Original Article

Kathrin Dohle[a], Daniel-Sebastian Dohle[a], Hazem El Beyrouti*, Katja Buschmann, Anna Lena Emrich, Lena Brendel and Christian-Friedrich Vahl

Short- and long-term outcomes for the surgical treatment of acute pulmonary embolism

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Abstract

Objectives: Acute pulmonary embolism can be a life-threatening condition with a high mortality. The treatment choice is a matter of debate. The early and late outcomes of patients treated with surgical pulmonary embolectomy for acute pulmonary embolism in a single center were analyzed.

Methods: All consecutive patients operated on for pulmonary embolism between January 2002 and March 2017 were reviewed. Patient demographics and pre- and postoperative clinical data were retrieved from our patient registry, and risk factors for in-hospital and long-term mortality were identified.

Results: In total, 175 patients (mean age 59 ± 3 years, 50% male) were operated on for acute pulmonary embolism. In-hospital mortality was 19% (34/175). No differences were found when comparing surgery utilizing a beating heart or cardioplegic arrest. Risk factors for in-hospital mortality were age >70 years [odds ratio (OR) 4.8, confidence interval (CI) 1.7–13.1, p = 0.002], body surface area <2 m^2 (OR 4.7, CI 1.6–13.7, p = 0.004), preoperative resuscitation (OR 14.1, CI 4.9–40.8, p < 0.001), and the absence of deep vein thrombosis (OR 9.6, CI 2.5–37.6, p < 0.001). Follow-up was 100% complete with a 10-year survival rate of 66.4% in 141/175 patients surviving to discharge. Once discharged from hospital, none of the risk factors identified for in-hospital mortality were relevant for long-term survival except the absence of deep vein thrombosis (OR 3.2, CI 1.2–8.2, p = 0.019). The presence of malignancy was a relevant risk factor for long-term mortality (OR 4.3, CI 1.8–10.3, p = 0.001).

Conclusion: Surgical pulmonary embolectomy as a therapy for acute pulmonary embolism demonstrates excellent short- and long-term results in patients with an otherwise life-threatening disease, especially in younger patients with a body surface area >2 m^2 and pulmonary embolism caused by deep vein thrombosis. Pulmonary embolectomy should therefore not be reserved as a treatment of last resort for clinically desperate circumstances.

Keywords: pulmonary embolism; surgical embolectomy.

Introduction

Pulmonary embolism (PE) is a common clinical condition with a broad variety of clinical presentations, and an age- and race-dependent annual incidence of up to 88/100,000 patients [1]. It is responsible for 12% of all deaths in Europe [2].

As Trendelenburg's procedure is one of the oldest heart operations and PE was Gibbon's trigger to invent the heart-lung machine, as the prerequisite for modern heart surgery, PE is an important disease for the cardiac surgeon. Historical results were fatal until Kirschner was successful in 1924. Decades later, mortality remained high despite the support of cardiopulmonary bypass (CPB). Therefore, in the current European guidelines, surgical embolectomy is only recommended in high-risk patients with failed lysis or contraindications to lysis [3]. Although often used in clinically desperate circumstances, current literature demonstrates good short- and long-term results for surgical embolectomy – comparable with those of thrombolytic therapy. This gives rise to a new debate about the role of surgical embolectomy in the treatment of PE [4].

In this retrospective single-center study, we analyzed the early and late outcomes of surgical embolectomy among patients with acute PE, and analyzed predictors for in-hospital mortality and long-term survival.

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Patients and methods

Study population and data source

According to our center's protocol, patients transferred for PE are reviewed by a multidisciplinary team. Patients with massive embolism, hemodynamic instability, postresuscitation status, or failed lysis or contraindications to lysis are referred for surgical embolectomy. Approval from our Institutional Ethics Committee was obtained for this retrospective data analysis (2018-13098-Epidemiologie). The International Classification of Disease codes, tenth revision, were used to identify patients operated on for acute PE from our institutional database. In total, 175 adult patients were operated on for acute PE between January 2002 and March 2017 in our institution. Patients' demographics, clinical data, and follow-up details were retrieved from our institutional database and medical records. Patients' demographics, preoperative clinical status, comorbidities and risk factors for PE, surgical strategy and findings, as well as in-hospital and long-term outcomes were analyzed.

Surgical techniques

All patients were given heparin after median sternotomy and cannulated for CPB. Embolectomy was performed using mild hypothermic or normothermic CPB, with or without aortic cross clamp, according to the surgeon's preference. The main pulmonary artery was opened longitudinally and, if necessary, the incision was extended into the left main pulmonary artery. In some cases, an additional incision was made in the right main pulmonary artery between the ascending aorta and superior vena cava. Clots were extracted under direct vision using forceps and suction. Temporary reduction of CPB flow was occasionally needed for optimal visualization.

Statistical analysis

Statistical computations and Figures 2 and 3 were done using GraphPad Prism version 7.0a for Mac (GraphPad Software, La Jolla, CA, USA), Wizard Pro data analysis version 1.9.7 (Evan Miller, Chicago, IL, USA), and SPSS 22.0 for MAC (SPSS Inc., Chicago, IL, USA).

Normal assumption of continuous variables was validated using the Shapiro-Wilk test. If the assumption did not hold, the Wilcoxon signed-rank test was used. The influence of the identified variables on in-hospital mortality and long-term survival was analyzed with a multiple logistic regression model using the identified covariates. All statistical tests were two-sided with the alpha level set at 0.05 for statistical significance. All frequency data are presented as percentages, and all continuous data as mean ± standard deviation. The confidence interval (CI) is 95%.

Results

Patient population and characteristics (Table 1)

A total of 175 adult patients underwent surgical embolectomy for acute PE during the study period. The mean age was 59 ± 17.2 years, and 87 patients (50%) were men. The mean body surface area (BSA) was 2.04 ± 0.253 m^2 across all patients. PE was diagnosed with computed tomography (CT) angiography in 151 patients and echocardiography alone in 24 patients. Nearly all the patients had a massive thrombus volume (97%) located centrally or bilaterally in the main pulmonary arteries (94%). Further details are shown in Tables 1 and 2.

Risk factors for in-hospital mortality

The overall in-hospital mortality was 19% (34/175). The mean age of hospital survivors (HS group) was significantly lower compared to the group of patients who died

Table 1: Patient characteristics, including predisposing factors for lung embolism, in in-hospital survivors and patients deceased in hospital.

	Total (n = 175)	In-hospital survivors (n = 141)	In-hospital deaths (n = 34)	p-Value
Patient characteristics				
Age (years)	59.3 ± 17.2	57.7 ± 16.8	66.3 ± 17.1	**0.008**
Male	87 (50%)	74 (53%)	13 (38%)	0.136
BSA	2.04 ± 0.25	2.06 ± 0.26	1.96 ± 0.22	**0.036**
Predisposing factors for PE				
Coagulopathy	22 (13%)	20 (14%)	2 (6%)	0.19
Nicotine use	31 (18%)	27 (19%)	4 (12%)	0.311
Oral contraception	9 (5%)	9 (6%)	0 (0%)	0.13
DVT	70 (40%)	66 (47%)	4 (12%)	**<0.001**
Prior pulmonary embolism	11 (6.3%)	9 (6%)	2 (6%)	0.914
Malignancy	50 (29%)	38 (27%)	12 (35%)	0.334

Significant p-values are marked bold.

Table 2: Clinical status at the time of presentation, surgical strategy, and operative findings.

	Total (n = 175)	In-hospital survivors (n = 141)	In-hospital deaths (n = 34)	p-Value
Preoperative clinical status				
CPR	40 (23%)	19 (13%)	21 (62%)	**<0.001**
Shock	112 (64%)	10 (7.1%)	11 (32.4%)	**<0.001**
Respiratory insufficiency	23 (13%)	21 (15%)	2 (6%)	0.163
Failed preoperative lysis	11 (6.3%)	4 (3%)	7 (21%)	**<0.001**
Surgical findings and surgical strategy				
Central or bilateral thrombus	165 (94%)	134 (95%)	31 (91%)	0.384
Massive thrombus volume	169 (97%)	138 (98%)	31 (91%)	0.054
Cardioplegic arrest	103 (59%)	86 (61%)	17 (50%)	0.242
Beating heart	72 (41%)	55 (39%)	17 (50%)	0.242
Re-sternotomy	20 (11%)	12 (9%)	7 (21%)	0.035

Significant p-values are marked bold.

in hospital (IHD group, 57.7 ± 16.8 vs. 66.3 ± 17.1 years, p = 0.008). The mean BSA of the HS group was significantly higher compared to the IHD group (2.06 ± 0.26 vs. 1.96 ± 0.22 m^2, p = 0.036).

Almost two-third of the patients in the IHD group were under cardiopulmonary resuscitation (CPR) at the time of presentation, which was significantly more compared to the HS group (62% vs. 13%, p < 0.001; Table 2). Significantly more patients who had failed previous lysis therapy were found in the IHD group (21% vs. 6.3%, p < 0.001). The rate of deep vein thrombosis (DVT) was significantly higher in the HS group (47%) compared to the IHD group (12%, p < 0.001; Figure 1). No differences were found regarding the surgical technique used (with or without cardioplegic arrest), or in the size and distribution of the thrombus material.

In a multivariate logistic regression model, age >70 years [odds ratio (OR) = 4.8, CI 1.7–13.1, p = 0.002], BSA <2 m^2 (OR 4.7, CI 1.6–13.7, p = 0.004), preoperative resuscitation (OR 14.1, CI 4.9–40.8, p < 0.001), and non-DVT-associated lung embolism (OR 9.6, CI 2.5–37.6, p < 0.001) were found to be relevant risk factors for in-hospital death (Table 3). The receiver-operating characteristic analysis showed a good fitting of this model [area under curve (AUC) = 0.84, Figure 2]. Based on this model, the predicted in-hospital mortality rate for patients older than 70 years, with lower body mass (<2 m^2 BSA), without DVT, and post-CPR status was 56%. The predicted in-hospital mortality rate for younger patients (<70 years), with a higher body mass (>2 m^2 BSA), with DVT, and without preoperative CPR was only 3.5%.

Table 3: Multivariate logistic regression model with risk factors for in-hospital mortality.

Risk factor	OR	95% CI	p-Value
Age >70 years	4.8	1.7–13.1	**0.002**
BSA <2 m^2	4.7	1.6–13.7	**0.004**
Preoperative CPR	14.1	4.9–40.8	**0.001**
No DVT	9.6	2.5–37.6	**0.001**

Significant p-values are marked bold.

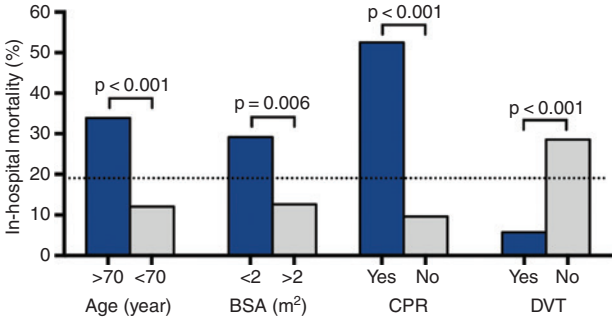

Figure 1: In-hospital mortality stratified for age, BSA, preoperative CPR, and DVT.

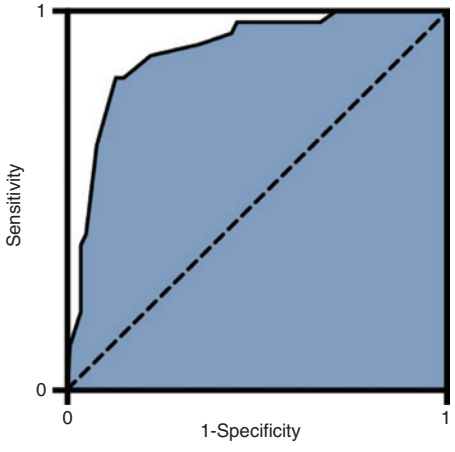

Figure 2: AUC of 0.84 demonstrating the good fitting of the chosen model.

Long-term results

The follow-up rate was 100% with a mean follow up time of 4.6 ± 3.3 years. The long-term survival rates of the HS group were 78% at 5 years and 66% at 10 years. Once discharged from the hospital, none of the risk factors identified for in-hospital mortality were relevant for long-term survival except for the absence of DVT (OR 3.2, CI 1.2–8.2, p = 0.019) or the presence of malignancy (OR 4.3, CI 1.8–10.3, p = 0.001; Figure 3). Approximately one-third of the PE patients without DVT were diagnosed with a malignant tumor. This was significantly more compared to those patients with a DVT (36% vs. 17%, p = 0.01). The 10-year survival rate of patients with a DVT and without cancer was 89%.

Discussion

In a nationwide US inpatient registry for surgical embolectomy after PE, including >2700 patients between 1999 and 2008, the overall mortality was 27.2% [5]. In a meta-analysis including 46 case series with 1300 patients, Stein et al. reported a mortality rate for surgical pulmonary embolectomy of 32% between 1961 and 1985, which declined to 20% between 1985 and 2005 [6]. Although these results look devastating, they should be considered in the context of the preoperative status of these patients assigned to surgical embolectomy with hemodynamic instability in 74% and preoperative cardiac arrest in 32%. Results from a German registry with >1000 patients treated non-surgically, with anticoagulation and thrombolysis alone, demonstrated mortality rates of 65% for patients with cardiac arrest, 25% for patients with cardiogenic shock, and 15% for patients with hypotension [7].

Our results, spanning a time period of 15 years from 2002, with an overall in-hospital mortality of 19%, are very similar to these meta-analysis and registry results. Like in other patient cohorts [6, 7], our in-hospital mortality was significantly higher in patients with cardiac arrest (53%) or cardiogenic shock (10%). By multivariate regression analysis, other significant risk factors could be identified. While age is always associated with more comorbidities and worse outcomes in cardiac surgery, our finding of a BSA of <2 m² and non-DVT-related PE as risk factors for in-hospital mortality are noticeable.

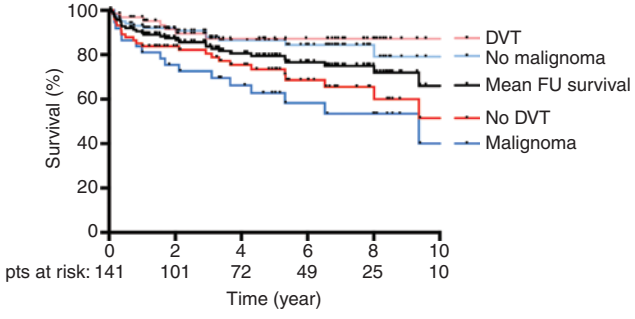

Figure 3: Kaplan-Meier survival curves of all patients, and then stratified for patients with or without DVT and with or without malignancy.

The paradox of lower mortality and morbidity in obese cardiac surgery patients is known and has recently been demonstrated in a meta- and registry analysis with >500,000 patients [8]. Thus far, no explanations have been proven but according to different hypotheses, higher BSA might reduce the diluting effects caused by extracorporeal circulation. Furthermore, relatively lower blood loss might prevent bleeding and its subsequent complications.

Non-DVT-related PE is often associated with a history of or a newly diagnosed cancer. Different retrospective studies and registries have proved an increased in-hospital mortality for acute PE in patients with cancer [9, 10]. Cancer is therefore a parameter in the PE severity index suggested by the current guidelines [3]. The different in-hospital mortality rates for DVT and non-DVT patients with acute PE might, *inter alia*, be caused by the natural history of the cancer, which is also demonstrated in our long-term results. Meanwhile, the thrombus architecture and mechanical characteristics of DVT and non-DVT thrombus might differ, as suggested by rare reports about the fibrin network in the surgically removed thrombus after PE in DVT patients [11, 12]. This might influence the technical success of surgical embolectomy and fibrinolytic agents.

According to the current European guidelines, early mortality risk-adapted treatment strategies are encouraged [3]. Primary reperfusion strategies with fibrinolytic agents in intermediate-risk patients showed no significant survival benefit but a significantly increased risk for major bleeding (11.5%), hemorrhagic stroke (2%) [13], and death [14]. Therefore, fibrinolysis is no longer recommended in intermediate-risk patients [15]. In high-risk patients, defined by shock or hypotension, systemic thrombolysis is currently the recommended treatment strategy. Surgical embolectomy is recommended if systemic thrombolysis is contraindicated (previous or current stroke, recent major surgery, or gastrointestinal bleeding) or has failed.

Interestingly, there is no evidence for the superiority of thrombolysis over surgical embolectomy in high-risk or intermediate-high-risk patients, while contemporary results for surgical embolectomy are improving and comparative studies show long-term benefits

for surgical embolectomy. In a recently published meta-analysis, including contemporary studies from 1998 until 2017 with 1101 surgical embolectomy patients and a preoperative cardiac arrest rate of 21%, the overall mortality rate was 14% and only 6.8% in patients were without preoperative CPR [16]. In a large retrospective study comparing the short- and long-term outcomes of 2111 patients undergoing thrombolysis (88%) or surgical embolectomy (12%), similar early mortality (15.2% vs. 13.2%) and 5-year survival rates (72.4% vs. 76.1%) were found despite the obviously different morbidity of the two groups and a significantly higher rate of recurrent PE after thrombolysis [17]. Another study comparing the postoperative results of systemic fibrinolysis and surgical embolectomy by single-photon emission CT found similar mortality rates but significantly less diffusion impairment after surgical embolectomy [18]. Other authors found significantly better right ventricular unloading after surgical embolectomy compared to systemic fibrinolysis, as measured using right ventricular diameter and pulmonary artery pressures [19].

With a growing body of evidence for a comparable safety profile, some authors suggest surgical embolectomy as the first-line therapy for patients with acute high- and intermediate-high-risk PE [4]. Like others [20], we see the urgent need for randomized controlled trials comparing the outcomes of surgical embolectomy with the current first-line treatment strategy. As our small retrospective study demonstrated, further differentiation of patients and their risk factors might lead to better patient-tailored treatment strategies. Most probably, surgical embolectomy should no longer be a treatment of last resort reserved only for clinically desperate circumstances.

Author Statement

Research funding: Authors state no funding involved. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent is not applicable.

Author Contributions

Daniel-Sebastian Dohle: Formal analysis; Methodology; Supervision; Writing – original draft; Writing – review & editing; Hazem El Beyrouti: Supervision; Validation; Katja Buschmann: Supervision; Anna Lena Emrich: Supervision; Lena Brendel: Supervision; Christian-Friedrich Vahl: Conceptualization; Supervision; Validation.

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Supplementary Material: The article (https://doi.org/10.1515/iss-2018-0024) offers reviewer assessments as supplementary material.
Article note: Presented at the 47th DGTHG (German Society for Thoracic and Cardiovascular Surgery) Annual Meeting, February 18, 2018.

Reviewer Assessment

Kathrin Dohle[a], Daniel-Sebastian Dohle[a], Hazem El Beyrouti*, Katja Buschmann, Anna Lena Emrich, Lena Brendel and Christian-Friedrich Vahl

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Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Sep 11, 2018

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	85

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	3
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	5 - High/Yes
Please rate the appropriateness of the figures and tables.	5 - High/Yes
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

The authors did a retrospective single-centre evaluation of 175 patients who underwent surgical embolectomy for acute pulmonary embolism. In-hospital mortality was about one fifth, two third of the initially surviving patients were alive at ten years.
The manuscript is clear-cut an well written. The results compare favourably to those in the literature and underline the take-home message to do embolectomy in patients with acute pulmonary embolism in selected subgroups.
One minor shortcoming is, why the authors do not explain why they used BSA rather than BMI for the estimation of body mass (the usefulness of BSA to determine the pump flow rate during cardiopulmonary bypass has been questioned recently).

Reviewer 2: anonymous

Aug 30, 2018

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	80

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	4
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

This is a manuscript, which describes a large series of patients who underwent surgical pulmonary embolectomy. The analysis is aimed at identifying prognostic factors for survival. The examined variables have been extensively analyzed in other publications on this subject, but the strength of this paper lies in the statistical power gained by an analysis of 175 contemporary patients. The paper is nicely written. The statistical evaluation is appropriate and complete. The discussion is well done and covers the important results. The conclusions they have drawn are valid.
However, I have some questions:
The indications for the surgical approach are needed to be clarified. A major weakness of this study is the lack of information on the time between onset of symptoms and treatment initiation. What was the time from admission to the operating room? Time is of the essence in these patients because of the serious hemodynamic burden. What diagnostic examination was done to confirm the diagnosis of pulmonary embolism? What is the denominator of all patients with PE and on what basis do you decide on a surgical procedure versus catheter-directed pulmonary embolectomy or localized thrombolysis?
How do you manage these patients postoperatively with anticoagulation?
Did you perform studies by transthoracic echocardiography to evaluate the right ventricular function pre- and postoperatively?
Based on your data, what is the specific role of surgical embolectomy and catheter-based thrombolysis?

Authors' Response to Reviewer Comments

Sep 17, 2018

Reviewer #1:
Question#1: Why using BSA rather than BMI for the estimation of body mass altough the usefulness of BSA to determine the pump flow rate during cardiopulmonary bypass has been questioned recently?
Answer#1: We thank the reviewer for this excellent question. While body mass index (BMI) is frequently used in studies investigating the association between obesity and outcome, body surface area (BSA) may be a preferable measure as it is better designed to account for the different densities of muscle and fat. Therefore BSA is usually the parameter pump flow rates during CPB are calculated. Nevertheless, both, BMI and BSA are calculated parameters from body height and weight and therefore closely correlated. Based on your comment we recalculated our results for BMI, but did not find any significant effect of BMI on in hospital mortality. Divided into two equal groups with 18 <bmi

Reviewer #2:
Question#1: What have been the indications for the surgical approach?
Answer#1: As described in the section study population and data source patients with massive embolism, hemodynamic instability, post resuscitation status, or failed- or contraindicated for lysis were referred for surgical embolectomy.
Question#2: Which period of time lapsed between onset of symptoms and treatment initiation?
Answer#2: Unfortunately, our database did not include the time of onset of symptoms, therefore we were unable to calculate the time until initiation of treatment. As patient files are only digitalized since 2010 data would be incomplete if we added this item.
Question#3: What was the time from admission to the operating room, because time is of the essence in these patients because of the serious hemodynamic burden?
Answer#3: We totally agree with the reviewer. According to our institutional protocol hemodynamic patients are directly admitted to the OR. Dependening on the time needed for transportation from different distances via helicopter or ambulance, times vary and are difficult to define clearly. Therefore, we were not able to include this important variable.
Question#4: What diagnostic examination was done to confirm the diagnosis of pulmonary embolism?
Answer#4: Diagnosis was made via CT-angiography in 151 patients. The remaining patients were diagnosed via echocardiography. A change was made in the section Patient population and characteristics.
Question#5: What is the denominator of all patients with PE and on what basis do you decide on a surgical procedure versus catheter-directed pulmonary embolectomy or localized thrombolysis?
Answer#5: According to our protocol patients referred for pulmonary embolism are seen by an interdisciplinary team of cardiologists and cardiac surgeons (Pulmonary Embolism Response Team, PERT). Today hemodynamically instable high risk patients are directly transferred to the OR or stabilized by ECLS implantation. High and low intermediate risk patients are treated by lysis or anticoagulation alone. Decisions are made case by case based on the risk factors and comorbidities within the PERT.
Question#6: How do you manage these patients postoperatively with anticoagulation?
Answer#6: Patients are anticoagulated orally for 6 month and reevaluated via CT thereafter.
Question#7: Did you perform studies by transthoracic echocardiography to evaluate the right ventricular function pre- and postoperatively?
Answer#7: Nearly every patient received intraoperative pre- and postoperative TEE, but the results have not yet been structured and included into our database. This structured evaluation is currently part of another project with our pulmonary embolism cohort.
Question#8: Based on your data, what is the specific role of surgical embolectomy and catheter-based thrombolysis?
Answer#8: In this current paper we only report about the results of surgical embolectomy. Our experience with catheter based therapy is limited. Especially with this retrospective cohort no clear comment about the role of catheter based lysis can be made. Based on the literature catheter based therapy seems to be a promising tool avoiding the surgical trauma. Nevertheless, only prospective randomized trials will show which patients benefit the most from either systemic or local lysis, endovascular thrombectomy or the surgical approach in high and intermediate high risk patients.

Reviewers' Comments to Revision

Reviewer 1: anonymous

Sep 19, 2018

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	85

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	4
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	5 - High/Yes
Please rate the appropriateness of the figures and tables.	5 - High/Yes
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:
The reviewers´suggestions have been met by the authors, the questions have been satisfactorily answered.

Reviewer 2: anonymous

Sep 22, 2018

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	70

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	4

Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	4
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	No: article should be accepted

Comments to Authors:
This is a rewritten manuscript of the first draft which seems now to be the final version. All previous remarks have been addressed and improvements were put in place.