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Ischemic Time is a Better Predictor Than Door-to-Balloon Time for Mortality and Infarct Size in ST-Elevation Myocardial Infarction

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Background: Current guidelines for ST-elevation myocardial infarction (STEMI) recommend early revascularization with optimal ischemic time (IT) < 120 min and door-to-balloon (D2B) time < 90 min. The focus of most studies has been D2B time, while IT is not frequently reported. We tested the hypothesis that total IT is a better predictor than D2B time for mortality and infarct size. Methods and Results: Between December 2008 and April 2013, 786 patients with STEMI were treated in our STEMI center, and 262 of these had cardiac magnetic resonance imaging 3–5 days after the index event. Total IT was defined as time from symptom onset to device activation, while D2B time was defined as hospital arrival to device activation. Patients were divided into three groups according to IT (<120, 120–239, ≥240 min) and into four groups according to D2B time (<30, 30–59, 60–89, ≥90 min). Baseline demographics including age, cardiac risk factors, and LAD infarct location were similar between groups. The 30-day mortality rate significantly increased across IT groups but did not correlate with D2B time groups. Similarly, infarct size significantly increased across IT groups but did not correlate with D2B time groups. Conclusions: In STEMI patients, IT was a better predictor than D2B time for 30-day mortality and infarct size. Our findings suggest that the focus of STEMI care should be directed at early initiation of therapy and minimizing IT rather than on D2B time alone. The potential impact of IT reporting in current STEMI registries merits further consideration.

Key words: angioplasty; myocardial infarction; revascularizations; magnetic resonance imaging

INTRODUCTION

Despite marked improvements in hospital treatment protocols with subsequent decline in hospital mortality, the median duration of pre-hospital delay for STEMI patients in the United States is still longer than proposed in guidelines, and this time interval remained unchanged from 1986 to 2005 [1,2]. While many different factors play a role in this time delay, reduction of infarct size, left ventricular dysfunction, and overall mortality following prompt restoration of coronary perfusion is well established. Delays lead to larger infarct size and increased cardiac morbidity and mortality [3–5]. Treatment guidelines have mainly focused on reducing door-to-balloon (D2B) time while often neglecting the pre-hospital time interval between symptom onset and hospital arrival [6]. As a result of national efforts to decrease D2B times, median D2B time decreased from 96 min in 2005 to 64 min in 2010 [7]. Yet despite this gratifying reduction, in-hospital mortality rates for STEMI patients undergoing primary percutaneous coronary intervention (PPCI) have not changed [8]. While shorter patient-specific D2B times were associated at the individual level with lower in-hospital and 6-month mortalities, risk-adjusted in-hospital and 6-month mortalities at the

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population level, independent of patient-specific D2B times, have risen in patients undergoing primary PCI (PPCI) [9].

Cardiac magnetic resonance (CMR) imaging with delayed gadolinium enhancement (DEcMRI) has gained acceptance as a reliable and reproducible imaging technique for identifying the location and extent of infarction [10–13]. Prolonged myocardial ischemia causes simultaneous necrosis of myocytes and capillaries, leading to capillaries becoming occluded by dying blood cells and debris, a phenomenon known as microvascular obstruction (MVO). DEcMRI permits in vivo visualization of MVO [14]. A proportional relationship between IT, transmural infarct size, and MVO has been reported [15,16]. The objective of this study was to examine whether IT is a better predictor than D2B time for 30-day mortality rate and DEcMRI measures of infarct size.

METHODS

Patients

From a prospectively maintained database, all patients with STEMI treated between December 2008 and April 2013 at Memorial Hermann Heart and Vascular Institute were included for this retrospective analysis. We excluded patients transferred from other hospitals, those with prior MI or prior coronary bypass surgery, those undergoing rescue PCI for failed thrombolysis, patients who did not undergo PCI for their STEMI, and patients with no 30-day follow up information available. We determined that this would yield a more uniform group of patients for analysis, especially for the CMR imaging. The 30-day post event data were gathered from outpatient clinic records and telephone contacts. Demographic, clinical, angiographic, and procedural data were tabulated, along with IT and D2B times. Patients were divided into three groups for IT analysis ($<$120, 120–239, $\geq$240 min) and into four groups for D2B analysis ($<$30, 30–59, 60–89, $\geq$90 min).

CMR Protocol

Although not specifically part of any protocol, CMR imaging after STEMI is common clinical practice in our institution. It is typically performed on patients at 3–5 days after STEMI. This is done using an MRI machine equipped with SQ-engine gradients (amplitude: 45 mT/m; slew rate: 200 mT/m/ms) and a 12-channel phased-array cardiac coil. After obtaining scout images, cine steady-state free precession (SSFP) CMR images were acquired from patients during short breath holds in the short-axis, two-chamber, and four-chamber planes; on short-axis images, the left ventricle was completely encompassed from the base to the apex, from which we acquired a total of 10–12 images. Cine SSFP images were obtained by use of the following parameters: repetition time (TR) 51.3 ms, echo time (TE) 1.21 ms, flip angle 80deg, 8-mm slice thickness, no interslice gap, matrix of 256 $\times$ 256, field of view ranging from 340 to 400 mm, and a voxel size of 1.7 $\times$ 1.7 $\times$ 8.0 mm. Short-axis [late gadolinium enhancement (LGE) images were obtained by use of a segmented inversion recovery technique and acquired 10–15 min after injection (Gadolinium-BOPTA, Multihance, Bracco, Milan, Italy; 0.1 mmol/kg body weight at 2 ml/s). Sequence parameters were the following: TR 700 ms, TE 4.33 ms, matrix 256 $\times$ 256, flip angle 30deg, slice thickness 8.0 mm, no interslice gap, and voxel size 1.7 $\times$ 1.4 $\times$ 8 mm.

Image Analysis

All CMR studies were analyzed off-line using a dedicated workstation . Left ventricular volume (LVV) was calculated from the short-axis SSFP cines. Infarct size (IS) and MVO were manually traced and calculated from the LGE short-axis images. Myocardial regions were considered infarcted if the signal intensity was $>$5 standard deviations above that of remote myocardium. The primary endpoint, myocardial scar index (%), was calculated as IS/LVV $\times$ 100%. The MVO was defined as a dark zone within the infarcted segments, usually located in the subendocardium. The secondary endpoint, MVO index (%), was calculated as MVO/LVV $\times$ 100%.

Statistical Analysis

Continuous variables are shown as averages with standard deviations, and were analyzed using the student's *t*-test. Categorical variables are shown as percentages and were analyzed with the chi-square test of Pearson. Differences were considered statistically significant at a P-value < 0.05.

RESULTS

Mortality Cohort Characteristics

Between December 2008 and April 2013, there were 928 STEMI patients treated. After exclusion criteria were applied, 786 patients remained and were included for analysis. Basic information by IT and D2B groups is shown in Tables I and II. Age, cardiac risk factors, glycoprotein IIb/IIIa inhibitor use, and left anterior descending artery (LAD) infarct rates were similar among the three IT groups as well as the four D2B groups. Rates of Killip class 4 increased

TABLE I. Mortality Cohort: Demographics and Baseline Values by IT

	Ischemic time (min)			
Variables	<120 ($n=111$)	120–239 ($n=423$)	≥240 ($n=252$)	*P*
Age, mean ± SD	55 ± 12	57 ± 11	56 ± 11	0.19
Male, *n* (%)	90 (81.0)	311 (73.5)	193 (76.5)	0.05
HLD, *n* (%)	51 (45.9)	219 (51.8)	120 (47.6)	0.41
Smoking, *n* (%)	77 (69.3)	268 (63.3)	176 (69.8)	0.17
IIb/IIIa use, *n* (%)	45 (40.5)	201 (47.5)	123 (48.8)	0.33
HTN, *n* (%)	73 (65.7)	271 (64.0)	171 (67.8)	0.60
DM, *n* (%)	20 (18.0)	92 (21.7)	53 (21.0)	0.69
Killip class 4, *n* (%)	1 (0.9)	21 (5.0)	18 (7.1)	0.04
LAD infarct, *n* (%)	71(64.0)	233 (55.0)	143(56.7)	0.24
30-day mortality, *n*(%)	3 (2.7)	24 (5.6)	36 (14.2)	0.001

IIb/IIIa = glycoprotein IIb/IIIa inhibitor; DM = diabetes mellitus; HLD = hyperlipidemia; HTN = hypertension; IT = ischemic time; LAD = left anterior descending coronary artery; SD = standard deviation.

TABLE II. Mortality Cohort: Demographics and Baseline Values by D2B Time

	Door to balloon time (min)				
Variables	<30 ($n=144$)	30–59 ($n=291$)	60–89 ($n=222$)	≥90 ($n=129$)	*P*
Age, mean ± SD	56 ± 12	57 ± 11	57 ± 12	55 ± 11	0.32
Male, *n* (%)	105 (72.9)	210 (72.2)	174 (78.4)	105 (81.4)	0.12
HLD, *n* (%)	63 (43.8)	150 (51.5)	105 (47.3)	72 (55.8)	0.18
Smoking, *n* (%)	99 (68.8)	192 (66.0)	140 (63.1)	90 (69.8)	0.54
IIb/IIIa use, *n* (%)	69 (47.9)	126 (43.3)	102 (45.9)	72 (55.8)	0.12
HTN, *n* (%)	93 (64.6)	179 (61.5)	150 (67.6)	93 (72.1)	0.17
DM, *n* (%)	30 (20.8)	57 (19.6)	57 (25.7)	21 (16.3)	0.17
Killip class 4, *n* (%)	6 (4.1)	12 (4.1)	12 (5.4)	10 (7.7)	0.43
LAD infarct, *n* (%)	81 (56.3)	168 (57.7)	132 (59.5)	66 (51.2)	0.49
30-day mortality, *n* (%)	9 (6.3)	21 (7.2)	21 (9.4)	12 (9.3)	0.34

Abbreviations as in Table I.

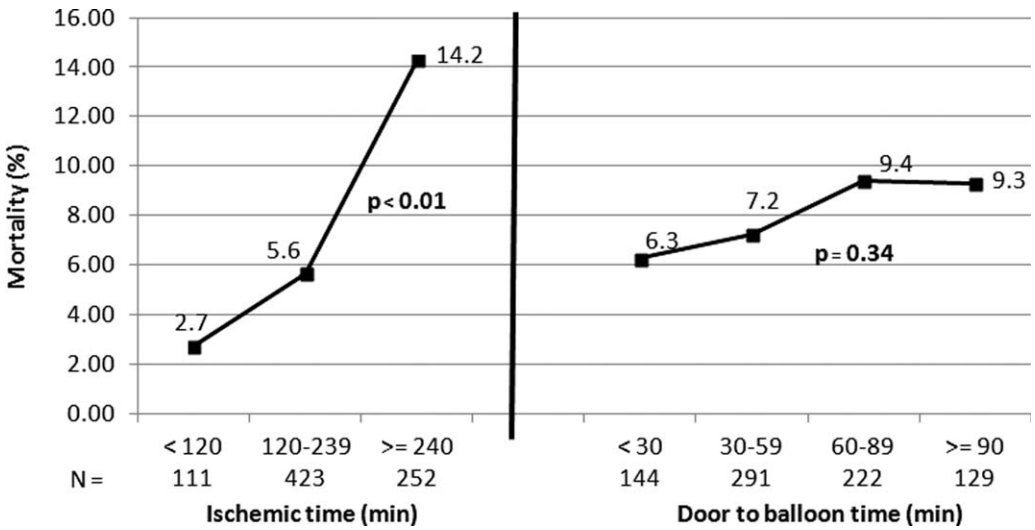

Fig. 1. 30-Day mortality rates by IT and by D2B time.

incrementally as IT increased from <120 min to 120–239 min to ≥240 min (0.9% vs. 5.0% vs. 7.1%, $P=0.04$), whereas rates of Killip class 4 were similar among D2B time groups ($P=0.43$).

Mortality Cohort Analysis (Fig. 1)

The overall 30-day mortality for the entire group of patients analyzed was 8.01% (63/786). The 30-day mortality rates significantly increased across IT groups.

TABLE III. CMR Cohort: Demographics and Baseline Values by IT

	Ischemic time (min)			
Variables	<120 ($n=37$)	120–239 ($n=141$)	≥240 ($n=84$)	*P*
Age, mean ± SD	55 ± 12	57 ± 11	56 ± 11	0.66
Male, *n* (%)	32 (86.5)	104 (73.8)	65 (77.4)	0.26
HLD, *n* (%)	17 (46.0)	73 (51.8)	40 (47.6)	0.74
Smoking, *n* (%)	21 (56.8)	79 (56.0)	50 (59.5)	0.88
IIb/IIIa use, *n* (%)	15 (40.5)	67 (47.5)	41 (48.8)	0.69
HTN, *n* (%)	22 (59.5)	88 (62.4)	55 (65.5)	0.80
DM, *n* (%)	5 (13.5)	30 (21.3)	17 (20.2)	0.57
Killip class 4, *n* (%)	0 (0)	3 (2.1)	3 (3.6)	0.62
LAD infarct, *n* (%)	25 (67.6)	77 (54.6)	47 (56.0)	0.36

Abbreviations as in Table I.

TABLE IV. CMR Cohort: Demographics and Baseline Values by D2B Time

	Door to balloon time (min)				
Variables	<30 ($n=48$)	30–59 ($n=97$)	60–89 ($n=74$)	≥90 ($n=43$)	*P*
Age, mean ± SD	56 ± 12	57 ± 11	57 ± 12	51 ± 11	0.03
Male, *n* (%)	35 (72.9)	70 (72.2)	58 (78.4)	38 (88.4)	0.18
HLD, *n* (%)	21 (43.8)	50 (51.5)	35 (47.3)	24 (55.8)	0.65
Smoking, *n* (%)	33 (68.8)	46 (47.4)	41 (55.4)	30 (69.8)	0.03
IIb/IIIa use, *n* (%)	23 (47.9)	42 (43.3)	34 (45.9	24 (55.8)	0.59
HTN, *n* (%)	31 (64.6)	53 (54.6)	50 (67.6)	31 (72.1)	0.16
DM, *n* (%)	10 (20.8)	19 (19.6)	19 (25.7)	4 (9.3)	0.20
Killip class 4, *n* (%)	0 (0)	2 (2.1)	0 (0)	4 (9.3)	0.01
LAD infarct, *n* (%)	27 (56.3)	56 (57.7)	44 (59.5)	22 (51.2)	0.85

Abbreviations as in Table I.

TABLE V. Comparison of DEcMRI Data Categorized by IT

Ischemic time (min)	<120 ($n=37$)	120–239 ($n=141$)	≥240 ($n=84$)	*P*
Scar volume (cc), mean ± SD	9.9 ± 10.0	19.7 ± 20.8	22.2 ± 18.0	<0.01
MVO (cc), mean ± SD	0.8 ± 1.5	3.1 ± 6.5	3.1 ± 5.0	0.06
Presence of MVO, *n* (%)	20 (54.1)	98 (69.5)	64 (76.2)	0.05
Scar index[a](%LV), mean ± SD	6.5 ± 6.3	11.9 ± 9.8	13.1 ± 8.7	<0.01
MVO/Scar volume (%),mean ± SD	5.5 ± 9.2	8.8 ± 10.2	9.1 ± 9.7	0.15
MVO index (%LV), mean ± SD	0.5 ± 0.9	1.7 ± 2.9	1.7 ± 2.6	0.04

[a]%LV = percentage of left ventricular myocardial volume; SD = standard deviation.

In contrast, 30-day mortality rates were similar across D2B groups.

CMR Cohort Characteristics

There were 262 STEMI patients who also had DEcMRI on hospital day 3–5. Typical reasons for not performing CMR include: presence of metal implants, inability to tolerate the MRI scanner, lack of patient consent, as well as various logistical reasons such as time of day or night, etc. Basic information on the CMR cohort by IT group and D2B group is shown in Tables III and IV, respectively. Age, cardiac risk factors, glycoprotein IIb/IIIa inhibitor use, Killip class 4, and LAD infarcts were comparable among IT groups. There were minor differences in these variables among D2B time groups. An infarcted region on DEcMRI was visualized in all patients and corresponded to the myocardial distribution of the infarct related artery.

CMR Cohort Analysis

There was a significant increase in myocardial scar index as IT increased. (Table V and Fig. 2) Specifically, the largest increase in scar index was noted after IT of 120 min. When IT increased from <120 to 120–239 min, scar index nearly doubled (6.5–11.9%,

$P < 0.01$), and MVO index more than tripled (0.5–1.7%, $P = 0.04$). In contrast, changes in both scar index and MVO index with increasing D2B times were less pronounced and not significant. (Table VI and Fig. 3) Figures 2 and 3 illustrate the relationships between myocardial scar index, IT, and D2B times.

DISCUSSION

This study shows that IT, that is, the time from onset of characteristic infarct pain until reperfusion, has better correlation with mortality and infarct size than does D2B time. The importance of prompt restoration of coronary patency in STEMI is well known. In spite of this knowledge, analysis of the pre-hospital time interval between symptom onset and hospital arrival has been largely neglected. In the Worcester Heart Attack Study that analyzed 5,967 AMI patients over a 20 year study period, Saczynski et al. [2] reported that mean and median pre-hospital delay times for AMI were 4.1 and 2.0 hr, respectively, in 1986, 4.7 and 2.2 hr in 1995, and 4.6 and 2.0 hr in 2005. Furthermore, a subgroup analysis of these patients revealed that PCI was performed within 90 min of hospital arrival in 10.8% of STEMI patients when pre-hospital delay was <2 hr, but was performed within 90 min in only 5.3% when pre-hospital delay was beyond 2 hr, suggesting that pre-hospital delay impacts later care [2].

National efforts have focused on reducing D2B time in hospitals, and these efforts have largely succeeded. In a recent study of 96,738 admissions involving PCI for STEMI, Menees et al. [8] reported that median D2B time declined significantly, from 83 min in 2005–2006, to 67 min in 2008–2009. Unfortunately, risk-adjusted in-hospital mortality rates appear not to have changed accordingly; 5.0% in 2005–2006, 4.6% in 2006–2007, 4.5% in 2007–2008, and 4.7% in 2008–2009. Likewise, 30-day mortality rates showed a similar nonsignificant trend.

CMR imaging has been found to correlate with clinical outcomes in STEMI patients. Wu et al. showed that infarct size and presence of MVO predicted major adverse cardiovascular events (MACE) such as cardiac death, nonfatal MI, congestive heart failure, stroke, and unstable angina requiring hospitalization. MACE occurred in 30% of patients with small infarcts, 43% with medium sized infarcts, and 71% with large infarcts ($P < 0.05$) [14]. Patients exhibiting MVO were more likely to experience MACE compared to patients without MVO (45% vs. 9%; OR = 5.7; 95% CI 1.84 to 51; $P = 0.016$) [14]. In a study of 110 STEMI patients, Hombach et al. [17] also showed that MVO was a significant predictor for MACE.

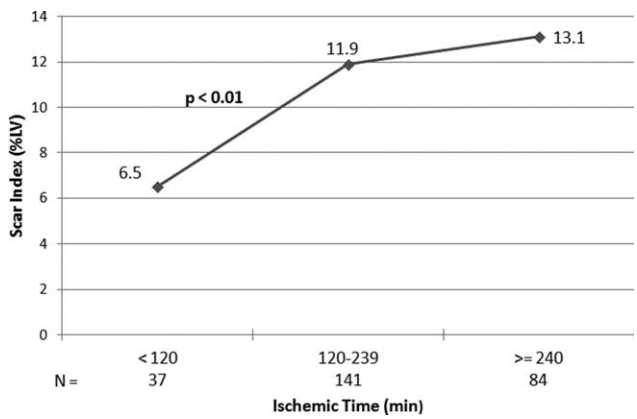

Fig. 2. Myocardial Scar Index by IT.

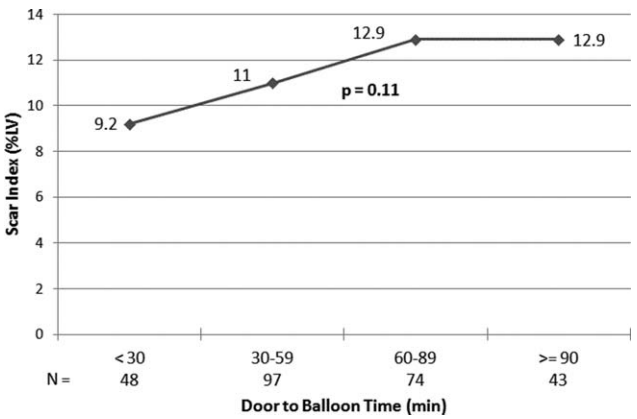

Fig. 3. Myocardial Scar Index by D2B Time.

TABLE VI. Comparison of DEcMRI Data Categorized by D2B Time

Door to balloon time (min)	<30 ($n = 48$)	30–59 ($n = 97$)	60–89 ($n = 74$)	≥90 ($n = 43$)	P
Scar volume (cc), mean ± SD	14.3 ± 15.6	19.2 ± 22.5	20.5 ± 17.2	21.8 ± 16.6	0.22
MVO (cc), mean ± SD	1.8 ± 3.8	3.0 ± 6.7	3.0 ± 4.7	3.0 ± 6.3	0.66
Presence of MVO, *n* (%)	27 (56.3)	66 (68.0)	56 (75.7)	33 (76.7)	0.09
Scar Index[a](%LV), mean ± SD	9.2 ± 9.3	11.0 ± 9.2	12.9 ± 9.4	12.9 ± 8.6	0.11
MVO/Scar volume (%), mean ± SD	6.6 ± 10.5	8.5 ± 9.5	9.4 ± 9.6	8.5 ± 11.0	0.51
MVO index (%LV), mean ± SD	1.2 ± 2.4	1.4 ± 2.2	1.8 ± 2.8	1.7 ± 3.5	0.55

[a]%LV = percentage of left ventricular myocardial volume; SD = standard deviation.

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Several CMR imaging studies have examined the relationship between IT and MRI findings. In a CMR study of 77 STEMI patients, Tarantini et al. [15] found that every additional 30 min of IT correlated with a 37% increase in the size of transmural infarct and a 21% increase in severe MVO. Francone et al. [16] also reported a similar relationship between IT and infarct size in STEMI patients, establishing a continuous, linear relationship between IT and infarct size ($r = 0.601$, $P = 0.0001$).

To the best of our knowledge, this is the first report comparing 30-day mortality rates and DEcMRI results between different IT and D2B time intervals. Our study's findings suggest that IT is a much better predictor than D2B time for 30-day mortality rate, myocardial salvage index, and MVO index. This study reinforces prior reports that suggest focusing more attention on IT rather than D2B time [18,19]. That is, the focus of STEMI care must be redirected toward minimizing IT rather than minimizing D2B time alone [6,20].

Limitations. A number of limitations must be acknowledged. A large number but not all STEMI patients underwent CMR imaging, and it was performed for regular clinical care. This no doubt introduces bias into the sample that cannot be directly measured nor accounted for, perhaps toward smaller infarcts and less-impaired patients. Finally, the sample sizes were not large enough for sophisticated multivariable statistical analyses, so only simple comparative analyses were performed. Nevertheless, we believe that these observations are clear and compelling.

CONCLUSIONS

In conclusion, the focus of STEMI management should be on minimizing IT rather than D2B time, and this can be accomplished by focusing on the pre-hospital phase, the time interval between symptom onset and hospital arrival. Total IT encompasses several different time intervals: symptom onset to EMS call, EMS call to EMS arrival, EMS arrival to hospital arrival, and then hospital arrival to device activation (D2B time). The D2B time is a small portion of the total IT, so successful strategies to shorten this time period have succeeded but yielded no significant changes in mortality. In contrast, pre-hospital delay for patients with STEMI has not improved much. Greater and more effective community and patient education is necessary to help inform patients regarding calls to emergency services agencies. Initiating therapies in the pre-hospital transport period, rapid communications with receiving hospitals, and regionalized system planning could also help lead to earlier coronary patency, better patient stabilization, and improved survival. With a stronger emphasis on decreasing overall IT, we strongly believe that STEMI mortality can be further decreased.

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