

## **ONLINE APPENDIX: Timing of metoprolol administration during STEMI on infarct size and ventricular function: A METOCARD-CNIC substudy**

### **ADDITIONAL METHODOLOGY**

Blinded analyses were undertaken by a core laboratory at the Spanish National Center for Cardiovascular Research (CNIC). Data were quantified with a dedicated software program (QMass MR 7.6; Medis, Leiden, the Netherlands). LV volume, LV mass, LVEF, and the extent of edema and necrosis were determined on day 5 to 7 CMR. MIS, expressed in grams or as a percentage of LV mass, was estimated from the extent of myocardial necrosis, defined according to the extent of abnormal delayed-gadolinium enhancement (9).

Sedation was induced by intramuscular injection of ketamine (20 mg/kg), xylazine (2 mg/kg), and midazolam (0.5 mg/kg). Buprenorphine (0.03 mg/kg) was used as an analgesic during the intervention. All animals were intubated and mechanically ventilated with oxygen (fraction of inspired O<sub>2</sub>: 28%) and anesthesia was maintained by IV administration of ketamine (2 mg/kg/h), xylazine (0.2 mg/kg/h), and midazolam (0.2 mg/kg/h). Central venous and arterial lines were placed and a single bolus of unfractionated heparin (300 mg/kg) was administered immediately before catheter introduction. During the procedure, pigs were monitored by continuous electrocardiography (ECG), pulse oximetry, and invasive measurement of systemic blood pressure and pulmonary artery pressure (using a Swan-Ganz catheter). Continuous infusion with amiodarone (300 mg, 150 mg/h) was maintained during the procedure in all pigs as prophylaxis for malignant ventricular arrhythmias.

Segmented cine steady-state free precession was performed to acquire 11 to 13 contiguous short axis slices covering the heart from the base to the apex to evaluate global and regional LV motion. CMR parameters include: (field of view [FOV] of 280 x 280 mm; slice thickness of 8 mm without gap; repetition time [TR] 2.8 ms; echo time [TE] 1.4 ms, flip angle 45; cardiac phases 25; voxel size 1.8 x 1.8 mm; number of excitations [NEX]: 3). Edema imaging (for quantification of myocardial area at risk) was performed with a T2-weighted, triple inversion-recovery fast spin-echo (T2W-STIR) sequence (FOV of 280 x 280; 11 to 13 short-axis slices with thickness of 8 mm and no gap; TR 2 to 3 heartbeats; TE 80 ms; voxel size 1.4 x 1.4 mm; STIR delay 210 ms; trigger delay longest; echo-train length 16; 2 NEX). A coil sensitivity correction algorithm for all T2W images was implemented in the scan acquisition. Finally, late-gadolinium enhancement imaging was performed 15 min after administration of 0.2 mmol/kg gadopentetate dimeglumine using an inversion-recovery, fast gradient-echo sequence to determine MIS (FOV of 280 x 280 mm; 11 to 13 short-axis slices with a thickness of 8 mm and no gap; TR 5.6 ms; TE 2.8 ms; voxel size 1.6 x 1.6 mm; time interval optimized to null normal myocardium; trigger delay longest; bandwidth, 304 Hz per pixel; 2 NEX).

The area of myocardium at risk (AAR) was defined as the extent of the LV demonstrating high signal intensity on T2W-STIR images (14). MIS (necrosis) was quantified from the extent of abnormal delayed-gadolinium enhancement. AAR and necrosis were identified as hyperintense regions using the basis of 50% of the peak myocardial signal intensities (full width half maximum) with manual adjustment when needed. If present, a central core of hypointense signal within the area of increased signal was included in the T2W-STIR or late-gadolinium

enhancement analysis. Finally, MIS was expressed both as a percentage of LV mass and normalized by AAR.

#### **ADDITIONAL REFERENCES**

1. Thiele H, Kappl MJE, Conradi S, et al. Reproducibility of chronic and acute infarct size measurement by delayed enhancement-magnetic resonance imaging. *J Am Coll Cardiol* 2006;47:1641-5.
2. Aletras AH, Tilak GS, Natanzon A, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation* 2006;113:1865-70.

**Online Table 1. Hemodynamic data from the animal study**

		Long interval	Short interval	60min post-reperfusion	Vehicle	p-value
Heart Rate (bpm)	Baseline	87.5 (15.3)	80.7 (7.5)	92.2 (15.3)	91.4 (15.9)	0.099
	Pre-reperfusion	91.8 (10.5)	79.9 (6.4)	88.2 (15)	95.2 (15.1)	<b>0.009</b>
	90min reperfusion	123.4 (13.6)	110.4 (19.5)	120.8 (18.5)	127.5 (18.1)	0.241
SAPm (mmHg)	Baseline	95.5 (4.1)	95.2 (5.9)	89.2 (10.7)	89.7 (10.6)	0.206
	Pre-reperfusion	66.5 (14.1)	63 (9.5)	65.6 (7.8)	67.5 (11.2)	0.793
	90min reperfusion	62.3 (10.3)	63.8 (11.2)	68.5 (8.1)	76.1 (10.0)	<b>0.046</b>
PAPm (mmHg)	Baseline	20.8 (3.6)	19.4 (2.5)	22.6 (7.1)	22.9 (6.5)	0.31
	Pre-reperfusion	27.8 (5.7)	25.8 (3.3)	25.6 (4)	24.9 (4.7)	0.673
	90min reperfusion	24.1 (4.4)	24.4 (4)	22.8 (3.3)	27.6 (5.9)	0.278
CI (L/min/m <sup>2</sup> )	Baseline	3.8 (0.8)	3.4 (0.6)	4.1 (0.6)	3.4 (1)	0.089
	Pre-reperfusion	2.3 (0.7)	2 (0.2)	2.4 (0.4)	2.1 (0.6)	0.062
	90min reperfusion	2.3 (0.6)	2.1 (0.4)	2.5 (0.5)	2 (0.8)	0.244
PCWPM (mmHg)	Baseline	7.4 (2.1)	7.8 (2.6)	6 (2.2)	5.9 (2.8)	0.246
	Pre-reperfusion	12.4 (1.3)	12.8 (1.8)	11.6 (2.6)	11.1 (2.5)	0.366
	90min reperfusion	12 (1.6)	12.4 (1.8)	12.8 (3.9)	11.9 (2.5)	0.882

Values are expressed as mean (SD); p-values were calculated by Welch ANOVA. CI, cardiac index. PAPm, mean pulmonary artery pressure. PCWPM, mean pulmonary capillary wedge pressure. SAPm, mean systemic arterial pressure.