PROCESS TIMES IN PRIMARY PERCUTANEOUS CORONARY INTERVENTION:
WHERE DOES THE TIME GO?

by

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ABSTRACT

ST-elevation myocardial infarction (STEMI) is a medical emergency and the treatment of choice, if available in a timely manner, is primary percutaneous coronary intervention (PPCI). It is in the best interest of the patient to receive this treatment as soon as possible to reduce ischemic injury to the heart. Using routinely recorded data from the Nova Scotia Health Authority on patients who receive PPCI between 2012-2014 we determined which components of the process contributed the most to total ischemic time. We determined that the majority of time and variation seen in total ischemic time was before the patient arrives at the hospital. Very little variation in process times were found once the patient arrives at the hospital. We also determined that sex is associated with longer total ischemic times after adjustment for cardiac history and process variables. The emphasis of future research should be reducing patients' decision time to seek medical care for acute coronary syndrome as hospital delay in our system was found to be minimal when considering the larger picture.

CHAPTER 1. INTRODUCTION

Cardiovascular disease is the second leading cause of death in Canada (1). In 2011, 19.7% of all deaths were due to cardiovascular disease (1). Ischemic heart disease accounted for 64.7 deaths per 100 000 people in Canada and in 2011, 33,569 Canadians died due to ischemic heart disease (2). Over the past decade, the percentage of deaths in Canada due to cardiovascular disease has decreased, but still remains a significant cause of mortality, morbidity and economic cost to Canada (3). In Nova Scotia, roughly a quarter of deaths, each year, are due to cardiovascular disease (2). Nearly half of these deaths are due to ischemic heart disease (2).

In the emergency setting, ischemic heart disease often presents in the form of 'Acute Coronary Syndrome' (ACS) where patients may experience a variety of symptoms like sudden onset of chest discomfort, weakness, sweating, nausea and vomiting (4). The underlying pathophysiology is rupture of the cholesterol plaque in the coronary artery leading to exposure of collagen under the coronary endothelium and this eventually leads to formation of blood clot and complete or partial occlusion of the coronary artery. The lack of blood flow interrupts oxygen from reaching the heart tissue, eventually causing the cells to die. Untreated, the patient's heart deterioration may lead to heart failure and death, depending on the extent of myocardial injury (5).

Patients presenting with symptoms suggestive of ACS are given a 12-lead electrocardiogram (ECG) to determine location and type of ischemic injury to the heart. If the ECG shows ST segment elevation, in appropriate clinical context it is suggestive of sudden occlusion of a coronary artery leading to acute ST-elevation myocardial infarction (STEMI). Without appropriate, emergent treatment, the patients are at risk of irreversible heart damage or death. Treatment of choice is timely reperfusion of the blocked blood vessel in the heart through primary percutaneous coronary intervention (PPCI) or fibrinolytic therapy.

Primary percutaneous coronary intervention (PPCI) has been shown to be more effective in reducing mortality among patients with STEMI (6). Despite effective interventions, recent studies have shown that not all patients receive

identical treatment. At least one study has suggested that women are not treated as aggressively as their male counterparts (7). Mortality rates among women after PPCI tend to be higher (8) and this difference may not explained through risk factors such as diabetes, hypertension, and higher BMI, which are more common among women receiving PPCI (9). Women are also less likely to report more 'typical' acute coronary syndrome symptoms (10). Furthermore, time to electrocardiogram and time to fibrinolysis (an alternate reperfusion strategy) were longer for women than for men (11). 'Door to balloon time,' a measure of the time it takes from arrival at hospital to achieving revascularization through PPCI, has been shown to be linked to mortality (12), and if there are delays in the process of receiving PPCI among women, it follows that they are likely to fare worse than males.

The majority of the literature that compares mortality outcomes among men and women who receive PPCI have examined the contribution of comorbidities, drug evaluation, and vital signs at presentation. Fewer still have researched the role of total ischemic time in predicting mortality (13-16). As acute myocardial infarction occurs rapidly and is a medical emergency, it is in the best interest of the patient to expedite the process from onset of event to intervention. The process of receiving PPCI has several points where there is room for delay. The duration of these steps may differ between men and women leading to one sex having more delays than others. To date, there remains to be few studies that examine the process of receiving PPCI from the patient perspective (17-19). It is imperative to assess whether women and men fare equally during the process of receiving PPCI. The study aims to answer the following research questions about patients in Nova Scotia:

1) In patients who are receiving primary percutaneous coronary intervention for ST elevation myocardial infarction, which parts of the process to receiving PPCI contribute the most to the total ischemic time in Nova Scotia?

2) In patients receiving primary percutaneous coronary intervention for ST elevation myocardial infarction in Nova Scotia, are process times equal among men and women?

To answer these research questions, all patients in Nova Scotia who received PPCI for STEMI in the Nova Scotia Health Authority from 2012-2014 will have their process times assessed. To perform this study, the existing database 'Cardiovascular Information System' (CVIS) will be accessed. This database routinely records pertinent patient data on all patients who receive PPCI in Nova Scotia. All PPCI are performed at the Queen Elizabeth II's Halifax Infirmary in Halifax, Nova Scotia. This is the only center in the province that performs this treatment. Descriptive statistics were used to calculate and compare total ischemic and process times in patients who received PPCI for STEMI. Regression modeling was used to explore which process time accounted for the most variation seen in total ischemic time. We compared total ischemic and process times by sex. We explored associations between sex and process times to determine if men and women fared equally using simple linear regression models. Multivariate linear regression models were then used to adjust for clinical and process variables.

CHAPTER 2. BACKGROUND

2.1 Ischemic Heart Disease in Nova Scotia

Ischemic Heart Disease is prevalent across all districts in Nova Scotia. In 2011, there were 2,282 deaths due to major cardiovascular diseases in Nova Scotia (2). Of those deaths, 464 were due to acute myocardial infarction (2). The number of ACS patients between 2002-2005 averaged 3,971 patients per year across Nova Scotia (20). According to Cardiovascular Health Nova Scotia, the Central Zone of the Nova Scotia Health Authority (NSHA) accounts for 1,325 ACS patients per year (20). In 2009, the Public Health Agency of Canada (PHAC) released a report summarizing heart disease and stroke across Canada and, unfortunately, the Maritime population is highly morbid with several risk factors that predispose them to heart disease (21). Smoking, being either overweight or obese, poor diet lacking adequate vegetables and fruit, lack of exercise, diabetes, and hypertension have all been well indicated in the development of heart disease (21). The rates of the above risk factors were all above the Canadian average in Nova Scotia (See Appendix A). Other risk factors have been shown to predict heart disease are dyslipidemia and increasing age (22,23). Additionally, Nova Scotia has the highest percent of residents living over the age of 65 compared to the rest of the country (16.6%) (24).

2.2 Primary Percutaneous Coronary Intervention in Nova Scotia

Percutaneous coronary intervention (PCI) is performed for a variety of cardiac pathologies like STEMI, Non STEMI and stable angina with the objective of improving blood flow though a blocked or severely narrowed coronary artery. PCI is an invasive procedure where a catheter, guided by X-ray, is inserted through either the patient's radial or femoral artery and moved into the patient's heart vasculature. Then a radio-opaque contrast agent is injected in to the coronary arteries and coronary anatomy is defined by repeated contrast injections and acquisition of pictures on the monitor. If a severe narrowing is visualized and if deemed suitable for PCI then a very thin wire is advanced in to the coronary artery and over that wire, first a balloon and then a stent is advanced across the narrowing. The stent is

like a wire mesh mounted over an expandable balloon, which is deployed in the artery at the site of the severe narrowing to relieve the blockage and to achieve a sustained blood flow to the cardiac tissue (20).

The two main reperfusion strategies to treat STEMI are PPCI and administration of intravenous fibrinolytic therapy. Fibrinolysis is the treatment of choice for patients who present within 12 hours, preferably 6 hours, of symptom onset and cannot receive PPCI within 90 minutes of first medical contact.. It is the mainstay of treatment for majority of patients presenting with STEMI in Canada. PPCI is the procedure of choice for patients who present within 12 hours of symptom onset and if it can be provided within 90 minutes following the first medical contact (6, 25, 26). It is also the treatment of choice for patients who have contraindications for fibrinolytic therapy regardless of the time, and for patients presenting in a state of shock (27). Contraindications to PPCI are patients with terminal illness with life expectancy of less than one year or severe dementia (27). Between 150-200 PPCIs are performed in the Nova Scotia Health Authority each year (28). PPCI has been associated with lower short-term (<6 weeks) and lower long-term (>1 year) mortality compared to fibrinolytic therapy (6, 25, 26).

2.3 Risk Factors associated with poor outcomes in Percutaneous Coronary Intervention

2.3.1 Delays in Process

The majority of the literature assesses mortality outcomes among men and women who receive PPCI examining the contribution of comorbidities, drug therapy, and vital sign presentation. Fewer have researched the role of 'total ischemic time' in predicting mortality (14-16). Total ischemic time is the duration between the onset of symptoms and restoration of normal coronary blood flow. Ideally PPCI should be performed in a timely fashion in order to reduce the amount of damage to the heart. It is important to recognize that timely performance PPCI requires a very well coordinated effort between the emergency medical services (EMS), emergency departments (ED), interventional cardiologists, cardiac catheterization laboratory staff i.e., nurses and radiation technologists and coronary

care unit staff. Especially after the regular hours of work a large team needs to be mobilized and there are inherent delays in the process. These include time of first medical contact to the performance of first electrocardiogram (ECG), time of diagnostic ECG to the activation of cardiac cathlab, time of cardiac cathlab activation to cathlab being ready to receive the patient, and time of patient arrival in the cathlab to the insertion of first device (balloon, stent or a thrombectomy catheter) in the infarct related artery. These steps can be broken down in to smaller steps and at each step there is a potential of a longer than expected delay. The recommended maximum delay between the first medical contact to the insertion of first device in the infarct related artery should be less than 90-120 minutes (29).

The length of time during each of these steps may also differ between men and women leading to one sex having more delays than the other. To date, there are few studies that examine the process of receiving PPCI from the patient perspective (17-19); most studies are outcome oriented, focusing on performance of care providers through risk adjustment to adjust for patient factors that may affect outcomes (See Appendix B). This study is an attempt to examine the process of PPCI, to determine the delays in the process and to suggest improvements if any in reducing the delays involved in the process of PPCI.

As stated earlier the treatment delay can occur at one or all of four levels; patient delay, pre-hospital delay, 'door to procedure' delay, and system delay. 'Patient delay' is the time between symptom onset and call to emergency services or decision to go to the hospital. 'Prehospital delay' includes time from dispatch of ambulance to arrival at hospital (this time includes pre-hospital patient assessment and transport). 'Door to procedure time' is the time it takes from arrival to the hospital to reaching the cardiac cathlab where PPCI is performed. 'System delay' is the sum of both the pre-hospital and door to procedure time delays. As the total ischemic time (time from the onset of symptoms to the insertion of first device in the infarct related coronary artery or administration of the fibrinolytic agents), increases mortality rate also increases (30). Timely decision-making and a well-coordinated team effort are the keys in reducing the total ischemic time. Figure 1 shows a flow diagram of the process of receiving

<u>Figure 1</u>: Flow diagram showing possible alternatives from simplified pathway of symptom onset to receiving PPCI. The red flow chart shows a simplified version of how a patient receives PPCI.
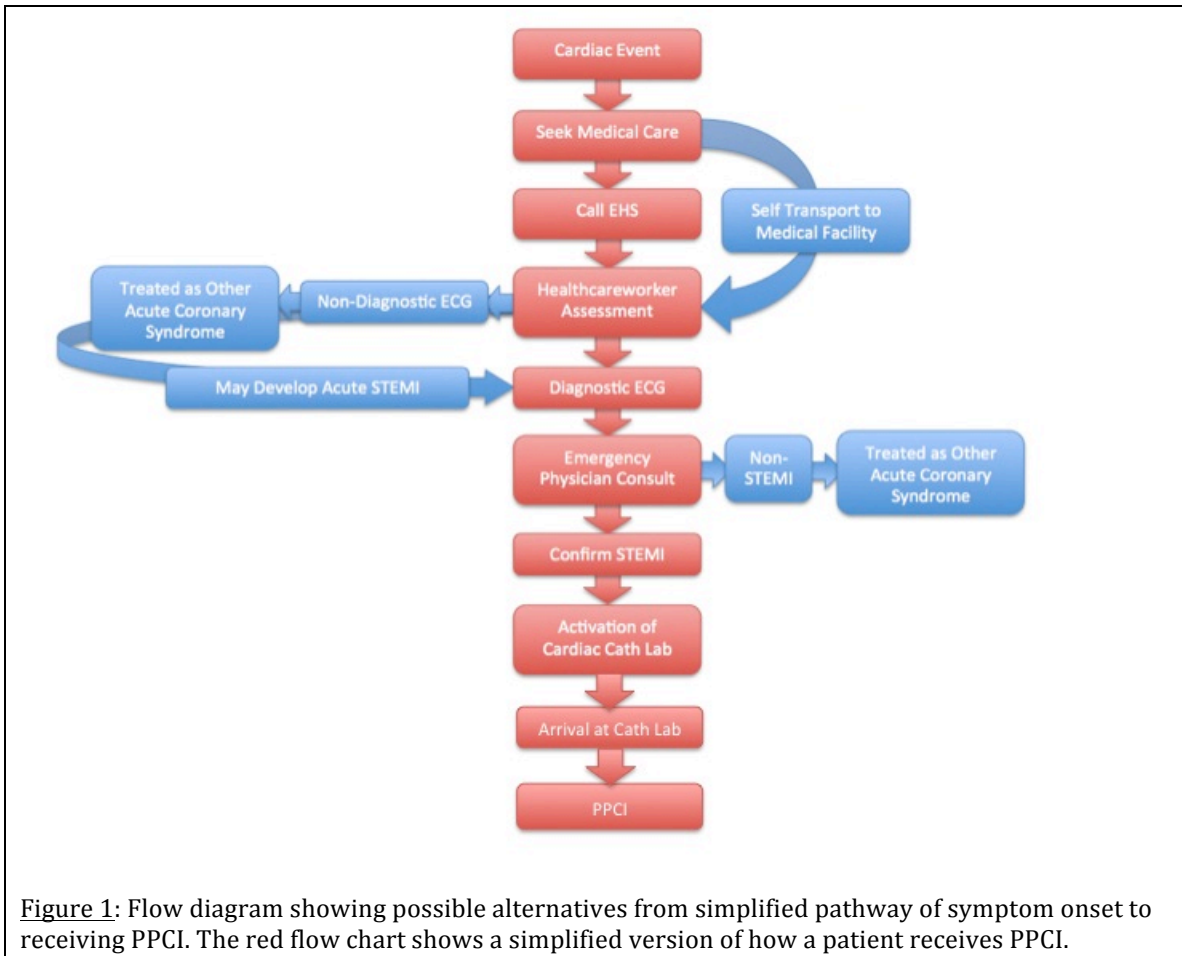
PPCI. The simplified pathway (in red) for receiving PPCI illustrates how a patient may experience this process. The pathway begins when a patient begins to have cardiac symptoms (symptom onset). In the simplified pathway, the patient contacts Emergency Health Services (EHS) for care. On arrival by the paramedics, the patient is assessed where they receive an ECG. The ECG shows signs of ST-elevation, and at this point, the paramedics would contact the Emergency room physician through radio-patch. The ECG is sent wirelessly to the hospital where the physician is able to see the new ECG and compare it to any previous ECG the patient may have had in the past. Should the ECG meet the diagnostic criteria for a STEMI (>1mm ST-segment elevation in anatomically contiguous limb leads and >2mm ST-segment elevation in anatomically contiguous precordial leads) the cardiac catheterization lab will be notified. The patient will bypass the emergency department and receive PPCI if the criteria are met.

As one might expect, delays could occur at all points of the pathway. Distance to tertiary center would increase total ischemic time due to either distance travelled or response time by paramedics. Depending on the presentation of the patient, evaluation by first medical contact may take more time especially if the patient presents atypically. Depending on where the patient experiences their symptoms, extrication of the patient also plays a role in ischemic time. From the hospital perspective there are the added challenges of having access to old ECGs, delays or interruptions in the transfer of ECGs through wireless network, as well as determining if the patient is having a new infarct as opposed to previous ischemic history (extensive cardiac history with no ability to find old serial ECGs). Furthermore, activation of the cardiac cathlab may be delayed due to after-hours presentation; cardiac cathlab personnel need to travel from their homes in order to set up the cardiac cathlab to perform PPCI. In many cases, the cardiac cathlab is not activated until cardiology sees the patient in the emergency department. This could arise due to poor ECG quality, lack of serial ECGs, or questionable ECG criteria. The specific reasons for why there are delays in each piece of the process are not routinely recorded, but time at each stage is collected in our hospital database. And finally, time from the arrival of the patient in the lab to insertion of first device in the infarct related artery will also vary depending on patient and practitioner. Given that patients may have different times to intervention, it is necessary to determine where the variation in time exists.

Also included in Figure 1 are the alternate pathways (shown in blue) a patient may take before receiving PPCI. For instance, not all patients will use the ambulance to travel to the hospital; they may self-transport or use a family member or friend to aid in their transport. Additionally, not all patients who are having chest pain will receive PPCI. Not all acute coronary syndrome patients are having acute STEMI; in fact some patients may be having a non-STEMI or their symptoms may not have a cardiac etiology. At every point in the alternate pathways there is room for delay, which would lead to variation in 'total ischemic time.' Total ischemic time can be visualized in Figure 2.

Figure 2: Total ischemic time and different points in the process of receiving PPCI. Total ischemic time can be measured at two points; at symptom onset or diagnostic ECG (either at first medical contact or during hospital visit).
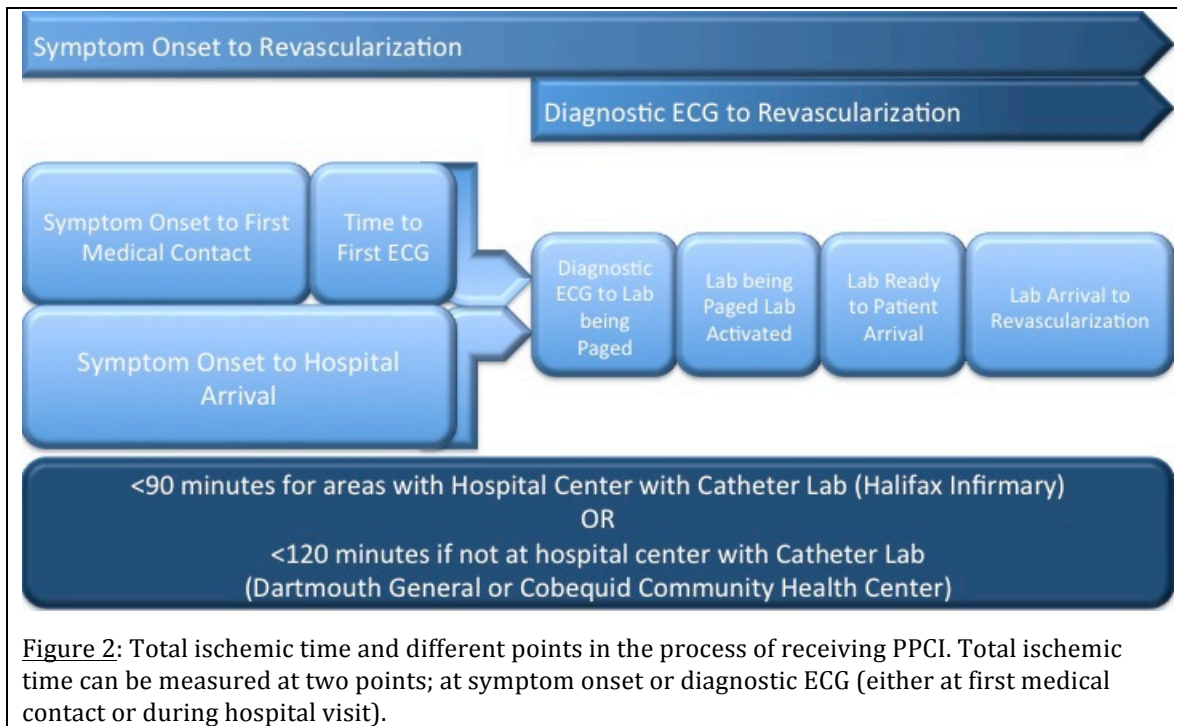
There is a paucity of research studying the process times between men and women. Women may be more likely to have system delays compared to men. A recent study by Pelletier et al. has shown that, in a few Canadian hospitals, women had longer 'door-to-ECG' times and 'door-to-needle' (fibrinolysis) time in comparison to men (11). This study, however, found that 'door-to-balloon' time (PCI) was not significantly different in comparison to men (11). System delay differences between men and women have not been investigated in the Nova Scotian population.

2.3.2 Differences in Presentation in Women

Symptoms of ACS occur at different frequencies between men and women. Women are more likely to exhibit back pain, jaw-pain, arm pain, shortness of breath, paroxysmal nocturnal dyspnea, nausea/vomiting, indigestion, loss of appetite, weakness/fatigue, cough, syncope, dizziness, and palpitations during an ACS in comparison to men (10,31). In one large cohort study of 1.1 million patients who had a myocardial infarction, two thirds of patients presented with chest pain but much fewer women presented with chest pain in comparison to men (32). This

same study also showed that these sex differences decreased with age suggesting that presentation of myocardial infarction was more uniform between the sexes with increasing age (32). Much of the current literature has suggested that instead of classifying symptoms as 'typical' and 'atypical' the symptoms for ACS should be broadened and standardized (33). A few studies have found that women report more symptoms than men, which may explain the perception that women have more 'atypical' symptoms (34). Atypical symptoms include describing the pain as sharp, pleuritic, burning, or the pain is reproducible by chest wall palpation. It has also been suggested that the misinterpretation of symptoms is largely responsible for delays in care. At least one study has suggested that severe chest pain/discomfort and previous myocardial infarction are the strongest predictors of timeliness of care (35). This study also showed that differences in severity of symptoms between men and women were not different and the gap in knowledge appears to be more related to chest pain being a prerequisite to myocardial infarction, which is not the case (33).

Atypical presentation may also be related to variation in process times. Women are known to present differently than males during ACS, and therefore the decision to seek medical care may be more delayed among women than men. Furthermore, patients who present atypically may be reluctant to contact EHS and therefore delay the time to their first ECG even further. These differences in process may account for the variation that is seen in mortality between men and women. Further study is needed to assess time delays and mortality outcomes among women who present with ACS.

2.4 Study Purpose & Research Questions

This study used hospital data that is routinely recorded for quality assurance in the Nova Scotia Health Authority (NSHA). The data allowed us to describe the total ischemic time of all patients who received PPCI in Nova Scotia from 2012-2014. We were able to identify the median times at each stage of the process of

receiving PPCI. These times were compared based on sex in order to determine if men and women had the same timeliness of care.

This study looked at the relationship between process variables influencing the total ischemic time. Additionally, we used sex as an explanatory variable to assess if total ischemic and process times differed between men and women. Given that there are differences in presentation and decisions to seek medical care, one can surmise that sex differences within the process of receiving PPCI may exist, but little or no research has examined this issue. This study assessed if there were associations between process times and sex.

The findings in this study served to illustrate the entire process of PPCI for STEMI from the patient perspective. Each piece of the process was described in terms of median time in order to show how long each stage of the process is expected to take. This study is unique as it illustrates the process of receiving PPCI in this level of detail. We were able to show the median times for each piece of the process by sex in order to determine if specific stages of the process were different for males and females. Additionally, we performed regression modeling in order to describe the variance of total ischemic time as well as the variation seen in process times. In doing so, we were able to show which areas could be improved not only in the general sense, but which areas were more sensitive based on sex. This study has the potential to show where we need to spend future efforts in reducing total ischemic time for patients who receive PPCI for STEMI.

This study intended to answer two research questions:

1) In patients who are receiving PPCI for STEMI, which parts of the process to receiving PPCI contribute the most to total ischemic time in Nova Scotia?

2) In patients receiving PPCI for STEMI in Nova Scotia, are process times equal among men and women?

CHAPTER 3. PROCESS TIMES IN PRIMARY PERCUTANEOUS CORONARY
INTERVENTION: WHERE DOES THE TIME GO?

(Manuscript)

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ABSTRACT

BACKGROUND: Primary percutaneous coronary intervention (PPCI) if provided in a timely fashion remains the treatment of choice for patients presenting with ST-elevation myocardial infarction (STEMI). Total ischemic time during STEMI (time from the onset of symptoms to the achievement of normal flow in the infarct related artery i.e., successful reperfusion) is an important predictor of the degree of myocardial injury and occurrence of other short and long-term adverse events including mortality. Several studies have examined 'door to balloon' times, but few studies have examined pre-hospital and in hospital process times as individual pieces that make up total ischemic time.

METHODS: Total ischemic and process times for patients who received PPCI from 2012-2014 in the Queen Elizabeth-II Halifax Infirmary were described. Median total ischemic times and process times were calculated and compared using the Kolmogorov-smirnov test. Regression modeling was performed to identify which process times and process variables explained the most variation seen in total ischemic times.

RESULTS: 438 patients who had successful PPCI and complete process times were identified in our center. Most of the total ischemic time was due to 'Symptom Onset to Hospital Arrival' and 'Symptom Onset to First Medical Contact.' Total ischemic time was found to differ based on the use of EHS and successful pre-activation of the cardiac cathlab. After hours procedures did not contribute significantly to 'Symptom Onset to Revascularization' time. Process times in hospital were found to be short and lack variation.

CONCLUSIONS: In our study we determined that most of the total ischemic time lies in 'Symptom Onset to Hospital Arrival' and 'Symptom Onset to First Medical Contact (FMC)' times. More research needs to be devoted to reducing patient delay, as there appears to be little room for improvement in hospital process times.

3.1 INTRODUCTION

ST-Elevation Myocardial Infarction is a medical emergency that requires immediate intervention. Longer 'total ischemic time,' or the time it takes from symptom onset to revascularization, is directly related to adverse outcomes in STEMI patients (36, 38, 39, 40). Fortunately, there are interventions that have proven to be highly effective in reducing adverse events including mortality among patients with STEMI and these include use of fibrinolytic therapy and primary percutaneous coronary intervention (PPCI). Several studies have shown that PPCI is superior to fibrinolytic therapy in reducing the adverse outcomes, if provided in a timely fashion(6). PPCI restores normal coronary circulation by removing the blockage in the artery through a stent (20). A successful PPCI is defined by the return of normal blood flow to the infarcted area on coronary angiogram. PPCI should be provided in a timely manner and the current guidelines suggest that the first medical contact to insertion of first device time in the infarct related coronary artery should be less than 90-120 minutes depending on the site of presentation of the patient (27, 29).

There is extensive literature on the outcomes following PPCI but only a few studies have examined process times in PPCI (13-16). Of these, most examined the total ischemic (the time from symptom onset to revascularization) and door to balloon (time from arrival at hospital to revascularization) times. To date, only a handful of studies attempt to show the detailed process of PPCI from a patient perspective (17-19). Total ischemic time for PPCI is made up of several component processes times that can each result in delays and contribute to variation in total ischemic time (Figure 3.1). For example, patients may not seek immediate attention for their symptoms or decide to self-transport to the hospital. ECGs may not be performed immediately in patients presenting with atypical symptoms, delaying diagnosis. Other process variables may also influence total ischemic time. For instance, patients who have a pre-hospital ECG can be confirmed prior to their arrival, bypassing the emergency department and heading directly to the cardiac catheterization laboratory (cathlab) for PPCI. Time of day may influence the total ischemic time. For patients presenting with STEMI during holidays or after regular

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hours, the cathlab team needs to come to hospital to perform the intervention, which can add delays.

The objective of this study was to determine which parts of the process of receiving PPCI for STEMI contribute most to total ischemic time, and explain variation in total ischemic time, in a large tertiary care center in Nova Scotia, Canada.

3.2 METHODS

We used data from 2011-2014 that was routinely recorded in the Philips Cardio Vascular Information System (CVIS)®. This database is used in the Queen Elizabeth II Health Sciences Center in Halifax, Nova Scotia to record patient data for those receiving cardiac catheterization, coronary angiography and percutaneous coronary intervention. Research ethics review and approval was obtained from the Nova Scotia Health Authority Research Ethics Board.

3.2.1 Study Population

This study was performed in the Province of Nova Scotia Canada. The province has a single, integrated health care system that serves a population of 940,000. PPCIs are exclusively performed in a single tertiary center in Halifax, equipped with four cardiac cathlabs. Approximately 400,000 people reside within 12 hours of symptoms and within 60 minutes of the total transport time to the center. Process times are routinely recorded as a quality assurance process. By describing the data from 2012-2014, for patients undergoing PPCI, we were able to disaggregate total ischemic time into its pre-hospital and hospital components, and identify which components make the largest contribution to, and explain the most variation in total ischemic time.

There were 517 patients identified in the database as having received PPCI for STEMI from 2012-2014. STEMI was defined as $\geq$1mm ST-segment elevation two contiguous leads. Four patients had PPCI for STEMI in hospital as inpatients and were excluded since they do not represent the majority of patients who receive PPCI for STEMI. Two other patients who received PPCI during 2012-2014 came from

satellite sites, which were outside the recommended transport times. Seventy-seven subjects had missing data and were removed from the final analysis. This left us with a total of 438 patients for the final analysis (Figure 3.2).

3.2.2 Variables of Interest

The dependent variables of interest were total ischemic time and each process time. Total ischemic time was defined in two ways as 'Symptom Onset to Revascularization' and 'Diagnostic ECG (in cases where first ECG was non diagnostic for STEMI) to Revascularization.' Using diagnostic ECG as the starting point of total ischemic time has its challenges; the diagnostic ECG confirms the STEMI, but it most likely occurred between the point of symptom onset and the diagnostic ECG. Process times were defined as 'Symptom Onset to Hospital Arrival,' 'Symptom Onset to First Medical Contact,' 'First Medical Contact to First ECG,' 'First Diagnostic ECG to cardiac cathlab being activated,' (using a paging system for the PPCI on call team trough the hospital telecommunication system) 'Lab being activated to Lab being Ready,' 'Lab being Ready to Patient Arrival in the lab,' and 'Lab Arrival to Revascularization.'

Additional "process variables" were included in the analysis, as they may explain variation in process times: 'Use of Emergency Health Services (EHS), 'Pre-activation of the Cardiac Cathlab,' and 'Activation After Hours.' 'Use of EHS' refers to the patient calling 911 and being transported via ambulance. Paramedics in Nova Scotia are trained to recognize STEMI on ECGs and can activate the cardiac cath laboratory prior to hospital arrival through consultation with emergency room physician through radio patch. 'Pre-activation of the Cardiac Cathlab' indicates that a diagnostic ECG was obtained prior to hospital arrival by paramedics and, through consultation with emergency room physician, have activated the cardiac cathlab and preparations are being made prior to the patient's arrival at the hospital. At our center, the cathlab has staff in hospital during the regular working days from 0900-17:00. On weekends, holidays, and outside the 09:00-17:00 window, the cardiac cathlab staff are on-call but are not in hospital and are called in for PPCI. Therefore cathlab activation after hours is an important variable that contributes to the total

ischemic time. The pieces of the process were also used to assess which process times contributed the most to total ischemic time.

3.2.3 Statistical Analysis

All statistical analyses were performed using STATA 13.1 statistics package (41). Median times with interquartile ranges (IQR) were calculated in order to describe total ischemic and process times. This allowed us to identify which process times were the largest contributors to total ischemic time as well as determine which pieces of the process are most amenable to intervention.

Total ischemic and process times were compared by process variables: 'Use of EHS,' 'Pre-activation of the Cardiac cathlab,' and 'Activation After Hours.' Kolmogorov-Smirnoff tests were used to determine if the distribution of total ischemic and process times differed by process variables.

We estimated the proportion of variance in total ischemic time attributable to each process time. Separate OLS regression models of each process time on total ischemic time were estimated. R-squared values for each regression measured the percent of variation in in total ischemic time explained by each process time. As the distributions of the dependent variable, total ischemic time, was positively skewed, it was log transformed. Coefficients were estimated from OLS regressions of each process variable on the log of each measure of total ischemic time in order to identify which process variables were associated with reductions in total ischemic time.

3.3 RESULTS

Among the 438 patients who received PPCI for STEMI at our center, 'Symptom Onset to Revascularization' had a median time of 173 minutes (IQR: 137-251 minutes). Using 'Diagnostic ECG to Revascularization' as total ischemic time, the median time was 87 minutes (IQR: 74 -104 minutes). Quintiles for total ischemic times and process times are shown in Table 3.1.

The longest process time was 'Symptom Onset to Hospital Arrival.' The median time was 88 minutes with an IQR of 56-155 minutes. Another process time

that was also by comparison much longer than the rest of the process times was 'Symptom Onset to First Medical Contact' (Median time: 60 minutes, IQR: 31-136 minutes).

The majority of the variation in total ischemic time was accounted for by the earlier stages in the process of receiving PPCI (Table 3.2). 'Symptom Onset to Hospital Arrival' and 'Symptom Onset to First Medical Contact' were found to account for most of the variation seen in 'Symptom Onset to Revascularization' (R^2= 0.53 and 0.58 respectively). All other process times were found to account for less than 10% of the variation seen (Table 3.2). Using 'Diagnostic ECG to revascularization' as total ischemic time, 'Cardiac cathlab Page to Lab Ready' had the largest R^2 of 0.19.

Process variables were strongly associated with total ischemic times. 'Symptom Onset to Revascularization' time was significantly associated with all three process variables (Table 3.3). 'Use of EHS' was found to have significantly shorter 'Symptom Onset to Revascularization times' ($p<0.001$). 'Pre-activation of Cardiac cathlab' was also found to significantly reduce 'Symptom Onset to Revascularization' time ($p<0.001$). 'Activation After Hours' of the cardiac cathlab was determined to influence 'Symptom Onset to Revascularization' time ($p=0.012$). However, when considering total ischemic time as 'Diagnostic ECG to Revascularization,' only 'Activation After Hours' was found to be associated ($p<0.001$).

Specific process times were also significantly associated with process variables (Table 3.4). 'Symptom Onset to First Medical Contact' time was found to be significantly shorter for those who called EHS ($p<0.001$). Those that contacted EHS also had shorter 'First Medical Contact to ECG' times ($p<0.001$). 'Use of EHS' was also found to have shorter process times even once the patient was in the hospital (see Table 3.4). 'Diagnostic ECG to Lab being activated' and 'Lab being activated to Lab being Ready' times were found to be significantly longer during after hours activation ($p=0.04$ and $p<0.001$ respectively). '

Process variables were found to be significantly associated with shorter total ischemic and process times (Table 3.5). When EHS was called, 'Symptom Onset to Revascularization' was reduced by 29% (Coefficient: -0.29, 95%CI: -0.39, -0.20). 'Pre-activation' was also found to have a similar effect (Coefficient: -0.27, 95%CI: -0.38, -0.17). Activation after hours was not found to be associated with 'Symptom Onset to Revascularization' time but was found to be associated with a 22% (95%CI: 0.17, 0.27) increase in 'Diagnostic ECG to Revascularization' time.

3.4 DISCUSSION

For patients who experience a STEMI, time to treatment is one of the biggest predictors of damage to the heart muscle, and timely PPCI is the preferred treatment for restoring blood flow to the heart muscle. The time from symptom onset to revascularization by PPCI (i.e. 'total ischemic time ') is a key determinant of outcomes in STEMI patients. Thus, understanding factors that contribute to ischemic time is critical for improving processes of care and patient outcomes.

The idea that total ischemic time may be more influenced by time before arriving at the hospital is not new (42), but no previous studies have examined the contribution of individual process times, prior to and after arrival at hospital, on total ischemic time. This study is the first to provide a detailed picture of total ischemic time in patients who received PPCI for STEMI. In our literature review we did not find any studies that attempted to describe process times that lead to PPCI in this detail. Additionally, this study also examined associations between the processes in place to expedite care and total ischemic time. For example, using EHS and pre-activation of cardiac cathlab showed a significant reduction in 'Symptom Onset to Revascularization' time

The time from symptom onset to hospital arrival, and not the process times within hospital, make the largest contribution to total ischemic time. Process times following arrival at hospital have far less of an impact on total ischemic time. There exists a surplus of literature addressing "door to balloon" times in order to reduce total ischemic time (43, 44). However, in our center, as with many others (12), there is limited potential for further reductions in process times within

hospital. The real potential for reduced total ischemic time is much earlier in the process, before contact with healthcare has even occurred. Considering this, the issue of total ischemic time is more related to the patient factors than hospital system issues. The delay in patients seeking medical care appears to have completely dwarfed any other process time in terms of variation and duration. Are patients unaware of symptoms related to acute coronary syndrome? What can be done to promote earlier recognition by patients of STEMI symptoms, rapid seeking of care? Reluctance to seek care is not a new phenomenon, and it would seem that patients may not benefit from education programs in symptom recognition (45,46). Perhaps what needs to occur is proper communication of the risk that a patient has of having a myocardial infarction. Thanks to studies using the Framingham Heart Study data, healthcare providers are well aware of what factors predict myocardial infarction and heart disease (47-49). Although the physician may know which patients are truly at risk for STEMI, this may not always be communicated to the patients themselves. The next step in reducing total ischemic times could come from an approach that identifies patients who are at the greatest risk of having STEMI and informing them of their risk. This could be performed at the physician level by educating their patients of their risk and what signs and symptoms that could indicate a STEMI.

  While delays in seeking treatment are the largest contributor to ischemic times, our results identify some system processes that significantly affect total ischemic time. When considering total ischemic time as 'Diagnostic ECG to revascularization,' there appears to be longer delay in the first steps of activating the cardiac cathlab. The most variable process time is 'Cardiac cathlab activated to Lab Ready'. This could be due to various reasons not recorded in this data set. For instance, delays due to overload in the cardiac cathlab or delays due to communication between departments. Even still, the data from our hospital center does not show any significant within-hospital system delays that explain much of the variation in total ischemic time.

  This study has certain limitations. It is single center, retrospective study with missing data for fifteen percent of subjects who were excluded from analysis.

However reviewing the coding practices and reasons for missing data, it is our opinion that results would be similar even with the inclusion of the subjects with missing data. On inspection of the missing data, it was noted that the majority was due to symptom onset not being routinely recorded. This is most likely a documentation issue at the healthcare provider level and highlights the importance of documentation. Symptom onset time was given as an approximation by the patient. Recall bias aside, these patients are in a critical state when seeking medical care and may not be able to provide an accurate time of when the symptoms started. Granted, using the diagnostic ECG as the start of the total ischemic time also has its challenges; the onset of STEMI most likely occurred before the ECG showed an injury pattern diagnostic of STEMI for reperfusion therapy. There is, however, no practical way other than these two measures in calculating total ischemic time for patients with STEMI.

Another limitation of this study is that only patients who received PPCI were included in analysis, those that died on the way to hospital, in-hospital prior to PPCI, or during PPCI were excluded. Even though these were very few in number, it was considered that these patients did not have the full process of receiving PPCI, and their exclusion may bias results. Potentially these are the patients who had the longest delay. For the purpose of this study, we wanted to examine the majority of patients who went through the entire process of PPCI in order to have a clear picture of where delays occur on average. In the big picture, finding which process time explains the majority of the variation would provide the most utility in reducing total ischemic time for PPCIs.

Finally, since our province has only one center that provides PPCI for a specified region, our results may have compromised generalizability. For instance, patients suffering from acute coronary syndrome may self-transport to their nearest hospital which may be one of the satellite sites (Dartmouth General Hospital or Cobequid Community Health Center). Those that called EHS would then be more likely to bypass the closest hospital in favor of the center that can perform PPCI, thereby shortening their total ischemic time.

In summary, this study identified where most of the total ischemic time actually occurs in the process of receiving PPCI for STEMI. The analysis in this study indicate that the majority of delay occurs in the earlier stages of total ischemic time, that is, prior to first medical contact or hospital arrival. This would suggest that patients are either unaware of the symptoms of acute coronary syndrome or reluctant to seek medical care for acute coronary syndrome symptoms. Further investigation into patient perspectives of acute coronary syndrome and patient delay in seeking medical care is warranted. Overall, however, it appears that the length of process times in receiving PPCI for STEMI are short from hospital arrival onward and that system delays are low at our PPCI center in Halifax Nova Scotia.
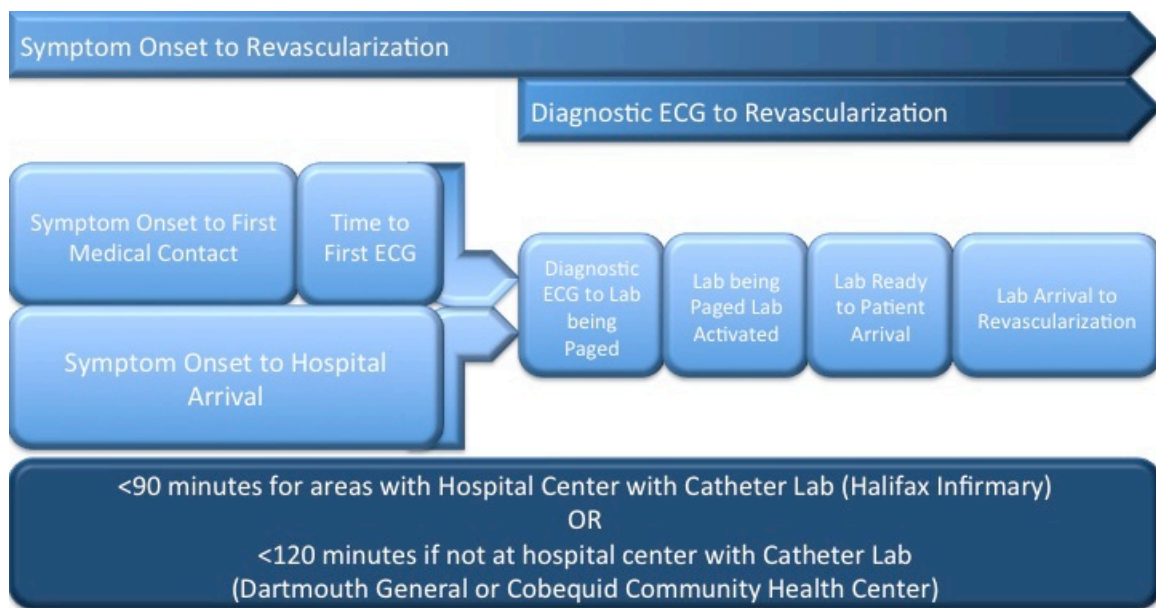
Figure 3.1: Total ischemic time and different points in the process of receiving PPCI. Total ischemic time can be measured at two points; at symptom onset or diagnostic ECG (either at first medical contact or during hospital visit).
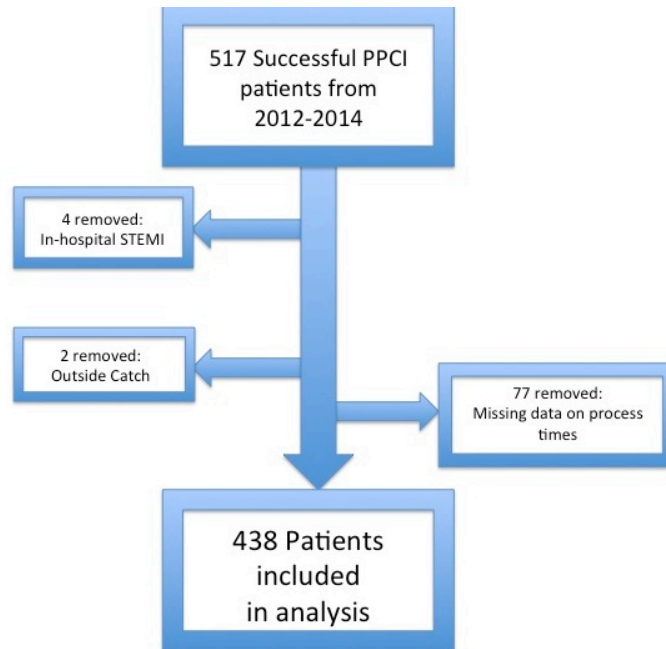
Figure 3.2: Flow diagram through which PPCI patients were determined to be included in the analysis.

Table 3.1: Quintiles of total ischemic and process times in minutes for patients who received PPCI for STEMI during 2012-2014.

Time N=438	10%	25%	50%	75%	90%
Total Ischemic Time					
Symptom Onset to Revascularization	107	137	173	251	421
Diagnostic ECG to Revascularization	63	74	87	101	121
Process Times					
Symptom Onset to Hospital Arrival	36	56	88	155	332
Symptom Onset to First Medical Contact	17	31	60	136	311
First Medical Contact to First ECG	0	4	8	13	21
Diagnostic ECG to Cardiac cathlab Page	5	9	14	22	33
Cardiac cathlab Page to Lab Ready	1	10	25	35	44
Lab Ready to Patient Arrival in the lab	5	10	10	16	32
Lab Arrival to Revascularization	20	25	31	39	48

Table 3.2: Percent of the variance in total ischemic time explained by each process time[a]

Time	Symptom Onset-Revascularization	Diagnostic ECG-Revascularization
Process Times	Percent	Percent
Symptom Onset to Hospital Arrival	0.53	*
Symptom Onset to First Medical Contact	**0.58**	*
First Medical Contact to First ECG	0.08	*
Diagnostic ECG to Cardiac cathlab Page	0.01	0.15
Cardiac cathlab Page to Lab Ready	0.01	**0.19**
Lab Ready to Lab Arrival	0.01	0.05
Lab Arrival to Revascularization	0.04	0.17

[*]Not calculated as these can't influence 'Diagnostic ECG to Revascularization'
[a] Percent variation explained is estimated as the R-squared from OLS regressions of each process time on the log of each measure of total ischemic time..

Table 3.3: Median total ischemic times comparing 'Use of EHS,' 'Pre-activation of Cardiac cathlab' and 'After Hours Activation.'

Time	Median Times (IQR) in minutes		
Total Ischemic Time	**Used EHS**	**Self-Transport**	**p-value[a]**
Symptom Onset to Revascularization	153 (126-199)	202 (150.5-320)	<0.001
Diagnostic ECG to Revascularization	87 (74-99)	87.5 (74-104)	0.449
Total Ischemic Time	**Pre-activation**	**No Pre-activation**	**p-value[a]**
Symptom Onset to Revascularization	147 (118-192)	192 (146-286)	<0.001
Diagnostic ECG to Revascularization	85 (74-97)	89 (74-104)	0.124
Total Ischemic Time	**Regular Hours**	**After Hours**	**p-value[a]**
Symptom Onset to Revascularization	169.5(119-242)	176.5(139-253.5)	0.012
Diagnostic ECG to Revascularization	75.5(60-92)	91 (80.5-105.5)	<0.001

[a] Kolmogorov-Smirnov test used to test for differences in the distribution of total ischemic times by process variables

Table 3.4: Median process times comparing 'Use of EHS,' 'Pre-activation of Cardiac cathlab' and 'After Hours Activation.'

Time	Median Times (IQR) in minutes		
Process Times	Used EHS	Self-Transport	p-value[a]
Symptom Onset to Hospital Arrival	87(60-132)	96.5(48-207.5)	0.002
Symptom Onset to First Medical Contact	44.5(26-90)	96.5(48-207.5)	<0.001
First Medical Contact to First ECG	6(0-10)	11(7-16)	<0.001
Diagnostic ECG to Cardiac cathlab Page	16(10-24)	12.5(8-19)	0.004
Cardiac cathlab Page to Lab Ready	25(10-34)	25(10-35)	0.979
Lab Ready to Lab Arrival	10(10-15)	10(10-20)	0.439
Lab Arrival to Revascularization	30.5(25-38)	32.5(26-41)	0.037
Process Times	Pre-activation	No Pre-activation	p-value[a]
Symptom Onset to Hospital Arrival	90(66-136)	86.5(49-175)	<0.001
Symptom Onset to First Medical Contact	48(27-91)	74(37-167)	<0.001
First Medical Contact to First ECG	6(0-9)	10(5-16)	<0.001
Diagnostic ECG to Cardiac cathlab Page	15(9-21)	14(8-23)	0.593
Cardiac cathlab Page to Lab Ready	26(15-35)	25(8-35)	0.139
Lab Ready to Lab Arrival	10(10-15)	10(10-20)	0.570
Lab Arrival to Revascularization	30(25-37)	32(26-40)	0.076
Process Times	Regular Hours	After Hours	p-value[a]
Symptom Onset to Hospital Arrival	84.5(56-163)	90(58-155)	0.907
Symptom Onset to First Medical Contact	60.5(31-144)	60(21-133)	0.999
First Medical Contact to First ECG	8(5-13)	8(4-13)	0.972
Diagnostic ECG to Cardiac cathlab Page	12(8-20)	15(9-23)	0.04
Cardiac cathlab Page to Lab Ready	5(1-20)	30(22-36)	<0.001
Lab Ready to Lab Arrival	10(10-20)	10(10-15)	0.161
Lab Arrival to Revascularization	32(25-38)	31(25.5-40)	0.948

[a] Kolmogorov-Smirnov test used to test for differences in the distribution of process times by process variables

Table 3.5: The effect of 'Use of EHS,' 'Pre-activation of Cardiac cathlab' and 'After Hours Activation on total ischemic time[a]

Time	Coefficient	CI (95%)	p-value
Total Ischemic Time with 'Use of EHS'			
Symptom Onset to Revascularization	-0.29	(-0.39, -0.20)	<0.001
Diagnostic ECG to Revascularization	-0.002	(-0.05, 0.05)	0.964
Total Ischemic Time with 'Pre-activation'			
Symptom Onset to Revascularization	-0.27	(-0.38, -0.17)	<0.001
Diagnostic ECG to Revascularization	-0.03	(-0.08, 0.2)	0.275
Total Ischemic Time during' After Hours'			
Symptom Onset to Revascularization	0.08	(-0.03, 0.18)	0.15
Diagnostic ECG to Revascularization	0.22	(0.17, 0.27)	<0.001

[a] Coefficient is estimated from OLS regressions of each process variable on the log of each measure of total ischemic time.

CHAPTER 4. PROCESS TIMES IN PRIMARY PERCUTANEOUS CORONARY INTERVENTION: ARE MEN AND WOMEN BOTH ON THE FAST TRACK?

(Manuscript)

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ABSTRACT

BACKGROUND: Primary percutaneous coronary intervention (PPCI) if provided in a timely fashion remains the treatment of choice for patients presenting with ST-elevation myocardial infarction (STEMI). Total ischemic time during STEMI (time from the onset of symptoms to the achievement of normal flow in the infarct related artery) is an important predictor of the degree of myocardial injury and occurrence of other short and long-term adverse events including mortality. Women have been identified as achieving less benefit from PPCI compared to men and it has been suggested that women may have longer total ischemic times. The objective of this study was to determine if women had longer total ischemic or process times compared to men.

METHODS: Total ischemic and process times for patients who received PPCI from 2012-2014 in the Queen Elizabeth-II Halifax Infirmary were described and compared in order to identify which pieces of the process differed between sexes. Median total ischemic and process times were calculated and compared by sex using the Kolmogorov-smirnov test. Regression modeling was performed in order to identify associations between sex and total ischemic and process times. Multivariate regression modeling was performed to adjust for process variables and cardiac history.

RESULTS: 438 patients who had successful PPCI and complete process times were identified in our center. Median times were found to be comparable between men and women at all stages of the process except for 'Symptom Onset to Hospital Arrival' (p=0.031). Sex was found to not be crudely associated with increased total ischemic or process times. Being female was associated with a 15% increase in the logarithm of 'Symptom Onset to Revascularization' time after adjustment of process variables and cardiac history.

CONCLUSIONS: In our study we determined that median process times did not differ by sex. However, one measure of total ischemic time was found to be associated with sex after adjustment for process and clinical variables.

4.1 INTRODUCTION

ST-Elevation Myocardial Infarction (STEMI) is a medical emergency and must be treated quickly.). Several studies have suggested that PPCI being superior to the fibrinolytic therapy in reducing the adverse outcomes if provided in a timely fashion (6). PPCI is the primary process of intervention in the infarct related coronary artery using devices like balloons and stents to restore normal coronary circulation during the process of a STEMI (20). A successful PPCI is defined by the return of normal blood flow in the infarct related artery on coronary angiogram.

The current literature has identified sex differences in outcomes of PPCI for STEMI. It has been argued that women may not fare as well with PPCI for STEMI compared to men (36). One of the reasons cited is a longer total ischemic time in women (37), which is one of the factors predictive of adverse outcome for patients presenting with STEMI (38-40). One possible reason for this is that women have more atypical presentations than males with STEMI, and therefore the decision to seek medical care may be further delayed among women than men (10). This, and other differences in process times may help account for the variation that is seen in the adverse outcomes between men and women presenting with STEMI.

Process times for receiving PPCI have been scarcely examined in the literature. There is a paucity of research examining the differences in process times between men and women. A recent study by Pelletier et al. has shown that, in a few Canadian hospitals, women had longer 'door-to-ECG' times and 'door-to-needle' (fibrinolysis) time in comparison to men (11). This study, however, found that 'door-to-balloon' time (PCI) was not significantly different between women and men (11). At each stage of the process of receiving PPCI (Figure 4.1) there is room for delay. Detailed system delay differences between men and women have not been investigated.

The objective of this study was to determine if there were significant differences among the process times between men and women who received PPCI for STEMI in our center during 2012-2014.

4.2 METHODS

We used data from 2012-2014 that was routinely recorded in Philips CardioVascular Information System (CVIS)®. This database is used in the Queen Elizabeth II Health Sciences Center in Halifax, Nova Scotia to record patient data for those who receive cardiac catheterization, coronary angiography and percutaneous coronary intervention. Research ethics review and approval was obtained from the Nova Scotia Health Authority Research Ethics Board.

4.2.1 Study Population

517 patients were identified as having PPCI for STEMI from 2012-2014. STEMI was defined as $\geq$1mm ST-segment elevation in two contiguous leads. Four patients had PPCI for STEMI in hospital as inpatients and were excluded since these patients do not represent the majority of patients who receive PPCI for STEMI. Two other patients who received PPCI during 2012-2014 came from satellite sites, which were outside the recommended transport times. Seventy-seven subjects had missing data and were removed from the final analysis. This left us with a total of 438 patients for the final analysis (Figure 3.2).

4.2.2 Variables of Interest

The dependent variables of interest were total ischemic time and each component process time. Total ischemic time was defined in two ways as 'Symptom Onset to Revascularization' and Diagnostic ECG to Revascularization.' Ischemic time was defined as two different measures as it is difficult to accurately determine when the blockage occurs. Patients may experience symptoms and have a first ECG that is not confirmatory. The blockage then rapidly develops and serial ECGs confirm STEMI. Using diagnostic ECG as the starting point of total ischemic time also has its challenges; the diagnostic ECG confirms the STEMI, but it most likely occurred between the point of symptom onset and the diagnostic ECG. This limitation is why we decided to measure total ischemic time in two ways: 'Symptom Onset to Revascularization' and 'Diagnostic ECG to Revascularization.' Process times were defined as 'Symptom Onset to Hospital Arrival,' 'Symptom Onset to First Medical

Contact,' 'First Medical Contact to First ECG,' 'First Diagnostic ECG to Cardiac cathlab being activated,' 'Lab being activated to Lab being Ready,' 'Lab being Ready to Lab Arrival,' and 'Lab Arrival to Revascularization.'

Independent clinical variables of interest included sex and previous cardiac history where cardiac history was defined as having a previous myocardial infarction, or previous PCI, or previous coronary bypass artery graft surgery (CABG). Process variables that were also measured to assess the variation in total ischemic time were 'Use of emergency health services (EHS), 'Pre-activation of Cardiac cathlab,' and 'Activation After Hours.' The cardiac cathlab staff is in hospital during the regular working days from 0900-17:00. On weekends, holidays, and outside the 09:00-17:00 window, the cardiac cathlab staff are on-call but are not in hospital and are called in for PPCI therefore cathlab activation after hours is an important variable that contributes to the total ischemic time.

4.2.3 Statistical Analysis

All statistical analyses were performed using STATA 13.1 statistics package (41). Student-t and chi-square tests were used where appropriate to describe the population. Stratifying by sex, median times with interquartile ranges were calculated. Kolmogorov-Smirnoff tests were used to determine if the distribution of total ischemic and process times differed among men and women. This allowed us to guide regression modeling to explore crude associations of sex and process times. To further compare medians, the Wilcoxon Rank Sum test was used to identify if process times that had significantly different distributions had comparable median times in men and women.

To achieve the objective of this study, regression modeling was performed to assess the association between sex and process times. As the distributions of the dependent variable, total ischemic time, was positively skewed, it was log transformed. Ordinary Least Squares linear regression models were performed regressing sex on each process time. We were able to determine if total ischemic and process times were associated with sex. Multivariable linear regression was used to adjust the effects of sex for age and previous history, as well as for process

variables, in order to identify factors that might account for sex differences in total ischemic and process times.

4.3 RESULTS

The majority of patients who received PPCI for STEMI in our center were male (75.3% male vs 24.7% female, p<0.0001). The mean age was 61.5 years. Women were significantly older with a mean age of 65.8 years vs. 60.1 years (p-value<0.0001). There was no difference in the presence of other clinical variables including hypertension, diabetes, dyslipidemia, history of previous PCI or CABG, and history of previous myocardial infarction (Table 4.1).

Table 4.2 shows the total ischemic and process time comparisons by sex. The distribution of total ischemic time was not significantly different between the two sexes, using either 'Symptom Onset to Revascularization' or 'Diagnostic ECG to Revascularization' as total ischemic time (p=0.305 and p=0.231 respectively). Medians were also compared using the Wilcoxon rank sum test (analyses not shown). Women were not found to have significantly different total ischemic times compared to men (p= 0.47 and p= 0.12 for either 'Symptom Onset to Revascularization' and 'Diagnostic ECG to Revascularization' respectively). 'Symptom Onset to Hospital Arrival Time' was significantly longer in women (p=0.031). Median time was compared and this was no longer found to be significantly different (p=0.22). A boxplot of 'Symptom Onset to Hospital Arrival' stratified by sex visualizes this difference (Figure 4.3). 'Lab Arrival to Revascularization' was also significantly longer in women (p=0.026). This should be interpreted with caution. Although these differences in process times are statistically significant, they are not large enough to affect the length of total ischemic time. The variations in 'Lab Arrival to Revascularization' times in both sexes were minimal.

Regression analyses yielded similar conclusions. Sex was not significantly associated with longer total ischemic nor process times. Using a model that adjusted for age, sex continued to not be associated with increase times. Adjusting for cardiac history (as defined as either having a previous MI, previous CABG, or previous PCI)

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also determined no significant sex effect. The models universally had low R^2 values, suggesting that the models did not fit the observed data.

4.4 DISCUSSION

This study uniquely examined sex differences in process times for receiving PPCI for STEMI in this detail. In our sample, we found that although women on average had longer process times, most were not significantly different than men. There appeared to only be one piece of the process where women had longer times; The 'Symptom Onset to Hospital Arrival' time was found to be longer for women when comparing distributions, but the median times were not found to differ. This highlights the fact that depending on the statistical test chosen, as the Kolmogorov-Smirnov test is more sensitive to differences in the tails of the distribution where comparison of the medians using the Wilcoxon-rank sum test was not. Future analysis should focus on sex differences in the risk of having long pre-hospital process times. This difference may be explained by the fact that women are more likely to have atypical symptoms that delays seeking care.

Regression modeling done in our study found that sex was not crudely associated with either total ischemic time or process time. There continued to be no significant sex effect when adjusting for age or cardiac history.

This study has certain limitations. It is single center, retrospective study with missing data for fifteen percent of subjects who were excluded from analysis. However reviewing the coding practices and reasons for missing data, it is our opinion that results would be similar even with the inclusion of the subjects with missing data. On inspection of the missing data, it was noted that the majority was due to symptom onset not being routinely recorded. This is most likely a documentation issue at the healthcare provider level and highlights the importance of documentation.

Another limitation of the study is the method used to calculate total ischemic time. Granted, using the diagnostic ECG as the start of the total ischemic time also has its challenges; the onset of STEMI most likely occurred before the ECG showed an injury pattern diagnostic of STEMI for reperfusion therapy. There is, however, no

practical way other than these two measures in calculating total ischemic time for patients with STEMI. Another limitation of this study is that only patients who received PPCI were included in analysis, those that died on the way to hospital, in-hospital prior to PPCI, or during PPCI were excluded. Even though these were very few in number, it was considered that these patients did not have the full process of receiving PPCI that their inclusion may skew the results. One could argue, however, that potentially these are the patients who had the longest delay. For the purpose of this study, we wanted to examine the majority of patients who went through the entire process of PPCI in order to have a clear picture of where delays occur on average. In the big picture, finding which process time explains the majority of the variation would provide the most utility in reducing total ischemic time for PPCIs.

This study was successful in giving a more detailed picture of total ischemic times and process times among men and women who received PPCI for STEMI in a tertiary care center in Nova Scotia. In our literature review, we did not find any studies that attempted to describe differences in process times between sexes in this level of detail. Most process times and total ischemic times were not found to be significantly different between the sexes and therefore in our sample we can conclude that men and women fare equally in the receiving PPCI for STEMI at our center.
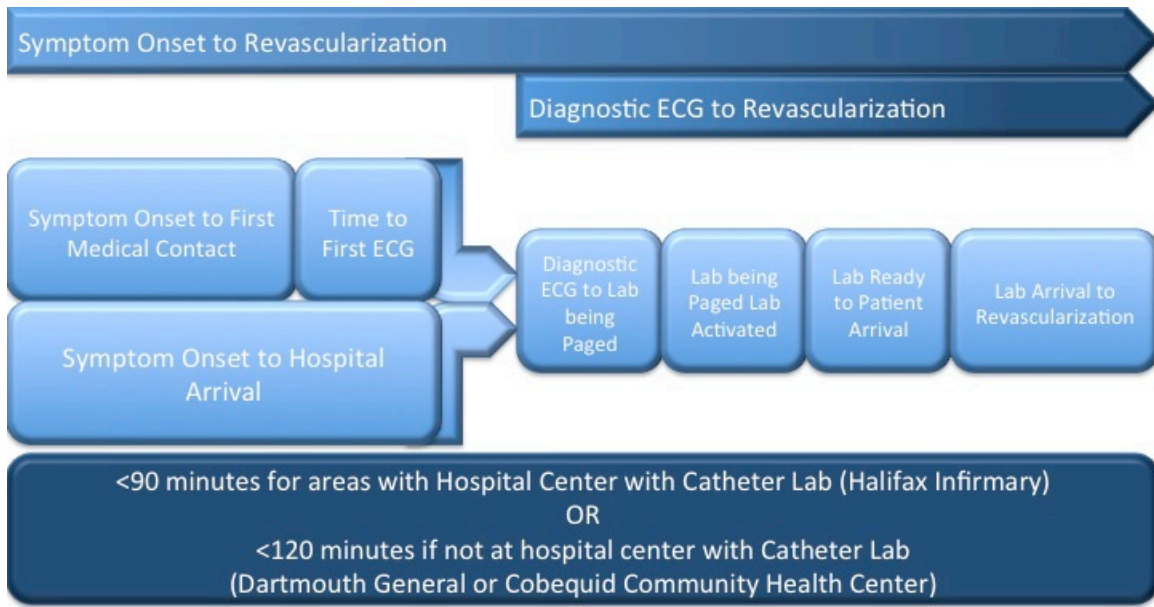
Figure 4.1: Total ischemic time and different points in the process of receiving PPCI. Total ischemic time can be measured at two points; at symptom onset or diagnostic ECG (either at first medical contact or during hospital visit).
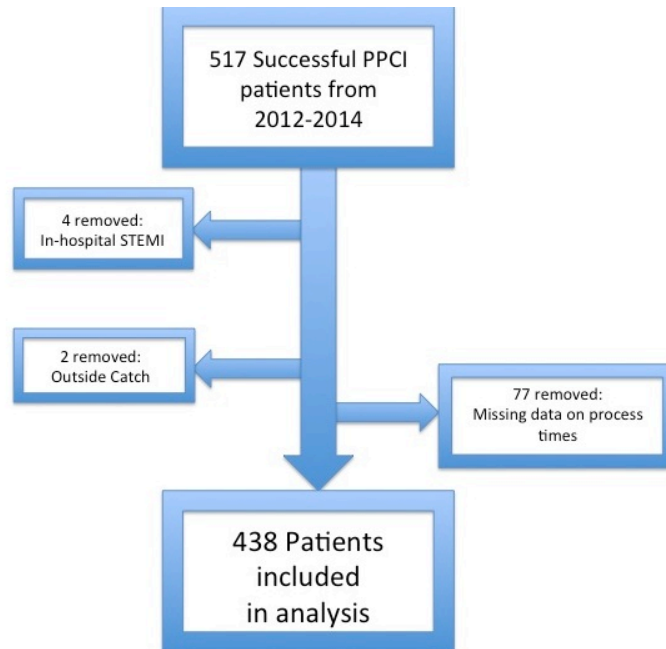

Figure 4.2: Flow diagram through which PPCI patients were determined to be included in the analysis.

Table 4.1: Description of patients who received PPCI for STEMI from 2012-2014 (N=438).

	Overall	Male (n=330)	Female (n=108)	p-value
Age	61.5	59.5	65.6	<0.0001
Hypertension	46%	44%	53%	0.098
Diabetes	17%	18%	15%	0.42
Dyslipidemia	40%	42%	37%	0.41
Previous PCI	10%	11%	8%	0.44
Previous CABG	2%	2%	3%	0.40
Previous MI	11%	11%	9%	0.57

Table 4.2: Median total ischemic and process times in minutes for males and females (N=438).

Time	Median time in minutes Male (IQR) n=330	Median time in minutes Female (IQR) n=108	p-value[a]
Total Ischemic Time			
Symptom Onset to Revascularization	174 (137-242)	169.5 (135.5-292.5)	0.305
Diagnostic ECG to Revascularization	87 (74-100)	91.5 (76.5-103)	0.231
Process Times			
Symptom Onset to Hospital Arrival	86 (56-151)	95 (57-207)	0.031
Symptom Onset to First Medical Contact	60 (32-132)	60 (30.5-182.5)	0.111
First Medical Contact to First ECG	8 (4-13)	8 (4-13)	0.986
Diagnostic ECG to Cardiac cathlab Page	14 (9-22)	15 (9-22)	0.968
Cardiac cathlab Page to Lab Ready	25 (10-35)	25.5 (10.5-33.5)	0.942
Lab Ready to Lab Arrival	10 (10-15)	10 (10-20)	0.589
Lab Arrival to Revascularization	30 (25-38)	34.5 (26-42.5)	0.026

[a] Kolmogorov-Smirnov test used to compare distributions of total ischemic and process times by sex
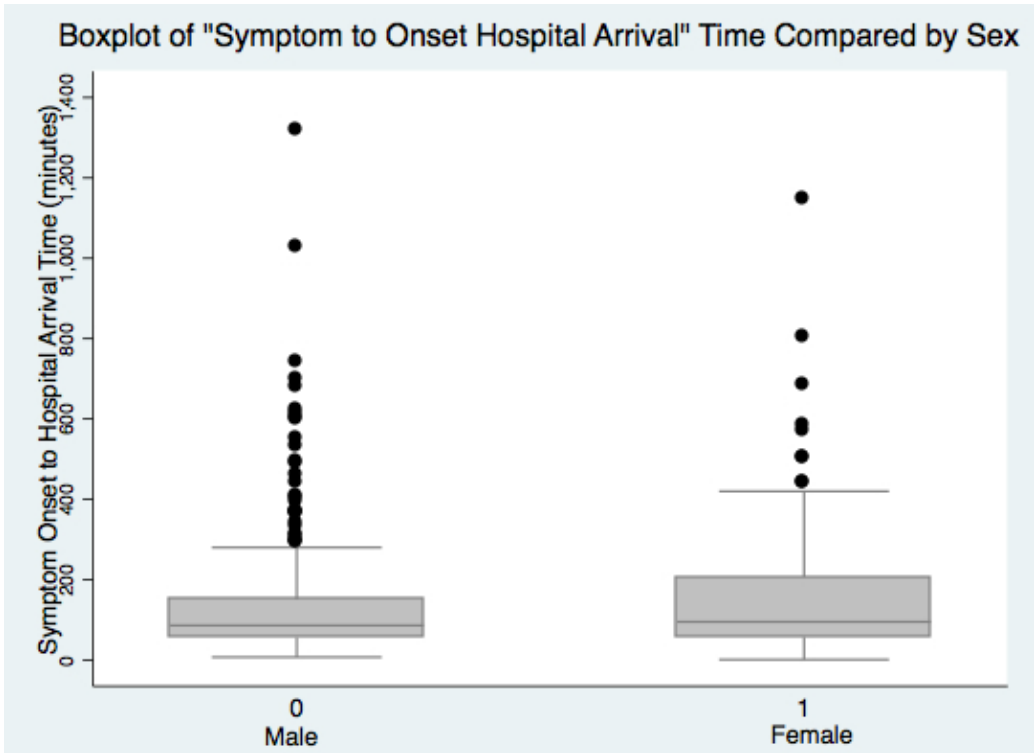
Figure 4.3: Boxplot of "Symptom Onset to Hospital Arrival" time compared by sex.

Table 4.3: Unadjusted and adjusted (for age and cardiac history) effects of sex on the log of total ischemic and process times: OLS regression models (N=438).[a]

Time	Unadjusted (95%CI)		Age adjusted (95%CI)		Cardiac History Adjusted (95%CI)	
	β-Coeff	R-Squared	β-Coeff	R-Squared	β-Coeff	R-Squared
Total Ischemic Time						
Symptom Onset to Revascularization	0.10 (-0.02,0.22)	0.006	0.087 (-0.032,0.20)	0.005	0.099 (-0.018,0.21)	0.005
Diagnostic ECG to Revascularization	0.054 (-0.005,0.11)	0.007	0.042 (-0.018, 0.10)	0.01	0.056 (-0.004, 0.11)	0.013
Process Times						
Symptom Onset to Hospital Arrival	0.16 (-0.038,0.35)	0.0005	0.11 (-0.08,0.31)	0.01	0.15 (-0.04,0.35)	0.01
Symptom Onset to First Medical Contact	0.055 (-0.18,0.29)	0.006	0.019 (-0.22,0.26)	0.02	0.048 (-0.19,0.29)	0.01
First Medical Contact to First ECG	0.075 (-0.098,0.25)	0.002	0.08 (-0.096, 0.26)	0.002	0.07 (-0.11, 0.24)	0.02
Diagnostic ECG to Cardiac cathlab Page	-0.042 (-0.21,0.13)	0.0006	-0.06 (-0.23, 0.11)	0.003	-0.04 (-0.20,0.13)	0.01
Cardiac cathlab Page to Lab Ready	0.027 (-0.15,0.21)	0.002	0.027 (-0.16,0.21)	0.0002	0.027 (-0.15,0.21)	0.0003
Lab Ready to Lab Arrival	0.069 (-0.072,0.21)	0.002	0.076 (-0.069,0.22)	0.003	0.072 (-0.069,0.21)	0.005
Lab Arrival to Revascularization	0.047 (-0.034,0.13)	0.003	0.026 (-0.057,0.11)	0.017	0.048 (-0.034,0.13)	0.004

[a] Log transformation of times were used for regression modeling with each process variable on total ischemic time

Table 4.4: Adjusted linear regression models for total ischemic times examining sex.[a]

Time	Sex (95%CI)	Adjusted for 'Use of EHS' (95%CI)	Model 1 (95%CI)[1]	Model 2 (95%CI)[2]
Symptom Onset to Revascularization	0.10 (-0.02,0.22)	0.15 (0.04,0.26)*	0.15 (0.04,0.26)*	0.15 (0.04,0.26)*
Diagnostic ECG to Revascularization	0.054 (-0.005,0.11)	0.06 (-0.005,0.12)	0.053 (-0.003,0.11)	0.05 (-0.0004,0.11)

*p<0.05
[a] Log transformation of times were used for regression modeling with each process variable on total ischemic time
[1] Model 1: Sex, 'Use of EHS,' 'Preactivation of Cardiac cathlab,' and 'Activation After Hours'
[2] Model 2: Sex, 'Use of EHS,' 'Preactivation of Cardiac cathlab,' and 'Activation After Hours,' Cardiac History

CHAPTER 5. CONCLUSIONS

In this study, we described the total ischemic and process times for patients who received PPCI for STEMI in Halifax Nova Scotia between 2012-2014. We found that the majority of time and the majority of the variation seen in total ischemic time was during the earlier stages of the process, that is, before calling the EHS or self transporting to the hospital. We found that once the patient is in the hospital or have had their diagnostic ECG, each stage of the process accounts for very little of the total ischemic time. Furthermore, these patients are unlikely to be delayed during any of these stages as the variation in time was found to be small once the patient had their diagnostic ECG.

Process variables were also found to be associated with process times. Using EHS and pre-activation of the cardiac cathlab was associated with shorter total ischemic times. After hour STEMI did influence the total ischemic time. Using total ischemic time as either 'Symptom Onset to Revascularization' or 'Diagnostic ECG to Revascularization,' patients were found to have longer times.

Nearly half of the total ischemic time from 'Symptom Onset to Revascularization' was accounted for by the first stage of the process of receiving PPCI. Since most of the variation in total ischemic either 'Symptom Onset to Hospital Arrival' or 'Symptom Onset to First Medical Contact' accounted for time. The idea that patients are reluctant to seek care for cardiac issues is well known and it would appear that patients are probably not well aware of the symptoms of acute coronary syndromes (45). Interestingly, education programs have been attempted to improve patient's awareness of symptoms congruent with acute coronary syndrome (46). Perhaps patient delay is not explained by symptom recognition, but if patients are actually aware that they are at risk for myocardial infarction. Our study would suggest that hospital delay accounts for very little in total ischemic time and more effort in describing patient delay to seek care is needed.

The study has shown that men and women fare equally in terms of total ischemic times at our center. This is in opposition to the existing literature that suggests that women have their first ECG taken later than men (10,11). There were

differences seen in one piece of the process 'Symptom Onset to Hospital Arrival,' but the difference was not seen in 'Symptom Onset to First Medical Contact.' Furthermore, when the medians were compared they were found to not significantly differ between men. However, using the Kolmogorov-Smirnov test showed a significant difference between men and women in the distribution of 'Symptom Onset to Hospital Arrival.' This indicated that women were more likely to have longer pre-hospital times. Future research into sex differences in the risk of having long pre-hospital times is warranted.

In summary, this study appears to be the one of few that has detailed the entire process of receiving PPCI for STEMI in this level of detail. Most of the other studies in the literature have examined either 'door to balloon' times or total ischemic times, but none have broken down total ischemic time into the sum of its parts as performed here. This study contributes to the literature by suggesting that more focus should be on patient delay as opposed to interventions to reduce hospital delays. Some have suggested that as long as 'door to balloon' times remain under 90 minutes, patients have no increase risk of mortality (12). This was met with criticism as it betrays to old adage 'time is muscle' for ischemic injury. Reducing hospital delay would only reduce total ischemic time by a few minutes, where interventions to reduce patient delay may lead to reductions of up to 30 minutes or more. Future studies into the awareness of patient's risk of develop acute myocardial infarction may improve patient outcomes after receiving PPCI for STEMI.

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