



# Diuretics Versus Volume Expansion in the Initial Management of Acute Intermediate High-Risk Pulmonary Embolism

Emile Ferrari<sup>1</sup> · Benjamin Sartre<sup>1</sup> · Mohamed Labbaoui<sup>1</sup> · Nathan Heme<sup>1</sup> · Florian Asarisi<sup>1</sup> · Nassim Redjimi<sup>1</sup> · Etienne Fourrier<sup>1</sup> · Fabien Squara<sup>1</sup> · Sithy Bun<sup>1</sup> · Nathalie Berkane<sup>2</sup> · Jean Philippe Breittmayer<sup>1</sup> · Denis Doyen<sup>3,4</sup> · Pamela Mocerri<sup>1,4</sup>

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## Abstract

**Aims** The very early management of pulmonary embolism (PE), a part from antithrombotic treatment, has been little studied. Our aim was to compare the effects of diuretic therapy (DT) versus volume expansion (VE) in patients hospitalized for PE with RV dysfunction.

**Methods and Results** We conducted a randomized open-label multicentric study including patients with intermediate high-risk PE. Patients were randomized between diuretics or saline infusion. The primary endpoint was time to troponin (Tp) normalization. Secondary endpoints were time to normalization of B-type natriuretic peptide (BNP), changes in echocardiographic RV function parameters and treatment tolerance. Sixty patients presenting intermediate high-risk PE were randomized. Thirty received DT and 30 VE. We noted no changes in Tp kinetics between the two groups. In contrast, faster normalization of BNP was obtained in the DT group: 56 [28–120] vs 108 [48–144] h:  $p=0.05$ , with a shorter time to 50%-decrease from peak value 36 [24–48] vs 54 [41–67] h,  $p=0.003$  and a higher rate of patients with a lower BNP concentration within the first 12 h (42% vs 12%  $p<0.001$ ). RV echocardiographic parameters were unchanged between the groups. One dose 40 mg furosemide was well-tolerated and not associated with any serious adverse events.

**Conclusion** In the acute management of intermediate high-risk PE, initial therapy including diuretic treatment is well-tolerated and safe. Although changes in Tp kinetics and echocardiographic RV dysfunction parameters did not differ, normalization of BNP is achieved more quickly in the DT group. This finding, which need to be confirmed in trials with clinical end points, may reflects a rapid improvement in RV function using one dose 40 mg furosemide.

**Trial Registry** Clinical Trial Registration NCT02531581.

**Keywords** Pulmonary embolism · Biomarkers · Diuretics · Volume expansion

## Introduction

Intermediate high-risk pulmonary embolism (PE) is a frequent and severe condition, characterized by right ventricular (RV) dysfunction and a high rate of in-hospital mortality [1]. Occurrence of RV failure must be prevented to avoid cardiogenic shock and death [2]. In these high risk patients, while the management of anticoagulants and thrombolytics is consistently improving, the relative benefit of volume expansion (VE) as opposed to diuretics have not been established [3–7]. According to the ESC recommendations for intermediate-risk PE, initial hemodynamic management remains empirical, consisting of reasonable VE and close monitoring [8]. The aim of our study was to compare the effects of diuretic therapy (DT) versus VE in patients

✉ Emile Ferrari  
ferrari.e@chu-nice.fr

<sup>1</sup> Cardiology Department, Centre Hospitalier Universitaire de Nice, 30, Avenue de la voie romaine, CS 51069, 06001 Nice Cedex 1, France

<sup>2</sup> Cardiology Department, Centre Hospitalier de Cannes, Cannes, France

<sup>3</sup> Medical Intensive Care Unit, Centre Hospitalier Universitaire de Nice, Nice, France

<sup>4</sup> UR2CA, Université Côte d'Azur, Nice, France

hospitalized for PE with RV dysfunction. The primary endpoint was troponin (Tp) normalization. The secondary endpoints were B-type natriuretic peptide (BNP) normalization, variations in RV function parameters and treatment tolerance.

## Methods

We performed a randomized multicentric open-label study. Patients with a confirmed intermediate high-risk PE were randomized on admission. They were treated with either an IV bolus of 40 mg furosemide on admission [supplemented with another 40 mg bolus if diuresis remained below 500 cc at the fourth hour (H4)] in the DT group or with a 500 mL saline infusion (sodium chloride 0.9%) delivered over 4 h, followed by one 1000 mL saline infusion per day in the VE group. The study flowchart is shown in Fig. 1. Anticoagulant therapy was initiated without delay, in accordance with the current guidelines [3].

## Patients

Patients were included in the study if they had an acute PE confirmed by computed tomography scan and all the following conditions: RV dilatation confirmed by echocardiography with a right-to-left ventricular end-diastolic diameter ratio  $> 0.9$  in the apical four-chamber view or  $> 0.7$  in the parasternal long-axis view, a tricuspid annular plane systolic excursion (TAPSE)  $< 16$  mm, a tricuspid annular peak

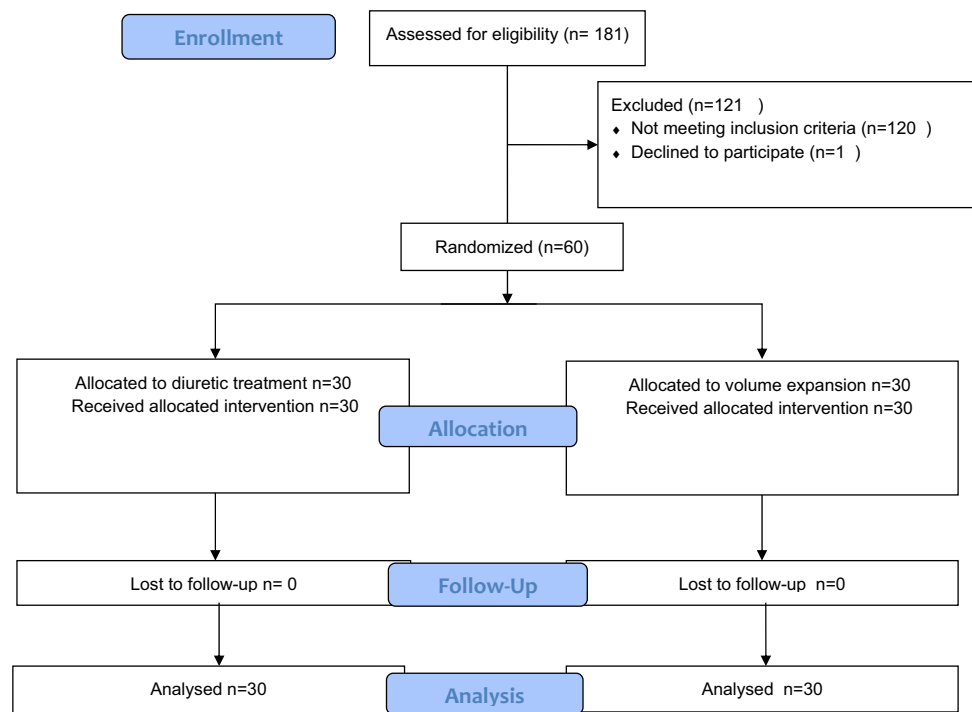
systolic velocity (S'-DTI)  $< 10$  cm/s, a myocardial injury confirmed by a positive Tp concentration  $\geq 70$  ng/L and a BNP concentration  $> 100$  pg/mL.

Patients presenting either cardiogenic shock, the need for thrombolysis or catecholamine infusion, cardiopulmonary resuscitation on admission, severe chronic renal disease (glomerular filtration rate  $< 30$  mL/min), an inferior vena cava (IVC) diameter  $< 21$  mm, or having received a diuretic or a fluid load infusion in the 24 previous hours were not included. Patients receiving chronic diuretic treatment for any other reason were also excluded. Randomization was done as soon as the patients arrived with a definite diagnosis in the participating centers. The maximum delay for randomization was 2 h. Maximum time from randomization to treatment was 1 h.

## Data Collection

Transthoracic echocardiography (TTE) measurements for the assessment of RV function were recorded in compliance with the latest guidelines [9, 10]. TTE was performed on admission with CX50 or Affinity 70 (Philips Medical Systems, Best, Netherlands) and was repeated 4 h after initiation of treatment (H4), then every day until normalization or after ICU discharge. RV and left ventricular (LV) diastolic diameters were measured in the parasternal long-axis view and the apical four-chamber view. TAPSE was assessed in the M-mode presentation by placing a cursor in the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole. Systolic pulmonary artery

Fig. 1 Flow chart



pressure (sPAP) was estimated by tricuspid regurgitation velocity using continuous-wave Doppler added to right atrial pressure as assessed by IVC size and collapsibility. RV systolic function normalization was defined by TAPSE > 16 mm and S'-DTI > 11 cm/s. All TTE were checked by two blinded readers.

High-sensitivity Troponin I (Tp) and BNP were measured at baseline, on admission, then at H12, and then every 12 h until normalization, with the Siemens Centaur® and the Alere Triage BNP kit (Beckman Coulter®), respectively. The positivity threshold was 70 ng/L for Tp and 100 pg/mL for BNP.

Blood pressure, heart rate, diuresis, and oxygen requirements (designed to maintain oxygen saturation > 95%) were recorded at H4, then twice a day until discharge.

### Follow-Up and Outcome Assessment

The primary endpoint was time to normalization of Tp concentrations. One of the second endpoints was time to normalization of BNP concentrations. Given that both biomarkers could increase immediately after hospitalization, we studied three criteria to evaluate the possible faster normalization: the total time to complete normalization defined as the time needed to reach Tp < 70 ng/L or BNP < 100 pg/mL, time to 50% concentration from baseline value (defined as the time needed to reach half the initial biomarker concentration), and the number of patients in whom biomarker decreased at first control at H12.

The other secondary endpoints were: improvement of RV echocardiographic dysfunction at H24 using TAPSE and S'-DTI and treatment safety outcomes measured by occurrence of hypokalemia (kaliemia < 3.5 mmol/L) and arrhythmia during initial hospitalization and acute kidney injury (increase of creatinine by 44 µmol/L or 25% from basal value [11]) during initial hospitalization and at day 30. All patients were followed for at least 30 days. Events were recorded during a consultation scheduled at day 30. The protocol was approved by our institutional ethics comity. This study was registered on clinical trials.gov NCT02531581. All patients gave their written informed consent for study participation.

### Statistical Analysis

Data characterized by a normal distribution are expressed as mean ± standard deviation while others are expressed as median with maximum and minimum ranges. Student's *t* test or the Mann–Whitney *U* test were used for comparisons between DT and VE groups. Khi2 test was used to compare discrete variables (with Yates's correction when needed). Kaplan–Meier analysis was used to establish event-free survival at day seven and cumulative survival at day 30.

All tests were two-sided. Data were considered significant at  $p < 0.05$ . All tests were performed using SPSS software, version 22.0 (SPSS, Inc., Chicago, IL, USA). We calculated that the inclusion of 44 patients would provide 90% potency to show the superiority of diuretics at a unilateral alpha level of 0.05, based on an estimated time of 72 h for Tp normalization. To offset possible study exits, we planned to include 60 patients.

## Results

Between January 2016 and December 2019, 181 patients admitted with PE were screened, of which 60 were randomized. Thirty were included in the DT group and 30 in the VE group. Demographic data and clinical and paraclinical status at baseline are reported for the whole population and for both groups in Table 1.

In the whole population, mean age was  $70.3 \pm 13$  years and 56% of patients were male. At baseline, mean heart rate and systolic blood pressure were, respectively,  $95 \pm 17$  beats/min and  $135.1 \pm 23$  mmHg. Mean Tp value was  $694 \pm 801$  ng/L and mean BNP value was  $430 \pm 653$  pg/mL. In the DT group, in compliance with the protocol, 29 patients received 40 mg IV furosemide and one received 80 mg.

Table 2 shows clinical and biological parameters used for safety monitoring of the DT group vs the VE group: At H24, urine output was  $5365 \pm 3238$  mL in the DT group vs  $2032 \pm 1682$  mL in the VE group ( $p < 0.001$ ). Systolic blood pressure, heart rate, creatinine and potassium concentrations decreased in both groups but with no difference between the two. Oxygen requirements also displayed no differences.

### Efficacy Endpoint

Table 3 reports biomarker changes. Whatever the criterion chosen, Tp kinetics did not differ between the groups. In contrast, time to complete BNP normalization was shorter in the DT group ( $77.9 \pm 55$  vs  $105.3 \pm 64$  h:  $p = 0.05$ ) as was the time to 50% concentration decrease ( $36.6 \pm 14$  vs  $53.6 \pm 15$  h:  $p = 0.003$ ). The number of patients with a decreased BNP concentration at the first control (H12) after randomization was higher in the DT group (45% vs 12.5% in the VE group:  $p < 0.001$ ).

The decrease in sPAP measured by echocardiography at H4 was higher in the DT group vs the VE group ( $7.7$  vs  $1.5$  mmHg  $p = 0.006$ ), as was the decrease in IVC diameter at H4 ( $2.9$  mm vs 0:  $p = 0.008$ ) (Table 4). In contrast, none of the studied RV echocardiographic parameters were modified, whatever the time chosen (Table 4).

**Table 1** Characteristics of patients

	Total population (n = 60)	Volume expansion (n = 30)	Diuretic (n = 30)	p
Age (years)	72 (63, 80)	75 (63, 82)	71 (62, 77)	0.31
Men (n (%))	37 (56)	17 (51)	20 (60)	0.46
HR (beats/min)	94 (85, 105)	94 (87, 108)	91 (81, 108)	0.56
SBP (mmHg)	135 (123, 150)	138 (128, 157)	132 (121, 148)	0.28
SpO <sub>2</sub> (%)	95 (94, 96)	95 (94, 96)	95 (94, 96)	0.44
Oxygen rate (L/min)	3 (2–4)	3 (2–4)	3 (1.5–4)	0.71
Creatinine (μmol/L)	90 (77, 104)	92 (76, 111)	89 (79, 107)	0.56
Troponin I (ng/mL)	480 (123, 1133)	456 (113, 1100)	620 (151, 1780)	0.39
BNP (pg/mL)	397 (214, 664)	384 (255, 865)	407 (211, 662)	0.39
RV/LV 4C	1.1 (1.0, 1.2)	1.15 (1.0, 1.27)	1.1 (1.0, 1.3)	0.76
TAPSE (mm)	14 (11, 15)	14 (12, 16)	13 (10, 16)	0.44
S'-DTI (m/s)	9.0 (7.5, 10.0)	9.0 (8.0, 10.5)	8.0 (7.0, 11.1)	0.61
sPAP (mmHg)	55 (49, 70)	54 (41, 57)	58 (50, 69)	0.096
IVC (mm)	21 (19, 24)	20 (19, 23)	20.8 (19, 23)	1
LVEF (%)	60 (55, 60)	60 (55, 60)	60 (55, 60)	0.64
Known CHF or RD	0	0	0	1

Unless specified, data are presented as median, 1st and 3rd quartile

HR heart rate, SBP systolic blood pressure, BNP B-type natriuretic peptide, RV right ventricular, LV left ventricular, TAPSE tricuspid annular plane systolic excursion, S'-DTI tricuspid annular peak systolic velocity, sPAP systolic pulmonary artery pressure, IVC inferior vena cava, LVEF left ventricular ejection fraction, CHF cardiac heart failure, RD respiratory disease

**Table 2** Variations in heart rate, systolic blood pressure, oxygen requirement, diuresis, potassium and creatinine in both groups

	Volume expansion (n = 30)	Diuretic (n = 30)	p
Δ HR at H4 (beats/min)	- 2 (- 9, + 3)	- 1 (- 7, + 3)	0.61
Δ SBP at H4 (mmHg)	- 9 (- 19, + 1)	- 2 (- 18, + 2)	0.42
Δ Oxygen requirements at H4 (L/min)	0 (0, 0)	0 (0, 0)	0.84
Δ HR at H24 (beats/min)	- 6 (- 14, 0)	- 4 (- 14, + 4)	0.65
Δ SBP at H24 (mmHg)	- 2 (- 13, + 7)	- 3 (- 12, + 9)	0.90
Δ Oxygen requirements at H24 (L/min)	- 1 (- 2, 0)	0 (- 2, 0)	0.42
Diuresis in first 24 h (mL)	1600 (725, 3750)	5350 (2800, 7200)	< 0.001
Δ Creatinine in first 96 h (μmol/L)	- 17 (- 21, 0)	- 7 (- 19, + 6)	0.22
Δ Potassium in first 96 h (mmol/L)	- 0.25 (- 0.36, + 0.10)	- 0.21 (- 0.50, + 0.10)	0.94

Data are presented as median, 1st and 3rd quartile. Except for diuresis in the first 24 h there are no significant changes between VE and DT groups

HR heart rate, SBP systolic blood pressure

The clinical status of two patients (one in each group) worsened during hospitalization. Both needed dobutamine infusion. One needed thrombolytic treatment but died. Both had a higher than average biomarker concentration on admission. No other clinical event occurred before day 30.

## Discussion

Currently, in patients with intermediate high-risk PE, the choice between a DT and VE, both of which aim to avoid

**Table 3** Biological endpoints

	Volume expansion (n = 30)	Diuretic (n = 30)	p
Primary endpoint			
Tp normalization (h)	72 (41, 120)	76 (41, 144)	0.74
Time to 50% Tp concentration	31 (23, 39)	32 (27, 47)	0.74
Patients with decreased Tp at H12 (%)	15 (50%)	16 (53%)	0.80
Secondary endpoint			
BNP normalization (hours)	108 (48, 144)	56 (28, 120)	0.05
Time to 50% BNP concentration	54 (41, 67)	36 (24, 48)	0.003
Patients with decreased BNP at H12 (%)	4 (13%)	14 (47%)	< 0.001

Unless specified, data are presented as median, 1st and 3rd quartile. There is no change in the kinetics of Tp (primary endpoint). However, the kinetics of BNP is normalized more quickly in the diuretic group with a clear tendency for normalization of BNP ( $p=0.05$ ) a significant faster 50% decrease in BNP ( $p=0.003$ ) and a significant higher number of patients with decreased of BNP at H12 ( $< 0.001$ )

Tp troponin, BNP brain natriuretic peptide

**Table 4** Variations in echocardiographic variables during the first 48 h

	Volume expansion n = 30	Diuretic n = 30	p
Δ TAPSE at H4	1.0 (0, + 3)	1.5 (0, + 4)	0.64
Δ S'-DTI at H4	0.4 (− 0.3, + 2)	1.0 (0, + 2)	0.29
Δ sPAP (mmHg) at H4	0.0 (− 5, + 5)	− 7 (− 18, − 1)	0.006
Δ IVC diameter (mm) at H4	0.0 (− 2, + 3)	− 3 (− 5, 0)	0.008
Δ TAPSE at H24	3.5 (0, + 5)	2.0 (− 1, + 6)	0.77
Δ S'-DTI at H24	1.0 (− 0.5, + 3)	2.0 (+ 1.3, + 3)	0.29
Δ sPAP at H24	− 1 (− 13, + 4)	− 9 (− 20, − 4)	0.18
Δ IVC diameter at H24	0 (− 4, + 1)	− 5 (− 9, + 3)	0.33
Δ TAPSE at H48	3.0 (+ 1, + 5)	2.0 (− 1, + 5)	0.36
Δ S'-DTI at H48	1.4 (− 1.2, + 4)	2.1 (− 0.3, + 4)	0.93
Δ sPAP at H48	0 (− 12, + 12)	− 12 (− 19, 0)	0.059
Δ IVC diameter at H48	− 3 (− 9, 0)	− 4 (− 9, + 1)	0.43

Unless specified, data are presented as median, 1st and 3rd quartile  
Δ change in

TAPSE tricuspid annular plane systolic excursion, S'-D tricuspid annular peak systolic velocity, sPAP systolic pulmonary artery pressure, IVC inferior vena cava

RV failure, remains empirical. The AHA and ACCP guidelines provide no recommendations on this issue [12, 13]. The 2008 European Society of Cardiology guidelines [14] favored modest VE in patients with a low cardiac index and normal blood pressure and the 2014 edition supplied no recommendations on hemodynamic conditioning [15], while the 2019 guidelines warned against inappropriate VE [3].

In intermediate high-risk PE [16, 17], the theoretical aim of VE is to maintain RV preload and stroke volume. Small

changes in RV preload can have a large impact on hemodynamics. Excessive fluid expansion on a distended right heart “crushing” the LV can have dramatic consequences on LV ejection, such as a modest hypovolemia on a RV that is not sufficiently preloaded. In intermediate high-risk PE, diuretics have been dogmatically contraindicated. However, in patients with RV dilatation, DT can reduce RV wall stress, thus providing a better adapted RV preload. Some experimental studies have shown that the overstretching related to VE can exacerbate RV dysfunction and precipitate hypotension and cardiogenic shock, [18–21]. In a porcine model of induced acute PE, Mortensen et al. compared in sixteen animals a VE (1 L/h for 2 h) versus a DT (40 mg of furosemide every 30 min with a total dose of 160 mg). These high doses of diuretic did not affect mean arterial pressure but decreased RV stroke and cardiac output [22]. One clinical study noted an increase in cardiac index from 1.6 to 2.0 L/min/m<sup>2</sup> after a 500 mL dextran infusion over 20 min in normotensive patients with acute PE and a low cardiac index [19] This cardiac index increase was inversely correlated to baseline RV end-diastolic volume index, supporting the idea that the greater the RV dilatation, the lower the beneficial effect of VE. Two single-center studies, one retrospective, the other prospective, have relaunched the debate [23, 24], suggesting that DT administered at admission in patients with intermediate high-risk PE is well-tolerated and could enhance systolic blood pressure, heart rate, oxygen dependency and RV dilatation, as compared with conventional VE.

Very recently, Lim et al. published the first randomized clinical trial in this context. An 80 mg bolus of furosemide was compared with placebo in 276 intermediate-risk PEs. The primary endpoint of this trial had different objectives: absence of oligo-anuria and normalization of heart rate, systolic blood pressure and arterial O<sub>2</sub> level at H24. The positive result obtained on this primary endpoint was mainly due to the lower incidence of oligo-anuria in the



diuretic group 95% vs 76%  $p < 0.001$ . There were no differences in the other three parameters. On the contrary, an HR > 110 was reported in 12.6% of patients in the diuretic group vs 3.6% in the placebo group ( $p = 0.008$ ) [25]. This may indicate that patients in the diuretic group achieved too high a urine output and became hypovolemic. A small but significant increase in serum creatinine level was observed in the diuretic group compared to the placebo group, confirming that 80 mg of furosemide may have been too high a dose. Suggesting that the choice of the dosage of diuretic treatment must be weighed and should probably differ according to the patient's condition.

In our randomized trial, we found that, unlike fluid expansion, a 40 mg furosemide bolus (translating into a higher urine output and a significant decrease in RV preload as measured by IVC diameter or sPAP decrease) does not modify Tp kinetics but tends to accelerate the normalization BNP.

According to the recent guidelines for acute PE management [3], a low BNP level justifies the safe discharge of hemodynamically stable patients, with an excellent negative predictive value. A more rapid decrease in BNP concentration is therefore a marker of good evolution [26], a faster normalization reflecting earlier RV function recovery. The lack of difference in Tp decrease (empirically chosen as our primary endpoint) was probably due to the longer half-life of this biomarker which does not enable rapid changes to be identified.

Of note, we included patients with RV dysfunction. Therefore, our results are relevant only for intermediate high-risk PE with RV dilatation but no hemodynamic instability and must not be extended to either low-risk or high-risk PE. However, most cases of hemodynamic impairment and death occur within the first few hours, the so-called “golden hours” [1]. Providing a better adapted RV preload could help patients get through these critical time.

In this randomized study focusing on very early management of patients with intermediate high-risk PE, a single intravenous bolus of 40 mg furosemide was well-tolerated. Compared with VE, intravenous DT modifies neither Tp kinetics nor RV echocardiographic parameters but accelerates BNP normalization, lower IVC diameter and sPAP significantly. These findings, which need to be confirmed in trials with clinical end points, may translate a rapid improvement in RV function using one-shot diuretic.

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## Declarations

**Conflict of interest** The authors declare that they have no competing interest.

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