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REVIEW

Door-to-Balloon Time for Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction

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ABBREVIATIONS
ECG = electrocardiogram
EMS = emergency medical system
FMC = first medical contact
PCI = percutaneous coronary intervention
pPCI = primary PCI
STEMI = ST-elevation myocardial infarction

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ABSTRACT

Over the recent years it has become clear that reperfusion by primary coronary intervention in patients with ST elevation myocardial infarction (STEMI) is superior to thrombolytic therapy and is the treatment of choice. However, this reperfusion strategy has some drawbacks, as cardiac catheterization laboratories are not always widely available 24 hours/7 days and long- time delays related to primary percutaneous coronary intervention (pPCI) could have negative impact on mortality. The shorter the delay from symptom onset to reperfusion, the greater the amount of the myocardium rescued as it is obvious that "time is muscle". Among pPCI related times the crucial time delay is the "door–to-balloon time", which is the time from arrival at the hospital until the mechanical restoration of the vessel patency. This time delay is usually accurately recorded and depends on the national (or even local) health care system. The European Society of Cardiology guidelines on myocardial revascularization suggest that total ischemic time should not exceed 120 min and especially 90 min for patients <65 years old, with anterior infarction and early presentation (<2 hours) from onset of symptoms, because these categories of patients have even worse outcomes and increased mortality with prolonged door-to-balloon times, compared to other categories.

Better education of the patient about symptoms suggesting myocardial ischemia, pre-hospital diagnosis of STEMI based on 12-lead electrocardiogram with immediate transportation to a PCI-capable center in order to eliminate inter-hospital delays, an effective emergency medical system capable of quick transportation, immediate activation of the cardiac catheterization laboratory from emergency physicians or an attendant cardiologist, the presence of an experienced team of high volume operators and skilled supporting staff capable of performing PPCI 24 hours/7 days, new and more effective antithrombotic drugs and angioplasty materials, are the key elements to achieve shorter door-to-balloon and PCI delay times and therefore to save the greatest amount of myocardium and reduce mortality.

INTRODUCTION

Recently published results from several trials (DANAMI-2,[1] PRAGUE-1,[2] and

-2[3], AIR -PAMI[4] which compared on site thrombolysis with primary PCI (defined as angioplasty and/or stenting without prior or concomitant fibrinolytic therapy), showed that primary PCI (pPCI) is the cornerstone for effective treatment of ST-elevation myocardial infarction (STEMI) patients, when it can be performed by an experienced team. Combined data from those trials put emphasis on the superiority of pPCI in significantly decreasing the composite endpoint of nonfatal myocardial infarction, stroke or death compared to fibrinolysis.[5] Primary PCI is associated with more effective restoration of vessel patency, less re-occlusion, improved residual left ventricular function and better clinical outcome.[6] However, the need for an experienced team including not only interventional cardiologists, but also skilled supporting staff available 24 hours/7 days in combination with an emergency medical system (EMS) capable of establishing quick diagnosis and fast transportation (within acceptable time limits) to a PCI–capable hospital, is the key to a successful treatment. Another challenge to avoid is long delay times of transportation between hospitals, as it is associated with worse clinical outcome and diminished advantage of primary PCI over thrombolytic therapy.

PRIMARY PCI DELAY TIMES-DEFINITIONS

The goal of treatment for patients with chest pain onset of less than 12 hours and persistent ST segment elevation or (presumed) new left bundle branch block is mechanical or pharmaceutical reperfusion of the infarct-related coronary artery with a thrombolysis in myocardial infarction (TIMI) 3 flow and myocardial blush grade 3 achieved as soon as possible.[7] Time from onset of symptoms to restoration of vessel patency is defined as total ischemic time which can be subdivided into time from symptom onset to first medical contact (FMC) and time from FMC (either ambulance crew or PCI capable hospital or non-PCI capable hospital) to balloon inflation (door-to-balloon) or time from symptom onset to administration of thrombolytic therapy (door-to-needle). PCI related time is the difference between the door-to-balloon minus the door-to-needle time. From randomized trials it was calculated that PCI-related time delay that can decrease the effectiveness of mechanical restoration of vessel patency over thrombolysis varies between 60 and 110 min.[8,9] Pinto et al[10] calculated the mean PCI-related time delay where two reperfusion strategies have equal mortality rates and that time was 114 min. However, this time delay varies according to age, time from symptom onset and infarct location. For example a patient <65 years old, with an anterior myocardial infarction presenting early (<2 hours from symptom onset) should undergo primary PCI within <1 hour, while for a patient >65 years old, with inferior infarction and presentation >2 hours after symptom onset, PCI related time could reach 3 hours.

DOOR-TO-BALLOON TIME: THE CRITICAL DELAY AND ITS IMPACT ON OUTCOMES

Although it seems that patients might have some benefit from reperfusion even after long delays including improved ventricular remodeling and less susceptibility to arrhythmias,[11] the longer the total ischemic time and duration of vessel occlusion, the greater the necrosis of the myocardium.[12] However, the impact on mortality of total ischemic time is often difficult to assess, because the part of time from symptom onset to hospital admission is based on patient's sometimes conflicting estimations and thus cannot be independently verified. In contrast, door-to-balloon times are usually more accurately recorded. Several studies indicate that any delay after hospital admission to balloon inflation is associated with worse outcome and higher mortality. In the GUSTO-IIb trial, 30-day mortality was increased with increasing time from randomization to balloon inflation.[13] Brodie et al[14] in a study cohort of 2300 patients indicated that in-hospital mortality was significantly higher with prolonged door-to-balloon times (0 to 1.4 h vs 1.5 to 1.9 h vs 2.0 to 2.9 h vs ≥3 h), with in-hospital mortality rate (4.9% vs 6.1% vs 8% vs 12.2% respectively, $p<0.0001$). Prolonged door-to-balloon times (0 to 1.4 h vs 1.5 to 1.9 h vs 2.0 to 2.9 h vs ≥3 h) were also associated with higher late mortality (12.6% vs 16.4% vs 20.4% vs 27.1% respectively at 7 years $p<0.0001$). According to classification in high and low risk patients presenting with STEMI, the impact on late mortality of delayed (≥2 h vs ≤2 h) door-to-balloon times was greater in high risk patients (32.5% vs 21.5% at 7 years, $p=0.0002$) and early (≤3 h) compared to late presenters (24.7% vs 15.0% at 7 years, $p=0.0001$). High risk patients were defined as patients with Killip class 3 or 4, age >70 years or anterior infarction. Unfortunately high risk patients along with women and diabetics were more likely to have longer door-to-balloon times. McNamara et al[15] in a cohort study including 29222 patients, indicated that longer door-to-balloon time was associated with increased in-hospital mortality (mortality rate of 3.0%, 4.2%, 7% and 7.4% for door-to-balloon times of ≤90 min, 91 to 120 min, 121 to 150 min and >150 min respectively, $p<0.001$). Increasing mortality with increasing door-to-balloon time was independent from time from symptom onset to presentation or presence of high risk factors. On the same wavelength, Rathore et al[16] in a large cohort study of 43801 patients indicated that longer door-to-balloon times were associated with higher risk of in-hospital mortality (mortality rate 3.0% for 30 min, 3.5% for 60 min, 4.3% for 90 min, 5.6% for 120 min, 7% for 150 min and 8.4% for 180 min $p<0.001$) suggesting that time to treatment should be as short as possible, even in centers capable of performing primary PCI within 90 min (absolute reduction in mortality 0.8% for reduction from 90 to 60 min).

REPERFUSION STRATEGIES AND IMPROVEMENT IN DOOR–TO–BALLOON TIMES

The European Society of Cardiology (ESC) guidelines indicate the preferred pathway[17] of treating STEMI patients. Patients referred to a PCI capable center should immediately undergo primary PCI by a team of high volume operators, while patients admitted to non PCI capable hospital should be transferred to a PCI capable hospital if time delay from FMC to balloon inflation is <2 h, or <90 min for patients with large anterior infarction, <75 years old and recent (<2 h) onset of symptoms. If primary PCI cannot be achieved within these time limits, the patient should receive fibrinolysis immediately (door-to-needle <30 min) and then be transferred to a PCI capable hospital in order to undergo angiography and rescue PCI in case of failed fibrinolysis, or angiography and delayed PCI if required, in case of successful fibrinolysis, in a time window of 3-24 hours. According to ACC/AHA guidelines, 75% of STEMI patients should undergo primary PCI within 90 min.[18] However, this task is not always easy to achieve. There are two key points for successful reperfusion with primary PCI: a) short delay times and b) a cardiac catheterization laboratory available 24 hours/7 days including experienced interventional cardiologists and supporting staff.

Despite the fact that better patient education about symptoms indicating myocardial infarction (in order to seek medical help as soon as possible) could minimize the time from symptom onset to FMC and consequently the total ischemic time, reduction of time delays in health care systems including transportation delay and door-to-balloon time, is the main target in order to achieve lower rates of in-hospital and late mortality. For this purpose, not only a well organized medical system is mandatory, but also a well functioning network of centers for safe and rapid STEMI patient transportation. Miedema et al[19] indicated that the greater delays from FMC at the referral hospital until arrival at the catheterization laboratory are observed when there is diagnostic dilemma, non-diagnostic ECG, hemodynamic compromise or bad weather conditions. In this particular study[19] of 2034 patients transferred for primary PCI, the authors reported the frequency, magnitude and clinical impact of specific delays. Each patient's total door-to-balloon time (arrival at referral hospital to balloon at PCI center) was divided into three segments: referral hospital door–in to door-out time, transport time and PCI center door-to-balloon time, with a delay limit of 45-45-30 minutes respectively, and a targeted total door-to-balloon time of 120 minutes. Of the above patients 30.4% were treated with pPCI in ≤90 min and 65.7% in ≤120 min. The most frequent delay was at the referral hospital (64% of the patients) followed by the PCI center (15.7%) and transport (12.6%).The most common reasons for delay at the referral hospital were awaiting transport and emergency department delay. Diagnostic dilemmas and non diagnostic ECG were the delays of the greatest magnitude, while delays caused by cardiogenic shock had the highest mortality. According to our own experience the main causes of inter-hospital and door-to-balloon time delays in our health system are summarized in Table 1 and discussed in detail below. Data from the National Registry for Myocardial Infarction (NRMI)[20] indicated that inter-hospital transfer from a non-PCI to a PCI-capable hospital is associated with low rates of door-to-balloon within time limits (4.2% for door-to-balloon <90 min, 16.2% for door-to-balloon <2 h). It is not surprising that Wang et al[21] indicated that STEMI patients requiring inter-hospital transfer for primary PCI had longer door-to-balloon times in comparison with direct arrival STEMI patients (median 149 vs 79 min $p<0.001$) and few received PCI at ≤90 min (10% vs 63% $p<0.001$). Very recently Pinto et al[22] reported that PCI-related delays are extensive among patients transferred for pPCI and are associated with poorer outcomes. As pPCI was performed with delays >90 minutes in 68% of transferred patients, there was no difference in mortality (5.7% vs 6.1%), in the composite end-point of death or myocardial infarction (6.7% vs 8.6%) and death, myocardial infarction or stroke (7.1% vs 9.3%), but the rate of in-hospital stroke was lower with pPCI (0.7% vs 1.8%) versus on-site thrombolysis; these results indicate the need for decreasing health care system delay by eliminating inter-hospital delay. Brown et al[23] indicated that pre-hospital diagnosis of STEMI with 12-lead electrocardiogram (ECG) and immediate pre-hospital activation of cardiac catheterization laboratory is associated with significant reduction in door-to-balloon time (73±19 min field STEMI, 130±66 min non-field STEMI, 141±49 min historical STEMI; $p<0.001$). Rokos et al[24] indicated that pre-hospital 12-lead ECG STEMI diagnosis and direct transportation to a PCI-capable hospital without any delay related to transportation to a non-PCI capable hospital and then inter-hospital transfer, achieved a door-to-balloon time of ≤90 min in 86% of patients. Also Dieker et al[25] showed that after ambulance-based diagnosis of STEMI, direct transportation to an intervention center with pre-hospital notification of the catheterization laboratory increases more than 3-fold the proportion of patients treated within the time window of the guidelines. Finally according to Postma et al,[26] pre-hospital triage in the ambulance, re-

TABLE 1. Major Causes of Specific Delays Associated With Door-to-Balloon Times in Greece

1. Awaiting transport (>60% of cases)
2. Prolonged time from symptom to first medical contact
3. Long distance, particularly in island population
4. Weather conditions in air- or by sea transport

duces time to treatment, infarct size and improves outcome especially for patients living at a long distance from the PCI center. Other key elements for reduction of door-to-balloon times that have been proposed include enabling of emergency-medicine physician to activate the catheterization laboratory without gaining approval from a cardiologist, or activation of the catheterization laboratory from an attendant cardiologist. Unnecessary intermediate admissions in the emergency room or the intensive care unit in PCI-capable centers should also be avoided. A drawback of primary PCI is that presentation during off-hours is common and seems to be associated with longer times to treatment. In contrast, off-hours presentation does not affect fibrinolytic therapy.[27]

According to ACA/AHA Guidelines, primary PCI should be performed by interventional cardiologists with high volume of such procedures (>75 elective per year and at least 11 for STEMI), in hospitals with an annual volume of >400 elective and >36 primary PCI procedures[28]. Recently, Krumholtz et al[29] presented data from a registry which included all patients undergoing primary PCI reported by hospitals to the centers for Medicare and Medical services in USA and demonstrated that door-to-balloon time declined from a median of 96 min in 2005 to a median of 64 min in 2010. There was corresponding increasing percentage of patients who had times <90 min (44.2% to 91.4%) and <75 min (27.3% to 70.4). These data indicate that significant improvement in door-to-balloon times has been achieved. Finally, significant advances in antithrombotic agents, including new antiplatelet agents with more rapid onset and stronger inhibition of platelet activity (prasugrel and ticagrelor), in combination with manual thrombus aspiration from the culprit lesion have a positive impact on successful mechanical reperfusion and outcome of STEMI patients.

With regards to Greece, official data concerning door-to-balloon time were recently presented by J. Kanakakis[30] (principal investigator for Greece), in the European meeting for the Stent for Life program. According to these data, the door-to-balloon time in our country is 63 min, almost identical with the one of 64 min reported by Krumholtz et al.[29] However, time from symptom to first medical contact (182 min) and time from first medical contact to balloon (142 min) remain, unfortunately, still prolonged. In general terms, regarding the implementation of the program Stent for Life in Greece, a significant improvement from August 2009 until today has been reported, in the rates of pPCI for the treatment of acute myocardial infarction. In particular, while in 2009 rates of pPCI were 9%, those of intravenous thrombolysis 41% and no reperfusion 50% for the total of patients with STEMI, those for 2011 are 32%, 40% and 28% respectively. In absolute terms the number of pPCIs in 2009 increased by 95/1.000.000 inhabitants (i.e. 1491 for the whole country) to 346/1.000.000 inhabitants (i.e. 3733 for the whole country) in 2011. The most important increase occurred in the metropolitan area of the capital, where the proportion of patients treated with pPCI rose from 31% to 59%, very close to the desired objective of 70%. The same registry demonstrated a mortality rate of 4.7% with pPCI, 5.7% with intravenous thrombolysis, 10% with rescue angioplasty and 11% when no reperfusion occurs.[30] Despite these very encouraging and positive early data, problems remain in the setting of pPCI in insular Greece and in the response time of the emergency medical system (EMS-EKAB) for inter-hospital transfers. Although, the various urban, suburban and rural areas of the country, are indeed adequately covered by existing catheterization laboratories, there are still major problems for insular Greece, given also the difficulties in air-transports. Regarding system transfer delays, it remains problematic because of the exceptional difficulties of successful response times from the staff of EMS-EKAB (drivers-paramedics-administrators), when it comes to transporting a patient who arrived to a hospital without catheterization facilities to a PCI center or when a patient with diagnosed STEMI is, by administration procedures, directed to a hospital without a catheterization laboratory. Improved however (as mentioned above) are the response times, when EMS-EKAB is called directly by the patient or his/her relatives on-site for transfer of the suspected patient with STEMI to the appropriate hospital. Satisfactory solutions to these problems may be given by the targeted and planned establishment and operation of catheterization laboratories in cities, which may better cover today's existing gaps. For example, new catheterization laboratories could open up in Tripoli or Kalamata for south-center Peloponnese, thus not streaming to Patras the whole traffic of STEMI patients for the entire Peloponnese; similarly a second catheterization laboratory can open up in Chania for Western Crete and relieve the load directed to Heraklion now serving the entire Crete; other places for new catheterization facilities may include Kavala for the axis of Thessaloniki-Alexandroupoli of Eastern Macedonia, Veria for Western Macedonia, Volos to assist Larissa for Thessaly, and Lamia or Chalkida for Central Greece.

With regards to a more appropriate response of the emergency system transport, positive results may be obtained by pre-hospital ECG diagnosis of STEMI (even via-telemedicine) and triage in the ambulance, direct transportation to a PCI-capable center without unnecessary admittance to a non-PCI capable hospital, pre-hospital activation of the catheterization laboratory before the patient's arrival in order to bypass the emergency department and the presence of high volume operators and skilled supporting staff available 24 hours/7 days. Nevertheless the dominant role, which will largely contribute and determine the success of the whole procedure to decrease as low as possible the door-to-balloon time, is the change of bureaucratic mentality, that still dominates a vast majority of professionals involved in our health system.

CONCLUSION

In conclusion, it is an established knowledge that door-to-balloon time delay is associated with increased mortality in STEMI patients undergoing primary PCI. Thus, reducing this time delay to the greatest extent possible for all patients, including those currently treated within 90 min, might reduce mortality. Better patient education about severity of symptoms, pre-hospital triage and direct transportation to a PCI center, improvements in the organization of the emergency medical system, wise distribution of PCI centers throughout the country, improvements in antithrombotic drugs, angioplasty materials and interventional cardiologist's skills and competence are the cornerstones for achieving short PCI delay times and increase survival.

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