Table 1. Blood Pressure and Heart Rate During HUTT With Placebo and Phenyilephrine Injection

	Physician Test (n = 15)		Patient Test (n = 10)	
	Phenylephrine	Placebo	Phenylephrine	Placebo
Systolic blood pressure (mm Hg)				
Supine	141 ± 20	129 ± 23	140 ± 16	142 ± 16
Tilting start	144 ± 23	128 ± 24	149 ± 18	144 ± 10
Symptoms onset	105 ± 19	96 ± 21	122 ± 23	106 ± 20
Injection	62 ± 13	61 ± 14	76 ± 16	74 ± 10
End point	121 ± 19*	50 ± 13	116 ± 32*	59 ± 9
Maximum effect	175 ± 35		177 ± 19	
Diastolic blood pressure (mm Hg)				
Supine	73 ± 12	68 ± 14	74 ± 14	73 ± 11
Tilting start	82 ± 14	76 ± 16	87 ± 3	85 ± 6
Symptoms onset	65 ± 12	62 ± 19	78 ± 15	72 ± 11
Injection	44 ± 11	45 ± 14	55 ± 13	51 ± 10
End point	73 ± 10*	37 ± 12	79 ± 20*	39 ± 8
Maximum effect	100 ± 16		102 ± 10	
Heart rate (beats/min)				
Supine	77 ± 16	75 ± 12	72 ± 10	74 ± 13
Tilting start	85 ± 19	93 ± 15	87 ± 11	88 ± 12
Symptoms onset	97 ± 26	97 ± 24	99 ± 21	105 ± 15
Injection	81 ± 30	88 ± 27	96 ± 26	98 ± 22
End point	68 ± 25	75 ± 21	70 ± 21	75 ± 26
Maximum effect	59 ± 21		55 ± 13	

*Phenylephrine vs. placebo: $p < 0.01$ (two-tailed paired Student t test).
End point = syncope or normal state of consciousness; HUTT = head-up tilt test.

Finally, in our study, all patients were able to activate easily the Algomed system at the time of prodromal symptoms, and injection of phenylephrine was effective in every patient. These results indicate that the modified Algomed pump is an efficient prototype of a patient-activated DDS for the treatment of VVS during HUTT. Obviously, our data are experimental, and further studies are needed to confirm these laboratory results in clinical practice.

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Association of Smoking With Improved Myocardial Perfusion and the Angiographic Characterization of Myocardial Tissue Perfusion After Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction

To the Editor: ST-segment elevation myocardial infarction (STEMI) may arise from different pathophysiologic processes ranging from plaque rupture to endothelial surface erosion. In the latter case, exposure of a denuded endothelium to a "high-risk blood phenotype" of elevated procoagulant factors and activated inflammatory cells may be the major trigger for thrombus formation. In particular, cigarette smoking is associated with increases in circulating fibrinogen and tissue factor (1), suggesting that thrombus in smokers with STEMI may be more fibrin-rich and, therefore, more amenable to fibrinolytic therapy.

Despite an increased risk of developing myocardial infarction, smokers with STEMI have a lower mortality compared with nonsmokers. This was first noted in the Thrombolysis In Myocardial Infarction (TIMI)-2 trial and has been largely attributed to fewer comorbidities and younger age among smokers. However, smoking has also been independently associated with lower mortality (2) and with better epicardial flow after fibrinolytic therapy (3). Although we were unable to detect differences in myocardial perfusion among a limited number of patients from older fibrinolytic trials (4), we hypothesized that in a larger population treated with current fibrinolytic therapy, smoking might be associated with improved myocardial perfusion as a potential unidentified explanation of the "smokers' paradox."

Data were drawn from patients in the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI), Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction

Table 1. Baseline Characteristics

	Nonsmokers (n = 644)	Smokers (n = 669)	p Value
Male gender (%)	79.5 (512/1,045)	79.7 (533/1,045)	0.94
Previous diabetes (%)	19.3 (124/186)	9.3 (62/186)	<0.001
Previous hypertension (%)	36.2 (233/394)	24.1 (161/394)	<0.001
Previous hyperlipidemia (%)	28.1 (181/328)	22.0 (147/328)	0.010
Previous coronary artery disease (angina or revascularization) (%)	39.1 (252/493)	36.0 (241/493)	0.245
Previous aspirin (%)	37.1 (239/446)	31.0 (207/446)	0.019
Previous beta-blocker (%)	21.3 (137/252)	17.2 (115/252)	0.060
Previous ACE inhibitor (%)	13.5 (87/137)	7.5 (50/137)	<0.001
Previous antihyperlipidemic (%)	16.6 (107/179)	10.8 (72/179)	0.002
Killip class 2–4 (%)	8.3 (53/108)	8.4 (55/108)	0.98
Combination therapy with glycoprotein IIb/IIIa inhibitor (%)	65.1 (418/841)	63.6 (423/841)	0.57
Age (yrs)	62 (54, 70) (n = 644)	53 (47, 61) (n = 669)	<0.001
Heart rate on admission (beats/min)	72 (62, 85) (n = 642)	72 (61, 86) (n = 669)	0.70
Systolic blood pressure (mm Hg) on admission	140 (129, 160) (n = 643)	137 (121, 150) (n = 669)	<0.001
Baseline white blood cell count ($\times 10^6$/ml)	9.6 (7.6, 11.8) (n = 419)	11.2 (9.1, 13.8) (n = 430)	<0.001
Baseline C-reactive protein (mg/l)	2.5 (1.0, 5.2) (n = 286)	3.2 (1.5, 7.2) (n = 318)	0.002
Baseline hemoglobin (g/dl)	14.6 (13.8, 15.4) (n = 634)	15.0 (14.1, 15.9) (n = 657)	<0.001
Baseline platelet count ($\times 10^3$/ml)	237 (201, 275) (n = 626)	250 (214, 294) (n = 652)	<0.001
Time to treatment (h)	3.0 (2.2, 4.0) (n = 636)	2.8 (2.0, 3.8) (n = 659)	0.004

Data are presented as the percentage (%) or median value (25th, 75th percentiles).
ACE = angiotensin-converting enzyme.

(ENTIRE-TIMI 23), and Fibrinolytics and Aggrastat with ST segment Resolution (FASTER) trials of reduced-dose fibrinolytic therapy with glycoprotein IIb/IIIa inhibitors for STEMI. Patients reporting active cigarette use were classified as smokers.

Angiographic analyses were performed by a core laboratory. Sixty-minute TIMI flow grade (TFG), corrected TIMI frame count (CTFC), and TIMI myocardial perfusion grade (TMPG) were assessed as previously described. Offline digital subtraction angiography (DSA) was performed, and blush intensity and rate of increase in blush intensity were quantified using a gray scale standard. The percentage of ST-segment resolution at 60 min was also assessed as a measure of myocardial perfusion.

All analyses were performed using Stata version 7.0 (Stata Corp., College Station, Texas). Continuous variables are reported as median values with 25% to 75% interquartile values, unless otherwise specified. Chi-square, Wilcoxon rank-sum, and Student *t* tests were used as appropriate. Backward stepwise logistic regression ($p < 0.05$ for entry, $p < 0.10$ for retention) was performed with TMPG as the outcome, incorporating smoking status, baseline characteristics, and known covariates of TMPG. A propensity score for smoking was used as a further adjustment in the model and in matching two cohorts of smokers and nonsmokers derived from the overall sample (5).

Of the 1,313 patients, smokers were younger, with a lower proportion of previous diabetes, hypertension, and hyperlipidemia, reduced number of medications, shorter time from symptom onset to treatment, and slightly lower blood pressure (Table 1). However, smokers had higher a white blood cell count (WBCC), hemoglobin, platelet counts, and C-reactive protein (CRP). There was no difference in the use of glycoprotein IIb/IIIa inhibitors between smokers and nonsmokers.

The incidence of multivessel disease was lower in smokers ($p = 0.02$). There were no significant differences in infarct artery location, lesion complexity, presence of residual thrombus, minimum lumen diameter, or percent stenosis among smokers compared with nonsmokers. Although the rate of 60-min TFG 3 was slightly higher and the CTFC was slightly faster among smokers, these differences were not statistically significant.

Smokers had improved myocardial perfusion by TMPG compared with nonsmokers (for TMPG 2/3: 59.2% vs. 47.9%, $p < 0.001$; for TMPG 3: 56.1% vs. 46.1%, $p = 0.001$). The association between smoking and improved TMPG was most pronounced among patients with patent epicardial arteries (Fig. 1) and among low- to moderate-risk patients in analyses stratified by TIMI risk score (TRS). Even among patients with TFG 3, smoking was associated with improved myocardial perfusion (76.8% TMPG 2/3 vs. 66.9%, $p = 0.006$). Smokers also had brighter blush intensity ($p = 0.02$) and a faster rate of increase in blush intensity ($p = 0.01$) quantified using DSA. The median ST-segment resolution was greater in smokers compared with nonsmokers ($p = 0.026$).

Smoking was associated with better myocardial perfusion after adjusting for differences in baseline characteristics, angiographic

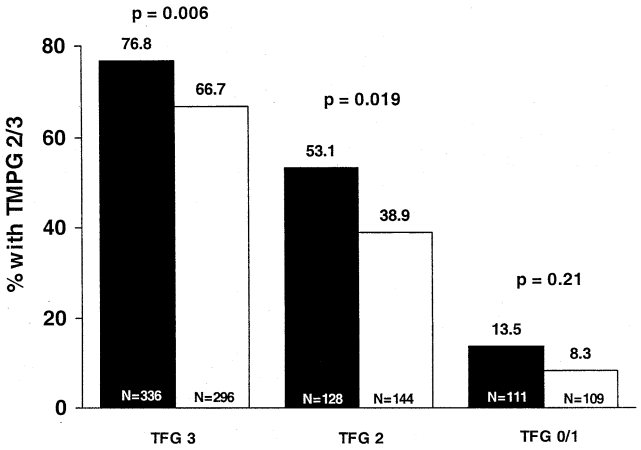

Figure 1. Smoking status and 60-min TIMI myocardial perfusion grade (TMPG) 2/3 stratified by TIMI flow grade (TFG). **Solid bars** = smokers; **open bars** = nonsmokers.

lesion characteristics, glycoprotein IIb/IIIa inhibitor use, and TFG 3 (odds ratio [OR] for TMPG 2/3 of 1.7, 95% confidence interval [CI] 1.3 to 2.3, n = 1,068, $p < 0.001$). This association persisted despite the inclusion of the propensity score for smoking, as well as in a model incorporating WBCC, hemoglobin, platelet count, and CRP (OR 2.0, CI 1.3 to 3.1, n = 461, p = 0.001). Finally, when the propensity score was used to generate matched cohorts of smokers and nonsmokers, the magnitude of the association between smoking and higher TMPG was similar to that in the overall unmatched population.

This analysis demonstrates that smokers with STEMI have improved myocardial perfusion after fibrinolytic therapy, as compared with nonsmokers, despite adjustment for differences in age, comorbidities, previous medications, and other potential confounders, and additionally in analyses stratified by TFG and TRS. This finding lends support to the hypothesis that smokers have more complete clot lysis after fibrinolytic administration, which results in improved myocardial perfusion independent of epicardial artery flow. Smoking has been associated with better clinical outcomes after fibrinolytic administration in STEMI patients, but the underlying mechanism responsible for the so-called "smoker's paradox" remains unclear. Several angiographic analyses have demonstrated faster epicardial flow among smokers, independent of baseline covariates (3). Although we observed no significant differences in 60-min epicardial flow, this may be due to the angiographic time point used, because among patients who had available 90-min data, the incidence of TFG 3 was significantly higher among smokers at 90 min (data not shown).

Smoking may not increase plaque vulnerability as much as it intensifies hypercoagulability. It is notable that the association between smoking and improved myocardial perfusion was independent of the higher WBCC and CRP levels in smokers. As elevated inflammatory markers are associated with impaired myocardial perfusion, this may reflect differing roles of inflammatory markers between smokers and nonsmokers. Smoking has been associated with higher levels of procoagulant factors (1), and soluble components of cigarette smoke have also been shown to impair fibrin cross-linking (6). These findings support the hypothesis that the pathogenesis of STEMI in smokers may be less atherogenic but more thrombogenic and therefore more responsive to fibrinolytic therapy.

It could be speculated that our findings may reflect more complete fibrinolysis with reduced distal embolization and microvascular dysfunction among smokers. Although our study was not powered to detect differences in clinical outcomes, insofar as improvements in myocardial perfusion have been associated with better outcomes in STEMI, the association between smoking and better myocardial perfusion may explain, at least in part, the improved prognosis of smokers in this clinical setting.

Spontaneous fibrinolysis and/or epicardial coronary vasospasm may have occurred more frequently among smokers, which may be a mechanism of a seemingly superior response to fibrinolytic therapy. Despite efforts to adjust for baseline characteristics and covariates, including the reperfusion regimen, this analysis is a nonrandomized, retrospective analysis of pooled clinical trials, and as such, it is possible that both identified and unidentified residual confounders may have influenced the outcomes.

Smoking is independently associated with improved myocardial perfusion after fibrinolytic therapy, despite adjustment for multiple baseline clinical characteristics. This finding may partly explain the improved outcomes of smokers with STEMI treated with fibrinolytic therapy.

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Letters to the Editor

Coronary Stenting Versus Balloon Angioplasty in Small Vessels

We read with interest the study by Moreno et al. (1), which demonstrated, through a meta-analytic technique, the significant reduction of restenosis due to stent in comparison to percutaneous transluminal coronary angioplasty in small-vessel coronary artery disease. However, the investigators failed to emphasize that substantial statistical heterogeneity was present, as shown in their overall analysis in Figure 1 (p for heterogeneity = 0.019).

We believe that this constitutes a methodological flaw in the study. Indeed, substantial heterogeneity is considered by several investigators to be a contraindication to quantitative pooling