CLINICAL RESEARCH

Diuretics versus volume expansion in acute submassive pulmonary embolism

Traitement diurétique versus remplissage dans l’embolie pulmonaire aiguë avec dysfonction ventriculaire droite

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KEYWORDS
Pulmonary embolism; Diuretic; Fluid loading

Summary
Background. — The benefit of volume expansion (VE) in submassive pulmonary embolism (PE) with right ventricular (RV) dysfunction is unclear.
Aim. — To compare the effects of diuretic treatment versus VE in patients hospitalized for PE with RV dysfunction.
Methods. — We prospectively included 46 consecutive patients with submassive PE treated on admission with a 40 mg bolus of furosemide (D group, n = 24) or 500 mL of saline infusion (VE group, n = 22). The primary endpoint was the timing of normalization of B-type natriuretic peptide and troponin Ic concentrations. The secondary endpoints were variations in RV function variables, recorded at baseline, at the 4th hour after treatment initiation (H4) and every day until discharge, and a clinical composite endpoint of thrombolysis or death at 7 and 30 days.

Abbreviations: BNP, B-type natriuretic peptide; H4, the 4th hour after initiation of treatment; H24, the 24th hour after initiation of treatment; HR, heart rate; IVC, inferior vena cava; LV, left ventricular; PASP, pulmonary arterial systolic pressure; PE, pulmonary embolism; RV, right ventricular; SBP, systolic blood pressure; S’-DTI, peak systolic velocity of tricuspid annulus by Doppler tissue imaging; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; VE, volume expansion.
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Results. — No differences were observed between patients at baseline. The primary end-point occurred earlier in the D group than in the VE group (67.5 ± 34.8 vs 111.6 ± 63.3 hours; \(P = 0.006\)). Furosemide treatment on admission was well tolerated, and was not associated with serious adverse events. At H4, substantial improvements were observed in the D group versus the VE group in terms of heart rate reduction (−8.15 ± 21.0 vs −0.71 ± 6.30 beats/min; \(P < 0.01\)) and peak tricuspid annular systolic velocity (Doppler tissue imaging) (11.4 ± 2.10 vs 9.90 ± 2.80 cm/s; \(P = 0.02\)). There was no significant difference between groups in terms of severe outcomes at 7 and 30 days.

Conclusions. — In the acute management of submassive PE patients, a single furosemide bolus on admission seems to produce significant and earlier improvements in RV function markers compared with VE, without adverse events.

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MOTS CLÉS
Embolie pulmonaire ; Traitement diurétique ; Remplissage

Résumé

Méthodes. — Nous avons prospectivement inclus 46 patients consécutifs hospitalisés pour une EP aiguë avec dysfonction VD traités à l’admission soit par un bolus de 40mg de furosémide (groupe D, \(n = 24\)), soit un remplissage de 500 cm³ de chlorure de sodium (groupe R, \(n = 22\)). Le critère de jugement principal était le temps de normalisation du Brain natriuretic peptide (BNP) et de la troponine Ic. Les critères de jugement secondaires étaient l’analyse de paramètres cliniques, biologiques et échographiques enregistrés à l’admission, après 4 heures de traitement, puis quotidiennement jusqu’à la sortie d’hospitalisation et la survenue d’un critère clinique composite (décès ou thrombolyse) aux 7e et 30e jours.

Résultats. — Il n’y avait pas de différence significative entre les 2 groupes à l’admission. La normalisation du BNP et de la troponine Ic est survenue plus rapidement dans le groupe D que dans le groupe R (67,53 ± 4,8 vs 111,6 ± 63,3 heures, \(p = 0,006\)). L’administration de furosémide à l’admission était bien tolérée et ne s’est pas compliquée d’effets indésirables graves. À la 4e heure, une réduction significative de la fréquence cardiaque et une amélioration significative du pic de vitesse systolique tricuspid (onde S, évaluée en doppler tissulaire pulsé) étaient observées dans le groupe D avec respectivement −8,15 ± 21,0 vs −0,71 ± 6,30 bpm dans le groupe R, \(p < 0,01\) et 11,4 ± 2,10 vs 9,90 ± 2,80 cm/s dans le groupe R, \(p = 0,02\). Il n’y avait pas de différence significative en termes de décès ou thrombolyse aux 7e et 30e jours entre les 2 groupes.

Conclusion. — Dans la prise en charge de l’EP aiguë avec dysfonction VD, un bolus de furosémide à l’admission entraîne une amélioration rapide et significative de paramètres pronostics cliniques, biologiques et échographiques sans survenue d’effets indésirables graves.

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Background
Submassive acute pulmonary embolism (PE) is a frequent and severe condition characterized by right ventricular (RV) dysfunction and a high rate of in-hospital mortality [1]. RV failure constitutes an emergency for the prevention of cardiogenic shock and death [2].

According to the current guidelines, fibrinolysis therapy is the cornerstone for patients with massive PE complicated with cardiogenic shock [3–6]. However, in intermediate-risk PE (RV injury with preserved blood pressure), the recent PEITHO trial [7], involving 1005 patients, showed no benefit from fibrinolysis therapy in terms of in-hospital or long-term mortality, but a high rate of bleedings. For intermediate-risk PE, except for anticoagulation therapy, initial haemodynamic management remains empirical, and consists of reasonable volume expansion (VE) [8] and close monitoring. In the above-mentioned randomized trial, no more information concerning concomitant therapies was given, except the potential use of dopamine infusion. Although careful VE is the standard of care in this particular situation, the volume and speed of administration are not well defined, and are at the discretion of the physician.

In submassive PE, pulmonary vascular resistances increase dramatically, leading to RV overload. One of the main consequences is RV dilatation, then both wall stress
and RV ischaemia contribute to decrease RV output, precipitating haemodynamic instability [9,10]. The theoretical goal of VE in submassive PE is to maintain sufficient RV preload and stroke volume, but is based on poor scientific evidence. Mechanically, some experimental studies have shown that the overstretching related to VE can worsen RV dysfunction and precipitate hypotension and cardiogenic shock [11–13]. In this situation, VE could even be deleterious, according to the Frank-Starling’s law [14].

In contrast, diuretics have been dogmatically counterindicated in acute submassive PE, to avoid RV preload reduction and potential worsening of RV systolic function. However, in patients with RV dilatation, diuretic treatment may reduce RV wall stress, providing a more adapted RV preload. A retrospective single-centre study has recently renewed the debate [15], showing that a diuretic treatment administered at admission in patients with submassive PE could significantly enhance systolic blood pressure (SBP), heart rate (HR), oxygen dependency and RV dilatation compared with conventional VE.

Therefore, in clinical practice, the choice between diuretics and VE is unclear, and is at the discretion of the clinician. In this prospective single-centre study, we sought to compare the effects of administration of a diuretic with careful VE (as a standard of care) in patients with acute intermediate-risk PE. It seemed to us preferable and ethical to assess with an open-label study, before the launch of a randomized controlled trial, if none of these two options was associated with haemodynamic impairment.

Methods

Study design

We performed an open single-centre prospective trial. The protocol was approved by the local ethics review board. The choice between furosemide and VE was at the discretion of the patient. Patients treated with a diuretic received a single intravenous bolus of 40 mg of furosemide at admission (D group). Patients treated with VE received a 500-mL saline infusion (sodium chloride 0.9%) delivered over 4 hours, followed by a 1000-mL saline infusion per day.

Anticoagulant therapy (low-molecular-weight heparin, enoxaparin) was initiated without delay, according to the current guidelines [3].

Patients

Patients were included in the study if they had an acute PE confirmed by computed tomography scan, RV dilatation confirmed by echocardiography (right-to-left ventricular end-diastolic diameter > 0.9 in the apical four-chamber view or > 0.7 in the parasternal long-axis view), RV dysfunction confirmed by echocardiography (tricuspid annular plane systolic excursion [TAPSE] < 16 mm and peak systolic velocity of tricuspid annulus by Doppler tissue imaging (S'-DTr) < 11 cm/s) and myocardial injury confirmed by a positive troponin Ic concentration (≥ 0.07 ng/mL) and a high B-type natriuretic peptide (BNP) concentration (> 100 pg/mL).

Subjects were not included in the study if they presented on admission a history of administration of thrombolytic agents, cardiogenic shock, a need for thrombolysis or catecholamine infusion, cardiopulmonary resuscitation, severe renal chronic disease (modification of diet in renal disease glomerular filtration rate < 30 mL/min) or an inferior vena cava (IVC) < 21 mm.

Echocardiography

Transthoracic echocardiography (TTE) measurements for the assessment of RV function were recorded according to the latest guidelines [16]. TTE was performed on admission with a CX50 (Philips Medical Systems, Best, the Netherlands), and was repeated at the 4th hour after initiation of treatment (H4) and every day until normalization.

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. Pulmonary arterial systolic pressure (PASP) was estimated with tricuspid regurgitation velocity using continuous-wave Doppler added to right atrial pressure as assessed by IVC size and its collapsibility. Flattening of the interventricular septum was assessed qualitatively in the parasternal short-axis or apical four-chamber view. RV systolic function normalization was defined by TAPSE > 16 mm and S'-DTr > 11 cm/s. RV dilatation normalization was defined by a RV basal diameter measured in the apical four-chamber view < 42 mm. PASP normalization was defined by PASP < 35 mmHg.

Biology

Troponin Ic measurements were performed with the Access AccuTnl + 3 kit (Beckman Coulter, Brea, CA, USA), with a positivity threshold of 0.07 ng/mL. BNP measurements were performed with the Alere Triage BNP kit (Beckman Coulter, Brea, CA, USA), with a positivity threshold of 100 pg/mL. Troponin Ic and BNP were measured at admission, then every 12 hours until normalization (Troponin Ic < 0.07 ng/mL and BNP < 100 pg/mL).

Follow-up and outcome assessment

All patients were followed for 30 days. Clinical variables (blood pressure, HR, diuresis, oxygen requirements) were recorded every day until discharge, and systematically at 30 days in consultation.

The primary efficacy outcome was the timing of normalization of BNP and troponin Ic concentrations, defined by troponin Ic < 0.07 ng/mL and BNP < 100 pg/mL. The secondary efficacy outcomes were timing of normalization of RV dilatation and systolic function as assessed by TTE; variations in HR, SBP and oxygen requirements from baseline; a clinical composite endpoint including death from any cause, cardiogenic shock, need for cardiopulmonary resuscitation, need for thrombolysis and/or catecholamine infusion between admission and day 7; and death from any cause between admission and day 30.

Safety outcomes were defined by the occurrence of hypokalemia (kalemia < 3.5 mmol/L) and possibly related arrhythmia, acute kidney injury (rise of creatinine by
Diuretics in acute submassive pulmonary embolism

44 μmol/L or 25% from basal value [17]) during initial hospitalization and the presence of severe renal disease at 30 days.

Statistical analysis

The main efficacy and safety analyses were based on all events that occurred in the treated population. Data characterized by a normal distribution are expressed as means and standard deviations. Variables without such a distribution are expressed as medians with maximum and minimum ranges. Student’s t test or the Mann-Whitney U test was used for comparisons between the D and VE groups. The χ² test was used to compare discrete variables (with Yates’s correction when needed). Kaplan–Meier analysis was used to investigate event-free survival at the 7th day and cumulative survival at the 30th day. All tests were two-sided. Data were considered significant at P < 0.05. All tests were performed with the use of SPSS software, version 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

Between January 2014 and June 2015, 141 prospective patients admitted with PE were screened, and 46 consecutive patients were included in the study. Twenty-two patients were treated with VE and 24 were treated with a diuretic.

Demographic data, clinical status and paraclinical status at baseline were not different between the two groups, and are reported in Table 1. Mean age was 70.9 ± 14.6 years in the VE group and 69.9 ± 18.8 years in the D group. At baseline, HR and SBP were, respectively, 100.4 ± 14.0 beats/min and 133.8 ± 31.6 mmHg in the VE group, and 102.2 ± 21.8 beats/min and 142.5 ± 25.0 mmHg

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of studied patients with acute pulmonary embolism.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume expansion (n = 22)</td>
</tr>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.9 ± 14.6</td>
</tr>
<tr>
<td>Men</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.5 ± 19.4</td>
</tr>
<tr>
<td><strong>Clinical status</strong></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>100.4 ± 14.0</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>133.8 ± 31.6</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>96.5 ± 2.10</td>
</tr>
<tr>
<td>Oxygen rate (L/min)</td>
<td>5.90 ± 3.30</td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Simplified PESI score</td>
<td>0.77 ± 0.75</td>
</tr>
<tr>
<td>Pulmonary infarction</td>
<td>2 (9.1)</td>
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<tr>
<td><strong>Medical history</strong></td>
<td></td>
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<tr>
<td>Active cancer</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Biological status</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>80.3 ± 13.5</td>
</tr>
<tr>
<td>GFR (MDR) (mL/min)</td>
<td>71.5 ± 16.7</td>
</tr>
<tr>
<td>Troponin l (ng/mL)</td>
<td>0.27 ± 0.23</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>526.4 ± 744.1</td>
</tr>
<tr>
<td><strong>Echocardiographic status</strong></td>
<td></td>
</tr>
<tr>
<td>RV4C (mm)</td>
<td>44.3 ± 4.20</td>
</tr>
<tr>
<td>RV/LV 4C</td>
<td>1.10 ± 0.19</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>12.8 ± 3.50</td>
</tr>
<tr>
<td>S’-DTI (m/s)</td>
<td>9.90 ± 1.80</td>
</tr>
<tr>
<td>Leftward septal deviation</td>
<td>22 (100)</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>IVC (mm)</td>
<td>24.5 ± 2.30</td>
</tr>
<tr>
<td>IVC collapsibility (%)</td>
<td>9.17 ± 6.91</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55 ± 5</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or number (%). BNP: B-type natriuretic peptide; GFR: glomerular filtration rate; HR: heart rate; IVC: inferior vena cava; LVEF: left ventricular ejection fraction; MDRD: modification of diet in renal disease; PASP: pulmonary artery systolic pressure; PESI: pulmonary embolism severity index; RV4C: right ventricular dimension in apical four-chamber view; RV/LV 4C: right ventricle/left ventricle ratio in apical four-chamber view; S’-DTI: peak systolic velocity of tricuspid annulus by Doppler tissue imaging; SBP: systolic blood pressure; SpO₂: pulse oximeter arterial oxygen saturation; TAPSE: tricuspid annular plane systolic excursion.
in the D group. Four patients in the D group and three patients in the VE group had a history of PE without previous chronic thromboembolic pulmonary hypertension. Hospitalization duration was similar in the two groups (5.4 ± 2.1 days). No significant differences were observed at admission between troponin Ic and BNP concentrations in the two groups (respectively 0.27 ± 0.23 ng/mL and 526.4 ± 744.1 pg/mL in the VE group, and 0.34 ± 0.31 ng/mL and 341.6 ± 291.5 pg/mL in the D group).

**Primary efficacy endpoint**

Normalization of BNP and troponin Ic occurred earlier in the D group than in the VE group: 67.5 ± 34.8 vs 111.6 ± 63.3 hours, respectively (P = 0.006).

**Secondary efficacy endpoints**

**Clinical outcomes**

A significant HR reduction was observed in the D group between baseline and H4 after treatment: −8.15 ± 21.0 vs −0.71 ± 6.30 beats/min in the VE group (P = 0.001; Fig. 1). The same HR improvement was observed between baseline and the 24th hour after initiation of treatment (H24): −16.4 ± 10.3 vs −5.02 ± 13.2 beats/min (P = 0.004). Variations in HR, SBP and oxygen requirements compared with baseline are presented in Table 2. At H24, we observed a trend towards an increase in SBP in the D group: 1.40 ± 23.8 vs −8.10 ± 26.5 mmHg in the VE group (P = 0.23). Urine output was higher in D group at H4 (833 ± 411 vs 185 ± 221 mL in the VE group; P < 0.001) and at H24 (1631 ± 654 vs 988 ± 546 mL in the VE group; P = 0.001). No significant difference was observed during hospitalization in the oxygen requirements of the two groups, but we observed a trend towards faster weaning off oxygen therapy in the D group than in the VE group: 92.0 ± 32.1 vs 109.4 ± 19.4 hours (P = 0.057).

Between admission and day 7, three clinical in-hospital events occurred in the VE group (one cardiogenic shock, necessitating thrombolysis in the first 48 hours of treatment, and two deaths [two cardiorespiratory arrests after 4 and 24 hours; both patients received rescue thrombolysis therapies]), whereas one event occurred in the D group (one cardiogenic shock, necessitating thrombolysis after 4 hours of treatment). Kaplan–Meier event-free curve analysis is presented in Fig. 2, and shows no significant difference (log-rank, P = 0.22).

![Figure 1](image1.png)

**Figure 1.** Evolution of heart rate values in beats/min at the 4th hour (H4) and the 24th hour (H24) after initiation of treatment (H0).

![Figure 2](image2.png)

**Figure 2.** Kaplan-Meier survival without thrombolysis analysis, according to treatment group, in 46 initially normotensive patients with acute pulmonary embolism.

<table>
<thead>
<tr>
<th>Table 2 Variations in heart rate, systolic blood pressure and oxygen requirement during the first 24 hours.</th>
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<tbody>
<tr>
<td><strong>Variation</strong></td>
</tr>
<tr>
<td>Δ HR at H4 (beats/min)</td>
</tr>
<tr>
<td>Δ SBP at H4 (mmHg)</td>
</tr>
<tr>
<td>Δ oxygen requirements at H4 (L/min)</td>
</tr>
<tr>
<td>Δ HR at H24 (beats/min)</td>
</tr>
<tr>
<td>Δ SBP at H24 (mmHg)</td>
</tr>
<tr>
<td>Δ oxygen requirements at H24 (L/min)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. Δ: variation in; H4: at the 4th hour after initiation of treatment; H24: at the 24th hour after initiation of treatment; HR: heart rate; SBP: systolic blood pressure.
Biological outcomes

BNP courses in the two groups during hospitalization are presented in Fig. 3. Normalization of BNP alone was faster in the D group (60.5 ± 38.5 vs 110.5 ± 64.7 hours in the VE group; P = 0.003), whereas normalization of troponin Ic was similar in the two groups (56.2 ± 29.1 in the VE group vs 50.5 ± 26.7 in the D group; P = 0.59). All biological efficacy variables are presented in Table 3.

Echocardiographic outcomes

A significant improvement in S'-DTI was observed at H4 in the D group: 11.4 ± 2.10 vs 9.90 ± 2.80 cm/s in the VE group (P = 0.023; Fig. 4A). We saw a trend towards improvement in TAPSE at H24 in the D group: 14.2 ± 4.31 vs 12.8 ± 4.15 mm in the VE group (P = 0.076). Also, PASP was lower at H4 in the D group than in the VE group (52 ± 7 vs 61 ± 8 mmHg; P = 0.003; Fig. 4B), but was similar at H24 in the two groups (51 ± 7 vs 54 ± 16 mmHg, respectively; P = 0.59). Evolutions of TAPSE, S'-DTI and PASP are presented in comparison with baseline in Table 4. Diameter and collapsibility of IVC at H4 was significantly different in the D group (respectively, 16.8 ± 3.48 mm and 22.9 ± 19.6% vs 23.8 ± 2.17 mm and 5.00 ± 8.32% in the VE group; P = 0.03 and P < 0.001); no significant variation in these two variables was observed during hospitalization.

We observed a significant decrease in the RV/LV ratio in the D group, from 1.16 ± 0.31 at baseline to 0.99 ± 0.28 at H4 (P < 0.01) and 0.97 ± 0.28 at H24 (P = 0.012). Meanwhile, no significant variations in the RV/LV ratio were observed in the VE group (Fig. 4C).

A trend towards faster recovery of RV function variables was observed in the D group, but this did not reach

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**Figure 3.** B-type natriuretic peptide (BNP) concentration course in the diuretic and volume expansion groups during hospitalization.

**Figure 4.** A. Annular tricuspid velocity course during hospitalization. B. Pulmonary artery systolic pressure (PASP) course during hospitalization. C. Right ventricular/left ventricular (RV/LV) ratio course during the first 24 hours. D: day; H: hour; S'-DTI: peak systolic velocity of tricuspid annulus by Doppler tissue imaging.

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**Table 3** Primary and secondary biological efficacy endpoints.

<table>
<thead>
<tr>
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<th>Volume expansion (n = 22)</th>
<th>Diuretic (n = 24)</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP and troponin normalization (hours)</td>
<td>111.6 ± 63.3</td>
<td>67.5 ± 34.8</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Secondary efficacy endpoint</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BNP normalization (hours)</td>
<td>110.5 ± 64.7</td>
<td>60.5 ± 38.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Troponin normalization (hours)</td>
<td>56.2 ± 29.1</td>
<td>50.5 ± 26.7</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. BNP: B-type natriuretic peptide.
statistical significance (Table 5). On average, normalization of RV systolic function took 83.4±21.0 hours in the D group vs 86.2±34.1 hours in the VE group (P=0.79). Normalization of PASP took 98.0±21.7 hours in the D group vs 102.2±51.3 hours in the VE group (P=0.72). Normalization of RV dilatation took 99.8±19.6 hours in the D group vs 107.7±46.5 hours in the VE group (P=0.48). Persistent RV abnormalities were noted in three patients (6.5%) at day 30, two in the VE group and one in the D group.

Survival at day 30
Between admission and day 30, two patients died in the VE group (both during the initial hospitalization) and one in the D group (death from respiratory distress on day 14). Kaplan–Meier cumulative survival curves are presented in Fig. 5, and show no significant difference (log–rank, P=0.42).

Safety outcomes
During hospitalization, acute kidney injury occurred in two patients in the D group versus none in the VE group. Management of renal failure consisted of VE, and no patients needed haemodialysis. Eleven patients from the D group (45.8%) had hypokalemia versus one patient in the VE group (4.5%; P=0.001), and no related arrhythmia was noted. Higher creatinine concentrations were observed in the D group than in the VE group on days 1 and 2, respectively, 92.5±30.4 vs 76.4±13.2 μmol/L (P=0.027) and 90.8±32.4 vs 72.2±13.0 μmol/L (P=0.019). After day 2, creatinine concentrations were not significantly different between the two groups until discharge. None of the patients in the two groups presented severe renal disease at day 30.

Figure 5. Kaplan–Meier survival analysis according to the treatment group in 46 initially normotensive patients with acute pulmonary embolism.

**Discussion**

In submassive PE, the choice between a diuretic and VE remains empirical. We sought to compare, in this first prospective open-label study with consecutive patients in whom choice between a diuretic and VE was at the discretion
of the clinician, the effects of these two therapeutic strategies. We found in this study that one single bolus of 40 mg furosemide, administered without delay after diagnosis assessment, is well tolerated and is not associated with RV function worsening. When compared with careful VE, it was associated with a greater improvement in HR, BNP, troponin Ic and echocardiographical markers of RV dysfunction, which are powerful prognostic factors in acute PE [2,18–26].

Our study supports the findings of Ternacle et al. [15], who reported, in 2013, a potential benefit of a diuretic treatment in submassive PE, with significant improvement in SBP, simplified PE severity index, shock index and oxygen requirement in a retrospective study with 40 patients.


In submassive PE, the two main physiological responses to the brutal RV afterload increase are catecholamine-driven tachycardia and RV dilatation [1,28–30]. Interestingly, we observed a very early significant improvement in HR in patients who received one single bolus of furosemide. This clinical variable is known to be a strong independent predictor of all-cause mortality in PE patients [31], and the lower the HR the better the prognosis. In parallel, we observed a significant decrease in the RV/LV ratio in the D group at H4 and H24. The enhancement of these two compensatory mechanisms — HR increase and RV dilatation — without SBP decrease, seems to indicate stroke volume enhancement. As supported by our findings on RV systolic function variables, we noticed an early significant S′-DTI improvement in the D group at H4.

We also noted that normalization of BNP and troponin concentrations was almost twice as fast in the D group. BNP secretion occurs in response to the increase in right-sided heart strain caused by sudden pulmonary hypertension [32]. In the recent guidelines for acute PE management [3], a BNP cut-off value of 90 pg/mL allows the safe discharge of haemodynamically stable patients, with an excellent negative predictive value. The course of its concentration during hospitalization follows clinical status and RV function evolution [33], and faster normalization may reflect an earlier RV function recovery.

In our study, a 500-mL VE of saline infusion was associated with an immediate increase in RV dilatation and a trend towards worsening of RV systolic function, highlighting the concept of reducing RV preload to decrease RV wall stress. Experimental studies confirmed that aggressive VE may worsen RV function by mechanical overstretch and/or reflex mechanisms that depress contractility [34]. On the other hand, a clinical study noticed an increase in cardiac index from 1.6 to 2.0 L/min/m² after a 500-mL dextran infusion over 20 minutes in normotensive patients with acute PE and low cardiac index [12]. This cardiac index increase was inversely correlated to baseline RV end-diastolic volume index, supporting the fact that the greater the RV dilatation the less the beneficial effect of VE. Indeed, their inclusion criteria were fundamentally different from ours: they included patients with a low cardiac index < 2.5 L/min/m², a condition in which hypovolaemia can occur, whereas we included only patients with dilated RV and IVC and systolic dysfunction. However, reducing RV preload strategy should only concern acute submassive PE with RV dilatation, but no haemodynamic instability, and must not be extended to low-risk PE or high-risk PE. Central venous pressure and RV preload are correlated to IVC size and collapsibility [35], and we found a significant improvement in both these variables at H4 after the diuretic injection. This reduced RV preload observed in the D group may explain our main results, and supports the hypothesis stated above.

Nevertheless, no improvement in SBP was observed in the two groups, and this finding has to be taken into consideration. To date, dobutamine has been used for years in high- and intermediate-risk PE [36,37]. However, the effects of dobutamine infusion in patients with acute PE, low cardiac index and normal blood pressure consist of a 35% increase in cardiac index and improvement in oxygen transport, but without any significant change in systemic arterial pressure [38,39].

Interestingly, in our study, the effects of the diuretic injection on RV function and HR occurred early in the first 24 hours, but most haemodynamic impairment and deaths occur in the first hours, called the “golden hours” by Wood in 2002 [1]. Providing a more adapted RV preload by a one-shot injection of furosemide could help patients to get through these critical hours.

In addition to all these variables being enhanced, we also showed that administering a diuretic to a patient with an acute PE with RV injury might be safe, questioning the dogma of the counterindication of diuretic treatment in this condition. Our results suggest that a diuretic treatment is feasible without any haemodynamic deterioration, and may be associated with faster improvement in the condition of these patients.

Study limitations

Our study had several limitations. The first was the small sample size of the study population, which still allowed similar baseline characteristics in the D and VE groups. This underpowered characteristic may explain the absence of difference concerning the secondary clinical endpoints. Second, this was an open-label single-centre study, and selection/exclusion bias cannot be excluded. Especially, TTE was performed in open-label, which can result in investigator bias, but the primary efficacy biological endpoint was chosen specifically for its objectivity and reproducibility. Third, it is possible that differences in BNP concentrations collected on admission, despite reaching no statistical difference, may have affected our conclusion regarding the primary endpoint. Finally, we did not assess RV preload or cardiac index using invasive right heart catheterization in this feasibility study. However, IVC diameter and collapsibility were very close in the two groups, suggesting a similar RV preload on admission, and cardiac index is no longer monitored routinely in high- and intermediate-risk PE. It is important to note that this was a feasibility study, and that no serious adverse events were observed after diuretic injection. The findings of this prospective series, despite all these biases, fully justify a randomized trial to compare these two strategies [40].
Conclusions

Compared with VE, one single bolus of furosemide seems to improve early clinical, biological and echocardiographic severity markers in patients with acute intermediate-risk PE and RV injury, without serious adverse effects.

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Disclosure of interest

The authors declare that they have no competing interest.

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