Cardioprotective effect of the short-acting betablocker Esmolol in experimental ischemia/reperfusion

Efecto cardioprotector del betabloqueante de acción ultracorta Esmolol en isquemia/reperfusión experimental

Jorge Nuche[1,2,3], MD; Sergio Huertas[2 3], MD; Carlos Galán-Arriola[1,2], PhD; Pedro López-Ayala[2], MD; Manuel Lobo[2 4], MD; Borja Ibáñez[1,2,4,*], MD PhD.

[1] Centro de Investigación Biomédica En Red de enfermedades CardioVasculares (CIBERCV), Madrid, Spain.

[2] Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

[3] Servicio de Cardiología, Hospital Universitario 12 de Octubre. Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12). Madrid, Spain.

[4] Servicio de Cardiología, IIS-Fundación Jiménez Díaz, Madrid, Spain

***Corresponding author:** Borja Ibáñez. Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC). Calle Melchor Fernández Almagro 3, 28029, Madrid (Spain). bibanez@cnic.es

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The intravenous administration of metoprolol during ongoing ischemia has been demonstrated to be associated with smaller infarct size in animal models[1,2] and in the METOCARD-CNIC clinical trial.[3] Clinical practice guidelines recommend (IIa-A) the use of intravenous beta-blockers at the time of presentation in patients with ST-segment elevation myocardial infarction (STEMI) who are hemodynamically stable.[4] However, in some cases, physicians do not prescribe i.v. betablockers to STEMI patients because of the fear that they can develop acute heart failure. There are betablockers with very short half-life that have the theoretical advantage that upon stopping infusion, its negative inotropic and chronotropic effects fade away within minutes. Given that not all betablockers are able to ameliorate ischemia/reperfusion injury,[2] there is a need for testing the cardioprotective abilities of short acting betablockers in a controlled experimental setting.

Esmolol is a highly beta1-selective, ultra-short acting betablocker with rapid onset of action (60 seconds) and which reaches steady state in 6 minutes after bolus administration. These pharmacological properties make esmolol a great candidate for its use in the setting of STEMI when hemodynamic instability is a potential concern. In this study we aimed to evaluate the infarct-limiting capacity of esmolol infusion during ongoing ischemia in a pig model of anterior STEMI. The benefits of esmolol were evaluated by state-of-the-art cardiac magnetic resonance (CMR) performed at 2 different timepoint: 7 and 45 days after reperfusion. Primary endpoint of the study was day7 indexed infarct size (IS, extent of delayed gadolinium enhancement, normalized to area at risk). AAR was quantified by cardiac computed tomography (CT) performed during index LAD occlusion following a previously reported methodology[5]. Main secondary endpoints were, indexed infarct size at 45-day and left ventricular ejection fraction (LVEF) on both CMR exams.

Before the actual ischemia/reperfusion experiments, a dose-response study with five animals was conducted to determine the most appropriate esmolol infusion rate: that achieving a 10% reduction of heart rate without sustained hemodynamic instability (250 µg/kg/min).

Fifteen male Large-White pigs underwent 40 min left anterior descending (LAD) coronary occlusion followed by reperfusion. Pigs were randomized to receive either esmolol (n=8) or control (vehicle infusion, n=7), which were initiated (without bolus) 20 minutes after LAD artery occlusion, and maintained for a total of 60 min (i.e. it was stopped 40 min after reperfusion). Since the main objective of the study was to test the infarct-limiting properties of esmolol, the infusion rate was not modified during the protocol, even in those pigs developing hemodynamic instability.

Three animals (2 esmolol and 1 control) died during STEMI induction. The 2 esmolol pigs died secondary to severe hemodynamic instability caused by esmolol infusion, while the control died because of refractory ventricular fibrillation. Three additional pigs (2 esmolol and 1 control) died between day7 and day 45 CMR.

CT-measured AAR was not different between groups (36.4%±6.1% vs 33.7±3.6% of LV in esmolol and control respectively; p=0.385), Figure 1A. IS was significantly smaller in the esmolol group both in 7-day (64.4±11.8% vs 84.1±9.4% of AAR; p=0.01) and in the 45-day CMR (52.9±9.1% vs 71.5±12.7%; p=0.04), Figure 1B. Animals in the Esmolol group presented a non-significant trend towards higher LVEF both at 7- and 45-day CMR (day 7: 39.7±4.1% vs. 34.0±6.2%; p=0.091; day 45: 43.4±6.6% vs. 35.3±11.8%; p=0.264), Figure 1C. There were no differences neither in microvascular obstruction nor in edema extension.

In this experimental setting, continuous esmolol infusion initiated during ongoing ischemia was associated with smaller IS and with a trend towards improved LVEF. The numerically higher death due to hemodynamic instability during index STEMI is explained by the experimental protocol aimed at addressing the infarct-limiting properties of esmolol. We speculate that in a clinical setting, these adverse effects will not occur since upon signs of acute

heart failure, infusion can be reduced or event stopped. Whether this tailored esmolol infusion will reduce IS is unknown, but highly plausible. The loss of 50% of the animals in the esmolol group and 29% in the control group represents the main limitation of this study. This experimental study complements previous clinical studies suggesting that esmolol can protect the heart during STEMI.[6] Given that not all betablockers exert infarct limiting effects[2], the effects seen with esmolol cannot be ascribed to other short-acting betablockers.

In conclusion, this study shows that esmolol infusion is able to reduce indexed IS in an experimental AMI model and shows a trend towards LVEF improvement. However, there are safety concerns regarding hemodynamic instability that requires further evaluation.

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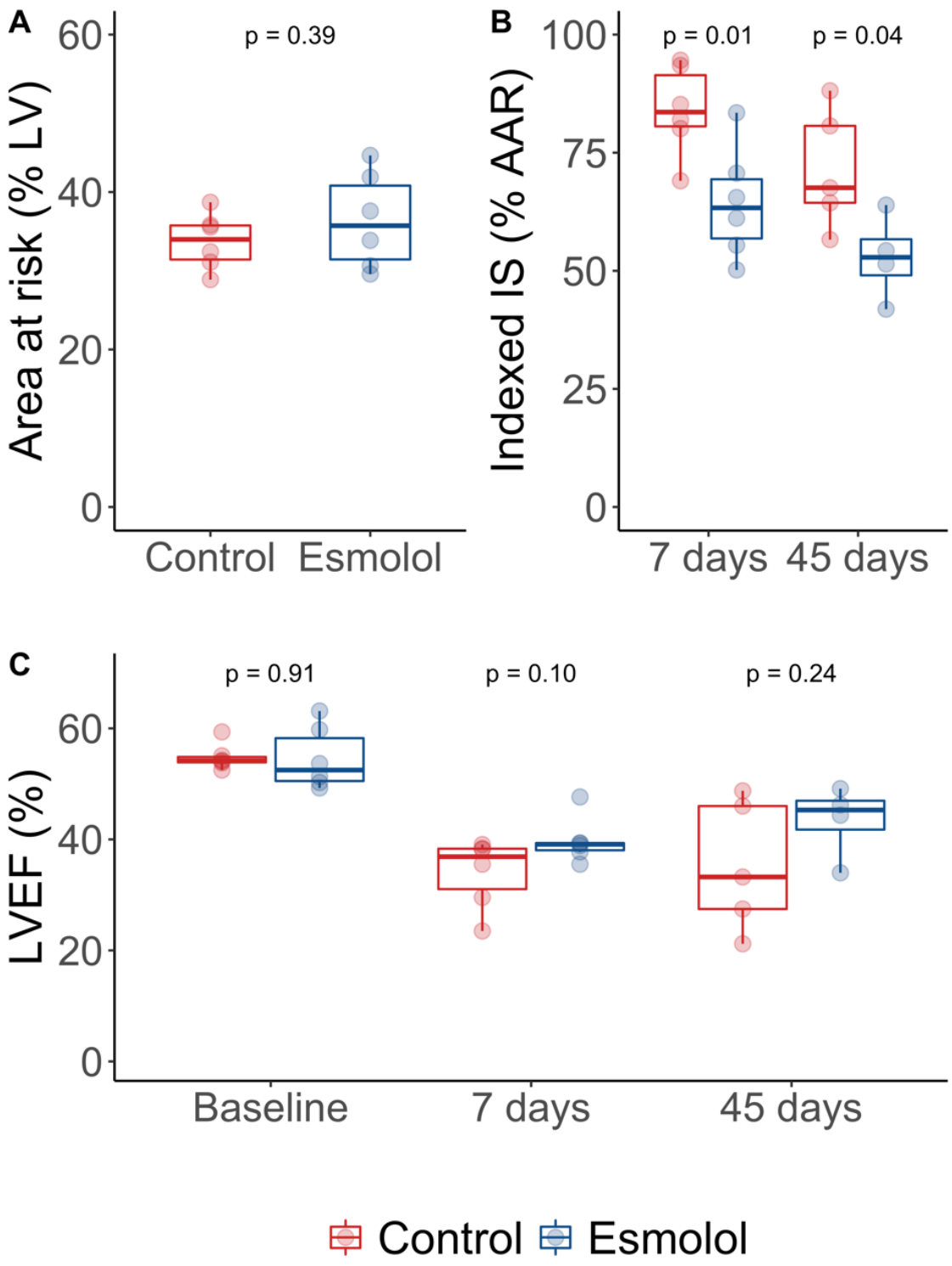
Figure Legends

Figure 1.

A: Area at risk (% of LV mass) on CT exam during index coronary occlusion; **B:** Indexed infarct size (% of area at risk with delayed gadolinium enhancement) on 7- and 45-day CMR. **C.** Left ventricular ejection fraction (LVEF) at different timepoints.

Boxplots represent median and interquartile range. Circles represent individual data.


A
Area at risk (% LV)
60
40
20
0
p = 0.39
Control
Esmolol
B
Indexed IS (% AAR)
100
75
50
25
0
p = 0.01
p = 0.04
7 days
45 days
C
LVEF (%)
60
40
20
0
p = 0.91
p = 0.10
p = 0.24
Baseline
7 days
45 days
Control
Esmolol