Má landiolol místo v kardiochirurgii?

Hynek Říha

Klinika anesteziologie a resuscitace

Kardiocentrum IKEM, Praha

Kongres ČSARIM, říjen 2023

Disclosures

- **AOP Orphan**

✓ **edukační přednášky**

Perioperační medikace u kardiochirurgických výkonů

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2017 EACTS Guidelines on perioperative medication in adult cardiac surgery

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Management of treatment with beta-blockers in perioperative settings

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative period			
It should be considered to continue beta-blocker therapy prior to cardiac surgery.	IIa	B	[125, 126, 176]
Postoperative period			
Postoperative long-term beta-blocker therapy is recommended in patients with a recent MI or reduced LVEF (<35%).	I	A	[171, 173–175]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Sousa-Uva M et al. Eur J Cardiothorac Surg 2018;53:5

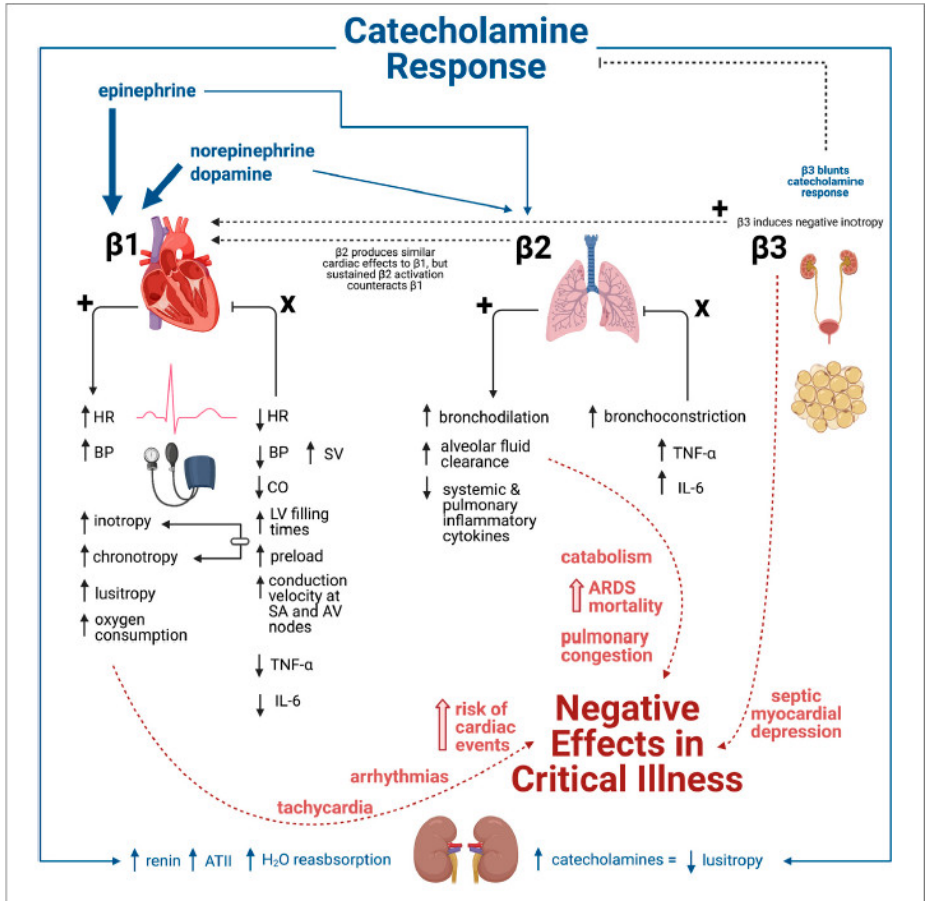
Betablokátory a kardiochirurgické výkony (perioperační období)

- Obava z negativně inotropního a chronotropního účinku betablokátorů
- ↓ Srdečního výdeje, a tím perfuze tkání (dodávky O2)

- Aplikace inotropik (beta-adrenergní agonisté)
- Aplikace vazopresorů (noradrenalin, …)

- Antagonizace účinků těchto farmak (?)

- Nástup a délka účinku (?)



Bruning R et al. Front Pharmacol 2021;12:735841

Esmolol a septický šok s vyšší vazopresorickou podporou

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

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Balik M et al. Wien Klin Wochenschr 2012;124:552

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

Martin Balik, Jan Rulisek, Pavel Leden, Michal Zakharchenko, Michal Otahal, Hana Bartakova, Josef Korinek

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/m^2]	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

Ultrakrátce působící β_1-selektivní blokátory a mortalita u sepse

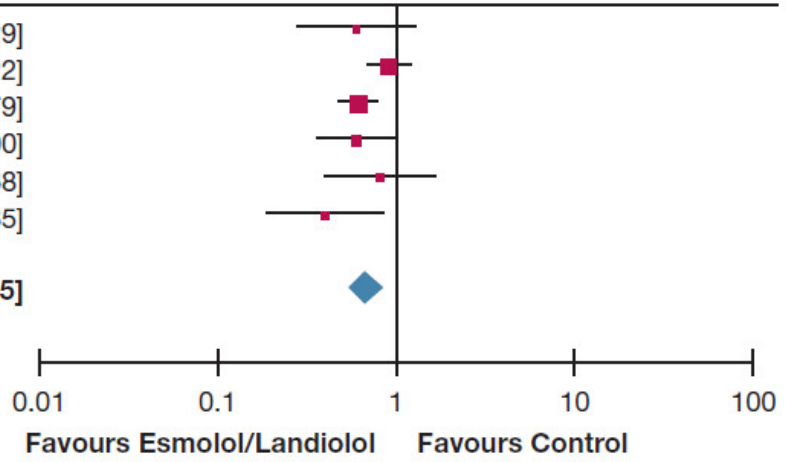
- **Sepse s perzistující tachykardií po iniciální resuscitaci**
- **Ultrakrátce působící β_1-selektivní blokátor (esmolol nebo landiolol)**

- **Metaanalýza 7 RCTs / 613 pacientů**
- **Z toho 6 RCTs / 572 pacientů => 28denní mortalita (all-cause)**

Study or Subgroup	Esmolol/Landiolol Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kakihana 2020	9	75	15	75	7.4%	0.60 [0.28, 1.29]
Liu 2019	31	50	34	50	29.3%	0.91 [0.68, 1.22]
Morelli 2013	38	77	62	77	33.2%	0.61 [0.48, 0.79]
Wang 2015	12	30	20	30	14.5%	0.60 [0.36, 1.00]
Wang 2017	9	30	11	30	8.2%	0.82 [0.40, 1.68]
Xinqiang 2015	6	24	15	24	7.5%	0.40 [0.19, 0.85]
Total (95% CI)		**286**		**286**	**100.0%**	**0.68 [0.54, 0.85]**
Total events	105		157			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.21$, df = 5 ($P = .21$); $I^2 = 31\%$

Test for overall effect: Z = 3.40 ($P = .0007$)



Hasegawa D et al. Chest 2021;159:2289

Ultra-krátce působící beta$_1$-selektivní blokátory u KCH pacientů

1. Cardioprotection during cardioplegic cardiac arrest	– **Cardioplegia adjuvant:** Esmolol, 1 mg/kg IV bolus after aortic cannulation, before aortic clamping + 2 mg/kg mixed with cardioplegia solution.[13]
2. After cardiopulmonary bypass	– **Prophylaxis of ventricular arrhythmia** Esmolol 1 mg/kg IV bolus prior to aortic clamp removal.[14] – **Treatment of atrial fibrillation** Landiolol, continuous infusion 0,5-2μg/kg/min until 40 μg/kg/min (reassessed every 10min) titrated on hemodynamic or electrocardiographic responses. Treatment duration 24 hrs.[15]
3. Systolic anterior motion (SAM) of the mitral valve after valve repair	– Step 1: intravascular volume expansion and simultaneously discontinuation of any inotropic drug. – Step 2: partial digital occlusion of the ascending aorta and simultaneous administration of an I.V. bolus of esmolol, 1 mg/kg. Patients with persistent SAM not responding to step 1 or 2 go to revision of mitral repair or valve replacement, immediately during the same surgical act.[16,17]
4. Aortic dissection	**Esmolol** 500 mcg/kg IVP over 1 min followed by continuous infusion at 25-50 mcg/kg/min, increase q 4 min by 25 mcg/kg/min to max rate of 300 mcg/kg/min.[18]
5. Acute myocardial infarction	– **Cardioprotective effects for myocardial ischemic injury during PCI:** – **Protocol with landiolol**: 20 μg/kg/min IV for 5 min immediately before reperfusion procedure. If after the 5 min, the patient's vital signs not meet the target (15% reduction in heart rate), landiolol is increased by 5–10 μg/kg/min every 1 min up to a maximum of 40 μg/kg/min. After completion of the PCI, landiolol is discontinued and followed by oral β -blocker (metoprolol, carvedilol or oral bisoprolol).[10] – **Protocol with esmolol**: (in patients with Killip class I or II STEMI, a baseline HR > 60 bpm and MABP > 65 mmHg) 500 μg/kg I.V. bolus over 5 min and start I.V. infusion at 50 μg/kg/min targeting HR of 60 bpm; if the target have not been reached 500 μg/kg I.V. bolus over 5 min and infusion 100 μg/kg/min; if the target have not been reached 500 μg/kg I.V. bolus over 5 min and infusion 150 μg/kg/min; if the target have not been reached 500 μg/kg I.V. bolus over 5 min and infusion to 200 μg/kg/min. Infusion for 24 hrs.[19] – **Prevention of atrial fibrillation after CABG**: Landiolol, 2μg/kg/min administered at the time of central anastomosis for 48 hrs.[20]
6. Critically ill septic patients in ICU	– Esmolol, infusion at 25 mg/hr and progressively increased the rate at 20 minute intervals in increments of 50 mg/hr (HR target between 80 and 94 bpm). Maximum dose 2000 mg/h.[21,22]
7. To improve arterial oxygenation in ECMO	– Esmolol IV bolus dose of 500 μg/kg and continuous infusion 50-80 μg/kg/min (SpO2 target > 92%).[23]
8. For anesthesia induction:	In patients predisposed to arrhythmias and in those with prolonged Pwd (P-wave dispersion) and prolonged QTc in their preoperative ECG: Esmolol 0.5 mg/kg IV bolus, followed by a continuous infusion at 100 μg/kg/h.[24]
9. Imaging (Coronary CT angiography)	If HR > 65 bpm: **esmolol** 0.8 mg/kg bolus, followed by another 0.8 mg/kg bolus if the HR is still > 65 beats/min.[25] If patients have a HR of 70–90 bpm: **landiolol**, 0.125 mg/kg IV bolus.[26]
10. Intraoperative period of non-cardiac surgery	– **Cardioprotective effects for myocardial ischemic injury** Esmolol, single dose bolus (usually 0.5-1 mg/kg) followed by a continuous infusion (between 100 and 300 μg/kg/min).[27]
11. Immediate post-operative period of non-cardiac surgery	– **Prevention of atrial fibrillation**: Landiolol, continuous IV infusion at 3 μg/kg/min during 72 h.[28] – **Treatment of atrial fibrillation**: Landiolol, continuous IV infusion 5-10 μg/kg/min (without bolus) for 48 hours, followed by 2.5–5.0 mg carvedilol orally daily for 1 month.[29]

Poveda-Jaramillo R et al. J Cardiothorac Vasc Anesth 2018;32:1415

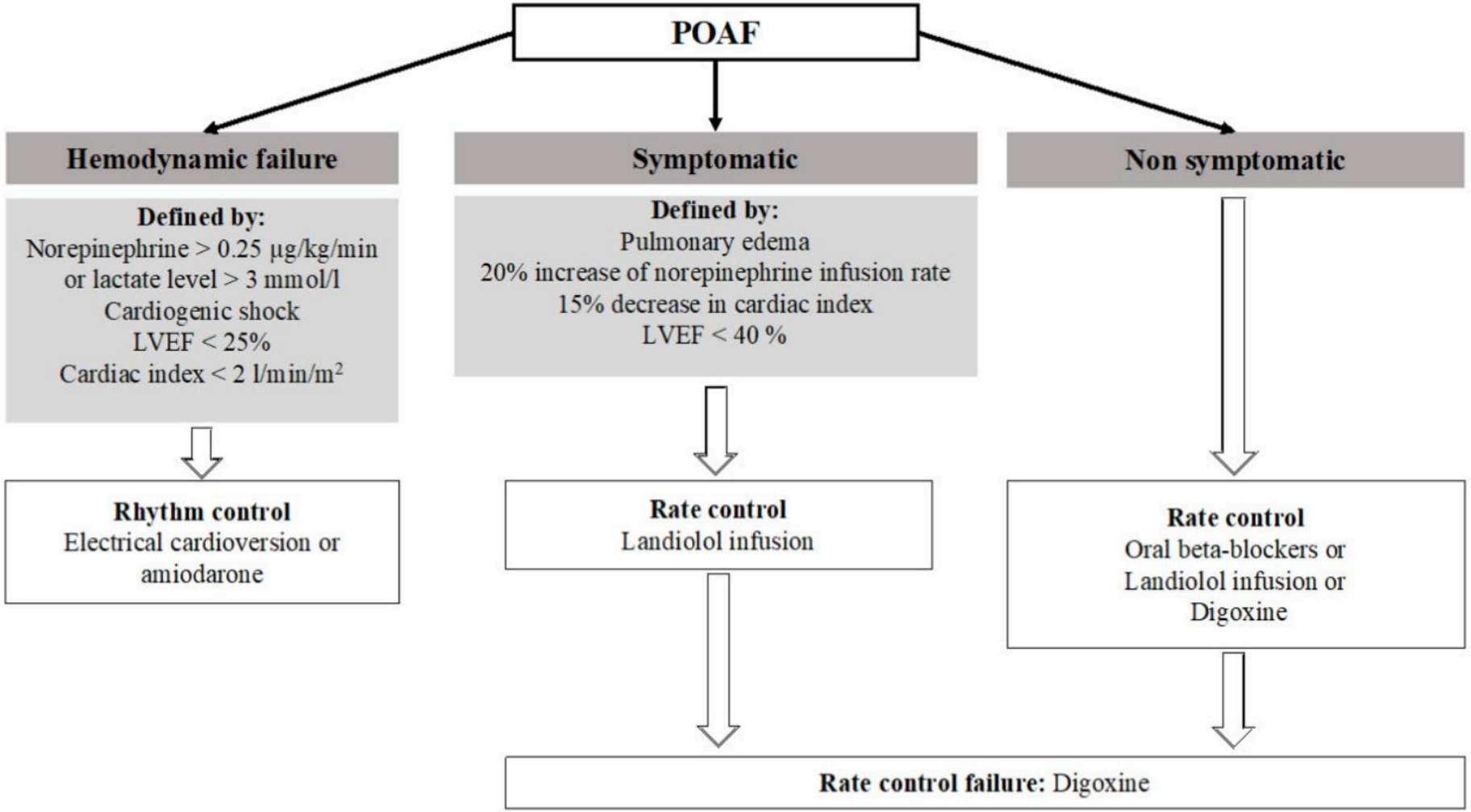
Fibrilace síní po kardiochirurgických výkonech

- **Prospektivní observační studie; 54 pacientů**

Baseline characteristics	
Age, years, mean (SD)	70 (7)
Gender, male, *n* (%)	44 (81.5)
Euroscore II, mean (SD)	4.8 (1.4)
NYHA	
Stage 1	23 (42.6)
Stage 2	24 (44.4)
Stage 3	7 (13)
Comorbidities, *n* (%)	
Cardiac insufficiency	3 (5.6)
Chronic kidney disease	6 (11.1)
Pre-existing AF	5 (11.1)
Surgery, *n* (%)	
CABG	36 (66.7)
Aortic valve replacement	23 (42.6)
Mitral valve replacement	5 (9.3)
Other	1 (1.9)
Respiratory support at baseline, *n* (%)	54 (100)
Invasive ventilation	9 (16.7)
Non-invasive ventilation	9 (16.7)
No mechanical ventilation	36 (66.7)
Medication at baseline, *n* (%)	
Norepinephrine	16 (30)
Amiodarone	5 (9.3)
Beta blockers	14 (25.9)
Onset of POAF after surgery, days, mean (SD)	2.4 (1.6)

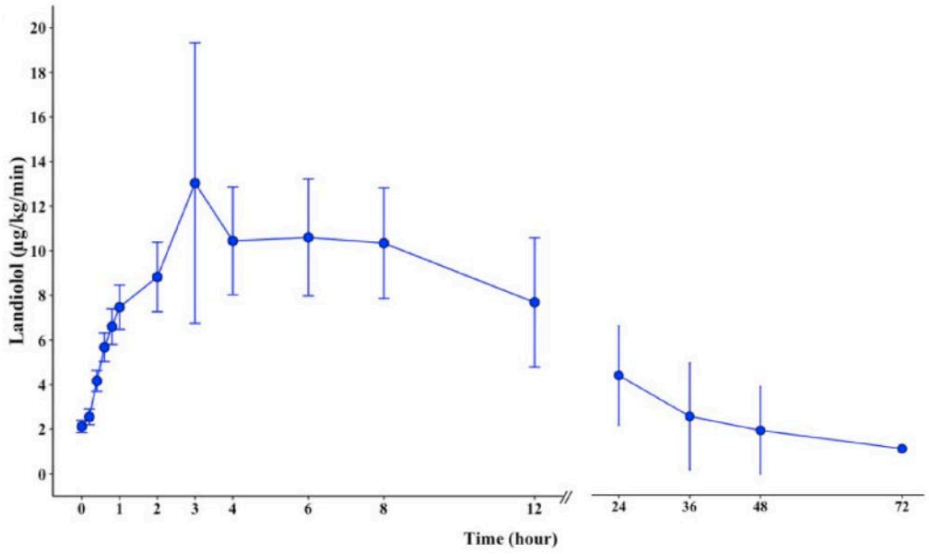
Chapalain X et al. Eur Heart J Suppl 2022;24 (Suppl D):D34

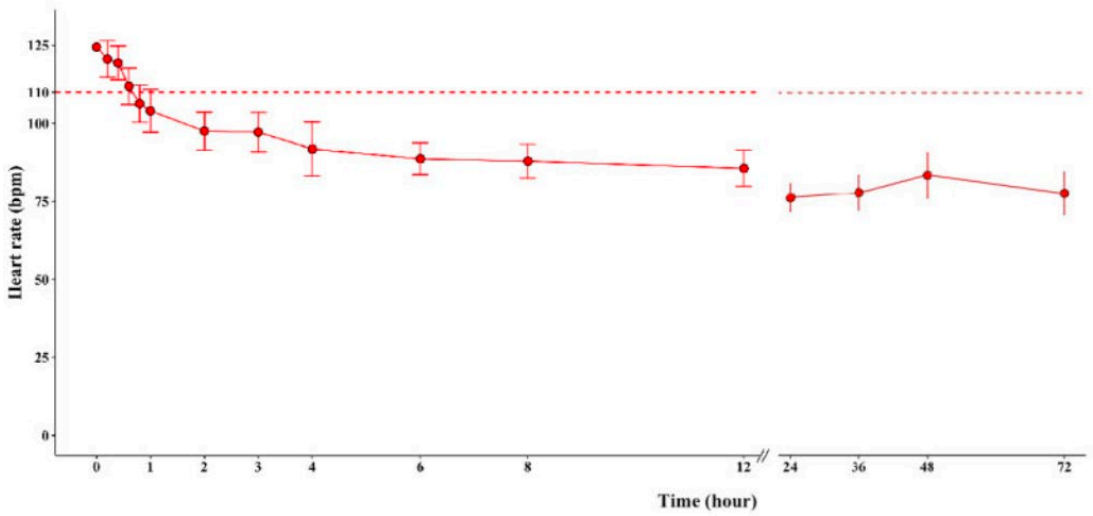
Fibrilace síní po kardiochirurgických výkonech

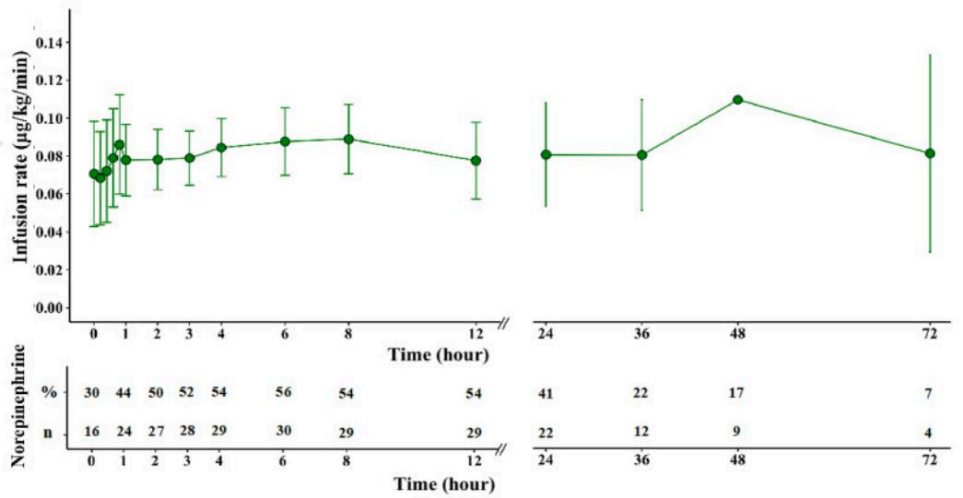


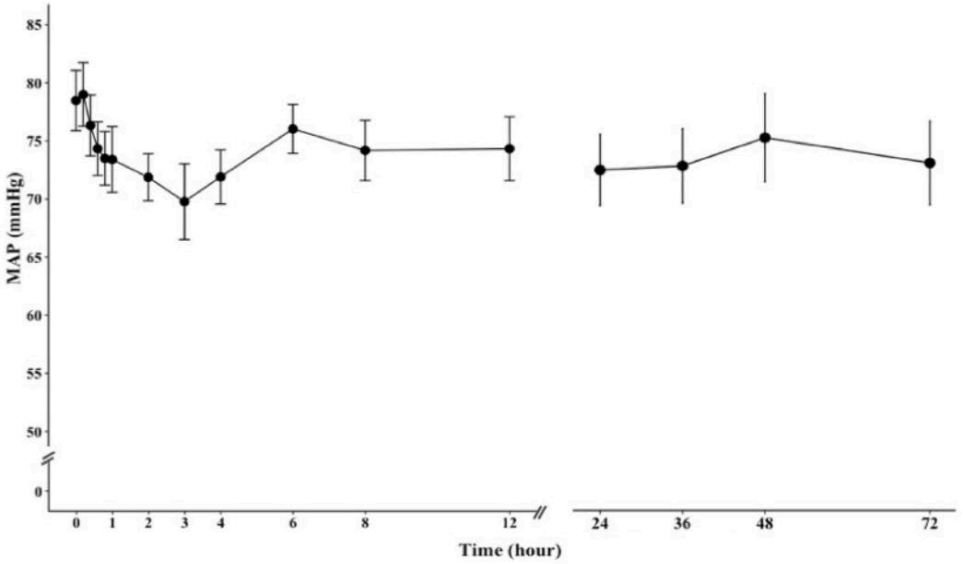
Chapalain X et al. Eur Heart J Suppl 2022;24 (Suppl D):D34

Fibrilace síní po kardiochirurgických výkonech





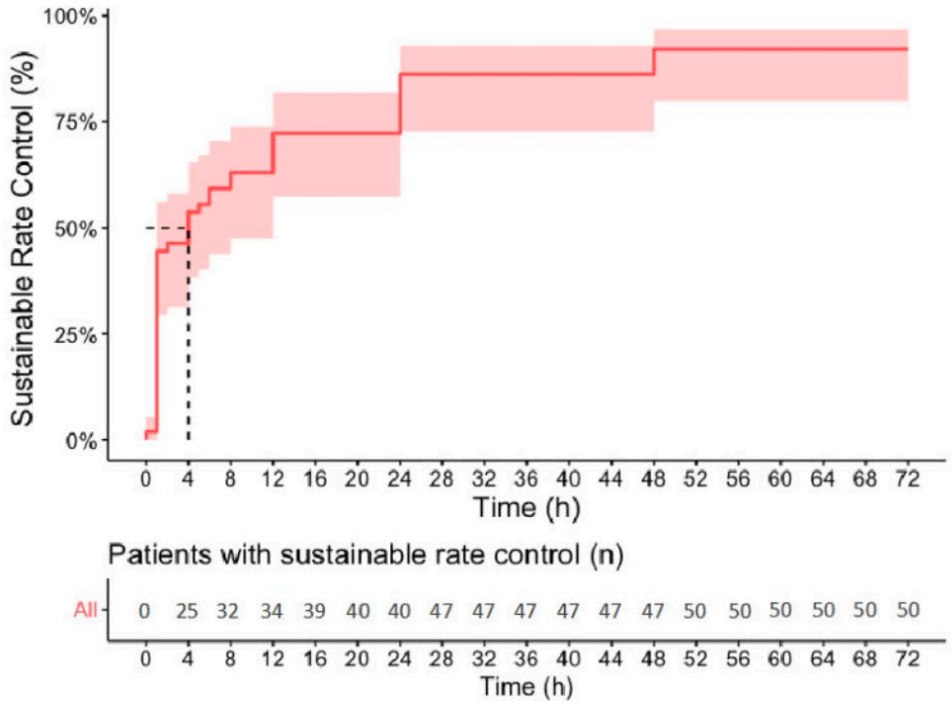


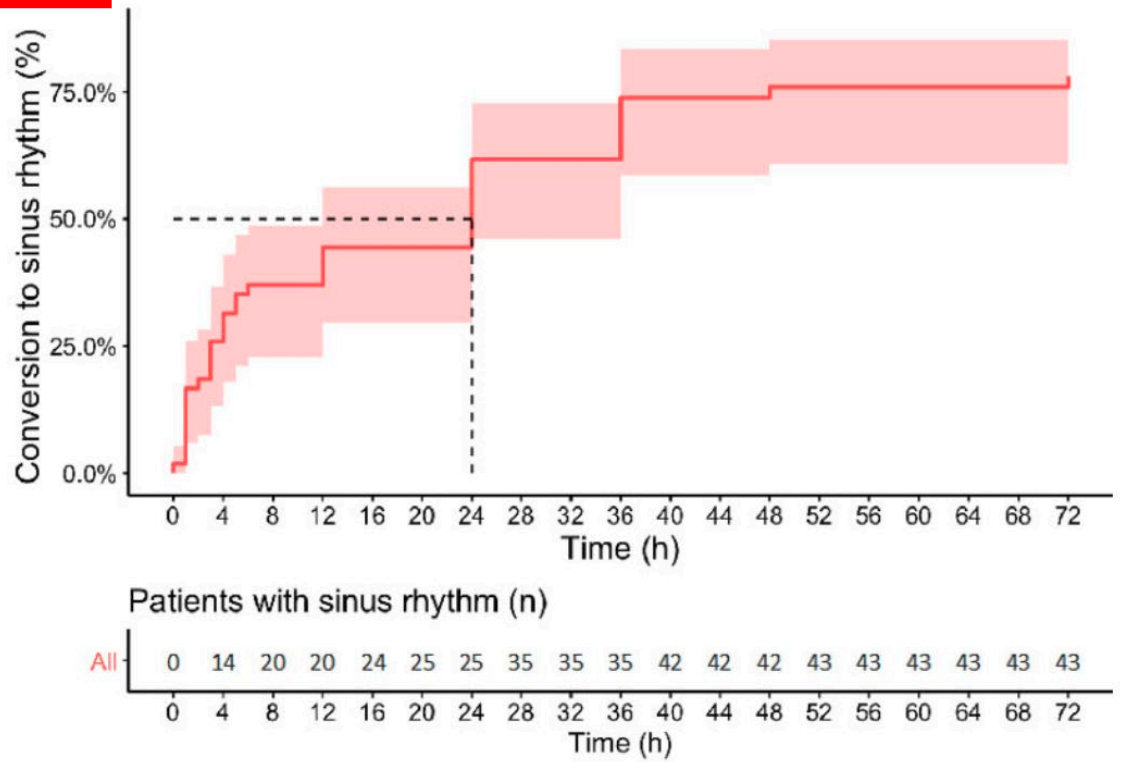


Chapalain X et al. Eur Heart J Suppl 2022;24 (Suppl D):D34

Fibrilace síní po kardiochirurgických výkonech

Rate control during landiolol infusion	
Sustainable rate control (HR < 110 b.p.m.), *n* (%)	49 (90.7)
Time until sustainable rate control was achieved, h, median (IQR)	4 (1-22)
Infusion rate of landiolol, µg/kg/min, median (IQR)[a]	10 (6-19)



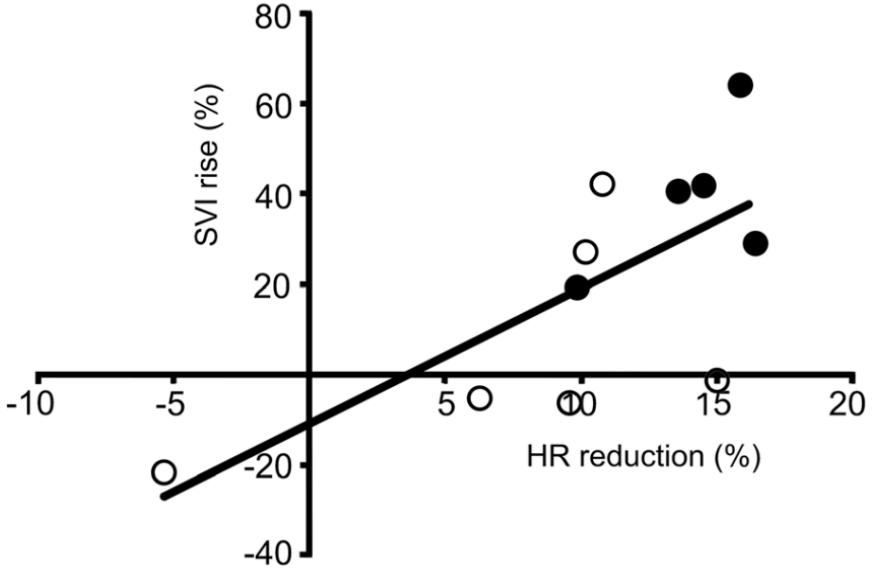


Chapalain X et al. Eur Heart J Suppl 2022;24 (Suppl D):D34

Sinusová tachykardie a katecholaminy po KCH výkonech

- **KCH výkon; 11 pacientů**
- **Landiolol 2,6±1,3 ug/kg/min (rozsah 1,1–5,0 ug/kg/min)**

	Pre-landiolol	Post-landiolol	*p*-value
HR	126.0 ± 7.6	112.4 ± 5.8	< 0.001
SVI	18.9 ± 4.2	22.4 ± 5.4	0.04
SV	30.8 ± 6.6	36.7 ± 10.5	0.033
CI	2.4 ± 0.5	2.5 ± 0.6	0.32
CO	3.9 ± 0.8	4.1 ± 1.1	0.28
SvO_2	63.1 ± 12.8	65.2 ± 13.3	0.42
sBP	86.6 ± 29.1	102.8 ± 19.6	0.082
dBP	54.9 ± 10.5	59.3 ± 8.7	0.11
mBP	80.3 ± 18.8	81.5 ± 15.7	0.71
sPAP	28.6 ± 5.1	29.6 ± 8.8	0.51
dPAP	20.3 ± 4.9	18.9 ± 5.6	0.14
mPAP	21.1 ± 7.6	22.5 ± 6.5	0.53
CVP	10.4 ± 3.6	10.5 ± 5.1	0.91
BT	37.4 ± 0.8	37.6 ± 0.6	0.17



Sakai M et al. J Cardiothorac Surg 2019;14:145

MMELPOAF study

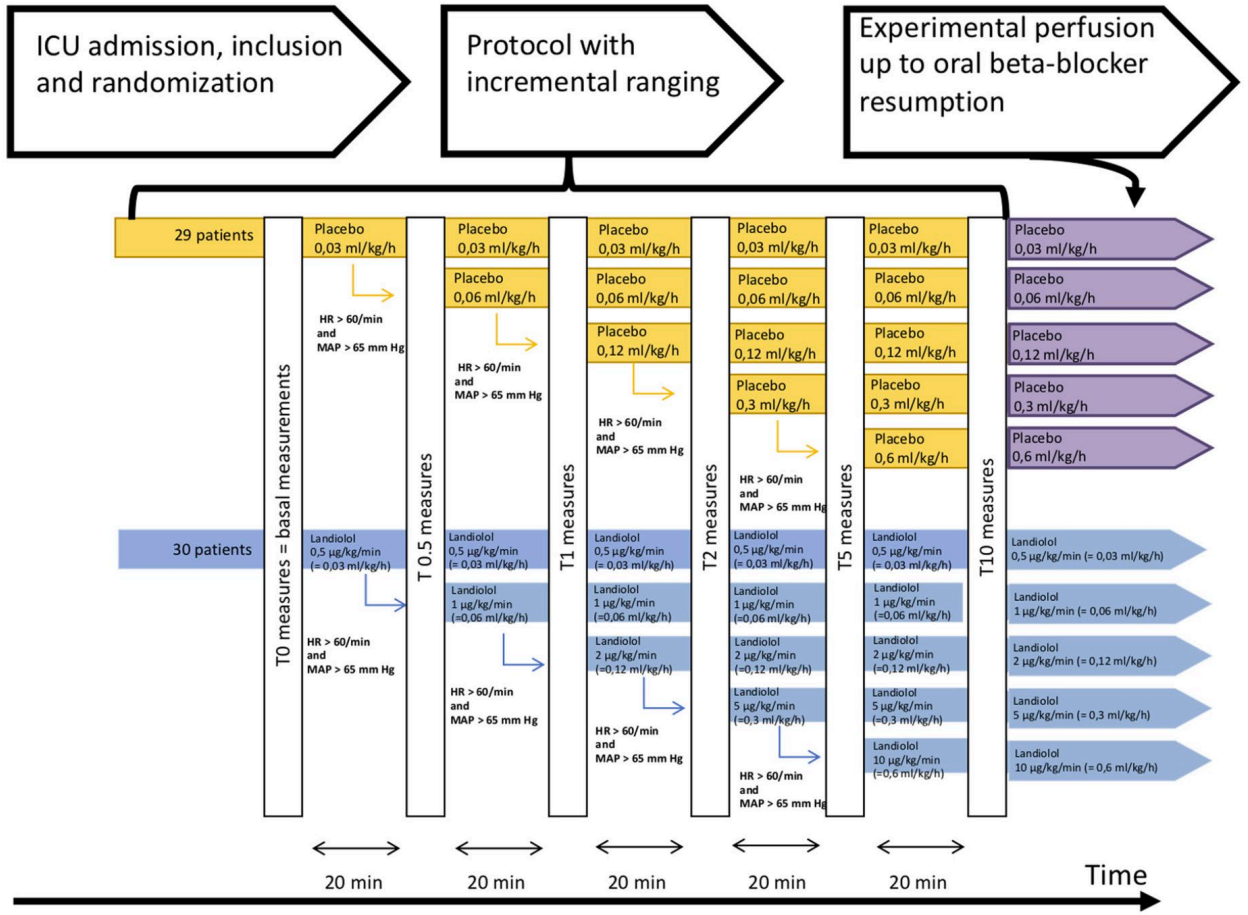
- **Micro- and Macrocirculatory Effects of Landiolol in Post-Operative AF**

	Placebo	Landiolol	
	n = 29	n = 30	p Value
Age, y	64 ± 10	63 ± 11	0.51
Men, n	21 (72)	23 (77)	1.0
Weight, kg	79 ± 19	77 ± 12	0.64
BMI, kg/m^2	27.4 ± 5.4	26.1 ± 3.2	0.24
Chronic heart failure, n	1 (3)	1 (3)	1.0
Diabetes mellitus, n	3 (10)	5 (17)	0.74
Hypertension, n	20 (69)	16 (53.3)	0.34
Chronic renal failure, n	4 (14)	5 (17)	1.0
COPD, n	0 (0)	3 (10)	0.25
Peripheral arterial disease, n	3 (10)	2 (7)	0.97
Chronic medications			
Beta-blockers	4 (14%)	4 (13%)	0.96
ACE inhibitors/ARB	14 (48%)	13 (43%)	0.52
Diuretics	4 (14%)	7 (23%)	0.37
Statins	13 (45%)	14 (47%)	0.89
Platelet inhibitors	15 (52%)	12 (40%)	0.37
Type of surgery			
Valvular replacement or repair	21 (73%)	15 (50%)	0.08
Coronary bypass	5 (17%)	10 (33%)	0.27
Combined surgery	3 (10%)	5 (17%)	0.48
Hemoglobin, g/L	123 [118-129]	122 [110-132]	0.42
Preoperative LVEF, %	49 [40-63]	50 [43-56]	0.94
Norepinephrine requirement, µg/kg/min	0.05 [0-0.1]	0.04 [0-0.1]	0.73

Ferraris A et al. J Cardiothoracic Vasc Anesth 2022;36:2864

MMELPOAF study

- **RCT: 59 pacientů (landiolol 30 a placebo 29); hodnocení 30/28 pacientů**
- **Landiolol: 0.5, 1, 2, 5 a 10 ug/kg/min během 2 h po KCH výkonu**



- HR >60 bpm a MAP >65 mmHg
- stabilizace 20 min před ↑ dávky

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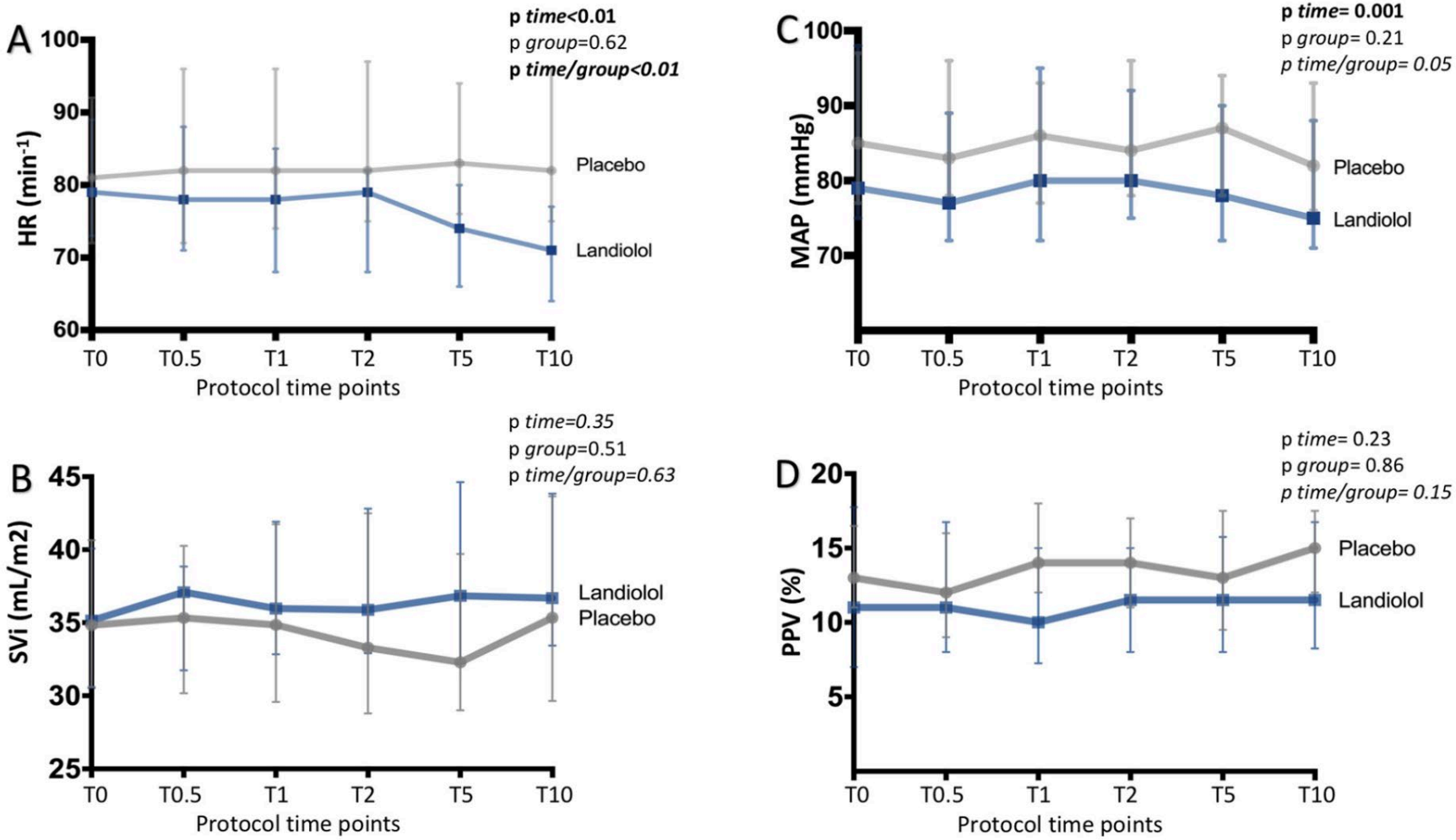
MMELPOAF study: parametry makrocirkulace



Ferraris A et al. J Cardiothoracic Vasc Anesth 2022;36:2864

MMELPOAF study: echokardiografické parametry

	T 0		T 10		*p* Time	*p* Group	*p* Time/Group
	Landiolol	Placebo	Landiolol	Placebo			
Left ventricle							
LVEF (%)	50 [43-56]	49 [40-63]	50 [42-59]	48 [44-58]	0.72	0.84	0.63
VTI (cm)	19 [15-22]	18 [15-23]	17 [14-22]	18 [16-24]	0.57	0.73	0.44
SVi	44 [36-61]	47 [30-57]	54 [39-58]	53 [42-58]	0.43	0.98	0.05
E/A	1 [0.8-1.2]	0.9 [0.8-1.1]	1.2 [0.9-1.4]	0.9 [0.7-1.1]	0.59	0.82	**0.02**
E/e'	9.3 [7.4-14.5]	13.4 [9.7-18]	10.5 [7.8-14.9]	13.6 [10.1-15.1]	0.85	0.02	0.62
Right ventricle							
TAPSE (mm)	13 [12-16]	13 [12-19]	12 [9-14]	14 [11-15]	0.17	0.31	0.37
FAC (%)	40 [34-44]	35 [25-41]	33 [30-36]	39 [29-40]	0.62	0.97	0.25
S tricuspid (cm/s)	8 [7-9]	9 [7-11]	7 [6-8]	9 [7-11]	0.43	0.36	0.34
E/A tricuspid	1 [0.8-1.2]	1.1 [0.8-1.2]	0.8 [0.7-1.0]	0.9 [0.8-1.2]	0.19	0.21	0.58
E/e' tricuspid	5.3 [4.7-6.5]	6.4 [5.3-7.5]	4.9 [4.3-6.1]	6.2 [4.7-7.1]	0.16	0.09	0.35

Ferraris A et al. J Cardiothoracic Vasc Anesth 2022;36:2864

MMELPOAF study: parametry mikrocirkulace

- **NIRS a sublinguální videomikroskopie**

Table 1 NIRS and sublingual videomicroscopy variables at baseline (T0) and during landiolol infusion (T1). Data are median [25th–75th]. No significant changes by [a linear mixed effect model] between T0 and T1 in both groups. NIRS, near-infrared spectroscopy.

	T0		T1	
	Landiolol	**Placebo**	**Landiolol**	**Placebo**
NIRS variables				
Resaturation speed (% s^{-1})	0.9 [0.7–1.6]	0.8 [0.6–1.5]	1.2 [0.7–1.6]	0.8 [0.6–1.6]
Desaturation speed (s)	225 [160–325]	210 [137–470]	190 [131–290]	205 [145–291]
ΔrSO2, (% point)	10 [6–13]	11 [7–13]	10 [7–14]	11 [9–14]
Videomicroscopy variables				
Proportion of perfused vessels (%)	89 [82–99]	91 [85–100]	95 [90–98]	93 [88–99]
Total vessel density (mm^2/mm^2)	19 [18–24]	19 [15–21]	21 [18–22]	19 [17–22]
Microvascular flow index	3 [2–3]	3 [2–3]	3 [3–3]	3 [2–3]
Heterogeneity index (%)	22 [2–42]	22 [1–38]	14 [2–30]	2 [0–14]

Ferraris A et al. Br J Anaesth 2021;126:e212

Betablokátory a kardiochirurgické výkony

β-Blocker	Relative β1 Selectivity	β1/β2 Affinity Ratio	β3	ISA
Acebutolol	+	2.4	-	+
Atenolol	++	4.7	-	-
Betaxolol	++	6.8	-	-
Bisoprolol	++	13.5	-	-
Carvedilol	-		-	-
Esmolol	++	33	-	-
Labetalol	-		-	+
Landiolol	+++	255	-	-
Metoprolol	++	2.3	-	-
Nadolol	-		-	-
Nebivolol	++	46	+	-
Pindolol	-		-	++
Propranolol	-		-	-

Abbreviations: ISA, intrinsic sympathomimetic activity.

Esmolol

50–300 ug/kg/min

Nasycovací dávka: 200–400 ug/kg

Landiolol

10–40 ug/kg/min

Lze až 80 ug/kg/min

Event. nasycovací dávka 1 ug/kg

β-Blocker	Absorption (%)	Bioavailability (%)	Lipophilicity	Half-life	Degradation/Excretion
Acebutolol	90	40	Yes	3-4 h	Hepatic metabolism 30-40% Renal 50%-60%
Atenolol	50	40	No	6-7 h	Renal 50%-80%
Betaxolol	90	89	Yes	14-22 h	Hepatic metabolism 15% Renal 80%
Bisoprolol	90	80-94	Yes	9-12 h	Hepatic metabolism 50% Renal 50%
Carvedilol	90	24	Yes	7-10 h	Hepatic metabolism 90%
Esmolol	n/a	n/a	N/A	9 min	Plasma esterases
Labetalol	90	33	Yes	5-8 h	Hepatic metabolism 50% Renal 50%-60%
Landiolol	n/a	n/a	N/A	2-4 min	Pseudocholinesterase Liver carboxyesterase
Metoprolol	90	65-70	Yes	3-4 h	Hepatic metabolism 95% Renal 5%
Nadolol	50	30	No	20-24 h	Renal 100%
Nebivolol	90	12-96	Yes	12-19 h	Hepatic metabolism
Pindolol	90	90	Yes	3-4 h	Hepatic metabolism 60-65% Renal 35%-40%
Propranolol	90	30-40	Yes	3-6 h	Hepatic metabolism Renal <1%

Oprea AD et al. J Cardiothorac Vasc Anesth 2019;33:817

Landiolol (Rapibloc®) vs. esmolol (Esmocard®)

Rapibloc®		Esmocard®
Čistý S-enantiomer molekuly landiololu		Racemická směs R- a S-enantiomeru molekuly esmololu
Žádná aktivita na kalciových a sodíkových kanálech		Blokuje kalciový kanál typu L a rychlý sodíkový kanál
Jen omezené negativně inotropní účinky Vysoká β-1 selektivita		R-enantiomer esmololu prokazatelně snižuje krevní tlak a má negativně inotropní účinek

Data from manufacturer

Landiolol: naše zkušenosti

- **Široké spektrum kardiochirurgických pacientů**
- ✓ **Operační sály**
- ✓ **Resuscitační oddělení**

- **Supraventrikulární tachyarytmie (fibrilace síní, …)**
- ➢ **Nepřiměřená tachykardie**

- **Vyloučeny ostatní faktory zvyšující srdeční frekvenci**
- ✓ **Hypovolémie**
- ✓ **Anémie**
- ✓ **Febrilie**
- ✓ **Bolest/diskomfort (analgosedace)**
- ✓ **Nízký/neadekvátní srdeční výdej**

Landiolol: naše zkušenosti

- Všechny typy KCH výkonů (včetně Tx srdce, VAD, ECMO, …)
- ✓ Významná systolická dysfunkce levé i pravé komory
- ✓ Kombinace s různými inotropními látkami i vazopresory

- Srdeční frekvence ≥120/min (individualizace)
- ➢ Cílová srdeční frekvence 100–110/min

- Kontinuální infuze landiololu v nízkých dávkách
- 0,5–10 (15) ug/kg/min; bez nasycovací dávky
- Zvyšování dávky po 10–15 min; snižování dávky (weaning) postupně

- ➢ Významné snížení srdeční frekvence bez poklesu TK a srdečního výdeje

Závěr

- ✓ SVT/fibrilace síní (kontrola srdeční frekvence, verze na SR, prevence)
- ✓ Nepřiměřená tachykardie
- ✓ Ischemicko/reperfuzní poškození myokardu

- Landiolol
- ➢ Velmi účinně snižuje srdeční frekvenci
- ➢ U většiny pacientů bez negativního vlivu na hemodynamiku

- Výborné farmakokinetické parametry ($T_{1/2}$ 2–4 min)
- Snadná titrovatelnost účinku, vysoká bezpečnost

- ➢ Nedílná součást farmakologického armamentaria u KCH výkonů