ORIGINAL CONTRIBUTION

Intravenous metoprolol during ongoing STEMI ameliorates markers of ischemic injury: a METOCARD-CNIC trial electrocardiographic study

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Abstract

Besides its protective effect against neutrophil-mediated injury at reperfusion, intravenous (IV) metoprolol was recently shown to reduce the progression of ischemic injury in a pig model of ST-segment elevation myocardial infarction (STEMI). Here, we tested the hypothesis that IV metoprolol administration in humans with ongoing STEMI blunts the time-dependent progression of ischemic injury assessed by serial electrocardiogram (ECG) evaluations before reperfusion. The METOCARD-CNIC trial randomized 270 anterior STEMI patients to IV metoprolol or control before reperfusion by percutaneous coronary intervention (PCI). In 139 patients (69 IV metoprolol, 70 controls), two ECGs were available (ECG-1 before randomization, ECG-2 pre-PCI). Between-group ECG differences were analyzed using univariate and multivariate regression models. No significant between-group differences were observed on ECG-1. On ECG-2, patients who received IV metoprolol had a narrower QRS than those in the control group (84 ms vs. 90 ms, $p = 0.029$), a lower prevalence of QRS distortion (10% vs. 26%, $p = 0.017$), and a lower sum of anterior and total ST-segment elevation (10.1 mm vs. 13.6 mm, $p = 0.014$ and 10.4 mm vs. 14.0 mm, $p = 0.015$, respectively). Adjusted analysis revealed similar results. Significant associations were observed between ECG-2 variables and cardiac magnetic resonance imaging measurements (extent of myocardial edema, infarct size, microvascular obstruction, and left-ventricular ejection fraction) after STEMI. In summary, IV metoprolol administration before reperfusion ameliorates ECG markers of myocardial ischemia in anterior STEMI patients. These data confirm that IV metoprolol is able to reduce ischemic injury and highlight the ability of ECG analysis to provide relevant real-time information on the effect of cardioprotective therapies before reperfusion.

Keywords ST-elevation myocardial infarction · Electrocardiography · Beta-blockers · Myocardial ischemia · Magnetic resonance imaging · Percutaneous coronary intervention

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Introduction

ST-segment elevation myocardial infarction (STEMI) originates in acute thrombotic occlusion of an epicardial coronary artery [1]. The severe ongoing myocardial ischemia produces visible alterations in the electrocardiogram (ECG). Indeed, the presence of ST-segment elevation in two or more contiguous leads in the appropriate clinical context is enough to initiate reperfusion strategies, with primary percutaneous coronary intervention (PCI) being the strategy of choice if available in a timely manner [1].

Paradoxically, reperfusion can trigger additional damage to the myocardium, known as reperfusion injury [2]. Therefore, the final extent of irreversible myocardial loss (infarct size) is the combined result of ischemic- and reperfusion-mediated injuries. Infarct size is the main determinant of poor clinical outcomes in STEMI survivors [3]. Large infarcts are also associated with low left-ventricular ejection fraction (LVEF), the main driver of chronic heart failure [4]. There is great interest in identifying cardioprotective therapies able to limit ischemia/reperfusion injury, and thus final infarct size [5]. Most experimentally and clinically tested cardioprotective interventions have focused on limiting reperfusion-mediated injury, with very few targeting ischemic injury [6]. Besides reperfusion itself, there are no interventions consistently associated with delayed ischemic injury.

The ECG has been largely used for the bedside assessment of the effectiveness of reperfusion and prognosis in myocardial infarction. The magnitude of ST-segment elevation [7–9] and QRS duration [10, 11] on initial ECG in STEMI patients shows a consistent direct association with morbidity and mortality. Conversely, successful myocardial reperfusion usually entails a significant and rapid resolution of ST-segment elevation [12, 13] and a reduction of QRS duration relative to the STEMI diagnosis value regardless of the reperfusion strategy [14, 15], which are associated with better prognosis. Therefore, ECG changes could serve as a surrogate marker of the effectiveness of cardioprotective therapies. The vast majority of studies in this regard have evaluated pre- and post-reperfusion ECGs changes with very few experimental works [16, 17] assessing the effect of peri- and pre-conditioning maneuvers on the ECG during ongoing ischemia (i.e., before reperfusion), limiting the ability to determine the contribution of cardioprotection-mediated reduced ischemic vs. reperfusion damage.

Metoprolol is a beta1-selective blocker with unique pharmacological properties [18] that has consistently shown an association with reduced infarct size in mice [19, 20], pigs [21, 22], and humans [23–25]. Metoprolol attenuates neutrophil-mediated reperfusion injury [19, 20].

Recent analysis of a pig model of ischemia/reperfusion showed that IV metoprolol can blunt the progression of ischemic injury [22]. However, the ability of metoprolol to reduce ischemic injury in humans has not been assessed before.

The aim of this study was to assess the impact of IV metoprolol administration during ongoing ischemia on ECG alterations that indicate ischemic injury. ECGs were obtained before and after IV metoprolol in patients with ongoing anterior STEMI from the METOCARD-CNIC trial. In addition, we examined the relationship between ECG alterations and infarct size and LVEF measured by cardiac magnetic resonance (CMR) performed 1 week after reperfusion.

Methods

Study design

This is a post hoc not pre-specified analysis undertaken in the patient population enrolled in the METOCARD-CNIC trial [26]. The study design has been published elsewhere [26]. Briefly, eligible patients aged between 18 and 80 years had symptoms compatible with STEMI for more than 30 min, an ST-segment elevation ≥ 2 mm in two or more contiguous leads from V1 to V5 on the initial or diagnostic ECG, and an anticipated time from symptom onset to reperfusion by primary PCI ≤ 6 h [26]. Exclusion criteria were Killip–Kimball class III or IV, systolic blood pressure (SBP) persistently below 120 mmHg, complete left bundle branch block, PR interval greater than 240 ms, type II or III atrioventricular block, heart rate (HR) persistently below 60 bpm, a history of previous myocardial infarction, chronic treatment with beta-blockers, or active treatment with bronchodilators. Patients were randomized 1:1 to IV metoprolol (target dose 15 mg) or control immediately after STEMI diagnosis. Patients randomized to the intervention group were scheduled to receive up to three 5 mg IV metoprolol boluses 2 min apart, with monitoring of blood pressure and heart rate between boluses. Within the intervention group, 67% of patients received 15 mg IV metoprolol, 15% received 10 mg, and 17% received 5 mg. The control group received no placebo IV formulation. Apart from IV metoprolol, all patients were treated according to clinical guidelines regardless of randomization arm. Relevant imaging parameters were assessed by CMR 5–7 days and 6 months after STEMI.

ECG analysis

From the total population included in the primary METO-CARD-CNIC trial analysis [24], all patients who had two 12-lead ECGs prior to reperfusion were included in this

sub-study. The first ECG was performed at the time of diagnosis, before randomization (ECG-1), whereas the second ECG (ECG-2) was performed after IV metoprolol administration in patients randomized to receive it (or at a comparable time in controls) and before reperfusion in all cases.

ECGs were performed with standard calibration (25 mm/s on the time axis and 10 mm/mV on the voltage axis) and were analyzed by two independent researchers blinded to treatment allocation using computer software with high-precision calibration and measurement rules (Image J or FreeRuler), manually guided and adjusted to hundredths of mm. The following parameters were analyzed: heart rate (HR), in beats per minute (bpm); PR interval duration (milliseconds, ms); QRS duration (ms); presence of QRS distortion in two or more contiguous leads; sum of ST-segment elevation in anterior leads (from V1 to V6, I and aVL, in mm), inferior leads (II, III and aVF), and lead aVR; and total ST-segment elevation, defined as the sum of the ST-segment elevation in anterior and inferior leads (mm).

A QRS distortion pattern was diagnosed when the ratio between the maximum R wave height and the J point was ≥ 0.5 in any lead or when there was S wave loss in leads V1 to V3 [27]. ST-segment elevation magnitude was measured 20 ms from the end of the QRS complex (or J point), taking the previous T–P segment as the isoelectric reference line.

CMR analysis

CMR images were analyzed as previously described [24, 25]. Briefly, images were analyzed by cardiac imaging experts blinded to ECG results, using a dedicated software package (QMass® MR 7.4, Medis, Leiden, The Netherlands). The CMR data used for this sub-study were extent of myocardial edema (grams of LV mass), infarct size (grams of LV mass), microvascular obstruction (grams of LV mass), and LVEF (%).

Statistical analysis

All analyses were performed "per protocol" (by treatment received). The primary endpoint was the between-group difference (IV metoprolol vs. control) in the sum of anterior ST-segment elevation on ECG-2, providing a measure of the effect of IV metoprolol on pre-reperfusion ECG.

A descriptive analysis was performed of demographic, clinical, hemodynamic, angiographic, and ECG variables and the treatment received during PCI. Continuous variables are expressed as mean and standard deviation (SD), and categorical variables are expressed as frequencies (n) and percentages (%).

In the univariate (unadjusted) analysis, between-group differences in continuous variables were analyzed by Student's t test for independent samples. Between-group differences in categorical variables were analyzed by the Chi-square test or Fisher's exact test. Differences are expressed as estimated mean differences and 95% confidence intervals (95% CI).

Similarly, in the unadjusted analysis of intragroup (IV metoprolol or control) ECG changes occurring between ECG-1 and ECG-2, continuous variables were examined by Student's t test for paired samples, whereas categorical variables were examined by the Chi-square test or Fisher's exact test. Intragroup change differences are expressed as estimated mean differences and 95% CI.

For the adjusted analysis of the effect of IV metoprolol on ECG-2 variables (QRS duration, presence of QRS distortion, sum of anterior, and total ST-segment elevation), multiple linear or logistic regression models were used depending on whether the dependent variable was continuous or binary, respectively. Three multivariate models were built for each of the ECG variables analyzed on ECG-2. Model 1 included the value of the variable of interest on ECG-1 as the main co-variate, in addition to the treatment received (IV metoprolol vs. control). Model 2 included variables from model 1 plus other clinically relevant variables that could act as confounders in the assessment of ischemic injury: age, sex, diabetes mellitus, ischemic symptoms duration, culprit artery, and initial TIMI coronary flow grade. Model 3 was the best reduced model (the most parsimonious model whose change in the β coefficient was less than 10% with respect to the reference model, and with a more precise 95% CI width) obtained through the *confound* user-written Stata command. The reference model, in addition to the variables in model 2, included body mass index, smoking habit, hypertension, dyslipidemia, initial SBP, and initial HR. The following independent variables were kept fixed in the different reduced models: treatment received (IV metoprolol vs. control), as this was the primary comparison of the study; and age and sex, as they constitute main demographic variables.

For multiple linear regression models, the values of the β coefficient and 95% CI were obtained by expressing the adjusted effect of IV metoprolol vs. control in each of the continuous ECG variables of interest analyzed on ECG-2, accompanied by the corresponding p value and the adjusted coefficient of determination (adjusted R^2). For multiple logistic regression models, the odds ratio and 95% CI values were obtained by expressing the increased risk of not administering IV metoprolol (vs. its administration) in the presence of QRS distortion on ECG-2, accompanied by the corresponding p value and the Nagelkerke psuedo-R^2 index (Cragg–Uhler–Nagelkerke R^2).

Two strategies were adopted for sensitivity analysis. The first consisted of an evaluation of the effect of IV metoprolol on ECG-2 variables in the patient subgroup with a pre-PCI TIMI grade 0–1 flow, since this variable can greatly influence the magnitude of ST-segment elevation and other ECG

measurements in the context of STEMI. The second strategy analyzed the between-group differences (IV metoprolol vs. control) in the changes occurring on ECG-2 compared with ECG-1.

To study the association between continuous ECG variables and CMR measurements, scatter plots were graphed to include the projection of the linear prediction fit line, as well as the coefficient of determination, Pearson's correlation coefficient (Pearson's *r*) and statistical significance. All analyses were performed using STATA version 15 (Stata-Corp, College Station, Texas).

Results

A total of 139 anterior STEMI patients were included; 69 patients received IV metoprolol during ongoing ischemia, while 70 patients did not and served as controls (Fig. 1). The baseline study population characteristics are shown in Table 1, both overall and by treatment group (IV metoprolol vs. control). There were no significant between-group differences in baseline characteristics. Overall mean age was 57.9 years (SD = 11.7), and 85.6% were men. Patients had a high prevalence of CV risk factors: hypertension 41%, active smoking 53%, dyslipidemia 25%, and diabetes mellitus 20%. Most patients presented no signs of heart failure (93% were in Killip–Kimball class I), and the most frequent infarct-related artery was the mid-left anterior descending coronary artery (LAD) (60%), followed by the proximal-LAD (28%), with 80% of patients having an initial TIMI grade 0–1 flow. No significant differences in baseline characteristics were found between the total population randomized in the METOCARD-CNIC trial and the population included in the present study (data not shown).

The main overall and by-group ECG characteristics at initial diagnosis (ECG-1) are shown in Table 2. Overall mean QRS duration was 88 ms (SD = 18), 19% of patients presented with QRS distortion in 2 or more contiguous ECG leads, and the sum of anterior and total ST-segment elevation was 13.8 mm (SD = 9.8) and 14.3 mm (SD = 10.9),

Fig. 1 Flowchart of METO-CARD-CNIC trial participants included in this study
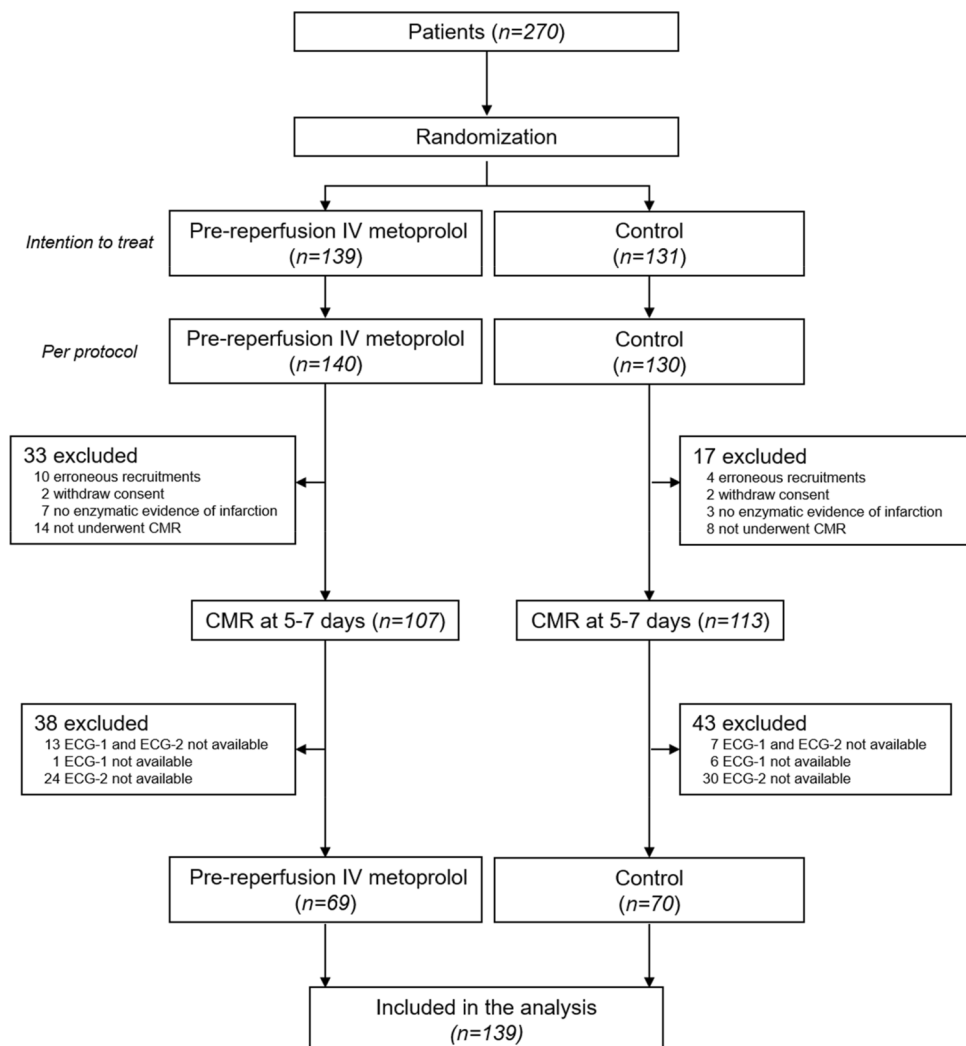
Table 1 Study population baseline characteristics, overall and by-group (IV metoprolol vs. control)

	All patients ($n=139$)	IV Metoprolol ($n=69$)	Control ($n=70$)	*P* values
Age, years	57.9 (11.7)	57.6 (12.7)	58.3 (10.7)	0.740
Male sex, *n* (%)	119 (85.6)	58 (84.1)	61 (87.1)	0.604
BMI, (kg/m^2)	27.6 (3.6)	27.4 (3.7)	27.7 (3.5)	0.628
Hypertension, *n* (%)	57 (41.3)	26 (38.2)	31 (44.3)	0.470
Smoking, *n* (%)				0.976
Active	73 (52.5)	35 (50.7)	38 (54.3)	
Ex-smoker ≤ 10 years	15 (10.8)	8 (11.6)	7 (10.0)	
Ex-smoker > 10 years	14 (10.1)	7 (10.1)	7 (10.0)	
Never smoked	37 (26.6)	19 (27.5)	18 (25.7)	
Dyslipidemia, *n* (%)	62 (44.6)	30 (43.5)	32 (45.7)	0.791
Diabetes mellitus, *n* (%)	28 (20.1)	13 (18.8)	15 (21.4)	0.704
Ischemia duration, (min)[a]	200 (66)	208 (63)	193 (68)	0.198
Killip–Kimball class at recruitment, *n* (%)				0.326
I	129 (92.8)	66 (95.7)	63 (90.0)	
II	10 (7.2)	3 (4.4)	7 (10.0)	
Infarct-related artery, *n* (%)				0.656
Proximal LAD	38 (27.5)	19 (27.9)	19 (27.1)	
Mid LAD	83 (60.1)	39 (57.4)	44 (62.9)	
Distal LAD	14 (10.1)	7 (10.3)	7 (10.0)	
Other location	4 (2.3)	4 (4.4)	0 (0.0)	
TIMI grade 0–1 flow before PCI, *n* (%)	110 (79.1)	52 (75.4)	58 (82.9)	0.810
Successful PCI, *n* (%)[b]	136 (97.8)	69 (100)	67 (95.7)	0.245
SBP at recruitment, (mmHg)	144 (19)	143 (17)	144 (20)	0.701
HR at recruitment, (bpm)	83 (13)	83 (12)	83 (14)	0.854
SBP after IV metoprolol, (mmHg)	–	131 (19)	–	–
HR after IV metoprolol, (bpm)	–	68 (10)	–	–
Treatment at the time of PCI, *n* (%)				
Heparin	132 (95.7)	67 (97.1)	65 (94.2)	0.681
Aspirin	137 (99.3)	69 (100)	68 (98.6)	1.000
Clopidogrel/prasugrel	136 (98.6)	68 (98.6)	68 (98.6)	1.000
Thrombus aspiration	116 (84.1)	59 (85.6)	57 (82.6)	0.642
GP IIb/IIIa during PCI	109 (79.0)	53 (76.8)	56 (81.2)	0.531

Values are presented as mean (standard deviation) for continuous variables or as frequencies (*n*) and percentage (%) for categorical variables. There were no significant between-group differences in any of the analyzed baseline characteristics

BMI body mass index, *GP* glycoprotein, *HR* heart rate, *IV* intravenous, *LAD* left anterior descending coronary artery, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure, *TIMI* thrombolysis in myocardial infarction

[a]Ischemia duration = time from symptom onset to reperfusion

[b]Successful PCI was defined as TIMI grade 2–3 flow after PCI

respectively. There were no significant between-group differences in ECG variables at this time point.

Overall and by-group ECG characteristics at pre-reperfusion (ECG-2) are shown in Table 2. In this unadjusted (univariate) comparison, the IV metoprolol group had a lower mean HR (81 bpm vs. 72 bpm, $p < 0.001$), a shorter mean QRS duration (90 ms vs. 84 ms, $p = 0.029$), a lower proportion of patients with QRS distortion (26% vs. 10%, $p = 0.017$), and a lower sum of anterior (13.6 mm vs. 10.1 mm, $p = 0.014$) and total (14.0 mm vs. 10.4 mm, $p = 0.015$) ST-segment elevation. There were no between-group differences in PR interval duration or the magnitude of ST-segment elevation in inferior leads or aVR.

Analysis of within-group ECG changes between ECG-1 and ECG-2 revealed a widening of the QRS complex in the control group and decreases in HR, QRS duration, QRS distortion prevalence, and the sum of anterior and total ST-segment elevation in the IV metoprolol group (Table 3).

Table 2 Characteristics of the ECG at initial diagnosis (ECG-1) and at pre-reperfusion (ECG-2), overall, and by-group (IV metoprolol vs. control)

ECG at initial diagnosis (ECG-1)	All patients ($n=139$)	IV Metoprolol ($n=69$)	Control ($n=70$)	Difference (95% CI)	P values
HR, (bpm)	81 (14)	81 (13)	81 (14)	0 (− 5 to 5)	0.984
PR interval, (ms)	169 (23)	169 (24)	168 (21)	1 (− 7 to 8)	0.853
QRS duration, (ms)	88 (18)	88 (20)	87 (17)	1 (− 5 to 8)	0.661
QRS distortion, patients (%)	26 (18.7)	11 (15.9)	15 (21.4)	− 5.5 (− 18.6 to 7.7)	0.407
Sum anterior ST-segment elevation, (mm)[a]	13.8 (9.8)	13.4 (8.8)	14.1 (10.8)	− 0.7 (− 4.0 to 2.6)	0.684
Sum inferior ST-segment elevation, (mm)	0.6 (2.2)	0.3 (0.9)	0.8 (2.9)	− 0.5 (− 1.2 to 0.2)	0.189
aVR ST-segment elevation, (mm)	0.3 (0.4)	0.3 (0.5)	0.2 (0.4)	0.1 (− 0.1 to 0.2)	0.300
Sum total ST-segment elevation, (mm)[b]	14.3 (10.9)	13.7 (9.1)	14.9 (12.4)	− 1.2 (− 4.8 to 2.5)	0.530
ECG at pre-reperfusion (ECG-2)					
HR, (bpm)	77 (16)	72 (14)	81 (16)	− 9 (− 14 to − 4)	**< 0.001**
PR interval, (ms)	169 (26)	173 (27)	165 (25)	8 (− 1 to 17)	0.080
QRS duration, (ms)	87 (18)	84 (19)	90 (16)	− 7 (− 12 to − 1)	**0.029**
QRS distortion, patients (%)	25 (18.0)	7 (10.1)	18 (25.7)	− 15.6 (− 28.3 to − 2.9)	**0.017**
Sum anterior ST-segment elevation, (mm)[a]	11.9 (8.4)	10.1 (6.9)	13.6 (9.5)	− 3.5 (− 6.3 to − 0.7)	**0.014**
Sum inferior ST-segment elevation, (mm)	0.3 (1.5)	0.3 (1.0)	0.4 (1.9)	− 0.0 (− 0.5 to 0.5)	0.922
aVR ST-segment elevation, (mm)	0.2 (0.5)	0.3 (0.5)	0.2 (0.4)	0.1 (− 0.1 to 0.2)	0.483
Sum total ST-segment elevation, (mm)[b]	12.2 (8.6)	10.4 (7.3)	14.0 (9.5)	− 3.6 (− 6.4 to − 0.7)	**0.015**

Values are presented as mean (standard deviation) for continuous variables or as frequencies (n) and percentage (%) for categorical variables. Differences between groups (IV metoprolol vs. control) are presented as mean differences and 95% confidence intervals (95% CI)

There were no significant between-group differences in any of the characteristics analyzed on the ECG at initial diagnosis (ECG-1)

[a] Sum of anterior ST-segment elevation is the sum of ST-segment elevation in leads I, aVL, and V1 to V6

[b] Sum of total ST-segment elevation is the sum of ST-segment elevation in anterior leads (I, aVL, and V1 to V6) and inferior leads (II, III and aVF)

P values <0.05 are in bold

Table 3 Within-group ECG changes between ECG at initial diagnosis (ECG-1) and ECG at pre-reperfusion (ECG-2)

	IV Metoprolol ($n=69$)	P values	Control ($n=70$)	P values
HR, (bpm)	− 9 (− 5 to − 12)	**< 0.001**	0 (− 2 to 3)	0.728
PR interval, (ms)	4 (0 to 9)	0.072	− 3 (− 6 to 0)	0.071
QRS duration, (ms)	− 4 (− 8 to − 1)	**0.015**	3 (1 to 6)	**0.011**
QRS distortion, % of patients	− 5.8 (− 13.9 to 2.3)	0.159	4.3 (− 6.0 to 14.6)	0.409
Sum anterior ST-segment elevation, (mm)[a]	− 3.3 (− 4.9 to − 1.7)	**< 0.001**	− 0.5 (− 3.3 to 2.3)	0.742
Sum inferior ST-segment elevation, (mm)	0.0 (− 0.2 to 0.3)	0.914	− 0.4 (− 1.0 to 0.1)	0.100
aVR ST-segment elevation, (mm)	0.0 (− 0.1 to 0.1)	0.505	0.0 (− 0.1 to 0.1)	0.720
Sum total ST-segment elevation, (mm)[b]	− 3.3 (− 5.0 to − 1.6)	**< 0.001**	− 0.9 (− 4.2 to 2.3)	0.579

Values are presented as mean changes (95% confidence intervals) for continuous variables or as mean percentage change (95% confidence intervals) for categorical variables

QRS distortion is the increase or decrease in the percentage of patients with QRS distortion on ECG-2 compared with ECG-1

[a] Sum of anterior ST-segment elevation is the sum of ST-segment elevation in leads I, aVL, and V1–V6

[b] Sum of total ST-segment elevation is the sum of ST-segment elevation in anterior leads (I, aVL, and V1–V6) and inferior leads (II, III, and aVF)

P values <0.05 are in bold

In the adjusted analysis, IV metoprolol showed similar effects on the ECG-2 variables to those observed in the unadjusted analysis. In the different multivariate models used, ECG-2 QRS duration in the IV metoprolol group ranged

Table 4 Adjusted analysis of the effect of IV metoprolol on QRS duration (ms) on pre-reperfusion ECG (ECG-2)

	Model 1	Model 2	Model 3
β coefficient (95% CI)	− 7.5 (− 11.4 to − 3.6)	− 7.4 (− 11.5 to − 3.3)	− 6.3 (− 10.0 to − 2.7)
P value	< 0.001	0.001	0.001
Adjusted R^2	0.548	0.578	0.643

Values of the β coefficient express the adjusted mean effect (95% CI) of IV metoprolol vs. control on QRS duration (ms) on ECG-2

Adjusted R^2 adjusted coefficient of determination of the model; 95% *CI* 95% confidence interval

Model 1 includes the value of QRS duration (ms) on ECG-1 (continuous variable) as the main co-variate, in addition to treatment received (IV metoprolol vs. control)

Model 2 includes variables from model 1, as well as age (continuous variable), sex (categorical), diabetes mellitus (categorical), ischemia duration (continuous), culprit artery (categorical), and initial TIMI coronary flow grade (categorical)

Model 3 was the best reduced model (most parsimonious model with a change in the β coefficient < 10% with respect to the reference model and with a more precise 95% CI width) obtained with the *confound* user-written Stata command. The reference model included the variables included in model 2, as well as body mass index (continuous variable), smoking habit (categorical), hypertension (categorical), dyslipidemia (categorical), initial SBP (continuous), and initial HR (continuous). In this case, model 3 (or the selected reduced model) included the following variables: QRS duration on ECG-1, age, sex, smoking, arterial hypertension, and initial TIMI flow grade

from 6.3 ms less (95% CI − 10.0 to − 2.7 ms; *p* = 0.001) to 7.5 ms less (95% CI − 11.4 to − 3.6 ms; *p* < 0.001) than in the control group (Table 4). The odds of having QRS distortion in two or more contiguous leads on ECG-2 ranged from 3.4 times higher (95% CI 1.2 to 10.3; *p* = 0.027) to 7.8 times higher (95% CI 1.9 to 32.7; *p* = 0.005) in patients who did not receive IV metoprolol (control group) than in those who did (Table 5). The sum of anterior ST-segment elevation on ECG-2 ranged from 2.9 mm less (95% CI − 5.5 to − 0.4 mm; *p* = 0.023) to 3.3 mm less (95% CI − 5.8 to − 0.8 mm; *p* = 0.010) in the IV metoprolol group (Table 6). Similar findings were observed for the sum of total ST-segment elevation on ECG-2 (Table 6). Sensitivity analyses revealed similar results (data not shown).

Associations between the sum of anterior ST-segment elevation on ECG-2 (the primary endpoint of the present study) and relevant CMR measurements are presented in Fig. 2. Overall, a positive correlation was observed between the sum of anterior ST-segment elevation on ECG-2 and CMR measurements at 5–7 days after STEMI of the extent of myocardial edema ($R^2 = 0.16$, $r = 0.40$, $p < 0.001$; Fig. 2A), infarct size ($R^2 = 0.24$, $r = 0.49$, $p < 0.001$; Fig. 2B), and microvascular obstruction ($R^2 = 0.17$, $r = 0.41$, $p < 0.001$; Fig. 2C). In contrast, the sum of anterior ST-segment elevation on ECG-2 showed a negative correlation with LVEF ($R^2 = 0.15$, $r = − 0.39$, $p < 0.001$; Fig. 2D), and this negative correlation was maintained 6 months after STEMI ($R^2 = 0.18$, $r = − 0.43$; $p < 0.001$). The direction and magnitude of these associations did not differ significantly between treatment groups. Similar associations were found for total ST-segment elevation (Fig. 3).

Table 5 Adjusted analysis of the effect of IV metoprolol administration on the odds of presenting QRS distortion on pre-reperfusion ECG (ECG-2)

	Model 1	Model 2	Model 3
Odds ratio (95% CI)	3.4 (1.2 to 10.3)	5.5 (1.3 to 22.9)	7.8 (1.9 to 32.7)
P value	0.027	0.018	0.005
Nagelkerke Pseudo-R^2	0.350	0.509	0.508

Values provided as odds ratios express the adjusted mean odds (95% CI) or increased risk of not administering IV metoprolol (vs. administration) in the presence of QRS distortion on ECG-2

Nagelkerke pseudo-R^2 index, Cragg–Uhler (Nagelkerke) pseudo-R^2 index of the model; 95% *CI* 95% confidence interval

Model 1 includes the value of presence of QRS distortion on ECG-1 (binary categorical variable) as the main co-variate, in addition to treatment received (IV metoprolol vs. control)

Model 2 includes variables from model 1, as well as age (continuous variable), sex (categorical), diabetes mellitus (categorical), ischemia duration (continuous), culprit artery (categorical), and initial TIMI coronary flow grade (categorical)

Model 3 was the best reduced model (most parsimonious model with a change in the odds ratio < 10% with respect to the reference model and with a more precise 95%CI width) obtained with the *confound* user-written Stata command. The reference model included the variables included in model 2, as well as body mass index (continuous variable), smoking habit (categorical), hypertension (categorical), dyslipidemia (categorical), initial SBP (continuous), and initial HR (continuous). In this case, model 3 (or the selected reduced model) included the following variables: presence of QRS distortion on ECG-1, age, sex, hypertension, dyslipidemia, culprit artery, and initial SBP

Table 6 Adjusted analysis of the effect of IV metoprolol on the sum of anterior and total ST-segment elevation (mm) on pre-reperfusion ECG (ECG-2)

Anterior ST-segment elevation	Model 1	Model 2	Model 3
β coefficient (95% CI)	− 3.3 (− 5.8 to − 0.8)	− 2.9 (− 5.5 to − 0.4)	− 3.0 (− 5.5 to − 0.6)
P value	0.010	0.023	0.014
Adjusted R^2	0.235	0.291	0.311
Total ST-segment elevation	Model 1	Model 2	Model 3
β coefficient (95% CI)	− 3.2 (− 5.8 to − 0.6)	− 2.9 (− 5.5 to − 0.2)	− 3.2 (− 5.8 to − 0.6)
P value	0.017	0.037	0.015
Adjusted R^2	0.183	0.234	0.244

Values of the β coefficient express the adjusted mean effect (95% CI) of IV metoprolol vs. control on the sum of anterior or total ST-segment elevation (mm) on ECG-2

Adjusted R^2 adjusted coefficient of determination of the model; 95% *CI* 95% confidence interval

Model 1 includes the sum of anterior or total ST-segment elevation (mm) on ECG-1 (continuous variable) as the main co-variate, in addition to treatment received (IV metoprolol vs. control)

Model 2 includes variables from model 1, as well as age (continuous variable), sex (categorical), diabetes mellitus (categorical), ischemia duration (continuous), culprit artery (categorical), and initial TIMI coronary flow grade (categorical)

Model 3 was the best reduced model (most parsimonious model with a change in the β coefficient < 10% with respect to the reference model and with a more precise 95% CI width) obtained with the *confound* user-written Stata command. The reference model included the variables included in model 2, as well as body mass index (continuous variable), smoking habit (categorical), hypertension (categorical), dyslipidemia (categorical), initial SBP (continuous), and initial HR (continuous). In this case, model 3 (or the selected reduced model) included the following variables: sum of anterior or total ST-segment elevation on ECG-1, age, sex, diabetes mellitus, ischemia duration, and initial TIMI flow grade (only for anterior ST-segment elevation)

Associations between QRS duration on ECG-2 and CMR measurements significantly differed by treatment group: whereas significant associations were found in the control group, no significant correlations were observed in the IV metoprolol group (Fig. 4).

Discussion

This study has evaluated the effect of IV metoprolol administration on ECG markers of ischemic injury in a population of patients with anterior STEMI enrolled in the METOCARD-CNIC trial. Compared with controls, the IV metoprolol group showed a narrowing in QRS duration, a reduction in the prevalence of QRS distortion in two or more contiguous leads, and a reduction in the sum of anterior and total ST-segment elevation. This attenuation of ECG markers upon IV metoprolol administration before reperfusion suggests an independent effect of this drug in blunting the progression of ischemic injury during ongoing coronary occlusion. To the best of our knowledge, this is the first study describing the effect of a cardioprotective therapy on ECG markers of myocardial injury in humans with ongoing STEMI.

IV metoprolol as a stabilizer of the QRS complex

Myocardial ischemia prolongs QRS duration due to the slowing of conduction velocity within the ischemic areas

[28]. Our results show a widening of the QRS complex in the control group between ECG-1 and ECG-2. This is in line with findings from other groups showing a direct association between ischemia time and QRS duration in the initial ECG in STEMI patients, possibly indicating a degree of irreversible microvascular damage [14]. Not only was this QRS widening abolished in the IV metoprolol group, but QRS duration even narrowed. IV–metoprolol-induced QRS shortening is smaller than the shortening observed after successful reperfusion (the most effective ischemia-reducing therapy); nevertheless, this finding suggests that IV metoprolol administration reduces ischemic injury per se. This could also explain the differential associations observed between QRS duration on ECG-2 and myocardial damage evaluated by CMR in the control group (direct association observed) vs. the IV metoprolol group (no association observed, Fig. 4).

The presence of QRS distortion in two or more leads on initial ECG in STEMI patients is associated with a larger extent of myocardial area at risk and infarct size than in patients with no QRS distortion [27]. Although no significant between-group differences were found on ECG-1, on ECG-2, the proportion of patients with QRS distortion was significantly higher in the control group (26%) than in the IV metoprolol group (10%). Since previous studies also indicated that persistent QRS distortion after revascularization is associated with larger infarct size and less myocardial salvage than in patients in whom this pattern disappears after
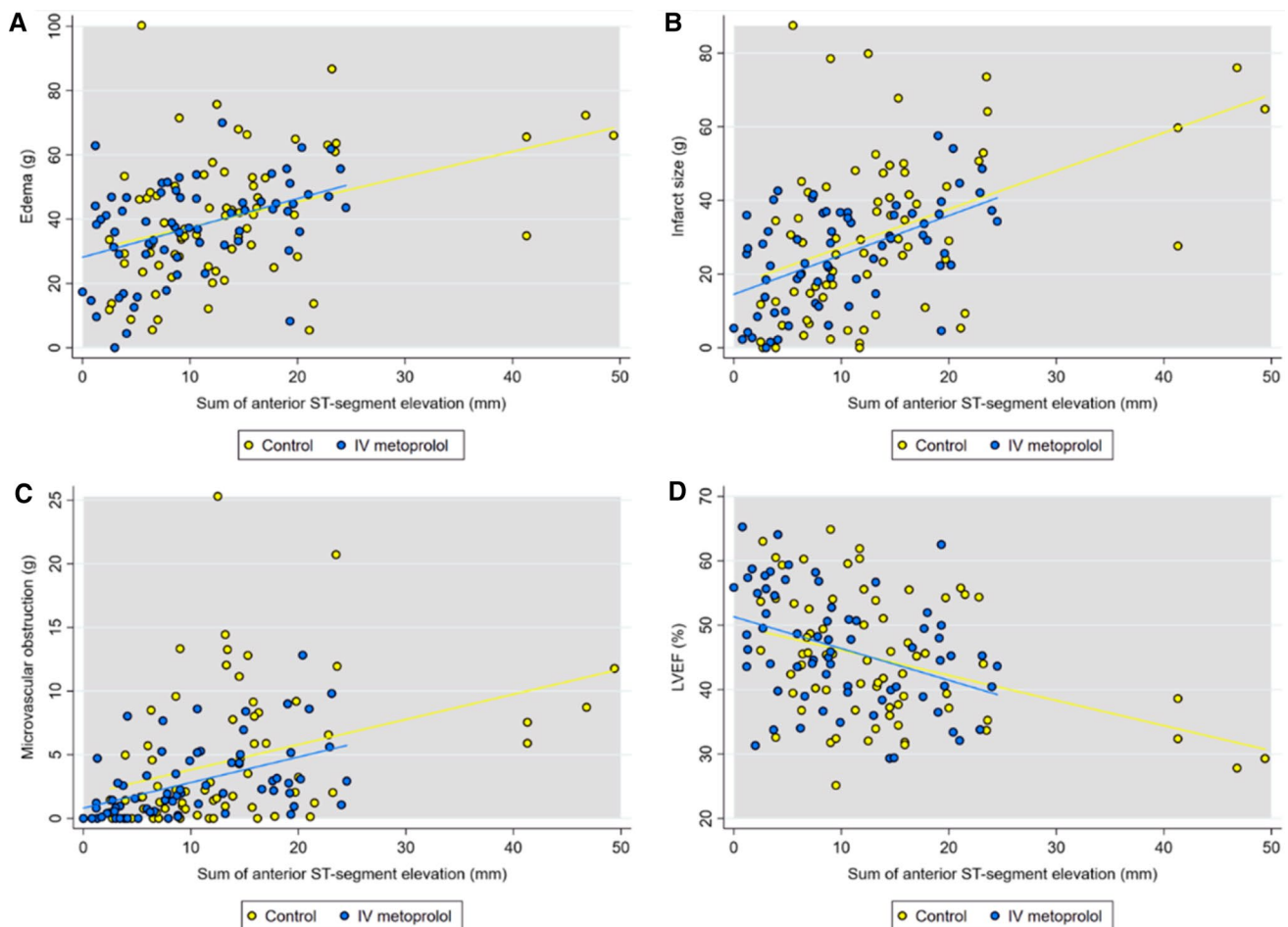
Fig. 2 Association between the sum of anterior ST-segment elevation on pre-reperfusion ECG (ECG-2) and cardiac magnetic resonance imaging measures 5–7 days after ST-segment elevation myocardial infarction. Panel **A** A positive correlation was observed between the sum of anterior ST-segment elevation on ECG-2 and the extent of myocardial edema ($R^2 = 0.16$, $r = 0.40$, $p < 0.001$). The direction and magnitude of this association was similar in the IV metoprolol group ($R^2 = 0.18$, $r = 0.42$, $p < 0.001$) and the control group ($R^2 = 0.14$, $r = 0.37$, $p = 0.001$). Panel **B** A positive correlation was observed between the sum of anterior ST-segment elevation on ECG-2 and infarct size ($R^2 = 0.24$, $r = 0.49$, $p < 0.001$). The direction and magnitude of this association was similar in the IV meto-prolol group ($R^2 = 0.28$, $r = 0.53$, $p < 0.001$) and the control group ($R^2 = 0.20$, $r = 0.44$, $p < 0.001$). Panel **C** A positive correlation was observed between the sum of anterior ST-segment elevation on ECG-2 and microvascular obstruction ($R^2 = 0.17$, $r = 0.41$, $p < 0.001$). The direction and magnitude of this association was similar in the IV metoprolol group ($R^2 = 0.23$, $r = 0.48$, $p < 0.001$) and the control group ($R^2 = 0.13$, $r = 0.36$, $p = 0.003$). Panel **D** A negative correlation was observed between the sum of anterior ST-segment elevation on ECG-2 and LVEF ($R^2 = 0.15$, $r = -0.39$, $p < 0.001$). The direction and magnitude of this association was similar in the IV metoprolol group ($R^2 = 0.15$, $r = -0.39$, $p = 0.001$) and the control group ($R^2 = 0.15$, $r = -0.38$, $p = 0.001$)

reperfusion [29], our findings again support a role for IV metoprolol in reducing ongoing ischemic damage.

Attenuation of ST-segment elevation after IV metoprolol administration during ongoing ischemia

Previous experimental studies showed an effect of local pre-conditioning maneuvers (intermittent cycles of occlusion and reperfusion in the coronary artery) on the magnitude of ST-segment elevation; however, until recently these changes were studied during episodes of pre-conditioning in the absence of myocardial infarction [30, 31]. Similar

findings have been reported in patients who underwent local pre-conditioning maneuvers prior to elective PCI [32] and in STEMI patients after primary PCI [33]. It is important to note that this finding has not been consistent in humans despite the demonstration of a simultaneous documented cardioprotection by imaging techniques, suggesting that ECG changes may be less sensitive than imaging [34].

In a recent pioneering experimental study by Klein-bongard et al., pigs were subjected to 60 min left anterior descending coronary artery occlusion and reperfusion [17]; this study demonstrated that cardioprotection mediated by remote peri-conditioning translates into an attenuation
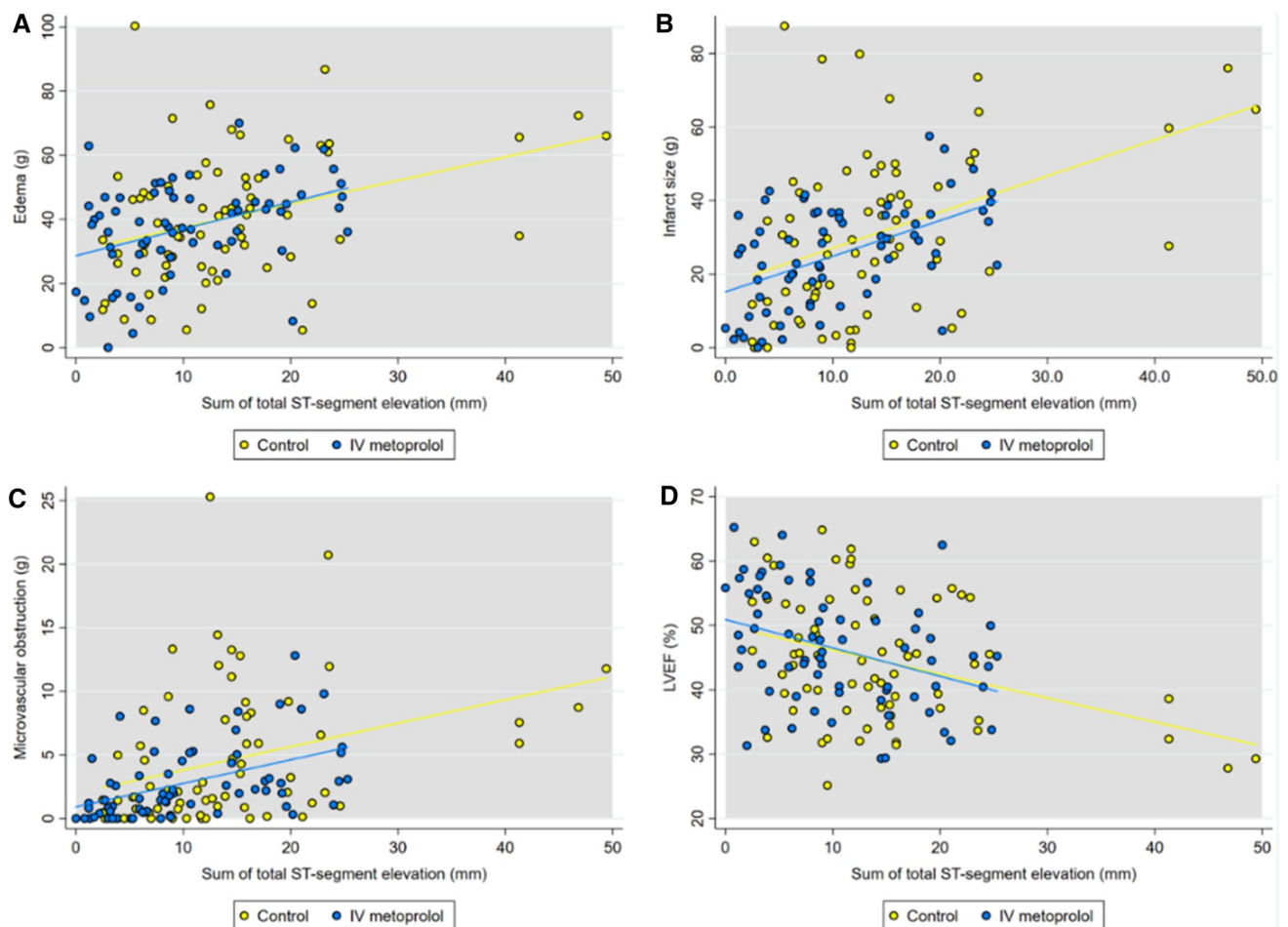
Fig. 3 Association between the sum of total ST-segment elevation on pre-reperfusion ECG (ECG-2) and relevant cardiac magnetic resonance imaging measures 5–7 days after ST-segment elevation myocardial infarction. Panel **A** A positive correlation was observed between the sum of total ST-segment elevation on ECG-2 and the extent of myocardial edema ($R^2 = 0.14$, $r = 0.38$, $p < 0.001$). The direction and magnitude of this association was similar in the IV metoprolol group ($R^2 = 0.17$, $r = 0.41$, $p = 0.001$) and the control group ($R^2 = 0.12$, r = 0.35, $p = 0.003$). Panel **B** A positive correlation was observed between the sum of total ST-segment elevation on ECG-2 and infarct size ($R^2 = 0.21$, $r = 0.46$, $p < 0.001$). The direction and magnitude of this association was similar in the IV metoprolol group ($R^2 = 0.26$, $r = 0.51$, $p < 0.001$) and the control group ($R^2 = 0.18$, $r = 0.42$, $p < 0.001$). Panel **C** A positive correlation was observed between the sum of total ST-segment elevation on ECG-2 and microvascular obstruction ($R^2 = 0.15$, $r = 0.39$, $p < 0.001$). The direction and magnitude of this association was similar in the IV metoprolol group ($R^2 = 0.21$, $r = 0.46$, $p < 0.001$) and the control group ($R^2 = 0.11$, $r = 0.33$, $p = 0.005$). Panel **D** A negative correlation was observed between the sum of total ST-segment elevation on ECG-2 and LVEF ($R^2 = 0.14$, $r = -0.37$, $p < 0.001$). The direction and magnitude of this association was similar in the IV metoprolol group ($R^2 = 0.13$, $r = -0.36$, $p = 0.002$) and the control group ($R^2 = 0.13$, $r = -0.37$, $p = 0.002$)

of ST-segment elevation immediately after the end of the peri-conditioning maneuvers, and before reperfusion. Compared with ECG performed 5 min after the onset of coronary occlusion, ECG performed at 55 min showed a partial resolution of the ST-segment elevation, and this reduction was greater in pigs that received peri-conditioning than in the control group (between-ECG reduction ~ 39% vs. 6%). The results also showed that ST-segment elevation resolution between 5 and 55 min of ischemia correlated inversely with histology-determined infarct size. Similar findings were reported in a later study by the same group, in which local and remote pre-conditioning maneuvers were performed

before infarction induction [16]; however, these maneuvers are not transferable to STEMI patients.

The ECG changes associated with a cardioprotective therapy in the acute phase of STEMI and before reperfusion in humans had never been described before. In the present study, we show that the reduction in ST-segment elevation between ECG-1 and ECG-2 after IV metoprolol administration was significantly higher than in controls (~ 25% vs. 4% reduction in the sum of anterior ST-segment elevation, Fig. 5). In agreement with the Kleinbogard et al.'s study, we found the sum of ST-segment elevation on ECG-2 correlated positively with both infarct size and the extent of myocardial
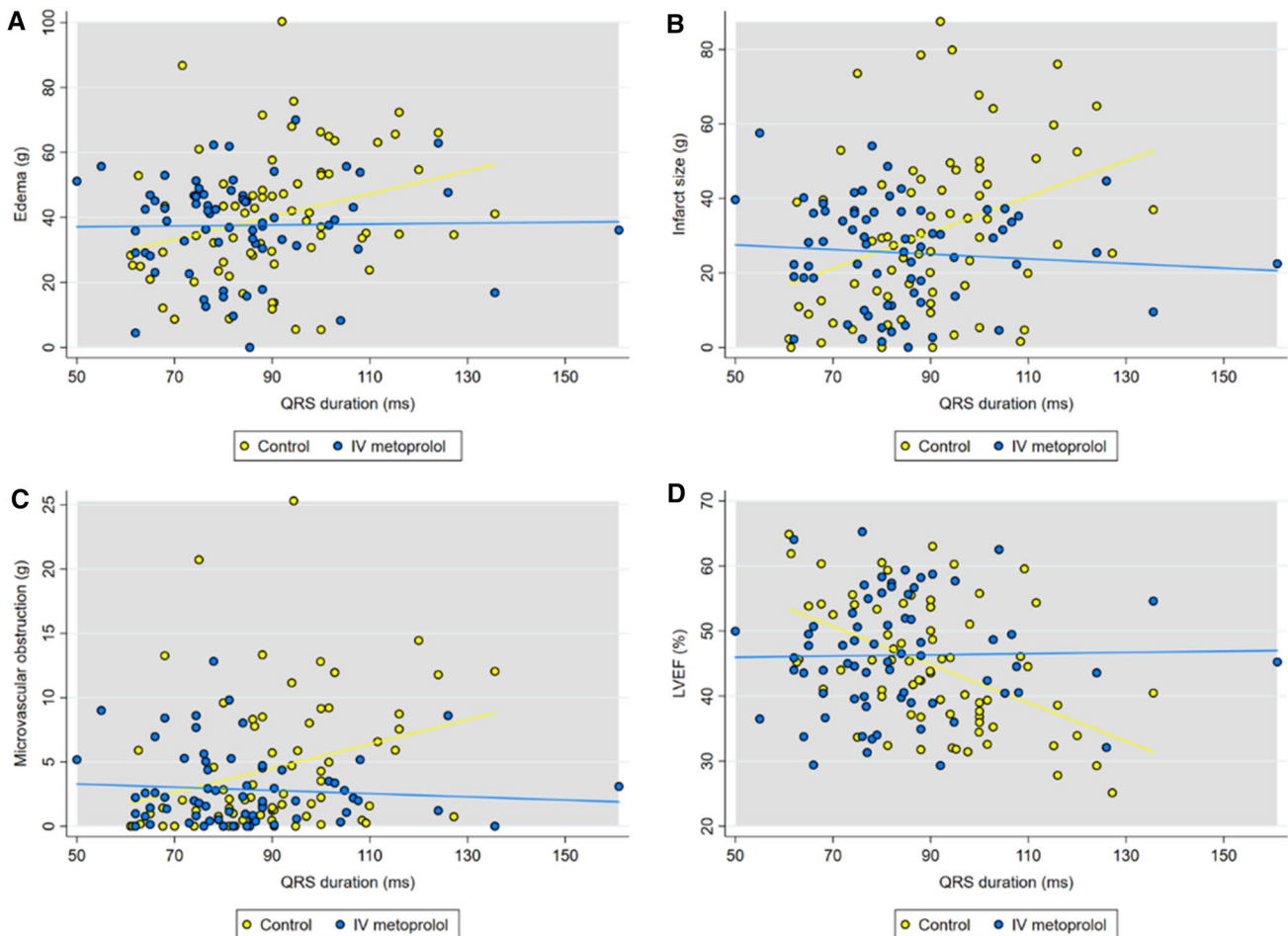
Fig. 4 Association between QRS duration on pre-reperfusion ECG (ECG-2) and relevant cardiac magnetic resonance imaging measure 5–7 days after ST-segment elevation myocardial infarction. Panel **A** A weak positive correlation was observed between QRS duration on ECG-2 and the extent of myocardial edema ($R^2 = 0.03$, $r = 0.17$, $p = 0.044$). This association differed significantly by treatment group: whereas the control group showed a positive correlation ($R^2 = 0.08$, $r = 0.29$, $p = 0.016$), no significant association was observed for the IV metoprolol group ($R^2 < 0.01$, $r = 0.02$, $p = 0.886$). Panel **B** A weak positive correlation was observed between QRS duration on ECG-2 and infarct size ($R^2 = 0.03$, $r = 0.19$, $p = 0.028$). This association differed significantly by treatment group: whereas the control group showed a positive correlation ($R^2 = 0.12$, $r = 0.35$, $p = 0.003$), no significant association was observed in the IV metoprolol group ($R^2 = 0.01$, $r = -0.08$, $p = 0.494$). Panel **C** A weak positive correlation was observed between QRS duration on ECG-2 and microvascular obstruction ($R^2 = 0.03$, $r = 0.17$, $p = 0.047$). This association differed significantly by treatment group: whereas the control group showed a positive correlation ($R^2 = 0.08$, $r = 0.29$, $p = 0.015$), no significant association was observed in the IV metoprolol group ($R^2 = 0.01$, $r = -0.08$, $p = 0.513$). Panel **D** A weak negative correlation was observed between QRS duration on ECG-2 and LVEF ($R^2 = 0.06$, $r = -0.24$, $p = 0.004$). This association differed significantly by treatment group: whereas the control group showed a negative correlation ($R^2 = 0.24$, $r = -0.49$, $p < 0.001$), no significant association was observed in the IV metoprolol group ($R^2 < 0.01$, $r = 0.02$, $p = 0.875$)

edema assessed by CMR. These findings are also consistent with previous findings in STEMI patients [8, 35]. Moreover, the negative correlation detected between the sum of ST-segment elevation on ECG-2 and LVEF is also in line with the previous findings [36].

Our results show that the beneficial impact of pre-reperfusion IV metoprolol on ST-segment elevation is already detectable on ECG before reperfusion. Since the attenuation of ST-segment elevation during ongoing ischemia translates into improved cardiac CMR parameters, the measurement of ST-segment elevation could provide relevant real-time clinical information about the potential success of cardioprotective therapies.

Timing and mechanisms underlying the cardioprotective effect of IV metoprolol

Primary PCI is the guideline-recommended revascularization procedure for patients with ongoing STEMI if the estimated time from diagnosis to reperfusion is ≤ 120 min [1]. Otherwise, immediate systemic fibrinolysis is recommended. However, fibrinolysis does not achieve effective

Fig. 5 Representative ECG from an anterior STEMI patient showing partial resolution of ST-segment elevation after administration of IV metoprolol and before primary PCI. The upper trace shows the diagnostic ECG (ECG-1), whereas lower trace shows the pre-PCI ECG (ECG-2) obtained after IV metoprolol administration to patient 101 in the METO-CARD-CNIC trial. The traces show an approximately 30% reduction in the sum of anterior ST-segment elevation on ECG-2 (arrows) relative to ECG-1

myocardial reperfusion in a significant proportion of patients and increases the risk of severe bleeding. Thus, any intervention to delay the progression of ischemic damage would be of great value in extending this time window, allowing more patients to benefit from primary PCI.

In this regard, an METOCARD-CNIC sub-study by García-Ruiz et al. showed that the sooner IV metoprolol is administered; the smaller the infarct size and the higher the LVEF in anterior STEMI patients undergoing primary PCI [21]. A subsequent experimental study showed that IV metoprolol can delay the progression of irreversible myocardial damage (CMR-determined infarct size) in pigs, suggesting that IV metoprolol decreases ischemic damage directly [22]. However, it is difficult to determine the contribution of reduced ischemic vs. reperfusion damage, because infarct size is always measured after reperfusion [37]. A previous study by García-Prieto et al. showed that IV metoprolol-mediated infarct size reduction is partly due to a direct effect of the drug on neutrophils and platelet–neutrophil interactions that translates into inhibited neutrophil migration and reduced microvascular obstruction, suggesting that the observed benefits of pre-reperfusion IV metoprolol in STEMI patients are, to some extent, a consequence of a reperfusion damage reduction [20]. The disruptive action of metoprolol on neutrophil dynamics has not been demonstrated for other beta-blockers [18, 19].

The present study is the first to use serial pre-reperfusion ECGs obtained before and after IV metoprolol administration (all during ongoing ischemia) to demonstrate the ischemia-limiting effect of a cardioprotective therapy in patients with ongoing STEMI. Over the course of myocardial infarction, pain, anxiety, and cardiac output reduction activate the sympathetic nervous system to produce a catecholaminergic response [38]. This sympathetic activation causes an increase in HR and myocardial contractility and, as a consequence, an increase in myocardial oxygen demand, which accelerates the progression of myocardial necrosis. The classically established mechanism of cardioselective beta-blockers is a reduction in myocardial oxygen consumption through their negative chronotropic, dromotropic, inotropic, and hypotensive effects [39].

As expected, HR on ECG-2 was lower and PR interval slightly longer in the IV metoprolol group than in the control group. However, no overall or by-group associations were found between HR or SBP and relevant CMR measurements (data not shown), previous experimental results showed that metoprolol is cardioprotective regardless of HR and blood pressure reduction [22], and no clear cardioprotective effect has been observed with other beta-blockers and HR-slowing drugs [19, 40]. These observations support the notion that the beneficial effects of IV metoprolol are not only due to its hemodynamic effects and that it also limits ischemic damage through other mechanisms. A possible neuro-mediated cardioprotective mechanism can be proposed, since metoprolol, unlike other beta-blockers, is lipophilic and can cross the blood–brain barrier [41].

This idea is consistent with the absence of a similar cardioprotective effect with other beta-blockers, such as IV propranolol or atenolol [18, 19]. Although a neuromodulatory effect has been proposed as a mechanism for other cardioprotective interventions, such as remote conditioning [42], this has not yet been described for IV metoprolol.

Limitations

The present study included ~ 63% of the patients from the primary analysis of the METOCARD-CNIC trial. Nevertheless, baseline characteristics remained comparable between the IV metoprolol and control groups, and results were similarly consistent in the analyses performed (including adjusted models and sensitivity analysis). The study included only patients with anterior STEMI and revascularized by primary PCI within a relatively short time window, which could limit the external validity of the results. Because ongoing myocardial ischemia is a dynamic process, the magnitude of ECG changes could depend on the timing of ECG collection. However, this potential error should be distributed similarly among participants in the IV metoprolol and control groups, given that ischemia duration was relatively short and most patients showed TIMI coronary grade < 2 flow before primary PCI, with no significant between-group differences. Finally, due to the limited sample size, this study did not analyze the association of ECG variables with the incidence of adverse events. However, the study does demonstrate an association of ECG parameters with prognosis-related CMR measures.

Conclusions

This study is the first to describe the effect of a cardioprotective therapy on ECG results in anterior STEMI patients before reperfusion, comparing patients who received IV metoprolol with patients who did not. Compared with no treatment, pre-reperfusion IV metoprolol induced a stabilization of the QRS complex and a reduction in the magnitude of anterior and total ST-segment elevation. Significant associations were found between relevant ECG measures and prognosis-related CMR imaging parameters obtained 5–7 days and 6 months after STEMI.

The administration of IV metoprolol before reperfusion attenuates ECG markers of myocardial ischemia, suggesting that this drug reduces ischemic damage through an independent effect. ECG analysis could provide useful real-time bedside clinical information about the effect of cardioprotective therapies administered before reperfusion.

Declarations

Conflict of interest Javier Sanchez-González is a Philips employee. All other authors state that they have no conflict of interests to declare.

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