TOTAL ISCHEMIC TIME VERSUS DOOR-TO-BALLOON TIME AS AN OUTCOME PREDICTOR IN ST-ELEVATION MYOCARDIAL INFARCTION

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Abstract

BACKGROUND
Acute Coronary Syndrome is a common presenting condition to the emergency department and early reperfusion therapy for patients with an ST-Elevation Myocardial Infarction (STEMI) with Percutaneous Coronary Intervention is the recommended treatment. The American Heart Association / American College of Cardiology has a 60 minutes goal for restoration of coronary flow from the time of patient arrival.

OBJECTIVE
To review the impact of rapidly identifying STEMI patients and expediting transfer to the interventional cardiology suite on restoration of blood flow times and metrics of cardiac injury, such as peak troponin and ejection fraction. To review the impact of total ischemic time on similar metrics.

METHODS
We conducted a single site retrospective review on STEMI patients undergoing the expedited process for reperfusion compared to standard process.

RESULTS
Expedited transfer of patients to the cardiac catheterization suite resulted in significantly lower door-to-balloon times for patients undergoing the “drive-by” process (mean 31.03, SD 4.05 vs mean 68.72, SD 45.09, p < 0.001), compared to usual care. The improved times, however, did not translate into improved metrics of peak troponin value or LVEF. There was a significantly lower peak troponin level (mean 57.14, SD 86.51 vs 97.73, SD 152.43, p=0.017) and a greater LVEF percent at six months (56.41, SD 10.46 vs 52.56, SD 11.93, p = 0.039) for those with < 4 hour symptoms than those with ≥ 4 hours of symptoms.

CONCLUSION
Symptom onset to balloon time has a greater impact on cardiac morbidity than door-to-balloon time.

INTRODUCTION

The term Acute Coronary Syndrome (ACS) includes the diagnosis of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. It is estimated that 625,000 patients experienced an ACS in 2010 and, overall, cardiovascular disease (CVD) accounted for 30.8% (807,775) of the 2,626,418 deaths in 2014. Coronary Heart Disease (CHD) is the leading cause of death attributed to CVD. In 2014, more than 360,000 people died of CHD.¹ Data from 2010 showed there were 4,640,000 emergency department visits with a primary diagnosis of CVD.²

STEMI is a medical emergency and prompt restoration of myocardial blood flow is essential to limit infarct size and reduce overall mortality.³ The 2013 ACC/AHA guideline for the management of STEMI recommends (class 1A) the use of primary percutaneous coronary intervention (PCI) as reperfusion therapy for any patient with an acute STEMI who can undergo the procedure in a timely manner by persons skilled in the procedure. Timely is defined as an first medical contact to PCI time of 90 minutes or less and arrival to PCI (door-to-balloon time, D2BT) of 60 minutes or less for patients transported to a PCI capable hospital.⁴ Prior studies have identified D2BT of less than 90 minutes as associated with reduced mortality.⁵,⁶

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Hospitals and Emergency Departments have implemented several initiatives to reduce D2B Time including obtaining pre-hospital 12-lead electrocardiograms (ECGs), transmitting ECGs from the field to the receiving hospital, and communicating with the hospital for pre-arrival preparation of the catheterization lab.

Reading Hospital implemented a “drive-by PCI” process in September 2012 to minimize the time spent in the Emergency Department (ED) and expedite patient movement to the cardiac intervention suite. When a pre-hospital 12-lead ECG showing STEMI is transmitted to the ED through electronic transmission the emergency physician activates an “MI Alert.” This alert notifies an interventional cardiologist and cardiac catheterization laboratory personnel, and together the team evaluates the patient upon arrival in the ED. The team evaluates the patient for clinical stability, candidacy for cardiac catheterization, and obtains procedure consent. All delays are kept to a minimum.

There is a general agreement that the “drive-by PCI” process leads to shortened D2B Time; however, clinical outcomes have not consistently improved compared to traditional treatment. More recent studies have shown that total ischemic time, defined by symptom onset to balloon time (SOBT) may be a better predictor of outcomes. Our study evaluated the effect of the “drive-by PCI” process for a US community hospital on D2BT and SOBT on intermediate endpoints.

METHODS

This study took place in a single center at the Reading Hospital, a large independent academic medical center with a population of 284,000 in our primary service area. The facility has full cardiac intervention capabilities with board-certified interventional cardiologists and cardiothoracic surgeons available 24 hours a day. The study site had had a median of 158 STEMI cases per year from 2010 through 2015. Data on all individuals presenting to the ED with a STEMI who underwent primary PCI is maintained in a secured local registry. This information is collected and managed by a designated individual on an ongoing basis.

Our study is a retrospective study on all patients presenting with a STEMI who underwent PCI from September 2012 to December 2014. Patients were divided into two broad groups, “drive-by PCI” and “non-drive-by PCI” respectively. “Drive-by PCI” included patients who followed the drive by protocol prior to PCI while “non-drive by PCI” included patients that arrived to the ED by either private vehicle or by an EMS unit that did not provide a pre-hospital ECG. We compared the outcome variables in both the groups.

Three individuals abstracted records for all patients (AS, YO, PR) during the study period. Additional clinical information on patients was obtained by accessing the electronic health records. We excluded patients who were under 18 years of age. Researchers were not blinded to whether the patients underwent “drive-by PCI” process or “non-drive-by PCI” process.

Data was kept in a limited access secure file on password protected computers. Data analysis was conducted on de-identified information. The Institutional Review Board of the Reading Hospital reviewed and approved the research protocol.

OUTCOMES AND DEFINITIONS

The following outcomes were pre-specified:

Door to Balloon Time (D2BT): for patients with STEMI identified outside the hospital, the time was defined as emergency department arrival to balloon time. For patients identified while in the emergency department, defined as time from ED triage to balloon time or time from a second ECG demonstrating STEMI to balloon time if the first ECG did not meet definition of STEMI.

Total ischemic time: defined as symptom onset to balloon time (SOBT).

Peak Troponin I value: measured in ng/mL.

Left Ventricular Ejection Fraction (LVEF): defined as percent by echocardiography, cardiac catheterization, or by nuclear studies.

Arrhythmias: supraventricular, ventricular and high degree atrioventricular blocks that required acute intervention with either medication, cardioversion or device implantation.

Heart Failure: Systolic dysfunction on echocardiography with LVEF less than 50%.

Cardiogenic shock: Persistent hypotension causing end organ hypofusion due to heart failure.

Mortality: during index visit or at 6 months as indicated in the medical record.

Length of Stay: both in intensive care unit and total inpatient hospital.

STATISTICAL ANALYSIS

This study used a combination of descriptive and inferential statistics. Discrete data were reported as count and percent within each category and continuous data were reported as mean and standard deviation (SD). These data were reported within the categories of “drive-by PCI” and “non-drive-by PCI”. Additional stratifications were made in the data for those patients who had SOBT of less than four hours and greater than or equal to four hours. Inferential statistics were computed for both discrete and continuous data. Discrete data were analyzed by chi-square test of association using the drive-by categories as the independent variable. For continuous level data, group t-tests were performed. For several of the time variables the data were windorsized because of the high positive skew for patients with times greater than 960 minutes. These patients represented the upper 5% of the distribution. Mann Whitney U test was used for analysis when outliers were present.

For all analyses, an apriori p-value of p < 0.05 was considered as statistically significant. Due to the exploratory nature of this analysis, there was not any need to apply corrections to the data analysis for multiple comparisons. All analyses were completed using SPSS version 24 (Chicago Illinois).
RESULTS

There were 336 patients in the study sample, 65 (19.3%) “drive-by PCI” and 271 (80.7%) “non-drive-by PCI”. Demographic variable comparisons between “drive-by” and “non-drive-by” patients can be found in Table 1.

There were no statistical differences between groups by age, Emergency Medical System minutes, peak troponin levels, total time of length of stay, or total ICU hours. There were no differences for time of symptom onset to ED arrival or SOBT in either group. Although the D2BT was significantly lower for patients undergoing the “drive-by” process (mean 31.03, SD 4.05 vs mean 68.72, SD 45.09, p < 0.001), the improved times did not translate into improved metrics of peak troponin value, LVEF, or intensive care of hospital LOS (Table 2).

Categorical variable analysis performed using Chi-square tests of association showed no differences for mortality, death in-hospital, cardiogenic shock, arrhythmia, stent, or heart failure while in hospital between the “drive-by PCI” and “non-drive-by PCI” cohorts. There was a difference based on gender with a higher percentage of patients in the “drive-by PCI” group being male (p=0.020). Those patients who activated the EMS system and underwent the “drive-by PCI” process were statistically more likely to have had symptoms for less than 4 hours than those in the “non-drive-by PCI” group (Table 2).

Using the same categorical variable for SOBT of < 4 hours as compared to ≥ 4 hours, there was a statistically significant lower peak troponin level (mean 57.14, SD 86.51 vs 97.73, SD 152.43, p=0.017) and a greater LVEF percent at six months (56.41, SD 10.46 vs 52.56, SD 11.93, p = 0.039) as determined by group t-test for the < 4 hour cohort. This analysis excluded patients with greater than 960 minutes as they were outliers. No significant differences were found for LVEF percent at admission, total length of stay hours or total ICU length of stay (Table 3).

Using the categorical variables for SOBT, those patients presenting at ≥ 4 hours from symptom onset had a higher percent of death at six months (4.9% vs. 0.6%, p = 0.018) as well as arrhythmias, (24.2% vs 13.3%, p=0.018). A higher percentage of patients with extreme troponin elevations (level of 75 ng/mL or greater) had SOBT in the ≥ 4 hours cohort (43.1% versus 23.6 %, p = 0.001) (Table 3). There were no statistically significant differences for gender mortality, death in-hospital, cardiogenic shock, stent, or heart failure in-hospital.

DISCUSSION

Despite the widespread adoption of 90 minutes as the standard for D2BT both nationally and internationally, there are conflicting data regarding the relation between time to treatment and morbidity and mortality outcomes in these patients. Quinn et al demonstrated that prehospital ECG use in patients with STEMI and NSTEMI was associated with survival advantage during the 30 days following hospitalization. Rathore et al in their study demonstrated longer D2BT were associated with higher one year mortality and concluded any delay in primary PCI was associated with increased mortality at the end of one year. They suggested efforts should focus on reduced time to treatment as much as possible even among PCI centers currently achieving the 90 minute D2BT. In contrast, Menees et al found no association between the trends in D2BT reductions and in-hospital and 30-day mortality from July 2005 to June 2009. However, for each year examined, unadjusted mortality was lower among patients with a D2BT of 90 minutes or less than among those with a D2BT longer than 90 minutes. Ho et al in 2014 examined the impact of shortening D2BT to 60, 45 and 30 minutes and did not find any association with 30-day mortality.

A number of the studies have emphasized that a relevant variable in assessing outcomes in STEMI is the total ischemic time. Reductions in D2BT may not have an effect on infarct size with prolonged total ischemic time and may have important consequences when total ischemic time is limited. Moreover, short term follow up for 30 days might not be an adequate end point to detect effects of infarct size limitation after PCI. Similarly, a number of the studies have questioned the emphasis on D2BT rather than other components of the total ischemic time such as SOBT. Hannan et al concluded that the combination of D2BT less than 90 minutes and SOBT less than 4 hours was associated with the lowest long term mortality rate. Similarly, Brodie et al found that D2BT of 90 minutes or less was associated with lower 1-year mortality rate in patients with SOBT of 90 minutes or less but not in those with SOBT greater than 90 minutes.

The primary objective of this study was to evaluate the influence of stringent D2BT and SOBT on the prognosis and outcome of patients with STEMI. Short D2BT were achieved after implementation of a “drive-by PCI” process in which patients had minimal intervention in the ED and were transported directly to the Cardiac Catheterization Suite. The new process did result in D2BT much lower than the recommended 60 minutes. These times did not translate into better outcomes with regards to key metrics such as peak troponin, cardiogenic shock, arrhythmias, heart failure or mortality. These results are similar to the experience in Japan, Canada and Italy. However, our study differs in that we were not able to show a clinical benefit with drastically shorter median D2BT of 60, 45 and 30 minutes and did not find any association with 30-day mortality.

While advances have been made in reducing D2BT, the delay in seeking care in the pre-hospital setting is the limiting factor in attempting to reduce the total ischemic time. Unfortunately studies aiming to reduce the SOBT have met with limited success. Measures should be directed to reduce overall ischemic time to possibly improve outcomes. Multidisciplinary system approach is required for overall reduction in the total ischemic time and should be the focus of continuous research.
Table 1 - Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Drive-by</th>
<th>Non-drive-by</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>65</td>
<td>771</td>
<td></td>
</tr>
<tr>
<td>Age in years – Mean(SD)</td>
<td>60.3 (12.6)</td>
<td>60.9 (13.7)</td>
<td>0.716</td>
</tr>
<tr>
<td>Gender (M - Male, F - Female)</td>
<td>M - 53 (81.5%)</td>
<td>F - 12 (18.5%)</td>
<td></td>
</tr>
<tr>
<td>Location of 1st EKG (A - EMS, E - Emergency Dept., O - other, P - Physician office)</td>
<td>A – 60 (52.3 %)</td>
<td>E – 0 (0.0 %)</td>
<td>P – 4 (6.2%)</td>
</tr>
<tr>
<td>Type of stent (BMS – Bare Metal Stent, DES – Drug Eluting Stent)</td>
<td>BMS – 16 (15.8 %)</td>
<td>DES – 46 (74.2%)</td>
<td>BMS – 52 (20.6 %)</td>
</tr>
<tr>
<td>EMS minutes – Mean (SD)</td>
<td>32.11 (13.69)</td>
<td>30.20 (10.72)</td>
<td>0.322</td>
</tr>
<tr>
<td>Door to Cath Suite Time in minutes – Mean (SD)</td>
<td>7.77 (4.05)</td>
<td>34.58 (42.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First Medical Contact to Balloon Time in minutes - Mean(SD)</td>
<td>63.42 (15.67)</td>
<td>76.64 (49.77)</td>
<td>0.035</td>
</tr>
<tr>
<td>Time from Symptom Onset to ED in minutes – Mean (SD)</td>
<td>243.71 (394.8)</td>
<td>459.97 (1142.8)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Table 2 – Outcomes by "Drive-by" versus "Non-drive-by" Cohorts

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Drive-by</th>
<th>Non-drive-by</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to balloon time in minutes - Mean (SD)</td>
<td>31.03 (8.38)</td>
<td>68.72 (45.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom onset to balloon time in minutes - Mean (SD)</td>
<td>258.81 (382.8)</td>
<td>465.23 (1031.1)</td>
<td>0.010</td>
</tr>
<tr>
<td>Peak troponin (ng/ml) – N (%)</td>
<td>&lt;10</td>
<td>10 – 75</td>
<td>&gt;75</td>
</tr>
<tr>
<td></td>
<td>16 (24.6%)</td>
<td>63 (21.7%)</td>
<td>123 (46.2%)</td>
</tr>
<tr>
<td>LVEF Percent on Admission - Mean (SD)</td>
<td>53.44 (11.91)</td>
<td>53.33 (10.74)</td>
<td>0.945</td>
</tr>
<tr>
<td>LVEF Percent at 6 Months - Mean (SD)</td>
<td>55.18 (11.6)</td>
<td>54.14 (12.16)</td>
<td>0.656</td>
</tr>
<tr>
<td>Arrhythmias – Number of patients</td>
<td>6 (10.2%)</td>
<td>30 (19.6)</td>
<td>0.101</td>
</tr>
<tr>
<td>Heart failure - Number of patients</td>
<td>1 (1.5%)</td>
<td>18 (6.8%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Cardiogenic shock - Number of patients</td>
<td>1 (1.7%)</td>
<td>16 (6.5%)</td>
<td>0.159</td>
</tr>
<tr>
<td>Mortality - Number of patients</td>
<td>1 (1.8%)</td>
<td>23 (9.4%)</td>
<td>0.057</td>
</tr>
<tr>
<td>Total Length of Stay (hours) - Mean (SD)</td>
<td>213.38 (1228.3)</td>
<td>110.24 (1166.1)</td>
<td>0.596</td>
</tr>
<tr>
<td>Total Length of ICU stay (hours) - Mean (SD)</td>
<td>87.13 (107.1)</td>
<td>117.85 (554.5)</td>
<td>0.798</td>
</tr>
</tbody>
</table>

Table 3 – Outcomes by symptom onset to balloon time < 4 hours versus ≥ 4 hours, excluding those with more than 16 hours as outliers

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>&lt; 4 hours</th>
<th>2 4 hours</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>214</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Peak troponin (ng/ml) – N (%)</td>
<td>&lt;10</td>
<td>10 – 75</td>
<td>&gt;75</td>
</tr>
<tr>
<td></td>
<td>55 (25.5%)</td>
<td>107 (50.5%)</td>
<td>56 (23.6%)</td>
</tr>
<tr>
<td>LVEF Percent on Admission - Mean (SD)</td>
<td>54.55 (10.52)</td>
<td>52.39 (11.36%)</td>
<td>0.112</td>
</tr>
<tr>
<td>LVEF Percent at 6 Months - Mean (SD)</td>
<td>56.41 (10.46)</td>
<td>52.36 (11.93)</td>
<td>0.039</td>
</tr>
<tr>
<td>Arrhythmias – Number of patients</td>
<td>28 (13.3%)</td>
<td>22 (24.2%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Heart failure - Number of patients</td>
<td>4 (2.2%)</td>
<td>4 (4.9%)</td>
<td>0.243</td>
</tr>
<tr>
<td>Cardiogenic shock - Number of patients</td>
<td>12 (5.7%)</td>
<td>6 (6.3%)</td>
<td>0.821</td>
</tr>
<tr>
<td>Mortality - Number of patients</td>
<td>12 (6.4%)</td>
<td>9 (10.3%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Total Length of stay (hours) - Mean (SD)</td>
<td>137.69 (1321.5)</td>
<td>151.95 (980.4)</td>
<td>0.931</td>
</tr>
<tr>
<td>Total Length of ICU stay (hours) - Mean (SD)</td>
<td>117.65 (624.5)</td>
<td>97.45 (129.4)</td>
<td>0.764</td>
</tr>
</tbody>
</table>
LIMITATIONS
This is a retrospective study and as such our findings are subject to the limitations of the study design. There were some unavailable data which could confound the interpretation of our data. Thirty-six patients did not have in hospital mortality data while 57 patients did not have data about mortality at 6 months. More than 50% of patients did not have a follow up trans thoracic echocardiogramat 6 months which was one of the variables studied to assess ventricular function. There are no definitive guidelines on follow up of STEMI patients and when a follow up transthoracic echocardiogram needs to be done. Most of these decisions are individualized and timing of data point collection at follow up varied. As this is a retrospective study, endpoints were not adjudicated and we relied on accuracy of chart information. Finally, we did not collect comorbidity information at baseline and as such could not adjust for this in our analysis which could impact the interpretation of outcome.

CONCLUSION
Our study confirms that SOBT impacts outcomes in patients with STEMI more than lowering D2BT, even when D2BT are aggressively reduced below the recommended ACC/AHA 60 minute criteria. Public health efforts should be utilized in increasing patient awareness about ischemic heart disease and its presentation, seeking early medical help, and expediting EMS transition for early transfer to reduce the symptom onset to balloon times and hence the overall outcomes.

FUNDING
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DISCLOSURES
The authors report no conflicts of interest.

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AUTHORSHIPS
AS, CB, VCM and MK involved in study design.
AS, OF, and PR performed data extraction.
OF, PR and TW performed data analysis
AS, CB, MK, OF and PR wrote and edited the manuscript

ABBREVIATIONS
CVD – cardiovascular disease, CHD – Coronary Heart Disease, D2BT –door-to-balloon time, SOBT – symptom onset to balloon time, LVEF – Left Ventricular Ejection Fraction, LOS – length of stay.

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