

Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy—should surgical indications be revisited?[†]

Thierry Aymard^{a,†}, Alexander Kadner^{a,†}, Alexandra Widmer^a, Reto Basciani^b, Hendrik Tevaearai^a,
Alberto Weber^a, Jürg Schmidli^a and Thierry Carrel^{a,*}

^a Department of Cardiovascular Surgery, Berne University Hospital, University of Berne, Berne, Switzerland

^b Department of Anaesthesiology and Pain Medicine, Berne University Hospital, University of Berne, Berne, Switzerland

* Corresponding author. Department of Cardiovascular Surgery, Inselspital, Berne University Hospital, University of Berne, Switzerland. Tel: +41-31-6322375; fax: +41-31-6324443; e-mail: thierry.carrel@insel.ch (T. Carrel).

Received 23 October 2011; received in revised form 9 January 2012; accepted 25 January 2012

Abstract

OBJECTIVES: The treatment of massive pulmonary embolism (PE) is a matter of debate. We present our institutional experience of patients suffering from massive PE with the aim of comparing the early results, the outcome and quality of life (QoL) between patients primarily assigned to either pulmonary surgical embolectomy (SE) or thrombolytic therapy (TL). A subgroup of patients (TS) with failed responses to TL requiring SE was separately analysed.

METHODS: All consecutive patients (January 2001–December 2007) with computed tomography (CT)-scan-confirmed massive bilateral central or paracentral PE were reviewed. All clinical data were retrieved from our patients' registry and completed by the evaluation of the CT-scan-derived right ventricle/left ventricle ratio (RV/LV ratio). Follow-up focused on clinical outcome and QoL was obtained.

RESULTS: Eighty patients were analysed including 28 SE (35%) and 52 TL (65%), of whom 11 (21%) required TS. Demographics and preoperative characteristics were similar between SE and TL. Analysis of the RV/LV ratio revealed a ratio of 1.66 for SE and 1.44 for TL. The early mortality rate was not significantly different between the two groups (SE: 3.6% versus TL: 13.5%), whereas early mortality was 27% in those patients treated initially with thrombolysis and subsequently requiring SE (TS-group). Severe bleeding complications were lower in the SE-group (3.6% versus 26.5% $P = 0.013$). Intracerebral bleeding rates and neurological events were not statistically different. After a mean follow-up of 63 ± 21 months, the mortality rate was 17.9% in the SE-group and 23.1% in the TL-group.

CONCLUSIONS: SE is an excellent treatment option in massive PE with comparable early mortality rates and significantly less bleeding complications than TL. Patients having surgery after inefficient thrombolysis have the worst early outcome. The RV/LV CT-scan ratio might serve as a predictor to differentiate patients, who could profit from direct surgical intervention than thrombolytic treatment attempts. Further studies are required to confirm these results.

Keywords: Pulmonary embolism • Embolectomy • Thrombolysis

INTRODUCTION

Patients presenting with acute massive pulmonary embolism (PE) are at high risk of circulatory collapse, medical and mechanical reanimation and late pulmonary hypertension. Their management is challenging and still a matter of debate. Although recent studies have repeatedly demonstrated good to excellent results following surgical embolectomy (SE), current guidelines recommend thrombolytic therapy (TL) as the treatment of choice, whereas surgical management is reserved for high-risk patients, in whom thrombolysis is absolutely contraindicated or has failed [1].

Unfortunately, there is no current study comparing the two treatment modalities. We reviewed our institutional experience with patients referred with acute massive PE, who underwent either TL or SE treatment.

PATIENTS AND METHODS

All consecutive institutional patients with acute massive central or bilateral paracentral PE who underwent treatment between January 2001 and December 2007 were retrospectively analysed.

The inclusion criteria were: acute massive PE defined in computed tomography (CT)-scan as central unilateral or bilateral or paracentral bilateral embolism. Massive PE was defined by >50% occlusion of pulmonary vasculature or occlusion of two or more lobar arteries or clinically as circulatory shock or moderate-to-severe right ventricular dysfunction (RVD) detected

[†]Presented at the 25th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Lisbon, Portugal, 1–5 October 2011.

[†]Both authors contributed equally.

Table 1: Baseline patient characteristics

Characteristics	Surgery (n = 28)	Lyse (n = 52)	P-value
Clinical			
Male	56%	44%	
Age (year)	56.3 ± 2.7	56.5 ± 2	0.92
Weight (kg)	82.9 ± 3.7	79.8 ± 2.7	0.45
NYHA	2.96	3.13	0.6
Systolic blood pressure (mmHg)	108	110	0.68
Heart rate	110	110	0.72
Deep venous thrombosis	39%	34%	0.1
Neoplasm	10.7%	16%	0.31
Immobilization	53.5%	78.8%	0.005
Post-PE	10.7%	13.4	1
Post-traumatic	7%	9.6%	1
Systolic PAP (mmHg)	72	53	0.01
Dyspnoea	14%	5.7%	0.23
Sat O ₂	86	85	0.45
NYHA ≥IV	46%	35.4	0.002
Cardiac insufficiency	82%	77%	0.77
Revised Geneva score ≥3	64%	52%	0.59
Shock index	1.1 ± 0.5	1.1 ± 0.5	0.86
Echocardiographic			
RV dilatation	3.5%	10.8%	0.4
LV EF (%)	59.4 ± 7.5%	60.4 ± 11.1%	0.25
CT-scan			
Central	21.5%	38%	0.14
Bilateral paracentral	78.5	59	0.13
R/L ventricular ratio	1.66	1.44	P = 0.04

PAP: Pulmonary artery pressure.

by echocardiography [2]. Submassive PE was defined as a haemodynamically stable condition with RVD, or with one or more of the following criteria present: cardiogenic shock (defined as systolic blood pressure <90 mmHg) associated with clinical signs of organ hypoperfusion and hypoxia, syncope, and pulmonary hypertension (>60 mmHg systolic pressure) or RVD. Patients older than 80 years and those with a life expectancy <6 months were excluded.

Two groups were defined: patients who underwent TL and patients who underwent SE. Patients who had undergone initial TL followed by surgery (TS) were analysed in a separate group. Clinical characteristics are summarized in Table 1. The revised Geneva score was calculated according to Klol *et al.*[3] and a high probability of PE was assigned when the score was superior or equal to three. In addition, right/left ventricle (RV/LV) ratio was calculated by measuring the RV/LV diameter at the level of the posterior papillary muscle in the CT-scan, as described previously by Lu *et al.* [4].

All in-hospital data were assessed and the follow-up focused on clinical statics and adverse events. In addition, the assessment of quality of life (QoL) was carried out by Short-Form-36 (SF-36) questionnaires.

Thrombolytic therapy

Indication for TL was based on the current guidelines of the American College of Chest Physicians and consisted of Alteplase started with a bolus of 15 mg followed by 85 mg infusion over 2 h.

Unsuccessful TL was defined as both persistent clinical instability (refractory cardiogenic shock, systemic arterial hypotension <90 mmHg, severe hypoxemia with oxymetry <90% or a PaO₂ without O₂ therapy of <55 mmHg or tachycardia >90 bpm) and residual RVD demonstrated at echocardiography during the first 36 h after the start of lysis.

Surgical therapy

Indication for SE was a central or paracentral bilateral massive PE with additional clinical criteria such as cardiopulmonary resuscitation, dysfunction of the RV, intracardiac thrombus or contra-indication for TL.

SE was performed through a median sternotomy using mild hypothermic or normothermic cardiopulmonary bypass (CPB). The main pulmonary artery was opened with a longitudinal incision, which was extended into the right or left pulmonary artery branches. The thrombotic material was extracted using a special forceps and by assisting suction. To ensure complete clot removal, the left and right pulmonary artery branches were inspected up to the segmental arteries using a flexible surgical angioscope. The right atrium and ventricle were explored routinely, all clot material was carefully removed and a patent foramen ovale was closed if present. The pulmonary arteriotomy was closed with a 4/0-running suture, and the patients weaned from CPB.

Post-intervention therapy

SE patients received intravenous unfractionated heparin immediately after surgery, which was maintained at a dosage of 1000 UI/h and later adapted to achieve an activated partial thromboplastine-time ratio of at least twice the control value.

All patients received oral anticoagulation therapy, starting on the second day and continued for at least 1 year with an International Normalized Ratio range between 2 and 3.

Definition of clinical endpoints

The clinical endpoints during hospitalization were: mortality, recurrent PE, neurological complications (ischaemic or haemorrhagic stroke confirmed by CT-scan) and bleeding complications requiring blood transfusion, surgical revision or discontinuation of TL.

Endpoints at the follow-up were: mortality, recurrent PE and QoL as assessed by SF-36.

Follow-up

All patients were contacted and a disease-specific questionnaire –focusing on the areas of current medication, especially anticoagulation therapy, thromboembolic or haemorrhagic complications, recurrent embolic events, re-hospitalization, assessment of NYHA class- was obtained, as well as the German version of the SF-36 Health Survey Questionnaire [5]. Details of this validated questionnaire have been published previously. Briefly, SF-36 consists of 36 short questions reflecting QoL in eight different areas: bodily pain (2 items); mental health (5); vitality (4); social functioning (2); general health (5); physical functioning

(10) and role functioning, both emotional (3) and physical (4). Role functioning reflects the impact of emotional and physical disability on work and regular activity (the individual's normal everyday role). Raw points were transformed, generating a score for each dimension ranging from 0 to 100, with 100 reflecting best functioning. Swedish normal population ($n = 8930$) scores are used as a standard population for comparison.

Statistical analysis

Analyses were performed using SPSS Statistics 17.0 for Windows. Patient characteristics are described using mean with standard deviation, or absolute numbers with percentages as appropriate. To minimize bias, continuous variables were generally assumed non-parametric and compared using the Mann-Whitney U -test. Proportions were compared using Fisher's exact test, and cumulative survival estimates using log-rank statistics. We performed logistic regression modelling for prediction of 30-day mortality, adjusting for the suspected confounding factors such as age and shock index. We performed linear regression analyses with the same set of independent variables to predict the two major aspects of QoL: physical and psychological health. Results are reported as hazard ratios for the logistic regression with 95% confidence intervals (CIs). The SF-36 questionnaire was analysed in accordance with the SF-36 manual.

All tests used were two-sided, and differences were considered statistically significant for $P < 0.05$.

RESULTS

Of the 125 identified patients, 80 consecutive patients with a complete clinical dataset were included, of whom 28 patients (35%) underwent SE, 52 patients (65%) underwent TL, including 11 patients (21%) undergoing surgery after failed lysis (TS).

No significant differences were found between the demographic and pre-interventional characteristics of the two groups (Table 1). Significant differences were seen in the preoperative pulmonary artery pressure, which was higher in the SE-group (72 ± 9 versus 52 ± 25 mmHg for TL-group; $P = 0.01$), and for the CT-scan RV/LV ratio, 1.67 for SE patients versus 1.43 for TL patients ($P = 0.04$). Interestingly, the analysis of the TS-group revealed a ratio of 1.63 close to the surgical group, while TL patients having an efficient lysis alone showed a ratio of 1.39.

Results and complications are shown in Table 2. The early mortality rate was not significantly different between the two groups, with 3.6% ($n = 1$) in the SE group and 13.5% ($n = 7$) in the TL group, whereas early mortality was 27% ($n = 3$) in those patients treated initially with thrombolysis and subsequently requiring SE-(TS-group).

Bleeding complications were significantly more frequent in the TL-group (27 versus 3.6% in the SE-group, $P = 0.01$). One patient suffered from intracerebral bleeding in the SE-group and two patients (4.4%) in the TL-group. Overall neurological complications were found in 17.9% ($n = 5$) in the SE-group and in 20.4% ($n = 10$) in the TL-group ($P = 1.0$).

The mean duration of the hospital stay was 14.0 ± 12.4 days after surgery and 10.9 ± 10.6 days after lysis therapy. In the TL-group, two patients underwent a second thrombolysis.

The follow-up was 95% complete with a mean of 63 ± 21 months, and the overall mortality was not significantly different

Table 2: Early and late outcomes

Characteristics	Surgery	Lyse	P-value
Early			
Mortality	3.6%	13.5% (26.5% for TS)	0.25
Duration of hospitalization	14 ± 12	10.9 ± 10.6	0.08
Bleeding	3.6%	26.5%	0.01
Cerebral bleeding	3.6%	4.4%	1
Neurological event	17.9%	20.4%	1
At follow-up			
Mortality	17.9%	23.1% (36.4% for TS)	0.6
Re-PE	0%	0%	1

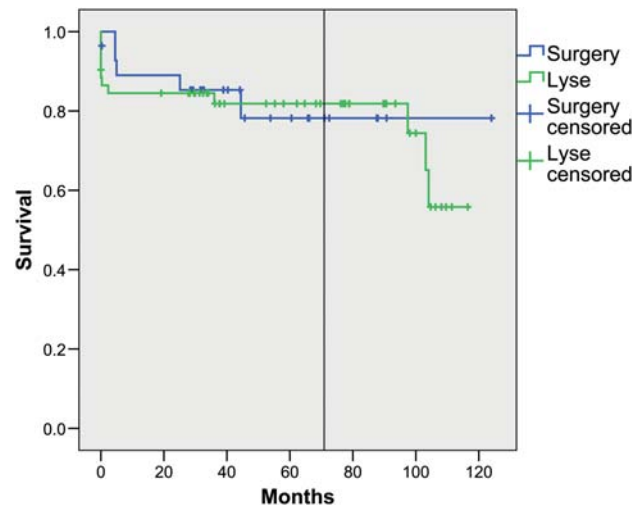


Figure 1: Kaplan-Meier survival.

between the two groups (17.9% SE-group versus 23.1% TL-group). Figure 1 shows the Kaplan-Meier survival curve with no difference between the groups for the 5-year survival probability (SE: 0.78; CI: 0.69–0.87; versus TL: 0.82; CI: 0.76–0.87).

QoL and adverse long-term events

A total of 82% of the SF-36 and disease-specific questionnaires were returned and answered correctly. The results (shown in Fig. 2) demonstrate a well-preserved QoL for the physical and psychological components with no significant difference between the two groups.

Recurrent PE was not reported in any patient. No deterioration of NYHA class was found. Figure 3 shows the trend for mortality, neurological events and the QoL.

DISCUSSION

PE is a common clinical condition, with a reported incidence rate of up to 2.3 per 10 000 [6]. In the majority of cases, acute PE can be well treated with supplementary oxygen, anticoagulation and, if necessary, intensive care management by intravenous fluids or vasopressin administration with careful attention to RV filling.

However, massive PE, especially if bilateral, is usually not well-supported, and standard medical therapy is often insufficient to avoid clinical decompensation. Several studies have demonstrated the ability of thrombolytic agents to dissolve pulmonary emboli, thus improving pulmonary perfusion and RV function [7]. Based on this data, current guidelines recommend treatment of more severe cases, such as submassive and massive PE, with TL.

On the other hand, several clinical reports have shown that surgical treatment of massive PE provides good to excellent results. Nevertheless, current guidelines reserve SE to high-risk patients only—patients in whom thrombolysis (TL) is absolutely contraindicated or has failed. Direct comparing studies for the two treatment modalities are missing.

As previously reported by us and others, the revealed early mortality and complication rate after SE is low, and thus favourably comparable to TL [8–13]. In contrast, in this study, we found a significantly higher mortality rate among patients who have undergone initially unsuccessful lysis, which had to be converted to SE. In this subgroup of patients, the mortality rate was as high as 27%.

The rate of unsuccessful lysis and the outcome of such patients in acute massive PE is not well documented in the literature. The rate varies between 5 and 10% and the mortality rate has been reported up to 38%. Furthermore, it has been shown that rescue SE may be offered to patients after a failed lysis with a better outcome than a repetitive TL attempt [14].

Consequently, early indicators would be of critical value for decision-making and primary treatment allocation.

An interesting and relatively easily accessible parameter was previously suggested to be the CT-based RV/LV ratio, whereby a ratio of >0.9 seemed to correlate with a worse outcome and a 5-fold increase of death within 30 days [15, 16].

Analysis of our data revealed a higher mean value of the RV/LV ratio for the two groups, with a significant higher value in the surgical group. In the subgroup of patients after failed lysis, we observed a similar RV/LV ratio as studied in the SE-group. Based on this finding, we propose that a LV/RV ratio of more than 1.5 may be considered as a cut-off value for allocating patients to SE instead of assigning to lysis therapy. Obviously, this has to be confirmed by further studies including a higher number of patients.

The overall complication rate was found to be lower for severe bleeding complications in the SE-group, but the rate of intracerebral bleeding events was not different among the two groups. Severe bleeding complications are well known after lysis therapy and have been reported in up to 25% of the patients with a rate of intracranial haemorrhage as high as 4% [9].

The long-term studied mortality is in accordance with the results by others, and appears to be mostly due to the underlying disease. The assessment of QoL shows a well preserved QoL in comparison with the normal population, without differences between the two treatment options.

In summary, this study reveals a low early mortality rate among patients undergoing SE. A comparison with lysis shows an even better early survival for surgery, however, this did not reach statistical significance and the low power of the study has to be considered when interpreting this finding. In contrast, patients who underwent SE after the failure of lysis clearly demonstrate a critically high mortality rate. If confirmed in additional studies, the CT-derived RV/LV ratio could be a useful parameter to identify candidates who might benefit from direct surgical therapy instead of thrombolysis. The limitation of surgical therapy for massive PE in patients in whom thrombolysis is absolutely contraindicated or has failed appears to be too restrictive. Current guidelines should be adapted with respect to the excellent clinical and functional results of SE. Multicentric studies and national registries should be conducted to provide missing data in order to improve patient allocation and treatment algorithms.

Conflict of interest: none declared.

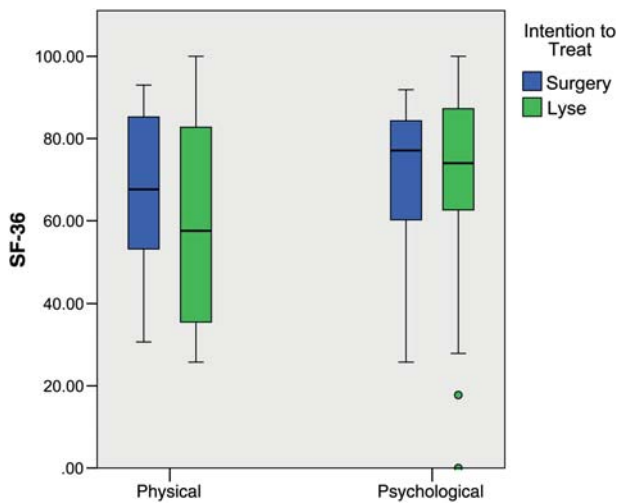


Figure 2: QoL assessment by SF-36.

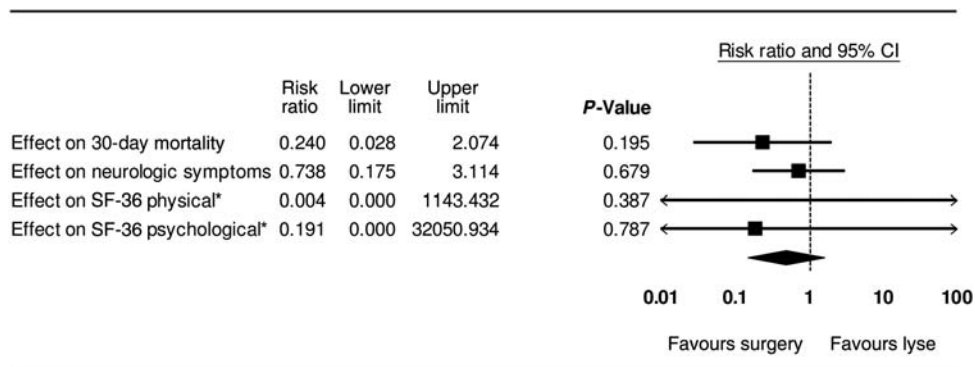


Figure 3: Plot representation shows trends in favour of surgery or lysis for major events such as mortality and neurological complications as well as for QoL. *The values displayed are exp(coefficient), exp(coefficient - 1.96 SE), exp(coefficient + 1.96 SE), respectively.

REFERENCES

- [1] Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2008;133(6 Suppl):454S-545S.
- [2] Wood KE. Major pulmonary embolism. *Chest* 2002;121:877-905.
- [3] Klol FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le Gal G *et al.* Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. *Arch Intern Med* 2008;168:2131.
- [4] Lu MT, Cai T, Whitmore AG, Quiroz R, Goldhaber SZ, Rybicki FJ. Interval increase in right-left ventricular diameter ratios at CT as a predictor of 30-day mortality after acute pulmonary embolism: initial experience. *Radiology* 2008;246:281-7.
- [5] Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998;51:903-12.
- [6] Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B *et al.* A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;151:933-8.
- [7] Lankeit M, Konstantinides S. Thrombolysis for pulmonary embolism: past, present and future. *Thromb Haemost* 2010;103:877-83.
- [8] Kadner A, Schmidli J, Schönhoff F, Krähenbühl 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.
- [9] Meyer G, Gisselbrecht M, Diehl JL, Journois D, Sors H. Incidence and predictors of major hemorrhagic complications from thrombolytic therapy in patients with massive pulmonary embolism. *Am J Med* 1998;105:472-7.
- [10] 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.
- [11] 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;3:265-70.
- [12] Ahmed P, Khan AA, Smith A, Pagala M, Abrol S, Cunningham JN *et al.* Expedient pulmonary embolectomy for acute pulmonary embolism: improved outcomes. *Interact CardioVasc Thorac Surg* 2008;4:591-4.
- [13] Maruna P, Kunstyr J, Plocova KM, Mlejnsky F, Hubacek J, Klein AA *et al.* Predictors of infection after pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension. *Eur J Cardiothorac Surg* 2011;39:195-200.
- [14] 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.
- [15] 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.
- [16] Schoepf HJ, Kucher N, Kipfmüller F, Quiroz R, Costello P, Goldhaber SZ. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. *Circulation* 2004;110:3276-80.

APPENDIX. CONFERENCE DISCUSSION

Dr H. Jakob (Essen, Germany): I have problems in understanding that you measured a systolic blood pressure of 72 in your surgical group. To my

knowledge, an untrained right ventricle is not capable of raising the pressure that high. So is there perhaps a chronic component in those patients?

Dr Roost: That could well be true; we don't know. But it's absolutely right, what you say, that it's a very high pressure for an untrained right ventricle to overcome.

Dr Jakob: And did you follow up the pulmonary artery pressures; did they come down to normal values over time?

Dr Roost: They do come down. I don't have the data here, but they do come down. We have not measured them routinely in the patients. But we have a smaller subset in a study which was published earlier on for surgical patients only, which showed nicely how they did come down immediately. But it is a problem if you end up with a patient in the OR and you find out that it's mostly a chronic problem; you, as a surgeon, have a problem there, so that's absolutely important.

Dr Jakob: What about the consequence of your study? I think you demonstrated nicely that this right ventricular/left ventricular ratio could perhaps be a cutoff point for decision-making; are your internal medicine colleagues accepting that in Berne?

Dr Roost: That's exactly the problem, because these patients are initially seen by the internist or the emergency medicine people. They first call the cardiologists who do the lytic therapy. Therefore the reason why we started to analyse our results was actually because we wanted to be there and involved in discussing the patients early on so that we can, perhaps, with that ratio, identify patients who would really profit from early surgery as opposed to lytic therapy. It's clear that in the great majority of patients you can avoid surgery, which is fine for them. But if you can save the few patients who probably need to have surgery later on, then you can really do something good.

So with that data, we wanted to address that in our hospital, which we have actually done. You can see that the ratio was different between the surgery and the thrombolytic therapy groups. I didn't present it here, but in the few patients, these 11 patients, who had to have surgery later on, they had a ratio much closer to the surgery group, so we do think it's actually an important parameter.

Dr Jakob: And one last question, these were all in-house patients?

Dr Roost: Yes.

Dr Jakob: But what are your colleagues doing in the peripheral hospitals? Do they contact you directly or do patients go to the internal medical department prior to surgery?

Dr Roost: Yes. We are not contacted first. And that's the problem. We only see the patients if the cardiologist or the people from emergency medicine contact us.

Dr Jakob: But you are losing time.

Dr Roost: Exactly. So we hope that with this data we hopefully can change that.

Dr T. Shah (Ahmedabad, India): I have two questions. What were the reasons for the 17.9% late mortality? Secondly, do you have a choice amongst the three thrombolytics that you enumerated? Is there anything which gives better results and fewer complications versus the others?

Dr Roost: Honestly, I do not have the data about the causes of death in the follow-up. You would have to contact Dr. Kadner, who actually gathered the data. And regarding the three agents, usually we use alteplase. And actually, that's the cardiologist's work, which agent is used, so I probably can't answer the question perfectly.

Dr S. Cebotari (Hannover, Germany): Do you have experience of using ECMO in failed right ventricle in these patients before operation, after operation?

Dr Roost: That's what we would do. If you have a patient that you cannot wean from bypass after removal of all the clots, what we would do is keep him on ECMO hoping that the right ventricle does recover. And I think in this group there was one patient we had to put on ECMO and who recovered.