Lung transplantation in patients with pulmonary arterial hypertension: The opinion of the Polish Cardiac Society Working Group on Pulmonary Circulation

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ABSTRACT

Pulmonary arterial hypertension is a rare but progressive disease that leads to death. Modern drug treatment slows the progression of the disease and prolongs patients' lives, but often, even maximal treatment with parenteral prostacyclin does not prevent deterioration. In the case of inadequate clinical response to drug treatment, lung transplantation (LTx) should be considered. This article aims to analyze thoroughly indications to refer a patient for consultation with a transplant center, the optimal timing of listing for LTx, contraindications for the procedure, bridging techniques, as well as tests needed before and after transplantation. We outline the technique of the procedure and evaluate psychological aspects of LTx.

Key words: lung transplantation, pulmonary arterial hypertension, pulmonary arterial hypertension treatment

EPIDEMIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

The prevalence of pulmonary arterial hypertension (PAH) in Poland in the adult population is 30.8 cases per million while the incidence is 5.2 cases per million per year [1, 2]. Women are affected more frequently than men (69.8% of the patient population). The majority of patients at the time of diagnosis are in functional class III (72.1%) and, less frequently, in functional class IV (10.9%), or II (16.4%). Idiopathic PAH is most commonly diagnosed (45.8%), followed by PAH associated with congenital heart defects (36.7%) and connective tissue diseases (13.6%). PAH associated with portal hypertension, human immunodeficiency virus (HIV) infection, or caused by drugs or toxins is less common. The mean age at diagnosis of PAH is 46.8 ± 22.3 years, with 33.2% of patients aged ≥65 years. Data obtained from the Polish Registry of Pulmonary Hypertension (BNP-PL) collected for this publication show that the mortality rate from PAH in the Polish population is 89 cases per year (6.8%). Therapy with three specific drugs is used in 13.8% of patients and with two drugs in 43% of patients. Among patients with PAH who died between October 1, 2018 and August 31, 2020, therapy with three specific drugs was used by 25.6% of patients, and treatment with parenteral prostacyclin was used by 45.1% of patients. Data collected from two centers in Poland that perform lung transplantation (LTx) (Gdansk Medical University, Silesian Center for Heart Diseases in Zabrze) show that in 2019–2020 a total of 8 transplants were performed in PAH patients aged 21 to 45, three of whom died as a result of graft failure, multiple organ failure, and brain edema (data collected for this publication).

The first successful LTx in a PAH patient performed by a team from the Department of Chest Diseases at the Institute of Tuberculosis and Lung Diseases in Warsaw took place in 2006 and was led by Prof. Walter Klepetko's team at AKH Vienna. The patient then remained under the care of the Zabrze team [3].

The above data indicate that maximal therapy is not used frequently enough in the PAH patient population and that an LTx program needs to be developed in this group of patients.

MAXIMAL MEDICAL THERAPY

PAH is an aggressive, rapidly progressive disease, whose essence is endothelial damage and remodeling of pulmonary arterioles. Abnormal functioning of three pathways involving endothelin, nitric oxide, and prostacyclin contributes to vascular changes [4]. Drugs used to treat PAH, affecting the above-mentioned three pathways, correct these abnormalities. All of these drugs exert a vasodilatory effect and also have antiproliferative effects.

According to the recommendations of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), assessment of the risk of death determines the choice of initial therapy and timing of treatment escalation. Risk can be estimated using the REVEAL scale, ESC risk tables, or based on the French, Swedish, and COMPERA registries. In Poland, ESC risk tables are most commonly used. The goal of treatment is always to achieve low-risk-of--death status, which is associated with a good prognosis [5].

If the patient is in the low- or intermediate-risk group at the time of diagnosis, combination therapy with two oral drugs from the groups of endothelin receptor antagonists (ERAs) and nitric oxide antagonists (phosphodiesterase-5 inhibitors [PDE-5i]) is started. If low-risk status is not achieved after 3–6 months, therapy must be escalated to oral three-drug therapy or, if the patient is in the intermediate-high or high-risk group, to maximal therapy. In contrast, if the patient is a high-risk patient at baseline, the maximal therapy is started immediately.

Maximal medical therapy is maximal conservative treatment of PAH, which consists of triple combination therapy with prostacyclin (PCA) intravenously (IV) or subcutaneously (SC) [6]. Using three drugs from different groups simultaneously corrects all the pathophysiological pathways responsible for vascular changes. Initial therapy with drugs from two groups (ERA plus PDE-5i) results in a greater reduction in pulmonary vascular resistance (PVR) than monotherapy with any drug, and initial triple-drug therapy (ERA plus PDE-5i plus PCA) results in the greatest reduction in PVR by about 70%. Parenteral prostacyclins are characterized by the strongest effects. In a randomized trial involving 81 patients in New York Heart Association (NYHA) class III and IV, three-month IV administration of epoprostenol resulted in a significant reduction in mortality compared to patients in the placebo group. The treatment also improved physical performance, quality of life, and hemodynamics [7]. The addition of sildenafil to long-term epoprostenol in the PACES trial resulted in a longer time to clinical deterioration and improved physical performance and hemodynamic parameters [8]. In two small observational studies of NYHA class III and IV patients who received maximal therapy as initial treatment, very good results were obtained. Eighteen patients patients who received combination therapy with epoprostenol plus bosentan plus sildenafil and 21 patients who received combination therapy with treprostinil SC plus ambrisentan plus tadalafil, showed improvement in functional, physical capacity, hemodynamics, and achievement of low-risk status after 4–6 months and after one year [9, 10]. Also, an observational study of 1611 patients based on the French registry showed that patients treated with maximal therapy from the start had the best chance of achieving low-risk status [11].

According to the ESC/ERS recommendations, implementation of maximal therapy in a patient or insufficient clinical response to initial oral combination therapy should be an indication to consider referring the patient for a consultation with an LTx center, and failure of maximal therapy should be an indication to place the patient on a waiting list for LTx [5].

CRITERIA FOR REFERRING A PATIENT TO A LUNG TRANSPLANT CENTER AND CRITERIA FOR PLACING A PATIENT WITH PAH ON THE LIST OF RECIPIENTS (INCLUDING CONTRAINDICATIONS)

Advances in drug therapy have changed the prognosis of patients with PAH, but some patients still do not achieve an adequate clinical response despite receiving maximum treatment. For these patients, LTx remains an important therapeutic option. The risk of perioperative death in patients with PAH is the highest of all indications for LTx. On the other hand, PAH patients have the best prognosis among those who survive the first 6 months if adequate preparation and optimal timing of transplantation are ensured [12]. Selecting potential candidates for transplantation is a difficult task not only because of the risks of surgery but also because the risk of infection and rejection is much greater than in other organ transplants.

Defining the optimal time to refer a patient with PAH and qualify for LTx is a key issue for successful transplantation.

The 2021 International Society for Heart and Lung Transplantation (ISHLT) recommendations [13] describe a candidate for LTx as a person who has:

- a high (>50%) risk of death from lung disease in the next 2 years;
- a high probability (>80%) of survival for more than 5 years after transplantation provided normal graft function.

The intensive development of pharmacological treatments affects the long-term prognosis of people with PAH, which requires using modern means of assessing prognosis, such as the REVEAL 2.0 scale, proposed in the recommendations of the 6th World Symposium on Pulmonary Hypertension (WSPH) in Nice in 2018 [14]. Ideally, survival assessment methods should be validated on a local population, and analysis of perioperative prognosis should take into account medical capabilities, experience, and post-transplant prognosis in the PAH population.

The arguments for earlier transplantation include:

- aggressive disease progression and cardiovascular decompensation;
- a high probability of complications that will prevent transplantation at a later stage, such as progressive cachexia, sarcopenia, and osteoporosis in the course of the disease;
- risk of sudden death in case of delayed surgery;
- progressive damage to other organs (kidneys, liver) by circulatory failure, which will increase the risk of transplantation.

Given the difficulties involved in determining the timing of LTx, it is essential for physicians treating PAH with pharmacological therapy to work closely with transplant centers and jointly determine the optimal individualized management strategy. For this reason, both ISHLT, as well as ESC/ERS and WSPH, present two stages of qualification:

- referral for transplantation at a transplant center;
- listing for transplantation by a transplant center.

The recent ESC/ERS guidelines published in August 2022 and endorsed by ISHLT indicate that consultation at a transplant center is recommended in the following situations [5]:

- potentially eligible patients for whom LTx might be an option in case of treatment failure;
- ESC/ERS intermediate-high or high risk or REVEAL risk score >7 on appropriate PAH medication;
- progressive disease or recent hospitalization for worsening PAH;
- need for IV or SC. prostacyclin therapy;
- known or suspected high-risk variants, such as pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis, systemic sclerosis, or large and progressive pulmonary artery aneurysms;
- signs of secondary liver or kidney dysfunction due to PAH or other potentially life-threatening complications of PAH, such as recurrent hemoptysis, which are expected to improve after successful transplantation.

The first stage of qualification includes a full medical evaluation for PAH severity, risk of death, and the presence of contraindications to transplantation. It allows the qualified person to get acquainted with the center, interact with transplant patients and prepare mentally for major surgery. Early referral gives time to fully evaluate the patient, perform necessary consultations, as well as take steps to eliminate potentially reversible contraindications, such as obesity or infection. It also makes it possible to take measures to reduce the risk of complications, such as diagnosis and potential embolization of bronchial vessels in cases of recurrent hemoptysis. Such evaluation should also include an assessment of exercise capacity to tailor pre- and postoperative rehabilitation programs to individual patient needs. Earlier initiation of collaborative patient care does not necessarily result in placing the patient on the waiting list if the patient responds well to the management used, but it will allow for immediate inclusion on the list if there is unfavorable disease progression.

Criteria for including patients on the waiting list for LTx according to ISHLT and ESC/ERS [5, 13] are:

- high risk score >10, according to ESC or REVEAL, on targeted PAH treatment including prostacyclins SC or IV;
- progressive hypoxemia, especially in patients with PVOD or pulmonary capillary hemangiomatosis;
- observation of progressive (but not end-stage) renal or hepatic failure resulting from PAH;
- life-threatening hemoptysis occurs.

Rather than placing importance on specific numerical cutoff points (e.g. six-minute walk test [6MWT distance]), especially in terms of hemodynamic criteria (pulmonary artery pressure, cardiac output, or right atrial pressure), attention should be paid to comprehensive assessment of risks and potential benefits by a multidisciplinary team. The same 6MWT, right atrial pressure, or cardiac output

values in a young person with rapid disease progression may indicate a significantly different prognosis than in an older person with other comorbidities and a slow disease course. Therefore, all measurements should be analyzed taking into account both the person's current situation, his/her history, and capabilities of the treating centers.

A key component of LTx eligibility is the exclusion of contraindications that unacceptably increase the risk of the procedure or subsequent treatment. The period between consultation and listing allows time to rule out or treat such comorbid conditions. According to ISHLT, absolute contraindications to LTx include [13]:

- lack of patient consent;
- malignant neoplasm with a high risk of cancer-related recurrence or death;
- renal failure with estimated-glomerular filtration rate (eGFR) <40 ml/min/1.73 m^2, unless multiorgan transplantation is considered;
- acute coronary syndrome or myocardial infarction in the last 30 days;
- stroke in the last 30 days;
- liver cirrhosis with portal hypertension or significantly impaired liver function (multi-organ transplantation to be considered);
- acute liver failure;
- acute renal failure with an increase in creatinine or the need for renal replacement therapy (with a low probability for the return of normal kidney function);
- septic shock;
- active extrapulmonary or disseminated infection;
- active tuberculosis;
- HIV infection with a detectable viral load;
- limited functional status (e.g., inability to move) with low potential for post-transplant rehabilitation;
- progressive cognitive impairment;
- repeated episodes of non-compliance with medical recommendations, lack of cooperation (in the case of pediatric patients, this is not an absolute contraindication and constant evaluation of non-compliance should be carried out, as children go through different stages of development);
- active substance use or addiction, including current smoking of cigarettes,
- e-cigarettes, marijuana, and intravenous drug use;
- another severe uncontrolled condition that can limit survival after transplantation.

In certain situations, despite the presence of relative contraindications, transplantation may be considered. It mainly depends on the experience of the transplant center. In its 2021 recommendations, ISHLT distinguishes two groups among relative contraindications [13]:

- Factors that cause an increased or significantly increased risk of transplant failure:
  - age >70 years;
  - coronary artery disease requiring coronary artery bypass grafting during transplantation;
  - reduced left ventricular (LV) ejection fraction (EF), EF <40%;
  - significant cerebrovascular disease;
  - severe esophageal motility disorders;
  - untreatable hematological disorders, including hemorrhagic diathesis, thrombophilia, or significant bone marrow dysfunction;
  - body mass index (BMI) >35 kg/m^2;
  - BMI <16 kg/m^2;
  - limited functional status, but with the possibility of rehabilitation after transplantation;
  - psychiatric, psychological, or cognitive conditions that may interfere with compliance with post-transplant recommendations;
  - lack of social support;
  - lack of understanding of the disease and/or pre- and post-transplant management despite education;
  - infection with *Mycobacterium abscessus*, *Lomentospora prolificans*, *Burkholderia cenocepacia*, or *Burkholderia gladioli*;
  - hepatitis B or C virus infection with detectable viral load and liver fibrosis;
  - a deformity of the thorax or spine that may cause restriction after transplantation;
  - the need for extracorporeal life-support techniques for transplant bypass.
- Factors causing a moderately increased risk of transplant failure:
  - age 65–70 years;
  - eGFR 40–60 ml/min/1.73 m^2;
  - coronary artery disease (including one that can be revascularized by percutaneous coronary intervention before transplantation);
  - history of coronary artery bypass grafting;
  - reduced LVEF, EF 40%–50%;
  - peripheral vascular disease;
  - systemic connective tissue diseases (scleroderma, lupus, inflammatory myopathies);
  - reflux disease or esophageal motility disorders;
  - thrombocytopenia, leukopenia, or anemia with a high probability of occurrence after transplantation;
  - osteoporosis;
  - BMI 30–34.9 kg/m^2;
  - BMI 16–17 kg/m^2;
  - frailty syndrome;
  - hypoalbuminemia;
  - uncontrolled diabetes;
  - oral marijuana use;
  - *Scedosporium apiospermum* infection;
  - HIV infection with an undetectable viral load;
  - history of thoracic surgery;
  - pleurodesis in anamnesis;
  - need for mechanical ventilation.

In justified cases of PAH with significant impairment of cardiac function, qualification for heart-lung transplantation (HLT) should be considered. This may be especially the case

in Eisenmenger syndrome with an inoperable heart defect [5]. It should be noted that the last successful lung and heart transplant in Poland took place in 2001 [15], and ISHLT reports only a few dozen such procedures per year [12].

Qualifying patients with PAH for LTx is a difficult and potentially lengthy process, and deciding whether to list them for LTx requires close cooperation among the patient's attending physicians, the transplant center, and the patient himself, along with his immediate family. The qualification procedure, which includes evaluation of disease progression and its natural course, exclusion of significant comorbid contraindications, and selection of optimal timing, are undoubtedly important elements affecting the outcome of transplantation.

SPECIFIC INDICATIONS FOR LUNG TRANSPLANTATION

Pulmonary artery aneurysm (PAA) is a rare anomaly of the pulmonary vessels. The incidence estimated from autopsy studies is 1 in 14 000 [16]. The etiology is varied and in more than 50% of cases is associated with congenital heart defects such as persistent Botallo duct, ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary valve defects, or connective tissue defects (Marfan and Ehlers-Danlos syndromes).

In other cases, PAA can occur in the course of vasculitis, PAH; the aneurysm can be also idiopathic. While PAA may be asymptomatic for a long time, it is known to lead to life-threatening conditions such as massive hemoptysis, rupture/dilatation, or compression of the left coronary artery trunk leading to acute coronary syndrome [17–23].

PAA (as opposed to pseudoaneurysm) refers to a focal dilatation involving the entire vessel wall. Currently, there is no defined dimension of the pulmonary artery at which we diagnose an aneurysm. Based on imaging studies, the normal dimension of the pulmonary artery in healthy adults is believed to be 25 mm ± 3 mm, with 29 mm being the upper limit of normal in men and 27 mm in women. Some authors consider any dilatation of the pulmonary trunk above this standard as an aneurysm, while others adopt a higher cutoff point, i.e., above 1.5 times the upper limit of normal without differentiating by sex. Currently, a dimension of 40 mm is most commonly accepted as the criterion for the diagnosis of PAA [24, 25] (according to Restrepo and Carswell, for the pulmonary artery trunk it is 45 mm, and for the pulmonary artery it is 30 mm).

Due to the rarity of the disease, there are no specific guidelines, but it is considered advisable to consider surgical treatment [26] when:

- maximum aneurysm diameter is >55 mm;
- PAA diameter increases by 5 mm in 6 months;
- there is a coexisting pulmonary valve pathology;
- there are symptoms of pressure on surrounding structures, such as symptoms from bronchial compression (cough, pneumonia, and bronchitis);
- a thrombus in the aneurysm is detected;
- there are clinical symptoms (shortness of breath, chest pain, fainting, palpitations);
- PAA occurs in the course of leaky heart defects;
- there are symptoms of rupture or dissection.

In patients with PAH, the presence of PAA should precipitate the decision to qualify for LTx. Qualification for LTx is not the sum of the indications for treatment of PAA and PAH, as each patient requires an individual assessment that takes into account the course and severity of both diseases.

Hemoptysis

The term hemoptysis refers to the expectoration of blood or sputum mixed with blood coming from the lung parenchyma or airways.

Depending on the amount of expectorated pure blood or its content in expectorated sputum, we distinguish:

- hemoptysis: a small/trace amount not exceeding 20 ml per day;
- massive hemoptysis (hemoptoe), 20–200 ml of blood per day;
- pulmonary hemorrhage >200 ml/day or 600 ml over 48 hours [27].

In practice, quantitative assessment of hemoptysis is often difficult and in many cases may be under- or overestimated by patients. Therefore, the concept of "life-threatening hemoptysis" is more commonly used and defined not only by the amount of expectorated blood but also by the rate of bleeding and its clinical consequences (e.g., hemoptysis requiring transfusion, intubation, airway obstruction, hypoxemia requiring mechanical ventilation) [28–33]. Massive hemoptysis refractory to interventional treatment is one of the elements that should always be considered in the qualification process for LTx in patients with PAH, chronic thromboembolic pulmonary hypertension (CTEPH), PVOD, and cystic fibrosis [34].

DIAGNOSIS OF THE PATIENT BEFORE REFERRAL TO THE TRANSPLANT CENTER

Before being referred to a transplant center, both at the stage of initial notification (referral), as well as for qualification for transplantation (listing), the patient should have a thorough evaluation confirming the key indications for the procedure and the absence of absolute contraindications. Studies should reflect the clinical status in recent months and confirm the failure to achieve prognostically relevant treatment goals. They should include

- clinical evaluation focused on right heart failure, NYHA functional class, and presence of syncope with consideration of the rate of disease progression and response to treatment escalation;
- assessment of cardiovascular capacity based on the 6MWT, spiroergometry, and measurement of natriuretic peptides;

- assessment of hemodynamics in right heart catheterization (SvO2-mixed venous oxygen saturation, cardiac index, and right atrial pressure);
- cardiac imaging (echocardiogram, MRI–CMR) always with attention to the presence/absence of fluid around the heart;
- if treatment goals have been achieved with parenteral drugs, then this is independent prognostic information.

The above data, once an LTx candidate is enrolled, should be systematically updated in communication between the attending cardiologist at the PAH center and the transplant center.

The expanded panel for evaluating a patient qualified for LTx includes elements of physical examination, laboratory tests, and imaging.

In terms of **physical examination**, blood pressure and heart rate, as well as the clinical diagnosis of renal failure, are complementary components of the assessment, using the REVEAL 2.0 calculator. Assessment of body mass index is necessary, allowing qualification of patients with BMI <35 kg/m^2. Any hospitalization in the preceding 6 months should be carefully reviewed. Before qualification, a psychological consultation is advisable, and in the case of PAH associated with connective tissue diseases, a rheumatologic evaluation of the involvement of individual organ systems [35]. It should specifically include an evaluation of esophageal involvement, with possible consideration of imaging and functional studies of the esophagus and bronchoalveolar lavage (BAL) for exclusion of hydrochloric acid/biliary accumulation and of the musculoskeletal system in relation to postoperative rehabilitation.

Extended **laboratory tests** should address the evaluation of renal function (GFR, proteinuria, and possibly cystatin). Elevated and dynamically rising bilirubin and creatinine levels may be important in determining the urgency of transplantation or disqualification from transplantation since belated qualification in the phase of multiple organ failure significantly worsens treatment outcomes [36].

Among the most commonly used **imaging tests** in patients transferred to transplantation units are echocardiography, CT scans, and, in recent years, cardiac MRI, which is considered the gold standard for evaluating the right ventricle (RV) in the course of PAH [37].

In terms of imaging tests, important are:

- Extended evaluation of the function of both chambers of the heart – for the success of LTx and further favorable course of treatment, proper functioning of the LV is also of great importance. Increasingly, before initiating specific therapy and before qualifying for surgical treatment, an in-depth assessment of its function is made by echocardiography (using the full capabilities of myocardial velocity and strain assessment and three-dimensional analysis), but also by MRI. Contrast-enhanced MRI allows for assessment of fibrosis within the ventricular walls (late enhancement) and estimating chances of retrograde remodeling and return of normal RV function after LTx.
- An up-to-date contrast-enhanced chest CT scan allows assessment of the bony structures of the chest, lung tissue, vasculature, and heart, facilitating surgical planning. It should be emphasized that the finding on CT of features suggestive of pulmonary capillary hemangiomatosis or pulmonary vein obliteration disease is a separate indication for transplant qualification due to the inability to treat in the manner typical of PAH.

Invasive testing includes right heart catheterization (RHC) and, in patients with suspected coronary artery disease, an up-to-date coronary angiography (similarly, exclusion of other locations of increased arteriosclerosis, such as the carotid arteries, by vascular testing). Current data from RHC (no older than 12 months) are indispensable for qualification at the optimal stage of the disease. Right atrial pressure >15 mm Hg and low cardiac index (<1.8–2 l/min/m^2) are among the criteria that increase the urgency of listing.

The described procedures before transplant qualification do not exhaust the examinations and consultations necessary to establish indications and contraindications for LTx used in most centers in Poland and around the world. These include also cardiological, pulmonological, and gastroenterological qualification, in the case of women, gynecological, psychiatric/psychological consultation, assessment of socioeconomic situation determining adequate cooperation in the postoperative period, panel of serological tests (cytomegalovirus [CMV], Epstein-Barr virus [EBV], toxoplasmosis, hepatitis C virus [HCV], hepatitis B virus [HBV], HIV), basic tumor markers and densitometries.

MONITORING A PATIENT LISTED FOR LUNG TRANSPLANTATION

Once a patient is qualified for LTx and placed on the active list of recipients, treatment management should be carried out in close cooperation with the transplant team. It is important to be aware that the waiting time for the procedure can be up to several years, so information about significant changes in the patient's condition should be promptly communicated to the transplant center. The goal of treatment should be to keep the patient as physically and mentally fit as possible, as well as to avoid performing procedures that could hinder the LTx procedure. Assessment of immunization levels with panel reactive antibody (PRA) should be updated every 3–6 months. For highly immunized patients, securing serum for cross-testing is recommended at 6-week intervals. It is important to remember to monitor and manage adverse effects of PAH drug treatment such as thrombocytopenia [38], anemia, hyperthyroidism [39], or hepatotoxicity. The function of central catheters [40], subcutaneous punctures, and implantable pumps [41] used for prostanoid therapy should also be closely monitored. Hospitalizations related to heart

failure exacerbations are associated with an unfavorable prognosis [42], with infections being the most common identifiable cause [43]. Infectious exacerbations during the waiting period for transplantation are also associated with poorer outcomes of the LTx procedure [44]. Every effort should be made to avoid cachexia and malnutrition in a patient awaiting LTx. In the case of symptomatic or asymptomatic iron deficiency, iron replacement therapy should be used [45]. Improvements in physical fitness and overall condition of the potential recipient can be achieved by conducting a program of supervised rehabilitation [46]. Patients should be vaccinated against influenza (once a year), pneumococcus (once every five years), and tetanus (once every 10 years), as well as COVID, hepatitis, and chickenpox if they have not had these vaccinations before [47]. As far as possible, standard oncological surveillance and periodic examinations recommended for the age category should not be neglected. Patients qualified for LTx should have ongoing access to psychological support and should be referred to palliative care if they are removed from the list of recipients [48]. Patients with uncontrolled fluid retention despite diuretic therapy or recurrent collapses should be considered for atrial septostomy [49], optimally with implantation of a device to ensure patency of the created cavity [50]. In patients with supra-systemic PAH, especially at a younger age, a Potts anastomosis between the pulmonary artery and descending aorta may be considered [51]. If the pulmonary artery is significantly dilated (>41mm), the risk of sudden death increases, most likely due to pulmonary artery dissection [23] or compression of the left coronary artery [22]. Implantation of a stent into the trunk of the left coronary artery is an effective method of managing its significant stenosis, but the choice of the stent and the timing of dual antiplatelet treatment should be discussed with the transplant team. The antiplatelet effect of prostacyclin derivatives should also be considered [52]. Hemoptysis and airway bleeding occur in advanced PAH and are associated with a poor prognosis in PAH unrelated to Eisenmenger syndrome [34]. Typically, the source of bleeding is dilated bronchial arteries, which can be successfully embolized [53]. Atrial arrhythmias associated with significant right atrial enlargement are also a complication typical of advanced PAH and should be expected in patients qualified for LTx. In the case of complex forms of atrial arrhythmias, ablation should be attempted, while taking into account the incomplete therapeutic effect of the procedure [54].

SURGICAL ASPECTS OF LUNG TRANSPLANTATION IN IPAH

General information

Donor-recipient selection takes into account the blood group (same or compatible), height (±5%), followed by clinical condition, age, and other variables. The individual immunization status of a given recipient may influence the decision to reject a given organ donor despite the aforementioned indications of desirable selection.

For the surgeon who is to perform the transplantation, the results of imaging studies of CT, X-ray, ultrasound (US; evaluation of anomalies of the thoracic structure, width of the pulmonary vessels, presence of intracardiac leaks, cardiac function, and structure, etc.), the results of coagulation tests (some of the drugs used in the treatment of IPAH deteriorate platelet function), as well as the evaluation of flows (US, Doppler US) in peripheral vessels (carotid and femoral) necessary for optimal selection of the site of implantation of cannulas of the extracorporeal membrane oxygenation (ECMO) system are important. Other tests are performed according to the standard qualification protocol for LTx.

Preparation of the patient in the operating room

- Intubation with a double-lumen endotracheal tube — the lung that is not currently being transplanted should be ventilated, as this avoids the need to maintain a high output on ECMO, and NO can be insufflated.
- Central puncture in the jugular vein.
- Swan-Ganz catheter and pulmonary artery pressure measurement.
- Cannulation with vascular catheters of the radial artery, femoral artery, and femoral vein — obtaining blood pressure measurements.
- DefiPads — high risk of arrhythmias including ventricular fibrillation (VF) and ventricular tachycardia (VT) and lack of rapid access directly to the heart.
- Cellsaver — long surgery and frequent clotting disorders necessitate blood-saving methods.
- Blood preparations — secured in the hospital blood bank.
- Drugs: antibiotics according to recent cultures of both recipient and donor or routinely used in the center.
- Immunosuppressive drugs depending on the protocol used at the center.
- Venous-arterial ECMO (ECMO VA) and a set of cannulas (in addition, a fully prepared, complete system for classic extracorporeal circulation [ECC] in the operating room).

Surgery

A feature that clearly distinguishes LTx in IPAH/PAH from transplantation in other disease entities is that these procedures are always performed using circulatory support techniques. With the widespread availability of ECMO technology, it has become the number one assistive technique for LTx surgery displacing classic ECC. A key feature of modern ECMO, because of which surgeons choose it more readily than ECC, is the lack of need for heparin during surgery and thus operating in a bloodless field.

Depending on the center's preferred protocols, different vascular access routes are used for cannulation, including femoral, subclavian, and carotid vessels, as well as directly by the aorta and cardiac structures. Direct can-

nulation or cannulation through synthetic vascular grafts sewn to the vessels is used. This shows the importance of the aforementioned multiple imaging techniques in the LTx qualification process. In most cases, the cannulation strategy is planned in advance. However, there are times when it is necessary to change plans on an ad hoc basis under the influence of unforeseen events. The wider is the range of surgical access routes available for the team, the easier it is to respond to difficult situations.

Finally connected and vented, the ECMO system starts working at the moment most convenient for the operating surgeon. It is not necessary to use heparin in the first 24 hours. The preferred access is an anterolateral mini-thoracotomy usually through the fourth or fifth intercostal space. The order in which lungs are transplanted is determined on an individual basis. Surgical steps are usually performed according to the scheme:

- release of the lung from adhesions if present and dissection of the hilar structures;
- separation of the pulmonary ligament from the diaphragm;
- pulmonary artery clamping;
- ligation of pulmonary veins as peripherally as possible;
- cutting off the inferior pulmonary vein then the superior pulmonary vein and later the pulmonary artery;
- bronchial resection;
- removal of the lung from the pleural cavity;
- opening the pericardial sac around the pulmonary veins;
- hemostasis in the pleural cavity.

At the same time, an assisting surgeon performs the separation and preparation of the donor's lungs for implantation.

If anterior access is used (preferred at the centers in Gdansk and Zabrze), the steps are as follows:

- Lung implantation begins with bronchial anastomosis, which can be immediately verified by bronchoscopy or video images from an endotracheal tube equipped with a camera (if available). The suture site is covered with tissue adhesive.
- The next step is to perform an arterial anastomosis frequently requiring surgical correction of the recipient's artery.
- Venous anastomosis is the connection of the recipient's left atrium to a portion of the donor's atrium, performed as the final step.

After completion of the anastomosis and before tying the sutures on the vessels, there is a need to remove air lingering in the donor's vascular bed. This is a critical moment. Once the blood flow is started, any air left in the pulmonary vessels and especially in the venous system is pushed out to the "left heart" and further to the aorta from where it has an open path to the coronary and cephalic vessels, potentially leading to air embolisms. The steps are as follows:

- unclamping and venting of the pulmonary artery — the vascular clamps are slowly loosened giving controlled blood flow to the lung — antegrade venting;
- venting from the pulmonary veins — retrograde venting;
- tying of the sutures on both vessels;
- removal of clamps;
- transesophageal echocardiography (TEE) control for the presence of air in the left heart and aorta;
- hemostasis;
- initiation of ventilation of the transplanted lung is preceded by recruitment maneuvers (opening of collapsed alveoli);
- insertion of a drain into the dorsal region of the costophrenic angle.

When the local and general condition is satisfactory, transplantation of the lung on the other side can begin. It seems important that the time between the unclamping of the vessels on the side transplanted first and the placement of the clamps on the pulmonary artery on the other side be no less than 1 hour. This allows the transplanted lung to adapt to the prevailing hemodynamic conditions minimizing the risk of lung swelling. After the second lung is transplanted, additional drains are placed into both pleural peaks, and the chest is closed once acceptable hemostasis is achieved. The patient is intubated with a typical cuffed endotracheal tube and has a bronchial tree lavage performed before leaving the operating room. The patient is then transferred to the postoperative ward.

With the use of ECMO systems for LTx surgery, especially in patients with IPAH/PAH, and a better understanding of the mechanisms leading to the hemodynamic crises and LV failure in the postoperative course after LTx, some centers have developed a program of routinely prolonging ECMO support, and some have developed less invasive methods to prevent such situations. In choosing this strategy, it is recognized that benefits of maintaining hemodynamic stability in the first few days after LTx and allowing time for the cardiovascular system to adapt to the new situation outweigh the patient's exposure to complications from prolonging the use of ECMO VA beyond the time of the operation itself, even though this involves the need for heparinization.

In contrast, other transplant teams have developed postoperative protocols seeking to avoid cardiorespiratory instability without invasive methods. In centers preferring this procedure, the ECMO system is usually (80%) disconnected from the patient in the operating room before transferring him/her to the postoperative ward. The use of new hemodynamic monitoring techniques, such as the ability to continuously measure cardiac output, has definitely improved immediate diagnosis and allows rapid implementation of non-invasive or less invasive treatment although also not without side effects. At the moment,

there are too few studies available to consider any of the already proposed strategies as more effective, but it is worth looking for new solutions since the early mortality rate after LTx in IPAH/PAH worldwide is the highest among all LTx performed for other conditions.

URGENT LUNG TRANSPLANTATION — CRITERIA, ROLE OF MAINTENANCE THERAPIES INCLUDING ECMO

Urgent qualification for LTx in patients with PAH includes situations in which the disease poses an immediate threat to life or is expected to lead to death within days or weeks.

Indications for emergency LTx in patients with PAH:

- Clinical deterioration is defined as:
  - functional class IV;
  - persistent RV decompensation (ascites, peripheral edema, jugular venous congestion, recurrent hemoptysis) despite optimal drug therapy; including treatment with intravenous, escalated to maximally tolerated, doses of parenteral prostacyclins
  - rapidly progressive disease, unresponsive to escalation of specific therapy, including maximal therapy.
- Signs of RV failure in patients with PVOD and/or pulmonary hemangiomatosis in whom pulmonary arterial targeted therapy is contraindicated or poorly tolerated.

Maintenance therapies, bridges to urgent transplantation:

- Atrial septostomy in its new form, Atrial Flow Regulator (AFR), a 4–10 mm diameter nitrile implant inserted into the atrial septum to create an artificial opening (shunt) in patients in whom maximal drug therapy, using parenteral prostacyclins, is ineffective [49]. The procedure decompresses the right atrium, reduces symptoms of heart failure, improves exercise capacity, and is an established option for bridging to LTx for patients with severe RV failure [50, 55, 56]. At the same time, by directing part of the output to the left side, it improves the output of the LV and, in this mechanism, enables it to "train", preparing it to receive a higher volume after LTx.
- Potts procedure is possible only in the case of supra-systemic pulmonary artery pressure. It provides a connection between the left pulmonary artery and the descending aorta reducing pulmonary artery pressure and is a transitional alternative to transplantation and/or a bridge to LTx for patients with severe RV failure and utilizing optimal drug therapy [57, 58].
- ECMO is used in 3 cases including:
  - bypass for transplantation — in the best transplant centers in the world this is the most commonly used bypass method. To ensure improved cardiac output and decompress the failing RV, only a veno-arterial configuration is used, i.e., blood is withdrawn from the right atrium (cannula[s] inserted through the right internal jugular vein and/or the right/left femoral vein) and returned after oxygenation through a cannula inserted through the right/left common femoral artery into the descending aorta (or, alternatively, through the right/left common femoral artery into the descending aorta), through the right subclavian artery/right common carotid artery as in the upper body ECMO configuration [59, 60];
  - for multiorgan conditioning — the failing heart and other failing organs in patients in the most advanced stage of PAH while constituting a bridge to decision c) as an absolute requirement and component of typical LTx surgery.
- Therapies whose theoretical basis and preliminary results of clinical trials are encouraging:
  - pulmonary artery sympathetic denervation (PADN) [61, 62];
  - the ARIA system, a fully implantable system that reduces RV work and simultaneously increases RV output by synchronously inflating and deflating a balloon inserted into the pulmonary artery trunk [63];
  - RV resynchronization/stimulation [64].

FOLLOW-UP AFTER LUNG TRANSPLANTATION

LTx aims not only to prolong life but also to improve its quality in patients with chronic respiratory diseases. Therefore, it is particularly important to manage patients after this procedure due to several complications that can occur both in the early postoperative period and later. Most patients experience acute graft rejection despite immunosuppressive therapy, and nearly 50% experience chronic rejection (after a year or more) [65]. Other common problems include infections, respiratory complications, graft failure, and serious extrapulmonary conditions [66–69].

Managing these patients requires experience and often engagement of specialists from different fields. The main issues involved are outlined below.

- An LTx patient should remain under constant monitoring by the transplant center where the procedure was performed and the periodic control of the center that referred the patient for transplantation and provided care for the patient before transplantation.
- Nearly half of the centers use induction of immunosuppression, administering interleukin-2 (IL-2) receptor antibodies or antithymocyte immunoglobulin or (most rarely) alemtuzumab in the first days after transplantation [67].
- Chronic treatment usually involves three-drug therapy, including (1) a calcineurin inhibitor: cyclosporine or tacrolimus; (2) a drug that inhibits lymphocyte proliferation: mycophenolate mofetil or azathioprine; and (3) a glucocorticosteroid [65, 67–69].
- Acute cellular rejection occurs in most patients within a year after transplantation, most often in the first six months. Symptoms of graft rejection are not very characteristic (fever, cough, shortness of breath) and

need to be differentiated from infection or failure of the transplanted lungs from other causes. It is necessary to perform a few tests including laboratory (CRP, procalcitonin), microbiological (material obtained from the airways during bronchoscopy), imaging (chest X-ray and CT), and histopathological [66–68].

- Antibody-dependent rejection requires a detailed immunological diagnosis [66], including determination of donor antigen-specific antibodies and the dynamics of their titer increase, if any, along with simultaneous evaluation of changes in the transplanted organ (complement system activation). Treatment includes inhibiting the production of antibodies and removing them. First-line treatment is administration of intravenous immunoglobulin (IVIg) and plasmapheresis [65, 69].
- In the treatment of acute rejection, intravenous methylprednisolone 500–1000 mg/day is used for 3 consecutive days, followed by oral prednisone at a dose of 0.5–1 mg/kg of body weight for another 1–2 weeks and a gradual reduction in its dose thereafter [67].
- Chronic rejection occurs in the majority of patients (in 70% at 10 years post-transplantation). In selected cases, it can manifest itself as early as 3 months after LTx and is the factor that most determines long-term survival. Chronic rejection of the transplant usually takes the form of bronchiolitis obliterans (BO), and spirometry testing is crucial in its diagnosis and monitoring of patients. However, the final diagnosis of the so-called bronchiolitis obliterans syndrome (BOS) is based on histopathological examination of a lung fragment. Due to the process of chronic rejection, which can be slowed but not inhibited by immunosuppressive treatment, chronic lung allograft dysfunction (CLAD) develops, leading to pulmonary fibrosis [65, 66, 68, 70]. There is no effective treatment for CLAD. Halting the progression of BOS after total irradiation of lymphoid tissue has been observed, but the method is not widely used. Another method is administration of alemtuzumab, which is a monoclonal antibody against the CD52 lymphocyte glycoprotein, or antithymocyte globulin [65, 71]. Lung retransplantation procedures are also being performed, but this is successful in a small number of patients [65, 69, 72]. The problem is selection of the optimal surgical technique and identification of patients for whom this procedure can provide the expected benefit.
- Infections associated with immunosuppression are usually caused by opportunistic bacteria characterized by drug resistance [68-70]. The most common etiological agents are *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, but infections with atypical microorganisms (*Legionella, Chlamydophila, Mycoplasma*) also occur. Infections of fungal etiology are dominated by mold (e.g., *Aspergillus*), and less frequently by *Pneumocystis jiroveci* (formerly pneumocystis carinii). Among viral infections, pneumonia caused by cytomegalovirus (CMV) is particularly dangerous. Infections that occur after LTx have a particularly severe clinical course.
- Caring for patients after LTx requires:
  - monitoring of immunosuppression in terms of pharmacology (determination of concentrations of immunosuppressive drugs to ensure desired levels), as well as toxicity (parameters of renal function, lipogram, glycemia, evaluation for the development of diabetes, hypertension, chronic kidney disease, osteoporosis, and the onset of cancer);
  - availability of a bronchoscopy laboratory with the ability to perform interventional bronchial procedures and transbronchial biopsies (preferably cryobiopsy);
  - availability of a specialized bacteriological and virological laboratory, with the ability to diagnose rare pathogens by the most sensitive methods (PCR, molecular diagnostics);
  - the possibility of performing total lymphoid irradiation (TLI) or photophoresis;
  - availability of a transplant immunology laboratory; an HLA laboratory, monitoring occurrence of *de novo* antibodies to donor-specific antibodies (DSA);
- Scheduled follow-ups for LTx patients are carried out every 14 days for the first 3 months, then every month for up to 6 months, then every 2–3 months until the end of the first year, and then every 3–6 months.

HOW TO TALK TO A PATIENT BEFORE A LUNG TRANSPLANT PROCEDURE?

The prospect of LTx as a treatment for PAH can be emotionally difficult. In the minds of some patients (but also doctors), this method of treatment is seen as definitive, associated with significant disease progression and "failure" of drug treatment. Others, on the other hand, may see it as "the beginning of the end" or simply replacement of one disease with another.

Although LTx can be a difficult process, discussing the possibility of transplantation early on (even before it is actually needed) will allow both the patient and family to consider it as a treatment option in the future.

PAH is a rare disease with an unfavorable prognosis. New drugs, opportunities for up-front combination therapies, and the strategy of pursuing a rapid low-risk profile to a greater extent than some years ago have increased (in the minds of both patients and doctors) the time to qualification for LTx. However, it is important that the option of transplantation should already be on the table when treatment first begins. The first hospitalization and initiation of therapy (and especially prostacyclin therapy) is an extremely important moment in the patient-doctor relationship. A conversation about the disease, its etiology, progression, and the chosen therapy regimen should clearly explain to the patient the process of treatment and monitoring of disease progression and the stage at which qualification for LTx should be considered.

It is important that all people with PAH who need or may need an LTx in the future understand what the transplant process is all about and receive information to make an informed decision. Early referral to a transplant center gives patients a chance to meet with a multidisciplinary transplant team before the qualification procedure and inclusion on the waiting list. Anyone living with PAH knows that the course of the disease can be unpredictable (especially in patients on parenteral prostacyclin therapy) and clinical deterioration can occur very quickly, necessitating urgent referral for LTx.

An important part of the conversation about LTx is to explain to patients the concept of the so-called "transplantation window", i.e., the optimal time to perform the procedure, in which the patient is sick enough to need a transplant, but also healthy enough to recover after the operation.

An important part of preparing for transplantation is giving the patient the opportunity to get to know the transplant team, who will explain the procedure to the patient and his or her relatives, as well as outline a plan for cooperation in the post-transplant period.

Once on the waiting list, the waiting period for a transplant begins, which can be unpredictable. The patient should be prepared emotionally for the possibility of a "false alarm" in the case of inadequate donor lungs and assured that this is not linked to removal from the transplant list. There are many emotions associated with the prospect of transplantation, including anxiety, depression, and even coming to terms with a progressive disease such as PAH. Support from the referring team, the transplant team, and the family is vital in overcoming these and other emotions surrounding transplantation. Difficulties with getting help to cope with emotional challenges should not affect transplant candidacy, but lack of help can hinder access to medical care, including transplantation.

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