Management of high risk pulmonary embolism — a single center experience

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Abstract: B a c k g r o u n d   a n d   A i m: Patients with acute pulmonary embolism (APE) associated with hemodynamic instability, i.e. high-risk APE (HR-APE), are at risk for early mortality and require urgent reperfusion therapy with thrombolysis or embolectomy. However, a considerable proportion of HR-APE subjects is not reperfused but only anticoagulated due to high bleeding risk. The aim of the present study was to assess the management of HR-APE in a single large-volume referral center.
M e t h o d s: A single-center retrospective study of 32 HR-APE subjects identified among 823 consecutive patients hospitalized for symptomatic APE.
R e s u l t s: Out of 32 subjects with HR-APE (19 women, age 69 ± 19 years), 20 patients were unstable at admission and 12 subsequently deteriorated despite on-going anticoagulation. Thrombolysis was applied in 20 (62.5%) of HR-APE subjects, limited mainly by classical contraindications in the remainder. Percutaneous pulmonary embolectomy was performed in 4 patients. In-hospital PE-related mortality tended to be higher, albeit insignificantly, in the patients who developed hemodynamic collapse during the hospital course compared to those unstable at admission (67% vs. 40%, p = 0.14). Also, survival was slightly better in 22 patients treated with thrombolysis or percutaneous embolectomy in comparison to 10 subjects who received only anticoagulation (54% vs. 40%, p = 0.2). Major non-fatal bleedings occurred in 7 of 20 patients receiving thrombolysis (35%) and in 2 (17%) of the remaining non-thrombolysed 12 HR-APE subjects.

Conclusions: Hemodynamically instability, corresponding to the definition of HR-APE, affects about 4% of patients with APE, developing during the hospital course in approximately one-third of HR-APE subjects. As almost 40% of patients with HR-APE do not receive thrombolytic therapy for fear of bleeding, urgent percutaneous catheter-assisted embolectomy may increase the percentage of patients with HR-APE undergoing reperfusion therapy. Further studies are warranted for a proper identification of initially stable intermediate-risk APE subjects at risk of hemodynamic collapse despite appropriate anticoagulation.

Key words: acute pulmonary embolism, high-risk pulmonary embolism, thrombolysis, embolectomy.

Introduction

Clinical manifestations of acute pulmonary embolism (APE) may vary from mild dyspnea to sudden cardiac death. Short term prognosis in APE is largely related to hemodynamic status. Hemodynamic collapse is a major risk factor for early mortality which exceeds 15% [1, 2]. According to the current European guidelines, this high risk group requires urgent reperfusion therapy with thrombolysis or pulmonary embolectomy. However, despite a significant reduction of in-hospital APE-related mortality in thrombolysed high risk patients [3, 4], a considerable proportion of hemodynamically unstable APE patients do not receive reperfusion therapy [5, 6], mostly due to high bleeding risk. There is an increasing evidence on potential value of percutaneous catheter-assisted embolectomy in the management of patients with HR-PE and even a subgroup of intermediate-risk APE [7–9].

Our aim was to assess therapeutic strategy in HR-APE pulmonary embolism in a high-volume APE referral center.

Materials and Methods

A single-center retrospective study was based on the analysis of medical records of consecutive patients managed in our referral center for symptomatic APE from January 2006 until June 2017.

Diagnosis of pulmonary embolism

APE was confirmed by contrast-enhanced multi-slice computed tomography (MSCT), when thromboemboli were visualized at least at the level of segmental pulmonary arteries or — in case of inconclusive MSCT findings — on the basis of a positive lower-limb venous compression ultrasound. MSCT angiography was performed using 64-row Toshiba Aquilion (Toshiba Medical Systems, Otawara, Japan) or 16-row GE LightSpeed Pro systems (General Electric Medical Systems,

Waukesha, Wisconsin, USA). The ultrasonographic lower-limb compression test was performed with a Philips XD11XE system (Philips Medical Systems, Best, the Netherlands). APE was diagnosed when a history of PE symptoms was no longer that 14 days prior to diagnosis. In hemodynamically unstable patients in whom MSCT was not immediately available, PE diagnosis was established by the suggestive clinical manifestations and right ventricular overload with typical findings on urgent transthoracic echocardiography [10]. In the remaining patients, transthoracic echocardiography after APE diagnosis was performed within 24 hours. Right ventricular (RV) dysfunction was defined as dilatation of the right ventricle (right/left ventricle diameter ratio >0.9 in the subcostal or apical four chamber view) combined with an absence of the inspiratory collapse of the inferior vena cava or an elevated systolic gradient through the tricuspid valve (>30 mm Hg), in addition to the lack of relevant left ventricular dysfunction or valvular heart disease. Typical echocardiographic findings included the McConnell sign, the 60/60 sign, and right heart thrombus [10]. Very interesting methods that can enrich and facilitate the diagnostic process are pocket-size imaging devices (PSID) [11]. Filipiak-Strzelecka *et al.* present that four-point compression venous ultrasonography and right ventricular size assessment with the use of PSID equipped with dual probe could positively influence the accuracy of clinical predictions.

Severity of Pulmonary Embolism

HR-APE was defined as shock or hypotension on admission with systolic blood pressure below 90 mm Hg and signs of peripheral hypoperfusion, if not caused by new arrhythmia, sepsis, or hypovolemia. Intermediate risk-APE was defined as systemic systolic blood pressure on admission ≥90 mm Hg with echocardiographic right ventricular overload and/or elevated serum levels of cardiac biomarkers: troponin T or N-terminal pro-B-type natriuretic peptide (NT-proBNP) [1, 2]. Low-risk APE was diagnosed in hemodynamically stable patients without right ventricular overload on cardiac imaging and with normal levels of cardiac biomarkers.

Treatment

Treatment decisions followed current ESC guidelines [1, 2]. High-risk APE was considered an indication for systemic thrombolysis (infusion of recombinant tissue plasminogen activator (rtPA) — either 100 mg over 1 h, or 0.6 mg/kg body mass, maximum 50 mg over 15 min). Hemodynamic deterioration in initially hemodynamically stable patients was also considered an indication for thrombolysis. In all cases, thrombolytic treatment was administered if deemed appropriate by the attending physician.

In HR-APE patients with contraindications to rtPA or after unsuccessful thrombolysis percutaneous pulmonary embolectomy with an Angiojet Thrombectomy System (Boston Scientific) was used since May 2016. The decision to perform percutaneous embolectomy was made by a dedicated PE response team which included an invasive cardiologist, intensivist and general cardiologist. After invasive therapy all patients received intravenous unfractionated heparin, followed by a body mass-adjusted dose of low-molecular weight heparin. Non-HR-APE patients were initially anticoagulated with low-molecular weight heparin. All intermediate-risk APE patients were monitored in our intensive care unit for at least 24 hours. During the hospitalization, oral vitamin K antagonist (international normalized ratio, INR: 2.0–3.0) or non-vitamin K oral antagonists (NOACs) were initiated unless contraindicated.

Study outcome

The cause of death was adjudicated by three of the authors (AF, MK, PP) by reviewing the patients' medical records and the results of autopsy if performed. Death was determined to be PE-related if it was confirmed by autopsy, or if it followed a clinically severe PE episode, either immediately or shortly after an objectively confirmed recurrent event, in the absence of an alternative diagnosis. Non-PE-related death included fatal bleeding, sepsis, progression of advanced neoplastic disease. Bleeding complications were defined according to ISTH criteria [12, 13].

Statistical analysis

Data are expressed as means followed by standard deviations or numbers with percentages. A chi-squared and Wilcoxon test were used to assess intergroup differences in dichotomized and continuous characteristics, respectively. A *P*-value below 0.05 was considered significant.

Results

Between January 2006 and June 2017, 823 consecutive APE patients (454 women, 369 men, aged 64 ± 19 years) were managed in our department. In 32 cases (3.9%) (19 women, 13 men; age 69 ± 19 years) HR-APE was diagnosed. In 27 of them APE was diagnosed with MSCT, while in 5 subjects APE by means of transthoracic echocardiography. In 542 patents (320 women, 222 men; age, 67 ± 17 years) the diagnosis of intermediate-risk APE was established, while the remaining 249 subjects formed a low-risk APE group (128 women, 121 men; age, 56 ± 19 years).

HR-APE patients included 20 patients hemodynamically unstable at admission, while 12 (2.2%) subjects, without hypotension at baseline, were initially diagnosed with

intermediate-risk APE and developed hemodynamic instability later despite full-dose anticoagulation. Of note, 9 out of these 12 patients deteriorated due to progressive right ventricular dysfunction during the first 24 hours of the index hospitalization, whereas 3 others, exhibiting multiple severe comorbidities, experienced a severe episode of recurrent APE after more than 7 days with consequent hemodynamic collapse (Table 1).

Table 1. Patients' characteristics.

Characteristic	Patients with HR-APE at admission n = 20	p	Patients with intermediate-risk APE at admission who deteriorated during the hospitalization n = 12	All HR-APE patients n = 32
Women/Men, n	13/7	ns	6/6	19/13
Age, years	76 ± 12	0.08	65 ± 20	71 + 18
Presence of coexisting diseases, n (%)	8 (40%)	ns	4 (33.3%)	12 (38%)
Thrombolysis, n (%)	10 (50%)	0.07	10 (83%)	20 (63%)
Percutaneous embolectomy, n (%)	3 (19%) (1 patient after unsuccessful thrombolysis)	ns	1 (6%) (1 patient after unsuccessful thrombolysis)	4 (12%)
PE-related mortality, n (%)	8 (40%)	0.14	8 (67%)	16 (50%)
Major bleeding, n (%)	5 (25%)	ns	4 (33%)	9 (28%)

Coexisting diseases: chronic obstructive pulmonary disease, chronic heart failure, active cancer; HR-APE: high-risk pulmonary embolism.

Treatment and clinical course

Thrombolytic therapy was used in 20 patients with HR-APE (62.5%), while 12 remaining subjects had coexistent conditions considered absolute contraindications to thrombolysis, including an episode of active major bleeding, recent major surgery, structural intracranial diseases or severe comorbidities resulting in high risk of bleeding. Two patients who experienced high risk APE in the first day after major surgery, were directly referred for percutaneous pulmonary embolectomy. In addition, rescue pulmonary embolectomy was performed in 2 other patients after failed thrombolysis. In sum, 22 (69%) patients with HR-APE received reperfusion therapy (Table 2).

Table 2. Characteristic of HR-APE patients according to PE-related death.

Characteristic	Survivors n = 16	p	Non survivors n = 16
Women/Men, n	9/7	ns	10/6
Age, years	64 ± 21	0.01	79 ± 9
Presence of coexisting diseases, n (%)	5 (31%)	ns	7 (44%)
Thrombolysis, n (%)	10 (63%)	ns	10 (63%)
Percutaneous embolectomy, n (%)	3 (19%) (1 patient after unsuccessful thrombolysis)	ns	1 (6%) (1 patient after unsuccessful thrombolysis)
Major bleeding, n (%)	6 (38%)	0.2	3 (19%)

In-hospital PE-related mortality was 50% in the whole group of 32 HR-APE subjects. The prognosis tended to be worse, albeit insignificantly, in the patients who were without hypotension at admission and developed hemodynamic collapse during the hospital course, as compared to those unstable at the beginning of the hospitalization (PE-related mortality risk: 67% versus 40%, $p = 0.14$) (Table 2). Also, the survival was slightly better ($p = 0.2$) in 22 patients treated with thrombolysis or percutaneous embolectomy (54%) in comparison to 10 subjects who received only anticoagulation (40%). As expected, survivors were significantly younger than non-survivors (Table 2).

Major non-fatal bleedings occurred in 7 of 20 patients receiving thrombolysis (35%) and in 2 (17%) of the remaining 12 HR-APE subjects. Out of 9 major non-fatal bleeding events, 7 (78%) occurred in 20 patients undergoing thrombolysis and 2 (22%) in the remaining 12 non-thrombolysed HR-APE subjects (Table 3).

Table 3. Bleeding events in HR-APE patients.

	Major bleeding n = 9	Clinically relevant non-major bleeding n = 5	All bleeding events n = 14
Thrombolysis, n (%)	7 (78%)	3 (60%)	10 (71%)
Hematomas, n (%)	3 (33%)	3 (60%)	6 (43%)
Gastrointestinal, n (%)	1 (11%)	1 (20%)	2 (14%)
Retroperitoneal, n (%)	1 (11%)	0	1 (7%)
Respiratory system, n (%)	0	1 (20%)	1 (7%)
Bleeding with a fall in haemoglobin level of ≥20 g/l or leading to transfusion of red blood cells, n (%)	4 (44%)	0	4 (29%)

Discussion

Despite a significant progress in the management of APE, HR-APE, i.e. hemodynamic instability, still remains one of the most challenging acute cardiovascular clinical conditions. The prevalence of HR-APE our study group is consistent with previous reports, estimating the prevalence of HR-APE in up to 5–10% of all APE patients [1, 2, 14]. Interestingly, 20 patients with HR-APE were unstable at admission, while further 12 subjects did not present baseline hypotension and developed hemodynamic collapse during the hospitalization. Thus, 12 (2.2%) out of 545 intermediate-risk PE patients progressively deteriorated with subsequent hemodynamic instability despite parenteral anticoagulation, mostly due to progressive right ventricular failure within the first 24 hours.

Recent data on anticoagulated intermediate-risk APE patients in PEITHO study showed that 5% of subjects with both right ventricular dysfunction and evidence of myocardial injury (elevated troponin levels), but normotensive at admission — termed intermediate/high risk APE — developed hemodynamic decompensation within the first 7 days despite standard anticoagulation [15]. In addition, the PEITHO investigators observed a 2-fold reduction in the primary outcome (a composite of death or hemodynamic collapse at 7 days) in the patients randomized to thrombolytic therapy. Accordingly, that study, jointly with our observation, supports the necessity of a close monitoring of intermediate-risk APE subjects with right ventricular dysfunction, preferably for 24–48 hours [1, 2], as well as consideration of a more aggressive therapeutic approach.

According to the current practice guidelines, primary reperfusion therapy by means of systemic thrombolysis or embolectomy is recommended in HR-APE [1, 2]. However, such aggressive therapeutic modalities remain still underused. Thrombolysis was applied in 40–50% of unstable HR-APE patients [5, 14], while the availability of surgical or percutaneous embolectomy is very limited. In the present series of patients, systemic thrombolysis was performed in 20 (62.5%) of HR-APE subjects, due to absolute contraindications to thrombolytic agents in the remainder. Since our previous data showed that the vast majority of high risk PE patients were anticoagulated only [6], we established a local PE response team. Since 2016, rescue urgent percutaneous pulmonary embolectomy was performed in 2 patients with HR-APE (APE within 24 hrs after major non-cardiac surgery), and in 2 others after unsuccessful intravenous thrombolysis.

In-hospital mortality in HR-APE is still unacceptably high and varies from 15 to 50% [1, 2, 16]. Importantly, it exceeds early mortality in ST-segment elevation myocardial infarction and is similar to that reported in cardiogenic shock accompanying an acute coronary syndrome [17, 18]. In our hands, PE mortality was slightly lower in 22 patients with HR-APE treated with systemic thrombolysis

or percutaneous embolectomy (46%), when compared to those on medical therapy only (60%) (p = 0.2).

In our opinion, percutaneous catheter-assisted embolectomy for urgent treatment of HR-APE patients with contraindications to thrombolysis or after unsuccessful thrombolysis should be available in referral centers of interventional cardiology. Moreover, a careful selection of intermediate-risk APE subjects who are risk of hemodynamic decompensation, appears a clinical challenge. Such patients might be eligible for systemic thrombolysis, embolectomy or catheter-directed thrombolysis, all the more because their prognosis tended to be worse in comparison to those unstable at admission (PE-related mortality risk: 67% vs. 40%, p = 0.14). Nevertheless, both a wider use of reperfusion therapy and its timing in non-HR-APE patients are still under debate.

Conclusions

Hemodynamically instability, consistent with HR-APE definition, affects about 4% of patients with APE, developing during the hospital course in approximately one-third of HR-APE subjects. As almost 40% of patients with HR-APE do not receive thrombolytic therapy for fear of bleeding, urgent percutaneous catheter-assisted embolectomy may increase the percentage of patients with HR-APE undergoing reperfusion therapy. Further studies are warranted for a proper identification of initially stable intermediate-risk APE subjects at risk of hemodynamic collapse despite appropriate anticoagulation.

Conflict of interest

None declared.

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