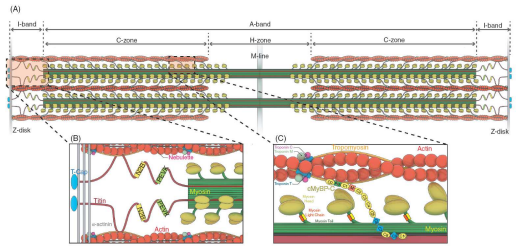
Postgraduate Course Kardiovaskuläre Intensivmedizin
Baden, 4. und 5. Mai 2017

Arbeitsgruppe der ÖKG
kardiovaskuläre Intensivmedizin

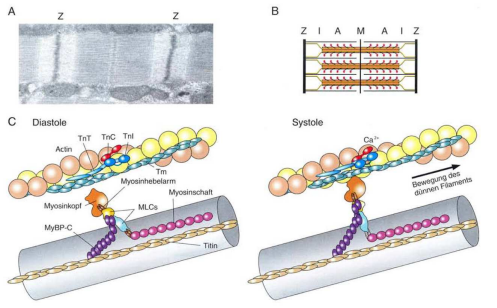
Show me the evidence: was ist Inotropie & welche Inotropika haben wir wirklich?

Die Sicht des Pharmakologen, pharmakologisches Rationale

Molekulare Struktur des Sarkomers

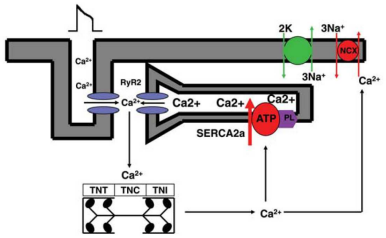


Molekulare Basis der Muskelkontraktion



Aktories et al. Allgemeine und spezielle Pharmakologie und Toxikologie
10., überarbeitete Auflage, Urban&Fischer

„Calcium Cycling“ in der Herzmuskelzelle

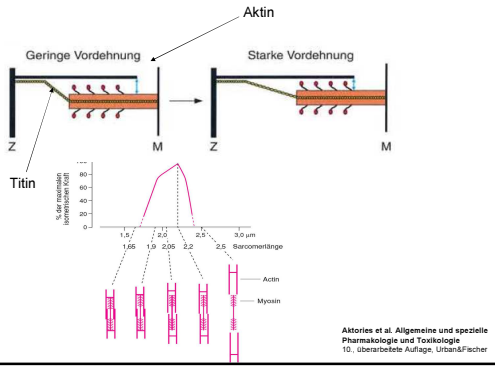


Hasenfuss G and Teerlink JR
European Heart Journal (2011) 32, 1838–1845

Show me the evidence:

Was ist Inotropie & welche selektiven Inotropika haben wir wirklich?

Frank-Starling Mechanismus

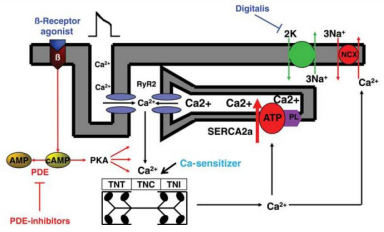


Aktories et al. Allgemeine und spezielle Pharmakologie und Toxikologie
10., überarbeitete Auflage, Urban&Fischer

Kontraktilität

Unter "Kontraktilität" versteht man die **Kontraktionsfähigkeit des Ventrikels an sich,** sie stellt also eine **von der Vordehnung unabhängige Größe** dar.

Inotropika: Molekulare Wirkmechanismen



Hasenfuss G and Teerlink JR
European Heart Journal (2011) 32, 1838–1845

Inotropie = Anzahl der aktivierten Querbrücken

(i) Die Menge an Ca^{2+} die für die Bindung an Troponin C verfügbar ist
(ii) Die Ca^{2+} - Affinität des Troponin C
(iii) Modulation der Querbrückeninteraktion
- Förderung der inotropen Querbrücken-Konformation
- Einheitskraft des Querbrückenzyklus
- Verlängerung der Bindungszeit der Myosinköpfe am Aktin

Nach Hasenfuss G and Teerlink JR
European Heart Journal (2011) 32, 1838–1845

Inotropika

- Calcium Mobilizer
  - Phasisch
  - Tonisch
- Calcium Sensitizer
  - Phasisch
  - Tonisch

Inotropika

- Calcium Mobilizer
  - Phasisch (Katecholamine, PDEIII-Hemmer)
  - Tonisch (Digitalisglykoside)
- Calcium Sensitizer
  - Phasisch (Levosimendan)
  - Tonisch (experimentelle Substanzen)

Show me the evidence:

Was ist Inotropie & welche lastunabhängigen Inotropika haben wir wirklich?

Table 12.5 Positive inotropes and/or vasopressors used to treat acute heart failure

Vasodilator	Bolus	Infusion rate
Dobutamine[a]	No	2–20 µg/kg/min (beta+)
Dopamine	No	3–5 µg/kg/min; inotropic (beta+)
		>5 µg/kg/min: (beta+), vasopressor (alpha+)
Milrinone[a,b]	25–75 µg/kg over 10–20 min	0.375–0.75 µg/kg/min
Enoximone[a]	0.5–1.0 mg/kg over 5–10 min	5–20 µg/kg/min
Levosimendan[a]	12 µg/kg over 10 min (optional)[c]	0.1 µg/kg/min, which can be decreased to 0.05 or increased to 0.2 µg/kg/min
Norepinephrine	No	0.2–1.0 µg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min	0.05–0.5 µg/kg/min

i.v. = intravenous.
[a]Also a vasodilator.
[b]Not recommended in acutely worsened ischaemic heart failure.
[c]Bolus not recommended in hypotensive patients.

European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Inotropika

- Calcium Mobilizer
  - Phasisch (Katecholamine, PDEIII-Hemmer)
  - Tonisch (Digitalisglykoside)
- Calcium Sensitizer
  - Phasisch (Levosimendan)
  - Tonisch (experimentelle Substanzen)

Table 3 Drawbacks of dobutamine and milrinone

(A) *Dobutamine*
- (i) Increased myocardial oxygen consumption
- (ii) Myocardial injury
- (iii) Tolerance/tachyphylaxis
- (iv) Interaction with beta-blockers
- (v) Arrhythmiogenesis
- (vi) Increased mortality

(B) *Milrinone*
- (i) Hypotension
- (ii) Arrhythmiogenesis
- (iii) Worsening prognosis in ischemic disease

Parissis JT et al.
Heart Fail Rev (2007) 12:149–156

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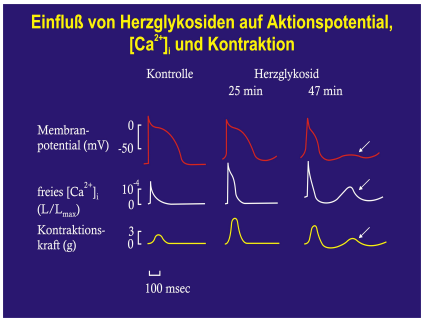
Parissis JT et al.
Heart Fail Rev (2007) 12:149–156

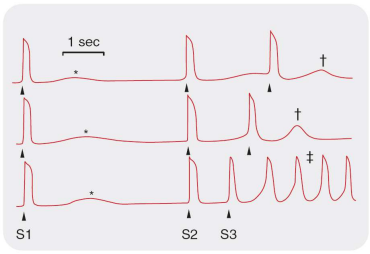
Einfluß von Herzglykosiden auf Aktionspotential, $[Ca^{2+}]_i$ und Kontraktion



Hess P, J. Gen. Physiol. 83, 395-415, 1984

Aktories et al. Allgemeine und spezielle Pharmakologie und Toxikologie
10. überarbeitete Auflage, Urban&Fischer

Späte Nachdepolarisationen – getriggerte Aktivität



Rang & Dale's pharmacology. – 7th ed
2012, Elsevier Inc. All

Wit A L, Cranefield P F 1977 Circ Res 41: 435

Therapeutic Advantages of Ca^{2+} Sensitizers

Potential Advantages

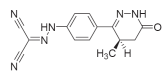
1. No risk for Ca^{2+} overload
   - Lack of arrhythmogenicity
   - Lack of myocardial cell injury and death
2. Energetic advantages
   - No increase in activation and metabolic energy
3. Effective in pathophysiological conditions
   - Acidosis
   - Stunned myocardium
   - Congestive heart failure
4. Permissible use with digitalis

Potential Disadvantages

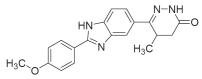
- Diastolic dysfunction

Endoh M Circ J 2008; **72:** 1915–1925

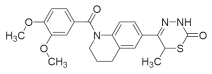
Calcium Sensitizer: Chemische Struktur



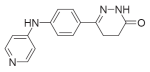
levosimendan



pimobendan



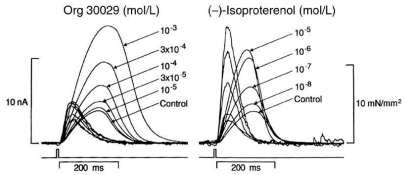
EMD-53998



MCI-154

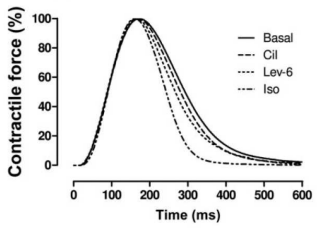
Endoh M Circ J 2008; **72:** 1915–1925

Kontraktions und Relaxationsdynamik der Herzmuskelfaser



Endoh M Circ J 2008; **72:** 1915–1925

Isolierte Herzmuskelfaser: Einfluss einiger Inotropika auf die Dynamik der Relaxation



Cil = Cilostamid (PDE3 Hemmer)
Lev-6 = Levosimendan
Iso = Isoprenalin

Ørstavik Ø et al.Br J Pharmacol (2014) **171** 5169–5181

Levosimendan

- positive Inotropie
- keine negative Lusitropie bzw. positive Lusitropie
- periphere Vasodilatation

Levosimendan

- positive Inotropie
- keine negative Lusitropie bzw. positive Lusitropie
- periphere Vasodilatation

> PDE3-Hemmung?

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ISSN 0901-9928

Functional and Antiischaemic Effects of the Phosphodiesterase Inhibitor Levosimendan in Isolated Rabbit Hearts

A. F. E. Rump, D. Acar, R. Rösen and W. Klaus
Institute of Pharmacology, University of Köln, Gleueler str. 24, D-50931 Köln, Germany
(Received October 4, 1993; Accepted December 20, 1993)

TABLE 2.

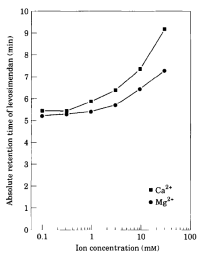
Relative potencies for Ca^{2+} sensitizers to inhibit PDE III and to increase Ca^{2+} sensitivity

Agents	Inhibition of PDE III (IC_{50}, μM)	Ca^{2+} sensitization (EC_{50}, μM)
EMD 53998 (racemate)	0.06[127]	4.8, 10[146]
EMD 57033 [(+)-isomer]	1.94[127]	1.7[146]
EMD 57439 [(−)-isomer]	0.05[127]	>100[146]
Pimobendan	2.4[147]	40[97]
Levosimendan	0.025[148]	0.3~1.0[68]
MCI-154	4.0[122,149]	>100[121]
Org 30029	37[139]	>100[71]
CGP 48506	>300[74]	10[73]
SCH00013	65[144]	~10[85]

References appear in superscript.

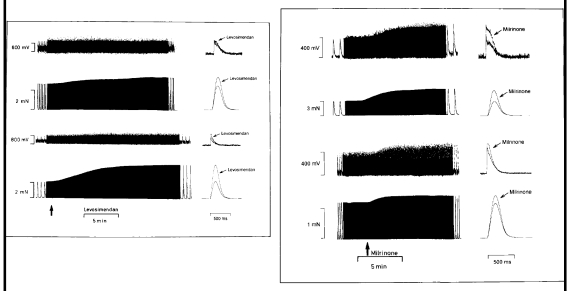
Endoh M J Cardiovasc Pharmacol **40**:323–338 2002

Die Bindung von Levosimendan an Troponin C ist Ca^{2+} - abhängig



Haikala H J Mol Cell Cardiol 27:1859-1866 (1995)

Intracelluläres Calcium und Kraftentwicklung in menschlichen Muskelfasern



Hasenfuss G et al. *Circulation*. 1998;98:2141-2147

BJP British Journal of Pharmacology

DOI:10.1111/bph.12047
www.brjpharmacol.org

RESEARCH PAPER

Inhibition of phosphodiesterase-3 by levosimendan is sufficient to account for its inotropic effect in failing human heart

Ø Ørstavik[1,2,3], S H Ata[1,2,3], J Riise[1,2,3], C P Dahl[2,3,4], G Ø Andersen[2,4], F O Levy[1,2,3], T Skomedal[1,2,3], J-B Osnes[1,2,3] and E Qvigstad[1,2,3]

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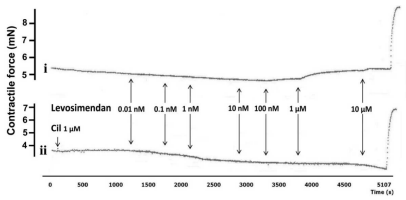
Received
8 January 2013
Revised
28 October 2013
Accepted
10 November 2013

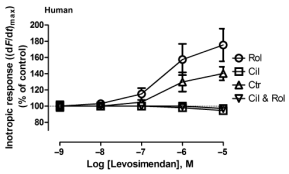
Isolierte Herzmuskelfaser: Vorbehandlung mit einem PDEIII-Hemmer verhindert die positiv inotrope Wirkung von Levosimendan



Cil = Cilostamid (PDE3 Hemmer)

Ørstavik Ø et al.Br J Pharmacol (2014) **171** 5169–5181

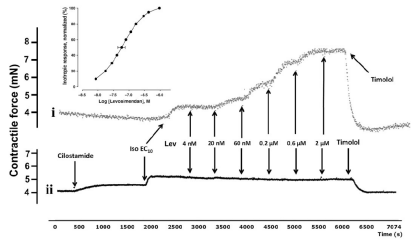
PDE4-Hemmung verstärkt, PDE3-Hemmung verhindert den positiv inotropen Effekt von Levosimendan



Cil = Cilostamid (PDE3 Hemmer)
Rol = Rolipram (PDE4 Hemmer)

Ørstavik Ø et al.Br J Pharmacol (2014) **171** 5169–5181

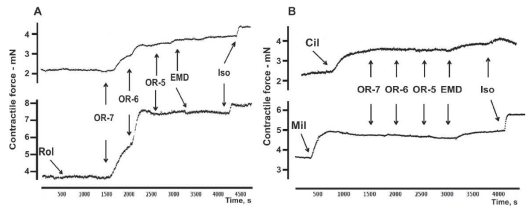
Potenzierung der inotropen Wirkung von Isoprenalin durch Levosimendan ist PDE3-abhängig



Cil = Cilostamid (PDE3 Hemmer)

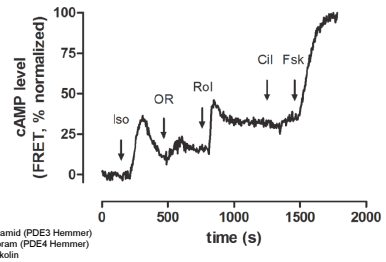
Ørstavik Ø et al.Br J Pharmacol (2014) **171** 5169–5181

Inotroper Effekt und PDE3 Hemmung durch den aktiven Levosimendan-Metaboliten OR-1896



Ørstavik Ø et. al. (2015) PLoS ONE 10(3): e0115547. doi:10.1371/journal.pone.0115547

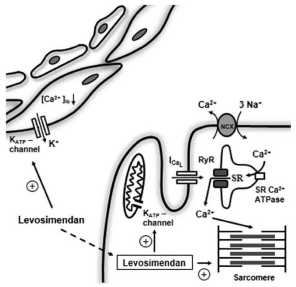
Inotroper Effekt und PDE3 Hemmung durch den aktiven Levosimendan-Metaboliten OR-1896



CiI = Cilostamid (PDE3 Hemmer)
RoI = Rolipram (PDE4 Hemmer)
Fsk = Forskolin

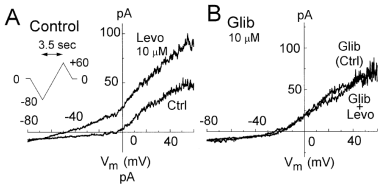
Ørstavik Ø et. al. (2015) PLoS ONE 10(3): e0115547. doi:10.1371/journal.pone.0115547

Multiple molekulare Angriffspunkte von Levosimendan



Nagy L et al. J Cardiovasc Pharmacol 2014;64:199–208

Levosimendan aktiviert K^+ Kanäle in arteriellen Myozyten



Yokoshiki H et al., Eur J Pharmacol 333 (1997) 249–259

Table 5. Treatment-Emergent Adverse Events[a]

	No. (%) of Patients		
	Levosimendan (n = 660)	Dobutamine (n = 660)	P Value[b]
Any adverse event	518 (78.5)	502 (76.1)	.32
Any serious adverse event[c]	196 (29.5)	217 (32.9)	.21
Hypotension	102 (15.5)	92 (13.9)	.46
Cardiac failure[d]	81 (12.3)	112 (17.0)	.02
Hypokalemia	62 (9.4)	39 (5.9)	.02
Atrial fibrillation	60 (9.1)	40 (6.1)	.05
Headache	55 (8.3)	31 (4.7)	.01
Ventricular tachycardia	52 (7.9)	48 (7.3)	.76
Nausea	45 (6.8)	49 (7.4)	.75
Ventricular extrasystoles	40 (6.1)	24 (3.6)	.05
Insomnia	37 (5.6)	29 (4.4)	.38
Tachycardia	33 (5.0)	33 (5.0)	>.99
Chest pain	32 (4.8)	47 (7.1)	.10
Diarrhea	30 (4.5)	21 (3.2)	.25
Pneumonia	30 (4.5)	24 (3.6)	.49
Congestive cardiac failure	26 (3.9)	22 (3.3)	.66
Constipation	26 (3.9)	28 (4.2)	.89
Renal failure	24 (3.6)	22 (3.3)	.88
Vomiting	22 (3.3)	24 (3.6)	.88
Pyrexia	22 (3.3)	19 (2.9)	.75
Urinary tract infection	21 (3.2)	30 (4.5)	.25
Cardiac arrest	20 (3.0)	26 (3.9)	.40
Anxiety	20 (3.0)	19 (2.9)	>.99
Pulmonary edema	20 (3.0)	18 (2.7)	.87
Dizziness	19 (2.9)	16 (2.4)	.73
Cough	19 (2.9)	21 (3.2)	.87
Pain in extremity	18 (2.7)	10 (1.5)	.18
Pruritus	16 (2.4)	7 (1.1)	.09
Cardiogenic shock	15 (2.3)	23 (3.5)	.25
Ventricular fibrillation	15 (2.3)	19 (2.9)	.63
Anemia	15 (2.3)	17 (2.6)	.86
Hyperkalemia	15 (2.3)	16 (2.4)	>.99
Epistaxis	14 (2.1)	7 (1.1)	.19
Back pain	13 (2.0)	18 (2.7)	.47
Muscle spasms	12 (1.8)	13 (2.0)	>.99
Angina pectoris	12 (1.8)	18 (2.7)	.36
Dyspnea	9 (1.4)	17 (2.6)	.16
Bradycardia	8 (1.2)	17 (2.6)	.10
Hypertension	9 (1.4)	15 (2.3)	.30
Cataract	7 (1.1)	14 (2.1)	.19
Delirium	7 (1.1)	0	.02

Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

Mebazaa A et al.
JAMA. 2007;297:1883-1891

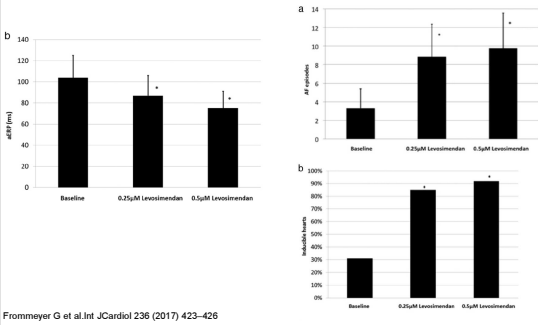
Table 3 Adverse Events Occurring With a Frequency ≥5% in REVIVE I and REVIVE II

	REVIVE I		REVIVE II	
	Levosimendan (n = 51)	Placebo (n = 48)	Levosimendan (n = 293)	Placebo (n = 294)
Hypotension	28 (54.9%)	23 (47.9%)	147 (50.2%)	107 (36.4%)
Headache	23 (45.1%)	13 (27.1%)	88 (30.0%)	44 (15.0%)
Cardiac failure	14 (27.5%)	13 (27.1%)	98 (33.5%)	108 (36.7%)
Ventricular tachycardia	12 (23.5%)	10 (20.8%)	72 (24.6%)	51 (17.3%)
Nausea	17 (33.3%)	11 (22.9%)	53 (18.1%)	46 (15.6%)
Dizziness	13 (25.5%)	4 (8.3%)	38 (13.0%)	35 (11.9%)
Hypokalemia	7 (13.7%)	8 (16.7%)	35 (11.9%)	36 (12.2%)
Renal failure	4 (7.8%)	1 (2.1%)	36 (12.3%)	40 (13.6%)
Insomnia	9 (17.6%)	7 (14.6%)	32 (10.9%)	37 (12.6%)
Constipation	5 (9.8%)	3 (6.3%)	34 (11.6%)	35 (11.9%)
Vomiting	4 (7.8%)	6 (12.5%)	27 (9.2%)	22 (7.5%)
Hyperkalemia	5 (9.8%)	5 (10.4%)	21 (7.2%)	19 (6.5%)
Diarrhea	4 (7.8%)	1 (2.1%)	21 (7.2%)	20 (6.8%)
Back pain	6 (11.8%)	5 (10.4%)	13 (4.4%)	20 (6.8%)
Urinary tract infection	1 (2.0%)	1 (2.1%)	20 (6.8%)	21 (7.1%)
Muscle cramp	6 (11.8%)	3 (6.3%)	20 (6.8%)	11 (3.7%)
Anxiety	1 (2.0%)	1 (2.1%)	17 (5.8%)	18 (6.1%)
Pain in extremity	1 (2.0%)	4 (8.3%)	14 (4.8%)	18 (6.1%)
Anemia	2 (3.9%)	3 (6.3%)	16 (5.5%)	15 (5.1%)
Angina pectoris	—	—	18 (6.1%)	18 (6.1%)
Atrial fibrillation	4 (7.8%)	1 (2.1%)	25 (8.5%)	6 (2.0%)
Pyrexia	—	2 (4.2%)	16 (5.5%)	18 (6.1%)
Cough	2 (3.9%)	4 (8.3%)	13 (4.4%)	15 (5.1%)
Ventricular extrasystoles	3 (5.9%)	2 (4.2%)	22 (7.5%)	6 (2.0%)
Dyspnea exacerbated	3 (5.9%)	3 (6.3%)	10 (3.4%)	15 (5.1%)
Hypoglycemia	1 (2.0%)	3 (6.3%)	15 (5.1%)	8 (2.7%)

Values are n (%). Versions of Medical Dictionary for Regulatory Activities + differed slightly between studies.
REVIVE = Randomized Evaluation of Intravenous LeVosimendan Efficacy trials.

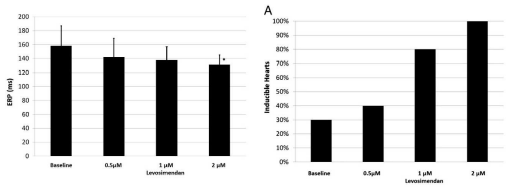
Packer M et al. J Am Coll Cardiol HF 2013;1:103–11

Isoliertes Herz: Levosimendan verringert atriale Refraktärzeiten und fördert Vorhofarrhythmien



Frommeyer G et al.Int JCardiol 236 (2017) 423–426

Isoliertes Herz: Levosimendan verringert ventrikuläre Refraktärzeiten und fördert ventrikuläre Arrhythmien



Frommeyer G et al.Int J Cardiol 228 (2017) 583–587

Elektrophysiologische Effekt von Levosimendan in Patienten mit normaler Herzfunktion

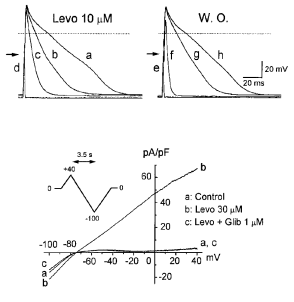
Drive cycle length	600 ms	500 ms	400 ms
Atrial effective refractory period			
Control	249 (25)	243 (28)	244 (18)
Levosimendan	226 (25)[a]	221 (26)[a]	211 (23)[b]
Ventricular effective refractory period			
Control	251 (17)	244 (17)	234 (15)
Levosimendan	246 (23)[a]	238 (18)[a]	225 (14)[a]

[a]$p < 0.01$, [b]$p < 0.001$, statistical significance in comparison to control phase.

TABLE 3. The effect of levosimendan on atrial and ventricular effective refractory periods

J Cardiovasc Pharmacol (2000) 35(4): 664-669

Levosimendan aktiviert myokardiale K_{ATP}-Kanäle



J Pharmacol Exp Ther (1997) 283:375–383

Postgraduate Course Kardiovaskuläre Intensivmedizin
Baden, 4. und 5. Mai 2017

Arbeitsgruppe der ÖKG
kardiovaskuläre Intensivmedizin

Show me the evidence: was ist Inotropie & welche Inotropika haben wir wirklich?

1. **Derzeit gibt es keine „lastunabhängigen“ Inotropika**
2. **Die positiv inotrope Wirkung von Levosimendan resultiert wahrscheinlich aus einer Kombination von Calcium Sensitizing und PDE3-Hemmung.**