Editorial

Chronic Thromboembolic Pulmonary Hypertension—Are Good Days Ahead?

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Chronic thromboembolic pulmonary arterial hypertension (CTEPH) is a debilitating and life-threatening pulmonary embolism complication that affects 0.79 percent[1] to 4.8 percent[2] of acute and 11.6 percent[3] of recurrent pulmonary embolism cases,[3] most commonly in first two years after a first symptomatic event.[4]

It is a distinct subset of pulmonary arterial hypertension (group IV PAH) with poor prognosis, resulting most often from long-term obstruction of the pulmonary arteries (main, lobar, and segmental), caused by fibrotic transformation of nonresolving thromboemboli (persisting in spite of greater than three months of effective anticoagulation treatment), which may be mediated by immunologic, inflammatory, and genetic mechanisms. However, most of these patients have high PH that cannot be fully explained by the severity of pulmonary vascular obstruction visible on imaging studies, suggesting a multifactorial mechanism for the development of PAH, which include progressive diffuse remodeling of the distal muscular pulmonary arteries (0.1–0.5 mm in diameter)[5] and thrombotic lesions causing obstruction in the distal arteries beyond the subsegmental level, which may all contribute to disproportionately elevated pulmonary vascular resistance (PVR) in approximately 40% of patients

On right heart catheterization, CTEPH is diagnosed by the presence of[1]: mean pulmonary arterial pressure (mPAP) $\geq$ 20 mm Hg, pulmonary artery wedge pressure (PAWP) 15 mm Hg, PVR $\geq$ 3 Wood units on right heart catheterization,[2] mismatched perfusion defects on V/Q scan, and[3] specific diagnostic signs such as ring-like stenoses, webs/slits, or chronic total occlusions (pouch lesions or tapered lesions) on computed tomography (CT) angiography, magnetic resonance (MR) imaging or conventional cineangiography[6] after 3 months of effective anticoagulation.

Because CTEPH is a progressive disease with severe patient consequences, early diagnosis and therapy initiation are critical. CTEPH needs to be differentiated from chronic thromboembolic disease (CTED), which may have similar presentation but does not have resting PAH.

Patients with CTEPH who are not treated are at a significant risk of developing PH, right heart failure, and early mortality. Those with mPAP $>$ 40 mm Hg had a 30% five-year survival rate, whereas those with mPAP $>$ 50 mm Hg have 10%.[7]

Over 40% of CTEPH patients were not considered for pulmonary thromboendarterectomy (PEA) (the gold standard treatment) in the international CTEPH registry,[8] either because of distal thrombi, extremely high risk of PEA due to prohibitive comorbidities, the patient's refusal to undergo complex surgery, or a high PVR disproportional to the degree of obstruction. Despite the fact that PEA surgery appears to be successful, up to a third of patients may have persistent (or residual) PH, and up to 51% may develop recurrent PAH.

Riociguat, the only medicine licensed for the treatment of inoperable or post-PEA CTEPH, has shown, at the best, a moderate benefit in improving 6-minute walking distance (6MWD) and reducing mPAP (by 10%). It was associated with serious adverse events in 54% of patients.[9]

Balloon pulmonary angioplasty (BPA) is a catheter-based therapeutic option for patients with CTEPH, who are not candidates for surgery or who have recurrent or chronic pulmonary hypertension after PEA, which is still the gold standard for CTEPH treatment. BPA is usually done in conjunction with medical therapy and is typically thought of as a supplement to medical treatment.

It has been proven in observational studies to enhance symptoms, right ventricular (RV) function, exercise capacity, and pulmonary hemodynamics.

In a meta-analysis of 14 studies (725 patients) by Zoppellaro et al, BPA was found to reduce mPAP (from 43 to 32.5 mm Hg), PVR (from 9.94 to 5.06 Woods units), increase

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cardiac index (from 2.35 to 2.62 L/min/m2), and improve 6MWD (from 345 to 442 m).[10]

The registry data also revealed a significant decrease in mPAP and PVR, and an increase in cardiac index, in patients undergoing BPA. The functional class of most patients improves after BPA, with the majority obtaining FC I/II. In almost all studies, the 6MWD improved by 50 to 100 m.[11]

Tanabe et al compared the safety and efficacy of BPA to medical therapy or PEA in a systematic evaluation of 13 studies (493 individuals). The 2-year mortality of 80 subjects who underwent BPA was significantly lower (13.2 percent vs. 1.3 percent) as compared with 68 subjects who received medical therapy; the risk ratio (RR) was 0.14 (95 percent confidence interval [CI]: 0.03–0.76).[12]

The largest multicentric study, which included 1408 surgeries in 308 patients, found that 36.3 percent of them experienced problems such as pulmonary injury (17.8%), hemoptysis (14.0%), and pulmonary artery perforation (14.0%). (2.9 percent). Within 30 days following BPA, there was a 2.6 percent mortality rate.[13]

Classical reperfusion pulmonary edema (RPE) is now considered to be a rare complication of BPA.

In this issue of the journal, Dr. M. Hanumantha Reddy et al. have reported their results of BPA in 11 patients (30 sessions) with distal CTEPH deemed inoperable by the CTEPH team. Like all other studies of BPA, to date, theirs is also an observational study (retrospective). This study has shown a significant improvement in exercise capacity, basal oxygen saturation, RV function, and decrease in PAP, right atrial (RA) pressure, RA diameter, inferior vena cava (IVC) diameter and RV diameter at 8 weeks after the last session of BPA, which are similar to studies from other parts of the world. These salutary results were achieved without any deaths and complications were less (18%), which were mostly lesser in nature when compared with similar studies. The benefit of BPA was achieved without the use of expensive imaging modalities like intravascular ultrasound (IVUS), optical coherence tomography (OCT), or pressure wire (which have been shown to reduce complications and optimize the procedure),[14] thus saving costs for patients, hospital, and third-party payers.

The study's limitations include the small number of patients, short follow-up time, retrospective observational design, lack of a control group, and lack of mention about the prior, concomitant or postprocedure medications received by the patients. Also, RV function was assessed by a single echo parameter, that is, tricuspid annular plane systolic excursion (TAPSE).

Other echo parameters of RV function which have been demonstrated to be useful in this setting include the following: RV fractional area change, RV outflow tract time velocity integral, peak RV free wall strain, tricuspid valve lateral annular systolic velocity, and eccentricity index, which can provide a comprehensive assessment of reverse RV remodeling. NT-proBNP levels can provide biomarker evidence of RV strain.[15,16]

These positive BPA findings come from expert centers and may not be generalizable. Despite all of the technical improvements, there is still a significant learning curve to execute BPA safely, successfully, and consistently. At experienced centers, the rate of adverse events has decreased significantly (from 15.8 percent in the first 444 sessions to 7.7 percent in the most recent 562 sessions)[17]

If done at specialist centers by competent interventionists following a complete multidisciplinary evaluation, refined BPA is now a recognized, safe, and successful therapeutic method for patients with inoperable CTEPH. The European Society of Cardiology and the European Respiratory Society[18] accepted BPA as a therapeutic strategy (IIb recommendation) for patients with technically inoperable disease or an unfavorable risk-to-benefit ratio for surgery in their 2016 guidelines for the diagnosis and treatment of PH.

Hybrid techniques combining BPA and medicinal therapy both before and after thromboendarterectomy may improve hemodynamics and long-term survival in CTEPH patients.

Furthermore, multicentre, prospective, large-scale randomized control trials (RCT) are needed to better understand the best patient and lesion selection, therapeutic techniques, complications, management, and long-term prognosis.

The beneficial results of this trial should act as a stimulus to establish more CTEPH expert centers with multidisciplinary teams comprising PH experts, PEA surgeons, radiologists, BPA interventionists, and anesthesiologists, who can deliver accurate, tailored treatment regimens for CTEPH patients.

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