Chronic thromboembolic pulmonary hypertension: More options, more awareness

Chronic thromboembolic pulmonary hypertension (CTEPH) (World Health Organization (WHO) group 4 pulmonary hypertension (PH)) is a rare complication of pulmonary embolism (PE), yet tantalisingly offers the potential for effective interventions. The precise incidence of CTEPH after PE is not known, with reported estimates ranging from 0.1% to 12% in the following 2 years. Furthermore, up to 50% of patients with CTEPH may not have a documented history of PE, which alludes to a complicated pathogenesis involving both obstruction of the pulmonary arteries by unresolved fibrotic clots and secondary vasculopathy.[1]

Fortunately, there is both increasing local awareness of CTEPH and increasing interventions and experience available, which makes the article by Davies-van Es *et al.*[2] in this issue of *AJTCCM* highly topical. The disease has traditionally been divided into four anatomical levels, involving the proximal main artery (level I) or the lobar (level II), segmental (level III) or subsegmental arteries (level IV), which are used as a guide to management. Surgery, in the form of pulmonary endarterectomy (PEA), remains the best therapeutic option for anatomically proximal disease (levels I - III), while balloon pulmonary angioplasty (BPA) and medical therapy are used for more distal disease and residual PH after PEA.[3]

PEA is a technically demanding operation, but it offers patients with CTEPH an opportunity for relief from this debilitating disease, with impressive results in experienced centres. The most important aspect of PEA is to perform as complete an endarterectomy as possible with removal of all the distal lesion tail ends from the pulmonary vascular tree. Perfect visualisation is essential, and the procedure is performed with the use of cardiopulmonary bypass and deep hypothermic circulatory arrest periods limited to 20 minutes at a time.[4]

Until very recently BPA was not available in South Africa, but fortunately it is now an option locally. BPA is reserved for the treatment of patients who are not suitable candidates for PEA,[5] which, depending on surgical expertise and the patient population, may constitute up to one-third of all CTEPH patients.[6] The first reported cohort of BPA patients had unacceptably high complication rates.[7] Subsequent refinement of the original technique, using a measured, conservative and step-wise approach along with improved patient selection, has resulted in improved effort tolerance, reduced pulmonary pressures and better quality of life with relatively low complication rates. A randomised controlled trial (Multicenter Randomized controlled trial based on Balloon Pulmonary Angioplasty (MR BPA))[8] confirmed that the outcomes in patients undergoing BPA are better than in those receiving medical therapy in the form of riociguat alone. Despite similarities in catheter and coronary wire manipulation as well as percutaneous balloon angioplasty, BPA is very different from coronary intervention. The approach to BPA is much more conservative, forgoing the immediate complete dilatation and stenting of stenotic lesions seen in coronary intervention in favour of progressive dilatation of lesions over multiple sessions. Stenting in BPA is very uncommon. Operator experience is essential to improve outcomes and decrease complications,[9] and for this reason it is recommended that BPA be performed in a dedicated PH centre with a sufficient volume of work to ensure upskilling and skill retention. Ultimately the goal of a BPA centre of excellence should be to perform >100 BPA procedures per year or perform BPA on >30 patients per year.[5]

Medical therapy should be reserved for inoperable or residual PH, and riociguat (an oral guanylate cyclase stimulator) and subcutaneous treprostinil (a prostacyclin agonist) are approved for patients with inoperable CTEPH abroad, but both therapies are expensive and not licensed locally. Other PH medications are used off-label in CTEPH; however, oral combination therapy is not infrequent in patients with severe haemodynamic disease.[1]

Against this backdrop of expanding available interventions for CTEPH, individual patient work-up becomes critical to determine the anatomical nature and extent of disease, to evaluate the haemodynamics in the context of a possible coexistent vasculopathy, and to exclude other pathologies. All investigations used provide important and often complementary information. Ventilation/perfusion (V/Q) and increasingly V/Q single-photon emission computed tomography (SPECT) scanning provide evidence of disease in the subsegmental areas, frequently below the resolution of most computed tomography (CT) scans, while CT scanning provides detail of both the vasculature and the lung parenchyma, including demonstration of lung regions that are unlikely to gain benefit from reperfusion (e.g. emphysematous or fibrotic areas). Echocardiography is important not only as the initial screening tool for diagnosing CTEPH, but also to assess functioning of both the right and left ventricles; however, it cannot replace right heart catheterisation in the measurement of important haemodynamic parameters. Invasive digital subtraction pulmonary angiography, performed at the same procedure as right heart catheterisation, is important because it arms the PH team with a tool that can accurately distinguish between primarily proximal disease, best managed surgically, and inoperable distal disease, better suited to BPA or medical therapy. It also assists in the identification of patients likely to have significant microvascular disease and therefore best treated medically.[5,10] In order to extract this anatomical information, high-quality angiographic images are required, but the acquisition of such images itself requires time and experience, and is one of the learning curves that must be overcome in the evolution of a PH service, particularly where BPA is available.[10]

The experience of Davies-van Es *et al.*[2] from a single centre is an important article and highlights the lack of standardisation of work-up for CTEPH patients, even within an institution. This lack of standardisation probably also reflects changing practice over the 16-year study period. It is interesting to note that over that study period, the majority of patients did not have V/Q imaging (29%) or right heart catheterisation (24%), and no patients had pulmonary

angiography, with the authors calling for a more standardised and protocolised approach to work-up in their institution.

There are additional important take-home messages from this article. Firstly, ~10% of the authors' original cohort did not have CTEPH, but pulmonary angiosarcoma. It is important for clinicians to appreciate that there are CTEPH mimics, which almost uniformly will have poor outcomes if not recognised prior to surgery. Secondly, the severity of disease presented for surgery appears worse than at other centres internationally, with 80% of the patients in WHO functional class III or IV, and almost half in clinical right heart failure. This is likely to be an indication of an underappreciation of CTEPH in the general community of physicians, with referral only after severe right ventricular failure occurs. This is an important finding in and of itself, as early diagnosis and early intervention are associated with improved outcomes, and is likely to be an important contributing reason for the high morbidity and mortality in this population compared with reported global norms. It serves as an important reminder to us, the pulmonology community, to advocate for increased awareness of the disease entity, follow-up after PE, and early referral for assessment and work-up.

Finally, despite the severe and late disease presentations in this study, many patients had life-changing outcomes after PEA, with notable improvement in WHO functional class. This finding emphasises that CTEPH is a condition that is potentially treatable. Unfortunately, loss to follow-up in this particular retrospective cohort limits accurate assessment of these outcomes, as only 75% of the patients were assessed after hospital discharge.

In summary, the future for patients with CTEPH is hopeful, with both PEA for proximal disease, and now BPA for more distal and residual disease, available locally. However, patients need to be identified as early as possible, and routine post-PE follow-up is advised for most patients after 3 - 6 months of anticoagulation. Work-up for CTEPH is advised in an experienced centre to ensure the best individualised management strategies and to improve outcomes.

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