Micro- and Macrocirculatory Effects of Landiolol: A Double-Blind, Randomized Study Following Cardiac Surgery

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Abstract

Background: Postoperative atrial fibrillation (POAF) increases morbidity and mortality after cardiac surgery. Landiolol, a selective ultra-short-acting betablocker has been recently suggested to prevent POAF in the cardiac surgical setting with a good safety profile. Micro- and detailed macrocirculatory effects of landiolol remain however largely unknown in that setting.

Methods: We conducted a prospective, randomized, double-blind study *versus* placebo in patients undergoing conventional cardiac surgery. Incremental doses of intravenous landiolol from 0.5 to 10 $\mu g^{-1}.kg^{-1}.min^{-1}$ or placebo were administrated postoperatively. Microcirculatory variables were assessed by both peripheral near-infrared spectroscopy (NIRS) in combination with a vascular occlusion test and sublingual videomicroscopy. Macrocirculatory variables were obtained from transpulmonary thermodilution and transthoracic echocardiography.

Results: Fifty-nine adult patients were allocated to the landiolol group (n=30) or the placebo group (n=29) from January to November 2019. Heart rate significantly decreased in the landiolol group (P<0.01) whereas mean arterial pressure (P=0.05) and stroke volume (P=0.63) were not significantly modified throughout the study. No modification was found in left and right systolic and diastolic ventricular functions except a significant increase in E/A ratio in the landiolol group (P=0.02). No difference was evidenced between groups in microcirculatory parameters at any landiolol dose. POAF occurred in 9 (32%) *vs.* 5 (17%) patients in placebo and landiolol groups, respectively (P=0.28).

Conclusions: Postoperative incremental doses of landiolol up to 10 $\mu g^{-1}.kg^{-1}.min^{-1}$ are efficacious to control heart rate without significant alterations in both micro- and macrocirculation following conventional cardiac surgery.

Background

Postoperative atrial fibrillation (POAF) is a major issue following cardiac surgery with cardiopulmonary bypass (CPB), leading to an increase in both morbidity and mortality [1]. Although not yet recommended in current guidelines, the use of landiolol, an intravenous ultra-short-acting betablocker recently introduced in Europe, could markedly reduce the incidence of POAF following cardiac surgery [2]. Its highly selective beta-1 blocker pharmacological properties associating a more selective chronotropic and less negative inotropic and hypotensive effects could be ideal during the perioperative period [3]. Despite a well-documented safety/efficacy profile in Japanese studies [4, 5], the benefit/risk ratio of landiolol in Caucasian surgical patients has to be further evaluated. Moreover, a better knowledge of both micro- and detailed macrocirculatory effects of landiolol is required before considering its wider use in routine practice.

Microcirculatory disorders have been reported following cardiac surgery and in septic shock patients [6–8]. Despite potential negative effects on macrocirculatory variables, beneficial effects of betablockers on microcirculation have been previously suggested both in clinical and experimental studies [9]. The

assessment of microcirculation is not yet a routine practice in intensive care unit (ICU) [10]. The use of peripheral near-infrared spectroscopy (NIRS) in combination with a vascular occlusion test (VOT) has been validated to assess regional oxygen saturation (rSO_2) and the microcirculatory response to an ischemic stress [11]. Besides, sublingual videomicroscopy is considered as the clinical reference method to analyze microcirculation abnormalities in various hemodynamic scenarios [12].

In this prospective, randomized, double-blind study, we assessed both micro- and detailed macrocirculatory effects of intravenous landiolol ranging from 0.5 to 10 $\mu g^{-1}.kg^{-1}.min^{-1}$ in patients undergoing conventional cardiac surgery. We hypothesized that landiolol titration would limit or reverse CPB induced-microcirculatory abnormalities compared to placebo without macrocirculatory alterations.

Methods

We conducted a monocentre, prospective, randomized, placebo-controlled and double-blind study. Patients were enrolled at the University Hospital Louis Pradel (Lyon, France) from January to November 2019 after Ethics Committee approval (Comité de protection des personnes Ouest VI, July 17th 2018; Agence Nationale de Sécurité du Médicament, July 10th 2018). The trial was registered with ClinicalTrials.gov (NCT03779178) on 12 April 2019. Each patient received appropriate information and written informed consent was systematically collected. CONSORT statement was respected in this study. 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). Patients with preoperative atrial fibrillation, contraindications to betablockers, cardiac index < 2.2 L/min, hyperlactatemia > 4 mmol/L, requiring inotropic drugs or norepinephrine > 0.3 $\mu g^{-1}.kg^{-1}.min^{-1}$ or major postoperative bleeding (> 200 mL/h) were not included into the study.

Patients' management and data acquisition

Patients were included within 2 hours following postoperative admission to the ICU. They were monitored with five-lead electrocardiogram, oxygen pulse oximetry, femoral invasive arterial blood pressure and transpulmonary thermodilution (PiCCO® device, Pulsion Medical systems, Germany). Propofol, vasoactive agents and oxygen intake with mechanical ventilation were kept constant throughout the study period.

After rubbing and cleaning the skin with an alcohol swab, a NIRS optode (INVOS oximetry adult sensor®, Medtronic, Minneapolis, MN) was carefully applied to the medial surface of the left or right forearm, 5 cm below the elbow. The sensor was attached to the skin of participants with opaque adhesive stickers so that the angle and position of the optode was kept constant. The sensor was connected to the INVOS oximeter 5100C® device (Medtronic, Minneapolis, MN). All rSO_2 values were recorded every 5 seconds. Data were recorded online, transferred to a specific software (INVOS analytics 1.2®, Medtronic, Minneapolis, MN) and stored for further analysis. A pneumatic cuff inflator was positioned at the upper extremity of the ipsilateral upper limb. A rapid arterial occlusion of the upper limb was provoked by

inflation of the pneumatic cuff at 50 mmHg above the systolic arterial pressure, until either rSO_2 values decreased to 40% or for a maximal period of 10 min, as previously described [7]. The arterial cuff was then rapidly deflated to initiate reperfusion. Recorded NIRS parameters were baseline rSO_2, the desaturation speed during ischemia (baseline rSO_2 minus rSO_2 min/time of ischemia), the resaturation speed during reperfusion (rSO_2 max minus rSO_2 min/time of reperfusion), and the variation in rSO_2 during reperfusion ($\Delta rSO_2 = rSO_2$ max $- rSO_2$ baseline). A regular VOT is depicted in Additional file 1.

Sublingual videomicroscopy was achieved with a dedicated device MicroScan® and AVA-3 software (Microvision medical, Amsterdam, The Netherlands). The technology uses sidestream darkfield imaging where illumination is achieved by surrounding the tip of the light guide with light-emitting diodes. We recorded 5 acquisitions of 5 different sites minimum at baseline and at the final time point (10 videos per patient) of 4 seconds minimum. Videomicroscopy records were performed according to current recommendations [12] to reach consensus statements in images acquisitions, quality and analysis. Video analyses were extracted in a specific and validated software [13], namely Capillary Mapper® 1.4.1 online version (https://capillary-mapper.uni-muenster.de), to collect the following data: microvascular flow index (MFI) quadrant, proportion of perfused vessels (PPV), total vessel density (TVD) and heterogeneity index (HI).

Macrocirculatory variables were derived from the PiCCO® device and assessed on-line after an initial calibration. A second calibration was performed before the last protocol time point. Heart rate (HR), mean arterial pressure (MAP), stroke volume index (SVi), cardiac index (CI) and pulse pressure variation (PPV) were systematically recorded. The transthoracic echocardiographic analysis (Vivid S6®, General Electric Healthcare, Boston, MA) was carried out twice : at baseline (T0) and at the final time point (T10) by two trained investigators (MJL and AF). Left ventricular parameters (end-diastolic and end-systolic dimensions and volumes with Simpson's biplane method, ejection fraction, aortic velocity time integral (VTI), mitral Doppler, and lateral tissular Doppler), right ventricular parameters (tricuspid Doppler, tissular Doppler, tricuspid annular plane systolic excursion (TAPSE), and fractional area changes (FAC)) were recorded. Echocardiographic SVi (VTI x aortic cross-sectional surface) indexed to body surface was determined as an additional measurement.

Arterial and venous blood gas analyses were sampled twice at baseline and at the final study time point to collect central venous saturation (SvO_2) and lactate.

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

Study protocol

Patients were randomized into a landiolol group and a placebo group according to a 1:1 repartition. Randomization was performed by using MedCalc Statistical Software version 18.11.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019). Both landiolol and placebo syringes 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 both to the patient and the investigator. 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) $\mu g^{-1}.kg^{-1}.min^{-1}$ converted into 0.03, 0.06, 0.12, 0.3 and 0.6 $mL^{-1}.kg^{-1}.h^{-1}$ 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 was inferior to 65 mmHg and/or HR decreased below 60/min, otherwise it was maintained at maximal dose up to oral betablocker resumption for a maximal period of 12 hours. The whole study protocol is depicted in Additional file 2.

Endpoints

The primary endpoint of the study was the assessment of the resaturation speed measured by NIRS combined to a VOT during incremental doses of landiolol. Secondary endpoints were: 1) The effects of incremental doses of landiolol on other microcirculatory variables given by NIRS and sublingual videomicroscopy; 2) The effects of incremental doses of landiolol on macrocirculatory variables given by transpulmonary thermodilution and transthoracic echocardiography; 3) The effects of incremental doses of landiolol on metabolic parameters.

Statistical analysis

The sample size was based on a previous study by our group using postoperative esmolol in the cardiac surgical setting and showing that resaturation speed grew up from 0.53%/min before esmolol to 0.82%/min at the highest esmolol dose [6]. 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. Continuous variables were analyzed with a linear mixed effect model using landiolol doses as a variable with a fixed effect according time points (T0.5 to T10), 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 [14]. Data are expressed as mean ± SD, or median [interquartile 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 adult patients were randomized into a landiolol group (n = 30) and a placebo group (n = 29) from January to November 2019. One patient was excluded from the analysis because of videomicroscopy technical problems. The flow chart of the study is depicted in Fig. 1. The main demographic and clinical characteristics of the whole cohort of patients are reported in Table 1. No significant difference was found between groups. Two patients did not receive the full dose regimen

because of MAP < 65mmHg in one case and HR < 60/min in the other case. Nine (32%) patients in placebo group *vs.* 5 (17%) in landiolol group experienced POAF between day 0 and day 5 ($P = 0.285$).

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

	Placebo	Landiolol	
	n = 29	n = 30	P 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/m²	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, $\mu g.kg^{-1}.min^{-1}$	0.05 [1-0.1]	0.04 [0-0.1]	0.73

Data are mean ± SD or median [25th -75th] 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.

Microcirculatory variables

Resaturation speed was similar in both groups over the study period (Fig. 2A). No significant difference was found between placebo and landiolol groups neither in baseline rSO_2 (74% [71−81] *vs.* 78% [71−82]; P = 0.72) nor in other NIRS variables (Figs. 2B and 2C). As well, the functional assessment of microcirculation by sublingual videomicroscopy at T0 and T10 was not significantly different between groups (Table 2).

Table 2

Sublingual videomicroscopy variables at baseline (T0) and maximal dose ranging (T10) in placebo (n = 28) and landiolol (n = 30) patients

		PPV (%)	TVD (mm^2/mm^2)	MFIq	Heterogeneity Index
T0	*Landiolol*	89 [82−99]	19.3 [18.3−23.9]	3 [2−3]	0.22 [0.02−0.42]
	Placebo	91 [85−100]	18.8 [15.1−21.2]	3 [2−3]	0.22 [0.01−0.38]
T10	*Landiolol*	95 [90−98]	20.6 [18.2−22.4]	3 [3−3]	0.14 [0.02−0.3]
	Placebo	93 [88−99]	19.3 [17.4−22.4]	3 [2−3]	0.02 [0-0.14]
P **time**		0.61	0.55	0.95	0.03
P **group**		0.75	0.38	0.99	0.53
P **time/group**		0.37	0.87	0.34	0.62
Data are median [25th -75th]					
PPV: Proportion of perfused vessels; TVD: Total vessel density; MFIq: Microvascular flow index quadrant.					

Macrocirculatory variables

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

Table 3

Echocardiographic variables 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*			
	Left ventricular function						
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 ventricular function						
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 [25th -75th]

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.

Metabolic variables

No significant difference was found on SvO_2 between landiolol and placebo 65% [60–71] *vs.* 64% [60–69] respectively (P = 0.19), but a time-effect was observed 74% [68–79] *vs.* 65% [60–71] (P < 0.01).

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 = 0.25), respectively.

Discussion

The main results of the present randomized study are that a dose regimen of intravenous landiolol from 0.5 to 10 µg^{-1}.kg^{-1}.min^{-1} following conventional cardiac surgery: 1) is not associated with hemodynamic microcirculatory effects, either beneficial or detrimental; 2) is responsible for a decrease in HR without changes in arterial pressure, stroke volume, and right and left systolic and diastolic ventricular performances; 3) is not associated with metabolic disturbances. Taken together, those results suggest that postoperative use of low-dose landiolol is efficacious to control heart rate with a good detailed hemodynamic safety profile.

While expected postoperative microcirculatory abnormalities were observed in both groups, no difference was found between landiolol and placebo groups. NIRS parameters were similar, including resaturation speed, a parameter assessing microvascular reactivity. In addition, no difference was detected in sublingual videomicroscopy analysis. Even if it is not yet a routine technology, an expert consensus for daily practical use and interpretation has been recently published [12]. We are in accordance with that consensus statement about images acquisitions and analyses. Video analysis was performed on-line in a free-of-charge software, namely Capillary Mapper (https://capillary-mapper.uni-muenster.de). This website was successfully validated for manual analysis of microcirculation videos against the gold standard analyzer software AVA 3 [13]. Thus, our results suggest that landiolol has neither beneficial nor detrimental effect on microcirculation according current monitoring of the study. Microcirculatory disorders have been mainly reported in sepsis, including heterogeneity in perfusion and obstructed capillaries [15]. Similar alterations could occur following cardiac surgery with cardiopulmonary bypass as microcirculation is known for being highly responsive to inflammatory mediators [16]. Such microcirculatory abnormalities can be independent from systemic hemodynamic alterations [15] and associated with adverse outcomes [17]. Previous studies reported potential beneficial effects of esmolol on microcirculation in both experimental and clinical settings [6, 9], the reason why we hypothesized landiolol could be beneficial as well. However, as there was no control group in our previous study [6], we might actually have only observed a time-related improvement in microcirculation, similar to current results.

As expected, we found a significant dose-dependent reduction in heart rate 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 indices 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. Overall, our results are in favor of a valuable safety profile of landiolol in that specific cardiac surgical setting.

If several strengths of the present study can be outlined (detailed and multimodal micro-and macrocirculatory approaches of landiolol hemodynamic effects, presence of a control group to differentiate a time-effect from a drug-effect, robust methodology), some comments are mandatory regarding its limitations. First, patients were strictly selected: normal cardiac function, sinus mode, elective conventional cardiac surgery. Subsequently, our results could not be extrapolated to more severe patients and/or surgical procedures. Second, we used peripheral NIRS in combination with a VOT, as previously described. We acknowledge physiological and technical limits of this method which cannot capture all the subtleties of the microcirculation. However, the simultaneous use of sublingual videomicroscopy reinforces the absence of significant microcirculatory effects of landiolol. Additional tools as capillary refill time could also be assessed in future issues. Finally, although not significant, one can argue that right ventricular echocardiographic parameters were slightly altered in the landiolol group. Thus, further studies should specifically focus on potential effects of landiolol on the right ventricle, especially in patients with right ventricular dysfunction.

Conclusions

In conclusion, the MMELPOAF study is the first randomized controlled trial describing the effects of a dose ranging of landiolol following cardiac surgery on both micro- and macrocirculation. No significant alterations were found, suggesting a good hemodynamic safety profile in that specific surgical setting.

Declarations

Details of authors' contribution

AF participated in the design of the study, patients inclusions and manuscript redaction. MJL participated in the design of the study, patients inclusions, statistical analysis and manuscript redaction. LC participated in patients inclusions. WF participated in the design of the study and patients inclusions. WJ participated in patients inclusions. NRS participated in the design of the study. BA, SJ and MP participated in coordination and helped to draft the manuscript. JLF participated in the design of the study, coordination and helped to draft the manuscript.

All authors read and approved the final manuscript.

Acknowledgments: Not applicable

Conflicts of interest:

-Arnaud Ferraris received lecture fees from Amomed Pharma France

-Jean-Luc Fellahi is member of the Scientific Advisory Board Amomed Pharma France and received consulting and lecture fees.

-The other authors have no conflicts of interest to declare

Acknowledgments : Not applicable

Availability of data : On demand to the corresponding author

Ethics Committee approval : Comité de protection des personnes Ouest VI, July 17th 2018; Agence Nationale de Sécurité du Médicament, July 10th 2018. Each patient received appropriate information and written informed consent was systematically collected.

Consent for publication : Not applicable

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14. version) JP (S. to 2007) DB (up, to 2002) SD (up, to 2005) DS (up, authors (src/rs.f) E, sigma) SH (Author fixed, et al. nlme: Linear and Nonlinear Mixed Effects Models [Internet]. 2018 [cited 2019 Mar 14]. Available from: https://CRAN.R-project.org/package=nlme.

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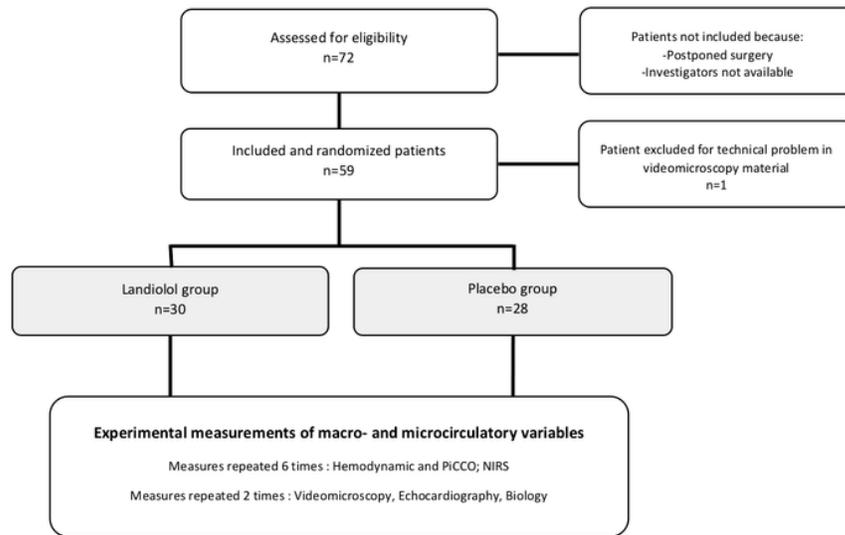
Figures

Figure 1
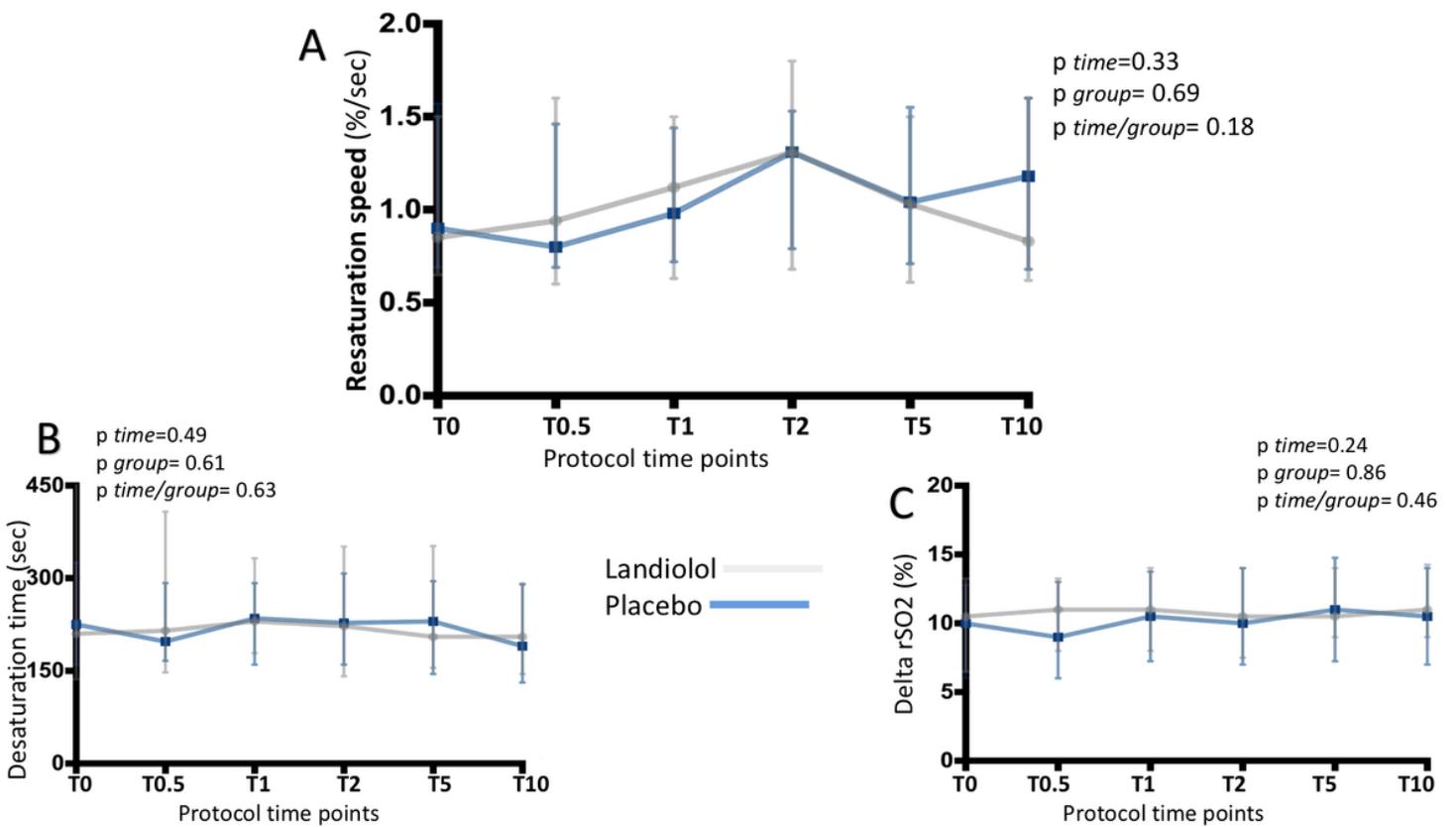
Flow-chart of the study

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Figure 2

Near-infrared spectroscopy variables combined with a vascular occlusion test at six different time points in placebo (n=28) and landiolol (n=30) patients. A: Resaturation speed (%/sec); B: Desaturation time (sec); C: Delta rSO2 (%). rSO2: regional oxygen saturation (%).

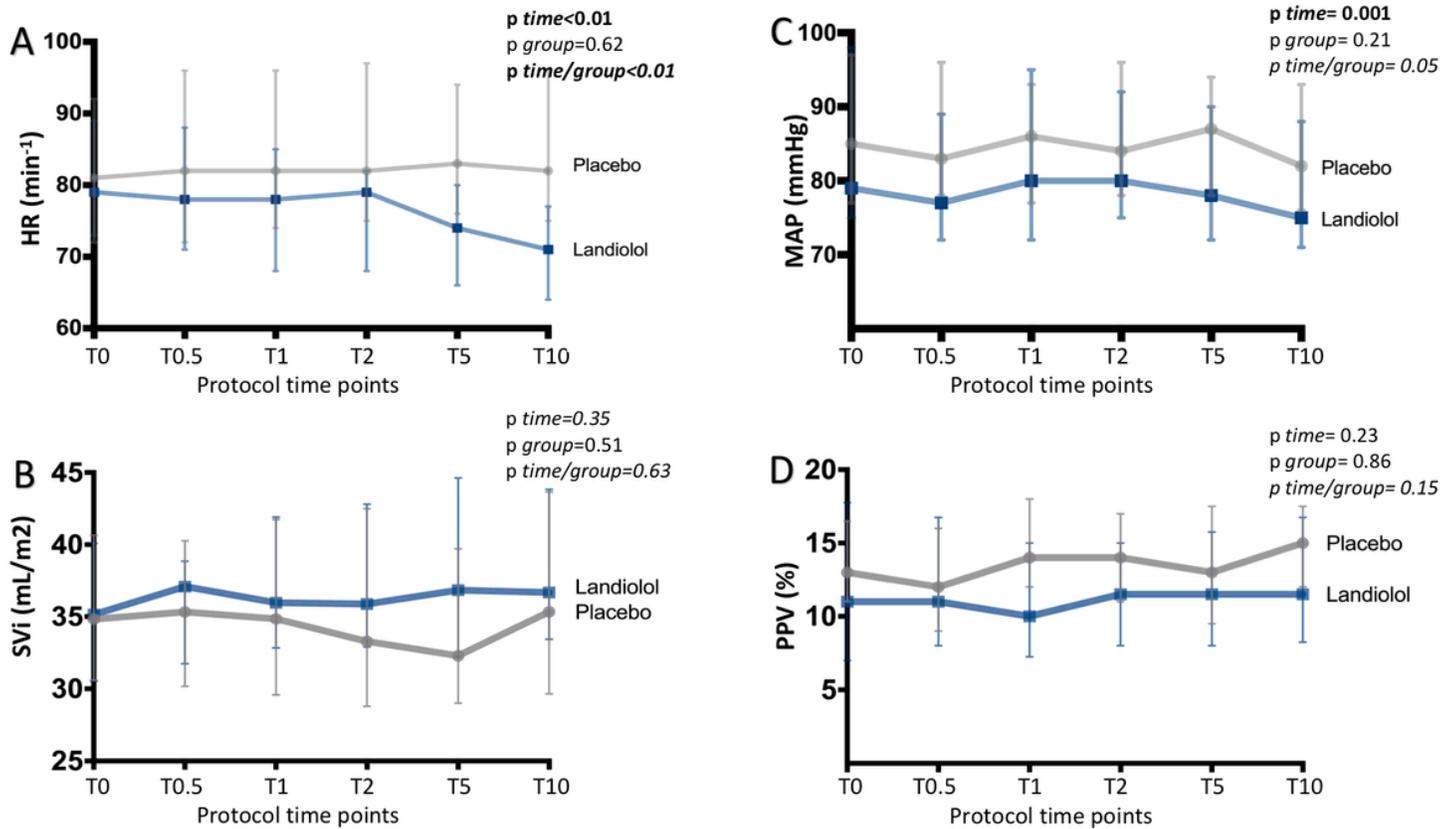## Figure 3

Macrocirculatory hemodynamic variables at six different time points in placebo (n=28) and landiolol (n=30) patients. A: Heart rate (HR, min-1); B: Indexed stroke volume (Svi, mL/m2); C: Mean arterial pressure (MAP, mmHg); D: Pulse pressure variation (PPV, %).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- Additionalfile2.tiff