Symptom-to-door time in ST segment elevation myocardial infarction: Overemphasized or overlooked? Results from the AMI-McGill study

Jonathan Afilalo MD¹, Nicolo Piazza MD², Sonia Tremblay MD², Nathalie Soucy PhD¹, Thao Huynh MD MSC²

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BACKGROUND: Ischemic time is a major determinant of infarct size in ST segment elevation myocardial infarction (STEMI). Emphasis is placed on reducing the door-to-reperfusion therapy time component, whereas the symptom-to-door time is often overlooked.

OBJECTIVES: To correlate the symptom-to-door time with left ventricular ejection fraction (LVEF) in patients with STEMI.

METHODS: Acute Myocardial Infarction (AMI)-McGill was a cohort study of consecutive patients with STEMI who presented to three adult university hospitals. Multivariate linear regression was performed to correlate the symptom-to-door time with postinfarction LVEF adjusted for reperfusion method, prior myocardial infarction and components of the Thrombolysis In Myocardial Infarction (TIMI) risk score.

RESULTS: There were 188 patients, with a mean age of 66 years. On arrival to hospital, 23% of patients were in Killip class II to IV and 87% received reperfusion therapy (20% fibrinolytic therapy and 67% primary percutaneous coronary intervention). The median symptom-to-door time was 120 min (first quartile: 60 min, third quartile: 290 min) and the median door-to-reperfusion therapy time was 93 min (first quartile: 54 min, third quartile: 155 min). Three variables were independently correlated with LVEF in the study's regression model: symptom-to-door time (beta: -0.66, 95% CI -1.18 to -0.14; P=0.01), Killip class II to IV on arrival (beta: -6.43, 95% CI -11.87 to -0.99; P=0.02) and anterior territory of the infarction (beta: -5.86, 95% CI -10.55 to -1.18; P=0.02).

CONCLUSIONS: Symptom-to-door time was negatively correlated with postinfarction LVEF in patients with STEMI. Strategies to shorten this delay, such as educating high-risk patients about the symptoms of AMI, should be considered.

Key Words: Angioplasty; Echocardiography; Fibrinolysis; Myocardial infarction; Thrombolysis

Ischemic time is a major determinant of infarct size in ST segment elevation myocardial infarction (STEMI) (1-3). Ischemic time may be subdivided into symptom-to-door and door-to-reperfusion therapy times. Although fibrinolytic therapy is less successful in restoring coronary flow in patients with prolonged symptom-to-door time (4-10), primary percutaneous coronary intervention (PCI) is successful in restoring coronary flow in approximately 90% of patients, regardless of symptom-to-door time (3,11). Previous studies have been conflicting as to whether symptom-to-door time (11,12) or door-to-reperfusion therapy time (13,14) is a superior predictor of clinical outcomes.

Le délai entre l'apparition des symptômes et l'arrivée à l'hôpital en cas d'infarctus du myocarde par élévation du segment ST : Surévalué ou négligé ? Les résultats de l'étude AMI-McGill

HISTORIQUE : La période d'ischémie est un déterminant majeur de la dimension de l'infarctus en cas d'infarctus du myocarde avec élévation du segment ST (IMEST). On s'attarde à la réduction du délai entre l'arrivée et la reperfusion, mais on néglige souvent le délai entre l'apparition des symptômes et l'arrivée à l'hôpital.

OBJECTIFS : Corréler le délai entre l'apparition des symptômes et l'arrivée à l'hôpital avec la fraction d'éjection ventriculaire gauche (FEVG) chez les patients atteints d'un IMEST.

MÉTHODOLOGIE : L'étude sur l'infarctus aigu du myocarde (AMI)-McGill était une étude transversale de patients consécutifs atteints d'un IMEST qui se sont présentés à trois hôpitaux universitaires pour adultes. Les auteurs ont procédé à une régression linéaire multivariée pour corréler le délai entre l'apparition des symptômes et l'arrivée à l'hôpital avec la FEVG après l'infarctus, rajustée selon le mode de reperfusion, l'infarctus du myocarde antérieur et les éléments de l'indice de risque de thrombolyse en cas d'infarctus du myocarde.

RÉSULTATS : Il y avait 188 patients, d'un âge moyen de 66 ans. À leur arrivée à l'hôpital, 23 % des patients étaient en classe Killip II à IV, et 87 % ont reçu une thérapie de reperfusion (20 % une thérapie fibrinolytique et 67 % une intervention coronaire percutanée primaire). Le délai médian entre l'apparition des symptômes et l'arrivée à l'hôpital était de 120 minutes (premier quartile : 60 minutes, troisième quartile : 290 minutes) et le délai médian entre l'arrivée et la reperfusion, de 93 minutes (premier quartile : 54 minutes, troisième quartile : 155 minutes). Trois variables étaient corrélées de manière indépendante à la FEVG dans le modèle de régression de l'étude : le délai entre l'apparition des symptômes et l'arrivée à l'hôpital (bêta : -0,66, 95 % IC -1,18 à -0,14; P=0,01). La classe Killip II à IV à l'arrivée (bêta : -6,43, 95 % IC -11,87 à -0,99; P=0,02) et le territoire antérieur de l'infarctus (bêta : -5,86, 95 % IC -10,55 à -1,18; P=0,02).

CONCLUSIONS : Le délai entre l'apparition des symptômes et l'arrivée à l'hôpital était inversement proportionnel à la FEVG après l'infarctus chez les patients atteints d'un IMEST. Il faut envisager d'adopter des stratégies pour raccourcir ce délai, telles que l'éducation des patients à haut risque quant aux symptômes d'AMI.

Current guidelines emphasize that door-to-reperfusion therapy times should be less than 30 min and 90 min for fibrinolytic therapy and primary PCI, respectively (15). With the emphasis on shortening door-to-reperfusion therapy time, symptom-to-door time may be overlooked. The objective of the present study was to correlate the symptom-to-door time with postinfarction left ventricular function (LVEF).

METHODS

Acute Myocardial Infarction (AMI)-McGill was a cohort study of consecutive patients with STEMI admitted at three adult McGill

¹Sir Mortimer B Davis Jewish General Hospital; ²Montreal General Hospital, McGill University Health Centre, Montreal, Quebec
Correspondence and reprints: Dr Thao Huynh, Montreal General Hospital, 1650 Cedar Avenue E-5200, Montreal, Quebec H3G 1A4.

Telephone 514-934-1934 ext 43241, fax 514-934-8318, e-mail thao.huynhthanh@mail.mcgill.ca

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Figure 1 Included and excluded patients from the Acute Myocardial Infarction (AMI)-McGill study. LVEF Left ventricular ejection fraction

University hospitals (Montreal, Quebec) during 2002. Patients were included if they were 18 years of age or older and had STEMI, defined as ST segment elevation of at least 1 mm in two or more contiguous leads. Patients were excluded if symptom-to-door time exceeded 12 h, STEMI had developed in hospital, they were transferred from other hospitals or an echocardiographic assessment of LVEF was not performed during the index hospitalization.

All three hospitals had onsite PCI facilities. Primary PCI was available with onsite personnel during working hours (8:00 to 17:00 during weekdays) and 24 h on-call personnel outside these hours. The choice of reperfusion therapy was at the discretion of the treating physician, with primary PCI being the preferred option during working hours.

Data collection

Patients with STEMI were identified by screening hospital discharges and coronary care unit admission censuses. Data abstraction was performed by cardiology research nurses. All echocardiograms were performed and interpreted by American Society of Echocardiography level III echocardiographers (16). Study approval was obtained from the directors of professional services at all three hospitals.

Study definitions

Symptom-to-door time was defined as the time of the onset of ischemic symptoms to patient arrival to the hospital. Door-to-reperfusion therapy time was defined as the time of patient arrival to the hospital to administration of the initial reperfusion therapy (first injection of the fibrinolytic drug or first inflation of the intracoronary balloon). The primary outcome was LVEF as measured by transthoracic echocardiography.

Statistical analysis

Categorical variables were presented as proportions and continuous variables were presented as mean $\pm$ SD. Medians and interquartile ranges were used to summarize continuous variables with skewed distributions (symptom-to-door and door-to-reperfusion therapy times). Multivariate linear regression was used to determine correlates of LVEF. The following covariates were entered into the regression model: symptom-to-door time, door-to-reperfusion therapy time, reperfusion method, prior myocardial infarction and the components of the Thrombolysis In Myocardial Infarction (TIMI) risk score (age older than 65 years, weight lower than 67 kg, diabetes mellitus, systolic blood pressure lower than 100 mmHg, heart rate greater 100 beats/min, Killip class II to IV on arrival and anterior territory of infarction) (17,18). All analyses were performed with SPSS version 12 (SPSS Inc, USA).

TABLE 1
Patient characteristics

Age, years (mean $\pm$ SD)	65.6 $\pm$ 13.8
Male sex, n (%)	136 (72.3)
Diabetes mellitus, n (%)	34 (18.1)
Dyslipidemia, n (%)	52 (27.6)
Hypertension, n (%)	76 (40.4)
Current smoking, n (%)	63 (33.5)
Prior myocardial infarction, n (%)	24 (12.8)
Killip class on arrival to the hospital, n (%)	
I	133 (70.7)
II	26 (13.8)
III	7 (3.7)
IV	7 (3.7)
Territory of the ST segment elevation myocardial infarction, n (%)	
Anterior	70 (37.2)
Other	101 (53.7)
Primary reperfusion method, n (%)	
Fibrinolytic therapy	37 (19.7)
Primary percutaneous coronary intervention	126 (67.0)
No reperfusion therapy	25 (13.3)
Time delay, min (median [Q1, Q3])	
Symptom-to-door time	120 (60, 290)
Door-to-reperfusion therapy time	93 (54, 155)
Symptom-to-reperfusion time	200 (134, 436)

STEMI ST segment elevation myocardial infarction; Q1, Q3 First, third quartiles

RESULTS

There were 303 patients admitted with STEMI at the three hospitals during 2002. Of these patients, 103 patients transferred from other hospitals and 12 patients without echocardiographic assessment during the index admission were excluded (four patients died and eight patients were discharged before an echocardiogram could be obtained) (Figure 1).

One hundred eighty-eight patients with a mean age of 65.6 $\pm$ 13.8 years were included; the majority were male (72.3%). Thirteen per cent of these patients had a prior myocardial infarction. On arrival to hospital, 21.2% were in Killip class II to IV and 37.2% had an anterior territory of infarction. Reperfusion therapy was administered in 86.7% of these patients. The primary reperfusion method was fibrinolytic therapy in 19.7% and primary PCI in 67.0%. The median symptom-to-door time was 120 min (first quartile [Q1]: 60 min, third quartile [Q3]: 290 min) and the median door-to-reperfusion therapy time was 93 min (Q1: 54 min, Q3: 155 min) (Table 1).

LVEF was measured a median of two days after the index STEMI (interquartile range: two days). In univariate analysis, LVEF was negatively correlated with symptom-to-door time ($r=-0.27$; $P=0.002$); it was not correlated with door-to-reperfusion therapy time ($r=-0.003$; $P=0.97$). In multivariate linear regression analysis, symptom-to-door time remained correlated with LVEF after adjusting for reperfusion method, prior myocardial infarction and the components of the TIMI risk score (beta: -0.66 , 95% CI -1.18 to -0.14 ; $P=0.01$ for each symptom-to-door hour). The following variables were also independently correlated with LVEF: Killip class II to IV (beta: -6.43 , 95% CI -11.87 to -0.99 ; $P=0.02$) and anterior territory (beta: -5.86 , 95% CI -10.55 to -1.18 ; $P=0.02$) (Table 2).

DISCUSSION

Symptom-to-door time was negatively correlated with early postinfarction LVEF in our patients after adjustment for reperfusion method

and the components of the TIMI risk score. Every symptom-to-door hour reduced postinfarction LVEF by approximately 1%. The results of our study may be more representative of real-world patients, because these patients were older and had more comorbidities than patients enrolled in clinical trials (19).

Our findings are in agreement with those of De Luca et al (12), who reported that symptom-to-door time exceeding 4 h was associated with increased one-year mortality, greater infarct size measured by cumulative enzyme release, and decreased TIMI-3 flow post PCI. Similarly, Lundergan et al (11) observed that symptom-to-door time in patients who underwent primary or rescue PCI was associated with greater infarct size measured by ventriculography at five to seven days. Door-to-reperfusion therapy time was not associated with infarct size or mortality in either of these studies (11,12).

There are three potential explanations for the stronger correlation of postinfarction LVEF with symptom-to-door time rather than door-to-reperfusion therapy time in our study. First, symptom-to-door time in our study was the major component of the total ischemic time (60%). Second, symptom-to-door time is spent without the benefits of antiplatelet and antithrombotic therapies, which may help to partially restore coronary flow before reperfusion therapy. Finally, the door-to-reperfusion therapy time may be a surrogate marker for quality of care delivered at a particular hospital. In support of this, door-to-reperfusion therapy time has been shown to be predictive of clinical outcomes mainly in multicentre studies as opposed to single-centre studies.

Killip class II to IV and anterior territory of infarction were negatively correlated with postinfarction LVEF. The presence of one of these correlates predicted a 6% decrease in postinfarction LVEF. We did not observe a correlation of door-to-reperfusion therapy time with postinfarction LVEF in our study.

Current guidelines for STEMI (15) recommend that health care providers educate patients about the symptoms of myocardial infarction (class I). Patients should be instructed to wait 5 min (10 min according to the Canadian Cardiovascular Society Working Group [20]) before notifying emergency medical services (class I). The National Heart, Lung, and Blood Institute developed the National Heart Attack Alert Program (21) and, more recently, a campaign called *Act in Time to Heart Attack Signs* (22,23). Educational materials such as wallet cards and pamphlets are provided to high-risk patients to promote early recognition of symptoms and expedite time to medical contact. These educational tools have not been evaluated in clinical trials, and their benefits are not yet known. The Rapid Early Action for Coronary Treatment (REACT) trial (23), an 18-month multifaceted community education program, did not shorten symptom-to-door time and did not reduce adverse outcomes.

Limitations

First, the retrospective design limited us to data available in the hospital charts. Second, early echocardiographic assessment might have underestimated postinfarction LVEF because of acute myocardial stunning. However, early postinfarction LVEF is a strong predictor of major adverse cardiac events in STEMI (24). Third, echocardiographic assessment was performed by various echocardiographers at the three hospitals. We did not measure interobserver and intraobserver variations, although all of these echocardiographers had American Society of Echocardiography level III training (16). Fourth, 13.3% of our patients did not receive reperfusion therapy. Thus, the smaller number of patients with available door-to-reperfusion therapy times limited our ability to detect correlations between this time delay and LVEF. Finally, we did not explore the potential complex interactions between symptom-to-door and door-to-reperfusion therapy times. The impact of door-to-reperfusion therapy time may be greater in patients with shorter symptom-to-door time and attenuated in patients with prolonged symptom-to-door time.

TABLE 2
Independent correlates of postinfarction left ventricular ejection fraction

	Beta	95% CI	P
Symptom-to-door time delay (per hour)	-0.66	-1.18 to -0.14	0.01
Killip class II to IV	-6.43	-11.87 to -0.99	0.02
Anterior territory	-5.86	-10.55 to -1.18	0.02

CONCLUSIONS

In patients with STEMI, symptom-to-door time is associated with a decrease in postinfarction LVEF independent of the reperfusion method. Thus, shortening symptom-to-door time may reduce the risk of LV dysfunction in STEMI. Strategies to shorten this time delay, such as educating high-risk patients about the symptoms of myocardial infarction, should be considered to avoid delays in seeking medical attention.

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