Arg389Gly beta-1-adrenergic receptor polymorphism determines neutrophil-stunning-associated cardioprotection by metoprolol

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**Background:** Cardioprotective strategies to limit infarct size (IS) have become crucial. The damaged inflicted on the myocardium is the result of the processes of Ischemia and Reperfusion (I/R). In the clinical trial METOCARD-CN1C, it was shown that the intravenous (i.v.) pre-reperfusion administration of the β1-selective antagonist metoprolol reduces IS and improves long-term cardiac function in patients after acute myocardial infarction (1). However, the small sample size precludes a definite conclusion. Despite not having demonstrated a solid clinical benefit in terms of hard endpoints reduction, the clinical guidelines for the management of ST-Elevation Myocardial Infarction (STEMI) recommend the early administration of i.v. β-blockers in patients undergoing Primary Coronary Intervention. Additionally, our group has recently described that the beneficial effect of metoprolol against myocardial I/R injury is due to neutrophil stunning (2), which represents a one-of-a-kind property not shared by other i.v. β-blockers, such as atenolol or propranolol (3).

**Purpose:** Since β1-adrenergic receptor (ADRB1) is one of major targets of pharmacological therapy, great efforts are now underway to account for the relevance of the polymorphic variation. Here we explore whether the cardioprotection exerted by metoprolol is dependent on genetic polymorphisms in human ADRB1.

**Methods:** Patients included in the METOCARD-CN1C trial were grouped into the different variants for the ADRB1, rs1801252 and rs1801253 (SerGly49 and Arg389Gly, respectively), which might affect their response to the beta-1 modulation exerted by metoprolol on neutrophils and thus its cardioprotective effect. Additionally, the polymorphic-dependent effect of metoprolol on neutrophil migration was evaluated in healthy volunteers, whose neutrophils were exposed across the transwell filter to the CXCL1 in the presence or absence of metoprolol. Drug-receptor interaction properties were evaluated in silico.

**Results:** We found that Arg389Gly polymorphism of the human ADRB1 impacts the cardioprotective effect of metoprolol in STEMI patients. Therefore, Arg389 homozygosity was associated with lower infarcts (Figure 1) and better long-term left ventricle ejection fraction when metoprolol was intravenously administered prior reperfusion. Moreover, the disrupting effect of metoprolol on neutrophil migration was only observed in Arg389 homozygote volunteers (Figure 2). These differences were attributed to alterations in the drug-receptor complex stability when Gly residues are present in position 389 of the ADRB1.

**Conclusions:** From our perspective, these results are the first showing a polymorphic implication in drug response against myocardial I/R injury. All the data presented refine cardiovascular pharmacotherapy, and have major implications for the prospective clinical trial design aiming at positioning metoprolol as the beta-blocker of choice to reduce hard endpoints in STEMI patients.
Cardioprotection

Figure 1. (A) STEMI patients included in the METOCARD-CNIC trial were grouped into the different variants for the ADRB1. (B) Frequency of the Arg389Gly ADRB1 polymorphism. Effect of early pre-reperfusion intravenous metoprolol administration on CK maximum peak (C) and infarct size (D), evaluated by cardiac magnetic resonance imaging (CMR), in the subset of patients with TIMI grade 0 to 1 flow before primary percutaneous coronary intervention. Linear regression models were used to evaluate association between ADRB1 polymorphisms and the outcome after adjusting for total ischemic time. * P<0.05.
Neutrophil migration

Figure 2. (A) Experimental scheme for CXCL1-induced transwell migration analysis. (B) Frequency of the Arg389Gly ADARB1 polymorphism. Baseline neutrophil migration across the transwell membrane was significantly blocked by metoprolol treatment in Arg389 homozygotes (C). Nevertheless, no effect was seen in Arg389Gly heterozygotes (D). Comparisons were made using one-way ANOVA for paired samples; * P<0.05. Data are presented as mean±SD.