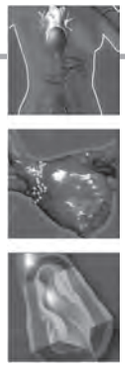

AngioJet® rheolytic thrombectomy: a new treatment option in cases of massive pulmonary embolism

Background: Pulmonary embolism (PE) with hemodynamic instability is associated with high mortality. While thrombolysis remains the treatment of choice for massive PE, percutaneous mechanical thrombectomy may be an alternative in selected cases. **Methods & results:** We performed a systematic review of the literature for articles dealing with the use of the AngioJet® (Medrad/Bayer Interventional, MN, USA) device (i.e., rheolytic thrombectomy) in the setting of massive/submassive PE. We identified 14 studies with a total of 197 patients: nine studies including 76 patients presenting exclusively with massive PE (group A, mean age: 59.2 ± 9.7 years), and five studies including 121 patients presenting with massive or submassive PE (group B, mean age: 61.8 ± 5.4 years). The success rate of the procedure, defined as technical ± clinical success, was reported as 86.8% in group A and as 94.3% in group B. Postprocedural thrombolysis was administered in 17.8 and 25.4% of cases, respectively. Periprocedural events (e.g., cardiovascular complications or other unexpected adverse events) were observed in 21.1% in group A, and 17.4% in group B. In-hospital mortality was 23.7 and 13.2%, respectively. Device-related major and minor complications were observed in 15.7% of cases. **Conclusion:** The AngioJet seems to be a safe and efficacious thrombectomy device in term of thrombus fragmentation/aspiration, as well as improvement of clinical parameters. However, mortality rate in these unstable settings remain high, and more data are needed before broadening the use of percutaneous mechanical thrombectomy in PE patients.

KEYWORDS: AngioJet® rheolytic thrombectomy ■ high-risk or massive pulmonary embolism ■ percutaneous mechanical thrombectomy

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Pulmonary embolism (PE) is one of the leading mortality causes in western countries, and accounts for more than 300,000 deaths worldwide every year [1,2]. In the case of massive PE (MPE), the complications and/or the clinical deterioration leading to death generally occurs in the first few hours after symptoms onset [3,4]. In the presence of cardiogenic shock or an episode of cardiac arrest, the in-hospital mortality may be as high as 60% [3,5].

International guidelines have stratified patients presenting with PE into three risk categories according to the initial clinical presentation: patients presenting with low-risk PE; those with intermediate or submassive PE (sMPE); and finally those with high-risk or MPE [6–8]. High-risk or MPE implies a hemodynamic instability, defined as shock index >1 or systolic blood pressure <90 mmHg for at least 15 min, or requiring inotropic support, while intermediate-risk or sMPE implies positive cardiac biomarkers and/or right ventricle dysfunction on trans-thoracic echocardiography [6–8].

Treatment modalities vary widely according to the initial clinical scenario, as well as the presence or absence of some PE-related complications. Accordingly, anticoagulation should be immediately administrated to all patients with suspicion of PE. Intravenous (iv.) unfractionated heparin, subcutaneous low-molecular-weight heparins or subcutaneous fondaparinux are the most prescribed anticoagulants in all types of PE, while systemic iv. thrombolysis, as well as mechanical thrombectomy, either percutaneous or surgical, are generally reserved for patients presenting with hemodynamic instability [5–7,9].

Intraveneous thrombolysis remains the gold-standard treatment modality for high-risk PE patients, although catheter-based mechanical thrombectomy procedures are an emerging field in treating MPE patients [10]. These percutaneous mechanical thrombectomy (PMT) procedures may be particularly attractive in some cases, especially if one considers that up to 40% of patients presenting with MPE may not be candidates for emergency surgical embolectomy (either too unstable or there is no surgical know-how), or may have absolute or relative contraindications to systemic fibrinolysis [6–8]. Indeed, thrombolysis-related bleeding complications, observed in up to 35% of cases (combined major and minor bleeding), with 2–3% of

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them being intra-cranial, remain a major source of morbidity and mortality in PE patients [11].

So far, PMT data in cases of MPE or sMPE were limited to several retrospective and a few prospective series. These reports differed widely because of different types of PMT devices used (i.e., fragmentation, rheolytic, aspiration PMT), enrolment of patients with different degrees of hemodynamic instability (i.e., MPE and sMPE) and frequent adjunctive use of thrombolysis (mainly intrapulmonary bolus ± perfusion). All of these elements challenge the interpretation of the findings and generate confusion over the role of a specific PMT procedure in case of PE [1,12–26].

Since 2009, at our tertiary center, we have been using the AngioJet® rheolytic thrombectomy system (ART; Medrad/Bayer Interventional, MN, USA) for the treatment of MPE in patients presenting with contraindications to thrombolysis, thrombolysis failure or as part of a clinical investigation. In this article, we review the most relevant studies dealing with the use of the ART in the treatment of PE, and propose current indications for this technique as well as a future perspective on the treatment of high-risk PE patients.

Materials & methods

We have performed a systematic review of all articles dealing with the use of the ART in the treatment of MPE/sMPE found by searching through the electronic database PUBMED using the words 'Angiojet', 'Rheolytic Thrombectomy', 'Percutaneous Mechanical Thrombectomy', 'Massive Pulmonary Embolism', 'Submassive Pulmonary Embolism', 'Acute Pulmonary Embolism', alone and in combinations.

We included in our review only articles concerning the use of ART either in the treatment of MPE alone or MPE and sMPE, which have included a minimum of two patients. All published articles up to April 2012 were taken into account. We also add in this review our personal (unpublished) experience with the ART in the case of MPE.

We have excluded single case reports as most of them relate to cases with favorable outcomes, which tend to bias the true value of the ART technology, and also because in some of them, data were not complete (e.g., missing hemodynamic or angiographic parameters or patient follow-up), and thus of less scientific interest. We also excluded articles limited to sMPE and experiences including other PMT devices in addition to ART. Abstracts, articles concerning nonhuman studies or use of ART in conditions other than PE were also excluded from the present review.

From all selected articles, we extracted data concerning: definitions of MPE/sMPE; definitions of successful procedures; methods used to investigate and evaluate the severity of PE; hemodynamic parameters (e.g., blood pressure, pulmonary artery pressures, shock index); angiographic parameters (i.e., Miller index); administration of adjunctive thrombolysis (intravenous ± intrapulmonary; bolus ± perfusion); periprocedural and postprocedural complications; and follow-up.

Results

Fourteen studies with a total of 197 patients were identified. Nine of them addressed the use of ART exclusively in patients presenting with MPE (group A: Tables 1 & 2), while five investigated ART in a combined population of patients presenting with MPE and sMPE (group B: Tables 3 & 4).

Group A (= MPE patients) and group B (= MPE + sMPE patients) included 76 and 121 patients, respectively. Patients enrolled in the group B studies were further divided as MPE (= 46 patients) and sMPE (= 75 patients).

The mean age was 60.1 ± 7.5 years (group A: 59.2 ± 9.7 years, group B: 61.8 ± 5.4 years). Out of the nine studies in group A, only two included patients in cardiogenic shock, namely Voigtländer *et al.* (n = 3, 60% of the total patients) and Bonvini *et al.* (n = 10, 100% of the total patients) [27,28]. In group B, 25 out of 107 (23.4%) patients were in cardiogenic shock. One study (Chauhan *et al.*), while claiming to have patients in cardiogenic shock, did not give any further details [22].

In two studies from group A there was no clear definition of the severity of MPE [28,29], while in the other 12 studies, MPE and sMPE were defined variably according to: the presence of pathological biomarkers; hemodynamic parameters (e.g., blood pressure, shock index); anatomic parameters (e.g., pulmonary artery obstruction as defined by computed tomography scan ± Miller index); and echocardiographic parameters (e.g., right ventricular dilation ± dysfunction) [20–33].

Concerning the use of thrombolysis, only two studies mentioned the use of preprocedural systemic thrombolysis (in group A: two [1%] patients [27] and in group B: one [0.5%] patient [22]). Postprocedural thrombolysis was delivered in 83 patients (43.2% of all patients):

35 (17.8%) in group A and 48 (25.4%) in group B.

In five studies, no definition of successful procedure was given [28–31,33]. In the remaining nine studies, successful procedure was variably defined as clinical success, technical success or procedural success [20–27,32]. A successful procedure was described in 66/76 cases (86.8%) in group A and in 99/105 cases (94.3%) in group B, respectively.

Hemodynamic data pre- and post-procedure (i.e., blood pressure, pulmonary artery pressure, Miller index and shock index) are not reported at all in several studies, but when mentioned they all demonstrate improvement of these parameters (Tables 2 & 4).

The duration between the establishment of the diagnosis of PE and the ART was mentioned for only one study in group A (Arzamendi *et al.*: 6.6 h from symptoms onset until thrombectomy) [30] and three studies in group B (Margheri *et al.*: 20.1 ± 22.9 h [23]; Chechi *et al.*: 22.9 ± 24.4 h [24]; Ferrigno *et al.*: sMPE patients: 21 ± 26 h [31]; MPE patients: 8 ± 10 h). The mean procedural time, defined as the time between the arrival of the patient to the angiography suite and their departure, was 105 ± 69 min, but was only available for six of the 14 studies.

Major periprocedural events were denoted in 31/197 (15.7%) patients: 23 (11.6%) episodes of bradyarrhythmia and two (1%) transient asystole, out of which 18 (9.1%) required temporary pacemaker implantation; one (0.5%) prolonged apnea requiring emergent intubation; and one (0.5%) hemoptysis. Finally, six (3%) deaths were observed during the ART procedure, out of which one occurred before the activation of the device. Of interest, all deaths occurring during the procedure were observed in the more unstable group A (death rate in group A: 7.9%; 0% death in group B).

Major postprocedural events were denoted in 61/197 (30.1%) patients: six (3.0%) episodes of hemoptysis; 13 (6.6%) major inguinal hematomas; two (1%) episodes of melena; five (2.5%) macro-hematuria; two (1%) retroperitoneal bleeding; four (2%) cerebral hemorrhage; 23 (11.7%) impairing of the renal function; three (1.5%) multiorgan failure; and seven (3.5%) significant thrombocytopenia. With respect to in-hospital mortality, it accounted for 29/197 patients (14.7%): 13/76 (17.1%) in group A and 16/121 (13.2%) in group B. For the survivors, after hospital discharge, no further deaths were reported up to 30 days.

Discussion

Massive pulmonary embolism carries very high mortality rates despite many efforts being made in the pharmacological and the pharmacomechanical treatment of this entity. Right heart strain and systolic blood pressure are strong predictors of increased early mortality [34,35]. Indeed, among the 2392 patients with acute PE involved in the International Cooperative Pulmonary Embolism (iCOPER) registry, the 90-day mortality rate was 52.4% (95% CI: 43.3–62.1) in patients with MPE, defined as systolic blood pressure <90 mmHg, whereas mortality rate was 14.7% (95% CI: 13.3–16.2) in those with systolic blood pressure >90 mmHg [35]. Of note, in patients presenting with MPE, death usually occurs within the first hours after clinical presentation, suggesting that anticoagulation and, when applicable, systemic thrombolysis should be given as soon as possible in this high-risk category of patients. However, in the case of contraindications to or failed systemic thrombolysis, catheter or surgical embolectomy remain alternative treatment modalities with a Class 2 recommendation in different PE guidelines. This class 2 level of evidence was attributed by a group of opinion leaders (i.e., level of evidence C) because so far no randomized trials or other strong evidence confirming the efficacy of this approach are available [6–8].

■ Percutaneous mechanical thrombectomy devices

The first PMT device to be used in the treatment of PE was the Greenfield suction embolectomy catheter in 1969, and this so far remains the only device with US FDA approval [36]. Since then, other PMT devices have been made available with variably good results; however, none of these have so far been rigorously evaluated in prospective clinical trials. Generally, PMT procedures can be classified into three main groups: aspiration thrombectomy; fragmentation thrombectomy; and rheolytic thrombectomy [10,37].

Despite the first use of the AngioJet catheter for the treatment of PE being described more than 15 years ago [29], its use for this indication remains off-label in the USA, and has only very recently (i.e., March 2011) gained the European approval for treating PE patients.

■ AngioJet technical aspects

The AngioJet thrombectomy catheter was initially designed for removal of thrombus in coronary arteries, and its use was gradually extended to peripheral vessels and peripheral arteries. Koning *et al.* described its first use in 1997 for two cases

Table 1. Studies including exclusively massive pulmonary embolism patients: baseline characteristics.

Study	Year	Patients (n)	Mean age (years)	Definition of MPE	Cardiogenic shock	Cardiorespiratory arrest prior ART	Mechanical ventilation prior ART	Echocardiography (TTE ± TEE) prior ART
Koning *et al.*	1997	2	73	N/A	0 (0)	0 (0)	0 (0)	Yes – 1 (50)
Voigtländer *et al.*	1999	5	56.8	N/A	3 (60)	0 (0)	3 (60)	Yes – 5 (100)
Zeni *et al.*	2003	17	52 ± 17	Clinical + anatomic (obstruction ≥2 lobar segments)	N/A	0 (0)	N/A	N/A
Siabilis *et al.*	2005	6	59 ± 17	HD impairment from interaction from embolus size and cardiopulmonary status	N/A	N/A	N/A	Yes
Spies *et al.*	2008	13	51 ± 20	PE causing at least HD compromise	N/A	N/A	6 (46.1)	Yes
Arzamendi *et al.*	2010	10	44 ± 19	PE in the presence of cardiogenic shock ± sustained hypotension (according to ACCP guidelines)	Yes (amount N/A)	N/A	N/A	Yes – 10 (100)
Hubbard *et al.*	2011	11	60	PE classified by CTPA criteria with Miller index >17 ± echocardiography evidence of right heart strain	N/A	3 (27.3)	N/A	Yes – 9 (82)
Wong *et al.*	2012	2	64	Acute PE with persistent systemic arterial hypotension (BPsyst <90 mmHg), cardiogenic shock or need for CPR	N/A	0 (0)	0 (0%)	Yes – 1 (50)
Bonvini *et al.*†	2012	10	73 ± 9	High-risk PE with cardiogenic shock with HD instability defined by shock index > 1	10 (100)	6 (60)	8 (80)	Yes – 10 (100)
		Total	***Mean***		***Total***	***Total***	***Total***	***Total***
		76 (mean 8.4 ± 5)	59.2 ± 9.7		13 (76.5)	9 (19.1)	17 (56.7)	36 (94.7)

Massive pulmonary embolism patient data concerning the year of publication of the study, the number of included patients, the MPE and submassive pulmonary embolism definitions, the clinical characteristics of the patients, and the use of thrombolytic regimen before, during or after the procedure.
†Unpublished data.
ACCP: American College of Chest Physicians; ART: AngioJet® rheolytic thrombectomy; BP: Blood pressure; BPsyst: Systolic blood pressure; Cardiogenic shock: Shock index >1 ± sign or symptoms of organ hypoperfusion; CI: Contraindications; CPR: Cardiopulmonary resuscitation; CT: Computed tomography; CTPA: Computed tomography pulmonary angiography; DVT: Deep venous thrombosis; HD: Hemodynamic; ip.: Intrapulmonary; iv.: Intravenous; IVC: Inferior vena cava; MPE: Massive pulmonary embolism; N/A: Not available; PE: Pulmonary embolism; TEE: Transesophageal echocardiography; TL: Thrombolysis; Trop: Troponines; TTE: Transthoracic echocardiography; V/Q: Ventilation/perfusion scan.

of severe pulmonary embolism with contraindications to thrombolytic therapy [29], and evidence for the use of ART for this condition only came in the last few years.

For the treatment of MPE, the 6-French ART devices (the largest device available on the market so far) should be used. This over-the-wire dual lumen catheter works according to Bernoulli's principle by creating a vacuum effect in a low-pressure zone generated by high-pressure saline jets emanating from the catheter tip (Figure 1). The recirculation of this high-pressure jet creates a vortex around the catheter tip (the Venturi effect) that fragments the thrombus, which is

Table 1. Studies including exclusively massive pulmonary embolism patients: baseline characteristics (cont.).

Scintigraphy – V/Q scan	CT	Cardiac marker	DVT	IVC filter	Thrombolysis	CI to systemic TL	Administered TL: iv.			Administered TL: ip.	Ref.
						Absolute or relative CI	*Pre-*	*Peri-*	*Post-*	*Bolus ± perfusion*	
0	0	N/A	N/A	0 (0)	No	2 (100)	No	No	No	No	[29]
0	0	N/A	N/A	0 (0)	No	5 (100)	No	No	No	No	[28]
Yes	Yes	N/A	Yes	12 (70.60)	Yes – 10 (58.82)	6 (35.30)	No	No	No	10 (58.82) perfusion overnight	[20]
Yes	Yes	N/A	Yes	0 (0)	Yes – 4 (66.66)	2 (33.33)	No	No	No	4 (66.66) bolus	[21]
0	Yes	N/A	N/A	5 (38.46)	Yes	13 (100)	No	No	No	4 (30.77) power-pulse spray mode	[25]
4 (40)	6 (60)	Mean peak Trop 1.1UI/l	6 (60)	2 (20)	Yes	10 (100)	0 (0)	0 (0)	0 (0)	2 (20) bolus	[30]
0	8 (72.72)	N/A	N/A	5 (45.45)	Yes – 8 (72.72)	1 (9)	No	No	No	5 (45.45) power-pulse spray mode and 8 (72.72) perfusion	[32]
0	2 (100)	N/A	N/A	0 (0)	No	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	[33]
0	3 (30)	N/A	N/A	1 (10)	Yes – 6 (60)	6 (60)	2 (20)	0 (0)	2 (20)	2 (20) bolus	[27]
Total, n(%)	***Total***		***Total***	***Total***	***Total***	***Total***	***Total***	***Total***	***Total***	***Total***	
4 (7.5)	19 (47.5)		25 (32.9)	28 (52.8)	47 (61.8)	2 (2.6)	0 (0)	2 (2.6)	35 (46.1)		

Massive pulmonary embolism patient data concerning the year of publication of the study, the number of included patients, the MPE and submassive pulmonary embolism definitions, the clinical characteristics of the patients, and the use of thrombolytic regimen before, during or after the procedure.
†Unpublished data.
ACCP: American College of Chest Physicians; ART: AngioJet® rheolytic thrombectomy; BP: Blood pressure; BPsyst: Systolic blood pressure; Cardiogenic shock: Shock index >1 ± sign or symptoms of organ hypoperfusion; CI: Contraindications; CPR: Cardiopulmonary resuscitation; CT: Computed tomography; CTPA: Computed tomography pulmonary angiography; DVT: Deep venous thrombosis; HD: Hemodynamic; ip.: Intrapulmonary; iv.: Intravenous; IVC: Inferior vena cava; MPE: Massive pulmonary embolism; N/A: Not available; PE: Pulmonary embolism; TEE: Transesophageal echocardiography; TL: Thrombolysis; Trop: Troponines; TTE: Transthoracic echocardiography; V/Q: Ventilation/perfusion scan.

then aspirated back in the catheter [32,36]. The device usually works in a standard fragmentation–aspiration mode, but it can also be used in a power-pulse spray mode. This latter mode can be simply activated in the new AngioJet console (Figure 2), or achieved by blocking the suction lumen with a stopcock if using the old version of the console [32]. With this power-pulse mode, the machine ejects the saline solution without immediately aspirating the fragmented thrombus. This allows for the powerful delivery of any type of drug (most of the time, recombinant tissue plasminogen activator) directly and deeply into the thrombus. After 5–15 min, the ART is activated

Table 2. Studies including exclusively massive pulmonary embolism patients: procedural details and outcomes.

Study	Year	Patients (n)	Definition of successful procedure	Successful procedures (%)	PA pressure (mmHg)	Mean Miller index		Duration of procedure	Procedural complications or events	In-hospital mortality	30-day survival (%)	Ref.
						Pre-	*Post-*	*Mean procedural time*				
Koning *et al.*	1997	2	N/A	2 (100)	sPA: Pre-ART, 48 ± 4; at 1 month, 24 ± 4	N/A	N/A	30 min	None	0 (0%)	2 (100)	[29]
Voigtländer *et al.*	1999	5	Definition N/A (assessed by HD improvement/ echocardiography/ angiography [Miller score/PA pressure])	3 (60)	mPA: Pre-ART, 34.7 ± 1.5; post-ART, 35.3 ± 3.8; at 24 h, 26 ± 4	28.8	26	N/A	3 transient bradycardia	2 (40%): 1 hemoptysis; 1 cerebral hemorrhage	3 (60)	[28]
Zeni *et al.*	2003	17	Technical success: >95% thrombus removal/clinical success: immediate relief of acute symptoms	Clinical: 16 (94.11)	N/A	N/A	N/A	N/A	1 third degree block; 1 bradycardia; 1 apnea; 1 death	2 (11.76%): 1 during PMT (hemoptysis/apnea/ bradycardia/death); 1 after 24 h/ hypotension + cardiac arrest	13 (76.5)	[20]
Siabilis *et al.*	2005	6	Clinical success: HD recovery with stable cardiac recovery + adequate peripheral perfusion (BPsyst >130 mmHg, SI <0.75)	5 (83.33)	N/A	18.83 ± 2.86	6.83 ± 2.79	3.37 ± 1.41 h	1 bradycardia; 1 apnea; 1 hemoptysis; 1 death	1 (16.66%): due to recurrent PE during the procedure	5 (83.3)	[21]
Spies *et al.*	2008	13	Technical success: immediate improved HD without complication/clinical success: when discharge status of patient is 'alive'	Technical: 12 (92.31) Clinical: 11 (84.6)	mPA: pre-ART, 47; post-ART, 45	18.1 ± 10.3	N/A	2.3 ± 0.6 h	2 bradycardia; 1 death	2 (15.38%): 1 during ART due to cardiac arrest after distal embolization of thrombus; 1 MOF	N/A	[25]
Arzamendi *et al.*	2010	10	N/A	9 (90)	mPA: pre-ART, 34.6; post-ART, 26.9	22.4 ± 2.8	9.8 ± 2.7	N/A	None	3 (30%): 1 due PE complications; 2 due to sepsis	N/A	[30]

Massive PE patient data concerning the technical aspects of the procedure, the success rate and the definition of a successful procedure, the pre- and the post-ART Miller index, the procedural and post-procedural complication rates, and the in-hospital and 30-day mortality rates.

[†]*Unpublished data.*

ART: AngioJet® rheolytic thrombectomy; BP: Blood pressure; BPsyst: Systolic blood pressure; HD: Hemodynamic; MOF: Multiorgan failure; mPA: Mean pulmonary artery pressure; N/A: Not available; PA: Pulmonary artery; PE: Pulmonary embolism; PMT: Percutanous mechanical thombectomy; SI: Shock Index; sPA: Systolic pulmonary artery pressure.

Table 2. Studies including exclusively massive pulmonary embolism patients: procedural details and outcomes (cont.).

Study	Year	Patients (n)	Definition of successful procedure	Successful procedures (%)	PA pressure (mmHg)	Mean Miller index		Duration of procedure	Procedural complications or events	In-hospital mortality	30-day survival (%)	Ref.
						Pre-	*Post-*	*Mean procedural time*				
Wong *et al.*	2012	2	N/A	2 (100)	N/A	N/A	N/A	N/A	N/A	0 (0%)	N/A	[33]
Bonvini *et al.*†	2012	10	Technical success: successfully perform all the attempted ART procedures; Clinical success: improvement in shock index ± decrease in catecholamine support	Technical: 10 (100); clinical: 8 (80)	sPA: pre-ART: 62.1 ± 17.4; post-ART: 50.6 ± 13.5	26.6 ± 3.3	20.5 ± 4.4	63 ± 20 min	2 deaths during ART (1 occuring during PMT performed under CPR conditions)	7 (70%): 2 MOF; 1 cerebral edema; 4 progressive right heart failure	3 (30)	[27]
		Total		***Total***	***Mean***	***Mean***	***Mean***	***Mean***	***Total***	***Total***	***Total***	
–		76 (mean 8.4 ± 5)		66 (86.8)	sPA: pre-ART: 55 ± 9.9; post-ART: 37.3 ± 18.8 mPA: pre-ART: 37.8 ± 5.8; post-ART: 33.9 ± 8.2	22.9 ± 4.2	15.3 ± 7.9	1.8 ± 1.3 h	11 events; 6 deaths	18 (23.7%)	36 (70.6)	

Massive PE patient data concerning the technical aspects of the procedure, the success rate and the definition of a successful procedure, the pre- and the post-ART Miller index, the procedural and post-procedural complication rates, and the in-hospital and 30-day mortality rates.

†*Unpublished data.*

ART: AngioJet® rheolytic thrombectomy; BP: Blood pressure; BPsyst: Systolic blood pressure; HD: Hemodynamic; MOF: Multiorgan failure; mPA: Mean pulmonary artery pressure; N/A: Not available; PA: Pulmonary artery; PE: Pulmonary embolism; PMT: Percutanous mechanical thombectomy; SI: Shock Index; sPA: Systolic pulmonary artery pressure.

Table 3. Studies including massive pulmonary embolism & submassive pulmonary embolism patients: baseline characteristics.

Study	Year	Patients (n)	Mean age (years)	Definition of MPE/sMPE	MPE (%)	sMPE (%)	Cardiogenic shock (%)	Cardiorespiratory arrest prior ART (%)	Mechanical ventilation prior ART (%)	Echocardiography (TTE ± TEE) (%)
Chauhan *et al.*	2007	14	63 ± 11	MPE: Large proximal PE + HD instability ± intractable hypoxemia; sMPE: Large PE with significant RV hypo/akinesis (TTE) and HD stable	10 (71.43)	4 (28.57)	Yes (amount N/A)	N/A	2 (14.28)	Yes (amount N/A)
Margheri *et al.*	2008	25	66	Group A: severe HD compromise/ shock; group B: moderate HD compromise (BP syst <100 mmHg, HR >100), group C: mild HD compromise	8 (32)	17 (68)	8 (32)	N/A	N/A	24 (96) (abnormal RV function)
Chechi *et al.*	2009	51	67 ± 14	MPE: PE with shock and hypotension ± RV dysfunction; sMPE: PE with stable HD but RV dysfunction (no clear definition)	14 (27.5)	29 (56.90)	14 (27.45)	N/A	N/A	51 (100) (RV size and function)
Nassiri *et al.*	2011	15	59 ± 16	MPE: saddle, main branch or >2 lobar PE with cardiogenic shock; sMPE: PE with HD stability + right heart strain by TTE or cardiac enzymes	1 (6.66)	14 (93.34)	1 (6.66)	1 (6.66%)	1 (6.66)	Yes (amount N/A)
Ferrigno *et al.*	2011	16	54 ± 16	According to ACCP definition (i.e., MPE: PE with BP syst <90 mmHg or drop in systolic BP > than 40 mmHg for more than 15 min)	5 (31.2)	11 (68.75)	2 (12.5)	2 (12.5)	2 (12.5) (1 sMPE after PMT; 1 MPE)	16 (100)
		Total	***Mean***		***Total***	***Total***	***Total***	***Total***	***Total***	***Total***
–		121 (mean 24.2 ± 15.6)	61.8 ± 5.4		46 (38.0)	75 (62)	25 (20.1)	3 (9.7)	5 (11.1)	91 (98.2)

MPE and sMPE patient data concerning the year of publication of the study, the number of the included patients, the MPE and sMPE definitions, the clinical characteristics of the patients and the use of thrombolytic regimen before, during or after the procedure.
†Thrombolysis was allowed (iv. or ip.) in all studies.
ART: AngioJet® rheolytic thrombectomy; BP: Blood pressure; Cardiogenic shock: Shock index >1 ± sign or symptoms of organ hypoperfusion; CI: Contraindications; CT: Computed tomography; DVT: Deep venous thrombosis; HD: Hemodynamic; ip.: Intrapulmonary; iv.: Intravenous; IVC: Inferior vena cava; MPE: Massive pulmonary embolism; N/A: Not available; PE: Pulmonary embolism; RV: Right ventricular; sMPE: Submassive pulmonary embolism; TEE: Transesophageal echocardiography; TL: Thrombolysis; TTE: Transthoracic echocardiography.

Table 3. Studies including massive pulmonary embolism & submassive pulmonary embolism patients: baseline characteristics (cont.).

Scintigraphy – V/Q scan (%)	CT (%)	Cardiac marker	DVT (%)	IVC filter	Thrombolysis†	CI to systemic TL (%)	Administered TL: iv.			Administered TL: ip.	Ref.
						Absolute or relative CI	*Pre-*	*Peri-*	*Post-*	*Bolus ± perfusion*	
0	12 (85.71)	N/A	Yes (amount N/A)	11 (78.60)	Yes	8 (57.14) absolute CI, 5 (35.71) relative CI	1 (7.15%)	0	0	5 (35.71%) bolus (including 4 [28.57] power-pulse spray mode)	[22]
Yes	Yes	N/A	21 (84)	11 (44)	Yes	Yes (amount N/A)	N/A	N/A	N/A	8 (32%)	[23]
3 (5.88)	43 (84.31)	35 patients Trop >0.01 ng/ml; D-dimer >500 in 49 patients	44 (86.27)	23 (45.10)	Yes	19 (37.25)	N/A	N/A	N/A	11 (21.57%) local infusion	[24]
0	Yes	13 patients Trop I > 0.01 ng/ml	10 (66.66)	10 (66.66)	Yes	Yes (amount N/A)	N/A	0	0	10 (66.66%) power-pulse spray mode	[26]
0	16 (100)	Trop I: sMPE: 0.08 ± 0.06; MPE: 0.58 ± 0.5	N/A	16 (100)	Yes	6 (37.5) absolute CI; 10 (62.5) relative CI	0	0	0	16 (100%) power-pulse spray mode	[31]
Total	***Total***		***Total***	***Total***		***Total***					
3 (3.1)	71 (93.4)		75 (82.4)	71 (58.7)		48 (59.2)					

MPE and sMPE patient data concerning the year of publication of the study, the number of the included patients, the MPE and sMPE definitions, the clinical characteristics of the patients and the use of thrombolytic regimen before, during or after the procedure.
†Thrombolysis was allowed (iv. or ip.) in all studies.
ART: AngioJet® rheolytic thrombectomy; BP: Blood pressure; Cardiogenic shock: Shock index >1 ± sign or symptoms of organ hypoperfusion; CI: Contraindications; CT: Computed tomography; DVT: Deep venous thrombosis; HD: Hemodynamic; ip.: Intrapulmonary; iv.: Intravenous; IVC: Inferior vena cava; MPE: Massive pulmonary embolism; N/A: Not available; PE: Pulmonary embolism; RV: Right ventricular; sMPE: Submassive pulmonary embolism; TEE: Transesophageal echocardiography; TL: Thrombolysis; TTE: Transthoracic echocardiography.

Table 4. Studies including massive pulmonary embolism & submassive pulmonary embolism patients: procedural details and outcomes.

Study	Year	Patients (n)	Definition of successful procedure	Successful procedures (%)	PA pressure (mmHg)	Mean Miller index		Duration of procedure	Procedural complications or events	Postprocedural complication	In-hospital mortality (%)	30-day survival (%)	Ref.
						Pre-	*Post-*						
Chauhan *et al.*	2007	14	Technical success: angiographic evidence of normal distal perfusion beyond the thrombus; Clinical success: clinical and HD improvement (14 technical/ 13 angiographic/ 12 procedural success)	Technical: 14 (100); clinical: 12 (85.71)	mPA: pre-ART, 32 ± 6; post-ART, 28 ± 8	N/A	N/A	139 ± 29 min	7 bradycardia; 2 transient asystolia → need for PM for all events	1 massive hemoptysis; 5 hematuria	3 (21.4): 1 intracranial bleed; 1 reccurent PE; 1 intractable cardiogenic shock	11 (78.6)	[22]
Margheri *et al.*	2008	25	Technical success: ability to deliver AngioJet® and aspirate thrombus in absence of procedural complications	Technical: 25 (100)	sPA: pre-ART, 48.4; post-ART, 38.2	20	10	N/A	3 bradycardia → 1 PM	7 worsening renal function; 10 major hematoma with transfusion; 3 thrombocytopenia	4 (16): 2 deaths due to persistent shock; 1 to recurrence of PE; 1 to cerebral hemorrhage	21 (84)	[23]
Chechi *et al.*	2009	51	Technical success: ability to deliver AngioJet and aspirate thrombus with at least 30% reduction of Miller index	Technical: 47 (92.2)	sPA: pre-ART, 49 mmHg; post-ART, 37 mmHg	19.5	9.5 ± 3.3	N/A	4 bradycardia → PM, 4 IABP	4 major; 8 minor; 12 minimal bleeding; 12 renal failure; 4 thrombocytopenia; 1 recurrent PE	8 (15.7): 6 persistent and refractory shock, 1 recurrent PE, 1 cerebral bleeding	43 (84.3)	[24]
Nassiri *et al.*	2011	15	Clinical success: clinical and HD improvement (no clear definition)	Clinical: 15 (100)	N/A	N/A	N/A	N/A	1 cardiac arrest (ART aborted)	2 acute renal failure	0 (0)	15 (100)	[26]

MPE and sMPE patient data concerning the technical aspects of the procedure, the success rate and the definition of a successful procedure, the pre- and the post-ART Miller index, the procedural and post-procedural complication rates, and the in-hospital and 30-day mortality rates.
→ indicates that as a consequence of some events of bradyarrhythmia, a certain amount of pacemakers needed to be implanted.
ART: AngioJet® rheolytic thrombectomy; HD: Hemodynamic; IABP: Intraaortic balloon pump; mPA: Mean pulmonary artery pressure; MPE: Massive pulmonary embolism; N/A: Not available; PA: Pulmonary artery; PE: Pulmonary embolism; PM: Pacemaker; sMPE: Submassive pulmonary embolism; sPA: Systolic pulmonary artery pressure.

Table 4. Studies including massive pulmonary embolism & submassive pulmonary embolism patients: procedural details and outcomes (cont.).

Study	Year	Patients (n)	Definition of successful procedure	Successful procedures	PA pressure (mmHg)	Mean Miller index		Duration of procedure	Procedural complications or events	Postprocedural complication	In-hospital mortality (%)	30-day survival (%)	Ref.
						Pre-	*Post-*						
Ferrigno *et al.*	2011	16	N/A	N/A	sMPE mPA: pre-ART, 31 ± 10.1; post-ART, 26 ± 8; MPE mPA: pre-ART, 40 ± 6; post-ART, 28 ± 6	sMPE: 17 ± 3.2; MPE: 18 ± 3.4	sMPE: 8.8 ± 3; MPE: 9.5 ± 4.4	All completed within 60 min	1 bradycardia	2 retroperitoneal bleeding + renal failure; 3 hemoptysis	1 (6.3)	15 (93.7)	[31]
		Total		***Total***	***Total***	***Mean***	***Mean***		***Total***	***Total***	***Total***	***Total***	
		121 (24.2 ± 15.6)		99 (94.3)	sPA: pre-ART, 48.7 ± 0.4; post-ART, 37.9 ± 0.8; mPA: pre-ART, 34.3 ± 4.9; post-ART, 27.3 ± 1.2	18.6 ± 1.4	9.4 ± 0.5		21 events	74× events	16 (13.2)	105 (86.8)	

MPE and sMPE patient data concerning the technical aspects of the procedure, the success rate and the definition of a successful procedure, the pre- and the post-ART Miller index, the procedural and post-procedural complication rates, and the in-hospital and 30-day mortality rates.
→ indicates that as a consequence of some events of bradyarrhythmia, a certain amount of pacemakers needed to be implanted.
ART: AngioJet® rheolytic thrombectomy; HD: Hemodynamic; IABP: Intraaortic balloon pump; mPA: Mean pulmonary artery pressure; MPE: Massive pulmonary embolism; N/A: Not available; PA: Pulmonary artery; PE: Pulmonary embolism; PM: Pacemaker; sMPE: Submassive pulmonary embolism; sPA: Systolic pulmonary artery pressure.

in the usual manner and results in a more efficacious thrombus fragmentation thanks to the adjunctive lytic effect [32].

The ART can be used in the lobar and segmental levels of the pulmonary branches, which have to measure at least 6 mm in diameter in order to assure a safe manipulation and decrease the risk of vessel wall damage [38]. After activation, the catheter is then slowly (i.e., 1 cm/s) advanced inside the thrombus for a total length of a single run of a maximum of 10 s. A longer activation period may create an unnecessary amount of thrombus fragmentation, leading to an important neurohormonal release, as well as a high tension of the pulmonary vessel walls, finally resulting in a massive bradycardia and hypotension [37,39–42]. The procedure should be continued until the hemodynamic conditions of the patient have improved, or a satisfactory angiographic result is obtained. Of note, even a very small thrombus aspiration (e.g., <30% of the total thrombus burden) in the case of MPE may be sufficient to re-establish an acceptable hemodynamic condition, thus suggesting that the duration of aspiration should be tailored more to the hemodynamic response of the patient than to the angiographic result.

Advantages of AngioJet

One of the main advantages of the AngioJet as part of the rheolytic thombectomy devices is that it works on a fragmentation–aspiration effect through the Venturi principle, thus reducing the risk of distal embolization that tends to frequently occur with other 'more classical' thrombectomy devices. Furthermore, by using the high-speed saline jet, it is considered far less 'aggressive' in terms of vessel damage than other thrombectomy devices [43].

Another important issue is that the ART can also be used in a spraying mode by adding a thrombolytic agent to the saline solution. By disseminating the thrombolytic agent into the thrombus, the lytic effect of the agent may be potentiated, finally increasing the efficacy of the thrombectomy procedure [32]. Furthermore, it should be mentioned that this power-pulse spray mode was widely used in several studies, even in patients with contraindications to systemic thrombolysis, and this is because the total amount of the administered lytic agent with this technology may be ten-times inferior to the one used during systemic iv. thrombolysis. Accordingly, Ferrigno *et al.* have reported the use of ART in the power-pulse spray mode in all of their 16 patients presenting with MPE as well as sMPE, who all had either contraindications to systemic thrombolysis or were at high risk of bleeding [31]. Interestingly, in this series, despite the occurrence of two retroperitoneal bleedings and three cases of hemoptysis, the 30-day mortality rate was only 6% [31].

Finally, the ART catheter and console appear to be quite user-friendly [30]. Observations from our review suggest that it seems to also be relatively safe in its use on a technical basis, since out of the 197 patients that benefited from this technique, only one death is suspected to be related to the device [20], and no other major device-related complications were reported.

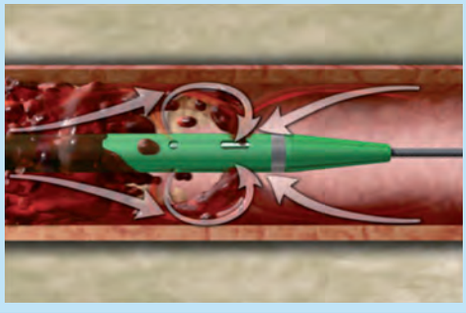

Figure 1. AngioJet® catheter tip showing the rheolytic effect of the saline jet associating the thrombus aspiration through the Venturi effect.

AngioJet-related complications

Despite the above-mentioned advantages, there still are concerns regarding the potential complications related to the use of ART in the setting of MPE. Indeed, in the meta-analysis published by Kuo *et al.* in 2009 on the use of PMT for the treatment of PE, the authors came to the conclusion that the ART had the highest rate of complication among all analyzed PMT devices [1]. This is a fact that must be taken into consideration before attempting any type of rheolytic procedure in the pulmonary vasculature. Accordingly, fragmentation of the clot induces significant hemolysis, which may be associated with a massive release of neurohormonal substances such as adenosine and bradykinins at the pulmonary vasculature level [15,39]. This phenomenon, associated with the concomitant activation of stretch receptors in the pulmonary arteries and in the right ventricle, is considered to be the leading cause of procedure-related bradyarrhythmias and hypotension [26,37]. As a consequence, this cascade of events may temporarily worsen the hemodynamic status of the patients. Measures to counterbalance these effects include the

placement of a transvenous temporary pacemaker wire in the right ventricle either at the beginning or during the procedure [37], as well as the administration of iv. medications such as catecholamine and aminophylline.

Accordingly, our review shows that out of the 197 patients, there were 23 (11.6%) episodes of significant bradyarrhythmia, and two (1%) episodes of transient asystole, out of which 18 (9.1%) required the implantation of a temporary pacemaker. However, the true rate of significant bradyarrhythmia may be significantly underestimated in our review, especially if one considers that in many centers the right ventricle stimulation with a temporary pacemaker is considered mandatory before every ART activation, and is thus considered as a normal procedural step of the intervention [37].

Another issue related to the hemolysis induced by ART is the occurrence of severe hyperkalemia and hemoglobinuria. Hyperkalemia may contribute to worsening the electrical instability, finally leading to severe ventricular arrhythmias, while hemoglobinuria causes further deterioration of renal function, which is often already impaired by the concomitant severe low cardiac output occurring during MPE. Among our study population we noted impairment or worsening of renal function in 11.7% of patients, which again may be underestimated because it was not routinely checked in all of the studies.

Finally, our observation also points out the risk of bleeding, which is associated with all percutaneous interventions. Despite the fact that only venous accesses are necessary to perform a PMT (one venous access for the catheter, a second in case a temporary pace maker is implanted), the bleeding risk of the procedure is not negligible. During the procedure, anticoagulation should be very aggressive (i.e., activated clotting time >300 s), and many of the treated patients have already had or are going to receive some kind of lytic therapy. Our study demonstrated a total of 14.5% of combined major and minor bleeding events; however, none of these were considered to be directly related to the death of the patient.

Figure 2. The new console of the AngioJet® device (Medrad/Bayer Interventional, MN, USA).

Unresolved issues related to AngioJet

Our observations point out a number of questions regarding the use of ART in the various studies we have analyzed. First of all, the average age of the population of 60.1 ± 7.5 years possibly shows that elderly patients, often more frail and presenting with more comorbidities, may have been excluded from these studies. There may also be a patients' selection bias related to the bleeding complications associated with ART. This may finally contribute to the observed high success rate of the procedure, which is reported to be up to 85%.

Furthermore, the absence in several studies of clear definitions regarding the severity of the PE and the absence of parameters such as biomarkers, hemodynamic parameters or echocardiographic findings (particularly right ventricular dimensions) has probably led to the inclusion of rather hemodynamically stable patients (i.e., sMPE), instead of those really suffering from MPE. Indeed, patients with MPE are more unstable and have a much worse prognosis with a higher risk of complications and death than those presenting with sMPE. This high degree of instability may be the main cause of the 3% periprocedural death rate observed among all patients, with all of these deaths occurring in the MPE group A of patients.

This is corroborated by all studies including both types of patients (i.e., sMPE and MPE), in which a clear difference between complications and mortality rates is reported in the MPE patients' group [24,31]. These higher complication and mortality rates may even be exacerbated if one analyzes only MPE patients presenting with cardiogenic shock or a previous episode of cardiac arrest. Accordingly, our group has

prospectively studied this very high-risk subgroup of MPE patients, and found an exceedingly high 24-h mortality rate (i.e., 70%), probably secondary to an irreversible condition of right heart failure [27].

It must also be pointed out that the scarcity of data concerning long-term follow-up of patients after ART makes it difficult to assess this technique as compared with the systemic lytic therapy. Data available so far do not allow for the precise definition of patients who would benefit the most from this technique.

■ Limitations of the study

Our observational study has some limitations. First, the studies included for analysis consist of a small pool of patients, most of the time retrospectively analyzed. Second, in our search, we mainly came across studies with favorable outcomes concerning the use of ART, suggesting that published data probably came from centers that already have experience of treating MPE patients, as well as experience with the AngioJet technology. Hence, data from centers with less experience or unfavorable outcomes have so far not been published.

Third, most of the series including more than ten patients are feasibility and safety studies, and thus do not exclusively include MPE patients. Accordingly, in these studies more technical or angiographic end points were analyzed, while in smaller studies including exclusively highly unstable patients, more clinical end points are mentioned, but most of the time these are only retrospectively analyzed. Finally, in more than 40% of the treated patients, some kind of thrombolysis (iv., intrapulmonary [bolus vs infusion vs power-pulse]) was administered, thus rendering the extrapolation of the sole efficacy, in terms of hard clinical end points, of the ART procedure in cases of MPE difficult.

Future perspective

Despite all of the ART-related issues, this technology presents some interesting features that need to be taken into consideration in the treatment of MPE.

Percutaneous mechanical thrombectomy procedures, such as the ART, may be further implemented in MPE treatment algorithms, especially if one considers that up to 40% of these patients may present with contraindications to iv. fibrinolysis or are at too high risk of bleeding events [1,6–8,11]. Accordingly, the total amount of thrombolytic agents used in the ART power-pulse spray mode could drastically be reduced, thus suggesting that lysis may be used also in those patients at high bleeding risk, who conversely would have been treated with heparin alone [26,31].

Finally, in the case of very unstable situations (i.e., impending cardiac arrest), the use of a cardiac assist device, such as extracorporeal membrane oxygenation, may be of great value, especially for these patients who cannot undergo surgical or percutaneous thrombectomy procedures in a timely fashion [44–46]. The percutaneous insertion of extracorporeal membrane oxygenation can be easily performed in the catheterization laboratory, and it guarantees a sufficient blood oxygenation, as well as organ perfusion in these highly unstable settings, in order to allow the operator the necessary time to safely and efficaciously perform the scheduled PMT procedure (Figure 3) [45].

Conclusion

MPE remains a life-threatening condition, despite a lot of improvements in the pharmacologic as well as the pharmaco-mechanical therapies being seen in the last 20 years. Intravenous thrombolysis should remain the treatment of choice in patients presenting with MPE, while this lytic regimen still remains a subject of debate in those presenting with sMPE.

In the last decade, a lot of interest has been given to the endovascular catheter-based approach for the treatment of PE: the PMT

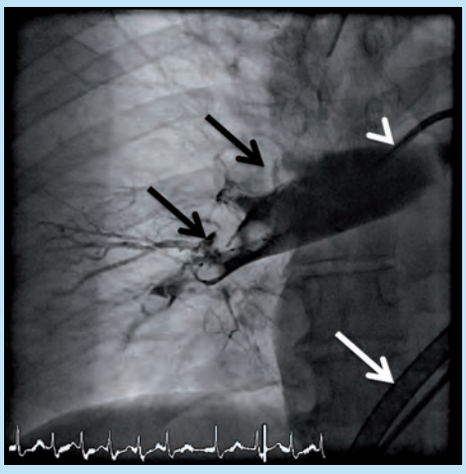

Figure 3. Right pulmonary angiography, showing an acute occlusion of the main lobar arteries (black arrow) performed after the insertion of extracorporeal membrane oxygenation (white arrow). White arrowhead: 8-French multipurpose guiding catheter used for the AngioJet® rheolytic thrombectomy procedure.

procedure. This minimally invasive procedure should be reserved for those patients presenting with a thrombolysis contraindication or those with a thrombolysis failure.

The ART procedure has proven its efficacy and safety in several retrospective, and a few prospective, clinical trials, suggesting that this technology, already available in many coronary catheterization laboratories, may be further implemented by treating MPE patients.

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Executive summary

Use of percutanous mechanical thrombectomy in massive pulmonary embolism

- The AngioJet® rheolytic thrombectomy system (ART), as part of the percutanous mechanical thrombectomy devices, is used mainly in patients with contraindications to or failed systemic lytic therapy.

ART technical aspects

- ART works by creating a vacuum effect generated by high-pressure saline jets emanating from the catheter tip. The recirculation of this high-pressure jet creates a vortex around the catheter tip, fragmenting the thrombus, which is then aspirated back into the catheter.
- The device can also be used in a power-pulse spray mode, ejecting powerful saline solution, sometimes mixed with a thrombolytic agent, directly into the thrombus, resulting in a more efficacious thrombus fragmentation.

Advantages of AngioJet

- The risk of distal embolization is greatly reduced by the fragmentation–aspiration principle.
- The spraying mode with a mixed saline solution and thrombolytic agent potentiates the lytic effect. It can be used as such even in patients with contraindications to systemic thrombolysis.
- The AngioJet catheter and console are quite user-friendly and safe in their manipulation.

AngioJet-related complications

- Complications related to the use of AngioJet include:
  - Procedure-related bradyarrhythmias and hypotension.
  - Impairment or worsening of renal function secondary to hemoglobinuria.
  - Electrical instability and ventricular arrhythmia due to hyperkalemia.
  - A risk of bleeding that is not negligible.

Future perspective

- ART is to be considered in massive pulmonary embolism treatment algorithms with regards to the considerable amount of patients with contraindications to intravenous fibrinolysis at too-high risk of bleeding.
- The concomitant use of a cardiac assist device, such as extracorporeal membrane oxygenation, may be of great value in order to allow the operator to perform the procedure more safely and efficaciously.

Conclusion

- Systemic thrombolytic therapy still remains the gold standard treatment for massive pulmonary embolism.
- Percutaneous mechanical thrombectomy procedures should be reserved for patients presenting with contraindications to thrombolysis or those with thrombolysis failure.
- The ART procedure has proven its efficacy and safety, suggesting that this technology should be further implemented in treating massive pulmonary embolism patients.

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