

Association of Epicardial and Tissue-Level Reperfusion with Left Ventricular End-Diastolic Pressures in ST-Elevation Myocardial Infarction

Ajay J. Kirtane MD^{1,3}, Anh Bui BS², Sabina A. Murphy MPH³, Dimitrios Karpaliotis MD¹, Ioanna Kosmidou MD³, Keith Boundy BA³, Aref Rahman MD¹, Duane S. Pinto MD¹, Julian M. Aroesty MD^{1,3}, Robert P. Giugliano MD, SM³, Christopher P. Cannon MD³, Elliott M. Antman MD³, C. Michael Gibson MS, MD^{1,3}, for the TIMI Study Group

¹Department of Medicine, Beth Israel Deaconess Medical Center; ²Harvard Medical School, and ³The TIMI Study Group, Department of Medicine, Brigham & Women's Hospital

Abstract. Unfavorable hemodynamics among patients with ST-elevation myocardial infarction (STEMI) have been associated with adverse clinical outcomes and may be linked to a failure to achieve complete reperfusion. We hypothesized that impaired epicardial and tissue-level perfusion after fibrinolytic therapy would be associated with adverse hemodynamics. The relationship between left ventricular end-diastolic pressure (LVEDP), baseline clinical characteristics, and angiographic findings were examined in 666 patients with STEMI treated with fibrinolytic therapy from the TIMI 14, INTEGRITI (TIMI 20), ENTIRE (TIMI 23), and FASTER (TIMI 24) trials. LVEDP was analyzed as a dichotomous variable with an elevated LVEDP defined as LVEDP >18 mmHg (median value). Higher post-fibrinolytic LVEDP was associated with age ≥65, female gender, Killip Class II–IV on presentation, and LAD culprit location. Elevated LVEDP was associated with both a closed infarct-related artery (58.8% of TIMI Flow Grade (TFG) 0/1 with elevated LVEDP vs. 46.6% of TFG 2/3, $p = 0.03$) and impaired myocardial perfusion (55.7% of TIMI Myocardial Perfusion Grade (TMPG) 0/1 with elevated LVEDP vs. 43.8% of TMPG 2/3, $p = 0.02$). In a multivariate analysis, impaired myocardial perfusion (OR 1.7, $p = 0.02$), abnormal Killip Class (OR 4.8, $p = 0.001$), age ≥65 (OR 1.6, $p = 0.04$), and female gender (OR 1.9, $p = 0.01$) were independently associated with elevated LVEDP. Elevated LVEDP was independently associated with a greater incidence of in-hospital (OR 11.8, $p = 0.02$) and 30-day congestive heart failure (OR 4.4, $p = 0.02$). In STEMI, angiographic indices of incomplete reperfusion are associated with an elevated LVEDP, and elevated LVEDP is associated with adverse clinical outcomes.

Abbreviated abstract. Successful reperfusion as well as the hemodynamic profile are associated with clinical outcomes among patients with STEMI. Elevated LVEDP was associated with both a closed infarct-related artery and impaired myocardial perfusion in univariate analyses. In multivariate analyses, impaired myocardial perfusion was independently associated with an elevated LVEDP.

Key Words. TIMI Myocardial Perfusion Grade, TIMI Flow Grade, ST Elevation Myocardial Infarction

Abbreviations. STEMI: ST-elevation Myocardial Infarction; LAD: left anterior descending artery; TFG: TIMI Flow Grade; TMPG: TIMI Myocardial Perfusion Grade; LVEDP: Left Ventricular End Diastolic Pressure.

Following the onset of ST-segment elevation myocardial infarction (STEMI), regional systolic and diastolic cardiac dysfunction occurs with associated increases in left-sided filling pressures [1–3]. The severity of hemodynamic alteration in STEMI is related to prognosis, including the development of congestive heart failure and death, particularly at pulmonary capillary wedge pressures >18 mmHg as originally described by Forrester and colleagues in 1974 [4–7]. In STEMI, adverse prognoses have also been associated with both slower epicardial blood flow [8,9] and impaired myocardial perfusion [10,11] following reperfusion therapy. While both impaired hemodynamic function and angiographic perfusion have been separately associated with adverse clinical outcomes following fibrinolytic administration, the association of these two metrics with each other has not been fully evaluated.

We hypothesized that a failure to observe normal epicardial and myocardial perfusion after fibrinolytic therapy would be associated with adverse hemodynamics in the setting of STEMI. Specifically,

Address for correspondence: C. Michael Gibson, M.S., M.D., 350 Longwood Avenue, First Floor, Boston, MA 02115, USA. Tel.: 617-525-6884; Fax: 888-249-5261; E-mail: mgibson@timi.org

we hypothesized that worsened TIMI Flow Grades and TIMI Myocardial Perfusion Grades after fibrinolytic therapy would be associated with an elevated left-ventricular end-diastolic pressure (LVEDP).

Methods

Clinical and angiographic data were analyzed from 666 patients from the TIMI 14, INTEGRITI (TIMI 20), ENTIRE/TIMI 23, and FASTER (TIMI 24) trials. The TIMI 14 trial was a 1,187 patient trial comparing full dose fibrinolytic (alteplase or reteplase) to abciximab plus reduced dose fibrinolytic in acute STEMI [12]. INTEGRITI was a 418 patient trial evaluating the safety and efficacy of eptifibatide in conjunction with varying doses of tenecteplase (TNK) in STEMI [13]. The ENTIRE/TIMI 23 trial was a 493 patient phase II trial comparing enoxaparin to unfractionated heparin in patients receiving TNK or reduced-dose TNK plus eptifibatide in STEMI [14]. FASTER was a phase II trial evaluating the efficacy of a combination of tirofiban, TNK, and unfractionated heparin in acute STEMI.

Angiographic and outcome analyses

In each of these trials, angiography was performed at 60 minutes following thrombolytic administration. Culprit lesions were identified by previously described methods in a dedicated core laboratory (TIMI Angiographic Core Laboratory) and were read by a single observer (C.M.G.). The optimal single plane projection was selected that identified the culprit vessel with minimal foreshortening or overlapping of branches. The TIMI Flow Grades (TFG) and TIMI Myocardial Perfusion Grades (TMPG) were measured as previously described [11,15,16]. LVEDP values and results obtained on left ventriculography were obtained from angiographic case report forms completed by individual sites participating in the TIMI trials. The timing of the measurement of LVEDP was at the discretion of individual operators. CK and CK-MB were obtained at individual sites in the TIMI trials.

Statistical analysis

All analyses were performed using Stata version 7.0 [17]. All continuous variable values are reported as the median \pm standard deviation, unless otherwise specified. Two-sided *t*-tests were used in the analysis of normally distributed continuous variables. The non-parametric Wilcoxon rank sum test was used when the data was not normally distributed. The Chi-square test and Fisher's Exact test (if less than 5 values in a category) were used for the analysis of categorical variables. ANOVA testing and the Kruskal-Wallis test were used for comparisons between groups. LVEDP was analyzed as a dichotomous variable with an elevated LVEDP defined as

LVEDP > 18 mmHg. This cut-point was the median value in our dataset and also has been well-described as the threshold at which pulmonary congestion occurs in AMI [6]. Multivariate logistic regression analyses were performed using elevated LVEDP as a dependent variable, incorporating variables related to elevated LVEDP with $p < 0.05$ in univariate analyses. Odds ratios are presented with 95% confidence intervals.

Results

Baseline characteristics

LVEDP ranged from 2 to 42 mmHg with a mean of 18.8 ± 7.7 , and a median of 18 mmHg (Fig. 1). The relationships between LVEDP and various baseline characteristics are shown in Table 1. A greater proportion of women with STEMI had an elevated LVEDP compared to men ($p = 0.001$), and age ≥ 65 was associated with elevated LVEDP ($p = 0.019$). There was a trend for an association between a prior history of hypertension and elevated LVEDP ($p = 0.15$). The presence of abnormal Killip Class (II–IV) on presentation was highly associated with elevated LVEDP ($p < 0.001$). There were no significant differences in LVEDP according to other baseline clinical presenting characteristics, including time to treatment > 4 hours or greater than the median (2.9 hours). There was also no significant correlation between time to treatment and LVEDP when time to treatment was analyzed as a continuous variable.

Coronary angiographic data and LVEDP

The associations between angiographic characteristics and LVEDP are shown in Tables 2 and 3. Occlusion of the left anterior descending (LAD) artery was associated with elevated LVEDP ($p = 0.019$).

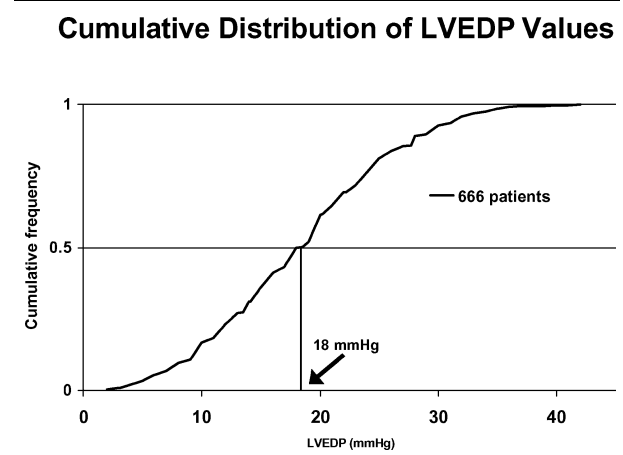


Fig. 1. Cumulative distribution of LVEDP values. The cumulative frequency of LVEDP values is displayed. The value on the y-axis represents the proportion of patients with LVEDP $<$ the x-axis value.

Table 1. LVEDP According to Baseline Characteristics

		n	LVEDP		P
			≤18 mmHg %	>18 mmHg %	
Age ≥65	+	205	42.9	57.1	0.019
	-	461	53.1	46.9	
Female	+	130	36.9	63.1	0.001
	-	536	53.2	46.8	
Prior diabetes	+	81	46.9	53.1	0.64
	-	585	50.3	49.6	
Prior HTN	+	200	45.5	54.5	0.15
	-	466	51.9	48.1	
Prior CHF	+	6	33.3	66.7	0.69
	-	660	50.2	49.8	
Prior high cholesterol	+	155	48.4	51.6	0.71
	-	511	50.5	49.5	
Prior MI	+	74	56.8	43.2	0.27
	-	592	49.2	50.8	
Prior smoker	+	335	52.0	48.0	0.25
	-	331	47.4	52.6	
Time to Rx > 4 hours	+	189	47.1	52.9	0.35
	-	476	51.3	48.7	
HR > 100	+	59	44.1	55.9	0.41
	-	607	50.6	49.4	
SBP < 100	+	13	53.9	46.1	1.0
	-	653	49.9	50.1	
Killip class 2-4	+	48	22.9	77.1	<0.001
	-	609	52.1	47.9	

Abbreviations: HTN: Hypertension; CHF: Congestive Heart Failure; HR: Heart Rate; SBP: Systolic Blood Pressure.

The percentage of patients with normal (LVEDP ≤18 mmHg) or elevated left-ventricular end-diastolic pressure (LVEDP >18 mmHg) is shown for each category.

Table 2. LVEDP and Angiographic Characteristics

		N	LVEDP		P
			≤18 mmHg %	>18 mmHg %	
LAD culprit	+	236	43.6	56.4	0.019
	-	430	53.5	46.5	
Lesion calcification	+	58	51.7	48.3	0.76
	-	585	49.6	50.4	
AHA lesion complexity	A	130	53.9	46.1	0.52
	B1	191	52.4	47.6	
	B2	205	48.3	51.7	
Number of diseased vessels	1	330	52.4	47.6	0.38
	2	210	49.1	50.9	
	3	120	45.0	55.0	

Abbreviations: LAD: Left Anterior Descending Coronary Artery; AHA: American Heart Association.

The percentage of patients with normal or elevated LVEDP is shown for each category.

There was no significant association between elevated LVEDP and the presence of residual thrombus, culprit lesion calcification, overall extent of disease, or AHA lesion classification. Worsened epi-

cardial flow after fibrinolytic therapy was associated with an elevated LVEDP (58.8% elevated LVEDP with a closed artery (TFG 0/1) vs. 46.6% elevated LVEDP with an open artery (TFG 2/3), $p = 0.033$, Fig. 2A). There was a trend towards an association between lower overall TIMI flow grades (TFG) in the culprit artery and an elevated LVEDP ($p = 0.17$). There was no significant association between TIMI frame counts (TFC) and LVEDP.

Impaired myocardial perfusion was also associated with an elevated LVEDP. A "closed myocardium" as assessed by TMPG (TMPG 0/1 = closed, TMPG 2/3 = open) was associated with elevated LVEDP (55.7% elevated LVEDP with closed myocardium vs. 43.8% elevated LVEDP with open myocardium, $p = 0.02$, Fig. 2B). Any abnormality of myocardial perfusion in the infarct-related artery territory was also associated with elevated LVEDP (54.7% elevated LVEDP with TMPG 0/1/2 vs. 44.3% elevated LVEDP with TMPG 3).

In multivariate logistic regression models incorporating age, sex, LAD infarct location and abnormal Killip Class on presentation, a closed myocardium by TMPG remained independently associated with elevated LVEDP (OR 1.7 [1.1-2.5], $p = 0.02$). Abnormal Killip Class on presentation (OR 4.8 [1.9-12.2], $p = 0.001$), female gender (OR 1.9 [1.1-3.2], $p = 0.01$), and age ≥65 (OR 1.6 [1.0-2.6], $p = 0.04$) were also independently associated with an elevated LVEDP. In a model in which the TFG was substituted for the TMPG, the presence of a closed epicardial artery tended to be associated with an elevated LVEDP (OR for elevated LVEDP 1.5 [1.0-2.5], $p = 0.07$), with Killip Class and female gender remaining significant in this model. In a model in which both the TMPG and TFG were included, a closed myocardium tended to be associated with elevated LVEDP (OR 1.6 [1.0-2.4], $p = 0.058$) whereas a closed epicardial artery was not (OR 1.2 [0.6-2.2], $p = 0.57$).

LVEDP and clinical outcomes

Elevated LVEDP was associated with a lower ejection fraction obtained during left-ventriculography ($55.0 \pm 16.1\%$ vs. $60.0 \pm 14.4\%$, $n = 567$, $p < 0.001$) as well as greater CK and CK-MB maximum values/upper limit of normal for each (median of 9.8 [4.4, 18.5] vs. 7.1 [3.5, 12.1], $p < 0.001$ for CK, $n = 545$; median of 16.5 [7.0, 40.2] v. 11.0 [5.2, 22.8], $p < 0.001$ for CK-MB, $n = 513$). Elevated LVEDP was associated with a more frequent incidence of in-hospital death/recurrent MI/CHF (7.8% vs. 3.6%, $p = 0.02$) (Fig. 3), as well as 30-day death/recurrent MI/CHF (10.8% vs. 6.0%, $p = 0.03$) (Fig. 4). This appeared to be in large part driven by a greater incidence of in-hospital CHF (3.6% with elevated LVEDP vs. 0.6% with normal LVEDP, $p = 0.01$) and CHF at 30 days (4.8% vs. 1.5%, $p = 0.02$). Although there were no significant associations between elevated LVEDP and

in-hospital or 30 day recurrent MI or death, the incidence of each of these endpoints was numerically higher in patients with elevated LVEDP.

In multivariate analyses, elevated LVEDP remained associated with both in-hospital CHF (OR 11.8 [1.5–94.7], $p = 0.02$) and 30-day CHF (OR 4.4 [1.2–16.3], $p = 0.02$), independent of age, gender, history of hypertension, time to treatment, Killip Class on presentation, LAD lesion location, artery patency, and myocardial perfusion. The only other variable with independent significance in this model was LAD infarct location (OR 4.6 [1.3–16.0], $p = 0.02$ for in-hospital CHF, OR 3.5 [1.3–9.6], $p = 0.01$ for 30-day CHF). Elevated LVEDP was independently associated with in-hospital death/recurrent MI/CHF (OR 3.0 [1.1–8.0], $p = 0.03$), and with a tendency to be associated with the 30-day composite of death/recurrent MI/CHF (OR 1.9 [0.9–4.3], $p = 0.10$).

Discussion

This study demonstrates that a failure to achieve normal epicardial flow and myocardial perfusion after fibrinolytic therapy is associated with an elevated LVEDP. Failure to restore myocardial perfusion was more strongly associated with an elevation of the LVEDP than failure to achieve epicardial patency. These results are consistent with the observation that impaired TMPGs are associated with larger SPECT infarct sizes at discharge and a worsened salvage index over 6 months following STEMI [18, 19].

Both systolic and diastolic myocardial function are impaired in acute STEMI [1]. Myocardial infarction has been associated with an increase in LV filling pressures and this association may be influenced by a variety of factors including infarct size, location, and clinical characteristics [6,7]. The goal of reperfusion therapy in the setting of STEMI is to restore early, full, and sustained epicardial and myocardial perfusion. Successful reperfusion, by aborting the further evolution of acute infarction, can have beneficial hemodynamic effects. Although left-sided filling pressures generally remain mildly elevated in patients with STEMI following successful reperfusion, the overall hemodynamic profile in these patients is more favorable than in patients who fail to achieve reperfusion. Experimental models have demonstrated that during ischemia the entire LV diastolic pressure-volume relationship shifts rightward and upward, leading to increases in both LVEDP and left ventricular end-diastolic volumes [1,20]. With early and successful reperfusion, the relationship can return to baseline although persistent myocardial dysfunction or “stunning” has been observed despite successful and complete reperfusion in several experimental models [21]. A similar obser-

vation has been made in clinical studies of patients with STEMI, where despite the successful restoration of epicardial flow, persistent microvascular dysfunction can be observed. Persistent perfusion abnormalities after fibrinolytic therapy in STEMI have been associated with greater infarct sizes, poorer myocardial salvage, and adverse clinical outcomes [11,18,19,22], even in patients who achieve epicardial TIMI 3 grade flow. Diminished myocardial perfusion in STEMI may reflect coronary microvascular dysfunction that can result from a variety of etiologies, including microvascular plugging with platelets and fibrin, spasm in the microvasculature, and free-radical and leukocyte-mediated injury [23].

In this study, although both epicardial flow and microvascular perfusion were associated with LVEDP in univariate analyses, epicardial flow grades after fibrinolytic therapy were less closely associated with an elevated LVEDP than impaired myocardial perfusion. This finding emphasizes the importance of “downstream” perfusion and suggests that incomplete tissue-level reperfusion in STEMI may lead to more profound myocardial dysfunction with resultant adverse hemodynamics. An alternative explanation for these findings is that the observation of diminished myocardial perfusion acutely is secondary to elevated LVEDP: i.e. an elevation in LVEDP causes slower flow into the myocardium by lowering the pressure gradient between the infarct-related artery and the myocardium. LVEDP has been well correlated with pressures resulting from extravascular compression forces and intravascular distending pressures, and this pressure can determine vascular resistance and flow [24–27]. However, perfusion abnormalities after STEMI have been shown to persist after treatment [28] and the presumed resolution of symptoms, suggesting that the regional decrement in perfusion is not solely a secondary phenomenon. In a substudy of the STOP-AMI trials, the TMPG assessed one to two weeks after STEMI was strongly associated with myocardial salvage assessed by SPECT imaging independent of ejection fraction or clinical status [19].

In multivariate models, elevated LVEDP was independently associated with an abnormal Killip class on presentation and with increased age and female gender in this study. Early observations of the hemodynamic alterations in STEMI demonstrated a correlation between symptomatic heart failure or pulmonary congestion and adverse hemodynamics, particularly at pulmonary capillary wedge pressures of >18 mmHg, the cut-point for LVEDP in this study [5–7]. This study further validates this relationship with the demonstration of a very strong and highly significant association between Killip classification and elevated LVEDP. The independent associations between age and female gender and elevated LVEDP are noteworthy, and may be related to age and gender differences in the response to fibrinolytic therapy

Table 3. LVEDP and Angiographic Characteristics of Flow and Perfusion

	n	LVEDP ≤18 mmHg	LVEDP >18 mmHg	P
		%	%	
<i>TIMI Flow Grade at 60 min</i>				
		n = 268	n = 256	
TFG 0	70	41.4	58.6	0.165
TFG 1	27	40.7	59.3	
TFG 2	129	55.8	44.2	
TFG 3	298	52.4	47.7	
TFG 0/1 (closed artery)	97	41.2	58.8	0.033
TFG 2/3 (open artery)	427	53.4	46.6	
TFG 0/1/2	226	49.6	50.4	0.538
TFG 3	298	52.4	47.7	
<i>TIMI Frame Count at 60 min</i>				
		n = 265	n = 250	
<i>Median CTFC (25, 75 CI)</i>				
		37.6	38.9	0.38
		(25.9,61.0)	(24.0, 100.0)	
CTFC < 40	275	53.1	46.9	0.427
CTFC ≥ 40	240	49.6	50.4	
<i>TIMI Myocardial Perfusion grade at 60 min</i>				
		n = 199	n = 192	
TMPG 0	115	42.6	57.4	0.087
TMPG 1	59	47.5	52.5	
TMPG 2	7	71.4	28.6	
TMPG 3	210	55.7	44.3	
TMPG 0/1 (closed myocardium)	174	44.3	55.7	0.02
TMPG 2/3 (open myocardium)	217	56.2	43.8	
TMPG 0/1/2	181	45.3	54.7	0.043
TMPG 3	210	55.7	44.3	

Associations between LVEDP and angiographic indices of epicardial flow (artery patency, TFG, TFC) and myocardial perfusion (TMPG) in infarct-related territories are shown by percentage of patients with normal or elevated LVEDP in each category.

Percentage of Patients with Elevated LVEDP in Relation to Epicardial Flow and Microvascular Perfusion

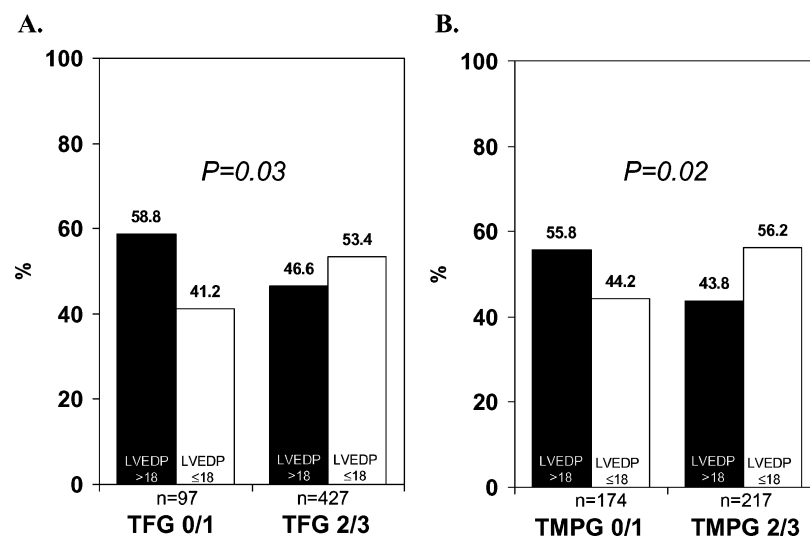


Fig. 2. (A) LVEDP and artery patency. The percentage of patients with elevated LVEDP is shown by TFG strata (TFG 0/1 = closed artery, TFG 2/3 = open artery). (B) LVEDP and myocardial perfusion. The percentage of patients with elevated LVEDP is shown by TMPG strata (TMPG 0/1 = closed myocardium, TMPG 2/3 = open myocardium).

Abbreviations: TFG: TIMI Flow Grade. TMPG: TIMI Myocardial Perfusion Grade.

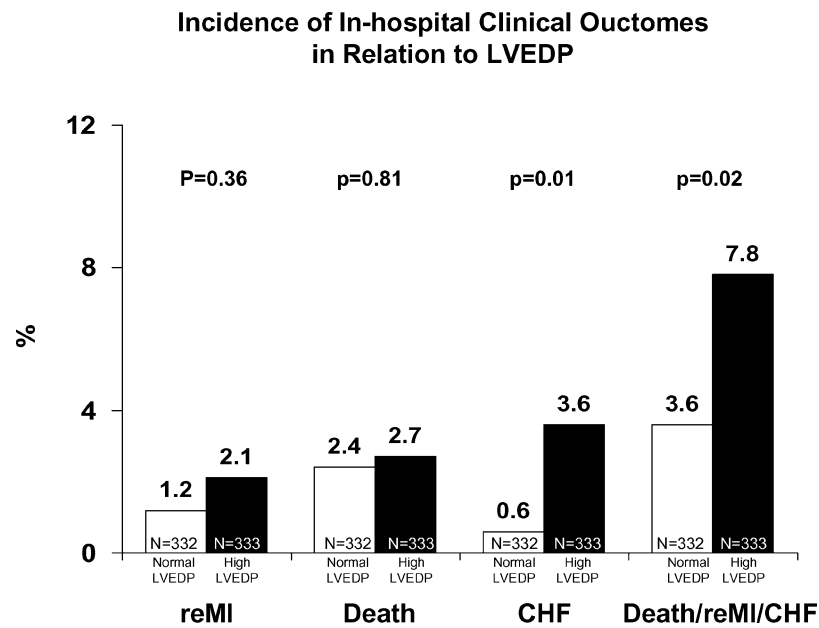


Fig. 3. LVEDP and incidence of in-hospital outcomes. The incidence of in-hospital clinical outcomes is shown stratified by LVEDP. Abbreviations: reMI: Recurrent Myocardial Infarction. CHF: Congestive Heart Failure.

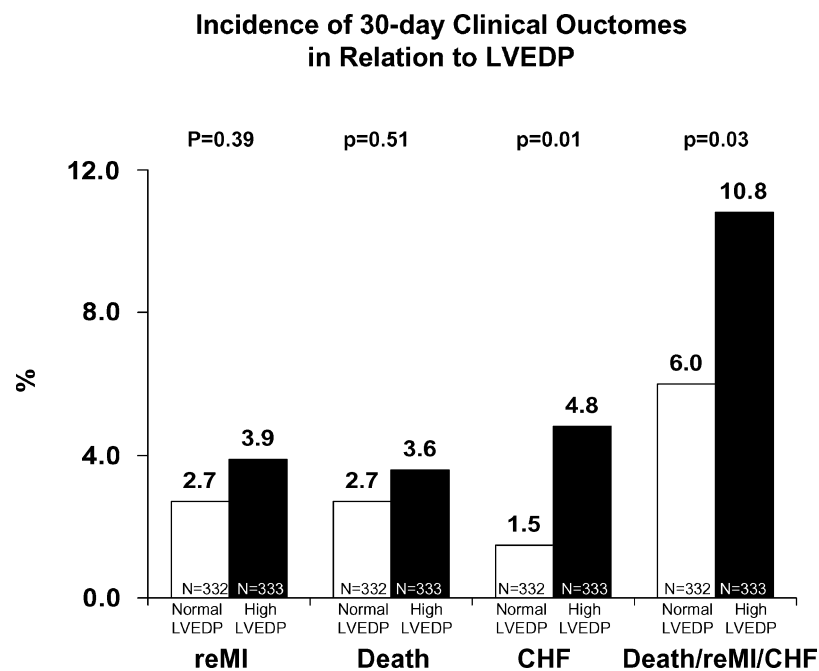


Fig. 4. LVEDP and incidence of 30-day outcomes. The incidence of 30-day clinical outcomes is shown stratified by LVEDP. Abbreviations: reMI: Recurrent Myocardial Infarction. CHF: Congestive Heart Failure.

[29], or a greater prevalence of pre-existing or sub-clinical systolic or diastolic heart failure in elderly patients or women in these studies. The lack of an association between LVEDP and a history of hypertension, time to treatment, and history of congestive

heart failure is surprising, and may have been due to an inadequate sample size. The association observed between an elevated LVEDP and the increased incidence of in-hospital and 30-day clinical outcomes is consistent with prior clinical observations [6,7].

Although the overall numbers of outcomes were small in this study, especially to demonstrate significant differences in outcomes such as overall mortality, our observations stress the importance of alterations in the acute hemodynamics of patients with STEMI.

Limitations

The study design was based upon pooled data from several trials analyzed retrospectively, and despite statistical adjustments, it is possible that both identified and unidentified confounders may have influenced the outcomes. Although recommended in all studies, the measurement of LVEDP was based upon the discretion of individual operators in the TIMI trials, and there is therefore the potential for selection bias. Patients with cardiogenic shock were excluded from these trials.

Conclusions

Successful reperfusion as well as the hemodynamic profile are associated with clinical outcomes among patients with STEMI. Elevated LVEDP was associated with both a closed infarct-related artery and impaired myocardial perfusion in univariate analyses. In multivariate analyses, impaired myocardial perfusion was independently associated with an elevated LVEDP.

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