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Available online 17 January 2018

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1885-5857/

Selection of the Best of 2017 in Pulmonary Hypertension

Selección de lo mejor del año 2017 en hipertensión pulmonar

To the Editor,

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling and the resulting increase in pulmonary vascular resistance. This increased afterload leads to hypertrophy of the right ventricle (RV), which is initially adaptive but ultimately maladaptive, causing right-sided heart failure and death.[1]

The World Health Organization has classified pulmonary hypertension (PH) into 5 major groups, according to clinical, hemodynamic, and histological similarities. The most prevalent entities are PH associated with left-sided heart disease (group 2) and PH resulting from respiratory disease and hypoxia (group 3). Despite their very low prevalence, PAH and its associated subtypes (group 1) have been the subject of considerable research. Continual advances in understanding the underlying physiopathological mechanisms in PAH and the development of new therapies have improved the survival of these patients,[1] but their prognosis remains ominous. Current treatments are unable to reverse disease progression and available diagnostic strategies often miss early-stage PAH.

In 2017, guideline recommendations have been widely implemented regarding the latest therapeutic approaches and risk assessment; knowledge of PAH pathophysiology and genetics has improved; and treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) has been established.

Three new drugs have appeared on the market, targeting each of the 3 available pathophysiological pathways involved in PAH[1]: *a)* macitentan, an endothelin receptor antagonist; *b)* riociguat, a soluble guanylate cyclase stimulator of the nitric oxide-mediated pathway, and *c)* selexipag, a prostacyclin I_2 receptor agonist that targets the prostacyclin pathway.

Following the AMBITION trial (initial therapy with a phosphodiesterase type 5 inhibitor [tadalafil] and an endothelin receptor antagonist [ambrisentan]), initial combination therapy has been established as the most widely-used therapeutic strategy for patients with newly-diagnosed PAH.[1,2]

The multidimensional approach to risk assessment recommended by guidelines has been validated. This type of risk assessment guides treatment decisions and determines survival by taking into consideration achievement of low-risk criteria in multiple risk markers.[3]

Regarding the advances in physiopathology and genetics, while vasoconstriction remains the key therapeutic target of available treatments, other mechanisms have found to be involved in the progressive obstruction of the pulmonary vascular bed characteristic of PAH. These mechanisms include cell proliferation, cell death inhibition, inflammation, immune alteration, excessive activation of signaling pathways and altered mitochondrial function and oxidative metabolism. This novel metabolic theory suggests that metabolic dysregulation goes beyond the vascular bed and is also present in the RV and skeletal muscle. In addition, immune system involvement due to bone marrow participation means that PAH is actually a systemic disease.[4]

This alteration of multiple metabolic pathways has a genetic component. The first gene linked to PAH was *BMPR2*, which encodes the morphogenetic protein receptor type 2 and regulates multiple cellular functions. Mutations in *BMPR2* have been described in 75% of the hereditary forms of PAH and 25% of the idiopathic forms. These mutations show an autosomal dominant inheritance pattern with incomplete penetrance (20%), varying by sex (42% in women vs 14% in men) and expressivity. There are more than 300 known mutations in *BMPR2*. Recently, new genes have been found to be involved in the development HAP, such as *KCNK3* (encoding for a pH-dependent potassium channel), *TBX4* (encoding for the TBX4 transcription factor involved in embryonic development), and *EIF2AK4*, which is linked to the development of pulmonary veno-occlusive disease. The presence of a mutation guides a correct diagnosis.[5] The door has been opened to genetic counselling and early diagnosis of patients' relatives.

The treatment of choice for CTEPH (group 4) is still pulmonary endarterectomy in a CTEPH center, where the outcome is low mortality and good long-term survival. In patients who are ineligible for endarterectomy, riociguat has shown benefit and is the only drug recommended by clinical practice guidelines for the treatment of CTEPH. In addition, in 2017 it has been demonstrated that balloon pulmonary

angioplasty (BPA)[6] is now a real therapeutic option for these patients. This intervention improves the hemodynamic parameters, symptoms and functional capacity of patients with inoperable CTEPH. Possible complications include hemoptysis, vessel rupture, reperfusion edema, and hemorrhagic pleural effusion. The results of BPA are highly satisfactory and long-term controlled studies are now underway.

Knowledge of the molecular and genetic components of PAH has improved in 2017. New therapies[4] are now being studied that involve the serotonin system, ion channels, regulation of cell proliferation, and others. These therapies will lead to the development of new drugs and therapeutic strategies that will work alongside current strategies to stop or even reverse disease progression.

Early diagnosis is an important pending issue because it increases survival.[1] Genetic studies, emerging imaging techniques, and a wider use of ergospirometry in at-risk populations will contribute to this achieve this goal.

Research into treatment of PH in groups 2 and 3 must also continue, because these highly prevalent diseases are still lacking in therapeutic options.

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Available online 8 January 2018

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https://doi.org/10.1016/j.rec.2017.12.008

https://doi.org/10.1016/j.rec.2017.10.043
1885-5857/

Selection of the Best of 2017 in Cardiac Transplant and Ventricular Assist Devices

Selección de lo mejor del año 2017 en trasplante cardiaco y asistencia ventricular

To the Editor,

December 2017 marked 50 years since Dr. Barnard performed the first ever heart transplantation (HTx) in Cape Town, South Africa. Since then, more than 100 000 patients worldwide have received a HTx, about 8000 in Spain alone.[1] In these 5 decades, HTx has been indisputably consolidated as the alternative treatment of choice for patients with refractory heart failure (HF).

Thanks to the subsequent successive therapeutic advances that have been made, the average survival of HTx recipients has progressively increased, reaching about 12 years in the most recent cohorts.[1] In parallel, there has been an expansion in the indications for the procedure, which currently has few absolute contraindications. The main Achilles heel of HTx is still the small number of available organs, which makes it difficult for this therapy to extend to the entire population of patients who could benefit from it.

The Spanish heart donor distribution system is based on priority criteria that are agreed among all HTx groups in the country and were extensively revised in 2017 (Table). The current system prioritizes candidates requiring short-term mechanical circulatory assist devices, who are conferred the highest priority level, called "urgency status 0" (high-urgent), given their high risk of short-term death. In recent years, the prolongation of waiting times for HTx has caused a progressive increase in the number of candidates receiving a transplantation through an urgent priority code.[1]

The multicentre study ASIS-TC[2] reviewed the results of the Spanish protocol for high-urgent HTx during the 2010 to 2015 period. This work showed the good performance of the system, which enabled 79% of the patients included in the waiting list with the highest priority level to receive a HTx with an average delay slightly longer than 7 days. In this series, early mortality after urgent HTx was high, especially among patients requiring preoperative support with biventricular devices or extracorporeal membrane oxygenation.

Another consequence of the limited availability of heart donors is the progressive increase in their average age and the acceptance of organs with long ischemia times.[1] Although some studies have shown good HTx results with these suboptimal donors, there is still reluctance regarding its widespread use. There is controversy as well, such as the need to perform angiography to exclude coronary heart disease from all donors older than 60 years.

Recently, some strategies have been proposed to increase the number of potential heart donors. First and foremost, ex vivo normothermic perfusion systems of the donated heart[3] allow the transport of beating and metabolically active hearts, which increases their ischemic tolerance and preserves their functionality. Some groups have also presented promising initial results from the use of hearts of deceased donors after circulatory-determined death.[4] Finally, some countries have implemented scouting programs involving the retrieval teams of the transplant centers, achieving a significant increase in the proportion of donated hearts that are finally implanted in a recipient.

In the current context of a limited availability of heart donors, the development of long-term left ventricular assist devices (LVADs) is of particular interest. In recent years, intracorporeal continuous-flow LVADs have replaced other support modalities, due to their excellent results in terms of