Dysregulation of Inflammatory and Fibrinolytic Biomarkers in Pulmonary Embolism Subcategories

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Purpose

Pulmonary embolism (PE) and deep vein thrombosis effects nearly 600,000 Americans, leading to 100,000 deaths annually[1]. Hemostatic activation, inflammation, cellular dysfunction and hemodynamic insults contribute to the outcomes in PE[2,3,4]. Due to the heterogeneity of this disease, presentation, diagnosis, and risk stratification remains challenging[5]. PE is currently classified into low-, intermediate-, and high- risk categories[6]. These current risk stratification models, however, lack positive predictive capability and phenotypic profiling with biomarkers may aid in this stratification. The purpose of this study was to profile inflammatory and fibrinolytic biomarkers, such as plasminogen activator inhibitor-1 (PAI-1), activated thrombin activatable fibrinolysis inhibitor (TAFIa), and C-reactive protein (CRP) in categorical PE patients categorized by risk.

Methods

Citrated blood samples from 174 patients with confirmed PE were collected at Loyola University Medical Center and an affiliated hospital under an IRB approved protocol. Frozen samples were retrospectively analyzed for biomarkers, including PAI-1, TAFIa, and CRP using commercially available sandwich ELISA methods. Normal controls were comprised of commercially available 25 male and 25 female citrated plasma samples (George King Biomedical, Overland Park, Kansas City). All PE patients were categorized into low risk (n=41), submassive (n=114), and massive (n=15) according to the American College of Cardiology/American Heart Association guidelines. Results were compiled as mean ± SEM and analyzed for significance and correlation. Percent change was calculated from the normal mean for each biomarker for each PE sample. Statistical analysis was evaluated using GraphPad Prism software.

Results

Marked increases were noted in PAI-1 (70.5±3.3, normal 10.5±2.8; $p<0.0001$), CRP (35.8±3.6, normal 0.5±0.2; $p<0.0001$), and TAFIa (113.8±3.1, normal 78.9±8.1; $p<0.005$) in PE patients compared to normal controls as shown in Table 1. Exhibited in Table 2, levels of PAI-1 in PE patients with massive risk demonstrated significant increase compared to low- and submassive- risk ($p<0.05$) patients. Levels of TAFIa in submassive and massive PE patients were significantly lower compared to patients with low-risk, as demonstrated in Figure 1. CRP demonstrated no significance difference between subcategories. A negative correlation was observed between TAFIa and CRP, shown in Table 3.

Table 1. Composite Biomarker Data in PE Patients Compared to Normal Controls

	PE Patients (n=174)			Controls (n=11-34)		
Marker	Mean ± SEM	Median	Range	Mean ± SEM	Median	Range
PAI-1 (ng/ml)	70.54 ± 3.32	64.79	8.3-199.77	10.47 ± 2.83	4.89	0.82-54.02
TAFIa (%)	113.82 ± 3.08	107.31	34.06-258.12	78.85 ± 8.13	76.54	21.07-110.56
CRP (ug/ml)	35.82 ± 3.64	13.36	0.03-208.5	0.51 ± 0.15	0.09	0-3.56

Table 2. Composite Biomarker Data in PE Patients with Low, Submassive, and Massive Risk

	Low Risk			Submassive			Massive		
Marker	Mean ± SEM	Median	Range	Mean ± SEM	Median	Range	Mean ± SEM	Median	Range
PAI-1 (ng/ml)	72.11 ± 5.97	75.38	12.6-194.25	66.23 ± 3.98	55.37	8.3-199.77	100.17 ± 13.85	83.1	27.11-197.43
TAFIa (%)	126.68 ± 6.19	122.23	48.77-220.1	111.11 ± 3.65	105.66	34.06-258.12	100.012 ± 11.66	92.92	36.76-219.24
CRP (ug/ml)	21.86 ± 5.01	12.73	1.29-199.1	39.45 ± 4.65	15.32	0.03-208.5	45.35 ±12.08	12.98	0.96-170.1

Figure 1. Percent Change of Biomarkers in PE Subcategories

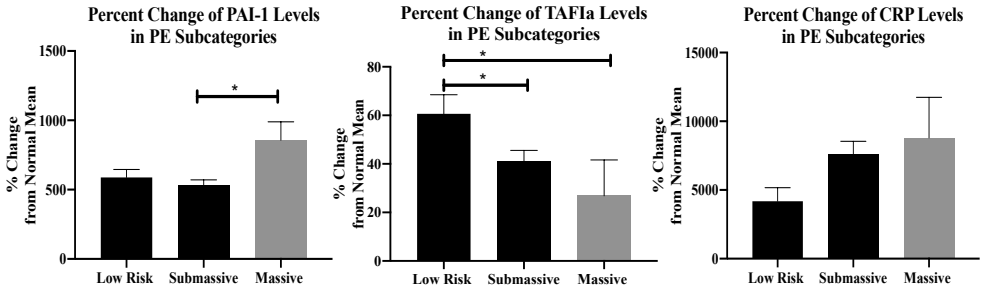

Table 3. Correlation Analysis of Biomarkers in PE Patients

	PAI-1	TAFIa	CRP
PAI-1	1	n.s.	n.s.
TAFIa	n.s.	1	**-0.21**
CRP	n.s.	**-0.21**	1

Conclusion

Our study found significant modulation in biomarkers in PE patients as compared to controls. Sever PE patients were found to have higher levels of PAI-1 and CRP suggestive of marked endothelial dysfunction and severe inflammatory response. Severe PE patients also were found to have decreased levels of TAFIa, contributing to the dysregulation of fibrinolysis.

Clinical Implications

These biomarkers may be useful for further risk stratification and outcome prediction of PE patients, and additionally serve as potential therapeutic targets for PE treatment.

References

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