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Balloon pulmonary angioplasty: does it have a role in CTED?

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In the current issue, Wiedenroth et al. report on the outcome of balloon pulmonary angioplasty (BPA) in ten patients with chronic thromboembolic disease (CTED), but without pulmonary hypertension (PH).[1] Six of the patients presented had completely normal pulmonary artery pressures (PAPs) (< 21 mmHg) at rest and five had a pulmonary vascular resistance (PVR) < 3 Wood units (WU), the level above which resistance is considered unequivocally elevated. Despite normal or near normal resting hemodynamics, these patients were highly symptomatic. After an average of nearly four trips to the catheter laboratory, 9/10 reported symptomatic benefit. In addition, favorable trends were reported in hemodynamics, effort tolerance, and biomarkers. The question therefore arises, does this offer hope to the many thousands of patients that remain symptomatic after suffering an acute pulmonary embolism (PE)? To address this question, I shall first outline the current state BPA and its place in our therapeutic armamentarium, then the natural history and consequences of CTED, and finally consider what steps should be taken before we accept BPA as having a role in CTED.

BPA in CTEPH

BPA is already an accepted therapeutic option for selected patients with chronic thromboembolic pulmonary hypertension (CTEPH).[2] Though the first case series was reported by Feinstein et al. in the United States in 2001, the technique has really been pioneered and refined by Japanese interventionists.[3] In the absence of randomized controlled trial data, only changes associated with the procedure or historical control comparisons have been reported. Such data suggest hemodynamic, symptomatic and survival benefit in patients with CTEPH. Exercise performance improves, the right ventricle structure and function normalize, and NTproBNP levels fall substantially. Follow-up for up to five years shows that the hemodynamic benefit persists.

Treatment is protracted, expensive, involves considerable radiation and contrast exposure, and, to date, is generally less effective than the gold standard treatment—surgical pulmonary endarterectomy (PEA).[3] However, direct comparisons are not necessarily appropriate as these interventions should be applied in different patient's populations. Each patient will spend 1 h or more in the catheter suite on 3–10 occasions, one week or more apart. Individual treatment sessions are limited by radiation exposure, the volume of contrast used (risk of contrast nephropathy if excessive volumes used), and patient tolerance—recurrent prolonged breath-holding is required to safely access lower lobe vessels. The aim in most centers is to treat all accessible lesions among the 19 segmental territories; within each segment, several sub-segmental branches may have to be accessed individually with a guide wire and balloon inflation performed on multiple occasions to deal with all the webs lesions, stenosis, slits, and/or occlusions.

Complications, while much less frequent in more recent series, remain relatively common, up to 10% per procedure, with each patient having multiple procedures. Pulmonary hemorrhage is most commonly due to wire perforation, but may also result from high pressure perfusion injury, arterial dissection, and pulmonary artery rupture. Consequences vary from asymptomatic opacities on radiography to hemoptysis coughing and desaturation to massive hemorrhage which may be fatal is uncontrolled. Reperfusion pulmonary edema (RPO) was a very common complication in early series in part due to the sudden exposure of previously low-pressure vasculature distal to the stenosis to very elevated PAPs, but also to vascular trauma from wire and balloon injury. Improved awareness of the risk factors for RPO (very elevated mean PAPs [mPAPs] > 40 mmHg or PVR > 7 WU, balloon to artery ratio > 0.8, exposing the distal vessel to pressures of > 35 mmHg) has significantly reduced the frequency and severity of this complication. Mortality, however, is uncommon in most published series.[3] At a BPA conference in NICE in November 2016, 11 centers (nine European, two Japanese) presented data on > 3400 procedures in 783 patients, hemoptysis occurred in 6% of procedures, RPO in 5%, and death in 0.5%. Each patient had an average of four procedures; therefore, the per-patient mortality was 2%. It should be noted that such data may represent a worst-case scenario, as all experience, including the learning curve, data were reported.

SAGE

As with the introduction of coronary angioplasty in 1977, BPA is a new therapeutic option that must find its place in a disease where established proven therapeutic options already exist. Pulmonary endarterectomy is the current gold standard therapy that has been shown to nearly normalize pulmonary circulation hemodynamics and improve prognosis. Peri-procedural mortality has improved and is now comparable with complex cardiac surgery (<5%), most patients achieve excellent improvement in functional status and quality of life (QoL) improvements, with near normal hemodynamics.[4] However, adverse events/peri-operable morbidity are common (around 50%). Not all CTEPH patients can benefit from PEA; around one-third of patients with CTEPH do not have surgically accessible disease. A further minority of patients are unsuitable for surgery because of co-morbidities. A proportion of patients after PEA surgery (17–31%)[3] have residual PH, though even most of these will have had significant hemodynamic improvement. Thus, while it is recommended that surgery must be considered in all patients with CTEPH, there are a significant number of patients for whom this option is not appropriate and some for whom the benefit is limited. If BPA were shown to offer the same outcomes with a lower morbidity, it could in the future challenge the paradigm that all patients should be offered surgery as the preferred intervention.

Survival among patients who are ineligible for surgery is much worse than for those undergoing surgery,[4] while for those with residual PH, post-surgery prognosis is improved but QoL and effort tolerance remain poor. The soluble guanylate cyclase stimulator Riociguat has been shown to increase effort tolerance in both these populations, but the hemodynamic benefits are very modest and the impact on prognosis is not yet clear. Drug therapy is believed to target the vasculopathy that develops in unobstructed vessels, thus does not address the underlying primary occlusive, fibrotic pathological issue.[3]

The prospect, therefore, for BPA is that by addressing the fundamental issue in inoperable patients with CTEPH and potentially those with residual post-surgery PH, it may alter the natural history, improve outcomes, and exercise performance. However, registry data alone will not be enough for this new contender.

Initial controlled trials are already underway. The RACE trial (ClinicalTrials.gov identifier NCT02634203) is a French trial where patients with inoperable CTEPH are randomized to Riociguat or BPA. Planned enrolment is 124 participants; the primary endpoint is change in PVR at 24 weeks and clinical secondary endpoints should provide the necessary data to power definitive trials. In Japan, the multicenter randomized controlled trial based on balloon pulmonary angioplasty for chronic thromboembolic PH (UMIN Clinical Trials Registry identifier UMIN000019549) will randomize 60 patients to BPA or Riociguat. The primary endpoint is change in mPAP at 12 months.

Future trials will also be required to compare outcomes to PEA in patients where the lesions are deemed suitable for both procedures (distal segmental/sub-segmental levels), and refining patient selection and comparing outcomes with different technologies as seen with the evolution of coronary angioplasty.

CTED

CTED refers to individuals where pulmonary emboli have failed to resolve, but resting PH has not been developed, i.e. the mPAP remains < 25 mmHg. This is because either the number of occluded segments is insufficient to affect resistance at rest or no secondary vasculopathy has developed. Whether the trigger for a vasculopathy (intimal and medial hypertrophy in unaffected sub 500-μm vessels) is primarily related to the degree of vascular obstruction or individual patient factors predisposing them to PH is unresolved. Although there is some disconnect between the volume of residual disease and the development of PH, it is worth noting that the standard risk factors for PH do not predict the development of PH after a PE.

Currently patients with CTED represent a very small proportion of the patients referred to PEA centers, not because CTED is rare but because referring centers will rarely investigate and refer such patients.[1] Those referred to PEA centers are thus likely to represent a very selected cohort and may not be typical of the general population of CTED patients. Certainly, they are highly symptomatic and have generally had other causes of effort limitation thoroughly excluded, but as this is done in a non-standardized fashion, it is difficult to know precisely in what way they differ pathobiologically from all other patients with CTED.

Within this highly selected cohort, we know that right ventricular diastolic function is impaired despite generally preserved structure and systolic function, so there is clear evidence of an RV response to increased afterload.[5] Held et al. compared ten patients with CTED to 31 CTEPH patients and 41 breathless control patients without pulmonary vascular disease or obstructions.[6] During right heart catheterization, exercise to 50 W resulted in an increase in mPAP from 21 mmHg to 44 mmHg among CTED patients; on cardiopulmonary exercise testing, CTED patients showed a similar reduction in maximal work rate and equivalent disturbance of indices of gas exchange to that observed among the CTEPH cohort. Thus, there are objective data to demonstrate that the vascular obstruction in these patients limits effort capacity and impacts right ventricular function.

PEA surgery has also been performed in a small number of patients with CTED. As with BPA, no control population was evaluated; apparent benefit with PEA surgery was slightly greater (6-min walking distance [6MWD] increased by 50 m, improved QoL scores, PVR and mPAP fell significantly).[7] While the changes in semi-objective data are more encouraging, the patient benefit is not hemodynamic, rather symptomatic and QoL-based, so the same questions remain in respect of the absence of a valid control group.

Looking to the larger population, among patients studied after apparent recovery from acute pulmonary embolic events, up to 50% have evidence of residual perfusion defects and a similar number remain breathless.[8] By contrast, $<4\%$ have CTEPH. It follows that, in principle, the numbers of patients that could be considered for interventions with CTED may, if a proven therapy were available, dwarf the population with CTEPH.

Registry follow-up after acute PE shows that around half the population have a reduced exercise tolerance associated with lower 6MWDs. Long-term mortality has been shown to be increased; however, death during follow-up is strongly associated with cancer or co-morbidity, while among those with first unprovoked PE and a low co-morbidity, 12-month mortality is only 3%.[8] The available data therefore do not address critical issues: Of patients that remain breathless post PE – what proportion are due to co-morbid diseases and what proportion represent the consequences of residual thromboembolic disease? Of those with effort limitation, residual clot burden, and no other cause of dyspnea, what proportion have objective evidence that perfusion mismatch is the likely cause of their effort limitation? Do some patients with effort-induced PH develop overt PH or exhibit a higher event rate during follow-up? What is the potential size of the population in whom BPA may have a role in improving symptoms and/or altering the natural history of the condition?

BPA for CTED: does it work?

While Wiedenroth et al. have demonstrated that BPA is feasible in CTED, the data reported are insufficient to demonstrate efficacy. Our understanding of underlying pathology and natural history of the CTED is very limited; therefore, all new interventions with both PEA and BPA should be applied only after careful balancing of benefits and risks. BPA is a complex, prolonged procedure associated with substantial radiation exposure (patients in the study had, on average, 3.5 procedures at separate sittings) and associated with a significant complication rate.[1] From CTEPH data, the complication rate of BPA per procedure is around 10%. The per-procedure complication rate in patients without PH may well be lower, but this has yet to be demonstrated in an adequately sized population. The only definitive outcome was the change in a subjective reporting of functional class. This is an unreliable measure where patients are recruited to undergo procedures without sham controls.

The pivotal importance of sham control when investigating outcomes of procedure has been shown in the recent ORBITA study of coronary angioplasty.[9] While percutaneous coronary angioplasty (PCI) has been accepted as providing superior symptomatic benefit when compared to medical therapy for the past 40 years, this study randomized 200 patients to PCI or a single-blinded sham angioplasty, where patients underwent pressure wire evaluation but not PCI. After six weeks, there was no benefit of PCI relative to sham procedure in terms of angina symptoms, increase in effort tolerance, time to ischemia on exercise testing, or improvement in cardiopulmonary exercise testing (CPEX). In previous unblinded studies, improvements in symptoms, exercise tolerance, and ischemia testing consistently demonstrated the superiority of PCI when compared to open-label medical therapy. This study demonstrates, as has been shown many times before, the very large placebo effect associated with interventional or surgical procedures.

It follows that simply demonstrating an improvement in symptoms with or without improvement in supporting tests such as CPEX will not be sufficient to establish the role for BPA in CTED. For coronary interventions, we have at least evidence that where pressure wire data are positive (as in the patients enrolled in the ORBITA trial), there is prognostic benefit from PCI. We do not currently have evidence that the natural history of CTED is adverse.

Future strategies

It therefore seems inevitable that before BPA could be accepted as a useful therapeutic approach in CTED, there is much work to be done. A much greater understanding of the natural history of CTED is required. Is there a significant cohort of CTED patients where symptoms and effort limitation are dominantly due to vascular occlusions and exercise associated elevation of pulmonary pressures? Do patients with CTED progress to CTEPH or do other adverse outcomes occur during follow-up? If a sizable population is identified, then sham procedures could be constructed, but would require some imagination (e.g. pressure wire evaluation of lesions that are treated or just interrogated). If long-term registries identified a sizable population with a high rate of adverse events, then demonstrating an improved outcome on objective measures with BPA might be sufficient. If, however, such studies show that the vast majority with CTED are symptomatic and have adverse outcomes for reasons that are independent of their CTED, then we can never have robust data and we will remain reliant on expert opinion to determine the optimal treatment strategy.

With improved management options for CTEPH (PEA, BPA, Riociguat) the medical profession is carefully expanding our experience to CTED patients. While our understanding of pathology and natural history remains very poor, any decision to treat has to be very carefully approached and should only considered in experienced PH/CTEPH centers.

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