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Microcirculatory effects of landiolol: a double-blind, randomised, controlled study after cardiac surgery

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Editor—Microcirculatory disturbances are commonplace after cardiopulmonary bypass.[1] Postoperative atrial fibrillation (POAF) occurs in nearly 30% of patients undergoing conventional cardiac surgery.[2] Landiolol, a short-acting i.v. beta blocker, could reduce both the incidence of POAF and postoperative microcirculatory abnormalities.[3] However, the effects of landiolol on microcirculation remain poorly documented. The aim of this prospective randomised, controlled, double-blind study conducted in patients undergoing cardiac surgery was to assess the microcirculatory effects of landiolol given at a moderate dose to prevent POAF. We tested the hypothesis that landiolol could limit cardiopulmonary-bypass-induced microcirculatory abnormalities.

From January to November 2019, 59 adult patients undergoing conventional cardiac surgery with cardiopulmonary bypass at the University Hospital Louis Pradel (Lyon, France) were enrolled on their arrival to the ICU after Ethics Committee approval. The trial was registered with ClinicalTrials.gov (NCT03779178). Patients with preoperative atrial fibrillation, contraindications to beta blockers, hyperlactataemia >4 mM, postoperative inotropic drug requirement, postoperative norepinephrine >0.3 μg kg^{-1} min^{-1}, acute respiratory distress syndrome, or haemodynamic instability were not included. Subjects were randomised into a landiolol group (n=30) and a control group (n=29). A complete set of measurements was carried out in all subjects before landiolol infusion (T0) and at 10 μg kg^{-1} min^{-1} i.v. (T1). Treatment was stopped if MAP was <65 mm Hg or HR <60 beats min^{-1}.

Microcirculation was assessed first with peripheral near-infrared spectroscopy (NIRS; INVOS™ Oximetry; Medtronic, Minneapolis, MN, USA) combined with a vascular occlusion test, as described.[1] We analysed the following variables: desaturation speed during ischaemia

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]

(baseline rSO_2 *minus* rSO_2min/time of ischaemia), resaturation speed during reperfusion (rSO_2max *minus* rSO_2min/time of reperfusion), and changes in rSO_2 during reperfusion (ΔrSO_2 = rSO_2max *minus* rSO_2 baseline). Microcirculation was also assessed with sublingual videomicroscopy (MicroScan® device; MicroVision Medical, Amsterdam, the Netherlands) according to current recommendations[4] and using validated software.[5] We computed the following variables: microvascular flow index, proportion of perfused vessels, total vessel density, and heterogeneity index. The primary endpoint was resaturation speed during reperfusion measured by NIRS combined with a vascular occlusion test. Secondary endpoints were the effects of landiolol on other microcirculatory variables from both NIRS and sublingual videomicroscopy.

All microcirculatory variables were similar in both groups over the study period (Table 1). Heart rate significantly decreased in landiolol compared with placebo (71 [64–77] *vs* 82 [75–96] beats min^{-1}; P=0.01), whereas MAP (75 [71–88] *vs* 82 [76–93] mm Hg; P=0.05) and stroke volume (36 [33–44] *vs* 35 [30–44] ml m^{-2}; P=0.63) remained unchanged. Nine (32%) patients in the placebo group *vs* 5 (17%) in the landiolol group experienced POAF between postoperative Day 0 and Day 5 (P=0.285).

Our results suggest that postoperative use of i.v. landiolol at 10 μg kg^{-1} min^{-1} reduces HR with neither beneficial nor detrimental effects on microcirculation. The incidence of POAF, although not statistically significant in the small study, was reduced by nearly 50%. This last result has been reported in patients undergoing cardiac surgery.[6] Microcirculatory disturbances have been mainly reported in sepsis,[7] but also after cardiac surgery with cardiopulmonary bypass, as microcirculation is known for being highly responsive to inflammatory mediators.[8] Thus, postoperative use of a moderate dose of landiolol could be efficacious to control HR with a good microcirculatory safety profile.

In conclusion, the Microcirculatory and Macrocirculatory Effects of Landiolol in Prevention of Postoperative Atrial Fibrillation (MMELPOAF) study is the first RCT describing the effects of landiolol on microcirculation in cardiac surgery. No significant alteration was found, suggesting its possible safety in that specific surgical setting.

Declarations of interest

AF has received lecture fees from Amomed Pharma France. J-LF is a member of the Scientific Advisory Board of Amomed Pharma France and has received consulting and lecture fees. The other authors have no conflicts of interest to declare.

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Physiologically variable ventilation and severe asthma. Comment on *Br J Anaesth* 2020; 125: 1107–16

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Editor—I read with interest the article by Dos Santos Rocha and colleagues[1] on the use of physiologically variable ventilation to improve gas exchange in an experimental model of severe asthma compared with pressure-controlled ventilation. We thank the authors for citing a series of prior articles on variable ventilation, which we named biologically variable ventilation, as we described.[2] They showed improved gas exchange, ventilatory pressures, lung tissue mechanics, and reduced lung injury with physiologically variable ventilation when compared with pressure-controlled ventilation. They state that '…the benefits of physiologically variable ventilation in the context of acute asthma exacerbations have not been characterised'. This latter statement is not entirely correct. We examined this question in a porcine model of severe bronchospasm, work that Dos Santos Rocha and colleagues cite, and came to the conclusion that there are advantages with biologically variable ventilation very similar to those described in their publication on physiologically variable ventilation.[2]

Apart from a difference in nomenclature to describe variable ventilation, the first experimental use of this mode of ventilation in a model of severe asthma was much earlier than they suggest. The work by Dos Santos Rocha and colleagues provides an important contribution to this area. Their development of an immunologic model based on ovalbumin sensitisation combined with methacholine nebulisation to induce bronchospasm is an important next step as a translational confirmation for this ventilatory approach that supports our prior work.

Declarations of interest

The author declares that they have no conflicts of interest.

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