

Outcomes-based systematic review for management of massive intra-cardiac or pulmonary thrombotic emboli during surgery

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ABSTRACT

Introduction: The management of massive intra-operative embolism remains controversial. Our hypothesis was that either surgical or medical thrombectomy offers survival benefit in these patients.

Methods: Published case reports were reviewed for intra-operative intra-cardiac or pulmonary embolism and outcomes for the following four intervention groups were evaluated for mortality benefit: surgical embolectomy; thrombolysis; anticoagulation; supportive care alone. We also assessed whether the use of diagnostic modalities prior to each embolism event resulted in a mortality benefit and, separately, whether post-intervention improvement in physiologic parameters resulted in improvement in outcomes. Univariate analyses and logistic regression were performed to assess the impact of the four primary interventions on mortality, the primary outcome.

Results: Seventy-eight cases were reviewed and therapeutic interventions resulted in improved survival (70 %) compared to supportive care (45 %), odds ratio = 0.38[0.15-0.98], $p = 0.04$. Univariate analysis of primary interventions with death as a primary outcome resulted in a lack of significantly different outcomes ($p = 0.08$). Mortality rates were 71 % in the thrombolytic; 28 % in surgical embolectomy; 18 % in anticoagulation and 43 % in the supportive care groups. The routine pre-event use of trans-esophageal echocardiography was not related with improved outcomes ($p = 0.36$) but the use of pulmonary artery or central venous catheters was ($p = 0.035$). Post-intervention improvements in the physiologic parameters of each diagnostic modality were associated with an improvement in mortality ($p < 0.05$).

Conclusions: Our data present some important trends among the intervention groups, raising significant concerns about the safety for the use of thrombolytics in the management of intra-operative embolism.

Keywords: *intra-cardiac, pulmonary emboli, outcome, intra-operative, case, review.*

INTRODUCTION

Pulmonary embolism is a major global public health concern, with an estimated 900,000 venous thromboembolic events occurring annually in the United States alone (1). Massive pulmonary embolism in non-surgical patients is relatively common and presents a high degree of mortality (25-65 %) (2).

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The incidence of massive intra-operative intra-cardiac or pulmonary emboli (IC/PE) is low but these intra-operative events have a high degree of mortality (68%) (3).

There is a lack of outcomes-based evidence to establish guidelines for intra-operative diagnosis and management of these rare events. Current recommendations and data emanates from case reports, case series, expert opinion, and extrapolation from other patient populations, with many practitioners relying on supportive care alone (4).

Additionally, as there is no consensus for management of intra-operative IC/PE, the utility of several diagnostic tools remains unclear. Thus, this review evaluated four commonly used diagnostic modalities under the primary end-point of in-hospital mortality to identify whether the use of more invasive modalities prior to the IC/PE event improved mortality and whether post-intervention improvements in the physiologic parameters for each modality correlated with improvement in patients' outcomes. Therefore, we conducted this systematic review with the primary intention of evaluating mortality outcomes for four intervention groups in the management of thrombotic IC/PE: surgical embolectomy (5, 6); thrombolysis (2, 7, 8); anticoagulation (9, 10); or supportive care alone. We hypothesized that either surgical or medical thrombectomy offers survival benefit in massive intraoperative IC/PE and also evaluated the use of more invasive techniques for early detection of IC/PE along with the improvement of physiologic parameters for each modality.

METHODS

To identify the relevant literature, we used computerized literature searches of the OVID and National Library of Medicine's PUBMED databases from 1957 to January

2012, in addition to the Google Scholar's database, limited to articles in or translated-to English. The search strategy was set up using the words: *pulmonary embolism, pulmonary emboli, thromboembolism, thrombosis, thrombus, embolus, intra-cardiac thrombosis, or cardiac thrombi*, in combination with *intra-operative, operative, or surgery*. Reference lists of relevant articles were checked for additional relevant articles. Four broad therapeutic intervention groups were selected and each of them assessed under the primary end-point of in-hospital mortality:

- 1) surgical embolectomy (encompassing both open surgical techniques and percutaneous embolectomy) (5, 6);
- 2) thrombolysis (with variability in choice of thrombolytic agent, dosing, mode of delivery, and frequency of administration) (2, 7, 8);
- 3) anticoagulation (typically heparin, but at variable doses and duration of therapy) (4, 9, 10) supportive care alone.

Additionally, four diagnostic modalities were assessed under the primary end-point of in-hospital mortality in two different ways: whether the use of more invasive modalities prior to the IC/PE event improved mortality and whether post-intervention improvements in the physiologic parameters for each modality correlated with improvement in patients' outcomes. The four diagnostic modalities were: invasive and non-invasive monitoring of vital signs; pulmonary artery catheter (PAC) or central venous monitoring device (CVP); end-tidal carbon dioxide monitoring (EtCO₂); and trans-esophageal echocardiography (TEE). A subgroup analysis for thrombotic type emboli was also performed to assess whether outcomes were different in the thrombotic subtype group. Invasive monitoring was defined as use of the PAC, CVP and arterial line monitoring. Non-invasive monitoring includes standard ASA

monitoring. Massive emboli were defined as events contributory to sudden hemodynamic instability.

The primary end-point of mortality was used for each diagnostic and therapeutic modality. All data were derived from case reports or case series outlined in the reference section. Inclusion criteria required that major embolic disease was present, but the diagnosis criteria were not objectively defined. Diagnosis was instead left to the discretion of the practitioner and institution, and in some cases the diagnosis was made post-mortem. All reports for extra-operative embolic events were excluded, as were reports of emboli or thromboembolic that did not result in hemodynamic compromise or were not classified as major embolic disease by the authors. There were 7 cases that met the above-mentioned inclusion and exclusion criteria, but were ultimately excluded because the presenting sign of IC/PE was sudden death, which did not allow for any of the four primary interventions assessed in this review to be initiated. Amniotic fluid embolism was not analyzed in this review. Additionally, non-thrombotic emboli's and neoplastic related emboli's were not included in the assessment of therapeutic modalities and mortality outcome. Funding was not obtained for this review.

Statistical analyses and data collection. Data were entered into a Microsoft Excel worksheet and transferred to a NCSS datasheet version 2007 (Salt Lake, UT). Data analysis was also limited by selective reporting within studies. Univariate analyses of categorical data (either binomial or multinomial) were done using chi-squared and Fisher's exact test and logistic regression to assess the impact of the four primary interventions on mortality. Odds ratios (OR_s) were reported with 95% confidence interval and Pvalues less than 0.05 were considered statistically significant. For the

analysis of each treatment modality, the supportive care group was used as the reference. Age was the only numerical data that was used in multivariate logistic regression as an independent factor to predict patient mortality. The results for numerical variables were reported as mean \pm standard deviation and were analyzed using one-way analysis of variance (ANOVA).

RESULTS

A total of 3,084 reports were screened. Data from a total of 78 cases meeting inclusion and exclusion criteria were reviewed (*Table 1*) but one case of amniotic fluid embolism and 7 patients who presented with sudden death were excluded for analysis of therapeutic intervention (*Table 1*).

Overall mortality was not statistically different between women (44%) and men (38%), with 50% of patients being female (*Table 1*). Although the number of the reported cases of intraoperative IC/PE increased over past 40 years, the mortality rate for this uncommon event has remained stable (40.9%) as depicted in *Figure 1*. Different types of emboli were not statistically significant predictors of mortality. Among all the cases reported, the thrombotic etiology (61.5%) was the most common type of emboli followed by gaseous (17.9%) (5, 10, 11-21) and neoplastic emboli (16.7%) (22-29). There were also two cases of fat emboli (30) and one case of amniotic fluid embolism (31) (*Table 1*). The mortality rates were similar among those with thrombotic and neoplastic etiologies (43.5% and 40.0%, respectively) which were significantly worse than those with air embolism (27.3%, $p < 0.05$). The type of surgery did not have a statistically significant impact on mortality.

Although there were reports of incidental diagnosis of IC/PE by use of TEE, the preoperative use of this tool did not alter

Table 1 - Demographic distribution of the reported cases between survivors and non-survivors.

	Survivors N = 46	Non-survivors N = 32	p value
Gender (female/male)	22/24	17/15	0.93
Age	54.5 ± 15.9	49.5 ± 21.1	0.31
Type of the embolus			
Thrombotic	28 (61%)	20 (63%)	0.41
Neoplastic	6 (13%)	8 (25%)	
Air (Gaseous)	10 (22%)	3 (9%)	
Other*	2 (4%)	1 (3%)	
Type of Surgery			
GI (stomach, intestine)	11 (73%)	4 (27%)	0.24
CNS (Central Nervous System)	1 (100%)	0 (0%)	
CVS (Cardiovascular System)	9 (75%)	3 (25%)	
GU (including Kidneys)	6 (67%)	3 (33%)	
Liver Transplant (8,9,46-56)	10 (59%)	7 (41%)	
Ortho/Spine	8 (50%)	8 (50%)	
Preoperative placement of PAC	23 (50%)	7 (21%)	0.035*
Preoperative placement of TEE	11 (24%)	5 (16%)	0.36

PAC = Pulmonary artery catheter; TEE = Trans-esophageal echocardiography.

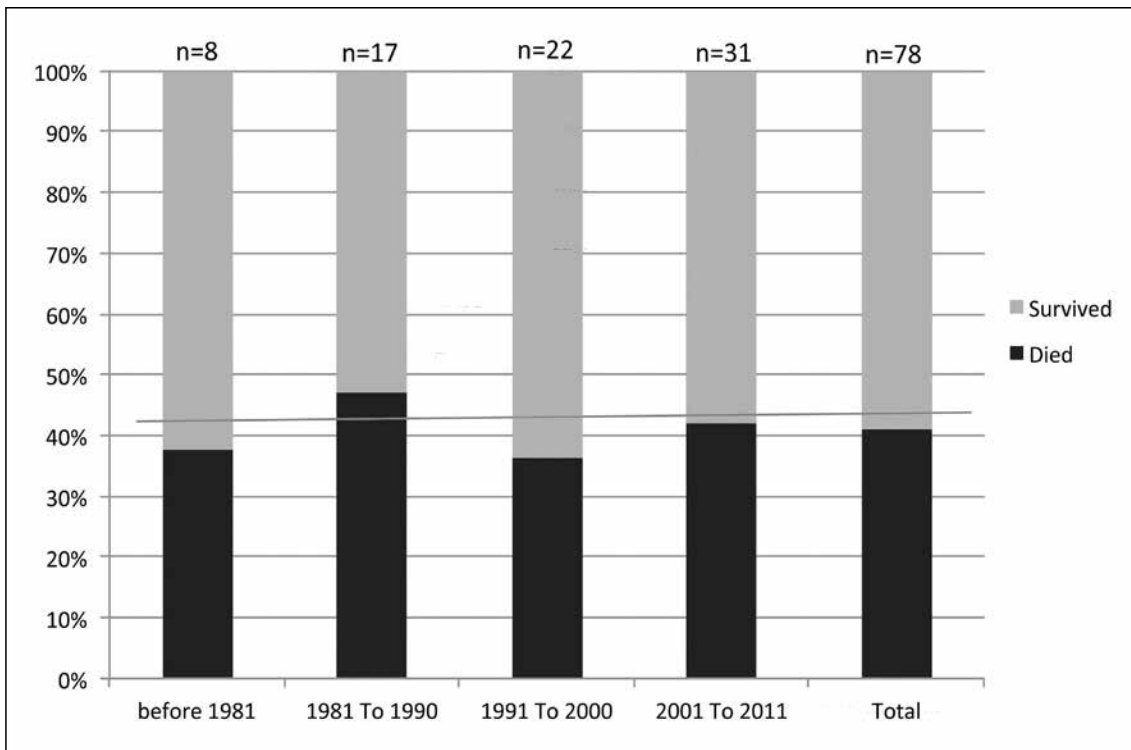


Figure 1 - The mortality rate of intra-operative intra-cardiac or pulmonary embolism over time.

Table 2 - Mortality outcomes per improvement in post-intervention physiologic parameters.

	Survivors	Non-survivors	p value
Vital Signs			< 0.001
Did Not Improve	0 (0%)	7 (100%)	
Improved	37 (84%)	7 (16%)	
End-tidal Carbon dioxide			0.002
Did Not Improve	0 (0%)	4 (100%)	
Improved	11 (85%)	2 (15%)	
Wall Motion Abnormality			0.034
Did Not Improve	2 (33%)	4 (67%)	
Improve	10 (83%)	2 (17%)	
Pulmonary Artery Pressures			< 0.001
Did Not Improve	0 (0%)	6 (100%)	
Improve	20 (87%)	3 (13%)	

mortality. However, the use of PAC prior to the embolic event was associated with improved mortality (OR = 0.3[0.1-0.8], $p = 0.035$, *Table 1*). For post-intervention monitoring, improvements in physiologic parameters for each of the four diagnostic modalities correlated significantly with

survival, but it is worthwhile noting that 13-16% patients that showed early improvement of vital signs did not survive (*Table 2*).

Of note, to assess the efficacy of each therapeutic intervention, we excluded 7 patients who manifested with sudden cardiac death

Table 3 - Mortality outcomes per primary intervention.

All Patients	Survivors N = 45	Non-survivors N = 25	OR [95% CI]
Embolectomy (Surgical)	21 (72%)	8 (28%)	0.8 [0.3-1.8]
Thrombolysis (Medical)	2 (29%)	5 (71%)	3.3 [0.5-20.4]
Anticoagulation	9 (82%)	2 (18%)	0.3 [0.1-1.6]
Supportive Care	13 (57%)	10 (43%)	Reference
Thrombotic Subgroup	N = 28	N = 20	
Embolectomy (Surgical)	11 (39%)	4 (20%)	0.3 [0.1-1.3]
Thrombolysis (Medical)	2 (7%)	5 (25%)	1.9 [0.3-13.2]
Anticoagulation	8 (29%)	2 (10%)	0.2 [0.0-1.2]
Supportive Care	7 (25%)	9 (45%)	Reference
Thrombotic Subgroup	N = 28	N = 20	
Embolectomy (Medical + Surgical)	13 (46%)	9 (45%)	0.6 [0.1-2.0]
Anticoagulation	8 (29%)	2 (10%)	0.2[0.0-1.2]
Supportive Care	7 (25%)	9 (45%)	Reference
Thrombotic Subgroup	N = 28	N = 20	
Intervention	21 (75%)	11 (55%)	0.4 [0.1-1.3]
Supportive Care	7 (25%)	9 (45%)	Reference

OR = Odds ratio; CI = Confidence interval.

that precluded them from further treatment modality. Overall, therapeutic interventions resulted in a better outcome compared to those received supportive care. Regardless of the cause of the embolus, 32 out of 47 patients (70%) survived when all types of therapeutic intervention were aggregated (e.g., surgical embolectomy, thrombolysis or conventional anticoagulation) while only 14 out of 31 patients (45%) survived with instituting a supportive care, OR = 0.38[0.15-0.98], $p = 0.04$. Univariate analysis of primary interventions with death as a primary outcome resulted in a lack of significantly different outcomes ($p = 0.08$), but some striking findings should be noted. After separating the type of the interventions, 9 out of 11 patients (82%) in the anticoagulation intervention group and 21 out of 29 patients (72%) in the surgical embolectomy group survived, compared to 2 out of 7 patients (29%) in the thrombolytic group and 13 out of 23 patients (57%) in the supportive care group (Table 3). However, the total number of patients was too low to provide sufficient power to show a significant difference among the groups.

Since the usefulness of the therapeutic interventions examined were most relevant to thrombotic emboli through decreasing the size of the embolus by preventing clot formation or by its lysis/removal, we reexamined their effect on mortality in thrombotic subtype alone (N = 48). Again, there were no significant differences in outcome among the treatment groups in comparison to supportive care ($p = 0.10$).

DISCUSSION

We confirmed that massive intra-cardiac and pulmonary emboli are rare events in the operating room but are associated with high rates of morbidity and mortality (3).

To our knowledge, this is the first study to provide evidence-based recommendations for management of intraoperative IC/PE. This review might offer a 2C level of evidence and a Grade B recommendation.

The presence of a triad of inflammation, venous stasis and hypercoagulability promotes thrombus formation, which may in turn result in massive IC/PE. During intra-operative period application/release of tourniquet or Esmarch band has been reported to cause massive IC/PE (32-36).

Although no statistically significant mortality differences were identified among the intervention groups, some striking findings should not be ignored. Primarily, mortality was far greater in the thrombolytic intervention group (71%) than in any of the other groups (surgical embolectomy, 28%; anticoagulation, 18%; supportive care, 43%). These results did not reach statistical significance because the data available from published reports resulted in an underpowered sample, but the degree of difference in mortality raises significant concerns about the safety of the use of thrombolytics for management of intraoperative IC/PE. Subsequent review of this topic with additional cases may yield adequate power to confirm this trend, but in the interim period it may be prudent for practitioners to consider thrombolysis as a therapy associated with a greater degree of mortality.

The finding that thrombolytic therapy is associated with worse outcomes contradicts recommendations from several sources, including the AHA/ACC guidelines for management of massive pulmonary emboli outside of the operating room environment (7). This discordance of results may be because use of thrombolytics is contraindicated for patients whom have undergone recent surgery, suggesting that intraoperative use of thrombolytics may be contraindicated altogether (37). The use of thrombolytics in the non-operative environment for treatment

of pulmonary embolus in patients with contraindications has been assessed and has been reported to be high (40%), but included a high incidence of complications (major bleeding in 92 of 478 patients and cerebral bleeding in 5 patients) (2).

Diagnostic tools were also assessed for their correlation to mortality outcomes. Use of PAC prior to the occurrence of the event significantly correlated with improvements in survival, which may be explained by allowing for early detection of changes in hemodynamic variables that would otherwise not have been monitored. Although early use of TEE (prior to the embolic event) has improved the diagnosis of IC/PE in some cases (38-44) the routine perioperative use of this device was not associated with an improved outcome. When intraoperative embolic events were suspected, however, TEE was often initiated intraoperatively, proving to be a useful diagnostic and prognostic tool. In addition to visualization the mass of thrombus or tumor, TEE was generally felt to increase the detection of wall motion abnormalities and post-intervention improvements in right ventricular wall motion that correlated positively with improved survival (40).

In fact, for each of the diagnostic modalities (vital sign monitoring, EtCO₂ monitoring, PAC, and TEE) post-intervention improvements in physiological parameters were positively correlated with an improvement in survival, but it is well worth noting that 13-16% of patients with improvement in these parameters subsequently died. This is cause for caution to each practitioner who might see improvement post-intervention, as there is still a high incidence of mortality for an undefined subset of patients.

Limitations

As this study is a systematic review of previously published literature, it is inherently burdened with multiple limitations but, al-

though a greater evidence grade would be preferable upon which to establish guidelines, it is currently impossible to perform a prospective randomized trial for management of massive intra-operative IC/PE. Aside from the standard limitations of a retrospective review (publication bias, recall bias of past reports, and inconsistent data reporting), perhaps the most obvious limitations in this particular study were the relative infrequency of events, the lack of standardization between cases, and the relatively low level of evidence, as all data were extracted from previous case reports or series. Secondly, in a study of liver transplant patients whose procedures were complicated by pulmonary emboli and/or intra-cardiac thrombi, the authors compared subgroups and reported that pulmonary embolus alone was associated with a greater mortality rate as compared to combination pulmonary emboli and intra-cardiac thrombi (3). Our review did not include such a subgroup analysis evaluating the effectiveness of each intervention based on anatomical distribution of emboli or thromboemboli. Additionally, there was inter-operator variability in the technique and/or delivery of each therapeutic intervention, and the resultant variation may have significant clinical implications that cannot be effectively accounted for with the current available data.

In regards to diagnostic modalities, there was a lack of consistency in reporting of the use of each diagnostic tool, predisposing this study's resultant statistical analysis to reporting bias. The use of intra-operative TEE has often been reported and is thought to be an effective diagnostic modality as it has the capacity to both directly visualize an IC/PE and, indirectly, to establish cardiac strain as indirect evidence of hemodynamic compromise caused by mass effect (45) but its use prior to a massive embolic event was not associated with improved mortality

outcomes (40). Nonetheless, improvement in visualized cardiac function was associated with improved outcomes. Amniotic fluid embolism was not analyzed in this review, which was in itself conducted under the assumption that mass effect contributes most significantly to the pathophysiology of massive intra-operative IC/PE events, but it has been postulated that immune modulatory pathways play a significant role in the pathophysiology of amniotic fluid emboli, perhaps more so than with other causes of IC/PE (11). Hence, it would have been inappropriate to assess whether therapeutic modalities such as surgical embolectomy (one of the four intervention groups) result in better or worse outcomes, considering that mass excision may not be possible for amniotic fluid emboli.

CONCLUSION

Prior to this review, recommendations for management of massive intra-operative IC/PE were limited to supportive care measures and analyses from data extrapolated from other patient populations. In this systematic review, anticoagulation and surgical embolectomy resulted favorable therapies for management of intra-operative IC/PE, while a trend toward harm from use of thrombolytic agents was noted.

When the size of the embolus is large enough to produce acute hemodynamic derangement, the surgical removal of the thrombus or tumor clearly offers early survival benefit and may decrease the mortality in the long run. Of note, not all institutions have the capacity to do surgical embolectomy or support a patient on cardiopulmonary bypass and, for those that do, it is worth emphasizing that anticoagulation resulted in an equally good outcome in those with thrombotic emboli, without introducing the morbidity associated with

cardiac surgery. It is of further value to re-emphasize that 13-16% of patients died despite post-intervention improvement in vital signs and other physiological measures, irrespective of the intervention utilized, and practitioners should remain vigilant in the post-intervention period as a significant as-of-yet undefined subset of patients appear to remain at higher risk for mortality. Further studies are necessary to obtain a higher level of evidence to strengthen recommendations for management of these often-catastrophic intra-operative events.

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