

Sex Differences in Timeliness of Reperfusion in Young Patients With ST-Segment–Elevation Myocardial Infarction by Initial Electrocardiographic Characteristics

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Background—Young women with ST-segment–elevation myocardial infarction experience reperfusion delays more frequently than men. Our aim was to determine the electrocardiographic correlates of delay in reperfusion in young patients with ST-segment–elevation myocardial infarction.

Methods and Results—We examined sex differences in initial electrocardiographic characteristics among 1359 patients with ST-segment–elevation myocardial infarction in a prospective, observational, cohort study (2008–2012) of 3501 patients with acute myocardial infarction, 18 to 55 years of age, as part of the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study at 103 US and 24 Spanish hospitals enrolling in a 2:1 ratio for women/men. We created a multivariable logistic regression model to assess the relationship between reperfusion delay (door-to-balloon time >90 or >120 minutes for transfer or door-to-needle time >30 minutes) and electrocardiographic characteristics, adjusting for sex, sociodemographic characteristics, and clinical characteristics at presentation. In our study (834 women and 525 men), women were more likely to exceed reperfusion time guidelines than men (42.4% versus 31.5%; $P<0.01$). In multivariable analyses, female sex persisted as an important factor in exceeding reperfusion guidelines after adjusting for electrocardiographic characteristics (odds ratio, 1.57; 95% CI, 1.15–2.15). Positive voltage criteria for left ventricular hypertrophy and absence of a prehospital ECG were positive predictors of reperfusion delay; and ST elevation in lateral leads was an inverse predictor of reperfusion delay.

Conclusions—Sex disparities in timeliness to reperfusion in young patients with ST-segment–elevation myocardial infarction persisted, despite adjusting for initial electrocardiographic characteristics. Left ventricular hypertrophy by voltage criteria and absence of prehospital ECG are strongly positively correlated and ST elevation in lateral leads is negatively correlated with reperfusion delay. (*J Am Heart Assoc.* 2018;7:e007021. DOI: 10.1161/JAHA.117.007021.)

Key Words: ECG • reperfusion delay • sex differences • ST-segment–elevation myocardial infarction

Women with ST-segment–elevation myocardial infarction (STEMI) receive timely therapy to achieve coronary reperfusion less frequently and experience more delays than similarly aged men.^{1,2} This sex gap exists not only among older individuals but also in young patients with STEMI.³ Of every 5 young women who present with STEMI in the United States, 2 exceed the guideline-recommended coronary reperfusion time.³ This delay is particularly concerning in young

patients, for whom survival advantage of coronary reperfusion is lost much sooner than among elderly patients.⁴ Higher premature mortality after myocardial infarction in women translates into more potential years of life lost compared with men.⁵ As such, young women with STEMI constitute a particularly vulnerable population, triggering the need to understand reasons behind departure from clinical guidelines in administering timely reperfusion among them.

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Clinical Perspective

What Is New?

- There are significant sex differences in the initial electrocardiographic characteristics of young patients with ST-segment–elevation myocardial infarction.
- ST-segment elevation occurs in fewer leads and is of lower magnitude in women, whereas positive voltage criteria for left ventricular hypertrophy are noted more frequently in men.
- Young women with ST-segment–elevation myocardial infarction are more likely to experience reperfusion delay compared with men, despite adjusting for differences in sociodemographic, clinical, and initial electrocardiographic characteristics.
- Absence of prehospital ECG and positive voltage criteria for left ventricular hypertrophy on the initial ECG were strongly correlated with reperfusion delay, whereas ST-segment elevation in the lateral leads was an inverse predictor.

What Are the Clinical Implications?

- Emergency personnel should be sensitized to sex differences in electrocardiographic characteristics of young patients with ST-segment–elevation myocardial infarction to enable appropriate and timely diagnosis.
- There remains a need to maximize the use of prehospital ECG to facilitate timelier diagnosis and reperfusion.
- Strategies to minimize delays secondary to misdiagnosis in patients with positive voltage criteria for left ventricular hypertrophy should be implemented.
- These may include recording serial ECGs for evolutionary changes and comparing with prior ECGs, if available.
- There is a need to focus our attention on other system- and patient-level factors that may cause sex disparities in treatment delay.

Differences in the initial ECG may explain, at least in part, differences in the time to reperfusion among women and men. Prior literature has documented differences in electrocardiographic characteristics of healthy women and men.^{6–8} For example, the normal limits of ST-segment amplitude or J-point elevation have been shown to be lower in healthy women compared with men.⁸ A consensus document of the universal definition of myocardial infarction, published by the major international cardiology societies, has acknowledged these differences and proposed differential criteria for significant ischemia in women versus men with J-point elevation.⁹ Despite this, only a few studies have investigated sex-related differences in electrocardiographic characteristics in patients with STEMI.^{10–12} Although these studies were limited by size and scope, some, but not all, suggested that women have less pronounced electrocardiographic changes than men.

Accordingly, we used data from the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study, which was specifically designed to address questions about the care of young women with acute myocardial infarction (AMI) in a large geographically diverse patient sample. A prespecified question was whether there are important sex differences in electrocardiographic findings that affect care. Our objectives were to evaluate sex differences in electrocardiographic characteristics at presentation in young patients with STEMI. We also sought to determine whether these differences explain sex differences in timeliness of coronary reperfusion. This information may lay a foundation for future efforts to improve guidance about diagnostic criteria, improve timeliness of guideline-recommended care, and ultimately improve outcomes, for young women with STEMI.

Methods

Study Population

The data that support the findings of this study are available from the corresponding author on reasonable request. Funding for deidentification of protected health information in the study would also need to be provided. The VIRGO study is the largest prospective observational study of young and middle-aged women and men with AMI and was designed to examine sex differences in the presentation, treatment, and outcomes of young and middle-aged patients with AMI. Details on the study design and method have been previously reported.¹³ In brief, young and middle-aged patients with AMI were enrolled from 103 hospitals in the United States and 24 hospitals in Spain, between August 21, 2008 and January 5, 2012, using a 2:1 female/male enrollment ratio. Eligible patients were between 18 and 55 years old, met AMI criteria, and presented or transferred to an enrolling institution within the first 24 hours of hospital presentation. AMI criteria included the following: (1) an increase in cardiac biomarkers (troponin I or T or creatine kinase-muscle/brain) with at least 1 value >99th percentile of the upper reference limit within 24 hours of admission; and (2) supporting evidence of myocardial ischemia, including symptoms of ischemia, electrocardiographic changes indicative of new ischemia (ST-segment changes, left bundle branch block, or the development of pathological Q waves), or other evidence of myocardial necrosis on imaging. Patients who developed elevated cardiac markers as a complication of elective coronary revascularization were not eligible for inclusion to this study. Additional exclusion criteria included the inability to speak English or Spanish, to provide informed consent, or to be contacted for follow-up. A total of 3572 patients were enrolled in the VIRGO study from the United States, Spain,

and Australia. Of these patients, we included 3501 (2349 women and 1152 men) in our analyses from the United States and Spain. We restricted our analyses to the 1359 patients presenting with STEMI (1132 from the United States and 227 from Spain). The most common cause for exclusion was refusing informed consent. Enrolled and nonenrolled patients had similar demographic characteristics. Data about reperfusion times were missing for 58 women and 30 men. These patients were excluded from analyses pertaining to treatment delay, for which the final sample included 1271 patients. Institutional review board approval was obtained at each participating center, and all patients provided written informed consent to participate.

Data Collection and Variables

Information on patient demographics, socioeconomic status, healthcare access, psychosocial risk factors, and symptoms was self-reported by the patient. Data on medical history, comorbidities, time to presentation, and clinical presentation were largely derived from the medical chart; however, in some cases, information from both the medical chart and patient interviews was combined to ensure variable completeness. Trained personnel conducted interviews and reviewed medical charts during the index AMI admission for the following: (1) sociodemographic factors, including age (categorized as 18–40 and 40–55 years), self-identified race (black, white, or other), Hispanic origin, socioeconomic status, and marital status; and (2) medical history, including prior coronary disease (AMI, percutaneous coronary intervention [PCI], or coronary artery bypass graft), presenting symptoms (typical/atypical chest pain and no symptoms), cardiac risk factors (diabetes mellitus, hypertension, dyslipidemia, obesity [body mass index ≥ 30 kg/m²], and smoking status), hemodynamic instability (ventricular tachycardia/fibrillation and blood pressure < 90 mm Hg), and the absence of a prehospital ECG. The timings of first hospital arrival, the qualifying ECG that prompted cardiac catheterization laboratory activation in either the emergency department or the field, and primary PCI balloon inflation or initiation of fibrinolytic therapy were recorded. We defined eligibility for reperfusion as ≥ 30 minutes of chest pain within 12 hours of presentation and ST-segment elevation > 1 mm in ≥ 2 consecutive leads or left bundle branch block that was new or of unknown duration. We defined treatment delay as door-to-needle time > 30 minutes for patients receiving fibrinolysis, door-to-balloon time > 90 minutes for in-house management of patients who received primary PCI, and door-to-balloon time > 120 minutes for patients who were transferred for primary PCI. An expert team of reviewers affiliated with the Yale Coordinating Center independently adjudicated electrocardiographic findings.

Electrocardiographic Analyses

The admission ECG for each patient was reviewed at a core laboratory, which included 4 researchers (J.A.B., A.P., J.G.A., and R.M.L.). The reviewers were blinded to patient sex or therapy. Reliability of electrocardiographic reading was tested in 100 randomly selected electrocardiographic tracings. Before starting electrocardiographic reading, intraobserver (1 reader [J.A.B.]) and interobserver (among the 4 readers of the core laboratory) variability was assessed in 100 randomly selected tracings for the following variables: abnormal Q waves, ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads (≥ 0.15 mV for V2–V3), ST-segment depression ≥ 0.05 mV in ≥ 2 contiguous leads, and negative T waves. Agreement between pairs of observations and the κ index was used as measures of variability. During the reading period, borderline and doubtful cases (ranging from selection of the index tracing when different tracings of the same patient were provided, to diagnosis of QRS fragmentation, hemiblocks, and abnormal Q waves) were discussed with 1 of the core laboratory members (J.B.) and an agreement was reached. Intraobserver agreement for 4 major electrocardiographic findings (abnormal Q waves, ST elevation, ST depression, and T-wave inversion) ranged between 96% and 99% (κ index, 0.89–0.98), and mean interobserver agreement for the same variables ranged between 87% and 90% (mean κ index, 0.61–0.80). We measured the magnitude of ST-segment elevation or depression in each lead to the nearest 0.5 mm from a scanned copy of the initial ECG. We defined Q waves as pathological when they had a duration of ≥ 30 ms in ≥ 2 contiguous leads or in the presence of an R wave of ≥ 40 ms in lead V1 and an R>S amplitude in lead V2.¹⁴ The presence of possible confounding factors, such as bundle branch block, ventricular hypertrophy, or poor ECG quality, was noted. We analyzed the following initial electrocardiographic variables: cardiac rhythm, heart rate, PR, QRS, and corrected QT interval duration, left ventricular hypertrophy (LVH) by Sokolow-Lyon criteria, pathological Q waves, number of leads with ST-segment elevation or depression, total elevation of the ST segment, total depression of the ST segment (in both cases, the summation in millimeters in all the leads affected), and negative T waves. ST-segment elevation was measured 0.02 seconds after the J point, and ST depression was measured 0.08 seconds after the J point, in the affected leads in comparison to the T-P segment. The infarction was considered to be anterior (leads V1–V4), inferior (II, III, and aVF), or lateral (leads I, aVL, and/or V5 and V6). Negative T waves were defined as symmetric T waves of ≥ 0.25 -mV amplitude in ≥ 2 contiguous leads with a prominent R or with R>S amplitude. In cases in which the electrocardiographic findings were complex or ambiguous, the primary reader included any comments or questions in a spreadsheet that

was reviewed by other core laboratory members to reach an agreement.

Statistical Analyses

We compared electrocardiographic characteristic variables between women and men, overall and by country, using χ^2 tests for categorical variables and Wilcoxon rank sum test for continuous variables. Categorical variables are presented as percentages in each category, and continuous variables are presented as medians. In addition, we compared electrocardiographic characteristics for each sex by reperfusion delay.

We developed a multivariable logistic regression model to assess the relationship between electrocardiographic characteristics at presentation and treatment delay. Presence of left or right bundle branch block and atrial fibrillation was missing for >25% of patients in our study, so those variables were excluded from the multivariable analysis. Our model included sex, sociodemographic characteristics (age, race, marital status, health insurance, and education level), prior cerebrovascular disease (stroke or transient ischemic attack) or heart disease (AMI, coronary artery bypass graft, or PCI), and presence of cardiovascular risk factors (diabetes mellitus, obesity, hypertension, hypercholesterolemia, and smoking). It also included additional clinical factors that have been previously identified as potential reasons for variation in time to reperfusion as covariates: the presence of atypical symptoms, presentation >6 hours of symptom onset, heart failure at presentation, and the absence of prehospital ECG. To account for differences in the baseline characteristics of patients from the United States and Spain, we performed sensitivity analyses and repeated the multivariable model assessing the relationship of electrocardiographic variables with reperfusion delay for US patients only. Given the exploratory nature of this study, no correction was applied for multiple testing. We rejected the null hypothesis for $P<0.05$. All analyses were performed in SAS, version 9.4 (SAS Institute, Cary, NC) by 1 of us (K.S.).

Results

Patient Characteristics

The baseline characteristics of all patients, stratified by sex and country, are in Table 1. The differences in baseline characteristics of the first ECG by sex and country are in Table 2. Overall, both young women and men did not have different heart rates and PR intervals. Young women had significantly shorter QRS intervals (87 versus 92 ms; $P=0.0001$) but longer corrected QT intervals (445 versus 425 ms; $P=0.0001$). Presence of LVH by voltage criteria was much more common in young men compared with women (3.7% versus 1.4%; $P=0.008$). Although the frequency of anterior and lateral pathological Q waves was

not significantly different between sexes, inferior Q waves were observed less frequently in women (17.1% versus 24.6%; $P<0.01$). The location of ST-segment elevation was not significantly different across all precordial and limb leads by sex. Women had ST-segment elevation in fewer leads compared with men (3 versus 4 leads; $P<0.01$). The extent of ST-segment elevation was significantly lower among women ($P<0.01$), with 1.6% of women having ≥ 6 -mm elevation compared with 6.1% of men; and 67% of women having ≤ 2 -mm elevation compared with 59.8% of men. The magnitude of ST-segment depressions was not significantly different across the precordial and limb leads between sexes. Women had higher frequency of T-wave inversions in the anterior leads (9.3% versus 5.6%; $P=0.01$).

Electrocardiographic Characteristics by Treatment Delay and Sex

Of 1271 patients with STEMI eligible to undergo coronary reperfusion, 485 had reperfusion delay (42.4% of women and 31.5% of men). We examined the differences in electrocardiographic characteristics by sex and treatment delay status (Table 3). In univariate analyses, young women who exceeded reperfusion times were more likely to have longer corrected QT intervals and less likely to have presented with ST-segment elevation in lateral and inferior leads and ST-segment depression in anterior and lateral leads than those who received timely reperfusion. Similarly, young men who experienced delay in reperfusion were more likely to have presented with ST-segment elevation ≤ 2 mm and T-wave inversions in lateral leads; and less likely to have presented with ST-segment elevation in anterior and lateral leads than those received timely reperfusion.

Electrocardiographic Predictors of Treatment Delay

In multivariable analyses (Table 4), female sex persisted as an independent predictor of treatment delay, despite adjusting for all the electrocardiographic variables (odds ratio [OR], 1.57; 95% confidence interval [CI], 1.15–2.15), in addition to the sociodemographic and clinical variables. LVH (OR, 2.84; 95% CI, 1.06–7.64) was a predictor of reperfusion delay, whereas ST-segment elevation in lateral leads (OR, 0.57; 95% CI, 0.41–0.78) emerged as an inverse predictor. Absence of prehospital ECG (OR, 1.64; 95% CI, 1.24–2.16) was also significantly associated with exceeding guideline-recommended reperfusion times. The effect sizes of most of the variables were comparable in sensitivity analyses including the US patients only. LVH was not a statistically significant predictor (OR, 2.57; 95% CI, 0.93–7.12), but the effect size was comparable.

Table 1. Baseline Characteristics of All Patients With STEMI in the United States and Spain by Sex

Characteristics	Overall			United States		Spain	
	Women (N=834)	Men (N=525)	P Value	Women (n=686)	Men (n=446)	Women (n=148)	Men (n=79)
Age range, y	20–55	25–55		23–55	26–55	20–55	25–55
Age, median (IQR), y	48 (44–52)	48 (44–51)	0.57	48 (44–52)	48 (44–52)	47 (42–51)	47 (42–50)
Race/ethnicity			0.002				
White	81.6	85.5		79.2	84.1	92.6	93.6
Black	13.9	8.0		16.4	8.7	2.7	3.9
Other	4.5	6.5		4.4	7.2	4.7	2.5
Hispanic	5.6	7.8	0.10	5.4	8.3	6.2	5.1
Married	51.0	55.9	0.08	49.0	55.5	60.5	58.4
Education			0.001				
Less than high school	6.7	2.3		1.0	1.4	34.8	8.3
Some high school	41.0	43.7		41.8	42.2	37.0	52.8
More than high school	52.3	54.0		57.2	56.4	28.2	38.9
Work full- or part-time	59.4	75.9	<0.001	60.0	75.1	56.6	80.5
Health insurance	81.1	78.5	0.24	77.5	75.1	98.0	98.7
Medical history							
Previous MI, PCI, or CABG	14.8	17.0	0.28	16.8	19.5	5.4	2.5
Angina	22.9	20.4	0.28	22.5	20.9	25.0	17.7
Congestive heart failure	1.8	0.8	0.11	2.2	0.9	0	0
Hypertension	58.2	58.9	0.80	61.8	61.7	41.2	43.0
Diabetes mellitus	29.1	15.1	<0.001	31.3	15.9	18.9	10.1
Hypercholesterolemia	61.3	68.0	0.01	63.3	69.1	52.0	62.0
Smoked within past 30 d	70.4	62.1	0.001	67.9	60.3	81.8	72.2
Smoking history			<0.010				
Never smoked	21.2	24.2		24.2	27.3	7.4	6.3
Ever smoked	11.9	19.1		11.4	18.4	14.2	22.8
Current smoker	66.9	56.8		64.4	54.3	78.4	70.9
Obesity (BMI \geq 30 kg/m ²)	48.3	41.9	0.02	54.2	44.8	20.4	25.3
Previous stroke/TIA	3.1	1.9	0.18	3.4	2.2	2.0	0
Renal dysfunction	8.7	7.9	0.61	9.5	8.6	4.7	3.9
Chronic lung disease	9.5	4.2	<0.001	10.8	4.9	3.4	0
Family history of CVD	74.2	71.2	0.03	75.7	74.7	67.6	51.9
Clinical characteristics at presentation							
Hemodynamic instability	13.8	11.8	0.29	12.1	11.4	21.6	13.9
Presented within 6 h of symptom onset	30.3	21.6	<0.001	32.0	22.5	22.3	16.5
Patient reported atypical symptoms	11.3	7.3	0.01	11.4	7.9	10.8	3.8
Ejection fraction <40%	13.8	14.2	0.84	14.0	14.8	12.8	10.4

Data are given as percentages unless otherwise indicated. BMI indicates body mass index; CABG, coronary artery bypass graft; CVD, cardiovascular disease; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; and TIA, transient ischemic attack.

Discussion

Using this prospective cohort study, we describe key findings related to sex differences in the presenting ECG and

timeliness of reperfusion in young patients with STEMI. First, we found several sex-related differences in the initial ECG in this population. For example, women had ST-segment elevation of lesser magnitude and in fewer leads compared with

Table 2. Baseline Electrocardiographic Characteristics of Young Patients With STEMI by Sex and Country

Electrocardiographic Characteristics	Overall (N=1359)		United States Only (n=1132)		Spain Only (n=227)	
	Women (N=834)	Men (N=525)	Women (n=686)	Men (n=446)	Women (n=148)	Men (n=79)
Heart rate, per min						
Median	76	75	77	75	72	75
IQR	65 to 88	64 to 86.5	66 to 89	64 to 86	60 to 84	60 to 87
QRS duration, ms						
Median	87	92	88	94	82	90
IQR	80 to 94	86 to 100	80 to 96	88 to 100	80 to 90	80 to 100
QTc duration, ms						
Median	445.1	425.4	450.5	427.4	422.7	416.3
IQR	421.3 to 471.4	407.0 to 449.6	427.9 to 475.7	408.2 to 452.9	395.8 to 445.6	395.1 to 434.5
PR interval, ms						
Median	152	156	152	156	156	156
IQR	140 to 170	142 to 170	140 to 170	142 to 170	136 to 170	140 to 170
Voltage (SV1+RV5), mm						
Median	13	15	15	15	11	16
IQR	11 to 19	11 to 20	11 to 19	11 to 20	11 to 15	7 to 21
LV hypertrophy, %	1.4	3.7	1.4	4.1	1.4	1.4
Atrial fibrillation, %	1.0	1.9	1.2	2.2	0	0
LBBB, %	0.7	0.4	0.6	0.2	1.4	1.3
RBBB, %	1.1	1.9	0.9	2.2	2.0	0
Pathologic Q wave, %						
V1-4 (anterior)	22.1	18.8	20.9	16.9	27.6	29.9
V5-6, I, and aVL (lateral)	7.5	7.7	7.8	6.3	6.3	15.6
II, III, and aVF (inferior)	17.1	24.6	16.5	24.1	19.9	27.3
ST-segment elevation, %						
V1-4 (anterior)	50.7	53.0	50.2	52.7	53.4	54.4
V5-6, I, and aVL (lateral)	46.2	45.5	45.3	45.3	50.0	46.8
II, III, and aVF (inferior)	58.3	60.0	59.5	61.7	52.7	50.6

Continued

Table 2. Continued

Electrocardiographic Characteristics	Overall (N=1359)		United States Only (n=1132)		Spain Only (n=227)	
	Women (N=834)	Men (N=525)	Women (n=686)	Men (n=446)	Women (n=148)	Men (n=79)
Extent of maximum ST-segment elevation, %						
≤2 mm	67.8	59.8	70.1	61.0	56.8	53.2
2–5 mm	30.7	34.1	28.3	33.2	41.9	39.2
≥6 mm	1.6	6.1	1.6	5.8	1.4	7.6
No. of leads with ST-segment elevation, median (IQR)	3 (2 to 5)	4 (2 to 5)	3 (2 to 5)	3 (2 to 5)	4 (2 to 5)	4 (2 to 5)
ST-segment depression, %						
V1–4 (anterior)	46.3	42.9	45.8	43.1	48.7	41.8
V5–6, I, and aVL (lateral)	60.0	63.8	59.0	63.5	64.2	65.8
II, III, and aVF (inferior)	23.3	24.0	21.6	22.0	31.1	35.4
Extent of maximum ST-segment depression, median (IQR)	0.0 (–0.5 to 0.0)	0.0 (–0.8 to 0.0)	0.0 (–0.5 to 0.0)	0.0 (–1.0 to 0.0)	0.0 (–0.8 to 0.0)	0.0 (–0.5 to 0.0)
No. of leads with ST depression, median (IQR)	–1.0 (–1.5 to –0.5)	–1.0 (–2.0 to –0.5)	–1.0 (–1.5 to –0.5)	–1.0 (–2.0 to –0.5)	–1.0 (–2.0 to –0.5)	–1.0 (–2.0 to –0.5)
T-wave inversion, %						
Anterior	9.3	5.6	10.1	6.1	5.5	2.6
Lateral	7.0	5.0	8.2	5.6	1.4	1.3
Inferior	4.5	4.0	5.0	4.7	2.1	0

IQR indicates interquartile range; LBBB, left bundle branch block; LV, left ventricular; QTc, corrected QT; RBBB, right bundle branch block; and STEMI, ST-segment-elevation myocardial infarction.

Table 3. Baseline Electrocardiographic Characteristics of Young Patients With STEMI by Sex and Treatment Delay Status

Electrocardiographic Characteristics	Women (N=776)			Men (N=495)		
	Treatment Delay (n=329)	No Treatment Delay (n=447)	P Value	Treatment Delay (n=156)	No Treatment Delay (n=339)	P Value
Heart rate, per min						
Median	78	74	0.001	77	75	0.17
IQR	67–92	65–86		65–88	63–86	
QRS interval, ms						
Median	88	86	0.25	92	94	0.78
IQR	80–94	80–94		86–100	86–100	
QTc interval, ms						
Median	450.7	444.7	0.03	427.5	425.8	0.31
IQR	425.1–477.8	421.2–466.8		409.6–456.4	407.5–448.9	
PR interval, ms						
Median	152	154	0.05	153	156	0.63
IQR	136–168	140–174		142–170	142–170	
Voltage (SV1+RV5), mm						
Median	14	13	0.99	20	12	0.11
IQR	11–19	10–22		17–21	10–18	
LV hypertrophy, %	1.7	1.0	0.40	6.2	2.9	0.08
Atrial fibrillation, %	1.2	0.9	0.66	2.6	1.8	0.56
LBBB, %	0.9	0.5	0.42	0.7	0	0.31
RBBB, %	1.8	0.7	0.14	2.6	1.8	0.55
Pathologic Q wave, %						
V1–4 (anterior)	21.2	22.2	0.73	13.5	20.7	0.06
V5–6, I, and aVL (lateral)	9.0	6.8	0.27	5.8	8.0	0.38
II, III, and aVF (inferior)	18.5	16.3	0.43	22.4	25.4	0.47
ST-segment elevation, %						
V1–4 (anterior)	55.0	47.9	0.05	45.5	56.2	0.03
V5–6, I, and aVL (lateral)	40.4	51.0	0.004	34.6	50.0	0.001
II, III, and aVF (inferior)	53.2	62.4	0.01	57.1	61.2	0.38
Extent of maximum ST-segment elevation, %			0.10			0.01
≤2 mm	73.0	65.8		69.9	55.8	
2–6 mm	25.5	32.7		25.0	37.4	
≥6 mm	1.5	1.5		5.1	6.8	
ST-segment depression, %						
V1–4 (anterior)	39.5	51.2	0.001	39.1	44.1	0.29
V5–6, I, and aVL (lateral)	54.7	63.3	0.02	60.3	64.4	0.37
II, III, and aVF (inferior)	24.0	22.6	0.64	18.0	24.7	0.09
T-wave inversion, %						
V1–4 (anterior)	9.2	9.5	0.88	7.1	5.0	0.35
V5–6, I, and aVL (lateral)	7.6	7.0	0.75	8.4	3.5	0.02
II, III, and aVF (inferior)	6.1	3.4	0.07	5.2	3.8	0.50

IQR indicates interquartile range; LBBB, left bundle branch block; LV, left ventricular; QTc, correct QT; RBBB, right bundle branch block; and STEMI, ST-segment–elevation myocardial infarction.

Table 4. Multivariable Analyses for Effect of Electrocardiographic Characteristics on Treatment Delay in Young Patients With STEMI

Variable	OR	95% CI
Female sex*	1.57	1.14–2.15
Heart rate	1.01	1.00–1.02
QRS interval	1.01	0.99–1.02
PR interval	1.00	0.99–1.00
LV hypertrophy*	2.84	1.06–7.64
Pathologic Q wave		
V1–4 (anterior)	0.67	0.44–1.02
V5–6, I, and aVL (lateral)	1.20	0.68–2.12
II, III, and aVF (inferior)	0.99	0.68–1.43
ST-segment elevation		
V1–4 (anterior)	1.42	0.97–2.08
V5–6, I, and aVL (lateral)	0.53	0.38–0.74
II, III, and aVF (inferior)	0.80	0.50–1.28
Extent of maximum ST-segment elevation groups		
≤2 mm	1.18	0.47–2.99
2–6 mm	0.95	0.38–2.39
≥6 mm
ST-segment depression groups		
V1–4 (anterior)	1.06	0.73–1.54
V5–6, I, and aVL (lateral)	0.78	0.53–1.16
II, III, and aVF (inferior)	0.88	0.55–1.40
T-wave inversion		
V1–4 (anterior)	0.86	0.49–1.50
V5–6, I, and aVL (lateral)	1.03	0.56–1.91
II, III, and aVF (inferior)	1.34	0.68–2.65
No prehospital ECG*	1.74	1.31–2.32

Multivariable logistic regression model to assess the relationship between electrocardiographic characteristics at presentation and treatment delay adjusted for sex. This model was also adjusted for sociodemographic characteristics (age, race, marital status, health insurance, and education level), prior cerebrovascular disease (stroke or transient ischemic attack) or heart disease (acute myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention), presence of cardiovascular risk factors (diabetes mellitus, obesity, hypertension, hypercholesterolemia, and smoking), presence of atypical symptoms, presentation >6 hours of symptom onset, and heart failure at presentation. CI indicates confidence interval; LV, left ventricular; OR, odds ratio; and STEMI, ST-segment–elevation myocardial infarction.

* $P < 0.05$.

young men with STEMI, and LVH was found more frequently in young men with STEMI compared with young women. Second, female sex persisted as an independent predictor of coronary reperfusion delay, despite adjusting for electrocardiographic variables in addition to other sociodemographic and clinical variables. Third, patients with positive voltage criteria for LVH were more likely, and those with ST-segment elevation in the

lateral leads were less likely to experience reperfusion delay. Finally, young patients without a prehospital ECG were much more likely to exceed reperfusion time guidelines compared with those who received an ECG before presentation.

This is one of the largest geographically diverse studies describing sex differences in electrocardiographic characteristics among patients with STEMI. We found that the extent of ST-segment elevations was significantly lower in women compared with men. This is consistent with a study that demonstrated that female sex is an inverse and independent predictor of marked ST-segment elevation in patients with STEMI.¹² Prior studies have also postulated that lower magnitude of ST-segment elevation in women could account for less frequent use of reperfusion therapies in these patients.^{12,15} We found that men with ST-segment elevation ≤ 2 mm exceeded the recommended time guidelines for PCI in bivariate analyses. A similar trend was noted among women, although it did not reach statistical significance. In our multivariate analyses, however, the extent of ST-segment elevation did not predict a delay in reperfusion.

One of our key findings is that sex differences in the presenting ECG do not significantly account for sex disparities in timeliness of coronary reperfusion. We have previously shown that female sex is an independent predictor of treatment delay in this population.³ Women had 1.72 times the odds (95% CI, 1.28–2.33) of exceeding reperfusion goals after adjusting for sociodemographic and clinical variables and transfer status in that study. In addition to these variables, adjusting for electrocardiographic variables at presentation in our current study appeared to only slightly attenuate the association, with women having 1.57 times the odds (95% CI, 1.15–2.15) of treatment delays in comparison with men in the full model and 1.77 times the odds (95% CI, 1.26–2.48) in the sensitivity analyses including patients from the United States only. This indicates the need to further investigate and act on other possible reasons behind departure from clinical guidelines for timely reperfusion in this vulnerable population. Some of these reasons include the need to create systems to mitigate delayed identification of worsening symptoms in patients with history of angina and delayed presentation to the hospital, both of which were significant predictors of reperfusion delay in our study.

We noted that young patients with STEMI had 1.74 times the odds of experiencing treatment delay if they did not receive a prehospital ECG compared with those who did. These results are consistent with results of various studies that have demonstrated that patients who receive a prehospital ECG receive reperfusion therapy faster than those with no prehospital ECG.^{16,17} The American Heart Association classifies a prehospital ECG as a class 1 recommendation for the diagnosis of patients with STEMI.¹⁸ In our study, $\approx 40\%$ of the patients with STEMI received an ECG before arrival to the

hospital. Data from the National Registry of Myocardial Infarction-4 for patients with STEMI had estimated the frequency of use of prehospital ECG at \approx 4.5% to 8% from 2000 to 2002.¹⁹ Our data reveal that the frequency of use of prehospital ECG has increased substantially in recent years, but there remains a need to maximize the use of this strategy that has the potential to reduce time to reperfusion.

In our multivariable analyses, we noted that patients who met electrocardiographic criteria for LVH had 2.84 times the odds of exceeding reperfusion times compared with those who did not. The effect size was comparable in our sensitivity analyses including only US patients, although not statistically significant. Presence of voltage criteria for LVH poses a challenge for accurate diagnosis of STEMI. In fact, in 1 study that evaluated effects of electrocardiographic characteristics on accuracy of interpretation for STEMI, the presence of voltage criteria for LVH led to a 64% reduction in odds of an accurate interpretation.²⁰ This likely leads to delayed diagnosis and treatment. Some ways of increasing the specificity of STEMI diagnosis in this setting include comparing the ECG in question with a tracing obtained sometime before the short-term event and recording serial ECGs in search of evolutionary changes. We also found that patients with ST-segment elevation in the lateral leads were 43% less likely to exceed reperfusion times. The reason for this is unclear and may need to be investigated in further studies.

Our study has several limitations. First, patients may have had several serial ECGs performed at presentation that may have led to discordance in the ECG used for our analyses and the one used for actual clinical decision making. For our analyses, we used either the first ECG or a subsequent ECG if it had more prominent ST-segment changes. We collected our data from chart extraction. We worked closely with each site coordinator to maintain the completeness and quality of each submission. Moreover, we used the universal definition for STEMI per the 2000 American Heart Association/American College of Cardiology guidelines that were current at the time of designing the study.²¹ The definition for STEMI has evolved during the past decade, with 2 different iterations.^{9,22} We anticipate that these differences are minor and may not impact the overall results of the article. In addition, reperfusion delay may have occurred as a result of other factors, including system-level delays, physician bias, or other patient-related factors. We did not perform qualitative interviews with the emergency personnel or other staff and cannot identify specific processes that may have contributed to the delay. Last, we did not collect information about presence or absence of strain pattern in patients with LVH, and this could potentially have confounded the interpretation of ST-segment and T-wave changes. However, only 3.7% of young women and 1.4% of young men had LVH by Sokolow-Lyon criterion, which is most strongly associated with strain pattern.

In conclusion, although there were significant sex differences in the presenting ECG between young women and men with STEMI, these differences only partially accounted for the sex disparities in timeliness of coronary reperfusion, triggering the need to focus our attention on other system- and patient-level factors that may cause sex disparities in treatment delay. Presence of voltage criteria for LVH and absence of prehospital ECG were strongly correlated with reperfusion delay, whereas presence of ST-segment elevations in lateral leads was a significant inverse predictor of reperfusion delay.

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References

- Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells O, Bozkurt B, LaBresh KA, Liang L. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118:2803–2810.
- Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med*. 2005;353:671–682.
- D'Onofrio G, Safdar B, Lichtman JH, Strait KM, Dreyer RP, Geda M, Spertus JA, Krumholz HM. Sex differences in reperfusion in young patients with ST-segment elevation myocardial infarction: results from the VIRGO study. *Circulation*. 2015;131:1324–1332.
- Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, Cutlip DE, Bates ER, Frederick PD, Miller DP. Hospital delays in reperfusion for ST-segment elevation myocardial infarction implications when selecting a reperfusion strategy. *Circulation*. 2006;114:2019–2025.
- Peeters A, Mamun A, Willekens F, Bonneux L. A cardiovascular life history. *Eur Heart J*. 2002;23:458–466.
- Simonson E, Blackburn H, Puchner TC, Eisenberg P, Ribiero F, Meja M. Sex differences in the electrocardiogram. *Circulation*. 1960;22:598–601.
- Macfarlane P, McLaughlin S, Devine B, Yang T. Effects of age, sex, and race on ECG interval measurements. *J Electrocardiol*. 1994;27:14–19.
- Macfarlane PW. Age, sex, and the ST amplitude in health and disease. *J Electrocardiol*. 2001;34:235–241.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.
- Dellborg M, Herlitz J, Emanuelsson H, Swedberg K. ECG changes during myocardial ischemia: differences between men and women. *J Electrocardiol*. 1994;27:42–45.
- Raitt MH, Litwin PF, Martin JS, Weaver WD. ECG findings in acute myocardial infarction: are there sex-related differences? *J Electrocardiol*. 1995;28:13–16.
- Galcerá-Tomás J, Melgarejo-Moreno A, Alonso-Fernández N, Padilla-Serrano A, Martínez-Hernández J, Gil-Sánchez FJ, del Rey-Carrión A, de Gea JH, Rodríguez-García P, Martínez-Baño D. Female sex is inversely and independently associated with marked ST-segment elevation: a study in patients with ST-segment elevation acute myocardial infarction and early admission. *Rev Esp Cardiol*. 2009;62:23–30.
- Lichtman JH, Lorenze NP, D'Onofrio G, Spertus JA, Lindau ST, Morgan TM, Herrin J, Bueno H, Mattera JA, Ridker PM. Variation in recovery role of gender on outcomes of young AMI patients (VIRGO) study design. *Circ Cardiovasc Qual Outcomes*. 2010;3:684–693.
- Barrabés JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Q-wave evolution of a first acute myocardial infarction without significant ST segment elevation. *Int J Cardiol*. 2001;77:55–62.
- Krumholz HM, Murillo JE, Chen J, Vaccarino V, Radford MJ, Ellerbeck EF, Wang Y. Thrombolytic therapy for eligible elderly patients with acute myocardial infarction. *JAMA*. 1997;277:1683–1688.
- Afolabi BA, Novaro GM, Pinski SL, Fromkin KR, Bush HS. Use of the prehospital ECG improves door-to-balloon times in ST segment elevation myocardial infarction irrespective of time of day or day of week. *Emerg Med J*. 2007;24:588–591.
- Canto JG, Rogers WJ, Bowlby LJ, French WJ, Pearce DJ, Weaver WD; National Registry of Myocardial Infarction 2 Investigators. The prehospital electrocardiogram in acute myocardial infarction: is its full potential being realized? *J Am Coll Cardiol*. 1997;29:498–505.
- The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: the era of reperfusion: section 1: acute coronary syndromes (acute myocardial infarction). *Circulation* 2000;102(Suppl):I172–I203.
- Curtis JP, Portnay EL, Wang Y, McNamara RL, Herrin J, Bradley EH, Magid DJ, Blaney ME, Canto JG, Krumholz HM. The pre-hospital electrocardiogram and time to reperfusion in patients with acute myocardial infarction, 2000–2002: findings from the National Registry of Myocardial Infarction-4. *J Am Coll Cardiol*. 2006;47:1544–1552.
- McCabe JM, Armstrong EJ, Ku I, Kulkarni A, Hoffmayer KS, Bhawe PD, Waldo SW, Hsue P, Stein JC, Marcus GM. Physician accuracy in interpreting potential ST-segment elevation myocardial infarction electrocardiograms. *J Am Heart Assoc*. 2013;2:e000268. DOI: 10.1161/JAHA.113.000268.
- Antman E, Bassand J-P, Klein W, Ohman M, Sendon JLL, Rydén L, Simoons M, Tendera M. Myocardial infarction redefined: a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959–969.
- Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50:2173–2195.

Sex Differences in Timeliness of Reperfusion in Young Patients With ST–Segment–Elevation Myocardial Infarction by Initial Electrocardiographic Characteristics

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