Peer reviewed article

Surgical treatment of chronic thromboembolic pulmonary hypertension

Eckhard Mayer

Department of Cardiothoracic and Vascular Surgery, Johannes Gutenberg University Hospital, Mainz, Germany

Summary

Chronic thromboembolic pulmonary hypertension is a commonly overlooked cause of physical incapacity and dyspnoea, with a higher incidence than is generally appreciated and a poor prognosis. The diagnosis can be suspected based on echocardiographic examinations and ventilation perfusion scanning of the lung. Pulmonary angiography still remains the gold standard for the diagnosis of thromboembolic pulmonary hypertension and the assessment of operability.

Pulmonary endarterectomy is a complex surgical procedure, which provides permanent relief of thromboembolic pulmonary hypertension and cure for most of the patients. The operation resembles a true endarterectomy of the pulmonary artery branches using extracorporeal circulation and periods of hypothermic circulatory arrest. In experienced centres, the operative risk has been decreased to an acceptable level. Following successful surgery, long-term survival and quality of life are excellent.

Earlier referral to surgery might avoid the occurrence of a secondary vasculopathy in the unaffected areas of the pulmonary vascular tree, and therefore further improve early and late results. A multidisciplinary approach and surgical experience are the prerequisites for success of this demanding procedure.

Key words: pulmonary endarterectomy; chronic thromboembolic pulmonary hypertension

Introduction

Acute pulmonary embolism is a frequent cause of morbidity and mortality with a higher incidence than is generally appreciated [1, 2]. Although it was believed that 0.1% to 0.5% of patients surviving acute pulmonary embolism develop chronic thromboembolic pulmonary artery obstruction due to unresolved embolic material or recurrent emboli or both [3, 4], the true incidence of chronic thromboembolic pulmonary hypertension (CTEPH) appears to be much higher. In a prospective study of 223 patients with acute pulmonary embolism symptomatic CTEPH occurred in 3.8% of the patients at 2 years after the acute episode [1]. CTEPH develops when more than 40–60% of major pulmonary artery branches are obstructed and is worsened by a secondary vasculopathy in the unaffected pulmonary vasculature due to increased pressure and flow. A subsequent persistent increase of pulmonary vascular resistance (PVR) is leading to progressive right ventricular dysfunction and failure. The occurrence of symptoms can be delayed for months or years depending on the degree of pulmonary artery obstruction and the development of microvascular disease in the unobstructed pulmonary arteries. Without intervention, the prognosis for patients with CTEPH is poor and survival is disproportional to the degree of pulmonary hypertension [5]. A mean pulmonary artery pressure of 30 mm Hg is considered to be the threshold for poor survival [6].

Pulmonary endarterectomy (PEA, pulmonary thromboendarterectomy, PTE) has proved to be an effective and potentially curative surgical treatment option for a majority of patients with CTEPH [7–9]. Based on a multidisciplinary team and a high level of surgical experience, the early mortality of pulmonary endarterectomy has become acceptably low. Long-term survival and quality of life of the patients after PEA is excellent [10].

This report summarises the current concepts of diagnosis, patient selection, surgical and postoperative management and outcome based on the literature and the experience with 335 of these operations performed at the Johannes Gutenberg University Hospital Mainz, Germany since 1989.

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Clinical manifestations and diagnosis of chronic thromboembolic pulmonary hypertension

The clinical presentation of CTEPH is often insidious and slowly progressive until right heart failure occurs and symptoms become more evident [11]. As a majority of patients has no history of venous thrombosis or acute pulmonary embolism, the diagnosis of thromboembolic pulmonary hypertension can be difficult and is often missed. Furthermore, there is still a general lack of awareness of this clinical entity and the option of successful surgical therapy. Characteristic symptoms are dyspnoea on exertion or at rest and a progressive decrease in exercise tolerance. In the later course of the disease, exertional chest pain, haemoptysis and syncope may occur due to massive pulmonary hypertension and right heart failure. As all symptoms are non-specific, pulmonary vascular disease should always be considered when no other specific causes of dyspnoea can be identified.

Transthoracic echocardiography is the standard investigation to detect pulmonary hypertension. It shows right atrial and ventricular enlargement and dysfunction with varying degrees of tricuspid regurgitation and a paradoxic motion of the interventricular septum leading to an impairment of left ventricular diastolic function [11–13].

Right heart catheterisation and measurement of cardiac output can determine the degree of pulmonary hypertension and pulmonary vascular resistance and rule out other (cardiac) causes of pulmonary hypertension.

Pulmonary ventilation perfusion scanning is an important screening method as it allows differentiation between CTEPH and idiopathic pulmonary arterial hypertension; mismatched segmental or lobar perfusion defects are characteristic for CTEPH, although the severity of the

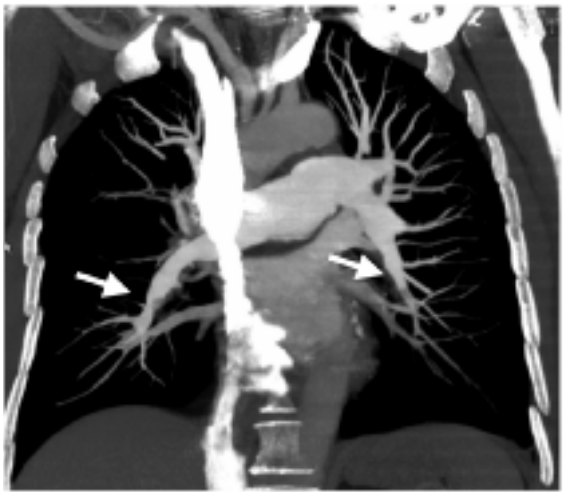


Figure 1

The distribution of obstructive pulmonary artery lesions at the main, lobar and segmental levels is detected by CT scanning.

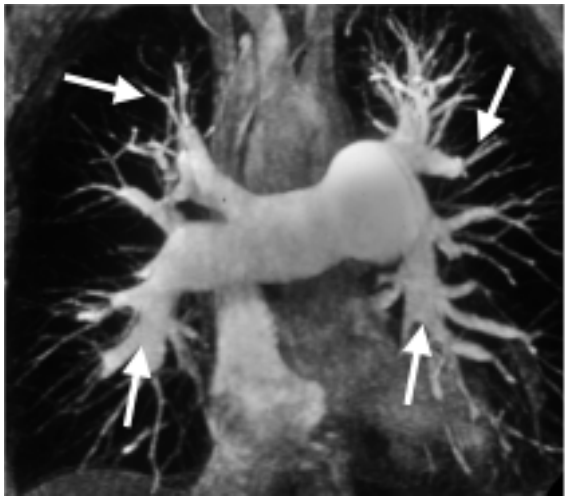
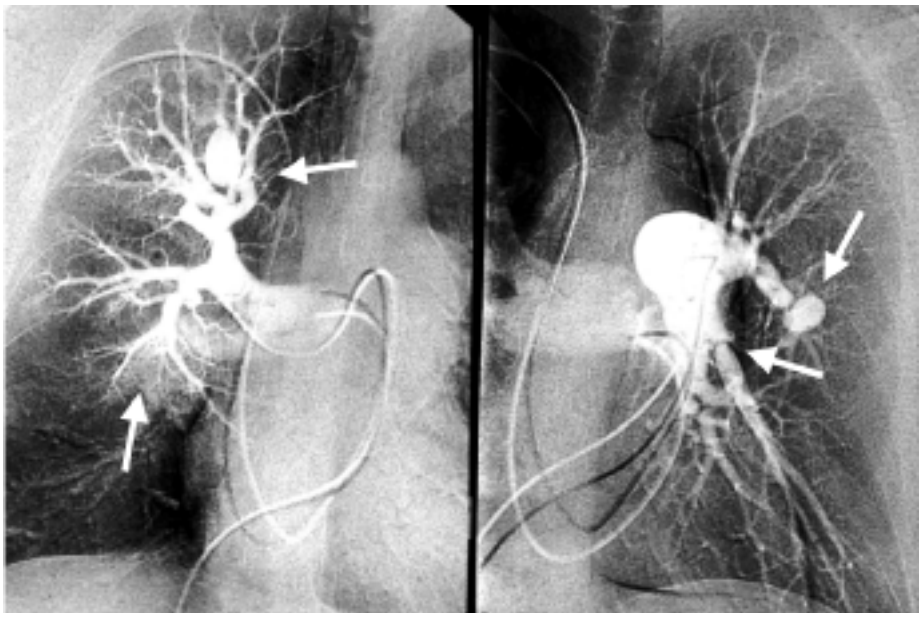


Figure 2

Three-dimensional MR angiography can precisely depict thromboembolic lesions down to the subsegmental pulmonary artery branches.

Figure 3

Pulmonary angiography demonstrates the occlusion of the right lower lobe artery with typical webs and bands and intraluminal filling defects and post-stenotic dilatations in bilateral segmental arteries.



disease is often underestimated by perfusion scanning [11].

High resolution helical computed tomographic scanning (CT) using maximal intensity projections (MIP) detects the distribution of obstructive pulmonary artery lesions at the main, lobar and segmental levels (figure 1) and a mosaic pattern of lung attenuation as a sign of regional perfusion differences. Although the absence of typical CT findings does not completely rule out surgically accessible thromboembolic disease, CT scanning gives important information on operability and perioperative risk of PEA [14].

Magnetic resonance imaging (MRI) has become a helpful noninvasive investigation in CTEPH patients as the obstructed lumen as well as the thickened vessel wall with incorporated thromboembolic material can be precisely depicted [15, 16] (figure 2). In addition, right ventricular function and pulmonary arterial and venous flow can be assessed. In 30–50% of patients undergoing pulmonary endarterectomy in our institution, the operation can be performed on the basis of MR imaging without conventional pulmonary angiography. In addition, differentiation between thromboembolic pulmonary artery obstructions and pulmonary artery sarcoma is possible by MR imaging [17].

Pulmonary angiography still remains the gold standard for the diagnosis of thromboembolic pulmonary hypertension and assessment of operability [11]. It can be performed safely regardless of the severity of pulmonary hypertension [18]. Multiplanar digital substraction imaging shows the exact localisation of pulmonary artery obstructions. Nevertheless, the interpretation of angiograms of CTEPH requires specific experience. The classical signs of chronic thromboembolic lesions include irregularities of the wall of pulmonary artery branches, intraluminal filling defects, stenoses or occlusion of central, lobar and segmental arteries caused by thrombus masses or webs and bands (figure 3). In patients with exclusively distal disease, the combination of pulmonary perfusion scanning and angiography allows exclusion of idiopathic pulmonary arterial hypertension and adequate assessment of surgical accessibility, operability and risk.

Patient selection

The decision for surgical treatment is made based on the severity of symptoms and the impairment of pulmonary haemodynamics. Patients considered for surgery are usually severely incapacitated in their daily activities with dyspnoea at low levels of exertion or at rest (New York Heart Association functional class III or IV). The mean preoperative pulmonary vascular resistance in surgical patients is 800 to 1000 dynes·s·cm^{-5}. Meanwhile, patients with exertional dyspnoea, almost normal pulmonary vascular resistance at rest and a significant increase at exertion are also accepted for surgery to improve ventilation perfusion balance and avoid secondary arteriopathy of the patent pulmonary arteries [4]. Patients with suprasystemic pulmonary artery pressures and excessive elevation of pulmonary vascular resistance (>1500 dynes·s·cm^{-5}) are also accepted for surgery although the operative risk is significantly increased [8].

Surgical accessibility of the thromboembolic lesions is an important prerequisite for a successful operation. It is heavily dependent on the surgeon's experience, and with the growing expertise of surgeons even patients with severe pulmonary hypertension and peripheral disease can be operated successfully. In order to achieve adequate early and late results, there should be no major discrepancy between the degree of pulmonary hypertension and the amount of surgically accessible thromboembolic material in the angiogram [19]. Right ventricular failure and concomitant hepatic and renal dysfunction are not considered as contraindications to surgery. However, patients with severe left ventricular dysfunction or significant obstructive or restrictive lung disease are not accepted for surgery. All patients over 45 years undergo coronary angiography before surgery to rule out coronary disease. If necessary, coronary artery bypass grafting can be performed at the time of pulmonary endarterectomy.

Medical treatment

A small percentage of CTEPH patients is not eligible for surgery due to significant small-vessel disease or severe comorbidity. Medical therapy based on prostanoids, phosphodiesterase-5 inhibitors and endothelin receptor antagonists or a combination of these substances may be an option for patients with inoperable CTEPH. However, the evidence that medical therapy may play a beneficial role for selected CTEPH patients is limited to the results of a small number of uncontrolled clinical studies only [2, 20–23]. Perioperative prostanoid therapy may be helpful for haemodynamic improvement before surgery or treatment of persistent pulmonary hypertension in the postoperative period [24]. Interventional balloon pulmonary angioplasty has been performed success-

fully in a very limited number of inoperable CTEPH patients [19]. However, this experimental procedure should only be considered in specialised centres for highly selected patients.

Operation

Although bilateral pulmonary endarterectomy has proved to be a potentially curative option for very sick patients with a poor prognosis, only 3000 to 4000 operations have been performed in a few centres worldwide with the largest experience accumulated at the University of California San Diego Medical Centre [7]. In 1989, a program for pulmonary endarterectomy has been established at the Johannes Gutenberg University Hospital in Mainz and 335 patients have undergone PEA since then.

The goals of the operation are restoration of lung perfusion and ventilation perfusion balance, reduction of right ventricular afterload and avoidance of a secondary vasculopathy in patent pulmonary arteries. The surgical techniques and modifications necessary to reach these goals at an acceptable operative risk have been well described by the San Diego group [7].

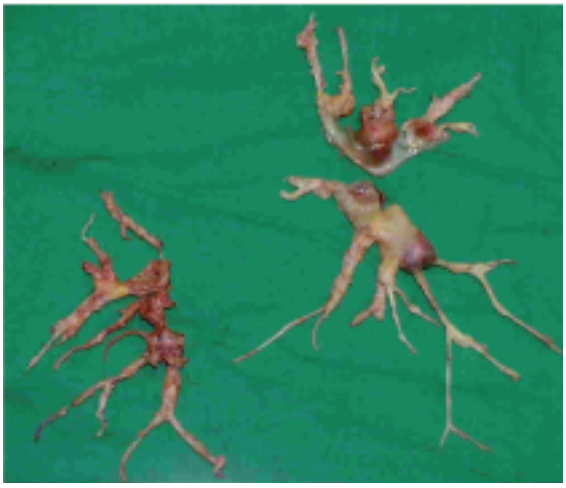


Figure 4

Surgical specimen with intimal thickening and fibrous webs and bands occluding all branches of the left PA and of the right middle and lower lobe arteries.

The operation is performed using extracorporeal circulation and periods of circulatory arrest under deep hypothermia, as good visibility in a bloodless field is essential for accurate endarterectomy. The operation is not a pulmonary embolectomy of thrombus material, but a true endarterectomy removing the organised fibrous material with its neointima and parts of the medial layer.

Following median sternotomy, cardiopulmonary bypass is instituted and cooling of the patient is initiated. When a 20 °C core temperature is reached, the aorta is cross-clamped and cold cardioplegic solution is administered. The superior vena cava is mobilised and the right pulmonary artery is incised intrapericarially. Following removal of gross thrombus material, the correct endarterectomy plane is established. The endarterectomy is performed in 20-minute periods of circulatory arrest. Using special suction dissectors, the endarterectomy specimen is circumferentially followed down to the segmental and subsegmental branches in each lobe, until a complete endarterectomy of the pulmonary vascular bed is achieved (figure 4). Following reperfusion and closure of the pulmonary artery incision, the left pulmonary artery is incised. Another period of circulatory arrest is necessary for the left pulmonary artery endarterectomy. Cardiopulmonary bypass is re-instituted and the left pulmonary artery incision is closed. Tricuspid valve repair is not necessary as tricuspid competence usually returns within days after successful pulmonary endarterectomy. Following rewarming, weaning from of cardiopulmonary bypass is cautiously performed. Following achievement of haemostasis, wound closure is routine.

Postoperative management

The postoperative course of patients undergoing pulmonary endarterectomy can be challenging with regard to haemodynamic and ventilatory management [25, 26]. The most significant problems are right ventricular dysfunction due to the effects of extracorporeal circulation, ischaemia, hypothermia or residual pulmonary hypertension and a reperfusion oedema within the endarterectomised segments of the lung. Basic tenets of postoperative care are the maintenance of adequate right ventricular function, organ perfusion, renal function, sufficient oxygenation and prevention of early pulmonary artery reocclusion [19]. Extensive ventilatory and circulatory monitoring including online measurement of cardiac output, mixed venous oxygen saturation and arterial blood gases have proved to be helpful. In our program, cautious fluid and vasoactive drug administration and pressure-controlled mechanical ventilation with a positive end-expiratory pressure of 8 to 10 cm H_2O allow prompt stabilisation of haemodynamics and gas exchange and early extubation on the first or second postoperative day in 85% of the patients. Fifteen percent of the patients require prolonged ventilation mainly due to reperfusion oedema and/or right ventricular dysfunction based on residual pulmonary hypertension. Reocclusion prophylaxis is started within 2 to 4 hours follow-

ing surgery using i.v. heparin and subsequent continuous anticoagulation with warfarin starting between postoperative day 5 to day 8. Lifelong anticoagulation is strongly recommended for all patients after endarterectomy. The routine preoperative insertion of an inferior vena cava filter to reduce the risk of perioperative or postoperative embolism is a matter of debate, as the filter by itself might be a cause of thrombosis and source of embolism.

Results

Pulmonary endarterectomy in CTEPH has not been assessed in randomised controlled studies, which are considered unethical in the absence of adequate alternative treatments. However, the outcome of pulmonary endarterectomy with regard to survival, functional status, haemodynamics, right ventricular function and gas exchange is very favourable for most patients.

Early results

Between June 1989 and March 2005, 335 patients underwent endarterectomy at the Johannes Gutenberg University Hospital Mainz. Multiple changes and modifications of the surgical and postoperative management have been implemented since January 1995 and the early results of 226 operations that have been performed since then are reported.

The mean age of 97 female and 129 male patients was 56 years, ranging from 21 to 82 years. Four patients underwent a PEA reoperation, two of them had their primary operation at another institution. Preoperative NYHA functional class was IV in 82 patients, III in 116 patients and II in 28 patients. In 91 patients, coagulation disorders were detected preoperatively. Mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) were elevated to 46 ± 11 mm Hg and 923 ± 195 dynes·s·cm^{-5} respectively (table 1).

The mean circulatory arrest time was 38 minutes (range 5 to 80 minutes). The in-hospital mortality rate was 8.5 percent (19 of 222) after primary operation and 2 of 4 after reoperation. Causes of death were persistent pulmonary hypertension in 9 patients, massive pulmonary reperfusion oedema in 4 patients, early reocclusion of the central pulmonary arteries in 3 patients, sepsis in 2 patients and unclear in 1 patient. The median duration of postoperative mechanical ventilation in 205 survivors was 31 hours (range 4 to 390 hours). Early results are summarised in table 2. At the end of ICU phase, PVR and mPAP were significantly reduced to 302 ± 145 dynes·s·cm^{-5} ($p < 0.001$) and 28 ± 12 mm Hg ($p < 0.01$) respectively.

Right ventricular dimensions measured by echocardiography were significantly reduced postoperatively with a persistent improvement of right ventricular function. Tricuspid valve regurgitation was significantly improved within a few days after surgery and in most of the patients, tricuspid competence returned to normal [12, 27, 28].

The early results in this series are similar to those of other specialised centres. The San Diego Group reported a 7.5% mortality in the largest program in the world with 1500 PEA operations [7]. In another large series from Paris, the hospital mortality rate was 10.9% and was closely related to the degree of pulmonary hypertension [8]. As in our patient group, persistent pulmonary hypertension was the predominant cause of death in both series [7, 8]. As there is a distinct surgical learning curve, mortality rates have been similarly improved in all centres with large numbers of patients to a level of 5–12%. However, with increased experience and without adequate treatment alternatives, the operation is also offered to patients with distal disease and very severe pulmonary hypertension. It is evident, that mortality rates in this group of patients are increased above the normal level.

Late results

Compared to the reported survival without surgery or with lung transplantation, long-term

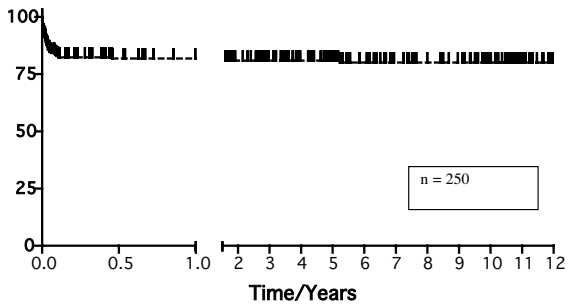
Table 1
Patient characteristics (Mainz, 1/1995 – 3/2005).

patients	n = 226
age (y.)	56 (21–82)
NYHA II/III/IV	28/116/82
mPAP (mmHg)	46 + 11
PVR (dynes·s·cm^{-5})	923 + 195
coagulation disorders	n = 91
additional cardiac operations	n = 32

Table 2
Early results (Mainz 1/1995 – 3/2005).

hospital mortality	8.5% (19 of 222)
hospital mortality after redo PTE	2 of 4
circulatory arrest time (min)	36 (5–80)
mechanical ventilation time (h)	31 (4–390)

Figure 5
Long-term survival after thromboendarterectomy is excellent (Mainz, 1989–2001, n = 250).



results after pulmonary endarterectomy are very favourable with a five year survival rate of 75 to 80% [29]. In 250 consecutive patients who underwent endarterectomy at the Johannes Gutenberg-University Hospital in Mainz in a thirteen-year-period between 1989 and 2001, the five-year-survival-rate was 77% with an initial decline of the survival curve representing early mortality and favourable long-term survival (figure 5).

Quality of life

More than 90% of the patients report a significant improvement of the quality of life and exercise tolerance after surgery. Before surgery, most patients are in New York Heart Association functional class III or IV; after surgery, more than 90% of them are in class I or II and able to resume normal activities [29].

Haemodynamic and angiographic findings

In several studies, significant and persistent decreases of pulmonary artery pressures and pulmonary vascular resistance after PTE surgery are reported [4, 10, 30]. More than five years after surgery, mean PAP and PVR are significantly lower compared to preoperative measurements with a normalisation of cardiac index in most of the patients. It is estimated that in 10–15% of the patients residual or recurrent pulmonary hypertension occurs. If a reoperation is not feasible, these patients should be treated medically in a specialised centre.

Conclusions

Pulmonary endarterectomy is an effective and potentially curative surgical treatment for patients with severe chronic thromboembolic pulmonary hypertension. Based on the experience of a multidisciplinary team, the operative risk has been reduced to an acceptable level. Long-term survival, NYHA functional status and exercise capacity are significantly improved. Earlier referral to surgery might avoid the occurrence of a secondary vasculopathy and therefore further improve early and late results. Lung transplantation is not an option for the vast majority of CTEPH patients and should only be considered for selected patients who are not accepted for endarterectomy in a centre with a large experience in this technically demanding surgical procedure.

Correspondence:
Eckhard Mayer, MD
Dept. for Cardiothoracic and Vascular Surgery
Johannes Gutenberg University Hospital
Langenbeckstrasse 1
55101 Mainz, Germany
E-Mail: emayer@uni-mainz.de

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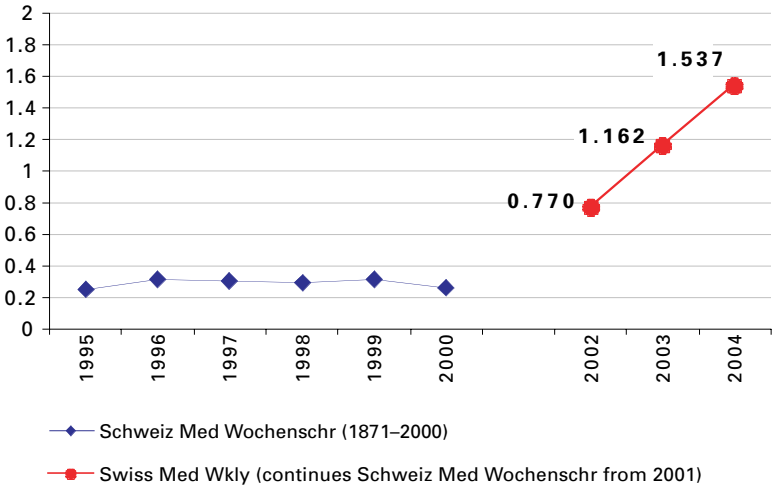

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