Surgical pulmonary embolectomy and catheter-based therapies for acute pulmonary embolism: A contemporary systematic review

Check for updates

Pranav Loyalka, MD,[a] Muhammad Z. Ansari, MBBS,[b,c] Faisal H. Cheema, MD,[d] Charles C. Miller III, PhD,[b] Sudarshan Rajagopal, MD, PhD,[e] and Keshava Rajagopal, MD, PhD[b,c]

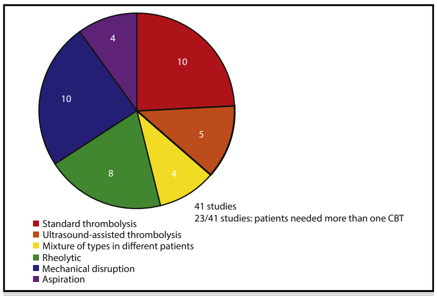
ABSTRACT

Objectives: Mortality in acute pulmonary embolism (PE) is believed to be principally due to the subgroup of PEs that are massive. Systemic thrombolysis is the therapeutic mainstay for acute massive PE, despite evidence suggesting limited survival benefits. Both catheter-based therapies (CBT) and surgical pulmonary embolectomy (SE) are well-accepted alternatives to treat acute PE. However, the comparative effectiveness of these approaches is difficult to study. We conducted a systematic review of CBT and SE for acute PE.

Methods: The PubMed database was queried for CBT- and SE-related publications between January 1998 and June 2017. A minimum of 10 patients undergoing intervention(s) was required for inclusion, and studies must not have excluded patients with massive PE. End points examined included hospital mortality, and additionally for CBT, procedural success rate.

Results: A total of 75 studies (41 of CBT, 34 of SE) were identified, with 1650 patients undergoing CBT and 1101 undergoing SE. Patients undergoing SE were more critically ill than those undergoing CBT (massive PE, 545 out of 975 [55.9%] for SE vs 742 out of 1553 [47.8%] for CBT). Cardiopulmonary resuscitation (CPR) was required in 217 out of 1015 patients undergoing SE (21.4%) versus 38 out of 983 patients undergoing CBT (4.0%). The hospital mortality of SE was 14.0%, versus 5.6% for CBT, in the entire patient group. However, the hospital mortality of SE in patients with pre-SE CPR was 46.3%, whereas it was 6.8% in those patients without pre-SE CPR. Although CPR was associated with an increased risk of mortality both for CBT and SE, it accounted for all of the mortality effect on SE (the adjusted odds ratio for CPR in a random effects model with treatment considered was 9.79 (95% confidence interval, 4.98-19.17; $P < .0001$). The adjusted odds ratio for mortality for SE relative to CBT was 1.36 (95% confidence interval, 0.80-2.32; $P = .84$). Moreover, CBT was associated with a procedural failure rate of 8.3%.

Conclusions: Both CBT and SE were associated with satisfactory published outcomes. SE is associated with greater absolute postprocedure mortality than CBT, but has been undertaken in more critically ill populations. The markedly higher incidence of CPR in SE accounts for the differential mortality between the patients undergoing SE and those undergoing CBT. Decision making with respect to best therapy must take into account potential needs for periprocedure artificial mechanical right ventricle and lung support, institutional experience and outcomes, anticipated therapeutic efficacy and benefit, and approach-specific risks. (J Thorac Cardiovasc Surg 2018;156:2155-67)



Heterogeneity of CBTs for acute PE.

Central Message

Outcomes of appropriately selected patients undergoing SE are at least equivalent to those undergoing CBTs to treat large-burden (ie, massive and submassive) PE.

Perspective

Both CBTs and SE have satisfactory published outcomes. Surgical therapy is associated with greater absolute postprocedure mortality than CBT, but has been undertaken in more critically ill populations. This accounts for the differential mortality of patients undergoing SE versus CBT.

See Editorial Commentary page 2168.

From the [a]Division of Cardiology, Department of Internal Medicine, and Departments of [b]Cardiovascular and Thoracic Surgery and [c]Advanced Cardiopulmonary Therapies and Transplantation, University of Texas-Houston McGovern Medical School and Memorial Hermann-Texas Medical Center, Houston, Tex; [d]Division of Cardiothoracic Transplantation and Circulatory Support, Texas Heart Institute at Baylor College of Medicine, Houston, Tex; and [e]Division of Cardiovascular Medicine, Department of Medicine, Duke University School of Medicine and Medical Center, Durham, NC.

Received for publication July 5, 2017; revisions received May 7, 2018; accepted for publication May 10, 2018; available ahead of print July 10, 2018.

Address for reprints: Keshava Rajagopal, MD, PhD, Division of Cardiology, Department of Internal Medicine, University of Texas-Houston McGovern Medical School and Memorial Hermann-Texas Medical Center, 6400 Fannin St, Ste 2350, Houston, TX 77030 (E-mail: keshava.rajagopal@uth.tmc.edu).

0022-5223/$0.00
Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery
https://doi.org/10.1016/j.jtcvs.2018.05.085

Abbreviations and Acronyms

CBT	=	catheter-based therapies
CPR	=	cardiopulmonary resuscitation
ECMO	=	extracorporeal membrane oxygenation
PA	=	pulmonary artery
PE	=	pulmonary embolism
RV	=	right ventricle
SE	=	surgical embolectomy

Scanning this QR code will take you to a supplemental video for the article.

Acute pulmonary embolism (PE) continues to be among the leading causes of mortality and morbidity, despite state-of-the art pharmacologic and procedural therapies. In the United States, it is estimated that ~ 400,000 cases of acute PE are diagnosed, with an annual mortality of ~ 50,000.[1] The vast majority of mortality due to PE is believed to be due to massive PE, or PE that elevates right ventricular (RV) afterload sufficiently, such that major adverse hemodynamic sequelae (eg, low cardiac output syndrome manifesting with systemic arterial hypotension, and/or overt shock) occur.[2-4] In addition, submassive PE, or PE that elevates RV afterload such that evidence of RV dysfunction and/or injury is present, but in the absence of low-cardiac-output syndrome or shock (ie, in the absence of satisfying massive PE criteria), is also associated with an increased risk of mortality relative to uncomplicated PE.[2-4] This is believed to be due to patients with submassive PE and high-risk features eventually deteriorating into massive PE physiology.

Standard-of-care therapy for patients with massive PE and submassive PE with high-risk features is centered on systemic thrombolysis,[5,6] first implemented in the 1970s, and popularized in the late 1990s. However, thrombolytic agents do not improve survival in unselected patients with PE.[7] Even in patients with massive and submassive PE, although right-sided hemodynamic parameters and echocardiographic data are improved with thrombolysis, it is unclear whether thrombolytic agents actually improve overall survival.[8,9] This is because although PE-related mortality may be improved by thrombolytic agents, this enhanced disease-specific mortality may be offset by intracranial hemorrhage-related mortality.[8]

In contrast to systemic fibrinolysis, the historical treatment for large-burden PE has been surgical embolectomy (SE). First attempted by Trendelenburg in 1908, successfully performed by Kirschner in 1924, and subsequently by Beall and Cooley using cardiopulmonary bypass,[10] SE has been associated with high mortalities in historical series and large contemporary databases. Kilic and colleagues[11] reported 27% hospital mortality for SE in a study of the Nationwide Inpatient Sample, the largest series of SE examined to date. However, in centers with particular expertise in mechanical circulatory support/extracorporeal membrane oxygenation (ECMO), a recent resurgence in SE has been experienced; many studies (reviewed below) have demonstrated good results. Finally, in the background of historically suboptimal SE results, and deaths and complications arising from systemic administration of thrombolytic agents, a variety of minimally invasive catheter-based therapies (CBTs) have been developed. These include a wide range of techniques: catheter-directed infusion of thrombolytic agents, direct catheter-mediated fragmentation, rheolytic catheter PE disruption, and suction embolectomy.[12]

To date, no comparative study of CBT has been conducted, and such a study would be difficult to conduct due to a sick patient population and significant variations in local practice. Still, with systemic fibrinolysis as the current standard, contemporary studies of CBT and SE are needed. We conducted a systematic review of the extant literature pertaining to CBT and SE in the era of systemic fibrinolysis.

METHODS

Search Strategy

An electronic search of the National Library of Medicine PubMed database was conducted (www.pubmed.gov). The beginning and ending time points for the search were January 1998 and June 2017. The beginning time point corresponds to being shortly after early stage and subsequent larger scale studies of systemic administration of thrombolytic agents in the treatment of acute PE. To identify CBT studies, the medical subject headings search terms used were *pulmonary embolism* OR *pulmonary embolus* AND *embolectomy* OR *thrombectomy* OR *thrombolytic therapy* AND *catheter* OR *percutaneous* OR *mechanical*. To identify SE studies, the medical subject headings search terms were *pulmonary embolism* OR *pulmonary embolus* AND *embolectomy* OR *thromboembolectomy* OR *cardiopulmonary bypass*. A total of 386 articles were initially identified in the CBT search strategy, and 511 were initially identified in the SE search strategy (by authors MZA, SR, and KR) (Figure 1). For CBT, studies were excluded if they were case reports or series (<10 patients) (n = 105), editorials or letters (n = 28), reviews (n = 83), not in English (n = 6), or did not clearly fit the inclusion criteria (n = 123), with a final 41 studies for analysis (Figure 1, *A*). For SE, studies were excluded if they were case reports or series (<10 patients) (n = 136), editorials or letters (n = 26), reviews (n = 73), not in English (n = 60), or did not clearly fit the inclusion criteria (n = 182), with a final 34 studies for analysis (Figure 1, *B*).

Inclusion and Exclusion Criteria

Articles were included if they were identified based on the initial search criteria, and if they satisfied the following inclusion criteria: either published in an English language journal or available in an English version,

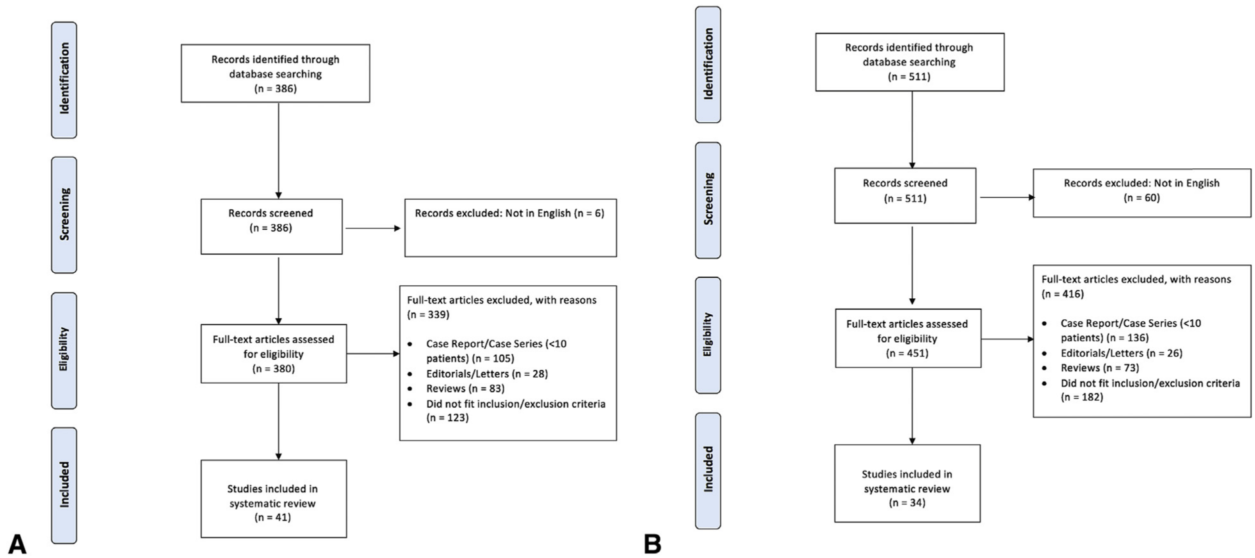


FIGURE 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagrams for methods for treating pulmonary embolism. A, Catheter-based therapies. B, Surgical embolectomy.

contained ≥10 patients who underwent procedural therapies, and did not exclude massive PE. Because false-positive results are possible; that is, SE articles could be identified within the CBT search and CBT articles could be identified within the SE search, studies were manually checked to determine whether in fact they belonged to the correct group (and were reassigned when appropriate). Finally, studies were manually checked to determine whether the same investigator groups and institutions published more than 1 study identified, with overlapping patients. If studies with overlapping patients were identified, only the most recent or largest study was chosen, excluding other studies. If overlapping patients were not identified; that is, totally chronologically sequential publications from an institution or investigator group, all pertinent publications were included.

Massive and Submassive PE

Massive and submassive PE were determined based on proposed definitions from a scientific statement from the American Heart Association published in 2011.[13] Massive PE was characterized by evidence of low-cardiac-output syndrome or clinical shock attributed to PE as the underlying cause, based on 1 or more of the following: systemic arterial systolic blood pressure <90 mm Hg, need for positive inotrope or systemic vasoconstrictor support, need for mechanical circulatory support, cardiac arrest, or profound bradycardia (heart rate < 40 bpm). This was with or without submassive PE criteria additionally being satisfied. Submassive PE was characterized by evidence of adverse effects on the RV (dysfunction and/or injury), in the absence of low-cardiac-output syndrome or clinical shock, based on 1 or more of the following: RV systolic hypokinesis, RV dilatation, elevated cardiac biomarkers (troponin I), elevated serum N-terminal probrain natriuretic peptide, or electrocardiogram changes suggestive of RV strain. All publications were manually checked to determine possible discrepancies between the authors' interpretation of their data and the standardized definitions reviewed above.

Statistical Analysis of the Effects of Cardiopulmonary Resuscitation on Outcomes

Because none of the studies cited made head-to-head comparisons between CBT and SE, a traditional meta-analysis that summarizes within-study treatment effects is not possible. In addition, because the reports are all series, no control treatment common to both SE and CBT across publications (eg, systemic thrombolysis) could be identified for use in a network meta-analysis. We therefore combined the studies using simple crude proportion analyses, and conducted heterogeneity analyses using forest plots of proportions, with mixed-effect pooled estimates and I^2 measures. We further used mixed effects meta-regression models to estimate the adjusted marginal means as described by Madden and colleagues,[14] and we followed the conceptual framework described by Benedetto and colleagues.[15] Further, because preintervention cardiopulmonary resuscitation (CPR) was much more common in the SE than the CBT series (see Results), and the mortality in patients requiring CPR was much higher, we evaluated the independent effect of SE while controlling for the effect of CPR in both simple stratified and adjusted mixed-effects models. Studies with fewer than 10 subjects were excluded from the regression analysis, and all models were weighted inversely to the variance of each study. A continuity correction was applied to allow for the inclusion of 0-event studies. Random intercepts were computed for study. All computations were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and SAS software (SAS Institute Inc, Cary NC).

RESULTS

Search Results

Using the search strategy outlined in the Methods section, 34 publications of SE outcomes and 41 publications of CBT outcomes were identified; these are listed in Tables 1 and 2, respectively. In the SE group, the mean ± standard deviation of patients per study was 32.4 ± 36.6 (median, 21 patients per study). In the CBT group, the mean ± standard deviation of patients per study was 40.2 ± 39.4 (median, 25 patients per study).

Outcomes of CBT

Overall, a total of 1650 patients across 41 publications underwent CBT. A breakdown of the different CBT approaches is depicted in Figure 2. Of note, a majority of publications (23 out of 41) utilized more than 1 CBT

TABLE 1. Studies included for catheter-based therapies. Studies in boldface type are included in Figure 3

Serial no.	Authors	Year	No. of patients	Massive PE	Submassive PE	CPR	Procedural success	Mortality overall	Mortality without CPR	Mortality with CPR	Technique
1	Bloomer and colleagues[16]	2017	137	16 (11.7)	121 (88.3)	ND	ND	5 (3.6)	ND	ND	Both standard and ultrasound-assisted catheter directed thrombolysis
2	Liang and colleagues[17]	2016	63	8 (12.7)	55 (87.3)	ND	58 (92.1)	2 (3.2)	ND	ND	Both standard and ultrasound assisted catheter directed thrombolysis
3	**Sag and colleagues[18]**	2016	13	13 (100)	0 (0%)	1 (7.7)	ND	0 (0)	0 (0)	0 (0)	Ultrasound-assisted catheter-directed thrombolysis
4	Kabhrel and colleagues[19]	2016	28	14 (50)	14 (50)	ND	ND	ND	ND	ND	Catheter-directed thrombolysis
5	Yoo and colleagues[20]	2016	28	12 (42.9)	16 (57.1)	5 (17.8)	ND	4 (14.3)	ND	ND	Catheter-directed thrombolysis + mechanical disruption
6	**Dilektasli and colleagues[21]**	2016	15	6 (40)	9 (60)	0 (0)	14 (93.3)	2 (13.3)	2 (100)	0 (0)	Catheter-directed thrombolysis + aspiration embolectomy
7	Piazza and colleagues[22]	2015	150	31 (20.7)	119 (79.3)	ND	ND	3 (2)	ND	ND	Ultrasound-assisted catheter-directed thrombolysis
8	George and colleagues[23]	2015	32	ND	ND	ND	ND	2 (6.3)	ND	ND	Catheter-directed thrombolysis
9	Kuo and colleagues[24]	2015	101	28 (28)	73 (72)	ND	90 (89)	6 (6)	ND	ND	Catheter-directed mechanical embolectomy or thrombolysis
10	**Engelberger and colleagues[25]**	2015	52	14 (27)	38 (73)	3 (6)	49 (94)	2 (4)	0 (0)	2 (100)	Ultrasound-assisted catheter-directed thrombolysis
11	Dumantepe and colleagues[26]	2015	36	11 (31)	25 (69)	ND	35 (97.2)	2 (5.5)	ND	ND	Mechanical aspiration embolectomy
12	**Quintana and colleagues[27]**	2014	10	2 (20)	8 (80)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0)	Ultrasound-assisted catheter-directed thrombolysis
13	**Mohan and colleagues[28]**	2014	50	20 (40)	30 (60)	0 (0)	46 (92)	2 (4)	2 (100)	0 (0)	Mechanical disruption plus catheter-directed thrombolysis
14	**Gaba and colleagues[29]**	2014	19	4 (21)	15 (79)	0 (0)	18 (95)	1 (5)	1 (100)	0 (0)	Catheter-directed thrombolysis
15	Akin and colleagues[30]	2014	17	5 (29)	12 (71)	ND	16 (94)	1 (6)	ND	ND	Catheter-directed thrombolysis
16	**Kennedy and colleagues[31]**	2013	60	12 (20)	48 (80)	1 (2)	59 (98)	3 (5)	3 (100)	0 (0)	Ultrasound-assisted catheter-directed thrombolysis
17	**Bonvini and colleagues[32]**	2013	10	10 (100)	0 (0)	6 (60)	8 (80)	7 (70)	3 (42.8)	4 (57.2)	Rheolytic embolectomy

(Continued)

TABLE 1. Continued

Serial no.	Authors	Year	No. of patients	Massive PE	Submassive PE	CPR	Procedural success	Mortality overall	Mortality without CPR	Mortality with CPR	Technique
18	**Nassiri and colleagues**[33]	2012	15	1 (7)	14 (93)	1 (7)	9 (60)	0 (0)	0 (0)	0 (0)	Rheolytic embolectomy
19	Cuculi and colleagues[34]	2012	63	17 (27)	46 (73)	3	57	4	ND	ND	Aspiration embolectomy plus catheter-directed thrombolysis
20	**Liu and colleagues**[35]	2011	14	5 (36)	9 (64)	0 (0)	14 (100)	0 (0)	0 (0)	0 (0)	Aspiration/mechanical disruption plus catheter-directed thrombolysis
21	**Gao and colleagues**[36]	2011	46	11 (24)	35 (76)	0 (0)	46 (100)	0 (0)	0 (0)	0 (0)	Aspiration embolectomy plus catheter-directed thrombolysis; mechanical disruption if aspiration failed
22	**Ferrigino and colleagues**[37]	2011	16	5 (31)	11 (69)	1 (6)	16 (100)	1 (6)	0 (0)	1 (100)	Rheolytic embolectomy plus catheter-directed thrombolysis
23	**De Gregorio and colleagues**[38]	2011	111	111 (100)	0 (0)	0 (0)	111 (100)	4 (4)	4 (100)	0 (0)	Mechanical disruption plus catheter-directed thrombolysis
24	Yamamoto and colleagues[39]	2009	50	12 (24)	38 (76)	5 (10)	50 (100)	3 (6)	ND	ND	Catheter-directed thrombolysis +/- either mechanical disruption or aspiration embolectomy
25	Lin and colleagues[40]	2009	25	ND	ND	ND	20/25 (80)	3 (12)	ND	ND	Ultrasound-assisted or standard catheter-directed thrombolysis
26	**Chechi and colleagues**[41]	2009	51	22 (43)	29 (57)	0 (0)	47 (92)	8 (16)	8 (100)	0 (0)	Rheolytic embolectomy plus catheter-directed thrombolysis
27	Spies and colleagues[42]	2008	13	13 (100)	0 (0)	ND	12 (92)	2 (15)	ND	ND	Rheolytic embolectomy
28	**Nakazawa and colleagues**[43]	2008	25	ND	ND	ND	18 (72)	0 ()	0 (0)	0 (0)	Mechanical disruption and aspiration embolectomy plus catheter-directed thrombolysis
29	Margheri and colleagues[44]	2008	25	20 (80)	5 (20)	ND	25 (100)	4 (16)	ND	ND	Rheolytic embolectomy
30	**Kuo and colleagues**[45]	2008	12	12 (100)	0 (0)	0 (0)	10 (83)	2 (17)	2 (100)	0 (0)	Mechanical disruption and aspiration embolectomy plus catheter-directed thrombolysis; rheolytic treatment if failed

(Continued)

TABLE 1. Continued

Serial no.	Authors	Year	No. of patients	Massive PE	Submassive PE	CPR	Procedural success	Mortality overall	Mortality without CPR	Mortality with CPR	Technique
31	**Eid-Lidt and colleagues**[46]	2008	18	8 (44)	10 (56)	0 (0)	16 (89)	1 (6)	1 (100)	0 (0)	Mechanical disruption plus aspiration embolectomy and catheter-directed thrombolysis
32	**Pieri and colleagues**[47]	2007	164	164 (100)	0 (0)	0 (0)	138 (84)	2 (1)	2 (100)	0 (0)	Mechanical disruption plus catheter-directed thrombolysis
33	**Chauhan and colleagues**[48]	2007	14	6 (43)	8 (57)	0 (0)	12 (86)	3 (21)	3 (100)	0 (0)	Rheolytic embolectomy
34	Barbosa and colleagues[49]	2007	10	10 (100)	0 (0)	1 (10)	9 (90)	1 (105)	0 (0)	1 (100)	Mechanical disruption
35	**Tajima and colleagues**[50]	2004	25	6 (24)	19 (76)	1 (4)	25 (100)	0 (0)	0 (0)	0 (0)	Mechanical disruption and aspiration embolectomy plus catheter-directed thrombolysis
36	**Tajima and colleagues**[51]	2004	15	ND	ND	ND	15 (100)	0 (0)	0 (0)	0 (0)	Percutaneous manual aspiration embolectomy
37	**Zeni and colleagues**[52]	2003	17	17 (100)	0 (0)	0 (0)	16 (94)	2 (12)	2 (100)	0 (0)	Rheolytic embolectomy plus catheter-directed thrombolysis
38	**De Gregorio and colleagues**[53]	2002	59	59 (100)	0 (0)	0 (0)	56 (95)	3 (5)	3 (100)	0 (0)	Mechanical disruption plus catheter-directed thrombolysis
39	**Schmitz-Rode and colleagues**[54]	2000	20	20 (100)	0 (0)	7 (35)	16 (80)	4 (20)	1 (25)	3 (75)	Mechanical disruption plus catheter-directed thrombolysis
40	**Fava and colleagues**[55]	2000	11	7 (64)	4 (36)	1 (9)	10 (91)	1 (14)	0 (0)	1 (100)	Rheolytic/aspiration embolectomy plus catheter-directed thrombolysis
41	Schmitz-Rode and colleagues[56]	1998	10	10 (100)	0 (0)	3 (30)	6 (60)	2 (20)	1 (50)	1 (50)	Mechanical disruption plus catheter-directed thrombolysis

Values are presented as n (%). *PE*, Pulmonary embolism; *CPR*, cardiopulmonary resuscitation; *ND*, no data.

approach to treat individual patients, to achieve therapeutic efficacy. Thirty-seven of 41 CBT publications (90%) provided information regarding PE classification. Of the 1553 patients in these studies, 742 (47.8%) had massive PE, and 811 (52.2%) had submassive PE. Twenty-eight of 41 CBT publications (68.3%) provided information regarding pretreatment CPR. Within these pre-CBT CPR publications, 596 out of 983 (60.6%) had massive PE, whereas 387 out of 983 (39.4%) had submassive PE. Twenty-seven of 41studies (65.8%) provided stratification of mortality based on CPR status. Mortality in the CPR group was 13 out of 25 (52.0%) compared with 38 out of 857 (4.4%) in the cohort without pre-CBT CPR. Twenty-five of 41 publications (61.0%) provided information both on PE classification and pretreatment CPR mortality classification. Of 842 patients in these studies, 25 (3.0%) required pre-CBT CPR. Mortality within pre-CBT CPR group was much higher: 13 out of 25 (52.0%) compared with 38 out of 817 (4.6%) in the group without pre-CBT CPR.

Procedural success (ie, technical adequacy of CBT determined by the authors as assessed either by angiographic or physiologic criteria) was reported in 35 out of 41 studies. Technically satisfactory outcomes were noted in 1157 of 1262 (91.7%) patients; that is, the failure rate was 8.3%.

One publication did not report mortality outcomes. Hospital mortality of the entire CBT group thus was 92 out of 1622 (5.7%). As in the SE group, mortality was

TABLE 2. Studies included for surgical embolectomy. Studies in boldface are included in Figure 3

Serial no.	Authors	Year	No. of patients	Massive PE	Submassive PE	Uncomplicated PE	CPR	Mortality overall	Mortality without CPR	Mortality with CPR
1	Lehrnet and colleagues[57]	2017	50	28 (56)	22 (44)	0 (0)	12 (24)	4 (8)	ND	ND
2	Edelman and colleagues[58]	2016	37	20 (54.1)	17 (45.9)	0 (0)	13 (35.1)	2 (5.4)	ND	ND
3	Cho and colleagues[59]	2016	26	26 (100)	0 (0)	0 (0)	11 (42.3)	4 (15.4)	ND	ND
4	**Keeling and colleagues[60]**	2016	214	38 (17.8)	176 (82.2)	0 (0)	28 (13.1)	25 (11.7)	16 (7.5)	9 (4.2)
5	**Neely and colleagues[61]**	2015	105	49 (47)	56 (53)	0 (0)	11 (10)	8 (8)	3 (38)	5 (62)
6	Azari and colleagues[62]	2015	30	30 (100)	0 (0)	0 (0)	12 (40)	5 (17)	ND	ND
7	**Worku and colleagues[63]**	2014	20	12 (60)	8 (40)	0 (0)	3 (15)	1 (5)	1 (100)	0 (0)
8	**Osborne and colleagues[64]**	2014	15	12 (80)	3 (20)	0 (0)	2 (13)	2 (13)	0 (0)	2 (100)
9	**Wu and colleagues[65]**	2013	25	16 (64)	7 (28)	2 (8)	8 (32)	5 (20)	1 (20)	4 (80)
10	Aymard and colleagues[66]	2013	39	ND	ND	0 (0)	ND	4 (10)	ND	ND
11	**Taniquchi and colleagues[67]**	2012	32	26 (81)	6 (19)	0 (0)	3 (9)	6 (19)	5 (83)	1 (17)
12	**Takahashi and colleagues[68]**	2012	24	16 (67)	8 (33)	0 (0)	11 (46)	3 (13)	0 (0)	3 (100)
13	**Marshall and colleagues[69]**	2012	10	10 (100)	0 (0)	0 (0)	6 (60)	4 (40)	1 (25)	3 (75)
14	**Malekan and colleagues[70]**	2012	26	7 (27)	19 (73)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
15	**Zarrabi and colleagues[71]**	2011	30	11 (37)	19 (63)	0 (0)	3 (10)	2 (7)	1 (50)	1 (50)
16	**Greelish and colleagues[72]**	2011	15	7 (47)	8 (53)	0 (0)	2 (13)	2 (13)	0 (0)	2 (100)
17	**Fukuda and colleagues[73]**	2011	19	17 (90)	2 (10)	0 (0)	4 (21)	1 (5)	1 (33)	0 (67)
18	Vohra and colleagues[74]	2010	21	21 (100)	0 (0)	0 (0)	9 (43)	4 (19)	ND	ND
19	**Sareyyupoqlu and colleagues[75]**	2010	18	12 (67)	6 (3)	0 (0)	7 (39)	4 (22)	0 (0)	4 (25)
20	**Carvalho and colleagues[76]**	2010	16	16 (100)	0 (0)	0 (0)	7 (44)	7 (44)	1 (14)	6 (86)
21	Kukla and colleagues[77]	2009	15	6 (40)	9 (60)	0 (0)	ND	5 (33)	ND	ND
22	**Sadaba and colleagues[78]**	2008	20	9 (45)	11 (55)	0 (0)	1 (5)	2 (10)	1 (50)	1 (50)
23	**Kadner and colleagues[79]**	2008	25	25 (100)	0 (0)	0 (0)	8 (32)	2 (8)	0 (0)	2 (100)
24	**Ahmed and colleagues[80]**	2008	15	7 (46.7)	6 (40.0)	2 (13.3)	0 (0)	3 (20)	3 (100)	0 (0)
25	**Diggonet and colleagues[81]**	2007	21	14 (67)	7 (33)	0 (0)	6 (29)	8 (38)	4 (50)	4 (50)
26	**Amirghofran and colleagues[82]**	2007	11	11 (100)	0 (0)	0 (0)	3 (27)	2 (18)	1 (50)	1 (50)
27	**Spagnolo and colleagues[83]**	2006	21	21 (100)	0 (0)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)
28	Meneveau and colleagues[84]	2006	14	14 (100)	0 (0)	0 (0)	ND	1 (7)	ND	ND
29	Sukhija and colleagues[85]	2005	18	18 (100)	0 (0)	0 (0)	ND	2 (11)	ND	ND
30	**Leachhe and colleagues[86]**	2005	47	28 (59.6)	15 (31.9)	4 (8.5)	6 (13)	3 (6)	2 (67)	1 (33)
31	**Dauphine and colleagues[87]**	2005	11	11 (100)	0 (0)	0 (0)	4 (36)	3 (27)	0 (0)	3 (100)
32	**Yalamanchili and colleagues[88]**	2004	13	4 (31)	9 (69)	0 (0)	2 (15)	1 (8)	0 (0)	1 (100)
33	**Ullmann and colleagues[89]**	1999	40	ND	ND	0 (0)	19 (48)	14 (35)	2 (14)	12 (86)
34	**Doerge and colleagues[90]**	1999	41	33 (80)	8 (20)	0 (0)	14 (34)	12 (29)	3 (25)	9 (75)

Values are presented as n (%). *PE*, Pulmonary embolism; *CPR*, cardiopulmonary resuscitation; *ND*, no data.

not classified based on PE classification. Mortality was classified based on pre-CBT CPR status; of 28 publications providing pretreatment CPR information, 25 classified mortality based on it. Within these publications, hospital mortality was 51 out of 842 (6.1%). Mortality was 13 out of 25 (52.0%) in those patients with pre-CBT CPR, whereas it was 38 out of 764 (5.0%) in those patients without pre-CBT CPR.

For the meta-analysis, no CBT study had 10 or more patients who received CPR, so no pooled estimates were

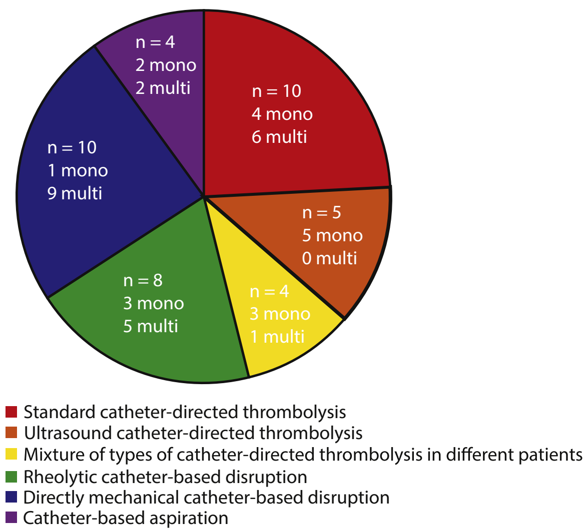


FIGURE 2. Representation of different types of catheter-based therapies (CBTs) in the CBT studies analyzed. Data are presented as a pie chart, with the indicated rainbow color legend. For a given type of primary CBT, studies in which the primary CBT was used exclusively as a single modality in patients are indicated as "mono." Studies in which the primary CBT was used as a first-line therapy, but as part of a strategy in which more than 1 type of CBT was used within individual patients, are indicated as "multi." Studies denoted as "multi" had individual patients who each received more than 1 type of CBT, but the first type of CBT used denoted as the primary therapy. Consequently, for a given type of primary CBT, mono and multi add up to the total number of studies for that type of primary CBT. The category in yellow refers to studies in which different types of primary CBT were reported; for 3 articles, several patients within a given study in this category had standard catheter-directed or ultrasound-assisted catheter-directed thrombolysis, but not a combination of the 2. In 1 article, 2 different types of CBT were employed, and some patients received an additional modality of CBT (also denoted as "multi").

computed for CBT-CPR. The overall weighted random effects estimate for CBT was 6% (95% confidence interval [CI], 4%-9%) (Figure 3).

Outcomes of SE

Overall, a total of 1101 patients across 34 publications underwent SE. Thirty-one of 34 publications (91.1%) provided information regarding PE classification (massive, submassive, or uncomplicated). Of 975 patients in these studies, 545 (55.9%) had massive PE, 422 (43.3%) had submassive PE, and 8 (0.8%) had uncomplicated PE. Thirty of 34 publications (88.2%) provided information regarding pretreatment CPR; of 1015 patients in these studies, 217 (21.4%) required pre-SE CPR. Procedural success (ie, technical adequacy of embolectomy) generally was not reported.

Hospital mortality of the entire SE group was 154 out of 1101 (14.0%). In the publications reporting PE classification, mortality generally was not categorized based on it. However, mortality was classified based on pre-SE CPR status when available; of 30 publications providing pretreatment CPR information, 25 classified mortality based on it. Within these publications, hospital mortality was 120 out of 834 (14.0%). Mortality was 74 out of 160 (46.3%) in those patients with pre-SE CPR, whereas it was 46 out of 674 (6.8%) in those patients without pre-SE CPR. Twenty-four of 34 publications (70.6%) provided information both on PE classification and pretreatment CPR mortality classification. Within these publications, 412 out of 794 (52.0%) had massive PE, 374 out of 794 (47.1%) had submassive PE, whereas 8 out of 794 (0.9%) had uncomplicated PE. Hospital mortality was 106 out of 794 (13.4%). Mortality was 62 out of141 (44.0%) in those patients with pre-SE CPR, whereas it was 44 out of 653 (6.7%) in those patients without pre-SE CPR. In SE patients not receiving CPR, the pooled random effect estimate of mortality was 9% (95% CI, 6%-11%). This was not statistically significantly different from CBT without CPR ($P = .14$) (Figure 3).

The shift in the percentages of PE types in the SE group when only the selected subgroup of publications (those that both classified PE type and stratified mortality based on CPR status) is considered, particularly relative to the analogous CBT subgroup, is solely attributable to a single outlier study of Keeling and colleagues (discussed in detail below),[24] the single largest SE study, with a ratio of massive to submassive PE < 1:4. If this study were excluded, of the remaining 23 studies, of 580 patients, 374 (64.5%) had massive PE, 198 (34.1%) had submassive PE and 8 (1.4%) had uncomplicated PE.

Effect of CPR and CPR Status on Differential Mortality Post-CBT Versus SE

As outlined in the Methods section, we conducted a statistical analysis of the effects of CPR status on the mortality of CBT and SE. It is important to note that in these statistical models, only the studies that had data regarding the presence or absence of CPR, and were further stratified based on mortality, were analyzed. Moderate heterogeneity between the studies was identified, as indicated by $I^2 = 18\%$. Mixed-model adjustment and inverse-variance weighting was used to estimate the adjusted odds ratio (OR) effects. The adjusted OR for CPR in a random effects model with treatment considered was 9.79 (95% CI, 4.98-19.17; $P < .0001$). However, as discussed above, 217 out of 1015 SE patients (21.4%) had a history of CPR, in comparison to 38 out of 983 CBT patients (4.0%). The adjusted OR for mortality for SE versus CBT was 1.36 (95% CI, 0.80-2.32). As a result, when controlling for the higher risk of the SE population, SE and CBT were found to have mortality risks that were not statistically significantly different ($P = .84$). Thus, even without individual-level risk adjustment, this analysis shows that

Study or Subgroup	Events	Total	Weight (fixed)	Weight (random)	IV, Fixed + Random, 95% CI
Group = CBT					
Engelberger CBT 10	0	49	0.5%	1.2%	0.00 [0.00; 0.07]
Gao CBT 21	0	46	0.5%	1.2%	0.00 [0.00; 0.08]
Piere CBT 32	2	164	2.0%	2.5%	0.01 [0.00; 0.04]
Nakazawa CBT 28	0	25	0.5%	1.2%	0.00 [0.00; 0.14]
Tajima CBT 35	0	24	0.5%	1.2%	0.00 [0.00; 0.14]
Ferrigino CBT 22	0	15	0.5%	1.2%	0.00 [0.00; 0.22]
Nassisi CBT 18	0	15	0.5%	1.2%	0.00 [0.00; 0.22]
Liu CBT 20	0	14	0.5%	1.2%	0.00 [0.00; 0.23]
Tajima CBT 36	0	14	0.5%	1.2%	0.00 [0.00; 0.23]
DeGregorio CBT 23	4	111	4.0%	2.9%	0.04 [0.01; 0.09]
Sag CBT 3	0	12	0.5%	1.2%	0.00 [0.00; 0.26]
Mohan CBT 13	2	50	2.0%	2.4%	0.04 [0.00; 0.14]
Fava CBT 40	0	10	0.5%	1.2%	0.00 [0.00; 0.31]
Quintana CBT 12	0	10	0.5%	1.2%	0.00 [0.00; 0.31]
Kennedy CBT 16	3	60	3.0%	2.7%	0.05 [0.01; 0.14]
DeGregorio CBT 38	3	59	3.0%	2.7%	0.05 [0.01; 0.14]
Gaba CBT 14	1	19	1.0%	1.8%	0.05 [0.00; 0.26]
Eid-Lidt CBT 31	1	18	1.0%	1.8%	0.06 [0.00; 0.27]
Schmitz-Rode CBT 39	1	13	1.0%	1.8%	0.08 [0.00; 0.36]
Zeni CBT 37	2	17	1.8%	2.4%	0.12 [0.01; 0.36]
Dilektasli CBT 6	2	15	1.8%	2.4%	0.13 [0.02; 0.40]
Chechi CBT 26	8	51	7.0%	3.2%	0.16 [0.07; 0.29]
Kuo CBT 30	2	12	1.7%	2.3%	0.17 [0.02; 0.48]
Chauhan CBT 33	3	14	2.4%	2.6%	0.21 [0.05; 0.51]
Total (fixed effect, 95% CI)		837	37.2%	--	0.07 [0.05; 0.09]
Total (random effects, 95% CI)		--		44.9%	0.06 [0.04; 0.09]
Heterogeneity: Tau^2 = 0.1959; Chi^2 = 29.46, df = 23 (P = 0.17); I^2 = 22%					
Group = SE−CPR					
Takahashi SE 12 (+CPR)	3	11	2.3%	2.5%	0.27 [0.06; 0.61]
Keeling SE 4 (+CPR)	9	28	6.3%	3.2%	0.32 [0.16; 0.52]
Neely SE 5 (+CPR)	5	11	2.8%	2.7%	0.45 [0.17; 0.77]
Ullmann SE 33 (+CPR)	12	19	4.6%	3.0%	0.63 [0.38; 0.84]
Doerge SE 34 (+CPR)	9	14	3.3%	2.8%	0.64 [0.35; 0.87]
Total (fixed effect, 95% CI)		83	19.3%	--	0.46 [0.35; 0.57]
Total (random effects, 95% CI)		--		14.3%	0.47 [0.31; 0.62]
Heterogeneity: Tau^2 = 0.2455; Chi^2 = 7.53, df = 4 (P = 0.11); I^2 = 47%					
Group = SE−no CPR					
Malekan SE 14 (-CPR)	0	26	0.5%	1.2%	0.00 [0.00; 0.13]
Spagnolo SE 27 (-CPR)	0	19	0.5%	1.2%	0.00 [0.00; 0.18]
Kadner SE 23 (-CPR)	0	17	0.5%	1.2%	0.00 [0.00; 0.20]
Neely SE 5 (-CPR)	3	94	3.0%	2.8%	0.03 [0.01; 0.09]
Osborne SE 8 (-CPR)	0	13	0.5%	1.2%	0.00 [0.00; 0.25]
Takahashi SE 12 (-CPR)	0	13	0.5%	1.2%	0.00 [0.00; 0.25]
Greelish SE 16 (-CPR)	0	13	0.5%	1.2%	0.00 [0.00; 0.25]
Zarrabi SE 15 (-CPR)	1	27	1.0%	1.8%	0.04 [0.00; 0.19]
Sareyyupoglu SE 19 (-CPR)	0	11	0.5%	1.2%	0.00 [0.00; 0.28]
Yalamanchili SE 32 (-CPR)	0	11	0.5%	1.2%	0.00 [0.00; 0.28]
Leachhe SE 30 (-CPR)	2	41	2.0%	2.4%	0.05 [0.01; 0.17]
Sadaba SE 22 (-CPR)	1	19	1.0%	1.8%	0.05 [0.00; 0.26]
Wu SE 9 (-CPR)	1	17	1.0%	1.8%	0.06 [0.00; 0.29]
Worku SE 7 (-CPR)	1	17	1.0%	1.8%	0.06 [0.00; 0.29]
Fukuda SE 15 (-CPR)	1	15	1.0%	1.8%	0.07 [0.00; 0.32]
Keeling SE 4 (-CPR)	16	186	15.2%	3.5%	0.09 [0.05; 0.14]
Ullmann SE (-CPR)	2	21	1.9%	2.4%	0.10 [0.01; 0.30]
Doerge SE 34 (-CPR)	3	27	2.8%	2.7%	0.11 [0.02; 0.29]
Taniquchi SE 11 (-CPR)	5	29	4.3%	3.0%	0.17 [0.06; 0.36]
Ahmed SE 24 (-CPR)	3	15	2.5%	2.6%	0.20 [0.04; 0.48]
Diggonet SE 25 (-CPR)	4	15	3.0%	2.8%	0.27 [0.08; 0.55]
Total (fixed effect, 95% CI)		646	43.5%	--	0.09 [0.06; 0.11]
Total (random effects, 95% CI)		--		40.8%	0.09 [0.06; 0.11]
Heterogeneity: Tau^2 = 0.0121; Chi^2 = 20.43, df = 20 (P = 0.43); I^2 = 2%					
Total (fixed effect, 95% CI)		**1566**	**100.0%**	**--**	**0.11 [0.10; 0.14]**
Total (random effects, 95% CI)		**--**		**100.0%**	**0.09 [0.06; 0.12]**
Heterogeneity: Tau^2 = 1.008; Chi^2 = 141.50, df = 49 (P < 0.01); I^2 = 65%					

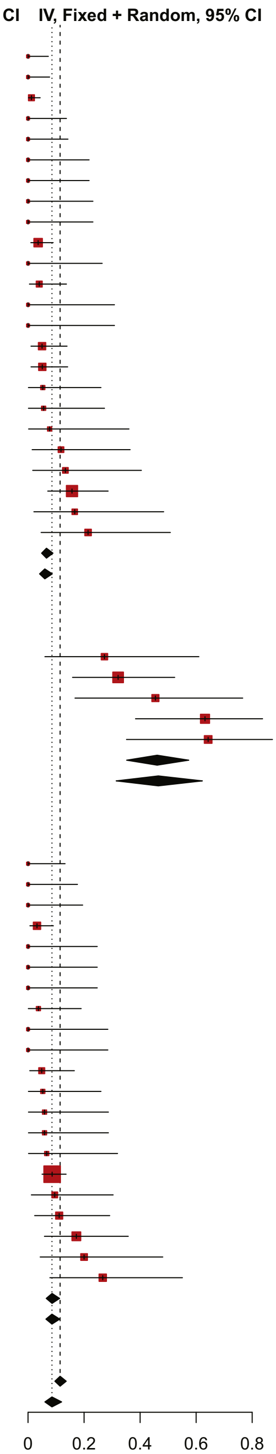


FIGURE 3. Forest plot of weighted proportions of mortality in studies with sample size for all subgroups. Study identifiers are first-author names and corresponding table entry numbers in Tables 1 and 2 (*boldface*). Weighted marginal proportions are shown for each subgroup. *CBT*, Catheter-based studies.

differences in the incidence of CPR in the CBT versus SE groups accounts for the differential mortality between the CBT and SE groups.

DISCUSSION

We found (Video 1) that published short-term outcomes of both CBT and SE for acute PE are, as expected, of

VIDEO 1. Pranav Loyalka, MD, and Keshava Rajagopal, MD, PhD, discuss the findings of their systematic review of catheter-based versus surgical therapies for acute pulmonary embolism. Video available at: https://www.jtcvs.org/article/S0022-5223(18)31520-4/fulltext.

good quality. SE was performed in a more critically ill patient cohort, with a higher proportion of patients with massive PE and a large number of patients with a pretreatment CPR history. In contrast, CBT was undertaken in a less critically ill cohort, with a relatively lower percentage of patients with massive PE. Unadjusted hospital survival outcomes of SE were inferior to CBT, but patients without pre-SE CPR were found to have survival outcomes equivalent to the CBT group as a whole. In addition, CBT was associated with a procedure failure rate of ~8%, which presumably does not exist for SE (although technical success or failure of SE was not documented in the literature surveyed). A majority of CBT studies reported needing to employ an additional modality of CBT distinct from the primary modality to achieve technically or physiologically satisfactory outcomes.

Substantial intercenter variations exist with respect to procedural expertise. As a result, in light of these findings, individual center and practitioner experiences are critically important in determining the best therapeutic strategy. However, some factors should prompt consideration of expanding the role of SE in the management of massive and possibly even submassive PE with high-risk features. First, and perhaps most important, patients with massive PE (and submassive PE on initial presentation that can subsequently evolve massive PE physiology) may require artificial mechanical support of the RV and/or lungs. Venoarterial ECMO and other techniques to mechanically support the RV and/or lungs are most easily undertaken in operating room environments. In centers with ECMO expertise, SE can be undertaken concomitantly or in a delayed fashion[70] after a period of RV and pulmonary support and end-organ resuscitation. This is perhaps particularly relevant in patients with pretreatment refractory shock and/or CPR. Moreover, in the majority of large-volume medical centers, cardiothoracic surgeons have the greatest experience and facility with these technologies. CBT, in contrast, rarely is performed by physicians and/or surgeons with experience in advanced mechanical cardiac and/or pulmonary support.

Second, clearance of the embolic burden is perhaps better accomplished via SE. Physiologic end points are of paramount importance, and even in early studies, both SE and CBT have been shown to reduce RV afterload and thereby improve hemodynamic parameters, and to reduce ventilation-perfusion mismatch and thereby improve gas exchange.[8,91-93] However, some evidence suggests that SE may be more physiologically effective than CBT. For example, in the recently conducted A Prospective, Single-Arm, Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (SEATTLE II)[22] large, prospective multicenter study of CBT, the mean RV to left ventricle ratio posttreatment was > 0.9, and mean pulmonary arterial (PA) pressure was reduced from 51.4 to 36.9; that is, substantial residual PA hypertension was observed. SE, on the other hand, appears to exhibit better physiologic results, including several of the studies reviewed in our study. Lehnert and colleagues,[57] in the most recent study we examined, investigated the efficacy of SE versus systemic thrombolysis (albeit not CBT) at removal of the embolic burden in the pulmonary vasculature. Using single-photon emission computed tomography scanning after the procedure, they found that SE was markedly superior to systemic thrombolysis. In addition, Keeling and colleagues[94] have shown dramatic improvements in ejection phase (ie, inversely proportional to afterload) indices of RV systolic function and tricuspid valve regurgitation.

However, the embolic burden may be nonlinearly related to pulmonary vascular impedance/RV afterload; that is, in critically ill patients with massive PE, small amounts of PE clearance may translate to large reductions in pulmonary vascular impedance and improvements in cardiac output. SE is conducted under direct vision, with the ability to extract a central clot, as well as clots extending into lobar and even segmental branch vessels. In contrast, incompleteness of PE burden clearance from CBT is well recognized, and in fact expected. This is true even of the SEATTLE II study,[22] which identified only a 30% improvement in angiographic PE burden, deeming these results procedural success. The mean modified Miller angiographic score based on computed tomography angiography was reduced from 22.5 pretreatment to 15.8 posttreatment. To place this in perspective, a normal score in the absence of any PE is 0, with a maximum score with complete involvement of all pulmonary vascular zones and totally absent pulmonary blood flow (ie, cardiac arrest) of 40 (the original maximum Miller score based on conventional catheter angiography is 34). Particularly in those studies that define procedural success by physiologic rather than angiographic criteria, modest PE burden clearance was found to result in physiologic improvements. However, whether further hemodynamic improvements would result from better PE clearance is unclear. Interpretation of surgical data in this regard is complicated. Most patients do not have pre-SE PA catheter data, and PA catheters generally are not placed in the setting of SE. In addition, cardiopulmonary bypass may have adverse effects on pulmonary vascular impedance.[95,96] Finally, postoperative invasive and even noninvasive positive-pressure mechanical ventilation also have variable effects on pulmonary vascular impedance.[97,98]

These arguments in favor of SE notwithstanding (particularly in critically ill patients such as those with massive PE), the optimal treatment of patients with lesser degrees of PE (ie, submassive or less) is unclear. However, a recent multicenter study of SE results, included in our study, may provide insights on this question. Keeling and colleagues[60] recently reported the results of a multicenter registry of SE. In this group of 214 patients undergoing SE, 82% had submassive PE, and only 18% had massive PE; that is, a ratio of massive to submassive PE < 1:4. As noted previously, these demographic characteristics represent not only a much lower risk profile than the existing SE literature, but also are a much lower risk profile than the existing CBT literature. Yet, hospital mortality in the study of Keeling and colleagues[60] was 11.7%, and in the subgroup of patients who did not experience pre-SE CPR, mortality was still 8.6%. If these findings are reproducible, they would suggest that aggressive use of SE in patients with submassive PE may be unwarranted, due to both apparently inferior survival outcomes relative to CBT, and more importantly, the lack of a survival benefit relative to the natural history of submassive PE.

Our study has several limitations. First, it is retrospective and uncontrolled. Second, when present, studies did not report at what times PE class was determined—at the time of initial presentation to any center, initial presentation to the treating center, or just before initiation of CBT or SE. This is important because submassive PE may deteriorate and convert to massive PE, and deaths due to submassive PE generally are believed to be due to this. Third, etiology of PE generally was not investigated in the studies analyzed. Fourth, mechanisms or modes of death also were not reported in the studies analyzed. Fifth, with respect to SE in particular, technical success or failure was not reported, but rather was presumed. Sixth, long-term follow-up was rare, and studies were limited to in-hospital or < 90-day outcomes. All of these data, if not absent, may provide important insights into PE and its treatment.

CONCLUSIONS

Based on the existing data, both SE and CBT have roles in the management of massive and submassive PE. These results demonstrate that both approaches achieve satisfactory outcomes. SE has practical utility in patients at high risk for needing mechanical RV and/or pulmonary support, and may be superior to CBT in those patients with central PE and larger embolic burden. In contrast, CBT may be better suited to patients for whom cardiac surgery is contraindicated or of extreme risk, and patients with more peripheral (ie, less surgically accessible) disease. Randomized controlled trials, although challenging to conduct in the setting of massive PE with labile patient conditions, will be valuable in identifying appropriate therapies for specific patient subsets.

Conflicts of Interest Statement

Authors have nothing to disclose with regard to commercial support.

References

1. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158:585-93.
2. Castillo C, Tapson VF. Right ventricular responses to massive and submassive pulmonary embolism. *Cardiol Clin*. 2012;30:233-41.
3. Konstantinides SV. Massive pulmonary embolism: what level of aggression? *Semin Respir Crit Care Med*. 2008;29:47-55.
4. Tapson VF, Humbert M. Incidence and prevalence of chronic thromboembolic pulmonary hypertension: from acute to chronic pulmonary embolism. *Proc Am Thorac Soc*. 2006;3:564-7.
5. Di Nisio M, van Es N, Buller HR. Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;388:3060-73.
6. Konstantinides SV, Vicaut E, Danays T, Becattini C, Bertoletti L, Beyer-Westendorf J, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. *J Am Coll Cardiol*. 2017;69:1536-44.
7. Riera-Mestre A, Jimenez D, Muriel A, Lobo JL, Moores L, Yusen RD, et al. Thrombolytic therapy and outcome of patients with an acute symptomatic pulmonary embolism. *J Thromb Haemost*. 2012;10:751-9.
8. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370:1402-11.
9. Tibbutt DA, Davies JA, Anderson JA, Fletcher EW, Hamill J, Holt JM, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonay embolism. *BMJ*. 1974;1:343-7.
10. Beall AC Jr, Cooley DA, Debakey ME. Surgical management of pulmonary embolism: experimental and clinical considerations. *Dis Chest*. 1965;47:382-91.
11. Kilic A, Shah AS, Conte JV, Yuh DD. Nationwide outcomes of surgical embolectomy for acute pulmonary embolism. *J Thorac Cardiovasc Surg*. 2013;145:373-7.
12. Kuo WT. Endovascular therapy for acute pulmonary embolism. *J Vasc Interv Radiol*. 2012;23:167-79.
13. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, 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;123:1788-830.
14. Madden LV, Paul PA. Meta-analysis for evidence synthesis in plant pathology: an overview. *Phytopathology*. 2011;101:16-30.
15. Benedetto U, Melina G, Takkenberg JJ, Roscitano A, Angeloni E, Sinatra R. Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. *Heart*. 2011;97:955-8.
16. Bloomer TL, El-Hayek GE, McDaniel MC, Sandvall BC, Liberman HA, Devireddy CM, et al. Safety of catheter-directed thrombolysis for massive and submassive pulmonary embolism: results of a multicenter registry and meta-analysis. *Catheter Cardiovasc Interv*. 2017;89:754-60.
17. Liang NL, Avgerinos ED, Marone LK, Smith MJ, Singh MJ, Makaroun MS, et al. Comparative outcomes of ultrasound-assisted thrombolysis and standard catheter-directed thrombolysis in the treatment of acute pulmonary embolism. *Vasc Endovascular Surg*. 2016;50:405-10.

18. Sag S, Nas OF, Kaderli AA, Ozdemir B, Baran I, Erdogan C, et al. Catheter-directed ultrasound-accelerated thrombolysis may be life-saving in patients with massive pulmonary embolism after failed systemic thrombolysis. *J Thromb Thrombolysis*. 2016;42:322-8.
19. Kabrhel C, Rosovsky R, Channick R, Jaff MR, Weinberg I, Sundt T, et al. A multidisciplinary pulmonary embolism response team: initial 30-month experience with a novel approach to delivery of care to patients with submassive and massive pulmonary embolism. *Chest*. 2016;150:384-93.
20. Yoo JW, Choi HC, Lee SJ, Cho YJ, Lee JD, Kim HC. Comparison between systemic and catheter thrombolysis in patients with pulmonary embolism. *Am J Emerg Med*. 2016;34:985-8.
21. Dilektasli AG, Demirdogen Cetinoglu E, Acet NA, Erdogan C, Ursavas A, Ozkaya G, et al. Catheter-directed therapy in acute pulmonary embolism with right ventricular dysfunction: a promising modality to provide early hemodynamic recovery. *Med Sci Monit*. 2016;22:1265-73.
22. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv*. 2015;8:1382-92.
23. George B, Wallace EL, Charnigo R, Wingerter KE, Kapadia P, Gurley JC, et al. A retrospective analysis of catheter-based thrombolytic therapy for acute submassive and massive pulmonary embolism. *Vasc Med*. 2015;20:122-30.
24. Kuo WT, Banerjee A, Kim PS, DeMarco FJ Jr, Levy JR, Facchini FR, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest*. 2015;148:667-73.
25. Engelberger RP, Moschovitis A, Fahrni J, Willenberg T, Baumann F, Diehm N, et al. Fixed low-dose ultrasound-assisted catheter-directed thrombolysis for intermediate and high-risk pulmonary embolism. *Eur Heart J*. 2015;36:597-604.
26. Dumantepe M, Teymen B, Akturk U, Seren M. Efficacy of rotational thrombectomy on the mortality of patients with massive and submassive pulmonary embolism. *J Card Surg*. 2015;30:324-32.
27. Quintana D, Salsamendi J, Fourzali R, Narayanan G. Ultrasound-assisted thrombolysis in submassive and massive pulmonary embolism: assessment of lung obstruction before and after catheter-directed therapy. *Cardiovasc Intervent Radiol*. 2014;37:420-6.
28. Mohan B, Aslam N, Kumar Mehra A, Takkar Chhabra S, Wander P, Tandon R, et al. Impact of catheter fragmentation followed by local intrapulmonary thrombolysis in acute high risk pulmonary embolism as primary therapy. *Indian Heart J*. 2014;66:294-301.
29. Gaba RC, Gundavaram MS, Parvinian A, Knuttinen MG, Minocha J, Owens CA, et al. Efficacy and safety of flow-directed pulmonary artery catheter thrombolysis for treatment of submassive pulmonary embolism. *AJR Am J Roentgenol*. 2014;202:1355-60.
30. Akin H, Al-Jubouri M, Assi Z, Acino R, Sepanski D, Comerota AJ. Catheter-directed thrombolytic intervention is effective for patients with massive and submassive pulmonary embolism. *Ann Vasc Surg*. 2014;28:1589-94.
31. Kennedy RJ, Kenney HH, Dunfee BL. Thrombus resolution and hemodynamic recovery using ultrasound-accelerated thrombolysis in acute pulmonary embolism. *J Vasc Interv Radiol*. 2013;24:841-8.
32. Bonvini RF, Roffi M, Bounameaux H, Noble S, Müller H, Keller PF, et al. AngioJet rheolytic thrombectomy in patients presenting with high-risk pulmonary embolism and cardiogenic shock: a feasibility pilot study. *EuroIntervention*. 2013;8:1419-27.
33. Nassiri N, Jain A, McPhee D, Mina B, Rosen RJ, Giangola G, et al. Massive and submassive pulmonary embolism: experience with an algorithm for catheter-directed mechanical thrombectomy. *Ann Vasc Surg*. 2012;26:18-24.
34. Cuculi F, Kobza R, Bergner M, Erne P. Usefulness of aspiration of pulmonary emboli and prolonged local thrombolysis to treat pulmonary embolism. *Am J Cardiol*. 2012;110:1841-5.
35. Liu S, Shi HB, Gu JP, Yang ZQ, Chen L, Lou WS, et al. Massive pulmonary embolism: treatment with the rotarex thrombectomy system. *Cardiovasc Intervent Radiol*. 2011;34:106-13.
36. Gao H, Huang GY, Ma LL, Wang LX. Combined catheter thrombus fragmentation and fibrinolysis for acute pulmonary embolism. *Intern Med J*. 2011;41:687-91.
37. Ferrigno L, Bloch R, Threlkeld J, Demlow T, Kansal R, Karmy-Jones R. Management of pulmonary embolism with rheolytic thrombectomy. *Can Respir J*. 2011;18:e52-8.
38. de Gregorio MA, Laborda A, de Blas I, Medrano J, Mainar A, Oribe M. Endovascular treatment of a haemodynamically unstable massive pulmonary embolism using fibrinolysis and fragmentation. Experience with 111 patients in a single centre. Why don't we follow ACCP recommendations? *Arch Bronconeumol*. 2011;47:17-24.
39. Yamamoto T, Murai K, Tokita Y, Kato K, Iwasaki YK, Sato N, et al. Thrombolysis with a novel modified tissue-type plasminogen activator, monteplase, combined with catheter-based treatment for major pulmonary embolism. *Circ J*. 2009;73:106-10.
40. Lin PH, Annambhotla S, Bechara CF, Athamneh H, Weakley SM, Kobayashi K, et al. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. *Vascular*. 2009;17(Suppl 3):S137-47.
41. Chechi T, Vecchio S, Spaziani G, Giuliani G, Giannotti F, Arcangeli C, et al. Rheolytic thrombectomy in patients with massive and submassive acute pulmonary embolism. *Catheter Cardiovasc Interv*. 2009;73:506-13.
42. Spies C, Khandelwal A, Smith TH, Jolly N, Kavinsky CJ. Percutaneous mechanical thrombectomy for massive pulmonary embolism using a conservative treatment strategy. *J Interv Cardiol*. 2008;21:566-71.
43. Nakazawa K, Tajima H, Murata S, Kumita SI, Yamamoto T, Tanaka K. Catheter fragmentation of acute massive pulmonary thromboembolism: distal embolisation and pulmonary arterial pressure elevation. *Br J Radiol*. 2008;81:848-54.
44. Margheri M, Vittori G, Vecchio S, Chechi T, Falchetti E, Spaziani G, et al. Early and long-term clinical results of AngioJet rheolytic thrombectomy in patients with acute pulmonary embolism. *Am J Cardiol*. 2008;101:252-8.
45. Kuo WT, van den Bosch MA, Hofmann LV, Louie JD, Kothary N, Sze DY. Catheter-directed embolectomy, fragmentation, and thrombolysis for the treatment of massive pulmonary embolism after failure of systemic thrombolysis. *Chest*. 2008;134:250-4.
46. Eid-Lidt G, Gaspar J, Sandoval J, de los Santos FD, Pulido T, Gonzalez Pacheco H, et al. Combined clot fragmentation and aspiration in patients with acute pulmonary embolism. *Chest*. 2008;134:54-60.
47. Pieri S, Agresti P. Hybrid treatment with angiographic catheter in massive pulmonary embolism: mechanical fragmentation and fibrinolysis. *Radiol Med*. 2007;112:837-49.
48. Chauhan MS, Kawamura A. Percutaneous rheolytic thrombectomy for large pulmonary embolism: a promising treatment option. *Catheter Cardiovasc Interv*. 2007;70:121-8.
49. Barbosa MA, Oliveira DC, Barbosa AT, Pavanello R, Kambara A, Egito ES, et al. Treatment of massive pulmonary embolism by percutaneous fragmentation of the thrombus. *Arq Bras Cardiol*. 2007;88:279-84.
50. Tajima H, Murata S, Kumazaki T, Nakazawa K, Abe Y, Komada Y, et al. Hybrid treatment of acute massive pulmonary thromboembolism: mechanical fragmentation with a modified rotating pigtail catheter, local fibrinolytic therapy, and clot aspiration followed by systemic fibrinolytic therapy. *AJR Am J Roentgenol*. 2004;183:589-95.
51. Tajima H, Murata S, Kumazaki T, Nakazawa K, Kawamata H, Fukunaga T, et al. Manual aspiration thrombectomy with a standard PTCA guiding catheter for treatment of acute massive pulmonary thromboembolism. *Radiat Med*. 2004;22:168-72.
52. Zeni PT Jr, Blank BG, Peeler DW. Use of rheolytic thrombectomy in treatment of acute massive pulmonary embolism. *J Vasc Interv Radiol*. 2003;14:1511-5.
53. De Gregorio MA, Gimeno MJ, Mainar A, Herrera M, Tobio R, Alfonso R, et al. Mechanical and enzymatic thrombolysis for massive pulmonary embolism. *J Vasc Interv Radiol*. 2002;13:163-9.
54. Schmitz-Rode T, Janssens U, Duda SH, Erley CM, Gunther RW. Massive pulmonary embolism: percutaneous emergency treatment by pigtail rotation catheter. *J Am Coll Cardiol*. 2000;36:375-80.
55. Fava M, Loyola S, Huete I. Massive pulmonary embolism: treatment with the hydrolyser thrombectomy catheter. *J Vasc Interv Radiol*. 2000;11:1159-64.
56. Schmitz-Rode T, Janssens U, Schild HH, Basche S, Hanrath P, Gunther RW. Fragmentation of massive pulmonary embolism using a pigtail rotation catheter. *Chest*. 1998;114:1427-36.
57. Lehnert P, Møller CH, Mortensen J, Kjaergaard J, Olsen PS, Carlsen J. Surgical embolectomy compared to thrombolysis in acute pulmonary embolism: morbidity and mortality. *Eur J Cardiothorac Surg*. 2017;51:354-61.
58. Edelman JJ, Okiwelu N, Anvardeen K, Joshi P, Murphy B, Sanderes LH, et al. Surgical pulmonary embolectomy: experience in a series of 37 consecutive cases. *Heart Lung Circ*. 2016;25:1240-4.
59. Cho YH, Sung K, Kim WS, Jeong DS, Lee YT, Park PW, et al. Management of acute massive pulmonary embolism: is surgical embolectomy inferior to thrombolysis? *Int J Cardiol*. 2016;203:579-83.

60. Keeling WB, Sundt T, Leacche M, Okita Y, Binongo J, Lasajanak Y, et al. Outcomes after surgical pulmonary embolectomy for acute pulmonary embolus: a multi-institutional study. *Ann Thorac Surg*. 2016;102:1498-502.
61. Neely RC, Byrne JG, Gosev I, Cohn LH, Javed Q, Rawn JD, et al. Surgical embolectomy for acute massive and submassive pulmonary embolism in a series of 115 patients. *Ann Thorac Surg*. 2015;100:1245-51.
62. Azari A, Beheshti AT, Moravvej Z, Bigdelu L, Salehi M. Surgical embolectomy versus thrombolytic therapy in the management of acute massive pulmonary embolism: short and long-term prognosis. *Heart Lung*. 2015;44:335-9.
63. Worku B, Gulkarov I, Girardi LN, Salemi A. Pulmonary embolectomy in the treatment of submassive and massive pulmonary embolism. *Cardiology*. 2014;129:106-10.
64. Osborne ZJ, Rossi P, Aucar J, Dharamsy S, Cook S, Wheatley B. Surgical pulmonary embolectomy in a community hospital. *Am J Surg*. 2014;207:337-41.
65. Wu MY, Liu YC, Tseng YH, Chang YS, Lin PJ, Wu TI. Pulmonary embolectomy in high-risk acute pulmonary embolism: the effectiveness of a comprehensive therapeutic algorithm including extracorporeal life support. *Resuscitation*. 2013;84:1365-70.
66. Aymard T, Kadner A, Widmer A, Basciani R, Tevaerarai H, Weber A, et al. Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy—should surgical indications be revisited? *Eur J Cardiothorac Surg*. 2013;43:90-4; discussion 94.
67. Taniguchi S, Fukuda W, Fukuda I, Watanabe K, Saito Y, Nakamura M, et al. Outcome of pulmonary embolectomy for acute pulmonary thromboembolism: analysis of 32 patients from a multicentre registry in Japan. *Interact Cardiovasc Thorac Surg*. 2012;14:64-7.
68. Takahashi H, Okada K, Matsumori M, Kano H, Kitagawa A, Okita Y. Aggressive surgical treatment of acute pulmonary embolism with circulatory collapse. *Ann Thorac Surg*. 2012;94:785-91.
69. Marshall L, Mundy J, Garrahy P, Christopher S, Wood A, Griffin R, et al. Surgical pulmonary embolectomy: mid-term outcomes. *ANZ J Surg*. 2012;82:822-6.
70. Malekan R, Saunders PC, Yu CJ, Brown KA, Gass AL, Spielvogel D, et al. Peripheral extracorporeal membrane oxygenation: comprehensive therapy for high-risk massive pulmonary embolism. *Ann Thorac Surg*. 2012;94:104-8.
71. Zarrabi K, Zolghadrasli A, Ostovan MA, Azimifar A. Short-term results of retrograde pulmonary embolectomy in massive and submassive pulmonary embolism: a single-center study of 30 patients. *Eur J Cardiothorac Surg*. 2011;40:890-3.
72. Greelish JP, Leacche M, Solenkova NS, Ahmad RM, Byrne JG. Improved midterm outcomes for type A (central) pulmonary emboli treated surgically. *J Thorac Cardiovasc Surg*. 2011;142:1423-9.
73. Fukuda I, Taniguchi S, Fukui K, Minakawa M, Daitoku K, Suzuki Y. Improved outcome of surgical pulmonary embolectomy by aggressive intervention for critically ill patients. *Ann Thorac Surg*. 2011;91:728-32.
74. Vohra HA, Whistance RN, Mattam K, Kaarne M, Haw MP, Barlow M, et al. Early and late clinical outcomes of pulmonary embolectomy for acute massive pulmonary embolism. *Ann Thorac Surg*. 2010;90:1747-52.
75. Sareyyupoglu B, Greason KL, Suri RM, Keegan MT, Dearani JA, Sundt TM III. A more aggressive approach to emergency embolectomy for acute pulmonary embolism. *Mayo Clin Proc*. 2010;85:785-90.
76. Carvalho EM, Macedo FI, Panos AL, Ricci M, Salerno TA. Pulmonary embolectomy: recommendation for early surgical intervention. *J Card Surg*. 2010;25:261-6.
77. Kukla P, Bryniarski L, Dlugopolski R, Krupa E, Nowak J, Kulak L, et al. Acute pulmonary embolism registry in the Malopolska region - clinical course. *Kardiol Pol*. 2009;67:735-41.
78. Sadaba JR, Greco E, Alvarez LA, Pulitani I, Juaristi A, Goiti JJ. The surgical option in the management of acute pulmonary embolism. *J Card Surg*. 2008;23:729-32.
79. Kadner A, Schmidli J, Schonhoff F, Krahenbuhl E, Immer F, Carrel T, et al. Excellent outcome after surgical treatment of massive pulmonary embolism in critically ill patients. *J Thorac Cardiovasc Surg*. 2008;136:448-51.
80. Ahmed P, Khan AA, Smith A, Pagala M, Abrol S, Cunninghan JN Jr, et al. Expedient pulmonary embolectomy for acute pulmonary embolism: improved outcomes. *Interact Cardiovasc Thorac Surg*. 2008;7:591-4.
81. Digonnet A, Moya-Plana A, Aubert S, Fletcher E, Bonnet N, Leprince P, et al. Acute pulmonary embolism: a current surgical approach. *Interact Cardiovasc Thorac Surg*. 2007;6:27-9.
82. Amirghofran AA, Emami Nia A, Javan R. Surgical embolectomy in acute massive pulmonary embolism. *Asian Cardiovasc Thorac Ann*. 2007;15:149-53.
83. Spagnolo S, Grasso MA, Tesler UF. Retrograde pulmonary perfusion improves results in pulmonary embolectomy for massive pulmonary embolism. *Tex Heart Inst J*. 2006;33:473-6.
84. Meneveau N, Seronde MF, Blonde MC, Legalery P, Didier-Petit K, Briand F, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest*. 2006;129:1043-50.
85. Sukhija R, Aronow WS, Lee J, Kakar P, McClurg JA, Levy JA, et al. Association of right ventricular dysfunction with in-hospital mortality in patients with acute pulmonary embolism and reduction in mortality in patients with right ventricular dysfunction by pulmonary embolectomy. *Am J Cardiol*. 2005;95:695-6.
86. Leacche M, Unic D, Goldhaber SZ, Rawn JD, Aranki SF, Couper GS, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *J Thorac Cardiovasc Surg*. 2005;129:1018-23.
87. Dauphine C, Omari B. Pulmonary embolectomy for acute massive pulmonary embolism. *Ann Thorac Surg*. 2005;79:1240-4.
88. Yalamanchili K, Fleisher AG, Lehrman SG, Axelrod HI, Lafaro RJ, Sarabu MR, et al. Open pulmonary embolectomy for treatment of major pulmonary embolism. *Ann Thorac Surg*. 2004;77:819-23; discussion 823.
89. Ullmann M, Hemmer W, Hannekum A. The urgent pulmonary embolectomy: mechanical resuscitation in the operating theatre determines the outcome. *Thorac Cardiovasc Surg*. 1999;47:5-8.
90. Doerge H, Schoendube FA, Voss M, Seipelt R, Messmer BJ. Surgical therapy of fulminant pulmonary embolism: early and late results. *Thorac Cardiovasc Surg*. 1999;47:9-13.
91. Greenfield LJ, Reif ME, Guenter CE. Hemodynamic and respiratory responses to transvenous pulmonary embolectomy. *J Thorac Cardiovasc Surg*. 1971;62:890-7.
92. Lualdi JC, Goldhaber SZ. Right ventricular dysfunction after acute pulmonary embolism: pathophysiologic factors, detection, and therapeutic implications. *Am Heart J*. 1995;130:1276-82.
93. Samoukovic G, Malas T, deVarennes B. The role of pulmonary embolectomy in the treatment of acute pulmonary embolism: a literature review from 1968 to 2008. *Interact Cardiovasc Thorac Surg*. 2010;11:265-70.
94. Keeling WB, Leshnower BG, Lasajanak Y, Binongo J, Guyton RA, Halkos ME, et al. Midterm benefits of surgical pulmonary embolectomy for acute pulmonary embolus on right ventricular function. *J Thorac Cardiovasc Surg*. 2016;152:872-8.
95. Toole JM, Ikonomidis JS, Szeto WY, Zellner JL, Mulcahy J, Deardorff RL, et al. Selective endothelin-1 receptor type A inhibition in subjects undergoing cardiac surgery with preexisting left ventricular dysfunction: influence on early postoperative hemodynamics. *J Thorac Cardiovasc Surg*. 2010;139:646-54.
96. Viitanen A, Salmenpera M, Heinonen J, Hynynen M. Pulmonary vascular resistance before and after cardiopulmonary bypass. The effect of PaCO2. *Chest*. 1989;95:773-8.
97. McConnell DH, Maloney JV Jr, Buckberg GD. Postoperative intermittent positive-pressure breathing treatments. Physiological considerations. *J Thorac Cardiovasc Surg*. 1974;68:944-52.
98. Powers SR Jr, Mannal R, Neclerio M, English M, Marr C, Leather R, et al. Physiologic consequences of positive end-expiratory pressure (PEEP) ventilation. *Ann Surg*. 1973;178:265-72.

Key Words: pulmonary embolism, surgery, embolectomy, thrombolysis, catheter