

## Original Article

# Early interventional therapy for acute massive pulmonary embolism guided by minimally invasive hemodynamic monitoring

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**Abstract:** Aim: The aim of this study was to investigate the clinical significance of minimally invasive hemodynamic monitoring in the early catheter-based intervention for acute massive pulmonary embolism (PE). Methods: A total of 40 cases with acute massive PE were randomized into experimental and control group with 20 cases in each group. In the experimental group, the hemodynamics was monitored via Vigileo/FloTrac system, while echocardiography was used in the control group. Twelve hours after systemic thrombolysis, catheter-based clot fragmentation and local thrombolysis were employed in the experimental group if Vigileo/FloTrac system revealed hemodynamic abnormality. For the control group, the application of catheter was determined by the findings in echocardiography at 24 hours after systemic thrombolysis. Results: A total of 12 cases in the experimental group underwent catheter therapy successfully while 4 cases in the control group received the same treatment. Compared to the control group, 12 hours after catheter intervention the experimental group had higher PaO<sub>2</sub>/FIO<sub>2</sub> and right ventricular ejection fraction (RVEF) but lower pulmonary artery systolic pressure (PASP), indicating the effectiveness of Vigileo/FloTrac monitoring. The 28-day survival rates were identical between the groups although one patient in the control group died. Both the RVEF and PASP were significantly improved in the experimental group in 6 months compared to the control group. Conclusions: In massive PE, hemodynamic monitoring via Vigileo/FloTrac system might be useful in the decision making for catheter intervention after systemic thrombolysis and might improve the outcomes for patients.

**Keywords:** Acute massive pulmonary embolism, hemodynamic, Vigileo/FloTrac

## Introduction

Pulmonary embolism (PE) is the third most common cause of death from cardiovascular disease after heart attack and stroke. It is estimated that there are more than 100,000 US cases annually and approximately 25% of patients presenting with sudden death [1]. Initial systemic anticoagulant therapy is the standard of care for PE, and treatment escalation depends on clinical presentation. Patients can be stratified according to hemodynamic status and imaging or cardiac biomarker assessment of right ventricular (RV) function. American Heart Association has defined massive PE as acute PE with hemodynamic instability, that is, sustained hypotension (systolic blood pressure < 90 mmHg for at least 15 min or requiring inotropic support), pulselessness,

or persistent profound bradycardia (heart rate < 40 beats per minute with signs or symptoms of shock) [2]. Treatment options for massive PE include systemic thrombolysis, catheter-based interventions, and surgical thromboembolectomy. Systemic intravenous thrombolysis is universally recommended by both American and European guideline bodies for massive PE but remains controversial for submassive PE [2, 3]. Thrombolytic therapy was associated with lower all-cause mortality and a lower risk of recurrent pulmonary embolism in patients with RV dysfunction [1]. The most widely suggested regimen is 100 mg of alteplase during 2 hours [4]. Transcatheter procedures are an alternative to systemic thrombolysis when patients are at higher bleeding risk or when thrombolysis has failed to improve hemodynamics. Transcatheter techniques include thrombus fragmentation

and/or aspiration. Hybrid catheter therapy includes both catheter-based techniques and local thrombolysis [5]. Surgical thromboembolectomy is recommended by The American College of Chest Physicians in patients with acute pulmonary PE associated with hypotension, if 1) patients have contraindications to thrombolysis; 2) patients have undergone failure of thrombolysis or catheter-assisted embolectomy; or 3) patients are in a state of shock that is likely to result in death before thrombolysis can take effect [6].

A correlation has been reported between RV dysfunction and clinical outcomes in PE [7]. Patients with RV dysfunction are known to be at risk of subsequent clinical worsening and PE-related death and may benefit from more aggressive therapeutic strategies [8]. In massive PE, systemic thrombolysis with heparin is recommended as the first line treatment to decrease the thromboembolic burden on the RV and increase pulmonary perfusion [6].

The conventional criteria for assessing the effectiveness of thrombolysis mainly depend on the hemodynamic data generated from computed tomography pulmonary angiography (CTPA) or echocardiography which provides the parameters for RV function [9]. At present, the only hemodynamic monitoring tool providing extensive and detailed data is the pulmonary artery catheter (PAC). There is a lot of controversy regarding the use of PAC. Some groups demonstrated that the PAC does not improve outcomes [10]. On the other hand, a meta-analysis revealed the use of PAC significantly reduced the morbidity and mortality [11]. A less invasive monitor that provides similar hemodynamic data as the PAC would be ideal for clinical application.

The Vigileo/FloTrac monitoring system monitors hemodynamic data by utilizing an existing radial or femoral arterial line and does not involve central venous access or PAC. Unlike other non-invasive systems, calibration is not necessary for Vigileo/FloTrac monitoring [12]. Patient specific hemodynamic data are generated by incorporating demographic characteristics [13]. Comprehensive hemodynamic data including cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR), stroke volume (SV), stroke volume index (SVI), stroke volume variation (SVV) and ScvO<sub>2</sub> (central venous oxygen saturation) can be obtained simultaneously [14]. We hypothesize that Vigileo/FloTrac moni-

toring is a valid tool for the guidance of catheter-based interventional treatment for massive PE and improves the patient outcomes. The hypothesis will be tested in a prospective study of massive PE patients in a tertiary medical center.

### Methods

#### *Study design*

This study was a single-center randomized study of patients diagnosed with massive pulmonary embolism between June 2010 and January 2014. The diagnosis was confirmed via CTPA. The study protocol was designed in adherence to the Declaration of Helsinki and approved by the Ethics Committee of Quzhou People's Hospital.

#### *Patient selection*

Patients were randomized into treatment group and control group upon study enrollment. The diagnosis of the massive PE was based on the standards of the American Heart Association [2]. The inclusion criteria are as follows: (1) diagnosis proved by CTPA and with proper clinical manifestations (systolic blood pressure < 90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate 40 bpm with signs or symptoms of shock); (2) onset of symptoms within 2 weeks; (3) the informed consent for Vigileo/FloTrac monitoring and catheter-based interventional therapy obtained. The exclusion criteria are as follows: (1) major surgery, organ biopsy or vascular injury within 2 weeks; (2) ischemic stroke within 2 months; (3) SBP > 180 mmHg or DBP > 110 mmHg; (4) post-resuscitation; (5) platelet count less than  $100 \times 10^9/L$ ; (6) post-delivery within 2 weeks; (7) infectious endocarditis; (8) severe liver and renal dysfunction; (9) hemorrhagic diabetic retinopathy; and (10) chronic obstructive pulmonary hypertension without newly onset of pulmonary embolism.

#### *Hemodynamic monitoring*

All the patients in the experimental group underwent right intra-jugular catheterization with specific central venous catheter kits (x3816s Edwards Lifesciences) and right radial catheterization connected to the FloTrac Sensor

**Table 1.** Baseline characteristics of each group

	Experimental group (n = 20)	Control group (n = 20)	p value
Age (yr)	61.70 ± 5.95	61.00 ± 5.65	0.705
Sex (male/female)	12/8	9/11	0.342
Left/right side	5/6 9 bilat	4/5 11 bilat	0.527
Body weight (kg)	64.06 ± 7.12	64.95 ± 6.81	0.453
Duration of symptoms (day)	5.90 ± 1.07	6.35 ± 1.46	0.274
Risk factors			
Previous DVT	14	15	0.723
Malignancy	1	2	0.99
Others	5	3	0.695
MAP (mmHg)	58.55 ± 7.72	61.8 ± 5.28	0.128
CVP (mmHg)	15.30 ± 2.13	15.55 ± 2.42	0.73
PaO <sub>2</sub> /FIO <sub>2</sub>	132.75 ± 19.95	128.75 ± 15.91	0.488
RVEF	43.90 ± 4.22	43.65 ± 4.00	0.849
PASP (mmHg)	58.05 ± 6.33	58.30 ± 1.57	0.906

MAP: mean arterial pressure; CVP: central venous pressure; PaO<sub>2</sub>/FIO<sub>2</sub>: oxygenation index; RVEF: right ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

**Table 2.** Hemodynamic parameters before catheter therapy within the experimental group

	Interventional therapy (n = 12)	Non-interventional therapy (n = 8)	p value
HR	132.4 ± 7.9	132.2 ± 5.1	0.955
MAP (mmHg)	66.3 ± 2.3	67.2 ± 1.1	0.139
CVP (mmHg)	14.0 ± 2.8	11.9 ± 1.3	0.062
PaO <sub>2</sub> /FIO <sub>2</sub>	198.4 ± 11.1	233.1 ± 11.8	< 0.01
ScvO <sub>2</sub>	62.1 ± 2.1	66.3 ± 1.2	< 0.01
CI (L/min/m <sup>2</sup> )	2.42 ± 0.15	2.90 ± 0.17	< 0.01
SVV	11.42 ± 1.31	18.88 ± 1.25	< 0.01

HR: heart rate; MAP: mean arterial pressure; CVP: central venous pressure; PaO<sub>2</sub>/FIO<sub>2</sub>: oxygenation index; ScvO<sub>2</sub>: central venous oxygen saturation; CI: cardiac index; SVV: stroke volume variation.

of the Vigileo Monitor (Edwards Lifesciences), in order to monitor SVV, CI and ScvO<sub>2</sub> continuously. The patients in the control group received right intra-jugular catheterization with double lumen deep vein catheters (Edwards Lifesciences) for central venous pressure (CVP) monitoring and right radial catheterization for mean arterial pressure (MAP) monitoring. RVEF and PASP were determined via echocardiography in both groups.

#### *Thrombolysis protocol and anticoagulation protocol*

All patients with acute massive PE received 7500 U of heparin subcutaneously and alte-

plase injection intravenously at the dose of 100 mg over 2 hours. The heparin was further administered every 12 hours for 3-5 days along with daily oral warfarin intake. The target range for INR was 2-3.

#### *Catheter-based interventions*

Catheter-based thrombus fragmentation and thrombolysis was performed under general anesthesia. Thrombus fragmentation was achieved via a pigtail rotational catheter which used an impeller to homogenize the thrombus [15]. Afterwards, urokinase 250,000 IU was administered locally [16]. Subsequent angiography showed opened pulmonary artery.

#### *Statistical analysis*

Continuous variables were expressed as mean ± standard deviation (SD) while categorical variables were expressed as values. Chi-square and Student's t test were used to examine categorical and continuous variables, respectively. Statistical analysis was performed with the SPSS 17.0 software.

The difference is considered statistically significantly if P < 0.05 .

#### **Results**

A total of 63 patients with acute massive PE diagnosed via CTPA between June 2010 and January 2014 were reviewed for the study. Forty patients were identified to meet the inclusion and exclusion criteria with 20 cases in each group. For the experimental group, the application of catheter-based thrombus fragmentation/thrombolysis therapy was determined by the hemodynamic parameters from FloTrac/Vigileo monitoring. For the control group, echocardiography was employed for the

**Table 3.** Effect of FloTrac/Vigileo-guided catheter therapy on hemodynamic parameters

	Experimental group (n = 20)	Control group (n = 20)	p value
MAP (mmHg)	71.30 ± 4.26	70.50 ± 3.85	0.54
CVP (mmHg)	10.40 ± 1.60	11.35 ± 1.76	0.08
PaO <sub>2</sub> /FiO <sub>2</sub>	264.90 ± 19.82	229.50 ± 29.35	< 0.01
RVEF	57.90 ± 5.40	52.20 ± 4.77	< 0.01
PASP (mmHg)	42.10 ± 4.20	47.75 ± 4.04	< 0.01

MAP: mean arterial pressure; CVP: central venous pressure; PaO<sub>2</sub>/FiO<sub>2</sub>: oxygenation index; RVEF: right ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

**Table 4.** Long term effect of FloTrac/Vigileo-guided catheter therapy

	Experimental group	Control group	p value
Survival	20	17	0.231
RVEF	64.35 ± 4.81	59.36 ± 3.50	< 0.01
PASP (mmHg)	31.06 ± 4.04	38.71 ± 4.66	< 0.01

RVEF: right ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

assessment of the necessity for catheter therapy. Patients were also monitored for MAP and CVP via traditional catheters. There were 21 male patients and 19 female patients ranging from 52 to 70 years old (mean, 60.3 ± 6.8) in the study group. There was no statistically significance in baseline characteristics such as CVP, MAP, PaO<sub>2</sub>/FiO<sub>2</sub>, RVEF and PASP between the two groups (**Table 1**). All patients were treated initially with unfractionated heparin plus systemic thrombolysis with 100 mg of alteplase during 2 hours.

Twelve patients in the experimental group underwent successful catheter therapy when FloTrac/Vigileo monitoring revealed abnormal hemodynamic status (SVV < 13%, SCVO<sub>2</sub> < 70%, and CI < 2.5 min/m<sup>2</sup>) 12 hours after systemic thrombolysis. Compared with the other 8 patients which catheter therapy was not performed, catheter therapy patients were significantly worse in PaO<sub>2</sub>/FiO<sub>2</sub>, ScvO<sub>2</sub>, CI and SVV. However, other parameters including HR, MAP and CVP were the same (**Table 2**).

Twenty-four hours after the systemic thrombolysis (12 hours after catheter therapy guided via FloTrac/Vigileo monitoring), the experimental group had significantly improved right ventricular function and oxygenation status including PaO<sub>2</sub>/FiO<sub>2</sub>, RVEF and PASP as compared with the control group (**Table 3**). Nevertheless, there

was no change in MAP and CVP. These data would support that FloTrac/Vigileo monitoring could identify target patients eligible for subsequent interventional therapy at an early stage.

In the mean time, patients in control group were evaluated for catheter therapy 24 hours after the systemic thrombolysis using echocardiography. Another 4 cases in the control group received successful catheter therapy. The 28-day survival rates were identical between the two groups however one patient in the control group died. Two more patients died 6 months after thrombolysis treatment. Both the RVEF and PASP were significantly improved in the experimental group at 6 months as compared to the control group (**Table 4**). These results suggest that FloTrac/Vigileo monitoring is a useful tool in monitoring hemodynamic status of PE patients for catheter-based intervention and improves long-term outcomes.

## Discussion

Our research goal was to determine whether minimally invasive Vigileo/FloTrac system is a valid method for guiding interventional therapy in acute massive PE. Our study demonstrated that FloTrac/Vigileo system in the experimental group allows for identify patients for early catheter-based intervention. The experimental group demonstrated improved right ventricular function and oxygenation status as compared with the control group 24 hours after the systemic thrombolysis. Furthermore, RVEF and PASP in the experimental group outperformed that of control group 6 months after the intervention.

For many years, PAC was the monitor of choice for hemodynamics in critical patients. PAC allows direct and simultaneous measurement of right atrial pressure, right ventricular pressure, pulmonary artery pressure, pulmonary artery occlusive pressure, mixed venous saturation (SvO<sub>2</sub>), and CO. However, the application of PAC is a highly invasive procedure. Furthermore, the outcome benefit for PAC has not been demonstrated in the literature [11, 17]. Echocardiography has been used as an effective monitoring tool for hemodynamic instability in the ICU and emergency medicine for many years. Echocardiography allows for evaluation

of RV dysfunction and CO in patients with PE. However, echocardiography measures parameters only in a single point and is not suitable for trend monitoring. Furthermore, there is difference in inter-observer interpretation [18]. The Vigileo/FloTrac system was first introduced in 2005 and allows pulse pressure-derived CO measurement without external calibration. The monitoring system derives hemodynamic values from the analysis of the arterial waveform [19]. This device monitors CO on a continuous basis by multiplying stroke volume with the heart rate. So far, the validation of this system in measuring CO has been assessed over 50 studies [20]. The Vigileo-FloTrac system has been used in emergency medicine setting for resuscitation of burn victims with good result [21]. A study was conducted to compare echocardiography and Vigileo/FloTrac device in the determination of changes in stroke volume induced by passive leg raising and found that Vigileo/FloTrac was able to predict fluid responsiveness with some limitation [22]. In another study, FloTrac/Vigileo has been demonstrated comparable to echocardiography in CO measurements in critically ill patients with the exceptions of patients with irregular heart rhythms and significant aortic stenosis [23]. However, the application of Vigileo/FloTrac system in acute PE has not been validated in the literature.

Treatment of acute PE usually results in improved pulmonary hemodynamic status [24]. However, reports showed more than half of PE patients still present with incomplete resolution 6 months after diagnosis. After which, there is no further resolution of thrombi [25]. When the acute PE was not resolved with 4 weeks, the embolic material was shown to be integrated into the pulmonary arterial wall at the main pulmonary artery, lobar, segmental, or subsegmental levels [26]. It has been documented that progenitor cells were identified in the neointima of occluded vessels in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Progenitor cells may enhance intimal remodeling and contribute to the development of CTEPH in the microenvironment formed by thromboemboli [27]. Our data demonstrated that catheter-based therapy guided by FloTrac/Vigileo system could reduce PASP six months after the procedure as compared with the control group. Therefore, this intervention might be helpful for reducing CTEPH.

There are several limitations in this study. First, this is a single-center prospective study with limited patient population. Second, our study did not directly compare the validity of FloTrac/Vigileo system with echocardiography. A direct comparison is necessary to generate more convincing data. Furthermore, this study is only limited to patients with acute massive PE. The validity of the FloTrac/Vigileo system in general PE patients has not been tested. Therefore, a large prospective study with broad PE population is warranted in the future.

In conclusion, due to the limitations and complications of PAC in the clinical practice, physicians are looking for less invasive devices to monitor hemodynamics in acute PE. The Vigileo/FloTrac system has been studied extensively in monitoring CO in many clinical situations. Vigileo/FloTrac system may have the potential to guide the anticoagulation, thrombolysis, and interventions via catheter and surgical thrombectomy for acute PE. Further studies needed to investigate the reliability of Vigileo/FloTrac system in improving outcomes of acute PE.

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### Disclosure of conflict of interest

None.

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