ВОЗМОЖНОСТИ РЕОЛИТИЧЕСКОЙ ТРОМБЭКТОМИИ В ЛЕЧЕНИИ ТРОМБОЭМБОЛИИ ЛЕГОЧНОЙ АРТЕРИИ

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Running head: AngioJet in acute pulmonary embolism

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Актуальность проблемы: тромбоэмболия лёгочной артерии (ТЭЛА) – распространённое сердечно-сосудистое заболевание, которое характеризуется высокой смертностью. Некоторым пациентам с ТЭЛА высокого хирургического риска не могут быть выполнены традиционные лечебные вмешательства, например, тромболизис или хирургическая тромбэктомия. Тем не менее, для улучшения прогноза таких больных требуется более агрессивная лечебная тактика, чем стандартная антикоагулянтная терапия. В таких случаях операцией выбора может стать реолитическая тромбэктомия (РТЭ), которая постепенно входит в клиническую практику лечения массивной ТЭЛА. В данной статье приводится опыт выполнения РТЭ посредством аппарата AngioJet у пациентов с массивной ТЭЛА высокого и среднего хирургического риска, которым не могли быть выполнены тромболизис или хирургическая тромбэктомия.
Методы и результаты: за период с сентября 2001 года по октябрь 2012 РТЭ была выполнена в общей сложности 91 пациенту с массивной ТЭЛА. Из них 28 пациентов относились к группе высокого риска, 63 - к группе среднего риска. Анализировались клинические характеристики пациентов: анамнез, особенности процедуры, периоперационные осложнения, выживаемость. У 15,4% пациентов дополнительно выполнялся локальный тромболизис. Технический успех был достигнут у 94,5% пациентов со значимым снижением индекса Миллера, отражающего объем эмболического поражения сосудов ($p<0,0001$). Общая госпитальная летальность составила 12,1% (11 пациентов). Из них 63,6% (7 больных) исходно относились к группе высокого риска. Частота развития крупных кровотечений составила 7,7%. При этом с накоплением опыта проведения РТЭ была отмечена выраженная тенденция к снижению частоты кровотечений ($p=0.03$).
Заключение: в опытных руках РТЭ может быть эффективным и безопасным методом лечения массивной ТЭЛА у пациентов, которым не могут быть выполнены тромболизис или хирургическая тромбэктомия.

PERCUTANEOUS ANGIOJET RHEOLYTIC THROMBECTOMY FOR MAJOR ACUTE PULMONARY EMBOLISM

Background. Pulmonary embolism (PE) is a common cardiovascular disease with significant mortality. Some patients with high-risk PE are not eligible for current treatment options, such as thrombolysis or surgical embolectomy; moreover, some patients with intermediate-risk PE may benefit from a more aggressive approach rather than the sole anticoagulation therapy. In these settings, catheter thrombectomy is an evolving technology and is becoming part of the treatment options for the management of major PE. We report our experience of percutaneous AngioJet Rheolytic Thrombectomy (ART) for the treatment of high and intermediate-risk PE in patients ineligible for current treatment options.
Methods and results. Between September 2001 and October 2012 a total of 91 patients with major PE referred for ART to our catheterization laboratory were included. Twenty-eight patients presented with high-risk PE and 63 with intermediate-risk PE. Clinical data including medical history, procedural characteristics, in-hospital complications and survival were collected. Adjunctive local thrombolysis was performed in 15.4% of patients. Technical success was obtained in 94.5% of patients, with a significant reduction of Miller index ($p<0.0001$). Total in-hospital mortality occurred in 11 patients (12.1%), of whom 7 (63.6%) presented with high-risk PE. The rate of major bleeding complications was 7.7%. Laboratory experience was significantly associated to a lower rate of major bleedings ($p=0.03$).
Conclusions. In experienced hands ART can be an effective and safe treatment option for major (i.e. high and intermediate-risk) PE in patients who may not be eligible for thrombolytic therapy or surgical embolectomy, or who may benefit from a more aggressive approach on top of anticoagulation therapy.

Introduction

Pulmonary embolism (PE) is a common cardiovascular disease with significant morbidity and mortality. Actually, acute obstruction of pulmonary circulation with subsequent increase in pulmonary pressure, in right ventricular afterload, dilatation and dysfunction, may become life-threatening. Despite major research efforts management is still suboptimal in many patients. Thrombolysis is the established therapy for patients with high-risk PE (i.e. cardiogenic shock and/or sustained hypotension) (1,2); while, when thrombolysis is contraindicated, surgical or percutaneous thrombectomy can be envisaged (1,2). Patients with intermediate-risk PE should be treated with anticoagulation therapy (1,2). However, there is growing evidence that some of the patients with intermediate-risk PE judged to be at poor prognosis, should be treated more aggressively, like those at high-risk, because outcome tends to be poor despite their mild hemodynamic compromise (3), with the basic objective of reestablishing patency of the pulmonary circulation and preventing further deterioration of right ventricular function and progression to cardiogenic shock (4). The net clinical benefit of thrombolysis in patients with intermediate-risk PE, seems to be not so good to justify this treatment in this subgroup of patients because of the increased bleeding risk (5). Whereas, percutaneous thrombectomy might be a promising option of effective and promptly thrombus clearing with no increase in major bleeding, even in the setting of intermediate-risk PE patients. Among percutaneous thrombectomy devices, rheolytic thrombectomy with AngioJet system (MEDRAD, INC., Warrendale, PA, USA) seems to be the most easy-to-use, and compared to other devices, seems to have the same effectiveness while being associated with a smaller risk of device-related complications (6).

We conducted the present analysis to appraise the impact of AngioJet rheolytic thrombectomy (ART) on angiographic and clinical endpoints in patients with acute high and intermediate-risk PE inelegible to receive current treatments options.

Methods

Study population

Consecutive patients with acute PE, either high or intermediate-risk PE, initially diagnosed by either computed tomography (CT), ventilation-perfusion scintigraphy or echocardiography, and referred to our catheterization laboratory for ART from September 2001 to October 2012, were retrospectively evaluated in the present analysis. ART was performed only in high-risk PE patients who had contraindications to thrombolysis, or were considered at high risk for bleeding with thrombolytics, or had failed thrombolysis; and in intermediate-risk PE patients judged to be at poor prognosis, due to the presence of severe right ventricular (RV) dysfunction or major myocardial necrosis.

According to criteria of the European guidelines, high-risk PE was defined as the presence of cardiogenic shock and/or sustained hypotension; while intermediate-risk PE patients, included in this analysis, were defined as those with both RV dysfunction, detected by transthoracic echocardiography, and high levels of myocardial necrosis markers (1). Available clinical history, risk factors predisposing PE, adjunctive medical therapy and in-hospital complications were systematically recorded. Written informed consent was obtained in all patients. Ethics approval was waived because of the observational retrospective design.

Procedure

Rheolytic thrombectomy was performed using the AngioJet device (MEDRAD, INC., Warrendale, PA, USA), which removes thrombus by means of the Bernoulli principle. Detailed descriptions of the procedure have been published previously (7,8). Briefly ART was performed by venous percutaneous transfemoral approach. All patients were administered unfractionated heparin, as an initial intravenous bolus of 70 IU/kg, followed by additional doses titrated to an activated clotting time >250 sec. When possible, principally according to the hemodynamic status of the patient, before and after ART, pulmonary angiography was performed by a 6 Fr angulated pigtail. An 8 Fr multipurpose catheter was then used to reach the thrombus mass, which was crossed either with a 300 cm 0.014'' hydrophilic wire (Choice PT Extra-support, Boston Scientific, Natick, MA) or a 260 cm 0.035'' hydrophilic wire (Terumo, Radifocus Guidewire, Terumo Corp., Tokyo, Japan) according to the AngioJet catheter used. The AngioJet catheter was then advanced over the guide wire, with the pump unit activated during slow catheter passages across the thrombus mass in a distal-to-proximal or proximal-to-distal direction under fluoroscopic guidance. Attempts were made to reposition the guide wire frequently through several locations in the large embolus, so as to perform thrombectomy in a

«Swiss cheese» fashion. The aim was to fragment and aspirate as much thrombus to improve hemodynamic status and pulmonary perfusion, rather than to achieve an optimal angiographic result. Only target thrombus lesions in vessels with reference diameter ∅3 mm (i.e. no segmental branches) were treated. The Xpeedior catheter was used when the reference culprit vessel diameter was >6 mm, whereas the Spiroflex catheter was used when smaller vessel (diameter 3-6 mm) were invol-

ved. Loco-regional fibrinolytic therapy was performed at the operator's discretion, either directly (infusion of 0.6 mg/kg of rt-PA over 15 minutes) or using the «power pulse spray» method (infusion of maximum 25 mg of rt-PA, obtained diluting 25 mg of rt-PA in 50 ml of saline solution and administered by advancing the AngioJet catheter by repeated steps of 1 mm each, therefore giving 0.6 ml of the solution for each AngioJet pump activation) (9). After the procedure patients were treated with unfractioned heparin, and subsequently switched to oral anticoagulation with warfarin unless contraindicated. Vena cava filters were also deployed at the operator's discretion to prevent further thromboembolic episodes, according to the results of lower limb venous Duplex ultrasound scan.

Angiographic analysis

Pulmonary artery pressure was monitored during the procedure, while pulmonary angiography was analyzed off-line by experienced angiographers according to established criteria described by Miller et al. (10), before and after the procedure. In detail, the Miller index (MI) was calculated by the sum in each patient of both obstruction and perfusion indexes. The obstruction index was calculated as follows: nine major segmental branches were identified in the right pulmonary artery (three in the upper lobe, two in the middle, and four in the lower), and eight major branches were identified in the left pulmonary artery (two in the upper lobe, two in the middle and four in the lower); the presence of filling defects in any of these branches was scored with one point per segment leading to a maximum score of 16. The perfusion index was scored as follows: each lung was divided into three zones (upper, middle and lower) and the flow in each zone was assessed as absent (three points), severely decreased (two points) and mildly decreased (one point) and normal (zero point) leading to a maximum score of 18. Thus the MI was computed by the sum of these two scores ranging from zero (best) to 34 (worst) (Figure 1).

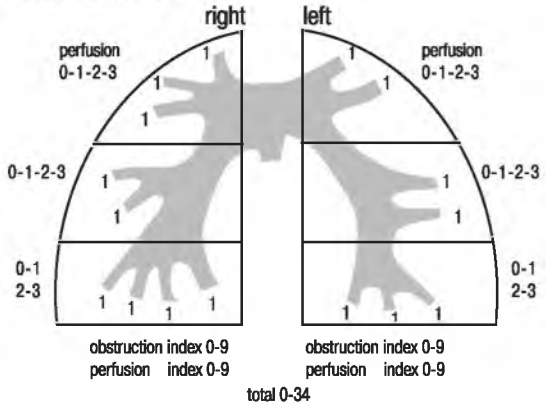

Fig. 1. *The Miller index.*

Рис. 1. *Расчет индекса Миллера.*

Definitions and in-hospital events

Patients were classified according to the early mortality risk in high and intermediate-risk PE patients (1), to explore throughly the impact of ART. Technical success was defined as the ability to deliver the AngioJet in the pulmonary vessels and to aspirate thrombus with at least 30% reduction of the MI; and procedural success as technical success in the absence of major procedural complications. The following events occurring during hospitalization were systematically abstracted by means of chart review: all-cause death, recurrence of PE, bleeding classified as major, minor and minimal according to the TIMI bleeding classification (i.e. major bleeding: any bleeding associated with a hemoglobin drop ≥5 g/dL or cerebral hemorrhage; minor bleeding: observed blood loss with a hemoglobin drop ≥3 g/dL or no observed blood loss with a hemoglobin drop ≥ 4 g/dL; minimal bleeding: any clinically overt sign of hemorrhage with a hemoglobin drop <3 g/dL) (11), renal failure (i.e. >25% postprocedural increase in serum creatinine) and severe thrombocytopenia (i.e. platelets <100.000 x 109/L).
The impact on in-hospital clinical events of laboratory experience in performing AngioJet RT, was evaluated comparing the outcome of the procedures performed during and after the first 24 months of the study period.

Statistical analysis

Continous variables were expressed as mean±standard deviation and categorical variables as number (%). Comparative analysis was performed using chi-squared test for categorical variables and t-test for continuos variables. Two-tailed statistical significance was set at the 0.05 level. SPSS version 20 sofware (SPSS, Chicago, IL) was used for all computations.

Results

A total of 91 consecutive patients with acute major PE were referred to our catheterization laboratory for ART. Baseline clinical, laboratory and instrumental data are listed in Table 1. The mean age was 67.4±14.1 years. Presenting symptoms were dyspnea (81.3%), chest pain (24.2%), syncope (22%) and cardiac arrest (4.4%). Of the 91 patients, 28 had high-risk PE (16 patients were in cardiogenic shock and 12 patients were hypotensive). Sixty-three patients had intermediate-risk PE with significant RV dysfunction on echocardiogram and high levels of myocardial necrosis markers.
In high-risk PE patients involved in the present analysis, use of thrombolytic agents was contraindicated, according to the guidelines criteria (1,2), in 13 (46.4%) patients due to recent surgery, major trauma, aortic dissection and prolonged and traumatic resuscitation. Significant comorbidities (i.e. active neoplasia) were felt to impose a significant risk of bleeding in the others

Table 1

Baseline clinical, laboratory and instrumental data of patients treated with AngioJet rheolytic thrombectomy

Исходные характеристики пациентов, включенных в исследование.

N = 91	n (%)
Male *Мужской пол*	41 (45.1)
Age (years) *Возраст (годы)*	67.4±14.1
Risk factors for pulmonary embolism: *Факторы риска ТЭЛА:*	
• current smoking *курение*	16 (17.6)
• obesity *ожирение*	18 (19.8)
• malignancy *опухоли*	23 (25.3)
• trauma/fractures *травмы/переломы*	9 (9.9)
• recent (<4 weeks) surgery *недавние (<4 недель) хирургические вмешательства*	18 (19.8)
	27 (29.7)
• immobilization *иммобилизация*	6 (6.6)
• coagulopathy *коагулопатии*	8 (8.8)
• autoimmune pathology *аутоиммунные заболевания*	4 (4.4)
• chronic heart failure *хроническая сердечная недостаточность*	
Contraindications to thrombolysis *Противопоказания к тромболизису*	36 (39.6)
Symptoms *Симптомы* :	
• dyspnea *одышка*	74 (81.3)
• hest pain *боль в груди*	22 (24.2)
• presyncope *пресинкопе*	9 (9.9)
• syncope *синкопе*	20 (22)
• palpitation *сердцебиение*	11 (12.1)
• cardiac arrest *остановка сердца*	4 (4.4)
Clinical presentation *Клинические симптомы:*	
• high-risk PE *Высокий риск*	28 (30.8)
- cardiogenic shock *кардиогенный шок*	16 (17.6)
- hypotension *гипотензия*	12 (13.2)
- intermediate-risk PE *Средний риск*	63 (69.2)
Lower limb venous Duplex ultrasound scan *Дуплексное сканирование глубоких вен нижних конечностей*	75 (82.4)
Deep vein thrombosis *Тромбоз глубоких вен*	61 (67%)

15 patients, except one who was treated with ART because of failure of thrombolysis. Of note that even 41.2% of the intermediate-risk PE patients showed a contraindication to thrombolysis (recent surgery, ischemic and hemorragic stroke, major trauma, bleeding diathesis and active bleeding), and that 15 (23.8%) of them were judged to be at high bleeding risk with thrombolysis due to the presence of comorbidities.

Technical success was achieved in 94.5% of cases, with a mean MI reduction rate of 50.4±15.2% (range 16.6–8 0%). Procedural success was obtained in 85 patients (93.4%) as one patient developed massive hemoptysis during the procedure.

Local infusion of rt-PA was performed directly in 13 patients and using the «power pulse spray» method in one patient (9). Of these 14 patients, 6 presented with high-risk PE and the benefit of fragmentation the thrombus and facilitationg aspiration with local fibrinolysis was judged to be superior to the risk of bleeding. Two of these patients presented bleeding complications (one major bleeding and one minor bleeding). A representative case treated with successfully ART is demonstrated in Figure 2.

Temporary transvenous pacing was needed in 4 subjects (4.4%) for bradycardia, as well as intra-aortic balloon pumping which was used in 4 patients (4.4%) in shock to reduce RV ischemia and improve cardiac output and mean arterial systemic pressure. Temporary vena cava filters were implanted in 23 patients (25.3%), in whom thrombi deemed at high risk for embolization

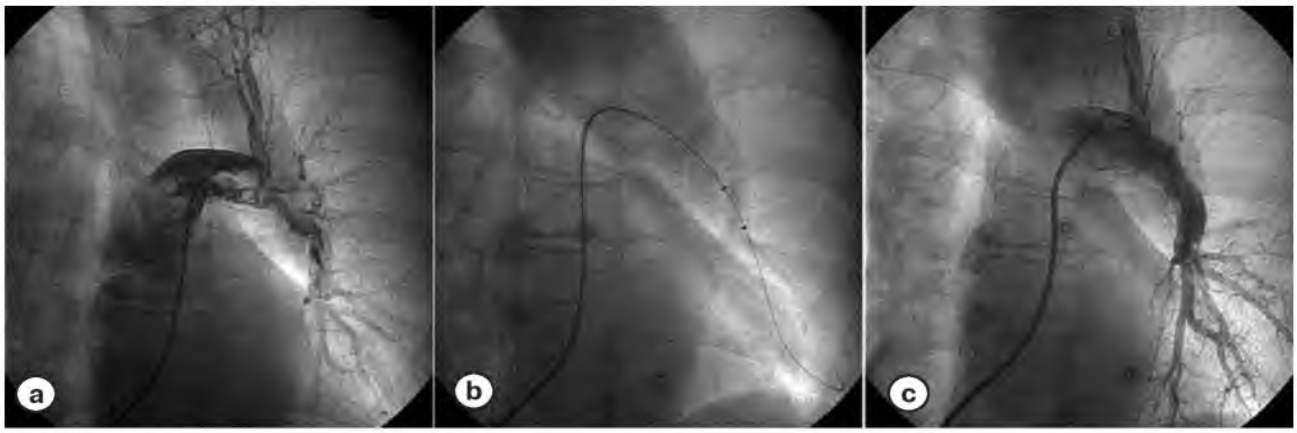

Fig. 2. *Catheter based rheolytic thrombectomy.*
a – perfusion and obstruction defects on the left pulmonary artery.
b – the AngioJet catheter is advanced to perform rheolytic thrombectomy.
c – the thrombus is removed from the main branches with improvement of perfusion and obstruction indexes.

Рис. 2. *Реолитическая тромбэктомия.*
a – дефекты заполнения в левой легочной артерии
b – катетер AngioJet установлен для проведения РТЭ
c – тромб удален, кровоток по левой легочной артерии восстановлен.

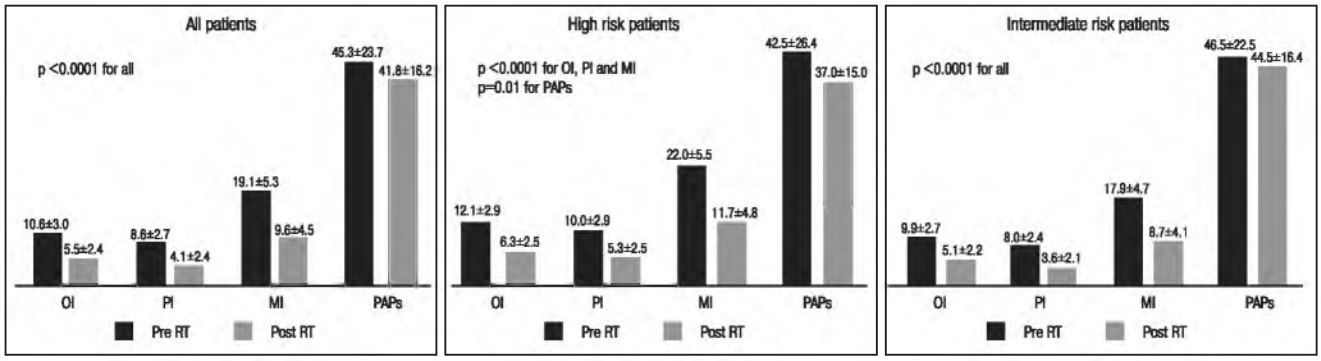

Fig. 3. *Improvement in obstruction, perfusion, Miller indexes and systolic pulmonary artery pressure before and after Rheolytic thrombectomy in high-risk and intermediate-risk PE patients (OI: obstruction index; PI: perfusion index; MI: Miller index; PAPs: systolic pulmonary artery pressure; RT: rheolytic thrombectomy).*

Рис. 3. *Динамика кровотока, индекса Миллера и систолического давления в легочной артерии до и после РТЭ у пациентов в зависимости от уровня риска.*

(i.e. mobile head) had been observed at lower limb venous Duplex ultrasound scan. Comparison of baseline to post-procedural angiographic data showed a statistically significant improvement in all angiographic endpoints, such as obstruction, perfusion and Miller indexes either in the high or in the intermediate-risk patients groups (Figure 3).

The clinical events which occurred during hospital stay are summerized in Table 2. Major bleeding were observed in 7 (7.7%) cases: one cerebral hemorrhage in a patient not treated with concomitant fibrinolysis; one groin hematoma plus melena and one groin hematoma plus hemoptysis in two patients who had received fibrinolytics; and two groin hematomas and two hemoptysis in patients who had not received fibrinolytics. Eleven patients (12.1%) died in-hospital: seven due to persistent and refractory shock, one for recurrence of embolism after a successful procedure, one for cerebral hemorrhage, one for massive hemoptysis and one for paralitic ileus. Patients with high-risk PE showed a higher in-hospital mortality than patients with intermediate-risk PE (25% vs 6.3%, p=0.01). More in detail, in-hospital mortality was higher in patients in shock (6 patients, 37.5%). The remaining 80 patients survived were discharged from hospital and all received oral anticoagulant therapy.

As regards the impact on in-hospital clinical events of laboratory experience in performing ART, a lower rate of major bleeding was observed in patients treated after the first 24 months (21.4% vs 5.2%, p=0.03) (Table 2),

Table 2.

In-hospital clinical events observed in patients treated with AngioJet Rheolytic Thrombectomy in the first 24 months compared to those treated after the first 24 months of activity.

Осложнения среди пациентов, которым РТЭ была выполнена в первые 2 года работы лаборатории и спустя 2 года после начала работы.

	N=91	First period Первый период (⩽24 months) N=14	Second period Второй период (>24 months) N=77	p
Major bleeding Большие кровотечения, n(%)	7 (7.7)	3 (21.4)	4 (5.2)	0.03
Minor bleeding Малые кровотечения, n (%)	10 (11)	1 (7.1)	9 (11.7)	0.6
Minimal bleeding Незначительные кровотечения, n(%)	9 (20.9)	5 (35.7)	14 (18.2)	0.1
Renal failure Почечная недостаточность, n (%)	13 (14.3)	4 (28.6)	9 (11.7)	0.8
Severe thrombocytopenia Тяжелая тромбоцитопения, n (%)	5 (5.5)	1 (7.1)	4 (5.2)	0.09
Recurrent pulmonary embolism Повторная ТЭЛА, n (%)	1 (1.1)	0 (0)	1 (1.3)	0.6
In-hospital mortality Госпитальная летальность, n (%)	11 (12.1)	3 (21.4)	8 (10.4)	0.2

being the patients' risk profile (mean age and number of patients in shock) similar in the two periods of activity (69.0±11.9 vs 67.1±14.5 years, p=0.6 nad 28.6% vs 15.6%, p=0.2 respectively), but with a higher rate of loco-regional fibrinolytic infusion in the first period of activity (35.7% vs 11.7%, p=0.02).

Discussion

PE is a common cardiovascular disease with significant morbidity and mortality, particularly during the in-hospital phase (3), and despite major research efforts, management is still suboptimal in many patients. Up to half of high-risk PE patients are not candidates for the recommended therapies, such thrombolysis or surgical embolectomy, when thrombolysis is contraindicated or failed (12,13). Actually, thrombolysis, despite it is associated with early reperfusion, decrease in pulmonary pressure and limitation of the extent of RV dysfunction in high-risk PE patients, have been associated, particularly in high-risk PE patients, with a significant risk of major bleeding (8–22%), especially intracranial bleeding (3%) (3,14,15). Furthermore, even in selected patients without absolute contraindications to thrombolysis, up to 20% of major hemorrhages and 3% to 5% of intracranial bleeding complications have been reported (3,16). Finally, even when thrombolysis is feasible, mortality remains exceedingly high in treated patients (52.4%) (17). On the other hand, the alternative option to thrombolysis, surgical pulmonary embolectomy, carries a mortality rate extremely variable, ranging from 11 to 30%, and despite the recent improvement in surgical outcomes, it is available only in few highly specialized centers (18-20). Anticoagulation is the recommended therapy for intermediate-risk PE patients (1,2). However, there is growing evidence that some patients among those at intermediate-risk are at higher risk with poor prognosis. The 30-day mortality in these patients could be as high as 15–20%, with a 10% of cases progressing to cardiogenic shock. The presence of RV dysfunction on echocardiography and elevated troponins, have been associated in non high-risk PE patients with a higher mortality with an odds ratio for short-term mortality of 2.53 (95% CI 1.17 to 5.50) (21) and 5.90 (95% CI 2.68 to 12.95) (22) respectively. Thus, decision making regarding whether more aggressive treatment is required in these patients, is difficult. In the MAPPET-3 study where patients with acute PE and pulmonary hypertension or RV dysfunction but without arterial hypotension or shock were enrolled, intravenous thrombolysis compared to standard treatment with heparin reduced the rate of clinical deterioration but not the rate of death (23). The PEITHO study (the Pulmonary EmboIism THrOmbolysis Study [PEITHO]; ClinicalTrials.gov Identifier NCT00639743) has been designed to assess the benefit of thrombolysis with tenecteplase as compared with anticoagulation in hemodynamically stable patients with RV dysfunction confirmed by echocardiography or spiral CT of the chest and a positive troponin test. The available preliminary results (5) report a significant reduction of the primary composite endpoint of all-cause mortality or haemodynamic collapse within 7 days in the group of patients treated with thrombolysis (2.6% vs 5.6%, p=0.015). This result however, was again main-

ly driven by the reduction of haemodynamic collapse (1.6% vs 5.0%, p=0.002) rather than by the reduction of mortality which was not significant (1.2% vs 1.8%, p=0.43). Patients treated with thrombolysis showed a significantly higher rate of major bleedings (6.3% vs 1.5%, p<0.001). Therefore, the net clinical benefit of thrombolysis in patients with intermediate-risk acute PE appears questionable because of bleeding concerns. Risk stratification of patients appears to be crucial, in that some intervention is needed to prevent the not unfrequent haemodynamic deterioration. If the PEITHO study results will be confirmed, thrombolysis probably is not going to be recommended for the treatment of intermediate-risk acute PE. In contrast, percutaneous thrombectomy might be considered instead of thrombolysis even for patients with intermediate-risk PE, mostly because of the observed efficacy in thrombus dissolution with no increase in major bleeding. No ongoing nor planned clinical trials are however investigating the potential role of percutaneous techniques in this patient subgroup, thus the role of percutaneous thrombectomy in this setting remains under debate.

Since many patients with major PE are ineligible for systemic thrombolysis or surgical embolectomy, or may benefit from aggressive therapies on top of anticoagulation, and promptly restoration of pulmonary flow is essential for better outcomes, percutaneous thrombectomy is an appealing alternative and is becoming part of the treatment options for the management of major PE. European Guidelines for management of PE (1) consider percutaneous thrombectomy an alternative to surgical treatment in high-risk patients when thrombolysis is contraindicated or has failed. Moreover, the recent American Guidelines states that percutaneous thrombectomy may be considered for patients with “submassive” acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction or major myocardial necrosis – Class IIb, Loe C) (2).

Catheter intervention techniques can de divided into three categories based on their mechanism of action: thrombus fragmentation, rheolytic thrombectomy and suction thrombectomy. The main objective of the different percutenous thrombectomy techniques is to eliminate central thrombi or fragment them so that they migrate to more distal branches, thus alleviating main pulmonary obstruction, which allows both an improved perfusion and a reduction of right ventricular pressure overload (24). The ART system (MEDRAD, INC., Warrendale, PA, USA) is a rheolytic device, which use the Bernoulli phenomenon, whereby a low-pressure zone is created around the catheter by the high speed retrograde saline jet. This results in mechanical disruption, aspiration, and retrieval of the surrounding thrombus.

To date, few data have been reported on the use of the ART for the treatment of high and intermediate-risk PE (Table 3) (8, 25–31). Overall, ART resulted effective in significantly improving the angiographic and hemodynamic parameters, with an in-hospital mortality up to 30%, either when AngioJet was used alone or in association with loco-regional thrombolysis, and with a rate of bleeding complications ranging from 0% to 31.2%.

The aim of our study was to provide more data in an attempt to confirm the effectiveness of ART in the treatment of high and intermediate-risk PE patients. Our data confirm the feasibility, efficacy and relative safety of ART in the treatment of acute PE, either high or intermediate-risk. Technical success was achieved in >90% of cases and in-hospital adverse events rate was generally low. In patients with intermediate-risk PE early mortality ranges from 8 to 17% (3,32), whereas in those with high-risk PE treated with heparin or thrombolysis is at least in the order of 10–50% (17) and may be as high as 65% in untreated patients (12). The in-hospital mortality in our series was 12.1%, therefore comparing favorably with the above figures, especially considering that 63,6% of patients who subsequently died presented with high-risk PE. Moreover, in intermediate-risk PE patients mortality rate was 6,3%, lower than the one reported in literature.

Percutaneous thrombectomy holds the promise of effective thrombus clearing minimizing bleeding adverse events. In our series, 39.6% of patients showed contraindications to fibrinolytic therapy, of whom 13 had high-risk PE (46.4% of all patients with high-risk PE). In our series, in-hospital rate of major bleeding was 7.7%. Published data on patients with acute PE who were treated with thrombolysis, report a rate of major bleeding up to 11–28% (17,33,34). Bleeding occurring in the setting of ART may be related to the presence of comorbidities resulting in a higher bleeding risk (i.e. malignancy), to vascular access complications or to issues related to the device (i.e. hemolysis, hemoptysis, and blood aspiration). It must be acknowledged, that in our series a low rate of major bleeding was observed, whereas we reported a no unimportant rate of minor and minimal bleeding (31.9%). This could be due to the use of AngioJet, but it also could be related to the high baseline bleeding risk of our population.

Laboratory and operator caseload and experience may influence the outcome of patients with acute PE treated with ART. As previously demonstrated (8) we confirm, in the light of the results of the present analysis, that 24 months and 14 patients treated represent the minimum required experience to effectively and safely use AngioJet in pulmonary intervention. We attribute our improved technical success and reduced procedural complications to several factors including: early recognition and treatment of patients who are otherwise ineli-

Table 3.

Prior reports of AngioJet use for acute pulmonary embolism
Наблюдения использования РТЭ для лечения ТЭЛА

	n	Clinical status Тип ТЭЛА	Reason for ART Причина выполнения РТЭ	Loco-regional TL Локальный тромболизис	Hemodynamic improvement Гемодинамическое улучшение	Angiographic improvement Ангиографическое улучшение	In-hospital mortality/complications Госпитальная смертность/осложнения
Koning 1997	2	Massive PE Массивная	Contraindication to thrombolysis Тромболизис противопоказан	No Нет	Yes Да	Yes Да	None Нет
Voigland er 1999	5	Massive PE Массивная	Contraindication to thrombolysis Тромболизис противопоказан	No Нет	Yes Да	3 patients 3 пациентов	Mortality/Смертность: 20%; Bleedings /Кровотечения: 20% (hemoptysis/ кровохарканье)
Zeni 2003	17	Massive PE Массивная	Contraindication to thrombolysis in 6 pts Тромболизис противопоказан	10 pts 10 пациентов	Not reported	16 patients 16 пациентов	Mortality/ Смертность: 11.7%; Bleedings/ Кровотечения: 5.8% (hemoptysis/кровохарканье)
Chauhan 2007	14	Massive PE Массивная (10 pts) and Submassive PE субмассивная (4 pts)	Contraindication to/failed thrombolysis Тромболизис противопоказан/ неэффективный тромболизис	5 pts 5 пациентов	Yes Да	Yes Да	Mortality /Смертность: 21.4%; Bleedings/Кровотечения: 28.5%
Arzamendi 2009	10	Massive PE Массивная	Contraindication to thrombolysis Тромболизис противопоказан	2 pts 2 пациентов	Yes Да	Yes Да	Mortality /Смертность: 30%; no bleedings/ Кровотечений нет
Chechi 2009	51	Massive PE Массивная (22 pts) and Sub-assive PE субмассивная (29 pts)	Ineligibility to thrombolysis for massive PE patients Не подходят для тромболизиса	11 pts 11 пациентов	Yes Да	Yes Да	Mortality /Смертность: 15.7%; Bleedings/ Кровотечения: 7.8% (major bleedings/ большие кровотечения)
Ferrigno 2011	16	Massive PE Массивная (5 pts) and Sub-assive PE субмассивная (11 pts)	Contraindication to thrombolysis Тромболизис противопоказан	16 pts 16 пациентов	Yes Да	Yes Да	Mortality /Смертность: 6.2%; Bleedings /Кровотечения: 31.2%
Hubbard 2011	11	Massive PE Массивная	Contraindication to thrombolysis in 2 pts Тромболизис противопоказан	9 pts 9 пациентов	Yes Да	Yes Да	Mortality /Смертность: 9%; Bleedings /Кровотечения: 9% (minor bleeding/ малые кровотечения)

ART: *AngioJet rheolytic thrombectomy; TL: thrombolysis, PE: pulmonary embolism; Pts: patients.*

gible or insufficiently treated with current treatment options; emphasis on «clot debulking» to restore distal perfusion rather than «clot resolution»; and lesser use and lower doses of adjunctive local trombolysis.

Conclusion

ART appears to be a promising treatment option for patients with major PE who are not eligible or insufficiently treated with current treatment options. Large ran-

domized clinical trials must be pursued to assess the safety, efficacy and long-term outcomes of rheolytic thrombectomy, alone or in combination with low-dose in situ thrombolysis, for the treatment of high and intermediate-risk PE.

Limitations

The main limitations of our study are those typical of any cohort study on new clinical applications of interventional devices (35). Because of the relatively small sample size of our population and the retrospective kind of analysis, large-scale, prospective clinical studies are warranted to confirm and expand our observations. Moreover, the population studied was heterogenous. Our series included 63 patients who had intermediate-risk PE, and the role of aggressive treatment is controversial in this group, and 28 patients with high-risk PE and contraindications to systemic fibrinolytic therapy, so that our results can only be applied to this subset of patients.

Finally, some patients underwent adjunctive local thrombolytic therapy that interferes with the evaluation of the pure effect of ART. We believe that patients with major PE should be evaluated by a multidisciplinary team, and ART should be performed by experienced operators in a timely fashion in a facility capable of dealing with significant medical and surgical emergencies. ■

References

1. Torbicki A., Perrier A., Konstantinides S. et al. Guidelines on the diagnosis and management of acute pulmonary embolism. The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *European Heart Journal* 2008(29):2276–2315.
2. Jaff M.R., McMurtry S., Archer S. et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011(123):1788–1830.
3. Goldhaber S.Z., Visani L., De Rosa M. Acute pulmonary embolism: Clinical outcomes in the international cooperative pulmonary embolism registry (ICOPER). *Lancet.* 1999;353:1386–1389.
4. Kucher N., Goldhaber S.Z. Management of massive pulmonary embolism. *Circulation.* 2005; 112:e28–e32.
5. Pulmonary embolism thrombolysis study (PHEITO). From ACC 2013.
6. Biederer J., Schoene A., Reuter M., Heller M., Muller-Hulsbeck S. Suspected pulmonary artery disruption after transvenous pulmonary embolectomy using a hydrodynamic thrombectomy device: clinical case and experimental study on porcine lung explants. *J .Endovasc. Ther.* 2003;10:99 –110.
7. Vecchio S., Vittori G., Chechi T. et al. Trombectomia reolitica percutanea con AngioJet nell'embolia polmonare: metodologia e risutati nell'esperienza di un centro ad alto volume. *G.Ital.Cardiol.* 2008;9(5):355–363.
8. Chechi T., Vecchio S., Spaziani G. et al. Rheolytic thrombectomy in patients with massive and submassive acute pulmonary embolism. *Catheter Cardiovasc. Interv.* 2009;73:506–513.
9. Bush R.L., Lin P.H. Percutaneous Mechanical Thrombectomy combine with Thrombolysis for the Treatment of Deep *Venous. Thromboses. Vasc. Disease Manage.* 2004;1:30-32.
10. Miller G.A., Sutton G.C. Kerr I.H., Gibson R.V., Honey M. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. Br. Med. J. 1971;2:681–4.
11. Chesebro J.H. Thrombolysis in myocardial infarction (TIMI) trial, phase I: A comparison between intravenous tissue plasminogen activator and intravenous stroptokinase. Clinical findings through hospital discharge. *Circulation.* 1987;76:142–154.
12. Konstantinides S., Geibel A., Olschewski M. et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: Results of a multicenter registry. *Circulation.* 1997;96:882–888.
13. Terrin M. Goldhaber S.Z., Thompson B. Selection of patients with acute PE for thrombolytic therapy: Thrombolysis in PE (TIPE) patients survey. The TIPE investigators. *Chest.* 1989;95(Suppl 5):279–S–281S.
14. Levine M.N. Thrombolytic therapy for venous thromboembolism. Complications and contraindications. *Clin. Chest Med.* 1995;16:321–328.
15. Wan S., Quinlan D.J., Agnelli G., Eikelboom J.W. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: A meta-analysis of the randomized controlled trials. *Circulation.* 2004;110:744–749.
16. Fiumara K., Kucher N., Fanikos J., Goldhaber S.Z. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. *Am.J.Cardiol.* 2006;97:127–129.
17. Kucher N., Rossi E., De R.M., Goldhaber S.Z.

Massive pulmonary embolism. *Circulation*. 2006; 113:577–82.
18. Gulba D.C., Schmid C., Borst H.G. et al. Medical compared with surgical treatment for massive pulmonary embolism. *Lancet*. 1994;343:576–577.
19. Aklog L., Williams C.S., Byrne J.G., Goldhaber S.Z. Acute pulmonary embolectomy: A contemporary approach. *Circulation*. 2002;105:1416–1419.
20. Stein P.D., Alnas M., Beemath A., Patel N.R. Outcome of pulmonary embolectomy. *Am.J.Cardiol*. 2007;99:421–423.
21. Sanchez O., Trinquart L., Colombet I., Durieux P, Huisman M.V., Chatellier G., Meyer G. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *Eur.Heart J*. 2008;29: 1569 –1577.
22. Becattini C., Vedovati M.C., Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*. 2007;116:427–433.
23. Konstantinides S., Geibel A., Heusel G. et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N.Engl.J.Med*. 2002;347:1143–1150.
24. Uflacker R. Interventional therapy for pulmonary embolism. *J. Vasc. Interv. Radiol*. 2001; 12:147–164.
25. Koning R., Cribier A., Gerber L. et al. A new treatment for severe pulmonary embolism: percutaneous rheolytic thrombectomy. *Circulation*. 1997; 96:2498–500.
26. Voigtlander T., Rupprecht H.J., Nowak B., Post F., Mayer E., Stahr P., Bickel C., Meyer J. Clinical application of a new rheolytic thrombectomy catheter system for massive pulmonary embolism. *Catheter Cardiovasc.Interv*. 1999;47:91–96.
27. Zeni P.T Jr., Blank B.G., Peeler D.W. Use of rheolytic thrombectomy in treatment of acute massive pulmonary embolism. *J.Vasc.Interv.Radiol*. 2003;14:1511–1515.
28. Chauhan S., Kawamura A. Percutaneous rheolytic thrombectomy for large pulmonary embolism: a promising treatment option. *Catheter Cardiovasc. Interv*. 2007;70:121–128.
29. Arzamendi D., Bilodeau L., Ibrahim R. et al. Role of rheolytic thrombectomy in massive pulmonary embolism with contraindication to systemic thrombolytic therapy. *Eurointervention*. 2009;5:716–21.
30. Ferrigno L., Bloch R., Threlkeld J. et al. Management of pulmonary embolism with rheolytic thrombectomy. *Can. Respir. J*. 2011;18:e52-e58.
31. Hubbard J., Saad W.EA., Sabri S.S. et al. Rheolytic thrombectomy with or without adjunctive indwelling pharmacolysis in patients presenting with right heart strain and/or pulseless electrical activity. Thrombosis 2011.
32. Kasper W., Konstantinides S., Geibel A., Olschewski M., Heinrich F., Grosser K.D., Rauber K., Iversen S., Redecker M., Kienast J. Management strategies and determinants of outcome in acute major pulmonary embolism: Results of a multicenter registry. *J.Am.Coll.Cardiol*. 1997;30:1165–1171.
33. Meyer G., Sors H., Charbonnier B. et al. Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: A European multicenter double-blind trial. *J.Am.Coll.Cardiol*. 1992;19:239–245.
34. Sors H., Pacouret G., Azarian R. et al. Hemodynamic effects of bolus versus two hour infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. *Chest*.1994;106:712–717.
35. Biondi-Zoccai G.G.L., Abbate A., Agostoni P. Parallel hierarchy of clinical research in cardiovascular medicine. *Ital.Heart J*. 2003;4:819–820.

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