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Review Article

Pulmonary Endarterectomy in Chronic Thromboembolic Pulmonary Hypertension: "State of the Art" and New Therapeutic Options

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Abstract

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is considered the only type of pulmonary hypertension (PH) with a potentially curative surgical treatment. Even today, this pathology is not easily recognized and frequently diagnosis is delayed, with the consequent impairment of the prognosis. CTEPH presents with nonspecific symptoms and general practitioners may not be aware of the condition or potential for treatment. Current medical treatment is, at best, palliative. Pulmonary endarterectomy (PEA) offers the only possibility of symptomatic and prognostic improvement, being curative in most cases in the short and long term.

Once the challenging diagnosis of the CTEPH has been done, the estimation of operability can be also difficult. The operability is based on the preoperative estimation of postoperative surgical classification and probable pulmonary vascular resistance (PVR), which determine the risk of intervention and the outcome. This complex procedure that includes, characterization of the pathology, the surgical intervention going through the whole decision process requires a multidisciplinary collaboration of experts in Pulmonary Hypertension, with a dedicated surgical team, and with very precise protocols. At our center, we have built a team of dedicated specialists including radiologists, cardiologists, cardiac surgeons, anesthesiologists and physiotherapists. Together, we have been able to obtain surgical results comparable to "big volumes" European centers, and also, we developed and implemented other therapeutic options such as pulmonary angioplasty with balloon, dedicated to patients at high risk and discarded for surgery.

In the present paper, we present an overview of the pathology and its main treatment, that is pulmonary endarterectomy. New therapeutic options are also exposed as well as our dedicated CTEPH team experience.

Keywords: *Pulmonary Hypertension; Deep Hypothermic Circulatory Arrest; Endarterectomy*

Introduction

Epidemiology

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is not such a frequent complication of acute pulmonary embolism (APE) and is associated with severe morbidity and mortality [1]. In the United States, an incidence of 0.1 - 0.5% has been estimated, based on the number of cases diagnosed as CTEPH and related to an annual incidence of patients surviving the acute event of pulmonary embolism (PE) [2,3]. The apparent low incidence CTEPH development after one or more episodes of PE, has been always a very controversial subject [4]. Pengo., *et al*. reported a cumulative incidence of 1%, 3.1% and 3.8% at 6, 12 and 24 months of the acute event, in the absence of a successive progression.

Multiple prospective studies, published between 2006 and 2010, refer to an incidence of CTEPH ranging from 0.6 to 1.3%, probably reflecting the real incidence of this disease [5-8].

In addition, in a recent work, Delcroix et al, determines some epidemiological data that give an idea of the real dimension of the problem. The CTEPH represents at least 19% of patients currently referred to dedicated centers in PH. The incidence of CTEPH approaches 5 cases per million of habitants per year and its prevalence could reach almost 40 cases per million inhabitants [9].

CTEPH is not only an unfrequent phenomenon after a diagnosed and treated APE; on the contrary, few patients with CTEPH refer a documented previous episode of APE. It is estimated that less than 40% of patients have an episode of acute pulmonary embolism [6] in their clinical history and this makes the differential diagnosis more difficult. This phenomenon is justified by the presence of few or sometimes complete lack of symptoms during the acute process, in those cases in which the thromboembolic fragments are of small caliber, in limited number and tend to obstruct distal arterial branches. Another reason that would explain the absence in anamnesis of the antecedent of the acute episode, is the recurrent thrombosis "*in situ*" of distal vessels, in those patients with paraneoplastic syndrome or in general with thrombophilic status.

The CTEPH is characterized by the intravascular fibrotic organization of the residual clot. This clot theoretically comes from the venous system, after one or repeated acute embolic events. Also intraluminal thrombosis in situ and not embolism, as previously mentioned, may be the acute event. In turn, a first embolic event, and the subsequent fibrotic transformation, involves an endovascular prothrombotic state, given the loss of endothelial protective characteristics, thus promoting repeated local thrombosis. In anatomical terms, the initial result is a reduction in the diameter of the vessel lumen due to the presence of intraluminal fibrotic bridles, and/or complete obstruction, giving rise to an increase in pulmonary pressure. The intensity of the symptoms is, first of all, directly proportional to the number of arteries involved in the process and to the degree of obstruction, which leads to an increase in the afterload of the right ventricle. In those cases in which the acute process does not cause a failure of the right ventricle and the "dead space" is not such to give respiratory symptoms, the patient may not even report any type of discomfort. In any case, also in the cases of patients who present typical symptoms of pulmonary embolism, after the first episode, they report well-being and absence of symptoms. It is a clearly defined time period, which can vary from months to years. During this time interval, recanalization of the arteries occurs with fibrotic transformation of the thrombus, which adheres firmly to the vascular wall. Simultaneously, an initially functional (vasoconstriction) and successively structural remodeling (hypertrophy) of the small healthy arteries not involved in the initial process ensues.

The vasoconstriction of the "healthy arteries" is a compensatory mechanism that allows to regulate the hyper-inflow of blood to the healthy lung territories. The prolonged vasoconstriction, gives rise to a phenomenon similar to what occurs in the venular and arteriolar postcapillary tree in pulmonary hypertension secondary to left ventricular failure. Changes occur in the histological architecture of the artery wall, with muscle hypertrophy of the tunica media and intimal hyperplasia. All these changes also involve alterations in the release of self-regulating substances such as nitric oxide or endothelin, contributing in turn to the process. The secondary arteriopathy of the pulmonary microcirculation is therefore very similar to the more classic forms of pulmonary hypertension and that can reach a state of irreversibility [10,11]. This double behavior, that is, the increase in pressure secondary to the remodeling of the fibrotic thrombus and the reduction of the caliber (anatomical component) and the compensatory remodeling of healthy small vessels (functional component or "secondary vascular changes"), is the reason why which this pathology is considered "double compartment": Dual Vascular Disorder. It has been theorized that this phenomenon occurs in 10 - 30% of patients and probably increases with time if surgery is not performed. Although concomitant pulmonary vascular disease predicts an adverse outcome [12,13], no biological mechanisms or indicators have been identified that can predict the degree of vascular compromise and reversibility. The disproportion between the severity and the level of occlusion of the vessels with respect to the degree of pulmonary hypertension may be indicators, but even today, it has not been demonstrated. The higher incidence of residual or recurrent HP in patients with medical conditions associated with CTEPH suggests that in these, pulmonary arteriopathy is more serious [14]. The new vision and the physiopathological knowledge of CTEPH have conditioned the routine of clinical practice. The main treatment continues to be pulmonary endarterectomy (PAD), although some cases may not be suitable, due to a predominance of secondary vascular pathology in hypertension and its irreversibility. Two aspects still difficult to identify today.

The pathogenesis of CTEPH is still largely unknown. The prevalence of hereditary thrombophilia (deficiencies of antithrombin, protein C or protein S, or mutations of factors II and V) is not significantly greater compared with other types of HP, such as idiopathic HP, or even in healthy individuals [15,16]. Antiphospholipid antibodies are detected in 21% of patients and elevated levels of factor VIII have been observed in 41% of patients with CTEPH. Multiple investigations [17] have documented that patients affected by CTEPH have a constant resistance to plasmin-mediated fibrinolysis. This abnormality has also been found in idiopathic HP and in some forms of acquired HP. The fibrin molecule or the same architecture in general of the fibrin clot probably presents a structural anomaly that makes it resistant to lysis. Prolonged exposure to fibrin or fragments thereof stimulates platelet adhesion and proliferation of endothelial cells, fibroblasts and pulmonary artery smooth muscle cells, thus suggesting a potential role in vascular remodeling and angiogenesis. Therefore, the traditional view of thrombosis as a plasmatic problem of clot formation is replaced by the idea that the core of thrombosis is the process of vascular repair that entails. Venous thrombi resolve by organization and recanalization, possibly similarly and resemble the formation of granulation tissue during wound healing.

The identification of clinical risk factors for CTEPH has shed new light on the molecular mechanisms underlying the persistence of the thrombus and its fibrous transformation. Clinical observations such as the frequent presentation of CTEPH in patients with arteriovenous shunts, splenectomized [17] or carriers of permanent venous access, and pacemakers have stimulated experimental research. Infections in these patients are frequent. Staphylococcus aureus or epidermidis are responsible for up to half of these device infections. It has been observed that the majority of CTEPH patients with these types of devices had a history of infection. *Staphylococcal* DNA has been found in PEA specimens of this type of patient.

Other interesting facts are that CTEPH is more common in patients with blood groups A, B and AB. In one study, 77% of patients with CTEPH had non-O blood group compared with 58% of patients with PAH ($p = 0.003$) [17,18].

Neoplastic patients have an increased risk of thromboembolic events, as a result of different mechanisms, including the activation of fibrinolytic and coagulation systems, inflammation and cytokine production.

Clinical presentation, diagnosis and selection of the candidate patient for EAP

The clinical presentation of CTEPH is not very specific, with progressive exertional dyspnea, palpitations, hemoptysis, syncope and, when right heart failure ensues, dilation of the neck veins and edema in the lower limbs. CTEPH is defined as the combination of these three factors: ≥ 3 months of effective anticoagulation and a mean pulmonary artery pressure (mPAP) > 25 mmHg with pulmonary capillary pressure ≤ 15 mmHg, and at least one perfusion defect (segmental). Some patients suffer from symptomatic chronic thromboembolic pulmonary disease without pulmonary hypertension at rest, and may also benefit from pulmonary endarterectomy (PEA) [19,20] this being still a very controversial argument.

The evaluation of operability in patients with CTEPH is crucial since surgery can be potentially curative. This type of assessment must be carried out by a team of multidisciplinary experts, including pulmonologists, cardiologists, radiologists and surgeons. Perhaps the most important factor in determining a suitable candidate is based on the correlation of severity of HP versus the extent and extent of the obstruction. Like any other surgical procedure, individual patient factors, including comorbidity and the level of expectations for long-term benefits, are crucial in the decision-making process.

As a general rule, symptomatic patients should be offered surgery regardless of the degree of hypertension or RV dysfunction, although these parameters are directly related to a corresponding degree of obstructive disease and the severity of the pathology. Although neither the value of pulmonary vascular resistance (PVR) nor the degree of RV dysfunction would exclude the patient from surgical consideration, PAD and postoperative care become more difficult. Generally, if the disease involves the main, lobar or even proximal branches of the segmental pulmonary arteries, surgical disengagement by endarterectomy is feasible. The segmental and subsegmental distal disease is much more difficult to eliminate and, in some centers, it can imply the inoperability of the patient. Hence the need to predict in the preoperative the level of obstruction and the type of postoperative specimen (Classification di Jamieson., *et al*. UCSD) [30,37]. This theoretical

forecast requires a careful and thorough analysis of pulmonary angiography and computed tomography (CT) with contrast. These images should be analyzed by comparing them with each other, in all the projections and in all the planes (axial, coronal and sagittal). Even so, the final decision on feasibility and surgical accessibility is still extremely subjective, which requires great experience.

Obviously, it is strictly necessary to know the degree of pulmonary hypertension, reasoning in terms of pulmonary resistances (data obtained with right catheterization) and also of commitment of right ventricular function, with echocardiography.

Other factors that will make the PEA a challenge, due to the potentially increased risk of "distal" disease and recurrence, are patients with risk factors such as venous access catheters, or pacemakers and patients who have undergone splenectomy. However, none of these are absolute contraindications for surgery, nor is age by itself a contraindication, since studies have indicated sustained benefits in patients older than 70 and 80 years of age [21,22].

As in the general practice of the surgeon and collaborators, it is essential to weigh not only the surgical risk, the risk of recurrence or the persistence of pulmonary hypertension, but also the likelihood of improvement of symptoms and quality of life after surgery. Therefore, it is necessary to consider the suitability of surgery in those patients with serious associated pathologies, such as terminal pulmonary disease or a life-limiting malignancy, which not only present a considerable perioperative risk, but also are unlikely to be possible. enjoy the benefits that would be achieved with the PEA.

Even so, thanks to the progressive increase of experience and the reduction of perioperative mortality rates, the surgical teams of CTEPH have shown themselves willing to operate increasingly complex cases [23-25].

On the other hand, almost opposite, it has been observed that some patients with significant chronic vascular occlusions but pulmonary hemodynamics almost normal at rest, are fit for CTEPH and therefore, are eligible for PEA. Some of these individuals have an mPAP that is higher than that observed in the healthy population, but below the threshold of definition of CTEPH [26]. Currently, there is a lack of adequate terminology for this fraction of patients and the term "CTEPH" is inappropriate. The Cambridge group has used the term chronic thromboembolic disease (CTED); others may use the term "chronic thromboembolic pulmonary vascular disease" [19]. Completely unilateral CTED is rare, although it may occur, however, most patients have bilateral disease, which may be greater (operable) on one side and less (inoperable) in the other: A series of 42 patients with CTED underwent pulmonary endarterectomy [26] in which there was no intrahospital mortality and patients experienced a clear improvement in symptoms, as well as functional class and quality of life. This suggests that patients selected with CTED can benefit from surgical treatment. It is obviously very important that the risks of surgery are previously weighed and that the patient is informed of them. Even if a patient has no symptoms, the restoration of the perfusion to a completely occluded lung may be beneficial (for example, eliminating the risks to the patient of the sudden loss of remaining lung function). In addition, the restitution of perfusion in these lungs allows to prevent chronic parenchymal changes, scars and secondary vasculopathy. However, as expressed by the same Cambridge group, it is not known if this strategy prevents the development of CTEPH or if they are two separate entities.

HPTEC Surgical Classification

One of the most complex aspects of CTEPH is therapeutic decision making. To propose the intervention of PEA, it is absolutely necessary to make a estimate, with the angiography and the CT, of the level of the pulmonary arterial tree that originates the fibrotic thrombus. The more distal it is, the more difficult it is to remove the thrombus. The group of experts from the University of California has recently proposed a surgical classification (UCSD Classification) [30]. They propose four levels of occlusive lung disease related to organized thrombus. Level 0 (zero) corresponds to absence of chronic thromboembolic disease. Level I indicates that the obstructive material and the plane of dissection affect one of the main pulmonary arteries. In case of complete obstruction of one of the main arteries the letter "C" (i.e. IC Level) is added; This distinction is important given the technical differences in the endarterectomy required in this context. In Level II the fibrous tissue begins in the lobar branches or beyond the takeoff of the superior lobe artery. Level III presents a more difficult surgical situation in which the disease is distal and begins in the segmental branches, where the occlusive disease may not be evident.

The endarterectomy plane must be carefully analyzed in each segmental branch. Level IV is the most challenging anatomical picture since endarterectomy can be quite difficult at this level (distal segmental branches or even sub-segmental) and extensive surgical experience is required to achieve optimal results.

Surgical technique

The intervention of pulmonary endarterectomy (PEA) requires a team of specialized and trained professionals not only in the intraoperative management but also in the intensive care in the postoperative period. As a general rule, the PEA follows four basic principles: (1) The endarterectomy must be bilateral and, therefore, performed through a median sternotomy approach; (2) perfect visualization is essential and is performed through cardiopulmonary bypass with periods of circulatory arrest in deep hypothermia (DHCA: Deep Hypothermic Circulatory Arrest) at approximately 20°C; (3) identification of the correct dissection plane is crucial; and (4) a complete endarterectomy is essential [19].

After the median sternotomy and pericardiotomy, the complete cardiopulmonary bypass is started with a cannula in the ascending aorta and two venous cannulae in the cava. It is advisable to introduce the cannula of the superior vena cava through the right atrial appendage. Positioning the cannula directly in the superior cava is not advisable since it can prevent the correct exposure of the right pulmonary branch. Two drainage cannulas of the left ventricle and the pulmonary tree are also introduced through the right superior vein and the main trunk of the pulmonary artery respectively. Once the extracorporeal circulation begins, the systemic cooling of the patient proceeds progressively, maintaining a minimum thermal gradient between the upper and lower body regions. The nasopharyngeal and bladder/rectal temperatures must be constantly monitored. The objective of temperature before proceeding with the circulatory stop are the 20 degrees of nasopharyngeal temperature. In general, it is easy that between the two temperatures there is a gradient of about 2 degrees, therefore, to obtain a temperature of about 20 degrees in the lower region of the body, the nasopharyngeal temperature must be further reduced to about 19-18 degrees. As the body temperature decreases, the ventricle will enter fibrillation. Under these conditions, if the ventricles are completely emptied and relaxed, the myocardium is protected. Even so, we prefer to complete the protection with cardioplegia: shortly before reaching the hypothermia temperature, we proceed with the clamping of the aorta and the cardioplegia in the ascending aorta. In our center we use the Custodiol or modified Brechtneider crystalloid cardioplegia. It is an intracellular cardioplegia, with low doses of sodium and potassium, enriched with ketoglutarate, histidine and tryptophan as main characteristics [34]. The dose of this cardioplegia is usually very abundant considering that about 25 ml/kg of the patient is calculated. Thus, a patient of about 75 kg needs a theoretical dose of 1875 ml of cardioplegia. This supposes an important dilution of the patient, with which it is possible to proceed to the extraction of the excess liquid with the hemofilter and/or as our team performs the retrograde aspiration through the right atrium, after right atriotomy. Once the cardioplegia dose is concluded, the state of the interatrial septum can be controlled. In the case of patent foramen, we tend to suture it, except in those rare cases in which we consider that the complete occlusion of the latter may be counterproductive for the function of an extremely compromised right ventricle. Initially, it is more convenient for the surgeon to stand on the left side of the patient and perform the endarterectomy on the right side. During the cooling phase, it is also possible to continue with the exposure of the right branch of the pulmonary artery, with a Ritcharson separator with the protected tips. The superior cellar that has to be perfectly controlled and mobilized. With the tip of the scalpel, the longitudinal arteriotomy is performed, which can be extended to "Y" at the level of the bifurcation, towards the superior and inferior lobar branches. The opening of the artery is maintained with two suspension points. The identification of the cleavage plane is then proceeded. It is not always thick enough as ideally the surgeon would like, so you have to take off the tunic intimately, circularly and with extreme delicacy. Successively with a dissector and with a specific aspirator that allows to suck and dissect, this plane continues to detach towards the different branches where progressively the intima increases in thickness, becoming frankly fibrotic. Already in this phase, when it begins to extend the dissection to the segmental branches of the different lobes it is absolutely necessary to proceed with the circulatory stop, hyper-oxygenating the patient previously. Interrupted systemic circulation, the lungs are completely emptied by manual hyperventilation. Once assured that the retrograde bronchial flow is completely absent or insignificant, we continue with the endarterectomy, gently pulling the fibrotic specimen and detaching it, always maintaining the correct plane of cleavage, even the different branches, even subsegmental.

The periods of hypothermic arrest, when they exceed 20 minutes duration, should be interspersed with hypothermic systemic perfusion phases. Anyway, when the initial phase of the endarterectomy (i.e. the arteriotomy, the identification of the plane etc.) is performed even in perfusion, it rarely takes more than 20 minutes to stop, for each side to finish the endarterectomy. Once the procedure in the right lung is concluded, the arteriotomy of the pulmonary branch is reconstructed. Successively, and in the same way described for the right side, proceed with the left endarterectomy.

We have previously described our myocardial protection technique. With regard to cerebral and systemic protection, deep hypothermia is already an optimal method of protection. Anyway, it has been demonstrated in multiple and consistent works, especially of the cortical arch surgery, that the probability of organic damage (especially cerebral) is directly proportional to the duration of the stopping period. Hence the need to intersperse stop periods with re-perfusion periods during the EAP. In our center we have a strong tradition with the use of moderate hypothermia (25 - 26 degrees) associated with selective anterograde cerebral perfusion for aortic surgery, having demonstrated the benefits of avoiding deep hypothermia at 20 degrees [38]. For this reason, at the beginning of our experience in EAP, we have tried to avoid deep hypothermia and stop, maintaining the temperature at 25 degrees and the normal systemic perfusion parameters, in particular mixed venous oxygen saturation (> 65%). In moderate hypothermia and following these parameters, the flow of extracorporeal circulation can be reduced to such a level (even to less than one liter per minute) that for the operator, in terms of retrograde flow is like working in a stop with the surgical territory practically bloodless [32,33]. The disadvantage of this technique is that in some cases, especially those patients who have a marked hypertrophy of the bronchial arteries, the surgical field is not sufficiently bloodless thus preventing a correct endarterectomy. In these cases, when it has already been shown that at 25 degrees it is impossible to continue correctly with the procedure, in order to reach deep hypothermia it was necessary to increase the pump flow again at nominal flow. During this phase, it was impossible to perform any surgical maneuver, significantly increasing the pump and cardioplegic stop times. For this reason and to stay in line with the greatest experts in EAP, we have decided to resort directly to deep hypothermia with stop, as previously described.

This decision was also reinforced by the results obtained in a clinical trial, the PEACOG (PEA and COGnition) [27] that investigated the benefits of cerebral perfusion by comparing selective cerebral perfusion and deep hypothermia during PAD in terms of cognitive function at 3 and 12. months The study showed no differences between the two techniques, which indicates that the PAD in standstill in deep hypothermia at 20°C provides excellent and reproducible results. However, the results of the registry suggest that a longer time of circulatory arrest may be associated with neurological complications [28].

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Postoperative management is as important, if not more so, of the procedure itself. The management of water balance, electrolyte control, cardiac output as well as peripheral systemic resistance, and anticoagulation are some of the fundamental aspects that require very delicate adjustments. A detailed description of the postoperative protocols would require another complex and interesting chapter.

Results of EAP

Hemodynamic and functional results

Postoperative hemodynamics becomes normal or almost normal in most patients after PEA. From the databases of the University of California, San Diego (UCSD, CA, USA) and international CTEPH records, improvements have been experienced from PVR 700-800 dyn·s·cm-5 to 250 dyn·s·cm-5 after surgery [23,32], that is, a fall of ~ 65%. Other parameters that improve markedly after PEA include mPAP (46 to 26 mmHg) and the median of the 6-minute road test (362 to 459m). Most patients experience a significant change in functional capacity (NYHA Class), as well as improvements in other measures of exercise capacity, such as Bruce's protocol, and quality of life

in general. The inverse remodeling of the right ventricle is constant, with structural and functional improvement. The hemodynamic improvements are practically immediate, while, depending on their mechanisms, structural and functional improvements may take longer [19,28,30].

In the immediate post-surgical period the problems that can be evidenced are: 1) persistence of HP, 2) parenchymal hemorrhage, 3) failure of the right ventricle, 4) and respiratory failure. The main cause of residual HP is surely the presence of secondary and irreversible vasculopathy associated with reperfusion edema. Other reasons could be the incomplete extraction of the thrombus or the extraction of the thrombus with a plane of cleavage that is too superficial. These two causes are quite infrequent, since it is known that although an PEA is not perfectly complete, the release of at least 70% of the vessels allows a hemodynamic response to be obtained. Also in expert hands, the plane of cleavage is evident. Even so, and in expert hands, the lesion of the wall of the vessels, especially distal, when the "tails" are removed from the thrombus, can favor parenchymal hemorrhage which, if severe, can be lethal. Severe failure of the right ventricle is a relatively rare phenomenon but one that should always be kept in mind when dealing with PEA intervention since in some cases it involves the implantation of a mechanical circulatory support with Extra Corporeal Membrane Oxygenator (ECMO). In general, the right ventricle of the CTEPH patient is hypertrophic and they are accustomed. The kinetics are usually depressed to a variable degree, but once the afterload is reduced, the contractility of the right ventricle improves rapidly and visibly. In some cases of very advanced pathology, the ventricular myocardium can present irreversible lesions with fibrotic substitution, as a result of imbalance of coronary perfusion in a severely hypertrophic right ventricle and with a disproportionate parietal tension. This phenomenon, if it occurs, occurs in very serious cases of HP, with probable secondary vascular pathology and long-term disease. If we add the long period of cardioplegic arrest, it is understandable that in some cases the right ventricle is not able to provide enough preload to the left ventricle. In these cases the low expenditure is evident and the interruption of extracorporeal circulation becomes impossible. In these situations it is necessary to implant the assistance with ECMO, Veno-arterial with femoro-femoral access. Respiratory insufficiency in gas analytic terms rarely assumes an indication to ECMO alone. In general, it accompanies the previously described phenomena. In the rare cases of isolated hypoxaemia, veno-venous ECMO may be sufficient. The advantages and disadvantages, as well as the technical particularities of one or another modality, are arguments of another more specific chapter.

Acute mortality and its predictors

The results of the PEA can vary depending on several factors, including the chronicity of the disease, the experience of the CTEPH team, the preoperative PVR, the exercise capacity, the NYHA functional class of the patient, the comorbidities and the distribution of the disease. In high-volume centers, in-hospital mortality is now < 5%, having improved over time [28]. Higher mortality rates have been reported, although some contributing factors have been identified; for example, a higher preoperative PVR may increase mortality. At the UCSD center, 4.1% of patients with preoperative RRP > 1000 dyn·s·cm-5 (about 12.5 Wood units, WU) died, while only 1.6% had a PVR < 1000 dyn·s·cm-5 died [30]. Data from the international registry of the CTEPH showed an intrahospital mortality approximately three times higher in those with PVR > 1200 dynes·cm-5 at diagnosis compared to PVR 400 - 800 dynes·cm·5. However, it is important to emphasize that those with high PVR also have more to gain from EAP surgery, since they have the greatest hemodynamic improvement and the best prognosis benefit. Patients with PVR > 1200 din·s·cm-5 (15 WU) with a poor right ventricular function and a more distal disease in the preoperative image are particularly at risk. These patients must be operated on in experienced centers [19]. In fact, this aspect, that is, the experience of the center, is a relevant factor that obviously conditions the results. The international consensus among experts is that EAP surgery should be performed in an experienced center, with the suggestion that there should be a center for every 40 - 50 million people making a consistent number of cases per year and with ≥ 5 years of experience [24].

In a recent prospective and multicenter European international registry (27 centers), which has included 679 patients affected by CTEPH, results have been compared between operated and non-operated patients. In the group of patients undergoing PAD (total 404 patients), the preoperative characteristics that increased mortality were dialysis-dependent renal insufficiency, pharmacological treatment with pulmonary vasodilators as bridging therapy and the need for additional cardiac procedures. Operative complications and residual postoperative pulmonary hypertension negatively affected mortality. In contrast, a greater preoperative mPAP and a history of acute VTE were associated with lower mortality [28].

According to the multivariate analysis, bridging therapy with drugs aimed at PH, in almost a third of operated patients, increased the risk of death. Possible explanations are: (1) delay in PAD due to the start of medical therapy, (2) the possible effects of therapies directed at PH on the properties of the chronic thromboembolic material that make surgery more difficult [31] (3) most importantly, the strictly observational nature of the medical therapy registry started more frequently in patients with more severe hemodynamics. In any case, the recorded data tend to discourage the use of bridge therapy in operable patients.

The survivors were 8 years younger, less frequently in the NYHA IV class, and managed to walk a longer distance in the 6MWT (350 versus 290 m), lower right atrial pressure (8 versus 12 mmHg) and PVR (710 versus 844 dynes) .cm-5), and a higher cardiac index (2.2 versus 2.0 L·min-1·m-2). In the postoperative period, the last measure of PVR was lower (241 versus 289 dynes, Cm-5) and only 14% and 8% of patients presented postoperative pulmonary hypertension and reperfusion edema compared to 37% and 20% respectively. the patient not survivors. Medical treatment with vasodilators directed against PH at any time started less frequently (34% versus 51%). The estimated survival at 1, 2 and 3 years was greater in the operated group, respectively, 93%, 91% and 89% respectively.

Center Experience

Our cardiovascular surgery center of Sant'Orsola Hospital was born in 1974, being an Italian and European reference in aortic surgery and also in cardiac transplantation. Thanks to our huge experience in those two fields and also to the close collaboration with Prof. N. Galié, world's leading expert in pulmonary hypertension, the PEA program to patients with CTEPH started in 2003. A local protocol was established thanks to experiences in referenced centers such as the San Diego center. From 2003 to the present, 145 PEA procedures have been carried out. In 49 cases, the operation was performed without circulatory arrest and with the management of extracorporeal circulation in moderate hypothermia as previously described in the surgical technique. In the rest of the cases we proceeded with the stop at 20 degrees of temperature. The mean stop time for bilateral EAP was 26.1 + 18 minutes. The number of stop periods was 1 or 2 at 43.5 and 24.8% respectively. Only in 10% of the cases was a number greater than 3 periods necessary.

In 80% of the cases an immediate reduction of 36% of the preoperative HP values was observed, which exceeded 50% in the 24 successive hours. In 32% of the cases, a complete normalization of the pulmonary pressure values was evidenced, before the suspension of the invasive monitoring.

In 12% of the cases it was necessary to implant an assistance system (peripheral Femoro-femoral ECMO) in the immediate postoperative period due to the persistence of HP and/or failure of the right ventricle. In the retrospective analysis, we have documented how precisely most of these patients experienced a markedly lower reduction in the values of pulmonary pressure and vascular resistance in the postoperative period (0.5% compared to 36% in the rest of the population). In the analysis of this group it was evident that most of these patients presented a more severe HP picture despite being treated with double therapy of pulmonary vasodilators (inhibitor of phosphodiesterase-5 and the antagonist of endothelin-1), which in itself could be an indicator of the severity of the pathology and the severity of the vasculopathy.

In this respect, that is, the use of preoperative vasodilators, (a topic that has been discussed by some experts), we have not observed differences in terms of the quality of the surgical specimen or technical difficulty in the removal of the fibrotic thrombus. On the contrary, the preparatory treatment allows us to appreciate the degree of reversibility of the concomitant vasculopathy, Pharmacological Reversibility Test type. On the other hand, the reduction in the degree of HP allows the patient to undergo surgery with a lower degree of dysfunction of the right ventricle and probably reduce the degree of reperfusion edema. Hence, patients who needed postoperative ECMO, were patients with a lower response to preoperative medical treatment and consequently had a lower response to the intervention. Obviously, patients who needed postoperative assistance had a higher mortality of 33%.

The results in terms of mortality, once the learning curve is exceeded, are stationary at less than 5% in recent years, although the overall mortality is 9.7%. The main cause of death was heart failure, pulmonary insufficiency and infectious complications. In our population, the predictors of mortality in the multivariate analysis were found to be low preoperative cardiac output, restrictive type COPD, and duration of hypothermic stop time.

We have observed that our PEA population presented extremely heterogeneous pictures in terms of hemodynamic and anatomical data. In fact we have distinguished 4 types of patients: on the one hand, those with favorable anatomy (proximal lesions: proximal or proximal segmental branches or Jamieson I and II classification) with less severe HP (giving as limit value the 12 Wood units of pulmonary vascular resistance, RVP) (group I) and with severe HP (group II) and, on the other hand, patients with distal anatomy (Jamieson III and IV), and with HP < 12 RVP (group III) and HP > 12 (group IV) (Figure 1).

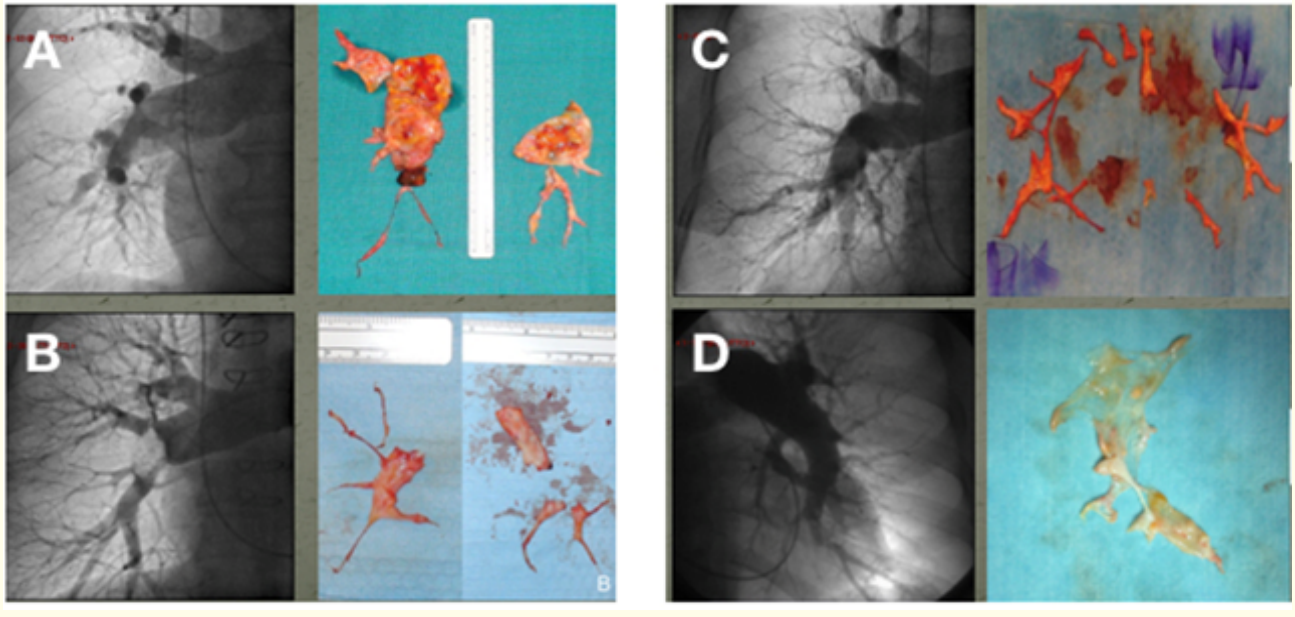

Figure: *In this image we present the comparison, we have carried out, simultaneously to the PEA between surgical sample and image of the preoperative pulmonary angiography. In picture A, the almost complete obstruction of the main pulmonary branch is evident. In image B, the presence of material at the origin of the lower right lobe branch is evident. In both cases, let A be B, the anatomy is considered absolutely favorable to the surgery and the correspondence between the angiographic image and the anatomical specimen is evident. In cases C and D the angiographic image shows a clear reduction in the caliber of the distal vessels with a marked poverty of subpleural vessels, an indirect sign of vasculopathy of the microcirculation. Also in these cases there is correspondence between angiography and surgical result, demonstrating how much in a case such as D, the probability of hemodynamic response is negligible.*

Despite being in all cases, fit in HPTEC, this subdivision into classes, relating anatomy and degree of pulmonary hypertension could facilitate the decision-making process, providing an estimate of the risk and the degree of response to the intervention. Although in our analysis we have not been able to demonstrate significant differences between the four groups, either because of the size of the sample, or because of the retrospective nature of the analysis, we have documented some interesting and somehow intuitive data. For example, group I patients are the patients who have had a better response not only in the postoperative period, but also in the long term. The patients of group II, despite having a favorable anatomy, had a worse response, with a smaller reduction of the PH and needing more significantly the postoperative ECMO. Astonishing thing that could be interpreted as that the association between the severe and irreversible peripheral vasculopathy together with the inexorable post-operative reperfusion edema, involves the persistence of HP, the failure of the right ventricle and consequently the need for ECMO.

In the rest of the groups we observed a less obvious or absent hemodynamic impact in groups III and IV respectively. In group IV, a higher incidence of complications was not observed, reflecting that the extraction of less fibrotic material not only has little impact at the hemodynamic level, but also causes less reperfusion edema, leaving the patient practically in the same preoperative conditions. What we have learned from our experience is that these patients (group IV) should not be proposed for surgery but rather for pulmonary balloon angioplasty (PBA), a treatment recently introduced in our center. As regards group II, PEA treatment should be and remains the primary treatment. It is necessary to foresee a more complex postoperative management in these patients. It is also essential to have experience in the management of ECMO. Surely, the ideal patient is the one that belongs to GROUP I, and where those patients affected by chronic thromboembolic disease (CTEVD) could probably be framed, although this argument is still extremely controversial.

The results in the follow up have shown stability of the results with 65.7% of patients with normalized values. All patients undergoing PAD continue with long-term anticoagulant therapy. Less than 7% of patients need vasodilator treatment. In two cases, it was necessary to subject patients to a second EAP at a distance of 6 and 5 years due to recurrence of CTEPH. Both cases presented with a LAC (anticoagulant lupus) syndrome.

We agree with the top experts that the specialized centers have to execute a consistent number of annual procedures. Even so, in our center we have attended to an annual reduction of cases, as a consequence of a super selection of patients, reducing the number of PEA procedures in extreme cases in anatomical and hemodynamic terms. This phenomenon has been accentuated in recent years as a result of the development of an optimal therapeutic alternative that is BPA. Despite the numerical reduction, years of team experience and knowledge acquired, these patients can be treated with PEA intervention with results in hemodynamic and mortality terms comparable to centers of greater volume.

New therapeutic alternatives in the HPTEC

With the coming into of pulmonary balloon angioplasty (BPA), the classification of patients as "operable" or "inoperable" may be less appropriate. Perhaps it is better to consider patients who are candidates for surgery (PEA), interventionist/percutaneous (BPA) or non-invasive (medical) therapy, and may receive two or three of these strategies in the course of their illness.

The initial experience with combined treatment PEA and BPA in highly selected cases has already been described in literature [35,36]. This can be applied as intraoperative planned BPA during PEA, acute rescue BPA after failure of PEA or BPA for residual or recurrent pulmonary hypertension months or years after PEA. BPA as a bridge to EAP is a strategy that has not been reported by any center so far, since it is theorized that BPA can change the fibrotic thrombus consistency and the quality of the vascular wall, increasing not only the complexity of a successive PEA, if not also the probability of parietal injury and risk of parenchymal hemorrhage.

In our center, several cases of BPA have been routinely carried out since 2015. The majority of patients treated are discarded patients for PAD, although in some cases they are patients previously submitted to PAD with residual PH and pathological distal vessels. In general, patients present clinical and hemodynamic improvements that are already noticeable in the first session of BPA, but it is usually a treatment that requires several sessions, since treating too many branches simultaneously predisposes excessively to the reperfusion edema observed in these patients. The results of this type of treatment will be published in a short time when they reach a consistent number.

Conclusions

CTEPH is a pathology considered rare, although there are no clear data on the incidence and real prevalence of this disease. There are multiple known risk factors as well as predisposing pathologies, but even so, in most cases these are not present, making diagnosis more difficult.

Regarding treatment, there are several lines of the CTEPH approach that are still evolving, since there are three therapeutic options available and some areas need to be refined and clarified. However, for patients with CTEPH that are considered operable, the message is clear: there is no better treatment than a full bilateral EAP carried out by an experienced team and therefore remains the treatment of choice for operable patients with CTEPH.

However, for a patient suffering from CTEPH to be a candidate for PEA, they must have enough thromboembolic material and be surgically accessible, with a proportional PVR that indicates the absence or minimal presence of secondary vasculopathy.

Being a rare surgical pathology, specialized centers must be numerically limited in order to acquire an experience that guarantees good results. The collaboration between the different experts is absolutely fundamental during the whole process, from the diagnosis, to the assessment of operability, the surgical treatment itself, the management of extracorporeal circulation, anesthesiological management and intensive care. Our center experience and our results clearly reflect this phenomenon.

The CTEPH, as well as its different therapeutic modalities require continuous research in order to be able to provide answers to so many aspects still to be known.

Bibliography

1. Auger WR., *et al*. "Chronic thromboembolic pulmonary hypertension". *Clinics in Chest Medicine* 28.1 (2007): 255-269.
2. Dalen JE and Alpert JS. "Natural history of pulmonary embolism". *Progress in Cardiovascular Diseases* 17.4 (1975): 259-270.
3. Fedullo PF., *et al*. "Chronic thromboembolic pulmonary hypertension". *New England Journal of Medicine* 345.20 (2001): 1465-1472.
4. Pengo V., *et al*. "Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism". *New England Journal of Medicine* 350.22 (2004): 2257-2264.
5. Lang IM., *et al*. "Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: A current understanding". *European Respiratory Journal* 41.2 (2013): 462-468.
6. Lang IM and Madani M. "Update on chronic thromboembolic pulmonary hypertension". *Circulation* 130.6 (2014): 508-518.
7. Pepke-Zaba J., *et al*. "Chronic thromboembolic pulmonary hypertension (CTEPH): Results from an internatio- nal prospective registry". *Circulation* 124.18 (2011): 1973-1981.
8. Guérin L., *et al*. "Prevalence of chronic thromboembolic pulmonary hypertension after acute pul- monary embolism Prevalence of CTEPH after pulmonary embolism". *Thrombosis and Haemostasis* 112 (2014): 598-605.
9. Delcroix M., *et al*. "Chronic thromboembolic pulmonary hyper- tension: Epidemiology and risk factors". *Annals of the American Thoracic Society* 13.3 (2016): S201-S206.
10. Moser KM and Bloor CM. "Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension". *Chest* 103.3 (1993): 685-692.
11. Simonneau G., *et al*. "The pathophysiology of chronic thromboembolic pulmonary hypertension". *European Respiratory Review* 26.143 (2017): 160112.
12. Skoro-Sajer N., *et al*. "Pulmonary vascular reactivity and prognosis in patients with chronic thromboembolic pulmonary hypertension: a pilot study". *Circulation* 119.2 (2009): 298-305.
13. Kim NH., *et al*. "Preoperative partitioning of pulmonary vascular resistance correlates with early out- come after thromboendarterectomy for chronic thromboembolic pulmonary hypertension". *Circulation* 109.1 (2004): 18-22.
14. Bonderman D., *et al*. "Risk factors for chronic thromboembolic pulmonary hypertension". *European Respiratory Journal* 33 (2009): 325-331.
15. Poli D and Miniati M. "The incidence of recurrent venous thromboembolism and chronic thromboembolic pulmonary hypertension following a first episode of pulmonary embolism". *Current Opinion in Pulmonary Medicine* 17.5 (2011): 392-397.

16. Miniati M., *et al*. "Fibrinresistance to lysis in patients with pulmonary hypertension other than thromboembolic". *American Journal of Respiratory and Critical Care Medicine* 181.9 (2001): 992-996.

17. Morris TA. "Why acute pulmonary embolism becomes chronic thromboembolic pulmonary hypertension: Clinical and genetic insights". *Current Opinion in Pulmonary Medicine* 19.5 (2013): 422-429.

18. Lang IM. "Advances in understanding the pathogenesis of chronic thromboembolic pulmonary hypertension". *British Journal of Haematology* 149.4 (2010): 478-483.

19. Jenkins D., *et al*. "Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension". *European Respiratory Review* 26.143 (2017): 160111.

20. Galiè N., *et al*. "2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)". *European Respiratory Journal* 46 (2015): 903-975.

21. Madani MM. "Surgical treatment of chronic thromboembolic pulmonary hyper- tension: Pulmonary thromboendarterectomy". *Methodist DeBakey Cardiovascular Journal* 12.4 (2016): 213-218.

22. Jamieson SW., *et al*. "Pulmonary endarterectomy: Experience and lessons learned in 1,500 cases". *Annals of Thoracic Surgery* 76.5 (2003): 1457-1462.

23. Berman M., *et al*. "Pulmonary endarterectomy: Outcomes in patients > 70". *European Journal of Cardio-Thoracic Surgery* 41.6 (2012): e154-e160.

24. Pretorius V., *et al*. "Should we offer pulmonary endarterectomy to octogenarians?" 5th World Symposium on Pulmonary Hypertension. 2013: CTEPH Nice, France (2013): 54-58.

25. Madani MM., *et al*. "Pulmonary endarterectomy: Recent changes in a single institution's experience of more than 2,700 patients". *Annals of Thoracic Surgery* 94.1 (2012): 97-103.

26. Ng C and Jenkins DP. "Surgical management of chronic thromboembolic pulmonary hypertension". *British Journal of Hospital Medicine* 74.1 (2013): 31-35.

27. De Perrot M., *et al*. "Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: The Toronto experience". *Canadian Journal of Cardiology* 27.6 (2011): 692-697.

28. Taboada D., *et al*. "Out-come of pulmonary endarterectomy in symptomatic chronic thromboembolic disease". *European Respiratory Journal* 44.6 (2014): 1635-1645.

29. Savini C., *et al*. "Safety of single-dose histidine-tryptophan-ketoglutarate cardioplegia during minimally invasive mitral valve surgery". *Innovations (Phila)* 9.6 (2014): 416-420.

30. Pacini D., *et al*. "Antegrade selective cerebral perfusion in thoracic aorta surgery: Safety of moderate hypothermia". *European Journal of Cardio-Thoracic Surgery* 31.4 (2007): 618-622.

31. Mikus PM., *et al*. "Pulmonary endarterectomy: An alternative to circulatory arrest and deep hypothermia: mid-term results". *European Journal of Cardio-Thoracic Surgery* 34.1 (2008): 159-163.

32. Mikus PM., *et al*. "Pulmonary endarterectomy: Is there an alternative to profound hypothermia with cardiocirculatory arrest?" *European Journal of Cardio-Thoracic Surgery* 30.3 (2006): 563-565.

33. Vuylsteke A., *et al*. "Circulatory arrest versus cerebral perfusion during pulmonary endarterectomy surgery (PEACOG): A randomised controlled trial". *Lancet* 378.9800 (2011): 1379-1387.

34. Delcroix M., *et al*. "Long-term outcome of patients with chronic thromboembolic pulmonary hypertension (CTEPH): Results from an international prospective registry". *Circulation* 133.9 (2016): 859-871.

35. Mayer E., *et al*. "Surgical management and outcome of patients with chronic thromboembolic pulmo- nary hypertension: Results from an international prospective registry". *Journal of Thoracic and Cardiovascular Surgery* 141.3 (2011): 702-710.

36. Kim NH., *et al*. "Chronic thromboembolic pulmonary hypertension". *Journal of the American College of Cardiology* 62.25 (2013): D92-D99.

37. Wiedenroth CB., *et al*. "Combined pulmonary endarterectomy and balloon pulmonary angioplasty in patients with chronic thrombo-embolic pulmonary hypertension". *Journal of Heart and Lung Transplantation* 35.5 (2016): 591-596.

38. Shimura N., *et al*. "Additional percutaneous transluminal pulmonary angioplasty for residual or recurrent pulmonary hypertension after pulmonary endarterectomy". *International Journal of Cardiology* 183 (2015): 138-142.

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