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Arnaud Ferraris, Matthias Jacquet-Lagrèze, Laure Cazenave, William Fornier, Wajma Jalalzai, et al.. Effects of Landiolol on Macrocirculatory Parameters and Left and Right Ventricular Performances Following Cardiac Surgery: A Randomized Controlled Trial. *Journal of Cardiothoracic and Vascular Anesthesia*, 2022, 22, 10.1053/j.jvca.2022.02.016 . hal-03658983

**HAL Id: hal-03658983**

**<https://hal.inrae.fr/hal-03658983v1>**

Submitted on 22 Jul 2024

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**Effects of landiolol on macrocirculatory parameters and left and right ventricular performances following cardiac surgery: A randomized controlled trial**

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**Clinical Trial number:** This trial was registered with ClinicalTrials.gov in number NCT03779178.

Registered 12 April 2019.

**Prior presentation:** None

**Abbreviated title:** The MMELPOAF study

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## **ABSTRACT**

**Objectives:** Postoperative atrial fibrillation (POAF) is a major complication following cardiac surgery and an early postoperative introduction of beta-blockers is recommended to reduce its incidence. Landiolol, a new intravenous short-acting  $\beta_1$ -blocker could present a useful and safe macrohemodynamic profile after cardiac surgery. Detailed metabolic and hemodynamic effects of landiolol on cardiac performance remain, however, poorly documented. We aimed to investigate the dose-dependent hemodynamic and metabolic effects of landiolol in that specific setting.

**Design:** A prospective, randomized, double-blind study *versus* placebo.

**Setting:** A tertiary university hospital.

**Participants:** Adult patients scheduled for elective cardiac surgery with cardiopulmonary bypass.

**Interventions:** Incremental doses of intravenous landiolol (0.5, 1, 2, 5 and 10  $\mu\text{g}/\text{kg}/\text{min}$ ) were given within the two hours after arrival in the intensive care unit. Macrocirculatory parameters and cardiac performances were derived from transpulmonary thermodilution and transthoracic echocardiography. Metabolic data were obtained from arterial blood tests.

**Measurements and Main Results:** From January to November 2019, 58 patients were analyzed and divided into a landiolol group (n=30) and a control group (n=28). Heart rate significantly decreased in the landiolol group ( $P<0.01$ ), whereas mean arterial pressure and stroke volume remained unchanged. No significant modification was found in both left and right systolic and diastolic performances. Metabolic variables were similar in both groups. New-onset POAF occurred in 9 (32%) vs. 5 (17%) patients in control and landiolol groups, respectively ( $P=0.28$ ).

**Conclusions:** Infusion of landiolol in the range of 0.5 to 10  $\mu\text{g}/\text{kg}/\text{min}$  during the early postoperative period presents a good macrohemodynamic safety profile in cardiac surgical patients and could be useful to prevent POAF.

**Keywords:** Postoperative atrial fibrillation; cardiac surgery; cardiac performance; landiolol.

## INTRODUCTION

Postoperative atrial fibrillation (POAF) is a major complication following cardiac surgery, leading to an increase in both morbidity and mortality<sup>1</sup>. While a rate control strategy using beta-blockers has not proved superiority when compared with a rhythm control strategy, the former is usually recommended when POAF is not associated with hemodynamic instability<sup>2,3</sup>. Although not specifically cited in current guidelines, intravenous short-acting beta-blockers can reduce POAF incidence<sup>4</sup>. Landiolol has recently been introduced in France<sup>5</sup>. This high-selective intravenous beta-1 blocker seems appropriate during the early phase of the postoperative period because of a very short half-life (4 minutes), a more selective chronotropic effect and less negative inotropic effect when compared to esmolol<sup>6</sup>. Marketed and studied in cardiac surgery for 15 years in Japan with interesting results in preventing and treating POAF<sup>4</sup>, the landiolol safety/efficacy ratio is well documented, permitting a significant heart rate reduction together with a nice arterial blood pressure stability<sup>4</sup>. Its detailed hemodynamic effects on macrocirculatory parameters like stroke volume and postoperative systolic and diastolic left and right ventricular performances are however not reported and available data only focus on heart rate and blood pressure changes<sup>7,8</sup>. Moreover, its metabolic effects remain unknown.

Therefore, the aim of this prospective, randomized, double-blinded study following conventional cardiac surgery with cardiopulmonary bypass (CPB) was to investigate the dose-dependent hemodynamic and metabolic effects of landiolol given at the early phase of the postoperative period in order to reduce POAF incidence. We hypothesized that low-dose landiolol would reduce heart rate without significant alterations in stroke volume and left and right ventricular performance.

## **METHODS**

The MMELPOAF (Micro- and Macrocirculatory Effects of Landiolol in Post-Operative Atrial Fibrillation) study was a monocentre, prospective, randomized, controlled, double-blinded trial designed to investigate both micro- and macrocirculatory hemodynamic effects of a postoperative dose ranging of landiolol between 0.5 and 10  $\mu\text{g}/\text{kg}/\text{min}$  following cardiac surgery with CPB. Specific data regarding microcirculatory effects have recently been published as a research letter<sup>8</sup>. The current paper focuses on macrocirculatory hemodynamic effects and left and right systolic and diastolic ventricular performances.

Patients were enrolled at the University Hospital Louis Pradel (Lyon, France) following Ethics Committee approval (comité de protection des personnes Ouest VI on 17 July 2018, and Agence Nationale de Sécurité du Médicament on 10 July 2018). The trial was registered with ClinicalTrials.gov (NCT03779178). Each patient received an appropriate information and a written, signed, informed consent was collected. We included adult patients scheduled for conventional cardiac surgery with CPB (coronary artery bypass grafting, aortic or mitral valve replacement or repair, and combined cardiac surgery). We excluded preoperative permanent atrial fibrillation, contraindication to beta-blockers (allergy, heart rate  $< 50/\text{min}$ , high degree atrioventricular block, asthma requiring treatment, metabolic acidosis with  $\text{pH} < 7.10$ ), patients with circulatory shock defined as cardiac index  $< 2.2 \text{ L}/\text{min}/\text{m}^2$  and hyperlactatemia  $> 4 \text{ mmol}/\text{L}$  or requiring inotropic treatment, patients with distributive shock defined as cardiac index  $> 2.2 \text{ mL}/\text{min}/\text{m}^2$  and norepinephrine  $> 0.3 \mu\text{g}/\text{kg}/\text{min}$ , patients with acute respiratory distress syndrome or major postoperative bleeding ( $> 200 \text{ mL}/\text{h}$ ), and pregnancy.

### ***Data collection***

Inclusion and protocol started within 2 hours following admission to the intensive care unit (ICU). Patients were monitored with five-lead electrocardiogram, oxygen pulse saturation ( $\text{SpO}_2$ ), femoral invasive arterial blood pressure and transpulmonary thermodilution (PiCCO device, Pulsion

Medical systems®, Germany). At the time of the study and throughout the study protocol (nearly 2 hours), no hemodynamic intervention was authorized. As well, propofol, vasoactive drugs, **fluid administration** and oxygen intake were kept constant throughout the study protocol.

Macrocirculatory parameters were derived from the PiCCO device and assessed on-line after initial calibration. A second PiCCO calibration was performed before the last time point. Heart rate (HR), arterial pressure, indexed stroke volume (SVi), cardiac index (CI) and pulse pressure variation (PPV) were systematically recorded. A transthoracic echocardiography (Vivid S6 General Electric Healthcare®) was carried out at baseline and at the final time point by trained investigators (MJL and AF). Left ventricular variables (end-diastolic and end-systolic dimensions and volumes, ejection fraction, aortic velocity time integral, mitral Doppler, lateral tissue Doppler), and right ventricular variables (tricuspid Doppler, tissue Doppler, tricuspid annular plane systolic excursion (TAPSE), fractional area changes (FAC)) were recorded. Arterial and venous blood gas analyses were sampled at baseline and at the final study time point to collect central venous saturation (SvO<sub>2</sub>) and lactate.

Finally, POAF incidence was assessed from postoperative day 0 in ICU (continuous five-lead electrocardiogram) to postoperative day 5 in the surgical ward (daily twelve-lead electrocardiogram).

### ***Study protocol***

All patients were randomized into 2 groups according to a 1:1 repartition: the landiolol group and the placebo group. Randomization was performed by using MedCalc Statistical Software version 18.11.6 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2019). Both treatment and placebo were prepared by a pharmacist as follows: landiolol 50 mg in 50 mL of NaCl 0.9%, and placebo 50 mL of NaCl 0.9%. The treatment distribution and perfusion was blinded to the patient and to the investigators. A complete set of measurements was carried out in all patients at six experimental time points: baseline (T0), landiolol 0.5 (T0.5), 1 (T1), 2 (T2), 5 (T5) and 10 (T10) µg/kg/min converted in 0.03, 0.06, 0.12, 0.3 and 0.6 mL/kg/h respectively, according to landiolol dilution (1mg/mL). A stabilization period of 20 min (5 half-lives) was respected at each step. The



treatment was stopped if MAP decreased below 65 mmHg and/or heart rate below 60/min. The intravenous solution (landiolol or placebo) was discontinued and oral bisoprolol was started on postoperative day 1. The detailed study protocol is depicted in Figure 1.

### ***Endpoints***

The primary endpoint was the effects of incremental doses of landiolol on macrocirculatory parameters (heart rate, blood pressure, stroke volume and echocardiographic variables of left and right ventricular performances). Secondary endpoints were the effects of incremental doses of landiolol on metabolic (SvO<sub>2</sub>, lactate) parameters and POAF incidence in both groups.

### ***Statistical analysis***

The initial sample size calculation was based both on a microcirculatory endpoint<sup>8</sup> and a previous study by our group showing that resaturation speed given by NIRS combined with a vascular occlusion test grew from 0.53%/min before esmolol to 0.82%/min at the highest esmolol dose<sup>9</sup>. Considering that microcirculatory abnormalities would be comparable, we determined that the enrollment of 58 patients assigned in a 1:1 ratio would give 90% power to detect a difference between both groups with an alpha risk of 0.05<sup>8</sup>. Continuous variables were analyzed with a linear mixed effect model using landiolol doses as a variable with a fixed effect according time points, and patient as a variable with a random effect for intercepts and slopes. Visual inspection of residual plots was performed to assess the absence of deviations from homoscedasticity or normality<sup>10</sup>.

Data are expressed as mean ± SD, or median (range), or number (%), according to their nature and distribution (Shapiro-Wilkinson test). We compared data by using a Wilcoxon test and/or a paired Student's t-test, as appropriate. All tests were two-tailed, and a *P* value less than 0.05 was considered statistically significant. Statistical analyses were performed using R software version 3.4.3 (R-project, GNU GPL).

## RESULTS

Fifty-nine patients were included into the study from January to November 2019. One patient was excluded because of technical problems and 58 patients were available for analysis. The flowchart of the study is depicted in Figure 2. Median age was 66 [55-71] years old, and left ventricular ejection fraction (LVEF) was 49% [43-58]. Two patients did not reach the maximal dose regimen because of MAP < 65mmHg and/or HR < 60/min. Twenty-three patients required low-dose norepinephrine support. Main patients' baseline characteristics in both groups are reported in Table 1. No significant difference was found between groups. Nine (32%) patients in placebo group vs. 5 (17%) in landiolol group experienced POAF between postoperative day 0 and postoperative day 5 ( $P=0.285$ ).

HR significantly decreased in landiolol group compared to placebo, whereas MAP slightly decreased in both groups without reaching statistical difference (Figure 3A and 3C). Stroke volume and pulse pressure variation remained unchanged throughout the study (Figure 3B and 3D). Echocardiographic parameters of left and right systolic and diastolic ventricular performances were similar in landiolol and placebo groups at the exception of E/A ratio which was higher in the landiolol group (Table 2).

No significant difference was found in SvO<sub>2</sub> between landiolol and placebo groups at baseline (65% [60-71] vs. 64% [60-69];  $P=0.19$ ), but a time-effect was observed over the study period (74% [68-79] vs. 65% [60-71];  $P<0.01$ ) in landiolol group. Lactate was similar in landiolol and placebo groups: 1.7 [1.4-2.2] vs. 1.9 [1.4-2.3] at T0, and 2.0 [1.7-2.4] vs. 1.4 [1.2-2.2] at T10 ( $P$  value time/group interaction = 0.25), respectively.

## DISCUSSION

The main results of the present randomized study are that an early postoperative dose regimen of intravenous landiolol (from 0.5 to 10  $\mu\text{g}/\text{kg}/\text{min}$ ) given in order to decrease POAF following conventional cardiac surgery with CPB: 1) is responsible for a significant decrease in HR; 2) is not associated with significant changes in arterial pressure, stroke volume, and right and left systolic and diastolic ventricular performances; 3) is not associated with metabolic disturbances; 4) **does not significantly reduce the incidence of POAF.**

As expected, we found a significant dose-dependent reduction in HR with landiolol. Besides, arterial pressure, stroke volume and metabolic parameters remained unchanged, suggesting the use of low-dose landiolol to control postoperative heart rate was safe. Further, echocardiographic systolic and diastolic parameters of right and left ventricular function were not affected by landiolol, the E/A ratio being even slightly improved. To the best of our knowledge, no detailed cardiac effects of landiolol had been previously reported in cardiac surgery patients. Overall, our results are in favor of a valuable safety profile of landiolol in that specific cardiac surgical setting. Landiolol is a high-selective beta-1 blocker which looks ideal in the perioperative period with a more selective chronotropic effect and less hypotension and negative inotropic effect when compared to esmolol<sup>6</sup>. Similar results from esmolol tolerance were found in a previous study with a similar phenotype of patients<sup>9</sup>.

Some strengths can be outlined regarding the present study. First, this is the first study that explores detailed macrocirculatory hemodynamic variables with landiolol in cardiac surgery patients by associating transpulmonary thermodilution, transthoracic echocardiography, and a metabolic approach. Subsequently, we can conclude to the safety profile of landiolol in such a dose ranging: arterial pressure, stroke volume and ventricular performances are preserved. Second, the presence of a control group gave the opportunity to differentiate between a time-effect and a drug-effect, in contrast with a previous work from our group using esmolol<sup>9</sup>.

Some limitations are however notable. We only included elective patients with normal cardiac function, postoperative sinus rhythm, and scheduled for conventional cardiac surgery. Subsequently, our results cannot be extrapolated to more severe patients and/or surgical procedures. Although not significant, one can argue that right ventricular echocardiographic parameters were slightly altered in the landiolol group. Thus, further studies should also focus on potential effects of landiolol on the right ventricle, especially in patients with right ventricular dysfunction. Further, more patients had valve surgery in the placebo group. Even if the difference was not statistically significant, it could have influenced the higher incidence of POAF. A huge decrease in POAF incidence has however repetitively been reported with landiolol in the setting of cardiac surgery<sup>3</sup>. Finally, our study was underpowered to show a significant decrease in POAF in the landiolol group, even if the incidence was reduced by nearly 50%. Since the vast majority of published studies with landiolol have been conducted in Japan, further studies including Caucasian people are mandatory before recommending a wider use of landiolol in Western countries to prevent POAF in the cardiac surgical setting.

In conclusion, the MMELPOAF study is the first randomized controlled trial describing detailed hemodynamic and metabolic effects of a dose ranging of landiolol given during the early postoperative period following cardiac surgery. We report a good hemodynamic safety profile of the drug in the range of 0.5 to 10 µg/kg/min.

## FIGURES

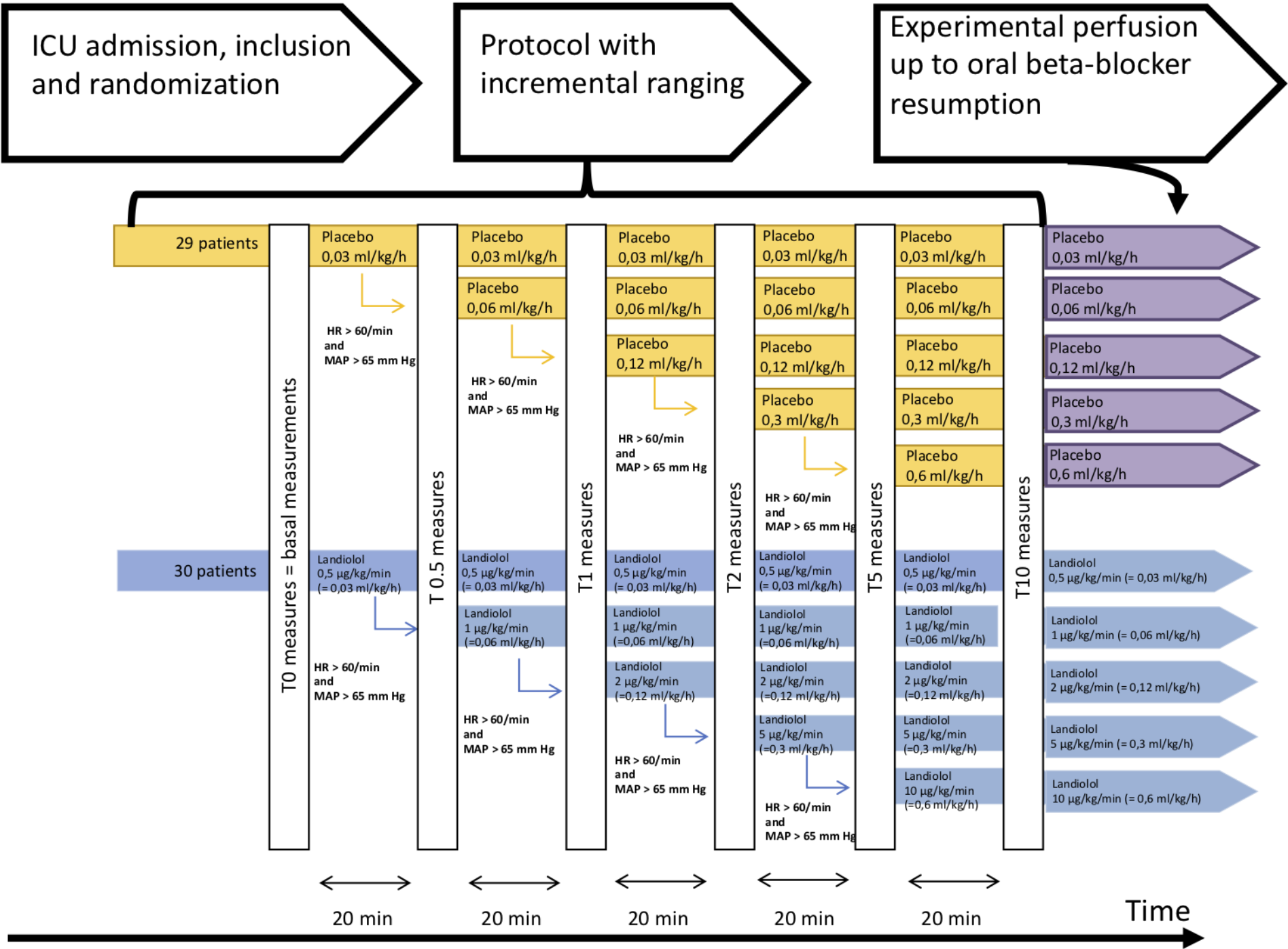
**Figure 1:** Study protocol with experimental time points. Landiolol doses were incremented if heart rate (HR) > 60/min and mean arterial pressure (MAP) > 65 mmHg. A 20 minutes stabilization period was respected between each time point. Six time points were predefined and named with equivalent landiolol dose from 0 to 10  $\mu\text{g}/\text{kg}/\text{min}$  (converted to intravenous solution administered in  $\text{ml}/\text{kg}/\text{h}$ ).

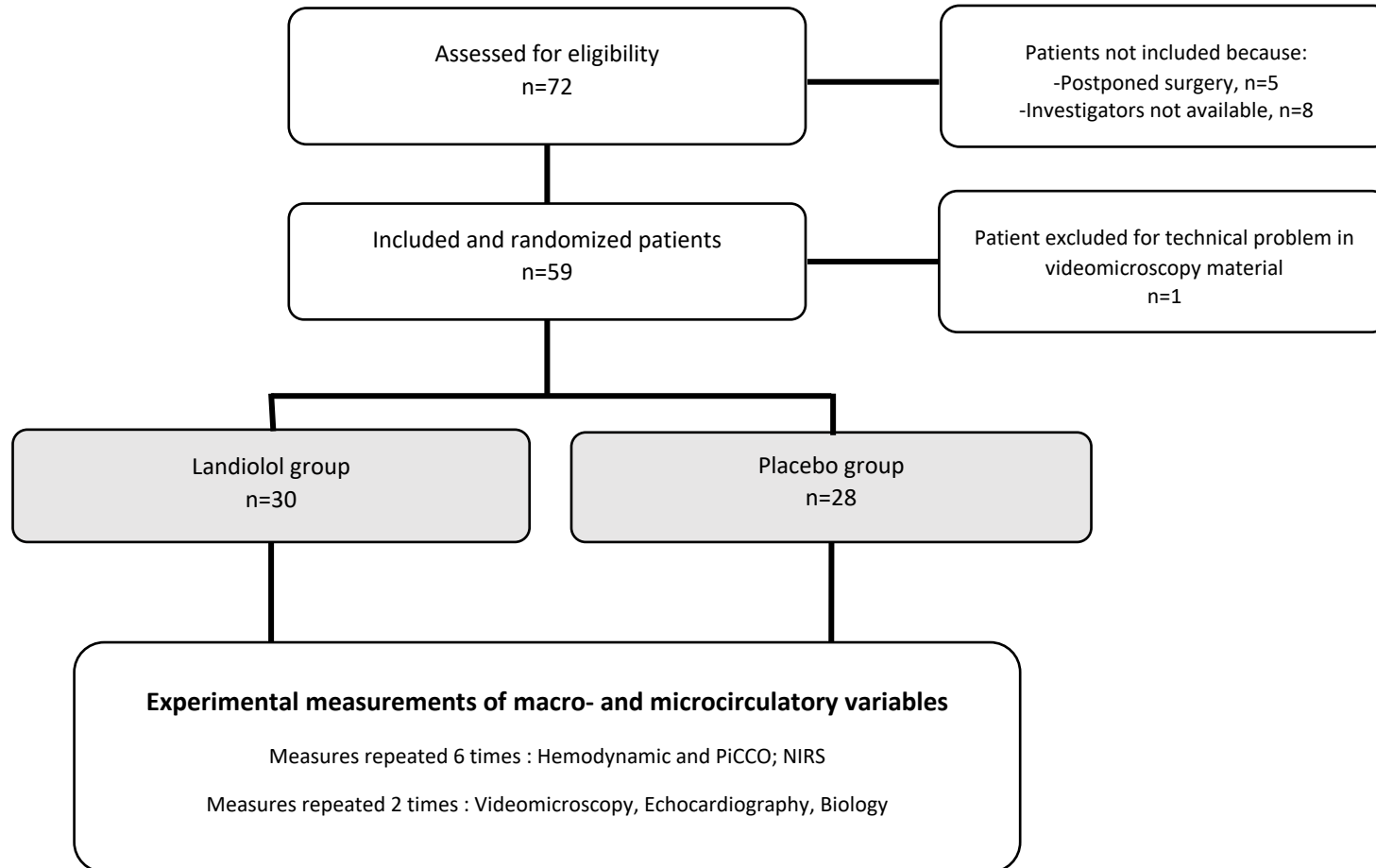
**Figure 2:** The flowchart of the study.

**Figure 3:** Macrocirculatory hemodynamic variables at six different time points in placebo (n=28) and landiolol (n=30) patients. A: Heart rate (HR, min); B: Indexed stroke volume ( $S_{vi}$ ,  $\text{mL}/\text{m}^2$ ); C: Mean arterial pressure (MAP, mmHg); D: Pulse pressure variation (PPV, %).

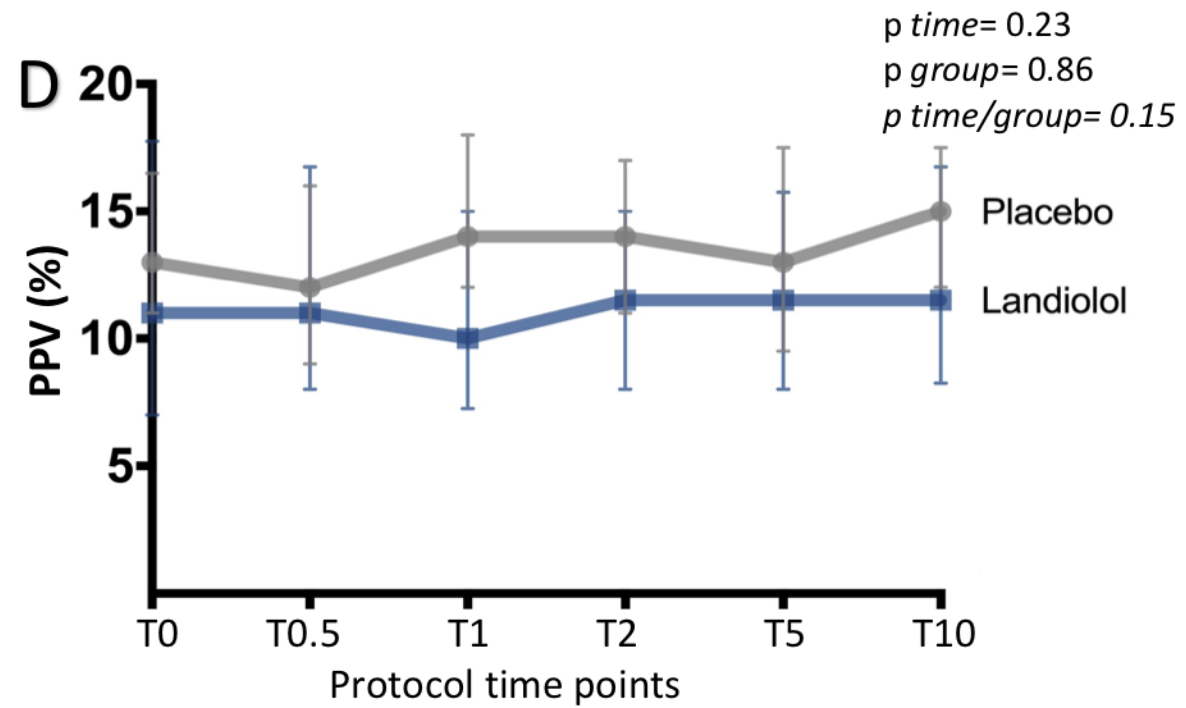
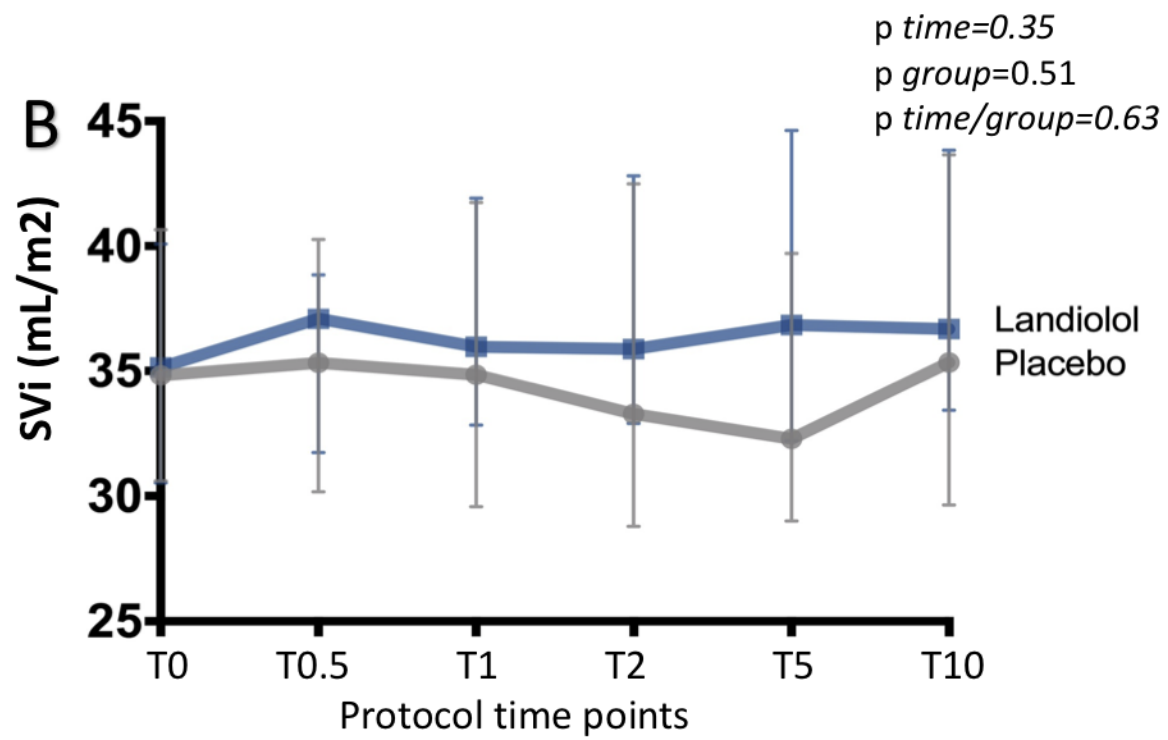
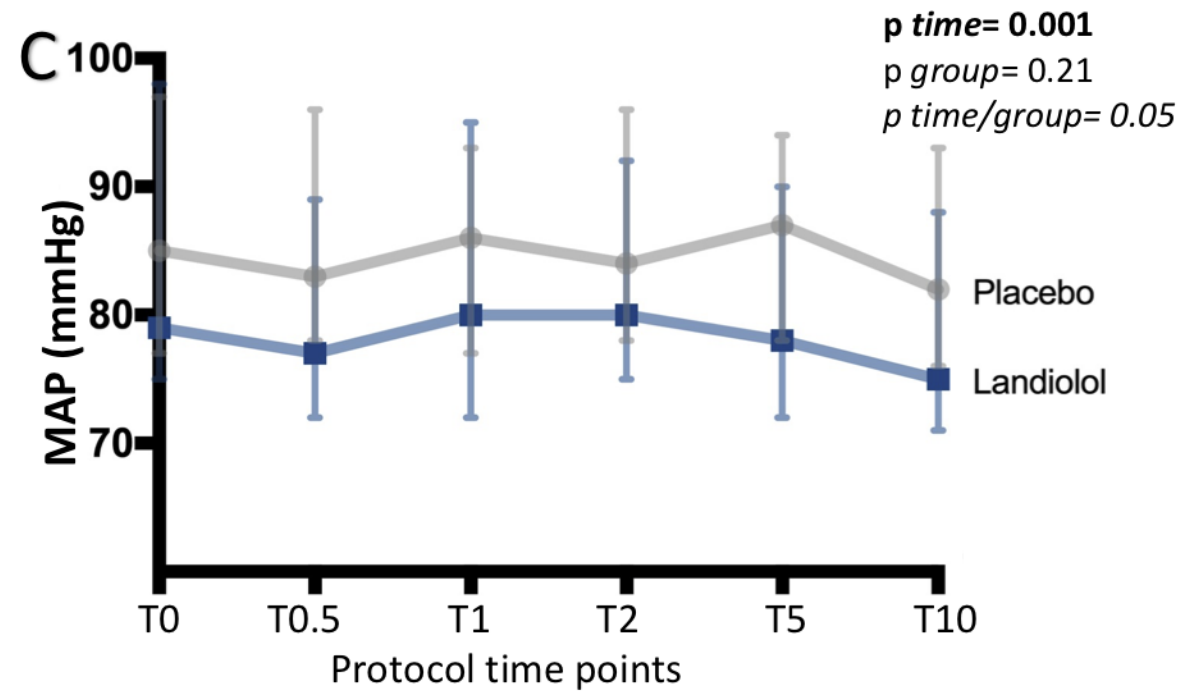
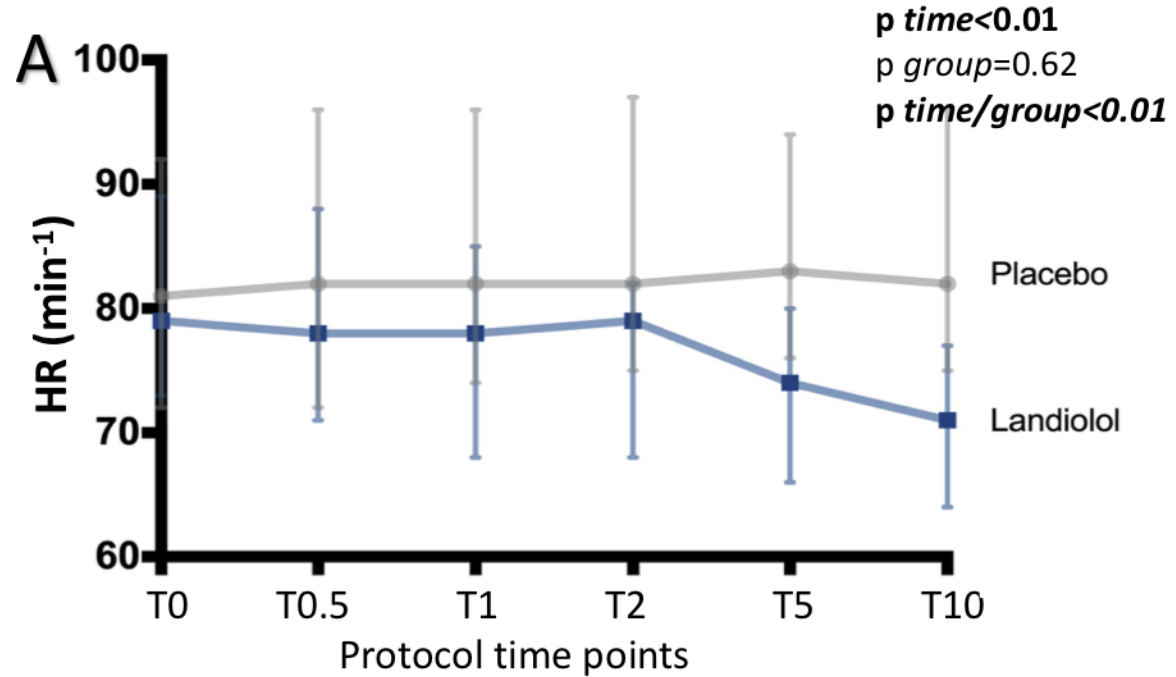
## REFERENCES

1. Maesen B, Nijs J, Maessen J, et al: Post-operative atrial fibrillation: a maze of mechanisms. *Europace* 14:159–74, 2012
2. Gillinov AM, Bagiella E, Moskowitz AJ, et al: Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. *N. Engl. J. Med.* 374:1911–21, 2016
3. Kirchhof P, Benussi S, Kotecha D, et al: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur. Heart J.* 37:2893–962, 2016
4. Fellahi J-L, Heringlake M, Knotzer J, et al: Landiolol for managing atrial fibrillation in post-cardiac surgery. *Eur. Heart J. Suppl.* 20:A4–9, 2018
5. Atarashi H, Kuruma A, Yashima M, et al: Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin. Pharmacol. Ther.* 68:143–50, 2000
6. Mio Y: [New ultra-short-acting beta-blockers: landiolol and esmolol--the effects on cardiovascular system]. *Masui.* 55:841–8, 2006
7. Li L, Ai Q, Lin L, et al: Efficacy and safety of landiolol for prevention of atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials. *Int. J. Clin. Exp. Med.* 8:10265–73, 2015
8. Shibata SC, Uchiyama A, Ohta N, et al: Efficacy and Safety of Landiolol Compared to Amiodarone for the Management of Postoperative Atrial Fibrillation in Intensive Care Patients. *J. Cardiothorac. Vasc. Anesth.* 30:418–22, 2016









**Table 1:** Patients' demographic and clinical characteristics (n=59).

	Placebo	Landiolol	
	n=29	n=30	<i>P</i> value
Age, years	64 ± 10	63 ± 11	0.51
Male, n	21 (72)	23 (77)	1.0
Weight, kg	79 ± 19	77 ± 12	0.64
BMI, kg/m <sup>2</sup>	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
<b>Chronic medications</b>			
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
<b>Type of surgery</b>			
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 [1-0.1]	0.04 [0-0.1]	0.73

Data are mean ± SD or median [25<sup>th</sup>-75<sup>th</sup>] or number (%).

BMI: body mass index; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor antagonist.

**Table 2: Left and right ventricular echocardiographic parameters at baseline (T0) and maximal dose ranging (T10) in placebo (n=28) and landiolol (n=30) patients.**

	T 0		T 10		P time	P group	P time/group
	Landiolol	Placebo	Landiolol	Placebo			
<b>Left ventricle</b>							
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	<b>0.02</b>
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
<b>Right ventricle</b>							
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

Data are median [25<sup>th</sup>-75<sup>th</sup>]

LVEF: Left ventricular ejection fraction; VTI: Velocity-time integral; SVi: stroke volume measured as VTI x aortic surface x corporeal surface; E/A: Mitral E and A waves velocities ratio; E/e': Mitral E wave velocity and annular e' wave velocity ratio; TAPSE: Tricuspid annular plane systolic excursion; FAC: right ventricular fractional area change; S tricuspid: tricuspid systolic annular velocity; E/A tricuspid: Tricuspid E and A waves velocities ratio; E/e' tricuspid: Tricuspid E wave velocity and annular e' wave velocity ratio.