Chronic thromboembolic pulmonary hypertension: clinical picture and surgical treatment

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Chronic thromboembolic pulmonary hypertension: clinical picture and surgical treatment. K.M. Moser, W.R. Auger, P.F. Fedullo, S.W. Jamieson.
ABSTRACT: Chronic, major vessel thromboembolic pulmonary hypertension (CTEPH), is an uncommon condition which, in the past, was an autopsy curiosity. Advances in diagnostic approaches, surgical techniques and postoperative management have transformed this disorder into a potentially curable form of pulmonary hypertension. The predominant symptom is unexplained dyspnoea on exertion. In patients with this complaint, CTEPH should be considered. Numerous pitfalls exist along the diagnostic path. Perfusion lung scans point toward the diagnosis, but often underestimate the extent of central arterial obstruction. Pulmonary angiography is the key diagnostic procedure, but the many patterns of thrombus organization-recanalization require a base of experience for proper interpretation. Criteria for selection of patients for surgery are evolving, but assurance of thrombus accessibility to surgery is critical. Surgical thromboendarterectomy bears no resemblance to acute pulmonary embolectomy. Recognition of thrombus (*versus* normal intima), meticulous dissection and a bloodless surgical field are essential for adequate restoration of pulmonary vascular patency. Multiple complications may arise postoperatively, and detailed attention to these is required for patient survival. With a co-ordinated, multi-speciality team effort, however, haemodynamic and clinical outcomes have been rewarding and persist long-term. Surgical mortality should steadily decline with such a co-ordinated effort, as well as earlier diagnosis and advances in surgical and postoperative management techniques.
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Many conditions, once considered to be rare, become recognized with increasing frequency as diagnostic approaches are developed and therapeutic initiatives become available. That is certainly the case with chronic, major vessel thromboembolic pulmonary hypertension (CTEPH). This entity has been known to exist for several decades [1–4]. At the outset, it was considered to be a rare autopsy curiosity. However, it has become apparent that CTEPH is not only more common than had been appreciated, but is also potentially subject to surgical cure [5].

The reasons for this transition are multiple. Firstly, diagnostic techniques such as lung scanning, right-heart catheterization and pulmonary angiography have become more widely applied. Secondly, the clinical picture and natural history of this disorder have been described [5] so that physicians are more suspicious of this diagnosis and less likely to attribute the patient's symptoms to alternative processes. Thirdly, with advances in cardiac surgical techniques, the potential for cure of the condition by surgical thromboendarterectomy has been demonstrated. Certainly, when any condition becomes subject to potential cure, there is increased impetus toward making the diagnosis.

These factors have combined to promote far greater recognition of chronic, major vessel thromboembolic hypertension in recent years. Our own experience with this condition has expanded remarkably. We reported an experience with 15 patients between 1970 and 1983 [6]; an additional 27 patients operated upon by 1987 [7]; and by mid-1991, we had seen and operated upon more than 270 patients. Reports from our institution and others now indicate that some 500 patients with this condition have been recognized and more than 300 have been operated upon [5, 8–11].

Our estimates of frequency, which remain rather crude, suggest that, in the United States alone, some 450 patients of the 500,000 who experience a pulmonary embolus each year probably enter this CTEPH patient pool. Furthermore, this appears to be a worldwide condition, with patients now having been recognized in virtually every nation with the capability for pursuing this diagnosis.

Clinical presentation and natural history

The usual course followed by a patient who survives an acute pulmonary embolic event is to resolve both the

acute embolus and, to a large extent, the venous thrombotic site from which the embolus arose. This course has now been amply documented in a number of studies [12–17]. Chronic thromboembolic pulmonary hypertension (CTEPH) is, therefore, an aberrant (and infrequent) outcome of acute pulmonary embolism. These patients, for reasons which remain to be defined, fail to achieve embolic resolution. Instead, their thrombi persist and become organized, fibrotic masses in major pulmonary arteries. The consequences of this failure of resolution are several: the creation of an alveolar deadspace (with total occlusion) or high ventilation/perfusion (V/Q) zones (with partial resolution); and an increase in pulmonary vascular resistance. It is well-recognized that pulmonary infarction is an unusual consequence of acute or chronic embolism [18], so that the majority of these patients do not suffer permanent parenchymal injury to the lung.

One of the features of this condition is its wide spectrum; that is, some patients emerge with minor residuals whereas others retain extensive vascular occlusion. Complete or partial obstruction of a few vessels - or even the right or left main pulmonary artery (given a normal lung on the contralateral side) - does not lead to pulmonary hypertension, even though an increased deadspace persists. However, when there is a more extensive loss of cross-sectional area of the pulmonary vascular bed, pulmonary hypertension appears at rest, or with minimal levels of exertion. Thus, depending on the extent of residual obstruction, one may encounter a spectrum of patients, from those who have virtually no symptoms to those with severe pulmonary hypertension and right-heart failure. This spectrum has recently been replicated by a canine model in which chronic pulmonary embolism was induced [19].

Not surprisingly then, the clinical presentations of these patients vary [5]. The one symptom that is common to all is dyspnoea on exertion. With minimal residual obstruction, this dyspnoea only appears at the extremes of exertion; with severe obstruction, it develops with even minimal activity. Therefore, in any patient with dyspnoea on exertion, this entity should be considered. Unfortunately, this diagnostic possibility is often overlooked for months and years because there are a number of diagnostic pitfalls which suggest alternative diagnoses. Furthermore, the findings of pulmonary hypertension in its early stages are subtle and easily overlooked.

The natural history of the disorder also contains other features which have often impeded diagnosis. For example, less than half of the patients have a history compatible with a prior episode of venous thrombosis and pulmonary embolism. Even among those with such a history, the venous thrombotic event may have been diagnosed as a muscle strain or cellulitis, and the pulmonary embolic event diagnosed as pneumonia, pleurisy or some other entity. Thus, one often encounters CTEPH in patients who either have no recall of a prior venous thromboembolic event or can relate only episodes of leg or lung symptoms that were attributed to other causes. This lack of a clear-cut history probably reflects the frequency with which both the diagnosis of deep venous thrombosis and pulmonary embolism are overlooked in the population at large [20–22]. Perhaps the critical point is that a negative history of a prior venous thromboembolic event cannot be used to exclude the diagnosis of CTEPH.

The natural history of this disorder contains a further curiosity. Even when very extensive residual occlusion is present, the patient often carries on relatively normal activities for periods of months to years before overt right ventricular failure or a marked decline in exertional capabilities becomes apparent. We have called this period of relatively minor symptoms the "honeymoon period". Sooner or later, however, the "honeymoon" ends and the patient enters a period of symptomatic decline. The potential bases for this decline are several. Firstly, there is the possibility that one or more recurrences of embolism have occurred. Available data indicate that, while recurrence is commonly suspected, it actually is an uncommon cause for deterioration. More likely is the second potential basis for decline; namely, the development of pulmonary hypertensive lesions in the "open" pulmonary arterial bed. These changes in the small pulmonary arteries further increase pulmonary vascular resistance and place an increased demand on the right ventricle [23]. A third possibility, suggested by observations we have made at surgery, is that the initial emboli induce *in situ* growth of thrombotic material, with such material further exaggerating the extent of vascular obstruction. The observations made at surgery are that whitish "distal" emboli are present, with reddish proximal extensions of more recent vintage (fig. 1).

Whatever the mechanisms of deterioration in a given patient, the historical facts are clear. The patient, at some juncture, begins to complain of increasing shortness of breath at lower levels of exertion and slowly demonstrates all of the other features of right ventricular dysfunction.

Diagnostic approach

Standard diagnostic approaches to the patient complaining of dyspnoea on exertion may provide some clues to the diagnosis of CTEPH; but there are also several diagnostic pitfalls that may lead away from the diagnosis. Physical examination, for example, is often unrewarding until the pulmonary hypertension is quite severe. The lung fields are usually clear to percussion and auscultation. However, there is one pulmonary auscultative diagnostic sign of great value; namely, murmurs which are heard over the lung fields [24]. These murmurs, systolic or continuous, are due to partial obstruction of major pulmonary arteries. They may be heard over any area of the lung fields. However, in order to appreciate them, the patient must hold his or her breath because the murmurs are easily obscured by the breath sounds. Because these murmurs are not heard in primary pulmonary hypertension, and rarely in other diseases of the pulmonary blood vessels, they are an important diagnostic clue.
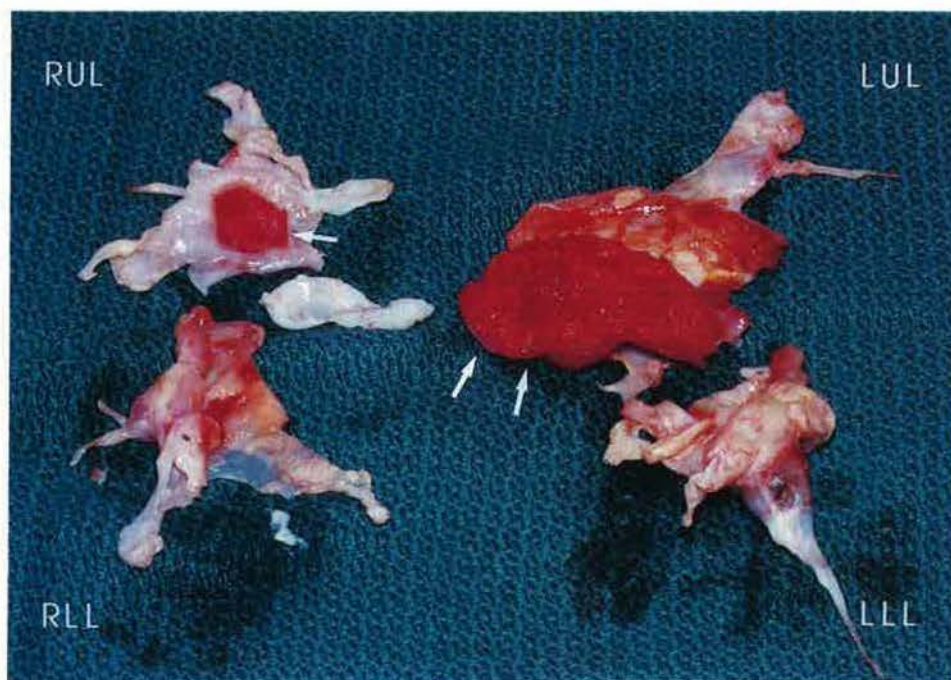
Fig. 1. – Partially organized, red thrombus (white arrows) frequently line the inner aspects of the fibrotic, well-organized thrombus endarterectomized from the pulmonary arteries.

Early cardiac examination is often normal apart from equivocal accentuation of the pulmonary closure sound. Later in the patient's course, pulmonary closure may be quite loud, there is usually tricuspid regurgitation and fixed splitting of the second sound; and still later, a right ventricular impulse along the left lower sternal border and a right ventricular S_3 and S_4 may be heard. Abdominal examination is unremarkable until congestive hepatomegaly appears late in the course; ascites may also then be observed. The lower extremities may or may not reveal evidence of venous stasis.

The blood count is normal until late in the course when hypoxaemia often induces an increase in haematocrit and haemoglobin. Studies searching for specific coagulopathies are usually unrewarding. Less than 1% of our patients have had protein C, protein S or antithrombin III deficiencies. The most common abnormality has been the presence of a lupus anticoagulant (in approximately 10% of the patients). Blood chemistry studies are normal until right ventricular failure induces hepatic and/or renal abnormalities.

The chest X-ray is often surprisingly normal, particularly early in the patient's course. However, there may be clues such as central pulmonary vascular shadows which should be of equal size and are not; for example, one main pulmonary artery may be very distended while the other is very small. Zones of avascularity may also suggest the diagnosis (fig. 2). Some patients will have pleural thickening as a residual of a prior embolus or infarct, although this is uncommon. Right ventricular cardiomegaly occurs late in the course.

The electrocardiogram is often quite normal early in the course; later, classical evidence of right axis deviation, right ventricular hypertrophy and strain will appear. One pitfall is the presence of marked T-wave inversions across the precordium due to right ventricular ischaemia which are often interpreted as evidence of an anterior myocardial infarction.

Echo-Doppler studies are extremely useful [25]. Doppler quantification of the tricuspid regurgitation (or pulmonary artery acceleration time) can estimate the pulmonary arterial systolic pressure. Depending on the point at which the patient is seen, the echo may also disclose right atrial and right ventricular enlargement, right ventricular hypertrophy and paradoxical motion of the interventricular septum. A very small percentage of patients will also have some evidence of right atrial thrombus which represents a residual of a prior embolus that has become incorporated into the right atrial wall.

Pulmonary spirometry is normal in the majority of patients. Patients with a long smoking history may show evidence of chronic obstructive pulmonary disease, while some nonsmokers may demonstrate expiratory obstruction due to bronchial hyperaemia related to the large bronchial arterial collaterals which these patients develop. One pitfall in the diagnostic approach is the fact that about 20% of these patients will have a restrictive pulmonary defect with reduction in lung volumes to below 80% of predicted [26]. The basis for this marked restriction has yet to be fully elucidated, but it appears to be due to a combination of pleural disease and small infarcts scattered throughout the lower lobes. Whatever its pathogenesis, such a finding often leads to a search for interstitial lung disease, leading away from the correct diagnosis. Finally, the diffusing capacity for carbon monoxide (D_{LCO}) is often within the normal range [27]. While it may be reduced, a normal D_{LCO} does not exclude the diagnosis of CTEPH.
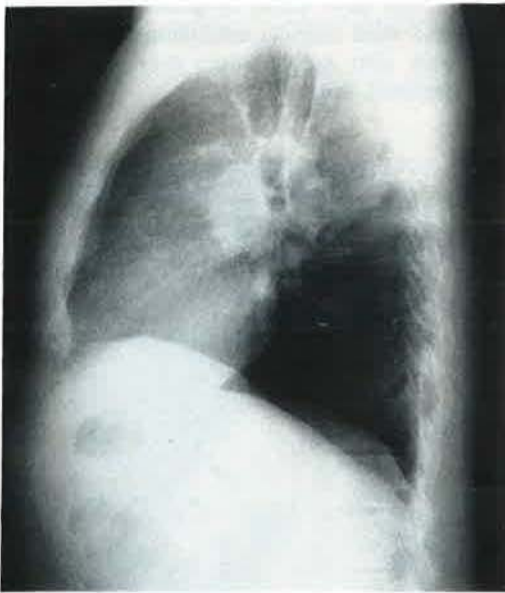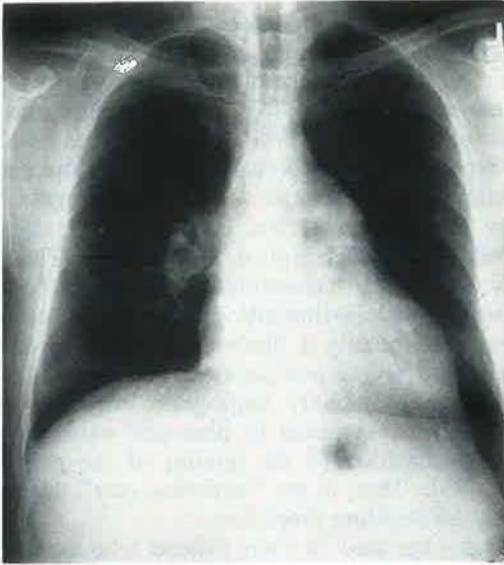
Fig. 2. – Chest radiograph of a patient with chronic, thromboembolic pulmonary hypertension. Remarkable features of this study include relative avascularity of the left upper lobe and entire right lung field, central pulmonary artery (PA) enlargement with a peculiar "beaked" appearance of the right descending PA, and right-sided cardiomegaly/pulmonary outflow tract enlargement as suggested by the obliteration of the retrosternal space.

Our speculation is that this normalization of the DLCO probably reflects the extensive bronchial arterial collateral flow. Ongoing measurements of bronchial arterial flow during surgery indicate such flow exceeds 10% of cardiac output in these patients. Since this flow "back-perfuses" the capillary bed, it should be capable of achieving substantial CO transfer.

Arterial blood gas studies at rest may be normal. However, with exercise, the majority of patients show a decline in arterial oxygen tension (Po_2) and a widening of the alveolar-arterial oxygen difference $D(A-a)o_2$ [27]. Later in the course, resting hypoxaemia is common. The mechanisms responsible for this hypoxaemia include ventilation/perfusion aberrations and a widening of the arterio-venous oxygen difference ($A-vo_2$) as the cardiac output declines [28].

Right-heart catheterization will reveal an elevated pulmonary arterial pressure with a normal wedge pressure. However, it is often difficult to obtain true wedge pressures in these patients and false elevations of the pulmonary capillary wedge pressure are often recorded. This is commonly due to "wedging" in a proximal pulmonary artery which is partially or totally occluded by thrombus. Direct measurement of the left ventricular end diastolic pressure may be necessary if elevated wedge pressures are consistently obtained.

While the Echo-Doppler studies and right-heart catheterization will indicate the presence of pulmonary hypertension, these studies cannot define the aetiology of the problem. The key non-invasive study which does so is the performance of perfusion and ventilation lung scans. In all patients encountered thus far, at least one segmental or larger perfusion defect has been observed; these defects are "mismatched" by a normal ventilation scan. While the discovery of significant perfusion defects usually leads most directly to the diagnosis, there is also a pitfall in this regard. Specifically, it has been found that the extent of perfusion deficits consistently underestimates the extent of central pulmonary arterial obstruction [29, 30]. Patients may have very severe central pulmonary arterial thrombotic obstruction with quite modest perfusion deficits on the scan (fig. 3a and b).

The procedure which best confirms the diagnosis and establishes surgical feasibility is the pulmonary angiogram. Again, there are pitfalls in pulmonary angiography. Firstly, there is the anxiety often generated by the idea of performing a pulmonary angiogram in a patient with severe pulmonary hypertension. While such anxiety is justified, following a series of relatively simple safeguards renders the procedure relatively risk free, as we have reported [31]. We perform only one injection into the right main pulmonary artery in the PA projection and another in the slight left anterior oblique position into the left main pulmonary artery. With sequential cut films, the status of the central pulmonary arteries can be clearly delineated, i.e. those arteries (main, lobar and segmental) which are the key to the diagnostic and therapeutic approach. Interpretation of these angiograms also presents difficulties because the changes characteristic of chronic embolism are quite different from those seen in acute embolism [32]. Interpretation of these unusual angiograms has been facilitated by observing the materials removed at surgery and correlating them with specific - but easily overlooked - changes on the pulmonary angiograms. Such changes included webs, bands, pouches and other irregularities, as well as "cut-off" and narrowed vessels (fig. 3b).
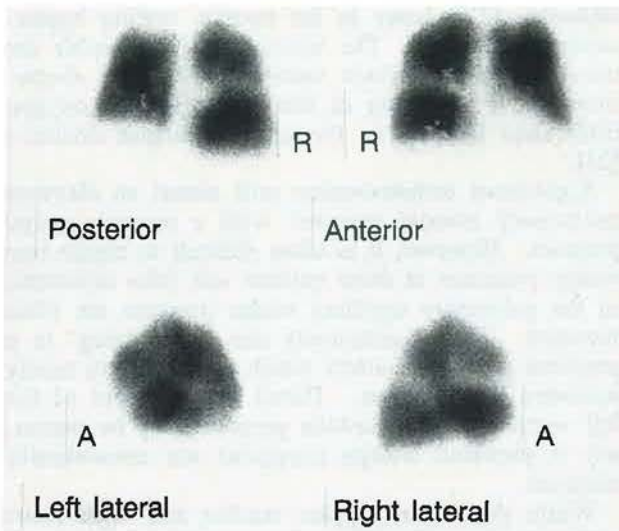
Fig. 3a. - Lung perfusion scan of a chronic thromboembolic pulmonary hypertension patient: absent flow to the apical left upper lobe, with decrement in perfusion to the right mid-lung field and segments of the right upper lobe, right lower lobe and left lower lobe. The perfusion defect at the base of the left lower lobe was matched by poor ventilation to the same area (left hemi-diaphragm elevation on chest radiograph). R: right; A: anterior.

patient and his family to accept the risks of surgery; 3) a pulmonary vascular resistance (PVR) of 300 dynes·s·cm^{-5} or greater; and 4) the absence of significant co-morbid disease [5]. None of these criteria, except for the patient's desire for surgery, is absolute.

Perhaps the most important criterion is the surgical accessibility of the thrombi. Unless the thrombi begin in the segmental arteries, they are not subject to removal by current surgical approaches. Therefore, assessment of such accessibility is crucial. If surgery is attempted and the thrombi prove to be inaccessible, the surgical mortality is likely to be high, especially in patients with severe pulmonary hypertension. At this time, if the pulmonary angiogram does not define accessibility, we proceed to fibreoptic angioscopy for direct visualization of the interior of the pulmonary arteries [33]. Thus, in the "borderline case", angioscopy is often the deciding procedure.

We have operated on some patients with a pulmonary vascular resistance below 300 dynes·s·cm^{-5}. These have predominantly been young patients with total unilateral occlusion. They have effort dyspnoea due to the large deadspace and wish surgical correction for relief of their dyspnoea and, also, so that they may continue in life with two perfused lungs.

Fig. 3b. - Pulmonary angiogram of the patient whose lung perfusion scan is pictured in figure 3a. Extensive involvement of the proximal right upper lobe vessels (open arrows), left upper lobe and both descending pulmonary arteries with chronic thrombi. Intimal irregularities (white arrows), absence of lobar and segmental vessels and abrupt vascular narrowing (black arrows) are typical angiographic features of this disease. Chronic thrombi removed at surgery are shown in figure 1.

Selection of patients for surgery

Our current criteria for considering patients for surgery include: 1) thrombi defined as accessible to current surgical approaches; 2) a willingness of the

While we would prefer patients without significant co-morbid conditions, we have followed the wishes of patients who elect surgery even in the presence of significant disorders such as co-existing coronary artery disease, lung disease, renal disease, etc. These

co-morbid conditions not only increase the risk of the procedure but also may diminish the extent of post-operative improvement. Coronary angiography is performed in all patients above 35 yrs of age who have significant coronary risk factors. If significant coronary lesions are encountered, these are corrected by bypass at the time of pulmonary thromboendarterectomy.

Extensive discussions are held with the patient and family regarding the risks of surgery, and the decision to proceed is left entirely with the patient. Our role is to present, in the most precise terms now possible, the risks of undergoing the surgical procedure and its potential benefits. Patients who are not certain they wish to proceed are advised to defer the decision for surgery.

Surgical approach

With the exception of those few patients with total unilateral occlusion, this is a bilateral disease. Pulmonary hypertension does not occur unless there is extensive involvement of both the right and left pulmonary arterial systems; and preoperative angiograms and scans have defined that this is a bilateral disease in the vast majority of patients.

Therefore, all patients are approached by median sternotomy to gain adequate bilateral exposure [5]. In addition, because the often luxuriant bronchial arterial flow makes it impossible to carry out the necessary delicate dissection, significant hypothermia (to approximately 20°C) is essential. This is a true thromboendarterectomy and not an embolectomy. Indeed, there is a steep learning curve in carrying out a satisfactory thromboendarterectomy. Often, there is reddish material proximal to those whitish lesions which represent the organized thrombus blocking off lobar and segmental arteries (fig. 1). If only this proximal reddish material is removed, the patient will not be improved. It is essential that the whitish, fibrotic material be dissected so that the lobar and segmental branches are opened. This material often looks much like normal "intima", although with experience the pits and ridges characteristic of organized thrombus will be recognized. To establish a satisfactory plane, it is necessary to incise into this "intima" so that the dissection distally can be carried out.

To achieve this dissection, bypass is interrupted for up to 20 min at a time, with reperfusion in between [34]. As experience is gained, the number and duration of these periods of bypass interruption can be sharply diminished. But, again, the lesions are so different in appearance from patient to patient that experience with a substantial number of cases is necessary before thromboendarterectomy can be carried out with a degree of dispatch. Naturally, extreme care must be taken in avoiding perforation of the pulmonary arterial wall during dissection. This is not an easy task since, often, after dissection of the thrombotic "neo-intima", the pulmonary arterial wall is rather thin.

To avoid injury to the phrenic nerves, the myocardium is cooled in a special cooling jacket so that no sludge is placed in the pericardial sac. This has eliminated a serious problem encountered early in our series: bilateral diaphragmatic paralysis due to hypotension. Finally, it is routine at surgery to inspect the atrial septum because of the high incidence of a small atrial septal defect (ASD) or patent foramen ovale encountered in this patient group (about 30%). If present, the communication is closed. Tricuspid regurgitation is present, often severe. However, this need not be surgically approached because it resolves after successful thromboendarterectomy [25].

In our experience, it is important that the medical members of the team, who are quite familiar with the angiographic, scan and angioscopic findings, be present in the operating room throughout the procedure to interact with the surgical team as issues regarding accessibility of thrombi in various arteries arise. The team is also present to interact with anaesthesiology in the immediate postoperative period to assure a smooth transition to the intensive care unit.

Postoperative management

The postoperative period of these patients is often complex. The usual problems that follow extensive open heart surgery are often encountered, including arrhythmias, the potential for bleeding, water and electrolyte disturbances and haemodynamic instability. In addition, however, complications specific to pulmonary thromboendarterectomy may be encountered. The most troublesome of these is reperfusion lung oedema [35]. This oedema involves only the lung zones from which proximal thrombi have been removed. It is a difficult problem because blood flow to these areas continues, even though they are oedematous and participate poorly in gas exchange. Therefore, significant postoperative hypoxaemia results. The hypoxaemia is managed in standard fashion by mechanical ventilation, providing sufficient oxygen to maintain the arterial oxygen tension at a reasonable level and, if necessary, some degree of positive end expiratory pressure. These patients may also be "position sensitive" with respect to hypoxaemia, depending on the distribution of the pulmonary oedema. The extent and severity of reperfusion oedema has been moderated in recent years by providing the patient with a large bolus of corticosteroids at the conclusion of the procedure and another dose the day after surgery, in the evening. The value of this empiric approach has been repetitively observed in these patients but, at this time, the basis for its effect has not been defined. We speculate that stimulation of surfactant production in the previously non-perfused lung zones may play a role.

The hypothermic-arrest sequence during the procedure has also been associated with transient psychiatric aberrations during the initial postoperative period [36]. These aberrations have correlated with the total duration of hypothermic-arrest, and they have been markedly reduced as these durations have declined over the last couple of years.

There is also, of course, concern about renewal of venous thrombosis and/or thrombosis *in situ* following this procedure. With rare exceptions, all patients facing pulmonary thromboendarterectomy have had a Greenfield filter placed in the inferior vena cava during their preoperative evaluation to guard against embolization from prior sites of venous thrombosis in the lower extremities [5, 37, 38]. In addition, the patients are placed on venous compression devices in the operating room and these are continued until the patient is fully ambulatory. Unless bleeding is a major problem, the patient is also started on subcutaneous heparin, 5,000–10,000 units subcutaneously every 12 h, the evening of surgery. This is maintained until coumarin therapy can be reinstituted several days after surgery.

In addition, atrial and ventricular pacing wires are placed at the time of surgery and these have proved useful in several regards. Firstly, the patients often emerge with sinus bradycardia from the surgery and the wires are helpful in achieving adequate cardiac rates to maintain the cardiac output. These patients often require atrial action to maintain optimal right ventricular function. Finally, the pacing wires may also be useful in dealing with the various arrhythmias that may arise.

To avoid accumulation of fluid in the pericardial space (even though the pericardium is not closed), a catheter is left in place in the posterior pericardium for the first 5–7 postoperative days. This has sharply reduced the incidence of pericardial effusion requiring drainage late in the patient's course.

It is clear that the many postoperative difficulties which these patients may encounter require the detailed attention of an experienced medical-surgical team. Their care is not "standard" in any regard and the dedicated attention of an experienced team is vital in dealing with the issues which arise.

The average duration of intubation and mechanical ventilation has approximated 3 days, with a 5 day intensive care unit stay. The average duration of post-surgical stay has been approximately 2 weeks.

Outcomes

The mortality risk of the procedure, over the first approximately 250 patients operated at our institution, has been close to 12%. The bases for these mortalities have been multiple. In the early days [7], prior to performance of coronary angiography as a routine, several died from unsuspected coronary lesions which expressed themselves postoperatively as acute myocardial infarction. Bilateral phrenic nerve paralysis was another complication which led to mortalities; as noted, this problem has been eliminated by use of the myocardial cooling pad. Sepsis has been rare, but also played a role in some deaths. At the present time, there are only two significant residual causes of mortality: 1) unrelenting reperfusion oedema; and 2) inability to remove sufficient thrombotic material at the time of surgery so that the postoperative course is marked by

persistent pulmonary hypertension and right ventricular dysfunction. Considering the fact that most of the patients upon whom we have operated are in New York Heart Association Classification III or IV, this mortality rate - while still unacceptable to us - is not unexpected. As already noted, extensive preoperative evaluation, including angioscopy when indicated, is designed to avoid operating on patients in whom pulmonary thromboendarterectomy will be less than optimal. However, it should be noted that a number of these patients, even when faced with an extreme estimate of risk and/or with our statement that resection may not be possible, elect to proceed because of their severe degree of disability and the lack of other therapeutic options.

Among the survivors of the procedure, the immediate postoperative haemodynamic results (table 1) demonstrate a marked reduction in pulmonary vascular resistance, a decline in pulmonary artery pressure and a rise in cardiac output. This degree of haemodynamic improvement is sustained long-term, as reflected in data we have collected when these patients return, months to several years after their procedure (table 2).

Table 1. – Haemodynamic results in 128 of 150 patients in whom postoperative values were obtained 48–72 h after intensive care unit admission (off all vasoactive agents)

	Preoperative	Postoperative
Ppa mmHg	47±12	28±9*
Ppa$_{sys}$ mmHg	76±21	47±16*
CO l·min^{-1}	3.7±1.1	5.7±1.2*
PVR dynes·s·cm^{-5}	901±467	261±163*

Ppa: pulmonary artery mean pressure; Ppa$_{sys}$: pulmonary artery systolic pressure; CO: cardiac output; PVR: pulmonary vascular resistance. Values are mean±SD. *: p<0.001 *vs* preoperative value.

Table 2. – Haemodynamic values obtained in 47 of the first 150 patients who returned for follow-up cardiac catheterization at 6–24 months after surgery

	Preoperative	Postoperative	Follow-up
Ppa mmHg	48±12	27±8*	24±10
Ppa$_{sys}$ mmHg	80±21	44±15*	39±17**
CO l·min^{-1}	3.7±1.17	6.0±1.1*	4.8±1.0$^+$
PVR dynes·s·cm^{-5}	971±551	232±111*	282±251

For abbreviations see table 1. *: p<0.001 *vs* preoperative value; **: p<0.0015 *vs* postoperative value; $^+$: p<0.0001 *vs* postoperative value.

There is a small subgroup of patients, however, in whom the postoperative reduction in pulmonary vascular resistance fails to return to normal or near normal levels. This subgroup is an object of particular focus at this time. It appears that, among these patients, severe intimal lesions have developed in the small pulmonary arteries in both the obstructed and

non-obstructed areas, maintaining their pulmonary arterial pressures above normal. Why these lesions develop, and how they might be predicted during the preoperative evaluation, is an object of ongoing study.

Perhaps the most gratifying aspect of long-term outcome in these patients is their functional status following surgery. As reflected in table 3, the majority return to Class I New York Heart Association status postoperatively, a state which they maintain for many years.

Table 3. – New York Heart Association functional classification of 117 patients of the first 150 who were evaluated at one year following surgery

Class	Preoperative	Follow-up
IV	63	0
III	49	6
II	5	26
I	0	85
Total	117	117

The long-term postoperative management of these patients is usually simple. We urge that they are maintained on coumarin therapy life-long, despite the usual presence of the caval filter. This policy has been invoked because we are concerned about the recurrence of venous thrombosis, which may lead to embolization of the filter; and we are also concerned about *in situ* rethrombosis in the pulmonary arteries. Thus far, during long-term follow-up, 3 patients who discontinued warfarin therapy have suffered recurrent venous thrombosis. Two patients have had recurrence of pulmonary vascular obstruction - either from *in situ* thrombosis or recurrent embolism - several years after the procedure; one of these patients had also discontinued his anticoagulant therapy. Most of the patients return to full-time, normal activity. Two of the young women operated upon have had successful pregnancies.

The future

Clearly, many questions regarding these patients remain to be resolved and are the object of intensive research at our institution. One major question is the reason for the aberrant outcome in these individuals after acute embolism; that is, why do they fail to resolve their emboli? Thus far, studies of the fibrinolytic system have not indicated that these patient differ significantly from control subjects; but these studies are being extended. Investigations of the reperfusion oedema issue have indicated that, biochemically and clinically, this represents a "focal" form of the adult respiratory distress syndrome [39]. Excessive elastase and oxidant release are evident, as are indications of surfactant abnormalities. Therapeutic initiatives to deal with these issues are underway. The changes in the small pulmonary arteries are also an area

of ongoing investigation. Lung biopsy specimens have indicated that these individuals frequently have "pulmonary hypertensive" lesions in the obstructed and the non-obstructed areas. This appears to be the basis for the many instances of postoperative "steal" that we have described [40]. Our current efforts are focused on means, without preoperative lung biopsy, for identifying patients with advanced lesions; and upon postoperative studies to determine to what extent these lesions may reverse with normalization of pulmonary arterial pressures. In addition, the search for excessive release of various mediators which may induce these changes are underway. While these issues are central to our ongoing research initiatives, many other questions have been catalysed by this same population. For example, the common occurrence of heparin-associated thrombocytopenia in the preoperative period; the remarkable capacity of the right ventricle to recover normal function; electrocardiographic studies; and attempts to improve thrombus definition by both angioscopy and ultrasound techniques [41] are all in progress.

In the clinical arena, one major goal is to promote earlier recognition of this condition. It is our hope that such early recognition will result in a progressive lessening of operative mortality as patients achieve operation before they enter advanced stages of right ventricular failure. We would suggest that all patients known to have significant pulmonary embolism should have a follow-up scan, even though they appear to be "doing well". Such a follow-up scan may indicate that there has been failure to achieve adequate resolution, and that the patient should be carefully watched for evidence of sustained or progressive pulmonary hypertension.

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