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Monitoring mixed venous oxygen saturation in patients with obstructive shock after massive pulmonary embolism

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Summary. *Background:* Patients with massive pulmonary embolism and obstructive shock usually require hemodynamic stabilization and thrombolysis. Little is known about the optimal and proper use of volume infusion and vasoactive drugs, or about the titration of thrombolytic agents in patients with relative contraindication for such treatment. The aim of the study was to find the most rapidly changing hemodynamic variable to monitor and optimize the treatment of patients with obstructive shock following massive pulmonary embolism.

Patients and methods: Ten consecutive patients hospitalized in the medical intensive care unit in the community General Hospital with obstructive shock following massive pulmonary embolism were included in the prospective observational study. Heart rate, systolic arterial pressure, central venous pressure, mean pulmonary-artery pressure, cardiac index, total pulmonary vascular-resistance index, mixed venous oxygen saturation, and urine output were measured on admission and at 1, 2, 3, 4, 8, 12, and 16 hours. Patients were treated with urokinase through the distal port of a pulmonary-artery catheter.

Results: At 1 hour, mixed venous oxygen saturation, systolic arterial pressure and cardiac index were higher than their admission values (31 ± 10 vs. $49 \pm 12\%$, $p < 0.0001$; 86 ± 12 vs. 105 ± 17 mmHg, $p < 0.01$; 1.5 ± 0.4 vs. 1.9 ± 0.7 L/min/m^2, $p < 0.05$; respectively), whereas heart rate, central venous pressure, mean pulmonary-artery pressure and urine output remained unchanged. Total pulmonary vascular-resistance index was lower than at admission (29 ± 10 vs. 21 ± 12 mmHg/L/min/m^2, $p < 0.05$). The relative change of mixed venous oxygen saturation at hour 1 was higher than the relative changes of all other studied variables ($p < 0.05$). Serum lactate on admission and at 12 hours correlated to mixed venous oxygen saturation ($r = -0.855$, $p < 0.001$).

Conclusion: In obstructive shock after massive pulmonary embolism, mixed venous oxygen saturation changes more rapidly than other standard hemodynamic variables.

Key words: Pulmonary embolism, thrombolysis, monitoring.

Introduction

Pulmonary embolism due to different causes is one of the premortem least recognized causes of death [1–5]. Massive pulmonary embolism (MPE) associated with shock is a devastating clinical event compared with hemodynamically stable patients with pulmonary embolism [6, 7]. The right-ventricular function is a crucial prognostic determinant and is positively associated with rapid resolution of pulmonary clots and effective supportive therapy. Although the indication for thrombolytic therapy in such patients remains unequivocal, there have been no randomized clinical studies on the optimal administration of volume infusion and vasoactive agents [8]. The ultimate hemodynamic goal is to ensure adequate systemic blood flow and oxygen supply, but evaluation of such therapeutic intervention necessitates invasive hemodynamic monitoring. The optimal mode of such monitoring also remains to be clarified.

Meyer et al. introduced serial calculations of total pulmonary vascular-resistance index (TPRI), determined by dividing mean pulmonary-artery pressure (MPAP) by cardiac index (Ci) obtained from thermodilution, to monitor the efficacy of thrombolytic therapy in patients with severe pulmonary embolism [9]. This method offered a better and more practical serial evaluation of pulmonary obstruction than from repeated estimation of angiographic indexes. However, Ci obtained from thermodilution can be inaccurate in low flow states and in the presence of tricuspid regurgitation, and does not provide information on the adequacy of oxygen transport [10].

The aim of our study was to find the most rapidly changing hemodynamic variable for monitoring the treatment of patients with obstructive shock after MPE.

Materials and methods

Patients

Ten patients who presented with shock secondary to MPE and who were treated with thrombolysis were enrolled in a prospective study during a 2-year period (May 1996 through December 1998). They were all admitted to an 11-bed, closed medical intensive care unit (ICU) in an 860-bed community general hospital. The study was approved by the institutional review board.

Diagnostic procedure

Transoesophageal echocardiography (TEE) using a 4–7 MHz multiplane probe (MPT7-4, HDI 3000, ATL, Bothell, Wa.) was performed after rapid initial assessment (clinical history, physical examination, and transthoracic echocardiography as a screening test before TEE in order to exclude diagnoses other than acute right-heart overload) within 15 min of admission to the ICU. We have described the detailed methodology previously [11, 12]. Briefly, right and left ventricles were examined from the transverse gastric short-axis view. Visualization of the atria and interatrial septum was achieved by slight withdrawal of the probe. The pulmonary trunk, proximal segment of the left pulmonary artery, and the whole right pulmonary artery were examined from the upper transverse view using extreme clockwise rotation of the probe. In the pulmonary artery or its branches, any abnormal intraluminal structure with echoicity different from blood and vessel was considered a thromboembolus.

In the case of negative TEE, pulmonary scintigraphy was performed as a confirmatory test after hemodynamic stabilization and thrombolysis. PIOPED criteria (prospective investigation of pulmonary embolism diagnosis) were used for evaluation and analysis of results [13]. Autopsy was performed routinely in patients who died.

Hemodynamic measurements

Systemic arterial pressure (SAP) and heart rate (HR) were non-invasively monitored (SC 960/961 or SC 6000, Siemens AG, Erlangen, Germany). Right-heart catheterization was performed in all patients. Continuous cardiac-output monitoring catheters with oxygen sensor and continuous display of mixed venous oxygen saturation (MVO_2) (Oxymetrics Swan-Ganz catheter, Baxter HealthCare Corp, Irvin, Ca) were used. Hemodynamic measurements included central venous pressure (CVP), MPAP, cardiac output and MVO_2 on admission and at 1, 2, 3, 4, 8, 12, and 16 hours after the start of thrombolysis. Ci was calculated as cardiac output divided by body surface area. TPRI was calculated as MPAP divided by Ci. Arterial lactate level was measured using a colorimetric enzyme method (Chronolab, Hitachi, San Jose, CA, USA).

Clinical presentation

Shock was defined as systolic arterial pressure < 90 mmHg and Ci < 2.1 l/min/m^2 with elevated serum lactate > 2.5 mmol/l.

None of the patients had acute trauma or signs and symptoms of systemic inflammatory response, sepsis or acute respiratory-distress syndrome.

Treatment

All patients received 100% oxygen through an Ohio mask or were mechanically ventilated. The ventilator settings remained constant during the study.

After the diagnosis was established, 80 IU/kg of heparin was given as an IV bolus, followed by one million I.U. of urokinase over 10 minutes through the distal port of a pulmonary artery catheter and then 1 million I.U. in 2-hour infusion. IV heparin infusion to achieve an activated partial thromboplastin time-ratio of two to three times the basal value was started at the end of urokinase infusion. Each patient received concomitant infusion of noradrenaline in stepwise incremental infusion (0.2–4.0 μg/kg/min). After noradrenaline, saline was infused (200–1000 ml/h) in patients with CVP < 20 mmHg. Dobutamine was used only as an adjunctive agent and was left to the discretion of the treating physician: its starting infusion was 3.5 μg/kg/min, continuing with incremental infusion to a maximum rate of 10.0 μg/kg/min. The therapy was titrated in an attempt to achieve mean systemic systolic arterial pressure > 80 mmHg and adequate urine output (50 ml/h).

Statistics

We used Student's t-test for comparison of continuous normally distributed data (heart rate, SAP, CVP, MPAP, MVO_2, Ci, TPRI, and urine output) and the chi-square test for comparison of noncontinuous variables. Results were expressed as mean ± SD unless otherwise specified. In patients who underwent repeated hemodynamic measurements, changes from baseline were evaluated with a paired t-test for each monitoring variable. Relative changes of variables that increased during treatment were calculated by dividing data by their baseline values (actual value/baseline value); those that decreased were calculated with the formula 1-actual value/baseline value. Rel-

Table 1. Characteristics, treatment, and outcome of 10 patients with massive pulmonary embolism and shock

Patient/sex/ age, yr	Risk factors for pulmonary embolism	Therapy in 16 hours			Outcome	
		Vol ml/kg	NE mg/kg	DOB mg/kg		
1/M/65	I-ST	0	0.025	0	Discharged	
2/F/70	MA	27.8	0.042	0	Discharged	
3/F/64	I-ST	15.3	0.069	0	Discharged	
4/F/48	I-ST	44.6	0.08	0	Discharged	
5/F/50	I-ST	0	0.025	0	Discharged	
6/F/73	I-MN	68.3	0.417	12.5	Died	MV
7/M/45	I-MN	90	0.017	4	Discharged	MV
8F/64	I-ST	62.5	0.028	0.42	Discharged	
9/F/67	I-MN	62.5	0.1	5.9	Discharged	
10/F/64	I-MN	47.1	0.259	0	Discharged	

M male; *F* female; *NE* norepinephrine; *DOB* dobutamine; *Vol* volume (saline) infusion; *MV* mechanical ventilation; *I-ST* immobilization due to surgical procedure or trauma; *I-MN* immobilization due to medical or neurologic disease; *MA* malignancy.

Table 2. Hemodynamics of patients with massive pulmonary embolism

	At admission N = 10	At 1 hour N = 10	At 2 hours N = 10	At 3 hours N = 10	At 4 hours N = 10	At 8 hours N = 10	At 12 hours N = 10	At 16 hours N = 9
Heart rate, bmp	129 ± 22	124 ± 16	123 ± 22	115 ± 24	115 ± 21*	113 ± 22*	108 ± 21*	103 ± 16†
SAP, mmHg	86 ± 12	105 ± 17*	131 ± 15§	130 ± 20§	129 ± 16§	129 ± 19§	121 ± 14§	130 ± 12§
CVP, mmHg	18 ± 3	18 ± 4	17 ± 4	16 ± 4	15 ± 3*	15 ± 3*	16 ± 5	16 ± 5
MPAP, mmHg	40 ± 9	36 ± 7	37 ± 7	34 ± 9*	32 ± 9†	33 ± 9*	32 ± 6†	32 ± 5†
MVO_2, %	31 ± 10	49 ± 12§	53 ± 10§	54 ± 9§	60 ± 8§	61 ± 10§	62±12§	66 ± 8§
Ci, l/min/m^2	1.5 ± 0.4	1.9 ± 0.7*	2.1 ± 0.6†	2.1 ± 0.5†	2.2 ± 0.5‡	2.3 ± 0.6§	2.5 ± 0.7§	2.5 ± 0.4§
TPRI, mmHg/l/min/m^2	29 ± 10	21 ± 12*	20 ± 10†	18 ± 8‡	16 ± 8§	15 ± 8§	15 ± 7§	12 ± 4§
Urine output, ml/h	16 ± 16	11 ± 8	16 ± 15	29 ± 22	50 ± 62	102 ± 76†	99 ± 94†	148 ± 126†

Values reflect data in patients with paired measurements. Data are mean (SD). *SAP* systolic arterial pressure; *MPAP* mean pulmonary artery pressure; *CVP* central venous pressure; *Ci* cardiac index; *MVO_2* mixed venous oxygen saturation; *TPRI* total pulmonary vascular resistance index. * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$; § $p < 0.0001$ for paired t-tests of mean of variable and corresponding value at admission.

ative changes of variables were compared using one-way ANOVA. Correlations were tested with the Pearson correlation coefficient. A 2-tailed value of $p < 0.05$ was considered statistically significant. SPSS 10.0 for Windows was used for statistical calculations.

Results

Ten consecutive patients (mean age 62 ± 5 years) with obstructive shock following MPE were enrolled in the study. Demographic and clinical data, treatment and outcome are shown in Table 1.

Nine patients (90%) had central thromboemboli diagnosed by TEE. All patients had right-ventricular dysfunction. In one patient, MPE was confirmed by high probability lung ventilation/perfusion scintigraphy after hemodynamic stabilization and thrombolysis.

All patients received noradrenaline infusion with a mean total dose of 0.106 ± 0.165 mg/kg over 16 hours, but in widely variable regimens. Mean total saline infusion over 16 hours was 41.8 ± 33.3 ml/kg. Two patients had excellent hemodynamic response to norepinephrine alone and required no volume support. Four patients received dobutamine with a mean total dose of 5.71 mg/kg over 16 hours.

Table 2 shows the changes in hemodynamic variables. At 1 hour MVO_2, SAP and Ci were higher than their admission values (31 ± 10 vs. 49 ± 12%, $p < 0.0001$; 86 ± 12 vs. 105 ± 17 mmHg, $p < 0.01$; 1.5 ± 0.4 vs. 1.9 ± 0.7 L/min/m^2, $p < 0.05$; respectively), whereas HR, CVP, MPAP and urine output remained unchanged. TPRI was lower than admission values (29 ± 10 vs. 21 ± 12 mmHg/L/min/m^2, $p < 0.05$). The relative change of MVO_2 at 1 hour was higher than the relative changes of all other studied variables ($p < 0.05$) (Fig. 1). The relative change of TPRI at 1 hour was not statistically different from those of SAP, MPAP and Ci. Urine output had the highest relative increase but the change occurred late during the treatment (at 3 hours or later).

At 16 hours serum lactate fell significantly (5.24 ± 2.5 vs. 1.83 ± 0.51 mmol/l). Serum lactate on admission and at 12 hours correlated strongly to MVO_2 ($r = -0.855$, $p < 0.001$) (Fig. 2). Values of $MVO_2 < 40\%$ were associated with lactate values > 2.5 mmol/l.

One patient died at 14 hours; despite effective initial treatment, she succumbed to sudden refractory electromechanical dissociation caused by repeated massive central re-embolism, later confirmed at autopsy. Of nine patients who survived to hospital discharge, eight received peroral anticoagulants and one received an inferior vena caval filter. No patient had major hemorrhage. One patient had a minor hemorrhage at the puncture site and required transfusion with one pack of blood.

Discussion

The present study shows that MVO_2 may offer better monitoring than standard hemodynamic variables; it changes rapidly and may enable goal-directed therapy. The study supports the view that central thromboemboli are present in the majority of patients with MPE and shock, and strengthens the role of TEE as a noninvasive bedside tool in this subgroup of patients [11, 12].

The ultimate goal of the treatment is to assure adequate tissue oxygenation in order to prevent further organ failure. To our knowledge this is the first, albeit small, study with continuous MVO_2 saturation monitoring in patients with MPE. Unlike other standard hemodynamic variables, MVO_2 allows estimation of the adequacy of tissue oxygenation. Thus, MVO_2 is a sensitive marker of therapeutic interventions in the early period of monitoring hemodynamically unstable patients with MPE. Since a great proportion of patients have contraindications for thrombolysis, this therapy can be terminated early after achieving adequate hemodynamic response [14]. We may also recognize patients refractory to thrombolytic therapy earlier and offer them different treatment.

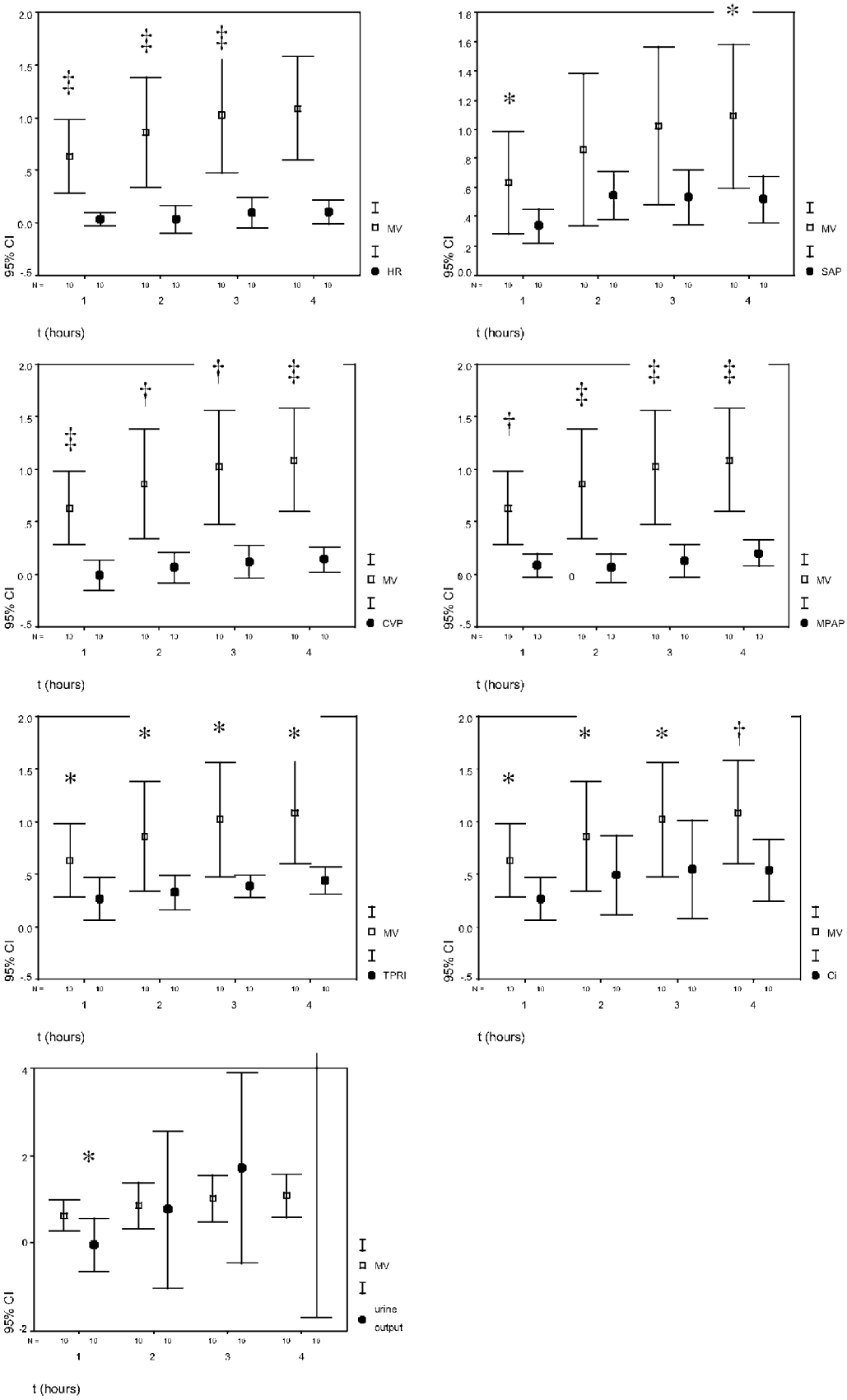

Fig. 1. Relative changes of hemodynamic variable in comparison with mixed venous oxygen saturation in patients with massive pulmonary embolism. *HR* heart rate; *SAP* systolic arterial pressure; *MPAP* mean pulmonary artery pressure; *CVP* central venous pressure; *Ci* cardiac index; *CI* confidence interval; MVO_2 mixed venous oxygen saturation; *TPRI* total pulmonary vascular resistance index. * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$; § $p < 0.0001$ for one-way ANOVA

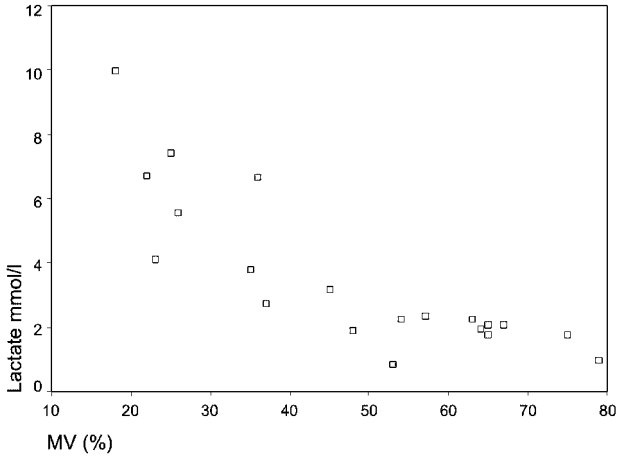

Fig. 2. Correlation between mixed venous oxygen saturation and serum lactate at admission and at 12 hours. *MV* mixed venous oxygen saturation

In our study, increased oxygen delivery increased MVO_2 in patients with stable oxygen demand and arterial oxygen content. In patients with MPE, cardiac output depends mainly on right-ventricular function, with its limited capacity to oppose an acute increase of afterload. Thus any clot reduction and/or improvement of right-ventricular contractile function increases MVO_2.

Michard et al. used MVO_2 measurements in patients with MPE and Miller score > 20/34 on admission in order to select patients for thrombolytic therapy [15]. He divided patients into responders with MVO_2 of $47 \pm 9\%$ and non-responders with MVO_2 $60 \pm 7\%$. In our group the average MVO_2 was 31%, which denotes extreme hemodynamic compromise, confirmed by other hemodynamic parameters and increased serum levels of lactate. It is possible that such patients are often excluded from studies, precluding realistic reporting of MPE. Patients with unstable MPE therefore manifest seriously impaired oxygen transport with low MVO_2 values. They seem to be the target group not only for the administration and monitoring of thrombolytic therapy but also for monitoring of volume infusion and vasoactive therapy. Mercat et al. confirmed the beneficial effects of 500 ml dextran without vasoactive therapy in patients with MPE who were normotensive [16]. It is well known that volume infusion should be used with caution in hypotensive patients with MPE. However, continuous MVO_2 monitoring allows individually tailored volume loading.

Most data for norepinephrine administration are extrapolated from animal models. Molloy et al. in a study of dogs found that norepinephrine improved right-ventricular performance by increasing blood pressure and right-ventricular perfusion and contractility [17]. In the same study all control dogs and those treated with volume and isoproterenol died. In our study patients rapidly increased MVO_2 values and decreased TPRI after receiving norepinephrine and thrombolytic infusion. It is impossible to avoid the confounding effects of such combined therapy, but norepinephrine seems to be an effective temporizing measure that enables thrombolysis and allows optimal volume loading.

The hemodynamic effects of dobutamine in patients with fixed cardiac output and hypotension can be potentially harmful. However, the hemodynamic improvement with dobutamine and concomitant noradrenaline and saline infusion in our four patients with MPE was similar to that found by Jardin et al., who used comparable doses of dobutamine in circulatory unstable patients [18].

Our report of a final TPRI reduction of –52% compares favorably with findings of –24% in the study by Meyer et al. [9], and is similar to the effects reported by Sors et al. [19] of 100 mg recombinant tissue-plasminogen activator (rt-PA) given as an intravenous bolus (–35%) or as a 2-hour continuous infusion (–42%). Short concentrated regimens of thrombolytic therapy are most effective in obtaining early rapid lysis [20]. In severely shocked patients, who have reduced systemic delivery, increasing the thrombolytic concentration in proximity to thromboemboli may be beneficial.

The drawback of pulmonary-artery catheterization is the increase of bleeding from vascular access sites. In our study there were no serious bleeding complications such as haematothorax or haemorrhagic shock, because cannulation via the subclavian route was performed before thrombolysis [21].

A further drawback of pulmonary-artery catheterization is loss of time. In ICU with very well trained staff, pulmonary-artery catheterization is performed in 15–20 minutes and possibly during TEE. Both procedures are probably performed more quickly than a CT scan. However, we have not found any study comparing short- or long-term mortality rates and the time needed to diagnose pulmonary embolism and initiate different diagnostic procedures in patients with suspected PE who have shock or hypotension.

We have not collected data on oxyhemoglobin saturation from the superior vena cava; this was shown to be effective in early goal-directed therapy in the treatment of severe sepsis and septic shock, and provided significant benefits in outcome [22].

In cases where the insertion of a pulmonary-artery catheter is impractical (such as thrombolysis), venous oxyhemoglobin saturation could be measured in the central circulation [23]; however, wide differences in range and confidence limits would lead to large errors if saturation in the superior vena cava or right atrium were substituted for true MVO_2 in calculations of oxygen transport or pulmonary venous admixture, especially in the face of high pulmonary arterial pressures and impairment of right ventricular function [24].

Our study has at least one limitation: we used urokinase, which is currently not as widely used as rt-PA. Despite this limitation a 38% reduction of TPRI and 102% increase of MVO_2 at 3 hours were achieved. Further studies with newer thrombolytic agents are needed.

In conclusion, we demonstrated that in patients with MPE and shock continuous MVO_2 more rapidly detects hemodynamic changes than standard hemodynamic variables and serial TPRI calculations. MVO_2 may become a promising monitoring tool in selected groups of patients with MPE, with potential to guide the titration of thrombolytic, volume and vasoactive therapy.

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References

1. Podbregar M, Voga G, Krivec B, et al (2001) Should we confirm our clinical diagnostics certainty by autopsy. Int Care Med 27: 1750–1755
2. Pablinger I, Grafenhofer H (2003) Pregnancy-associated thrombosis. Wien Klin Wochenschr 115: 482–484
3. Kyrle PA, Eichinger S (2003) The risk of recurrent venous thromboembolism: the Austrian study on recurrent venous thromboembolism. Wien Klin Wochenschr 115: 471–474
4. Watzke HH (2003) Clinical significance of gene-diagnosis for defects in coagulation factors and inhibitors. Wien Klin Wochenschr 115: 475–481
5. Schobersberger W, Hauer B, Sumann G, et al (2002) Travelers thrombosis: incidence, etiology, prevention. Wien Klin Wochenschr 114: 14–20
6. Janata K, Holzer M, Domanovitis H, et al (2002) Mortality of patients with pulmonary embolism. Wien Klin Wochenschr 114: 766–772
7. Urokinase Pulmonary Emboly Trial (1970) Phase 1 results: a cooperative study. JAMA 214: 2163–2172
8. Tapson VF, Witty LA (1995) Massive pulmonary embolism: diagnostic and therapeutic strategies. Clinics in Chest Medicine 16: 329–338
9. Meyer G, Sors H, Charbonnier B, Kasper W, Bassand JP, Kerr IH, et al (1992) Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: a European multicenter double-blind trial. J Am Coll Cardiol 19: 239–245
10. Nunez S, Maisel A (1998) Comparison between mixed venous oxygen saturation and thermodilution cardiac output in monitoring patients with severe heart failure treated with milrinone and dobutamine. Am Heart J 135: 383–338
11. Krivec B, Voga G, Žuran I, Skale R, Pareznik R, Podbregar M, et al (1997) Diagnosis and treatment of shock due to massive pulmonary embolism: approach with transesophageal echocardiography and intrapulmonary thrombolysis. Chest 112: 1310–1316
12. Podbregar M, Krivec B, Voga G (2002) Impact of morphologic characteristics of central pulmonary thromboemboli in masssive pulmonary embolism. Chest 122: 973–979
13. Prospective investigation of pulmonary embolism diagnosis (PIOPED) investigators (1990) Tissue plasminogen activator for the treatment of acute pulmonary embolism: a collaborative study by the PIOPED investigators. Chest 97: 528–533
14. Kasper W, Konstantinidis S, Geibel A, Olschewski M, Heinrich F, Grosser KD, et al (1997) Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registy. J Am Coll Cardiol 30: 1165–1171
15. Michard F, Meyer G, Wysocki M, Diehl JL, Mercat A, Sors H (1999) Cardiorespiratory efficacy of thrombolytic therapy in acute massive pulmonary embolism: identification of predicitve factors. Eur Respir J 13: 610–615
16. Mercat A, Diehl JL, Meyer G, Teboul JL, Sors H (1999) Hemodynamic effects of fluid loading in acute massive pulmonary embolism. Crit Care Med 27: 540–544
17. Molloy WD, Lee KY, Girling L (1984) Treatment of shock in a canine model of pulmonary embolism. Am Rev Respir Dis 130: 870–874
18. Jardin F, Genevray B, Brun-Ney D, Margairaz A (1985) Dobutamine: a hemodynamic evaluation in pulmonary embolism and shock. Crit Care Med 13: 1009–1012
19. Sors H, Pacouret G, Azarian R (1994) Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism: a randomized controlled multicenter trial. Chest 106: 712–717
20. Blinc A, Francis CW (1996) Transport processes in fibrinolysis and fibrinolytic therapy. Thromb Haemost 76: 481–491
21. Lee HS, Quinn T, Boyler RM (1995) Safety of thrombolytic treatment in patients with central venous cannulation. Br Heart J 73: 359–362
22. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368–1377
23. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM (1989) Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. Chest 95: 1216–1221
24. Edwards JD, Mayall RM (1998) Importance of the sampling site for measurement of mixed venous oxygen. Crit Care Med 26: 1356–1360

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