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Assessment of Time Delay Threshold Values till Primary Percutaneous Coronary Intervention and their Effects on Coronary Artery Flow, Myocardial Perfusion and Left Ventricular Systolic Function

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Abstract

***Background:** Primary percutaneous coronary artery intervention (PCI) in patients with acute ST-elevation myocardial infarction (STEMI) leads to myocardial salvage.*

***Objectives:** To test whether shorter periods to primary PCI improve coronary flow, myocardial perfusion and left ventricular systolic function. Methods: 170 patients with acute anterior STEMI treated by primary PCI were evaluated. Time periods from onset of chest pain to first medical contact (FMC) and from FMC to primary PCI (FMC- PCI) and from pain to primary PCI (Pain - PCI) were recorded.*

***Results:** Patients with pain-PCI<300 min, tended to achieve TIMI grade III more frequently (51%vs 33%), p=0.06 and more frequent MBG≥2, (53% vs 36%), p=0.08. Partial ST-elevation resolution was achieved more frequently in patients with pain- PCI<180min (87% vs 65%), p<0.05. Lower peak troponin levels were found in patients with pain- PCI<300 min (49.2±45.2 vs 84.2 ±43 ng/ml), p=0.03. In patients with pain-PCI< 180min, left ventricular ejection fraction (LVEF) increased by 10±8% vs 5.5±5%, p<0.05. In patients with pain-FMC < 90 and < 120 min the increase in LVEF was larger than in others, p<0.05. FMC- PCI less< 180min was associated with larger increase in LVEF, p<0.05.*

***Conclusion:** Decreasing pain to PCI intervals, improves myocardial perfusion and LVEF.*

Keywords: *STEMI; Primary coronary angioplasty; coronary flow; Left ventricular function.*

Abbreviations

PCI: Primary percutaneous coronary artery intervention; **STEMI:** ST-elevation myocardial infarction; **FMC**: first medical contact; **FMC- PCI:** FMC to primary; PCI; **Pain – PCI:** pain to primary PCI**; LVEF:** left ventricular ejection fraction; **MCI:** Mild Cognitive Impairment; **AD:** Alzheimer's disease; **SSRIs:** Selective Serotonin Reuptake Inhibitors

Introduction

Primary percutaneous coronary intervention (PCI) is the optimal therapy for ST-segment elevation myocardial infarctions (STEMIs) when promptly available (1-5). After occlusion of a coronary artery, the wave front of necrosis progresses from the center of necrosis in the subendocardium, towards the epicardial and adjacent ischemic but still viable regions (6). Rescue of these peri-necrotic viable but ischemic regions, must be performed promptly, since the time from hospital arrival to primary PCI—the door-to-balloon time—is associated with morbidity and mortality (7-8). Door-to-balloon time became a quality measure of hospital performance, and thus, North American and European guidelines recommend a door-to-balloon time of ≤90 minutes (9-12).

Coronary artery flow (13) and left ventricular systolic function (14) after primary PCI are important predictors of prognosis. Coronary artery flow is very important in predicting recovery of left ventricular systolic function in patients with acute STEMI treated by primary PCI (15-16). Coronary artery and myocardial flow after primary PCI are dynamic and reflect the dynamic nature of the coronary microcirculation after primary PCI (17).

The present study was performed to test the hypothesis that time delays after the onset of the chest pain of STEMI and hospital arrival till primary PCI affect coronary artery flow, myocardial perfusion and left ventricular systolic function and to find significant time thresholds.

Materials and Methods

One hundred and seventy consecutive patients with acute anterior STEMI undergoing PPCI were enrolled in the study. All fulfilled the following criteria: 1) First anterior wall STEMI. 2) Primary PCI within 12 hours of the onset of symptoms. 3) Routine informed consent to perform primary PCI. Anterior STEMI was defined as continuous chest pain for at least 30 minutes and ST elevation of at least 2.0mm in ≥2 contiguous precordial ECG leads. Exclusion criteria included one of the following clinical or angiographic findings: Prior bypass surgery, previous anterior STEMI, significant left main artery disease, failed primary PCI. Pain to first medical contact (FMC), FMC to PCI and pain to PCI time intervals (18) were registered for all patients during the study period from the beginning 2007 to the end of 2013.

Primary PCI was performed in standard fashion. All subjects were treated with either loading oral clopidogrel (600 mg) and aspirin (300 mg) in the emergency department and maintenance dose of clopidogrel 75mg/day and aspirin 100mg/day or with prasugrel loading 60mg orally and maintained later on 10mg/day with the same regimen of oral aspirin. Anticoagulation before was achieved with heparin bolus 50-70 units/kg body weight to achieve coagulation time≥250msec or with bivalirudin bolus 0.75mg/kg body weight and maintenance dose of 1.75mg/kg/hour intra-venously for 4 hours after the procedure. Coronary angiography and PPCI were performed subsequently. Bare metal stents were deployed by high-pressure implantation techniques. Low magnification angiogram at either the right 30 º or 90 º lateral projections with prolonged cine was performed to optimize myocardial blush grade (MBG) documentation at the end of the intervention as previously described (19). All patients were treated with clopidogrel or prasugrel and aspirin for 12 months after the procedure.

Fourteen-lead electrocardiograms were performed at admission and after primary PCI. Measurement of ST-segment in mm was performed from the lead of highest elevation. The ratio of difference of ST-elevation before and after primary PCI to ST elevation before primary PCI was calculated. When the ratio exceeded 70% ST-elevation resolution was considered complete, a ratio between 30% and 70% was considered partial, and no resolution of ST elevation was diagnosed when the ratio was less than 30%.

All patients had routine clinical evaluation and determination of Killip class. Routine blood tests and assessment of troponin and creatine phosphokinase blood levels were measured daily.

All patients had complete Doppler echcardiographic studies, within the first 6 hours after primary PCI, 48 hours later, and 5 days after the intervention. Siemens, Acuson Sequoia echocardiographic system, California, equipped with 3.5-7MHZ transducers was used. All patients had complete Doppler echcordiographic studies, within the first 6 hours after primary PCI, 48 hours after PPCI, and 5 days after primary PCI. Chamber diameters and usual measurements were performed according to recommendations of American Society of Echocardiography. Ejection fraction of LV (LVEF) was measured from biplane apical views.

For the calculation of wall motion score index

$$LV - WMSI = \frac{\sum score\ of\ 16\ segments}{16} \quad (1)$$

assigning a value of 1 for normal LV wall motion, 2 for hypokinesis and 3 for akinesis. Using the same values of wall motion scores, LAD 9 segmental score index was calculated as:

$$LAD - WMSI = \frac{\sum score\ of\ 9\ segments}{9} \quad (2)$$

In order to obtain LAD flows, the color Doppler Nyquist limit was set at 17 cm/sec. From low parasternal short axis view, search for diastolic color flow in the anterior

interventricular groove followed by clockwise rotation was performed, while form apical foreshortened two chamber views LAD diastolic flow was located in the interventricular groove and the counterclockwise rotation of the transducer was performed.

Parameters of LAD velocity patterns were averaged from 3 beats, all in sinus rhythm. Diastolic LAD deceleration Time (DDT) was measured as the time from peak diastolic velocity to the intercept of tangent of the velocity envelope with baseline.

Statistical Analysis

Statistical analysis was conducted using SPSS software version 16. Continuous parameters were expressed as means and standard deviations, and categorical variables were expressed by numbers or percentage. Two-tailed student's-t test was performed to compare changes in continuous parameters. Categorical variables were compared by the $\chi 2$ test. $p<0.05$ was considered as statistically significant.

Results

One hundred and seventy patients with acute anterior STEMI treated by primary PCI, age 61±12.7 years, were evaluated. Most of the patients were men and the clinical characteristics are summarized in table 1.

Variation of Time Intervals

After 2010, FMC to PCI time decreased significantly, and caused a reduction in Pain to PCI time despite the fact that Pain to FMC did not change, table 2.

Effects of Pain to PCI Time Intervals

Angiographic Findings: Post primary PCI, patients with pain to PCI<300 min, tended to achieve TIMI grade III more frequently (51%) compared to others (33%), p=0.06 and more frequent MBG≥2, (53% vs 36%), p=0.08.

ST-Elevation Resolution: Partial ST-elevation resolution after PCI, was achieved more frequently in patients with pain to PCI<180min (87% vs 65%), p<0.05, table 4.

LAD Velocity Parameters: Early assessment after PCI revealed lower LAD systolic velocities in patients with pain to PCI less than 300min, tables 5. Patients with pain to PCI intervals less than 90 and less than 120 min had lower LAD diastolic time velocity integrals compared to others. Patients with pain to PCI intervals less than 180 min had shorter LAD diastolic deceleration time table 5.

Late after PCI, lower diastolic velocities and integrals were found in those with pain to PCI less than 90min, table 6. Systolic LAD velocities were lower in those with pain to PCI less than 300 min.

Myocardial Damage: Lower peak troponin blood levels were found in patients with pain to PCI<300 min (49.2±45.2 vs 84.2±43 ng/ml), p=0.03, table 7.

Left Ventricular Systolic Function: Patients with pain to PCI intervals less than 180 min and less than 230 min had larger increase in LVEF before discharge, table 8.

Effects of Components of Pain to PCI Time Intervals

Angiographic Findings: TIMI and myocardial blush grades after PCI were not affected by pain to FMC and FMC to PCI intervals, table 3.

ST-Elevation Resolution: Complete and partial ST elevation resolution was not affected by pain to FMC; while FMC to PCI intervals less than 90 min were associated with higher prevalence of partial ST-elevation resolution, table 4.

LAD Velocity Parameters: Early LAD systolic velocity was lower in those with pain to FMC less than 180min, table 5. In patients with FMC to PCI intervals less than 90 and 135min had lower early LAD systolic velocities and integrals, table 5. Late diastolic LAD velocities were lower in those with pain to FMC less than 90min, table 6. While late LAD systolic velocities were lower in those with FMC to PCI less than 180min, the late diastolic deceleration and pressure half times were longer, table 6.

Myocardial Damage: Maximal blood levels of myocardial biomarkers were not affected neither by pain to FMC nor by FMC to PCI intervals, table 7.

Left Ventricular Systolic Function: In patients with pain to FMC less than 90 and less than 120 min, the increase in LVEF was larger than in others, p<0.05. FMC to PCI less than 180min was associated with larger increase in LVEF, p<0.05, table 8.

Table 1. *Patients' Characteristics.*

Characteristics	Patients
Patients (number)	170
Women (%)	25.9%
Age (yrs)	61±12.7
HTN (%)	47%
Obesity (%)	30.6%
FH of CAD (%)	27.7%
HLP (%)	56.5%
DM2 (%)	18.2%
Smoker (%)	49.4%
Killip I class (%)	92.4%
Pain to PCI	219.7± 155.7

Abbreviations: HTN=Hypertension; HLP= Hyperlipidemia; DM2= Diabetes Mellitus type 2; FH of CAD= Family history of coronary artery disease.

Table 2. *Change overtime of time intervals till primary percutaneous coronary intervention.*

	Pain to FMC	FMC to PCI	Pain to PCI
Before 2010	150.1±177.7	98.3±124.8	**225.01±167.5**
After 2010	131.5±127.4	75.6±46.1	**188.6±98.6**
P-value	0.332	0.037	**0.0304**

Abbreviations: FMC= First Medical Contact.

Table 3. *Angiographic coronary flow and myocardial blush*

			pre	post	pre	post	
	TIME (min)	**Patients (%)**	**TIMI 3(%)**	**TIMI 3(%)**	**MBG ≥2(%)**	**MBG =3(%)**	**MBG ≥2(%)**
Pain to PCI	**<=90**	4.1%	0%	50%	0%	38.9%	55.6%
	>90	95.9%	5.3%	47.4%	2%	30.9%	49.7%
	P-value		ns	ns	ns	ns	ns
	<=120	27%	4.4%	48.9%	2.2%	30.4%	52.2%
	>120	73%	4.8%	46.8%	1.6%	32.3%	49.2%
	P-value		ns	ns	ns	ns	ns
	<=180	53.5%	4.4%	46.2%	1.1%	30.8%	46.2%
	>180	46.5%	5.1%	49.4%	2.5%	32.9%	54.4%
	P-value		ns	ns	ns	ns	ns
	<=230	67%	5.3%	50%	2.6%	33.3%	49.1%
	>230	33%	3.6%	42.9%	0%	28.6%	51.8%
	P-value		ns	ns	ns	ns	ns
	<=300	80.6%	5.3%	51.1%	2.2%	34.3%	53.3%
	>300	19.4%	0%	33.3%	0%	21.2%	36.7%
	P-value		ns	(0.06)	ns	0.1	0.08

Pain to FMC	**<=60**	45%	3.4%	95.2%	1.7%	71.4%	90.5%
	>60	55%	8.2%	90%	2.7%	57.4%	97.1%
	p-value		ns	ns	ns	ns	ns
	<=90	68%	4.1%	93.3%	1.02%	55.6%	91.1%
	>90	32%	8.7%	88.6%	4.3%	64%	97%
	p-value		ns	ns	ns	ns	ns
	<=120	73%	4.03%	91.5%	1.6%	59.3%	91.5%
	>120	27%	17.4%	90%	1.2%	63.3%	96.7%
	p-value		<0.05	ns	ns	ns	ns
	<=180	88%	5.3%	91.03%	2%	59%	93.6%
	>180	12%	0%	90.9%	0%	72.7%	90.9%
	p-value		ns	ns	ns	ns	ns
FMC to PCI	**<=45**	24%	4.9%	88%	2.4%	41.5%	93.6%
	>45	76%	6.3%	91.1%	1.5%	28.5%	94.7%
	p-value		ns	ns	ns	ns	ns
	<=90	63.5%	51.9%	2.8%	36.1%	3.7%	14.8%
	>90	36.5%	40.3%	0%	24.2%	4.8%	12.9%
	p-value		ns	ns	ns	ns	ns
	<=135	74.1%	8.8%	2. 4%	4.7%	4.2%	14.3%
	>135	25.9%	9.3%	0%	5.9%	4.8%	4.8%
	p-value		ns	ns	ns	ns	ns
	<=180	84.1%	90.5%	2.1%	3.1%	16.1%	4.2%
	>180	15.9%	100%	0%	3.7%	3.7%	4.8%
	p-value		ns	ns	ns	ns	ns

Abbreviations: FMC= First Medical Contact; Time (min)= pain to FMC time (minutes)/Door to Balloon/Pain to Balloon; Pre TIMI= TIMI grade prior to PPCI; Post TIMI= TIMI grade after PPCI. TIMI3 post%=percentage of patients with TIMI grade flow 3 after PPCI; Pre MBG= Myocardial blush grade prior to PPCI; Post MBG= Myocardial blush grade after PPCI; MBG 3 Post%= percentage of patients having MBG=3 post PPCI; MBG≥2post% =Percentage of patients having MBG≥2 post PPCI. ns= non significant.

Table 4. *ST-Elevation resolution*

	TIME (min)	**Patients(%)**	**Complete Resolution ≥70%**	**Partial Resolution 30% - 70%**	**No resolution < 30%**	**Resolution Average**
Pain to PCI	<=90	4.1%	22%	77.8%	11%	50% ± 32.03%
	>90	95.9%	15.8%	53.9%	19.7%	48% ± 29.8%
	p-value		ns	ns	ns	ns
	<=120	27%	16.7%	83.9%	12.5%	45.4% ± 29.2%
	>120	73%	26.2%	73.8%	21.3%	49.3% ± 30.3%
	p-value		ns	ns	ns	ns
	<=180	53.5%	13.3%	86.7%	15.6%	45.1% ± 27.1%
	>180	46.5%	35%	65%	22.5%	51.17% ± 32.7%
	p-value		<0.05	<0.05	ns	ns
	<=230	67%	22.4%	77.6%	17.3%	48.4% ± 29.6%
	>230	33%	25.9%	74.1%	22.2%	47.8% ± 31%
	p-value		ns	ns	ns	ns
	<=300	80.6%	24.7%	75.3%	17.8%	48.8% ± 30%
	>300	19.4%	16.7%	83.3%	25%	44.7% ±29.9%
	p-value		ns	ns	ns	ns

Pain to FMC	<=60	45%	35%	60%	5%	56.7%± 28.2%
	>60	55%	20%	56.9%	23.1%	45.6%± 30.1%
	p-value		ns	ns	ns(0.07)	ns
	<=90	68%	26.8%	63.4%	9.8%	51%± 28.2%
	>90	32%	20.4%	52.3%	27.3%	45.6%± 31.4%
	p-value		ns	ns	0.039<0.05	ns
	<=120	73%	23.2%	58.9%	17.9%	48.1%± 30.1%
	>120	27%	24.1%	55.2%	20.7%	48.3%± 29.9%
	p-value		ns	ns	ns	ns
	<=180	88%	24.6%	56.2%	19.2%	48.5%± 30.5%
	>180	12%	16.7%	66.6%	16.7%	46.4%± 26.9%
	p-value		ns	ns	ns	ns
FMC to PCI	<=45	24%	18.8%	59.3%	21.9%	43.4%± 30.9%
	>45	76%	26.4%	56.6%	17%	51.1%± 29.2%
	p-value		ns	ns	ns	ns
	<=90	63.5%	17.2%	64%	18.8%	46%± 28.2%
	>90	36.5%	42.8%	38.1%	19.1%	54.8%± 34.4%
	p-value		<0.05	<0.05	ns	ns
	<=135	74.1%	18.7%	61.3%	20%	46.1± 29.2%
	>135	25.9%	60%	30%	50%	63.4%± 31.7%
	p-value		<0.05	ns	<0.05	ns
	<=180	84.1%	23.2%	58.5%	18.3%	48.4% ± 29.8%
	>180	15.9%	33.4%	33.3%	33.3%	41.7%± 38.2%
	p-value		ns	ns	ns	ns

Abbreviations: FMC= First Medical Contact; Time (min)= pain to FMC time (minutes); ns= non significant.

Table 5. *Early LAD Doppler velocity parameters.*

	TIME (min)	**Patients (%)**	**LAD Diam (mm)**	**VD (cm / sec)**	**VS (cm/sec)**	**TVI D (cm)**	**TVI S (cm)**	**PHT (msec)**	**DDT (msec)**	**DDT>600 (msec)(%)**	**HR (bpm)**
Pain to PCI	**<=90**	4.1%	2± 1.4	36.9 ± 11.7	6.9 ± 16	9.28 ± 2.8	2.23 ± 2.6	167 ± 170.3	351.7 ± 234.3	25	72.5± 6.9
	>90	95.9%	2.52 ± 0.44	42.9 ± 16.2	13.4 ± 11.4	12.02 ± 5.1	2.79 ± 2.12	162.3 ± 96.3	563.6 ± 330.3	47.4	76.7± 9.6
	p-value		ns	ns	ns	0.038<0.05	ns	ns	0.044	ns	ns
	<=120	27%	2.57± 0.68	39.6 ± 14.5	10.9 ± 13.2	10.4 ± 4.03	2.48 ± 2.2	153.1 ± 135.2	447.1 ± 313.7	28.6	75.1 ± 9.3
	>120	73%	2.45 ± 0.41	43.2 ± 16.3	13.3 ± 11.7	12.2 ± 5.3	2.83 ± 2.2	167.7 ± 93.8	580.6 ± 326.8	52.3	76.5 ± 9.4
	p-value		ns	ns	ns	<0.05	ns	ns	ns	ns	ns
	<=180	53.5%	2.44 ± 0.6	43.03 ± 16.1	10.1 ± 15.34	11.1 ± 5.2	2.48 ± 2.62	146.5 ± 123.4	454.4 ± 329.6	30.3	76.07 ± 9.02
	>180	46.5%	2.53 ± 0.41	40.9 ± 15.35	15.2 ± 6.03	12.2± 4.6	2.98 ± 1.5	182.04 ± 84.7	623.1 ± 304.3	59.38	76 ± 9.8
	p-value		ns	ns	ns	ns	ns	ns	0.035	0.018<0.05	ns
	<=230	67%	2 . 5 ± 0.56	42. 2± 14.6	12 ± 13.7	11.6± 4.9	2.7 ± 2.34	160.7 ± 118	525.4± 342.9	42.2	74.9± 9.3

	>230	33%	2.47± 0.9	41.7± 18.4	13.86 ± 7.5	11.7 ± 5.08	2.78 ± 1.65	169.2 ± 75.9	564.7 ± 291.5	50	79.6± 8.7
	p-value		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=300	80.6%	2.5 ± 0.51	40.9 ± 15	11.9 ± 12.6	11.5 ± 5.04	2.69 ± 2.2	166.5 ± 110.8	552.2 ± 333.5	45.8	75.6 ± 8.9
	>300	19.4%	2.3 ± 0.56	51.3 ± 19.6	17.8 ± 4.48	12.7± 4.09	3± 1.56	127 ± 67.1	392.3± 227.8	33.3	81.75± 3.2
	p-value		ns	ns	0.032<0.05	ns	ns	ns	ns	ns	ns
Pain to FMC	**<=60**	45%	2.48± 0.43	42.3± 16.1	16.1± 6.8	11.5± 4.4	3.46± 1.78	160± 140.1	487.1± 323.5	33.3	72.2± 10.5
	>60	55%	2.49± 0.54	42± 15.7	11.4± 13.2	11.7± 5.16	2.48± 2.23	164± 96.7	552.6± 328.7	48	77.5± 8.5
	p-value		ns	ns	ns	ns	ns	ns	ns	ns	0.09
	<=90	68%	2.45± 0.65	40.7± 13.5	12.4± 11.5	11.25± 4.6	2.63± 2	151.3± 1219	484.9± 317.7	35.5	73.8± 9.5
	>90	32%	2.52± 0.32	43.4± 17.6	12.7± 12.9	12.04± 5.3	2.8± 2.3	173.9± 93.5	586.2± 331.3	52.9	78.6± 8.5
	p-value		ns	ns	ns	ns	ns	ns	ns	ns	0.057
	<=120	73%	2.48± 0.57	42.6± 15.3	11.6 ± 13.6	11.3± 4.6	2.61± 2.3	151.1± 115.5	318.7± 288.8	36.4	75.5± 9.3
	>120	27%	2.49± 0.34	40.8± 16.9	14.5± 8	12.5± 5.7	2.97± 1.8	188.2± 86.8	648.4± 320.6	61.9	77.3± 9.4
	p-value		ns	ns	ns	ns	ns	<0.05	0.06	ns	ns
	<=180	88%	2.47± 0.52	41.4± 15.3	11.8± 12. 7	11. 4± 4.9	2.61± 2.2	162.6± 113.2	534.5± 339.4	42.9	75.6± 9.03
	>180	12%	2. 7± 0.4	47.2± 18.7	18.03± 3.9	14.2± 5.35	3.7± 0.99	166.2± 45.9	567± 156.2	66.7	80.6± 11.7
	p-value		ns	ns	0.0175<0.05	ns	ns	ns	ns	ns	ns
FMC to PCI	**<=45**	24%	2.42± 0.72	44.4± 16.7	6.6± 16.6	1 1 . 8 5 ± 5.86	1.8± 2.7	143.9± 105.1	506.3± 357.8	40	77.8± 8.72
	>45	76%	2.5± 0.55	40.7± 15.1	15.7± 7.3	11.5± 4.4	3. 2± 1.6	175.4± 109.2	577± 307.9	47.5	74.8± 9.9
	p-value		ns	ns	0.033	ns	0.039	ns	ns	ns	ns
	<=90	63.5%	2 . 5 ± 0.52	41± 16	11± 13.4	11.2± 5.04	2.98± 2.3	159.8± 115.9	521.6± 344.5	42	76.6± 9.1
	>90	36.5%	2.56± 0.42	45.5± 14.6	17.4± 4.1	13.1± 4.4	3.47± 1.45	174.9± 75.9	598.2± 259.2	53.3	74.4± 10.2
	p-value		ns	ns	0.0103<0.05	ns	ns	ns	ns	ns	ns
	<=135	74.1%	2 . 5 ± 0.52	41.1± 15.3	11.8± 12.7	11.5± 5.03	2.6± 2.2	162.4± 109.3	530.5± 326.9	43.9	7 6 . 0 4 ± 9.12
	>135	25.9%	2.32± 0.39	48.7± 17.9	17.4± 5.03	12.8± 4.4	3.4± 1.9	167.8± 102.9	587.4± 338.2	50	76.2± 11.2
	p-value		ns	ns	0.04<0.05	ns	ns	ns	ns	ns	ns
	<=180	84.1%	2.5± 0.49	41.1± 15	12.4± 12.3	11.6± 5	2.77± 2.17	165.4± 107.3	549.8± 323.7	46.03	75.8± 9.2
	>180	15.9%	1.7± 0.02	65 ± 21.2	15± 4. 2	12.75± 6.2	1.4± 0.42	33± 0.4	150± 50.9	0	88± 9
	p-value		<0.05	ns	ns	ns	0.034	<0.05	0.0007	ns	ns

Abbreviations: FMC= First Medical Contact; Time (min)= pain to FMC time (minutes); VD=Peak diastolic velocity; VS=Peak systolic velocity; TVI D= Diastolic time velocity integral; TVI S=Systolic time velocity integral; PHT=Pressure half time; DDT=Diastolic deceleration time; bmp: Beat per minute; ns= non significant.

Table 6. *Late LAD Doppler velocity parameters*

	TIME (min)	Patients (%)	LAD Diam (mm)	VD (cm/sec)	VS (cm/sec)	TVI D (cm)	TVI S (cm)	PHT (msec)	DDT (msec)	DDT > 600 (msec) (%)	HR (bpm)
Pain to PCI	**<=90**	4.1%	1.8 ± 1.13	30.8± 7.2	0.75± 19.24	9.12± 3.48	1.2± 2.74	197.4 ± 155.5	672.8 ± 535.9	60	78.4 ± 19.8
	>90	95.9%	3.26 ± 3.19	40.3 ± 13.9	15.96 ± 8.9	13.9 ± 4.3	3.67± 2.4	202.9 ± 78.8	654.8 ± 258.8	64.3	69.9 ± 11.5
	P		ns	0.037<0.05	ns	0.033<0.05	ns	ns	ns	ns	ns
	<=120	27%	2.56 ± 0.61	36.15 ± 8.66	13± 13.9	12.3 ± 2.76	2.88 ± 2.38	193.1 ± 95.1	657.95 ± 326.5	70	72.45 ± 14.5
	>120	73%	3.46± 3.73	41.17 ± 15.4	15.7 ± 8.7	14.1 ± 4.95	3.76± 2.5	207.2 ± 81.4	655.5 ± 265	61	70.03 ± 11.9
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=180	53.5%	2.63 ± 0.54	37.8± 13.3	13.2± 13.27	12.6 ± 3.9	2.98 ± 2.48	196.97 ± 88.1	674.1± 300.9	68.8	71.5 ± 14.23
	>180	46.5%	3.83± 4.6	41.7 ± 14.1	16.54± 6.5	14.7± 4.9	4.01 ± 2.43	208.8± 84.01	636.7± 267.7	58.6	70.3± 11
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=230	67%	2.61 ± 0.51	37.95± 12.3	13.8 ± 11.61	12.82± 3.8	3.34± 2.7	196.3± 84	667.3± 283.5	65.9	70.88± 13.5
	>230	33%	4.33± 5.3	43.2± 16.2	17± 7.62	15.1± 5.4	3.79 ± 1.99	215.2± 90.2	633.8± 290.6	60	71.3 ± 11.6
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=300	80.6%	3.24± 3.4	38± 12.56	13.89± 10.67	13.04 ± 4.2	3.33 ± 2.44	208.5 ± 87.2	675.6± 291.7	66.04	70.73± 12.9
	>300	19.4%	2.88± 0.38	50 ± 17.2	20.75 ± 7,17	17.2 ± 4.98	4.49 ± 2.69	156.7 ± 60.5	528.25 ± 192.7	50	72.7 ± 13.6
	p		ns	0.09	0.038<0.05	ns	ns	ns	ns	ns	ns
Pain to FMC	**<=60**	45%	2.7 ± 0.37	35.6± 8.1	16.7± 5.3	13± 4.2	3.9± 1.6	194.9± 99.9	664.4± 344.7	64.3	69.2± 12.03
	>60	55%	3.3 ± 0.35	40.7± 14.8	14.3± 11.6	13.7± 4.5	3.4± 2.7	204.7± 81.9	653.9± 267.4	63.8	71.5 ± 13.3
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=90	68%	2.62± 0.6	35.6± 9.1	13.5± 11.8	12.4± 3.8	3.4± 2.9	187.03± 85.9	631± 291.7	60	70.1 ± 10.6
	>90	32%	3.6 ± 0.41	43.2± 16.2	16.1± 9.25	14.6± 4.8	3.6± 2.1	217.2± 84.3	680.8± 278.7	67.7	72.0 ± 15.2
	p		ns	0.026<0.05	ns	ns	ns	ns	ns	ns	ns
	<=120	73%	2.6 ± 0.5	39.2± 14.4	14.1± 12.1	12.9± 4.16	3.4± 2.8	188.8± 84.4	640.6± 286.5	62.5	75.1 ± 11.6
	>120	27%	4.4 ± 5.5	40.3± 12.4	16.25± 6.6	14.9± 4.8	3.6± 1.9	228.8± 84.2	686.2± 283.2	66.7	70.7 ± 15.8
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=180	88%	3.2 ± 3.3	38.7± 13.4	14.3± 10.6	13.1± 3.9	3.4± 2.5	206.2± 88.6	671.9± 293.6	66.04	70.8 ± 11.4
	>180	12%	3 ± 0.41	45.5± 15.4	18.5± 9.2	16.6± 0.25	3.95± 2.7	174.1± 57.3	553.1± 190	50	73.1 ± 21.9
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns

FMC to PCI	**<=45**	24%	3.9± 5.2	40.7± 14.6	12.2± 14.35	13.4± 4.5	2.8± 2.5	185.5± 84.9	627.5± 275.8	68	70.8 ± 11.8
	>45	76%	2 . 8 ± 0.38	38.7± 13.1	16.49± 7	13.6± 4.4	3.9± 2.4	214± 85.4	676.3± 291.5	61.1	71.1 ± 13.8
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=90	63.5%	3 . 3 ± 3.6	38.6± 13	13.95± 11.2	13.14± 4.03	3 . 0 6 ± 2.05	206.4± 89.4	667± 299	68.1	69.9 ± 10.5
	>90	36.5%	2.83± 0.53	42.8± 15.95	17.6± 7.8	14.9± 5.6	4.8± 3.2	188.5± 72.5	618.4± 231.3	50	74.1± 18.5
	p		ns	ns	ns	ns	ns(0.076)	ns	ns	ns	ns
	<=135	74.1%	3.29± 3.3	39.5± 14.1	14.6± 11	13.48± 4.3	3.2± 2.2	205.6± 86.5	667.4± 287.9	66.7	70.2 ± 11.3
	>135	25.9%	2.46± 0.29	39.86± 10.1	16.9± 6.09	13.8± 5.4	5.6± 3.4	173.7± 78.95	570.3± 253	42.9	76± 20.3
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=180	84.1%	3 . 2 ± 3.17	39.4± 13.9	14.6± 10.6	13.4± 4.4	3.4± 2.5	206.6± 84.1	669.3± 279.3	66.1	70.04± 11.14
	>180	15.9%	2.5± 0.3	45± 2.8	23± 1.9	16.2± 6.6	5.35± 0.78	82.5± 19.1	273± 69.3	0	87.7± 30.3
	p		ns	ns	2.9×10^{-7} <0.05	ns	ns	<0.05	<0.05		ns

Abbreviations: FMC= First Medical Contact; Time (min)= pain to FMC time (minutes); VD=Peak diastolic velocity; VS=Peak systolic velocity; TVI D= Diastolic time velocity integral; TVI S=Systolic time velocity integral; PHT=Pressure half time; DDT=Diastolic deceleration time; BPM: Beat per minute; ns= non significant.

Table 7. *Myocardial biomarker maximal blood levels*

	TIME (min)	Patients(%)	MAX.CPK [u/l]	MAX. TROPONIN[ng/ml]
Pain to PCI	**<=90**	4.1%	3068.9± 2213.7	77± 55.5
	>90	95.9%	1477.2± 1252.3	50.9± 45.1
	p-value		ns	ns
	<=120	27%	2122.2± 1922	58.5± 47.1
	>120	73%	1464± 1197	51.6± 46.8
	p-value		ns	ns
	<=180	53.5%	1664.9± 1670.8	55.9± 44.7
	>180	46.5%	1638.5± 1217	51.3± 49.3
	P-value		ns	ns
	<=230	67%	1634.7± 1561	50.8± 44.6
	>230	33%	1689.2± 1245	60.03± 51.5
	p-value		ns	ns
	<=300	80.6%	1573.9± 1491	49.2± 45.2
	>300	19.4%	1689.2± 1245	84.2± 43
	p-value		ns	0.03

Pain to FMC	**<=60**	45%	1969.7± 1829.6	52± 48.6
	>60	55%	1550.8± 1322.3	54.3± 46.5
	p-value		ns	ns
	<=90	68%	1720.5± 1635.7	50.8± 45.9
	>90	32%	1588.1± 1269.5	56.6± 47.8
	p-value		ns	ns
	<=120	73%	1693.6± 1568.7	55.8± 47.7
	>120	27%	1571± 1246.8	49.4± 49.5
	p-value		ns	ns
	<=180	88%	1598.4± 1471.8	52.1± 47.7
	>180	12%	2005.8± 1395.6	64.4± 39.8
	p-value		ns	ns
FMC to PCI	**<=45**	24%	1849.5± 1654.4	52.4± 43.5
	>45	76%	1534.3± 1334.2	54.6± 49
	p-value		ns	ns
	<=90	63.5%	1725.3± 1591	49.9± 43.8
	>90	36.5%	1422.5± 937.2	65.9± 54.6
	p-value		ns	ns
	<=135	74.1%	1689.6± 1517.2	53.7± 44.9
	>135	25.9%	1379.2± 967.2	53.8± 61.3
	p-value		ns	ns
	<=180	84.1%	1620.5± 1471.2	53.2± 56.7
	>180	15.9%	2579.7± 760.3	68.3± 54.9
	p-value		ns	ns

Abbreviations: n= number of patients; FMC= First Medical Contact; Time (min)= pain to FMC time (minutes); Max. Trop=Maximal Troponin level; Max. CPK=Maximal Creatine phosphokinase level; ns= non significant.

Table 8. *Left ventricular systolic function*

	TIME (min)	**Patients (%)**	**LVEF-EARLY (%)**	**LVEF-LATE (%)**	**ΔLVEF (%)**	**LV WMSI EARLY**	**LV WMSI LATE**	**Δ LV WMSI**	**LAD WMSI EARLY**	**LAD WMSI LATE**	**Δ LAD WMSI**
Pain to PCI	**<=90**	4.1%	34.6 ± 4.4	41.3 ± 5.6	6.7 ± 4.8	1.64 ± 0.27	1.82 ± 0.46	0.16 ± 0.34	1.99 ± 0.41	2.13 ± 0.31	0.16 ± 0.84
	>90	95.9%	36.9 ± 6.6	45 ± 9.1	8 ± 8.1	1.6 ±0.26	1.52 ± 0.35	-0.12 ± 0.31	1.94 ± 0.49	1.73 ± 0.51	-0.27 ± 0.45
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=120	27%	33.8 ± 5.3	44.7 ± 7.9	10.3 ± 8.8	1.69 ± 0.27	1.64 ± 0.36	-0.05 ± 0.34	2.09 ± 0.5	1.91 ± 0.51	-0.15 ± 0.57
	>120	73%	37.9 ± 6.5	44.5 ± 9.3	6.8 ± 7.2	1.58 ± 0.27	1.52 ± 0.36	-0.11 ± 0.31	1.9 ± 0.5	1.72 ± 0.5	-0.26 ± 0.42
	P		0.0022 <0.05	ns	ns	ns	ns	ns	ns	ns	ns
	<=180	53.5%	36.2 ± 6.7	46.3 ± 8.4	10.1 ± 8.8	1.6 ± 0.26	1.57 ± 0.33	-0.08 ± 0.35	1.98 ± 0.5	1.85 ± 0.46	-0.21 ± 0.58
	>180	46.5%	37.1 ± 6.1	42.7 ± 9	5.5± 5.8	1.61 ± 0.27	1.53 ± 0.39	-0.1 ± 0.3	1.92 ± 0.47	1.69 ± 0.54	-0.25 ± 0.35
	p		ns	0.054	0.005 <0.05	ns	ns	ns	ns	ns	ns
	<=230	67%	36.8 ± 6.7	45.9 ± 8.7	9.1 ± 8.3	1.57 ± 0.25	1.49 ± 0.33	-0.12 ± 0.32	1.93 ± 0.48	1.73 ± 0.48	-0.27 ± 0.53
	>230	33%	36.4 ± 5.8	41.8 ± 8.6	5.3± 5.8	1.67 ± 0.27	1.64 ± 0.41	-0.05 ± 0.31	1.98 ± 0.49	1.81 ± 0.55	-0.18 ± 0.33

	p		ns	0.041 <0.050	0.0145 <0.05	ns	ns	ns	ns	ns	ns
	<=300	80.6%	36.8 ± 6.5	45 ± 9	8.1 ± 7.9	1.59 ± 0.27	1.51 ± 0.35	-0.12 ± 0.32	1.93 ± 0.5	1.73 ± 0.52	-0.26 ± 0.49
	>300	19.4%	35.6 ± 5.6	41.9 ± 7.9	6.3± 7.4	1.67 ± 0.19	1.68 ± 0.43	0 ± 0.33	2.01 ± 0.44	1.89 ± 0.46	-0.13 ± 0.3
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
Pain to FMC	**<=60**	45%	36.1 ± 6.47	43.3 ± 7.43	7.86± 8.4	1.57±0.23	1.54 ± 0.4	-0.1 ± 0.5	1.86 ± 0.36	1.72 ± 0.47	-0.16 ± 0.59
	>60	55%	36.8 ± 6.5	44.97 ± 9.3	7.87 ± 7.66	1.62± 0.27	1.55 ± 0.36	-0.1 ± 0.31	1.97 ± 0.52	1.78 ± 0.52	-0.25 ± 0.42
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=90	68%	35.5 ± 6.6	45.35± 9	9.67± 8.9	1.63± 0.25	1.56 ± 0.35	-0.16 ± 0.37	2.02 ± 0.48	1.58 ± 0.48	-0.25 ± 0.47
	>90	32%	37.8 ± 6.13	43.8 ± 8.8	6.13± 6.2	1.59± 0.27	1.54 ± 0.39	-0.07 ± 0.34	1.88 ± 0.48	1.69 ± 0.52	-0.22 ± 0.46
	p-value		ns	ns	0.034<0.05	ns	ns	ns	ns	ns	ns
	<=120	73%	35.9 ± 6.6	45.03± 9.2	9.1± 8.3	1.58± 0.26	1.51 ± 0.33	-0.14 ± 0.36	1.95 ± 0.5	1.78 ± 0.51	-0.24 ± 0.5
	>120	27%	38.2 ± 5.9	43.7 ± 8.3	5.4± 6.2	1.66± 0.26	1 . 6 ± 0.42	-0.07 ± 0.35	1.95 ± 0.45	1.73 ± 0.52	-0.23 ± 0.4
	p		ns	ns	0.02 <0.05	ns	ns	ns	ns	ns	ns
	<=180	88%	36.5 ± 6.6	44.5 ± 9.1	7.9± 7.9	1.58± 0.27	1.51 ± 0.34	-0.14 ± 0.35	1.93 ± 0.49	1.73 ± 0.51	-0.26 ± 0.47
	>180	12%	37.4 ± 5.3	44.8 ± 7.6	7.4± 7.5	1.57± 0.01	1.79 ± 0.42	0.05 ± 0.39	2.05 ± 0.48	1.99 ± 0.43	-0.08 ± 0.35
	p-value		ns	ns	ns	ns	ns	ns	ns	ns	ns
FMC to PCI	**<=45**	24%	35.03± 5.9	44.6 ± 8.2	8.9± 8.5	1.7± 0.21	1.54 ± 0.37	-0.14 ± 0.34	2.18 ± 0.38	1.84 ± 0.46	-0.29 ± 0.52
	>45	76%	37.7 ± 6.6	44.6 ± 9.4	7.2± 7.3	1.58± 0.27	1.55 ± 0.37	-0.08 ± 0.31	1.87 ± 0.49	1.73 ± 0.52	-0.21 ± 0.44
	p-value		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=90	63.5%	36.7 ± 6.5	45.2 ± 8.9	8.5 ± 7.9	1.62± 0.27	1.59 ± 0.4	-0.06 ± 0.35	1.94 ± 0.48	1.79 ± 0.5	-0.2 ± 0.51
	>90	36.5%	36.6 ± 6.3	42.7 ± 8.9	6.1± 7.6	1.57± 0.24	1.44 ± 0.2	-0.15 ± 0.24	1.96 ± 0.49	1.71 ± 0.52	-0.3 ± 0.31
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=135	74.1%	37.03 ± 6.6	45.2 ± 8.7	8.1± 7.8	1.62± 0.26	1.55 ± 0.38	-0.11 ± 0.33	1.97 ± 0.47	1.76 ± 0.501	-0.25 ± 0.49
	>135	25.9%	33.8 ± 4.3	40± 9.3	6.2± 7.7	1.52± 0.27	1.55 ± 0.26	-0.02 ± 0.23	1.85 ± 0.57	1.81 ± 0.58	-0.12 ± 0.24
	p		ns	ns	ns	ns	ns	ns	ns	ns	ns
	<=180	84.1%	36.8 ± 6.5	45.04 ± 8.7	8.14± 7.8	1.61± 0.26	1.55 ± 0.37	-0.09 ± 0.33	1.94 ± 0.49	1.75 ± 0.5	-0.24 ± 0.47
	>180	15.9%	31.7 ± 2.9	31.7 ± 2.9	0 ± 0	1.62± 0.22	1.54 ± 0.32	-0.07 ± 0.09	2.11 ± 0.4	1.97 ± 0.56	-0.13 ± 0.16
	p		ns	0.004 <0.05	3.23×10^{-15} <0.05	ns	ns	ns	ns	ns	ns

Abbreviations: FMC= First Medical Contact; Time (min)= pain to FMC time (minutes); LVEF-Early= Early left ventricular ejection fraction; LVEF-Late= Late left ventricular ejection fraction; ΔLVEF= (LVEF-Late) – (LVEF-Early); LV WMSI EARLY= Early left ventricular wall motion index; LV WMSI LATE= Late left ventricular wall motion index; ΔLV WMSI=(LV WMSI LATE) – (LV WMSI EARLY); LAD WMSI EARLY= Early wall motion score index of segments supplied by the left anterior descending coronary artery; LAD WMSI LATE= Late wall motion score index of segments supplied by the left anterior descending coronary artery; ΔLAD WMSI= (LAD WMSI LATE) – (LAD WMSI EARLY); ns= non significant.

Discussion

In the present, study, the effects of time delays from onset of chest pain till primary PCI on infract related artery coronary flow, myocardial perfusion parameters, myocardial injury and recovery of LV systolic function were evaluated. Shorter intervals of pain to PCI were associated with better angiographic infarct related coronary artery flow and myocardial perfusion, less myocardial damage, and larger improvement in LV systolic function. In addition, shorter pain to FMC, and shorter FMC to PCI intervals were associated with larger improvement in LV systolic function.

In the current study, the recently recommended terminology of time intervals till PCI (2017 European guidelines for the management of patients presenting with acute STEMI) was adopted (18). Thus chest pain to FMC, FMC to PCI and pain to PCI time intervals were evaluated according to the new guidelines.

It is important to mention that the patient factor, chest pain to FMC time intervals, did not change over the years; however the medical system factor, FMC to PCI and consequently pain to PCI time intervals decreased significantly after 2010. The more recent European society of cardiology guidelines (18) recommend to keep the interval between STEMI diagnosis to PCI less than 120min, and in primary PCI hospitals less than 60 min; while the previous recommendations from 2014 (20), suggest to keep door to balloon time intervals less than 60 minutes and pain to PCI times less than 2-3hours (20).

The hypothesis of the present study that time delays from the onset of chest pain till primary PCI affect both the coronary flow and myocardial perfusion in the infarct related coronary artery tended to reach statistical significance. While shorter pain to PCI intervals tended to be associated with better angiographic outcome, pain to FMC and FMC to PCI time intervals did not affect the angiographic results. In concordance with the findings of the present study, prevalence of slow flow in the infarct related artery in patients with STEMI undergoing primary PCI was reported to be higher when the pain to balloon time was larger than 4 hours (21). Moreover it was reported that only the combination of a short (< 90 min) door to balloon time and a short chest pain-to-door time was associated with the improvement of clinical outcome (22,23). Previously a threshold value for door to balloon time was examined (i.e., ≤ 30 vs > 30 min,≤ 45 vs > 45 min, and ≤ 60 vs > 60 min) and surprisingly, the prevalence of final TIMI flow less than or equal to 2 was not affected by these time intervals(24).

Concerning the function of coronary microcirculation, shorter pain to PCI intervals were associated with better ST-elevation resolution, while shorter FMC to PCI time intervals had more partial ST-elevation resolution. Since the function of the coronary microcirculation and coronary artery velocities are dynamic and changing during the course of hospitalization after PPCI (17), LAD velocity parameters were evaluated early after primary PCI and before discharge from the hospital. A trend towards lower LAD velocities in patients with shorter time intervals was noticed, possibly related to a trend of larger LAD diameters in these patients.

Regarding myocardial injury; shorter pain to PCI time intervals (less than 300 min) was associated with lower maximal troponin blood levels. As a result, the increase in LVEF was larger in patients with shorter pain to PCI intervals (less than 180 and 230 min). In addition, shorter pain to FMC and FMC to PCI intervals, were associated with large improvement in LV systolic function. Similar to the findings of the present study, it was reported that shortening of the duration between chest pain onset and reperfusion to less than 4.0 hours was critical in reducing myocardial necrosis and improving heart function and 30-day mortality (23). Ultrashort door to balloon time (<45min) did not improve left ventricular systolic function (23), and did not improve mortality (24, 25).

Shortening of door to balloon time has been verified to benefit patients presenting early and/or with high risk in terms of reducing mortality (23, 26-28). The emphasis regarding time is on "presenting early". As already mentioned, in the present study, the patient factor-pain to FMC- did not change overtime, while the medical system factor-FMC to PCI time did shorten and lead to reduction in the ischemic time from chest pain till primary PCI. More importantly, further shortening of FMC to PCI time did not improve outcome (24, 29). These findings are in parallel with the patho-physiology of the time course of development of myocardial injury in acute STEMI. Following the abrupt thrombotic occlusion of

an epicardial coronary artery, a wave front of necrosis begins from the subendocardial necrotic area to the periphery and towards the epicardium (6). Thus, time is muscle, and the reopening of the occluded vessel should be performed as fast as possible. Pain to PCI interval should be as short as possible; however, if pain to FMC is so long, shortening FMC to PCI interval will not yield significant improvement in outcome. Therefore, future efforts to reduce pain to FMC time rather than achieving ultra-short FMC to PCI time intervals seems warranted in order to achieve better primary PCI outcomes.

Limitations

This was a single center, small study without long term follow up. Apparently, large long term multicenter studies and registries are needed.

Conclusion

In conclusion, decreasing pain to primary PCI time intervals improves myocardial perfusion and thus, improves LVEF. Since pain to FMC time intervals did not change overtime, reduction of total ischemic time by decreasing pain to FMC time intervals seems to be more effective than achieving ultra-short FMC to PCI time intervals.

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