SVR (dyn·s/cm⁵)	721 ± 212	751 ± 171	733 ± 209	763 ± 203	764 ± 213	749 ± 200	NS
Lactate (mmol/l)	1.7 ± 0.5	1.7 ± 0.4	2.0 ± 0.6	2.1 ± 0.4	1.7 ± 0.3	1.8 ± 0.5	NS
DO_2 (ml/min)	1309 ± 207	1311 ± 206	1314 ± 204	1316 ± 199	1311 ± 185	1308 ± 198	NS
SvO_2 (%)	70 ± 8	67 ± 5	65 ± 5	63 ± 5	60.2 ± 4	64 ± 5	NS
VO_2 (ml/min)	326 ± 130	345 ± 108	367 ± 101	376 ± 101	394 ± 70	385 ± 103	NS
OER (%)	25 ± 8	26 ± 6	28 ± 7	29 ± 7	31 ± 6	30 ± 8	NS
Echocardiography							
LV EF (%)	62.7 ± 12	60.5 ± 11	57.9 ± 10	59.7 ± 9	57.9 ± 6	60.3 ± 9	NS
TAPSE (mm)	21 ± 4	22 ± 3	22 ± 4	21 ± 3	21 ± 3	22 ± 3	NS

Parameters presented as means ± SD. All changes were insignificant except decrease in heart rate ($p < 0.001$, repeated measures ANOVA)
Nor norepinephrine, *HR* heart rate, *MAP* mean arterial pressure, *PAMP* mean pulmonary artery pressure, *PAWP* pulmonary artery wedge pressure, *CO* cardiac output, *CI* cardiac index, *SV* stroke volume, *SVR* systemic vascular resistance, DO_2 systemic oxygen delivery, SvO_2 mixed venous oxygen saturation, VO_2 systemic oxygen consumption, *OER* oxygen extraction ratio, *LV EF* left ventricular ejection fraction, *TAPSE* tricuspid annular plane systolic excursion

Concomitant use of beta-1 adrenoreceptor blocker and norepinephrine in patients with septic shock

Martin Balik, Jan Rulisek, Pavel Lubin, Michal Zakharchenko, Michal Otahal, Hana Bartakova, Josef Kuchyna

Wien Klin Wochenschr (2012) 124:552–556
DOI 10.1007/s00508-012-0209-y

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- 25 Septic Shock pts, unkontrolliert
- 24h Stabilisierung
- Esmolol bis <95/min

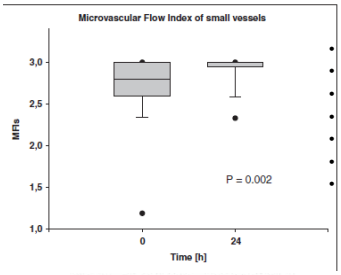
TABLE 2. Hemodynamic Data of the Study Patients ($n = 25$)

Variable	Baseline	24 Hr	p
Cardiac index (L/min/m²)	4.0 (3.5; 5.3)	3.1 (2.6; 3.8)	< 0.001
Stroke volume index (mL/beat²/m²)	34 (27; 46)	40 (31; 46)	0.31
Heart rate (/min)	117 (112; 126)	86 (80; 89)	< 0.001
Mean arterial pressure (mm Hg)	71 (68; 75)	72 (70; 74)	0.67
Mean pulmonary arterial pressure (mm Hg)	31 (28; 34)	31 (28; 34)	0.73
Pulmonary arterial occlusion pressure (mm Hg)	17 (15; 20)	18 (16; 20)	0.50
Central venous pressure (mm Hg)	13 (11; 16)	14 (12; 17)	0.09
Left ventricular stroke work index [g m/beat/m²]	25 (22; 31)	29 (21; 34)	0.56
Right ventricular stroke work index [g m/beat/m²]	8.0 (6; 12)	9.0 (6; 12)	0.89
Norepinephrine dosage (µg/kg/min)	0.53 (0.29; 0.96)	0.41 (0.22; 0.78)	0.03

Microvascular Effects of Heart Rate Control With Esmolol in Patients With Septic Shock: A Pilot Study*

Morelli, Crit Care Med 2013;41:2162-68

Mikrozirkulation nicht schlechter!



- 25 Septic Shock pts
- Sublinguale Messung
- MicroScan, MicroVision
- 3 Felder
- 15 sec
- DeBacker Score
- Flow index
  - normal (3)
  - sluggisch (2)
  - intermittent (1)
  - absent (0)

Microvascular Effects of Heart Rate Control With Esmolol in Patients With Septic Shock: A Pilot Study*

Morelli, Crit Care Med 2013;41:2162-68

ß Blocker in der Sepsis/SS

Zusammenfassung der Effekte

- MAP besser unter Propranolol, Überleben 25/32 Propranolol, 6/22 unbehandelt
  - » *Berk, JL, Ann Surg 1969;169:74-81*
- MAP Anstieg, Noradrenalin & Vasopressin Reduktion unter Milrinon und Propranolol
  - » *Schmittger, Dünser, Crit Care 2008;12(9):R99*
- Noradrenalinbedarf fallend unter Esmolol, MAP & SV konstant, Mikrozirkulation +-besser (sublingual MFI 2.8->3.0)
  - » *Morelli, Crit Care Med 2013; 41:2162-8*
- HR Rückgang, MAP und Noradrenalin unverändert
  - » *Balik Wie Kli Wo 2012;124:552-56*
- SWI Anstieg von 31->47ml/min/m2 unter Esmolol
  - » *Aboab, ICM 2011;37:1344-1351*

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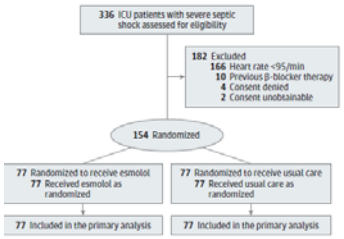
Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

JAMA 2013;310:1683-91



JAMA 2013;310:1683-91

…übliches Sepsis Bündel

After 24 hours of hemodynamic optimization aimed at es-
tablishing an adequate circulating blood volume (adjudged by
pulmonary artery occlusion pressure of ≥12 mm Hg and cen-
tral venous pressures of ≥8 mm Hg), a mixed venous oxygen
saturation higher than 65% and a MAP of 65 mm Hg or higher,
we enrolled patients if they were still requiring norepineph-
rine and their heart rate persisted at 95/min or higher. Pa-
tients were randomly assigned by a computer-based random-

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

JAMA 2013;310:1683-91

Ausschlußkriterien

- **CI <2.2l/min/m²**
- **PCPW >18mmHg**
- **Herzklappenerkrankung**
- **ß Blockertherapie**
- **<18 Jahre**
- **Gravidität**

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
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JAMA 2013;310:1683-91

Endpunkte

primär

- **HR Reduktion unter 95 Schläge/min**

sekundär

- **28d Mortalität**
- **Hämodynamik, Oxygenation, Organfunktion**
- **NE 24/48/72/96hr**

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

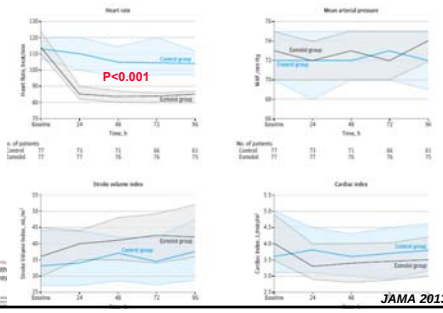
JAMA 2013;310:1683-91

Esmololtitration

- Start 25mg/h
- 50mg/h Steigerungsschritte in 20min Abständen
- Max Dosis 2000mg/h
- Ziel HR <95/min
- 96h

JAMA 2013;310:1683-91

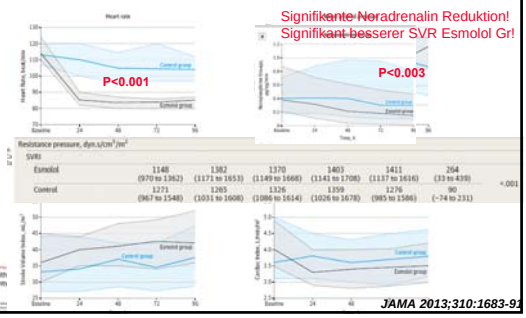
... CI und MAP nicht schlechter unter Esmolol



JAMA 2013;310:1683-91

... CI und MAP nicht schlechter unter Esmolol

Signifikante Noradrenalin Reduktion!
Signifikant besserer SVR Esmolol Gr!



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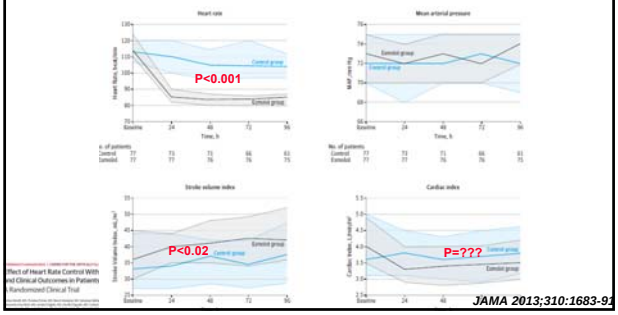


JAMA 2013;310:1683-91

signifikant bessere aber immer noch schwer reduzierte Schlagarbeit unter Esmolol !

aber klinisch bedeutend?

Table 2. Hemodynamic Variables of Study Patients

Group	Median (Interquartile Range)					Area Under the Curve	*P* Value, Wilcoxon-Mann-Whitney
Stroke work index, mL/m²	Baseline	24 Hours	48 Hours	72 Hours	96 Hours		
Left ventricle							
Esmolol	27 (23 to 33)	31 (24 to 34)	32 (26 to 37)	32 (25 to 39)	34 (28 to 41)	3 (−1 to 8)	.03
Control	24 (19 to 31)	26 (19 to 31)	28 (21 to 34)	27 (21 to 32)	31 (23 to 36)	1 (−3 to 5)	

JAMA 2013;310:1683-91

Afterload-“insensitive“ Params of LV Cardiac Function

LVSWI = SVI * MAP * 0.0144

Datenbuch Intensivmedizin p366

CPI = CI * MAP * 0.0022

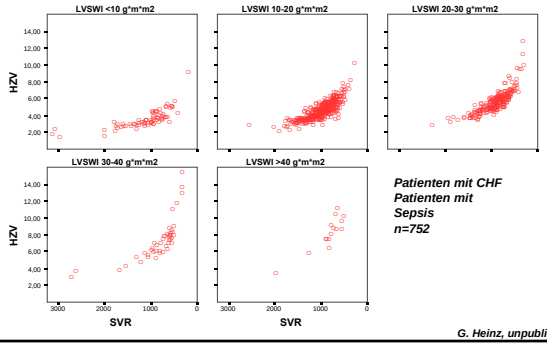
Eur J Heart Fail 2003;5:443-451

LVSWI

56 ± 6 g*m/m²

Datenbuch Intensivmedizin, Gustav Fischer, 3. Auflage 1992, S366

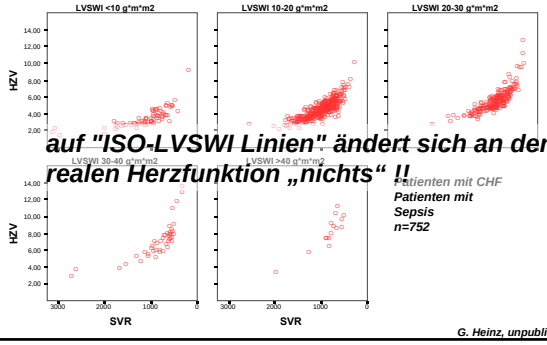
HZV – SVR stratifiziert nach "gleicher Funktion"



Patienten mit CHF
Patienten mit Sepsis
n=752

G. Heinz, unpublished data

HZV – SVR Beziehung stratifiziert nach LVSWI



auf "ISO-LVSWI Linien" ändert sich an der realen Herzfunktion „nichts“ !!

Patienten mit CHF
Patienten mit Sepsis
n=752

G. Heinz, unpublished data

signifikant bessere und immer noch schwer reduzierte Schlagarbeit unter Esmolol !

aber klinisch bedeutend?

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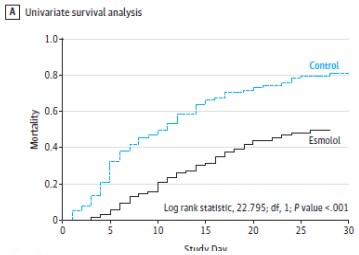
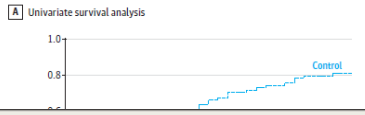
JAMA 2013;310:1683-91

...klinische Konsequenz



JAMA 2013;310:1683-91

...klinische Konsequenz



Outcome	No. (%) Esmolol (n = 77)	Control (n = 77)	*P* Value
Mortality			
28 d	38 (49.4)	62 (80.5)	<.001
ICU	44 (57.1)	68 (88.3)	<.001
Hospital	52 (67.5)	70 (90.9)	<.001

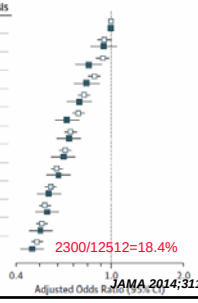
Ungewöhnlich hohe Mortalität!!! contemporär ~30%

JAMA 2013;310:1683-91

Zunehmend mehr Sepsis Überlebende…..

A Mortality

Year of ICU Admission	No. of Patients		No. of Events	
	Sepsis	No Sepsis	Sepsis	No Sepsis
2000	2708	35014	949	4807
2001	3783	45000	1271	5855
2002	4668	51972	1455	6484
2003	5221	58393	1573	6996
2004	6375	65292	1841	7383
2005	6987	72220	1833	7825
2006	7627	75926	1961	7765
2007	8529	78297	2090	7844
2008	8797	77379	2106	7541
2009	10277	84842	2264	7943
2010	11367	93385	2386	8302
2011	12213	98045	2418	8535
2012	12512	100286	2300	8010



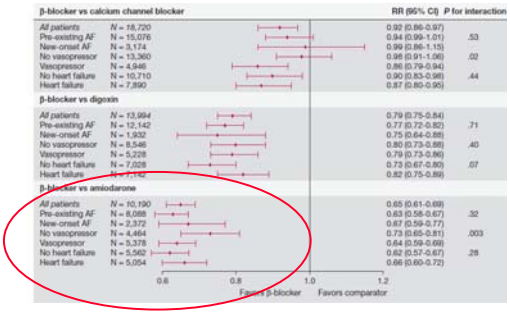
JAMA 2014;311:1308--16

Limitationen/Kritik

- **Unüblich hohe, nicht mehr zeitgemäße Mortalität in der Kontroll wie Behandlungsgruppe!!!**
- **Hohe Inzidenz an multiresistenten Organismen (Klebsiella, Acinetobakter) !! Langlieger??!!**
- **AB Therapie – Empfindlichkeiten, adäquat?**
- **Hoher Prozentsatz excludiert da sie <95 HR hatten – gilt also nur für eine Subgruppe??**
- **SAPS II Score unterschiedlich in Gruppen: 52 (Esmolol) vs 57 (Kontrollgruppe)**
- **Bias: nicht geblindet, Conflict of Interest Autoren!!!**

ß Blocker bei AF in der Sepsis

Mortalität



Chest, 2016;149:74-83

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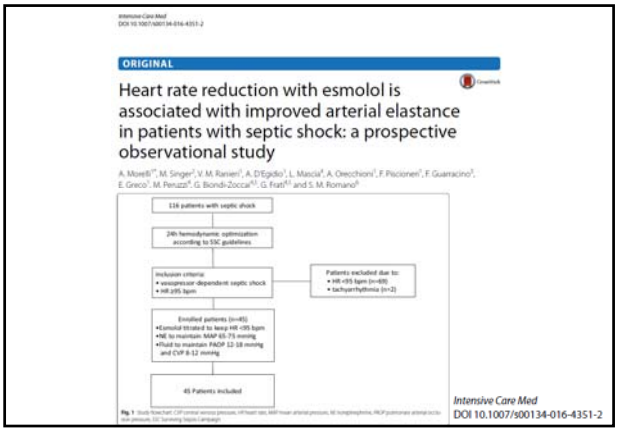
- **Unkontrollierte Serie Morelli 2016**
- Guidelines

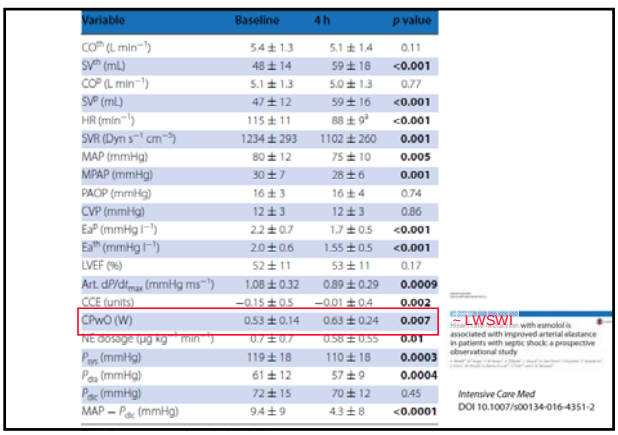


ORIGINAL

Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study

A. Morelli[1*], M. Singer[2], V. M. Ranieri[3], A. D'Egidio[1], L. Mascia[4], A. Orecchioni[1], F. Piacionen[1], F. Guarracino[5], E. Greco[1], M. Penuzzi[6], G. Biondi-Zoccai[4,7], G. Frati[4,7] and S. M. Romano[5]

Intensive Care Med
DOI 10.1007/s00134-016-4351-2



Variable	Baseline	4 h	*p* value
CO^{Th} (L min^{-1})	5.4 ± 1.3	5.1 ± 1.4	0.11
SV^{Th} (mL)	48 ± 14	59 ± 18	**<0.001**
CO^{P} (L min^{-1})	5.1 ± 1.3	5.0 ± 1.3	0.77
SV^{P} (mL)	47 ± 12	59 ± 16	**<0.001**
HR (min^{-1})	115 ± 11	88 ± 9[$]	**<0.001**
SVR (Dyn s^{-1} cm^{-5})	1234 ± 293	1102 ± 260	**0.001**
MAP (mmHg)	80 ± 12	75 ± 10	**0.005**
MPAP (mmHg)	30 ± 7	28 ± 6	**0.001**
PAOP (mmHg)	16 ± 3	16 ± 4	0.74
CVP (mmHg)	12 ± 3	12 ± 3	0.86
EaP (mmHg l^{-1})	2.2 ± 0.7	1.7 ± 0.5	**<0.001**
Ea^{Th} (mmHg l^{-1})	2.0 ± 0.6	1.55 ± 0.5	**<0.001**
LVEF (%)	52 ± 11	53 ± 11	0.17
Art. dP/dt_{max} (mmHg ms^{-1})	1.08 ± 0.32	0.89 ± 0.29	**0.0009**
CCE (units)	−0.15 ± 0.5	−0.01 ± 0.4	**0.002**
CPwO (W)	0.53 ± 0.14	0.63 ± 0.24	**0.007**
NE dosage (μg kg^{-1} min^{-1})	0.7 ± 0.7	0.58 ± 0.55	**0.01**
P_{sys} (mmHg)	119 ± 18	110 ± 18	**0.0003**
P_{dia} (mmHg)	61 ± 12	57 ± 9	**0.0004**
P_{dic} (mmHg)	72 ± 15	70 ± 12	0.45
MAP − P_{dic} (mmHg)	9.4 ± 9	4.3 ± 8	**<0.0001**

~LWSWI

Intensive Care Med
DOI 10.1007/s00134-016-4351-2

CPI & LVSWI im *kardiogenen* Schock univariat mit Überleben assoziiert

univariat, kardiogener Schock

Table 2. Univariate Logistic Regression Results of Hemodynamic Parameters for In-Hospital Mortality

Parameters*	n	Mean ± SD†	Unit for Odds Ratio	Odds Ratio (95% CI)	p Value
Cardiac power output	189	0.62 ± 0.30	0.20	0.55 (0.41, 0.73)	<0.001
Cardiac power index	253	0.33 ± 0.14	0.10	0.61 (0.49, 0.77)	<0.001
Cardiac output	204	3.86 ± 1.60	1	0.62 (0.49, 0.78)	<0.001
Stroke volume	196	40.8 ± 18.5	10	0.69 (0.56, 0.84)	<0.001
Left ventricular work index	244	1.36 ± 0.74	0.4	0.69 (0.58, 0.82)	<0.001
Left ventricular work	182	2.63 ± 1.54	0.7	0.70 (0.58, 0.84)	<0.001
Stroke work	180	27.2 ± 16.5	8	0.71 (0.59, 0.86)	<0.001
Stroke work index	134	14.8 ± 9.1	5	0.72 (0.58, 0.91)	0.005
Cardiac index	282	2.07 ± 0.79	0.5	0.73 (0.62, 0.87)	<0.001
Left ventricular ejection fraction	196	30.0 ± 12.8	7	0.81 (0.69, 0.96)	0.013
Systolic blood pressure	525	89.2 ± 22.2	10	0.84 (0.77, 0.92)	<0.001
Mean arterial pressure	460	66.7 ± 15.9	8	0.84 (0.76, 0.93)	<0.001
Coronary perfusion pressure	329	33.4 ± 14.4	7	0.84 (0.75, 0.94)	0.002
Diastolic blood pressure	460	54.3 ± 14.8	7	0.85 (0.78, 0.94)	<0.001
Right ventricular diastolic pressure	88	14.4 ± 7.5	4	0.98 (0.78, 1.24)	0.877
Heart rate	520	96.5 ± 26.0	10	1.00 (0.93, 1.07)	0.923
Right atrial pressure	204	13.9 ± 6.6	3	1.01 (0.89, 1.15)	0.862
PCWP	378	24.0 ± 8.7	5	1.09 (0.97, 1.22)	0.159
Pulmonary artery diastolic pressure	260	23.7 ± 7.4	4	1.10 (0.96, 1.26)	0.164
Pulmonary artery systolic pressure	259	40.3 ± 11.8	6	1.14 (1.00, 1.29)	0.047
	144	2,266 [1,782, 2,860]†	600	1.14 (0.93, 1.39)	0.203
	143	1,257 [938, 1,620]†	400	1.16 (0.93, 1.44)	0.186
	93	43.7 ± 15.8	8	1.17 (0.94, 1.46)	0.161

Cardiac Power Is the Strongest Hemodynamic Correlate of Mortality in Cardiogenic Shock: A Report From the SHOCK Trial Registry

JACC 2004;44:340-8

CPI im *kardiogenen* Schock multivariat bester Prädiktor der Spitals-Mortalität

multivariat, kardiogener Schock

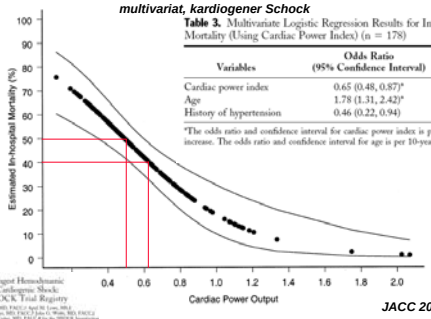


Table 3. Multivariate Logistic Regression Results for In-Hospital Mortality (Using Cardiac Power Index) (n = 178)

Variables	Odds Ratio (95% Confidence Interval)	p Value
Cardiac power index	0.65 (0.48, 0.87)*	0.004
Age	1.78 (1.31, 2.42)*	<0.001
History of hypertension	0.46 (0.22, 0.94)	0.033

*The odds ratio and confidence interval for cardiac power index is per 0.10 W/m² increase. The odds ratio and confidence interval for age is per 10-year increase.

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Steifigkeit ↓ = Compliance ↑

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$Ea = \frac{MAP}{SV}$

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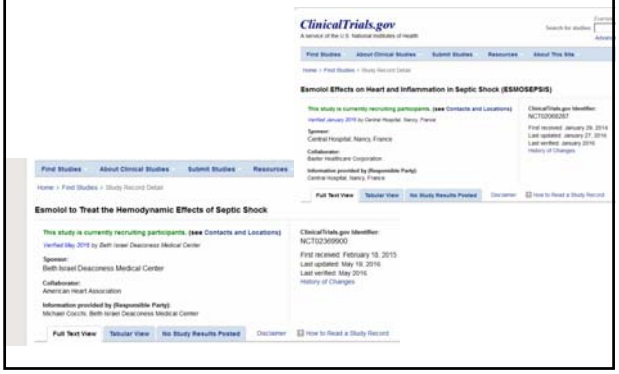
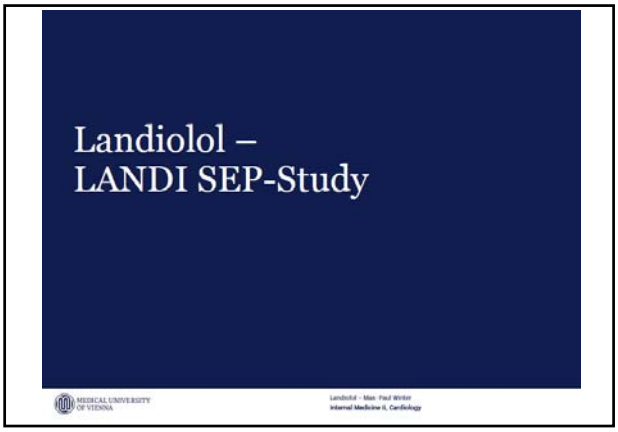
- **Guidelines**

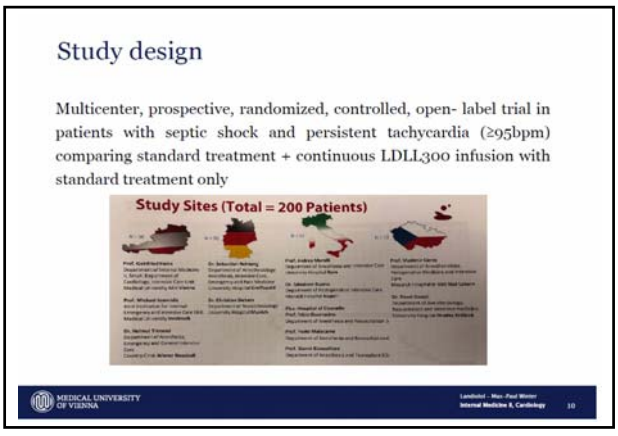
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

ß Blocker – keine Empfehlung/kein Treffer
Esmolol – keine Empfehlung/kein Treffer

Ausblick


ClinicalTrials.gov
Esmolol Effects on Heart and Inflammation in Septic Shock (ESMOSEPSIS)
Esmolol to Treat the Hemodynamic Effects of Septic Shock
Beth Israel Deaconess Medical Center
American Heart Association
NCT02369900


Landiolol –
LANDI SEP-Study
MEDICAL UNIVERSITY OF VIENNA
Landiolol - Max-Paul Winter
Internal Medicine II, Cardiology


Study design
Multicenter, prospective, randomized, controlled, open- label trial in patients with septic shock and persistent tachycardia (≥95bpm) comparing standard treatment + continuous LDLL300 infusion with standard treatment only
Study Sites (Total = 200 Patients)
MEDICAL UNIVERSITY OF VIENNA
Landiolol - Max-Paul Winter
Internal Medicine II, Cardiology
10

Study endpoints

Primary efficacy endpoint:

Heart rate response (i.e. HR = 80-94 bpm) and maintenance thereof and no increase in vasopressor requirements during the first 24 hours after treatment start

Secondary efficacy endpoints:

Change in vasopressor requirements over the study period (dose and duration)

28-day mortality (all cause)

ICU mortality (all cause)

Duration of ICU stay (survivors/non-survivors)

Duration of hospital stay (survivors/non-survivors)

SOFA score (as long as the patient is treated with vasopressors) on day 1, 2, 3, 4, 7, 10, 13, 16, 19, 22, 25 and 28

Daily Inotropic requirements (as long as the patient is treated with vasopressors)

Inclusion criteria

- Age ≥18 years
- **Confirmed septic shock:**
  - Confirmed or suspected infection
  - Acute increase of ≥2 points on SOFA Score
  - Need for continuous vasopressor therapy to maintain a mean arterial pressure (MAP) of >65 mmHg despite adequate fluid resuscitation
  - Blood lactate >2mmol/L (18mg/dl)
- **Presence of blood lactate >2mmol/L (18mg/dl) and increase of ≥2 points on SOFA Score are only necessary for the diagnosis of septic shock but not at time of study inclusion**
- Tachycardia and/or tachyarrhythmia with heart rate ≥95 beats/min
- Norepinephrine infusion rate **≥0.2 µ g/kg**/min at the time of study inclusion
- **Patients must have undergone a haemodynamic optimization period of at least 24 hours but a maximum of 36 hours, during which period they received continuous vasopressor treatment and standard treatment for septic shock according to the SSCG 2016 guidelines**

Exclusion criteria

- Any form of compensatory tachycardia
- **β -blocker treatment within * days prior randomization**
- Sick Sinus syndrome, or 2nd or 3rd degree AV block
- Patients with any form of cardiac pacing
- A known, serious cardiovascular condition such as ischemic stroke or transient ischaemic attack within last 6 months, or preexisting heart failure New York Heart Association Class III or IV
- Cardiogenic shock
- MAP <65 mmHg
- Known pulmonary hypertension
- Known terminal illness other than septic shock with expected patient's survival <28 days
- Known presence of an advanced condition to withhold life- sustaining treatment
- Patients for whom a "Do Not Resuscitate" (DNR) exist
- Known sensitivity to any component of the study medication (e.g. Landiolol, nanandrol)
- Participation in a clinical drug trial within 30 days prior randomization
- Any condition that, in the Investigator's opinion, makes the subject unsuitable for study participation (to be documented)
- Pregnant or breast feeding patients
- Untreated Pheochromocytoma

Wrap it up

- ß Blocker und Vasopressoren kombinierbar und gut toleriert
- MAP Anstieg/Noradrenalin Reduktion
- CO Abfall aber Schlagvolumenanstieg
- LVSWI erhalten bis gering signifikant steigend, CPI steigend
- Weitere Sepsis Studien mit ß Blockern unterwegs
- Sepsis *noch keine* guideline-etablierte Indikation für ß Blocker

Iceland 1993, G.Heinz©

Arnhem Land, NT, Australien 1994, G.Heinz©

Landiolol

Landiolol (Rapibloc^{R})

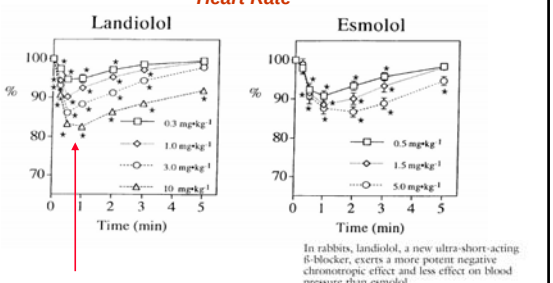
- 20mg/2ml Konzentrat
- 0.1-0.3mg/kg
- **300mg Lyophilisat, linksdrehendes Racemat**
- **10-40µg/kg/min (loading downgegraded!!, evtl. 100µg/kg/min),**
- **1-10µg/kg/min bei kardialer Dysfunktion, Sepsis!!**
- **Keine Wirkung auf Na^{+} & Ca^{2+} Kanäle (≠ Esmolol)**
- **Geringere Blutdruckwirkung vs Esmolol**
- **t/2 4min, Wirkdauer 15min**
- **8-fach höhere $ß_1$ Selektivität als Esmolol**
- **Keine Tachyphylaxie**

Kurzwirksame ß Blocker

	Onset	t/2	Dauer	Dosis µg/kg/min	Selektivität	HR/BP	Elimi-nation
Landiolol	1-2 min	4 min	15min	5-40	$ß_1$>>>$ß_2$	HR ↓↓ RR +-	RBC Esterasen
Esmolol	2 min	9 min	10-20min	50-300	$ß_1$>>$ß_2$	HR ↓ RR ↓	RBC Esterasen

Landiolol vs Esmolol

Heart Rate



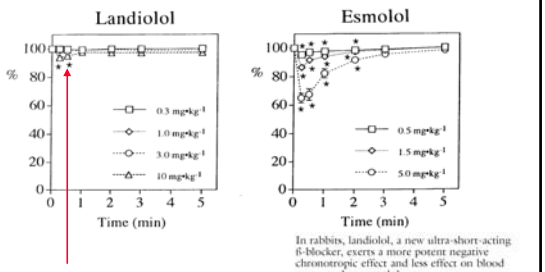
Raschere HR Senkung

In rabbits, landiolol, a new ultra-short-acting ß-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol

CAN J ANESTH 2001 / 48: 10 / pp 985-989

Landiolol vs Esmolol

MAP



Geringe Blutdruckwirkung
nur in der höheren Dosis

In rabbits, landiolol, a new ultra-short-acting ß-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol

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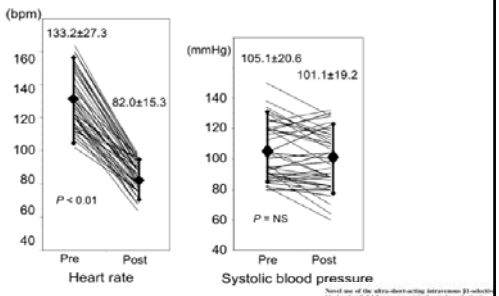
Weniger SAP Senkung bei CHF



Heart Vessels (2014) 29:464–469