

Residual pulmonary hypertension after retrograde pulmonary embolectomy: long-term follow-up of 30 patients with massive and submassive pulmonary embolism

Khalil Zarrabi^a, Abdolali Zolghadrasli^{b,*}, Mohammad Ali Ostovan^c, Azimeh Azimifar^d and Leila Malekmakan^e

^a Department of Cardiac Surgery, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

^b Shiraz Cardiovascular Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran

^c Department of Cardiology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

^d Department of Physiology, International Unit of Shiraz University, Shiraz, Iran

^e Department of Community Medicine, Shiraz Nephro-Urology Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran

* Corresponding author. Shiraz Cardiovascular Research Center, Shahid Faghihi Hospital, P.O. Box 7134844119, Shiraz, Iran. Tel/fax: +98 711 2343529; e-mail: abdolali_zolghadr@yahoo.com (A. Zolghadrasli)

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Abstract

OBJECTIVES: Pulmonary hypertension is a major cause of morbidity and mortality in patients following acute pulmonary embolism. Although thrombolytic therapy decreases pulmonary arterial pressure, compared with anticoagulation alone, it has the propensity for haemorrhagic complications, distal embolization and incomplete recanalization, with the potential risk of late pulmonary hypertension. Surgical embolectomy—once performed solely on critically-ill patients—has now gained favour in a wider range of patients. In this paper we present the outcomes of patients who underwent surgical embolectomy complemented with retrograde technique and follow-up systolic pulmonary arterial pressure (SPAP).

METHODS: From January 2004 to December 2010, 30 consecutive patients with a mean age of 58 ± 15 years underwent pulmonary embolectomy at our centre. The patients were followed for a mean period of 30.5 ± 12 months. Their New York Heart Association (NYHA) classifications were assessed and their SPAPs were measured by echocardiography.

RESULTS: The overall mortality rate was 13.2% (4/30). Of the remaining patients, 19 patients (73.1%) were in NYHA classes I and II, 7 patients (26.9%) in class III and no patient in class IV. The patients' preoperative and postoperative mean SPAPs were 44.9 ± 5.7 and 34.9 ± 7.1 mmHg, respectively, which showed a significant reduction ($P < 0.001$). The mean SPAP in the follow-up was 29.4 ± 11.5 mmHg, which again showed significant reduction compared with early postoperation values ($P < 0.001$). No significant correlations were found between the level of SPAP reduction in patients' follow-up with age ($P = 0.727$) and total days of ICU admission ($P = 0.700$), but weak correlations with sex ($P = 0.016$) and total intubation time were noticed ($P = 0.035$).

CONCLUSIONS: This is the first series reporting the long-term outcome of patients undergoing surgical embolectomy complemented by retrograde embolectomy technique, demonstrating the safety and favourable long-term outcome of this technique. It is also a new element in the growing body of evidence regarding the relevance of surgical embolectomy in patients with acute pulmonary embolism. We concluded that, following surgery, not only does the pulmonary arterial pressure drop immediately, but also the trend toward normalization continues long after operation.

Keywords: Surgical pulmonary embolectomy • Retrograde pulmonary embolectomy • Acute pulmonary embolism • Chronic thrombo-embolic pulmonary hypertension

INTRODUCTION

Chronic thrombo-embolic pulmonary hypertension (CTPH), defined as mean pulmonary arterial pressure above 25 mmHg persisting 6 months after the diagnosis of acute pulmonary embolism, is a relatively rare complication that is estimated to occur in 2–4% of patients after the acute event [1, 2]. This complication causes considerable morbidity and, although late mortality is determined mainly by comorbidities—particularly cancer—it may also cause mortality, mainly due to progressive right ventricular (RV) failure [1–4].

Following acute pulmonary embolism, thrombolytic therapy and catheter embolectomy have been proved to be effective in decreasing pulmonary arterial pressure by restoring patency of vessel, thereby reducing right ventricular pressure and stabilizing patients' haemodynamics [1, 5, 6]. However, these procedures are associated with haemorrhage, distal embolization and failure to completely resolve the intraluminal thrombus, rendering the patient amenable to development of chronic thrombo-embolic pulmonary hypertension [6–8]. Whilst surgical embolectomy has usually been reserved for patients who were critically ill, there has been a resurgence in recent years—driven by improved surgical

technique, better postoperative care and, especially, lower mortality rates in recent series—which has resulted in enhanced indications for the use of surgical embolectomy in patients with acute pulmonary embolism [6–18].

Previously, we presented an improved technique for retrograde pulmonary embolectomy, which complemented the current conventional antegrade technique, and published the short-term results on 30 patients; herein we present the long-term follow-up and analysis of the pulmonary arterial pressures of the patients who underwent surgical embolectomy with retrograde technique.

PATIENTS AND METHOD

Patient population

From January 2004 through 30 December 2010, patients with massive and submassive pulmonary embolism underwent pulmonary embolectomy in two university teaching hospitals. The study included 15 men and 15 women with a mean age of 58.2 ± 15.6 years, ranging from 28 to 80 years. The most common risk factors for development of pulmonary embolism were deep vein thrombosis (14.46%), followed by recent surgery (7.23%).

The indications for surgery were severe haemodynamic and/or respiratory compromise in 11 patients (36%) judged to be on the verge of cardiac arrest, with three of them actually experiencing cardiac arrest at some point before operation; lack of response to intravenous thrombolysis in 10 patients (30%); contraindication for thrombolysis in 7 patients (23%) and, in 2 patients (6%), because of concomitant patent *foramen ovale*.

Surgical technique and hospital course

Surgery involved median sternotomy with bicaval cannulation and total circulatory bypass. Then the main pulmonary artery was opened distal to the pulmonary valve and the incision was extended as needed up to the bifurcation of the artery. The clots were removed by means of atraumatic forceps, bolus saline flush and suction. Thereafter, an atrial septostomy was created and pulmonary vein orifices in the left atrium were identified and cannulated, one by one, with a 5-French to 5.5 French endotracheal tube and irrigated with oxygenated blood with a mean pressure of 30–45 mmHg for 60–120 s for each vein. In this way, any peripherally lodged thrombus fragments were washed out in a retrograde manner. At the end of the operation, the atrial septal defect was closed and the systolic and diastolic pulmonary artery pressure was directly measured before and after cardiopulmonary bypass. The patients were then transferred to the intensive care unit (ICU). All the surviving patients were anticoagulated with unfractionated heparin and then warfarin, and were discharged from hospital for the care of their primary physician.

Study design

For the purposes of this study, the surviving patients were contacted and asked to refer to our outpatient clinic. The study objectives were explained to them and informed consent was obtained. A full physical examination was performed; their New York Heart Association (NYHA) classification was evaluated by a physician and they underwent transthoracic echocardiography to assess

their systolic pulmonary arterial pressures (SPAP), carried out by a cardiologist who was unaware of the study goals. The SPAP was estimated from the tricuspid valve regurgitant jet velocity plus the right atrial pressure estimated from the inferior *vena cava*, and is expressed in mmHg.

Statistical analysis

Repeated measure design was used to compare the SPAPs of patients in the three periods of preoperation, postoperation and long-term follow-up because of variable follow-up in our patient population. We used repeated measure without any covariates that were significant ($P < 0.05$). Accordingly, we included age as a covariate and sex as a factor and used the full model (sum of squares type III) to construct our model.

In order to analyse correlation of numerical and nominal variables with preoperation and postoperation SPAP values, Spearman's rho- and Mann-Whitney *U*-tests were used, respectively. P -value < 0.05 was considered weakly significant and < 0.001 strongly significant.

RESULTS

The mean postoperative follow-up was 30.5 ± 12 months with a range of 6–61 months. The overall mortality rate in our study was 13.2% (4/30). A 60-year-old woman died during operation, due to severe right ventricular dysfunction; a 79-year-old man after 2 months of ICU care, due to heart and renal failure; a 65-year-old man after 6 months, due to renal cell carcinoma related complications and a 75-year-old woman with Cushing's syndrome died after 20 months, due to sepsis. In total, twenty-six patients completed the study; 12 women (46.2%) and 14 men (53.8%) with a mean age of 56.3 ± 15.8 years. The mean intubation time for this group of patients was 52.7 ± 37.1 h and the mean stay in ICU was 7.3 ± 11.7 days. Nineteen patients (73.1%) were in NYHA class I and II—indicative of only slight limitation of activity—and 7 patients (26.9%) were in NYHA class III—showing marked limitation of activity—with no patients in NYHA class IV.

Measured directly in the operating room, the patients' preoperative and postoperative mean SPAPs were 44.9 ± 5.7 and 34.9 ± 7.1 , respectively, which showed a significant reduction ($P < 0.001$). The mean SPAP in the follow-up, measured by transthoracic echocardiography, was 29.4 ± 11.5 , which showed significant reduction compared with both preoperation and early postoperation values ($P < 0.001$), which was independent of age and sex after insertion of these factors (P -values of 0.294 and 0.147, respectively) (Table 1, Fig. 1).

We performed a correlation study for baseline SPAP, the immediate fall in SPAP following operation and the further diminution of SPAP in follow-up with different variables (Table 2). There was no correlation between age of patients on admission and total days in ICU with the level of SPAP reduction in patients' follow-up, compared with preoperation values ($P = 0.727$ and 0.700 , respectively) but there was a weak positive correlation with intubation time ($P = 0.035$) and sex of the patients ($P = 0.016$). There was no meaningful correlation between age of patients on admission and total days in ICU ($r = 0.144$, $P = 0.483$) but there was a weak correlation with total intubation time ($r = 0.404$, $P = 0.041$).

Table 1 Mean pressures and minimum and maximum ranges of pulmonary systolic pressures measured at three intervals in the study group

Systolic pressure	Mean \pm SD (mmHg)	Minimum (mmHg)	Maximum (mmHg)	P-value
Preoperation	44.9 \pm 5.7	35.50	55.00	0.001
Early postoperation	34.9 \pm 7.1	22.50	50.00	
Follow-up study	29.4 \pm 11.5	16.00	60.00	

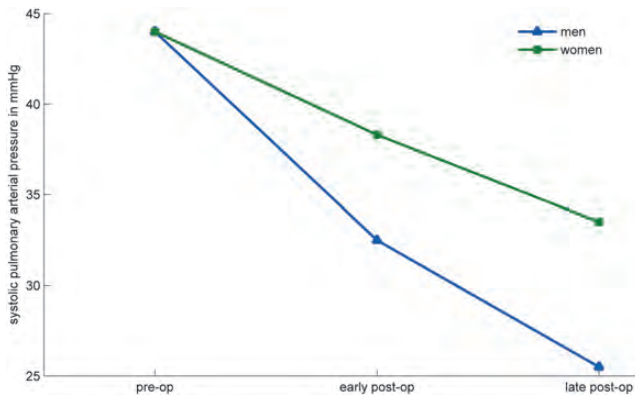


Figure 1. Repeated measure of the systolic pressures in the study group.

Table 2 Correlation coefficients of age, intubation time and ICU admission days with baseline SPAP and the fall in this value immediately after operation and in the follow-up

	Preop SPAP	Differences in Preop and early postop SPAP	Differences in early and late postop SPAP
Age	0.057	-0.077	0.146
Intubation time	0.039	0.085	0.442*
ICU admission	0.065	0.146	0.357

SPAP: systolic pulmonary arterial pressure; ICU: intensive care unit.
* $P < 0.05$.

DISCUSSION

Historically, surgical embolectomy has always been reserved for critically ill patients. Current guidelines still recommend thrombolytic therapy for patients with massive and submassive pulmonary embolism with haemodynamic compromise, and propose surgical embolectomy as a substitute in case thrombolytic therapy is either contraindicated or ineffective [19]. Nevertheless, due to the overwhelmingly encouraging results of surgical embolectomy, many centres now offer this procedure as first-line therapy for such patients and have added patients with right ventricular failure, patent *foramen ovale* and intracardiac thrombi to the list of patients eligible for surgery [6–18, 20]. A recent paper by Aymard et al. proposed computed tomography scan derived right

ventricle/left ventricle ratio (RV/LV CT ratio) as a new index for eligibility of patients for surgery [18].

Thrombolytic agents lyse organized clots, restore flow in the pulmonary artery, improve haemodynamics and have been shown to decrease short-term mortality and the likelihood of development of pulmonary hypertension, compared with anticoagulation alone [1, 2, 5, 6]. Despite these favourable outcomes, thrombolytic therapy is associated with long-term morbidity and is contraindicated in up to 50% of patients [6]. It is associated with the risk of bleeding in as much as 21.9% of patients and intracerebral haemorrhage rate of 0.7–6.4% [5–7, 9, 10]. Another concern that is not addressed in current guidelines is the limited time window available in critically ill patients before thrombolytic agents take effect, since most deaths are reported within the first few hours: what is more distressing is the delay in definitive management in patients with lack of response to thrombolytic therapy, who show higher mortality rates after surgery [6, 9, 11, 18]. Operative mortality increases significantly in patients with preoperative cardiac arrest, with reports as high as 30%, even with preoperative percutaneous cardiopulmonary support, prompting some authors to advocate a strategy of aggressive and early surgery in all patients with impending RV failure [9, 10]. Considering all these shortcomings of thrombolytic therapy, in parallel with emerging reports of favourable outcomes of surgery with comparable and even superior mortality benefit and higher symptomatic relief, many institutes including our centre were encouraged to revise their eligibility criteria for surgical embolectomy [6–18, 20]. The mortality rate in our study was 13.2% (4/30) in a mean follow-up of 30.5 ± 12 months. This is within the range reported by other studies and imitates the trend of decreased mortality rates in recent series [6, 7, 9–18]. The mortality rate was reported to be around 35% before 1985, 20% in the following decade and from 5.3 to 27.2% in recent series, attributed to better surgical techniques, improved perioperative care, early surgery and widened indication for surgery including patients with more stable haemodynamics [9, 11]. In our study, the mortality rate in the subgroup of patients with preoperative cardiac arrest was 33.3% (1/3) again reflecting the need to allocate such patients for earlier operation. It is widely believed that, during the first 30 days after the index event of acute embolism, the main cause of death is RV failure, whereas underlying comorbidity is the primary cause thereafter [14, 21]. In line with this belief, our only mortality in the first 30 days was a woman who died during operation due to RV failure and the other three mortalities were related to underlying problems.

As stated earlier, CTPH is a major cause of late morbidity and even mortality in patients surviving acute pulmonary embolism [2, 3, 8]. Thrombolytic embolectomy lessens the risk of development of CTPH, compared with anticoagulation alone, and surgical embolectomy can also prevent clot organization and thromboembolic scarring, resulting in decreased possibility of CTPH [1, 5, 14]. Clot fragmentation with showering to distal arteries is commonly seen with catheter-based embolectomy and incomplete recanalization is always a possibility in patients receiving thrombolytic therapy, rendering the patient amenable to the development of pulmonary hypertension, although no clinical trial has directly compared these two methods in this respect [6]. Retrograde pulmonary embolectomy, which was first performed in 1966 with subsequent modifications, has the advantage of dislodging the remaining clots in distal pulmonary vasculature not approached in antegrade technique [22, 23]. Consequently, compared with the antegrade technique alone, this will help to prevent pulmonary hypertension, without injury to lung parenchyma or the pulmonary

arterial wall by forceps or Fogarty catheters [8, 16]. Few studies have directly addressed the issue of patient follow-up based on SPAP. In this study, we have shown that the pulmonary artery pressure falls immediately after operation and the normalization of pulmonary artery pressure continues even in the long-term follow-up. This is in agreement with the findings in other reports demonstrating the dynamic nature of the pulmonary vasculature and its propensity toward higher or lower values, especially in the first two years after the acute event [2]. Potential risk factors for the development of CTPH are multiple episodes of pulmonary embolism, younger age, larger perfusion defect and idiopathic presentation of pulmonary embolism [2]. In our study we analysed age, sex, intubation time and days spent in the ICU and found that higher age is associated with longer intubation time after operation which, in turn, may be associated with higher SPAP in follow-up. Moreover it was demonstrated that female gender may be associated with less favourable response, compared with male gender (Table 2, Fig. 1). These findings, although interesting, were found in correlation studies and need to be confirmed in larger observational studies in order to be relied upon.

NYHA classification is a useful and simple index to evaluate the symptoms of the patient. Both thrombolytic and surgical embolectomy have favourable effects on the symptoms of patients with acute pulmonary embolism, with at least one report indicating a lower proportion of patients having subjective complaint of dyspnoea after surgical embolectomy, compared with thrombolytic therapy [20]. In our report 73.1% of patients were in NYHA class I and II, which is near the range of 73.3–86% reported in other studies [7, 20]. Some of these reports excluded patients with left-sided systolic dysfunction and valvular disease while, in our series, five surviving patients had moderate-to-severe left-sided dysfunction (ejection fraction <40%) in the follow-up echocardiography, which can be a cause of dyspnoea. In addition, considering the fact that some patients with CTPH are asymptomatic and some symptomatic patients have causes of dyspnoea not attributable to pulmonary hypertension, and that we did not actively seek for the causes of dyspnoea in our patients, this seems to be an acceptable result [1, 2, 20]. In our study, there was a close association between NYHA classification and SPAP; while 73.1% of patients were in NYHA classes I and II, 76.9% (20/26) had SPAP below 40 mmHg at follow-up. Whether or not NYHA classification is an accurate clinical indicator to follow the patients after pulmonary embolism needs to be validated in larger studies, with at least one study reporting acceptable correlation between NYHA classification and SPAP [20].

This is the first series published regarding the long-term outcome of patients undergoing surgical embolectomy complemented by modified retrograde embolectomy technique, demonstrating the safety and encouraging long-term outcome of this technique. It is also a new piece in the growing body of evidence regarding the relevance of surgical embolectomy in patients with pulmonary embolism. Additionally, this is one of the few studies to follow the patients with an objective and reproducible index, i.e. systolic pulmonary arterial pressure. It was also interesting to notice that the pulmonary arterial pressure does not fall only immediately following surgery, but that the pressure normalization continues well into long-term follow-up. Considering the overall safety of pulmonary embolectomy, even in the context of more unstable patients usually selected for this approach, the time has perhaps come to conduct a large, clinical, randomized trial to compare the short-term and long-term outcomes of this approach with thrombolytic embolectomy.

This study has its own limitations: first of all, it is a non-randomized study, subject to bias of patient selection. Additionally, the patients' SPAPs were measured by echocardiography in the follow-up study, while their immediate preoperative and postoperative SPAPs were measured directly in the operating room. Although there is close correlation between echocardiographic and catheter-based measurement of pulmonary arterial pressure, this discrepancy in measurement methods should be considered when analysing the study data [24]. Finally, this is a retrograde study and patients were investigated at different stages of the postoperation period. If patients could be followed prospectively, and echocardiography was performed in the same stage for all patients, more consistent results could be obtained.

Conflict of interest: none declared.

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eComment. Paradigm shift in surgery for massive pulmonary embolism: If not now then when?

Author: Anand Sachithanandan

Serdang Hospital, Kuala Lumpur, Malaysia

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This retrospective study by Zarrabi *et al.* adds to the growing repository of contemporary evidence regarding the safety and efficacy of surgical embolectomy for massive and submassive pulmonary embolism [1]. The authors highlight the potential for chronic thromboembolic pulmonary hypertension, an important but often overlooked sequelae of suboptimal therapy which may result following anticoagulation only, or catheter directed thrombolysis due to incomplete recanalization. The significant consistent reduction in pulmonary arterial systolic pressures reported on serial studies immediately before and after surgery and on follow-up is most encouraging.

Despite improved outcomes, a surgical embolectomy largely remains a second line or last resort alternative therapy, perhaps burdened by historical outcomes. However, with the increased availability of cardiopulmonary bypass support and more detailed imaging (computed tomography and transoesophageal echocardiography), a surgical embolectomy should feature early in the treatment algorithm of any patient with a large volume central thrombus burden in the main pulmonary artery or proximal branch pulmonary arteries. Surgery should also be considered for the haemodynamically stable patient who may have features of impending right ventricular dysfunction, a known prognosticator for an embolism-related early (in-hospital or 30 day) death [2].

In carefully selected patients, an early surgical embolectomy may offer the best opportunity to rapidly and completely reperfuse the pulmonary arterial vasculature, thereby avoiding potential future complications such as chronic thromboembolic pulmonary hypertension.

Conflict of Interest: None declared

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