



Long-term outcomes after pulmonary endarterectomy

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) that is potentially curable with pulmonary endarterectomy (PEA). PEA is considered the first-line treatment as it can remove the chronic, fibrotic, flow-limiting organized thrombus within the pulmonary arterial bed, addressing the primum movens of CTEPH. In fact, after successful PEA, there is rapid reverse remodeling (usually within 2–3 weeks) of the right ventricle (RV) resulting in reduced volume and increased ejection fraction. As RV function is a major determinant of prognosis in PH, it is easy to understand the impact of PEA on long-term outcome of CTEPH patients; in most registries the 3-, 5- and 10-year post-operative survival is 84–92%, 76–86% and 72–77% (1-6), respectively. This is significantly higher than the survival of patients with inoperable CTEPH, which in most registries is 70%, 50–59% and 40% at 3, 5 and 10 years, respectively (2,6). Moreover, when compared to the general population, the life expectancy following PEA is shorter, but the difference is quite small (2), and prognosis may be primarily related to comorbidities as half of long-term follow-up deaths are attributable to conditions other than RV failure (3).

Nevertheless, we cannot simply consider PEA as a cure-all. First of all, PEA has an in-hospital mortality that is, in high-volume centers, less than 5% (1,6,7). Secondly, 10% to 50% of patients (according to the different definitions utilized) may have persistent PH after surgery (3) and this can impact long-term outcomes, reducing exercise capacity (8) and, in some clinical records, survival as well (5,6,8). The severity of persistent PH that seems to be prognostically relevant is still debated. However, the cut-offs of 34–38 mmHg of mean pulmonary arterial pressure (mPAP) and of 5.3–7.3 Wood units (WU) of pulmonary

vascular resistance (PVR) after PEA seem to be predictive of death (3,5). Thirdly, symptoms of reduced exercise tolerance may persist after PEA regardless of residual PH and may require up to 1 year to recover despite the immediate hemodynamic improvement (7). A possible explanation is that the normalization of the hemodynamic profile at rest may not be translated into an immediate functional recovery of the pulmonary vascular bed (9). In addition, comorbidities can play an important role; PEA performed in octogenarians results in a similar 5-year survival rate as compared to patients a decade younger, but the improvements in cardiac index and functional capacity are blunted in the elderly (10). Finally, recurrent CTEPH after normalization of pulmonary hemodynamics by PEA can occur. It is a very uncommon event (around 1%) and can be related to recurrent acute embolic events that occur in <2% of patients (preferentially in those with inferior vena cava filters and/or antiphospholipid syndrome or in patients with inadequate anticoagulant therapy) or related to progression of distal pulmonary arterial disease over time (3,7).

In our experience between 2003 and 2020, 170 patients with CTEPH (median age of 63 years) underwent PEA. The Kaplan-Meier (KM)-estimated 3-, 5- and 10-year survival rates were 88% [95% confidence interval (CI): 82–92%], 87% (95% CI: 80–91%) and 75% (95% CI: 66–82%), respectively. Survival was significantly better than for the cohort of 173 inoperable CTEPH patients (median age of 73 years) treated with medical therapy; the KM-estimated 3-, 5- and 10-year survival rates were 84% (95% CI: 78–89%), 72% (95% CI: 63–79%) and 39% (95% CI: 29–49%), respectively. We arbitrarily split our cohort into two timeframes, before and after 2011, to

consider the surgical learning curve and assess whether there has been an improvement in outcome over time. The in-hospital mortality for the early cohort was 15% and the 5-year survival rate was 83% (95% CI: 73–89%); the in-hospital mortality for the late cohort was 5% and the 5-year survival rate was 91% (95% CI: 80–96%). Conditional 3-, 5- and 10-year KM-estimated survival for patients surviving the in-hospital post-operative period was 99% (95% CI: 94–100%), 97% (95% CI: 92–99%) and 84% (95% CI: 74–90%), respectively. In the early cohort, conditional 5-year survival was 97% (95% CI: 90–99%), and in the late cohort, it was 96% (95% CI: 84–99%). Forty-three percent of patients discharged from hospital have persistent PH (defined as a mPAP \geq 25 mmHg and PVR \geq 3 WU at 6 months after PEA) and 61% of them received PH-specific drugs (18% of the latter were also treated with balloon pulmonary angioplasty). No statistically significant difference in conditional 5-year survival was observed between patients with or without persistent PH after surgery ($P=0.225$), or between patients with persistent PH treated or not with PH-specific drugs ($P=0.802$). However, patients with persistent PH after PEA treated with PH-specific drugs have significantly higher median (interquartile range) mPAP {34 [30–43] *vs.* 29 [26–32] mmHg; $P<0.001$ } and PVR [5.2 (4.3–6.8) *vs.* 3.5 (3.3–4.5) WU; $P<0.001$]. Thus, it can be speculated that PH-specific treatment may have improved the prognosis of those patients with a worse hemodynamic profile.

In conclusion, PEA is the gold standard of care for patients with CTEPH deemed operable as it can provide excellent long-term outcomes with low mortality rates in high-volume centers. However, a favorable long-term outcome is not only dependent on a successful intervention, but is also related to the post-operative management of PEA-treated patients; a close clinical follow-up aimed at maintaining proper anticoagulation and monitoring the long-term clinical, functional and hemodynamic effects of PEA is mandatory. In fact, in the event of residual PH, additional strategies should be considered to potentially target both distal pulmonary vasculopathy (with PH-specific drugs) and residual chronic thrombotic lesions in subsegmental arteries (with balloon pulmonary angioplasty). However, the degree of residual PH requiring treatment has yet to be clearly defined.

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Footnote

Conflicts of Interest: The authors declare no conflicts of interest.

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