AB008. Prosthetic tracheal replacement using stented aortic matrices

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Abstract: Airway transplantation remains a great surgical and biological challenge. This is still an unsolved problem for patients in therapeutic impasse because of major tracheobronchial lesions requiring surgical resection and airway reconstruction. Schematically, 5 principal ways of research have been explored with the use of synthetic prostheses, airway bio-prostheses, tracheal allografts, various autologous substitutes and more recently bioengineered conduits. The lack of prospective human studies did not allow standardizing surgical approaches. In 1997, we initiated a research program on airway transplantation using stented aortic matrices in the Laboratory of the Alain Carpentier Foundation, Paris. A series of 7 preclinical animal studies using a sheep model showed that autologous and fresh or cryopreserved allogeneic aortic grafts could be valuable tracheal, carinal and bronchial substitutes. The regeneration of epithelium and de novo generation of cartilage were observed within the aortic matrices, thus allowing stent removal at a mean of 6 months. These favorable results led to the first human applications in patients with extensive tracheal diseases or complex tumors that would otherwise require pneumonectomies. Recently, we confirmed that airway bioengineering using cryopreserved aortic allografts was feasible for complex tracheal and bronchial reconstruction in 13 human cases (Martinod et al. Feasibility of bioengineered tracheal and bronchial reconstruction using stented aortic matrices. JAMA 2018;319:2212-22). Twenty patients were prospectively included in the TRACHEOBRONCART study. Thirteen patients underwent tracheal (n=5), bronchial (n=7), or carinal (n=1) replacement. Airway transplantation was not performed in 7 patients because of medical contraindication (n=1), unavoidable pneumonectomy (n=1), exploratory thoracotomy only (n=2), and a lobectomy or bilobectomy was possible (n=3). The overall 90-day mortality rate was 5%. There was no mortality at 90 days among patients who underwent tracheal or bronchial reconstruction. The only mortality was observed in the patient who had a massive stroke after carinal transplantation. There was no adverse event directly related to the innovative surgical technique. Stent removal was performed at a postoperative mean of 18.2 months. At a median follow-up of 3 years 11 months, 10 of the 13 patients were alive. Of these 10 patients, 8 breathed normally through newly formed airways after stent removal. Regeneration of epithelium and de novo generation of cartilage were observed within aortic matrices from recipient cells. We confirmed in human the possibility of epithelium regeneration, de novo cartilage generation and stent removal. Our previous work has shown that the −80 °C cryopreserved aortic allografts contained viable cells at time of implantation, as assessed by their ability to migrate and proliferate from explants. They released a large panel of cytokines and growth factors and exerted
significant chemoattractant and proangiogenic effects toward endothelial cells when assessed \textit{in vitro}. Thus, cells from cryopreserved aortic allografts could have orchestrated the regenerative process by stimulating progenitor/stem cell homing and organ healing. The recipient body was used as a natural bioreactor and allowed \textit{in vivo} airway tissue engineering. After approval by French Regulatory Authorities (Assistance Publique Hôpitaux de Paris DRCD and DAJ), we started the prospective observational study TRITON01 (TRacheobronchial bIoengineering using aorTic matrices for airway recONstruction) as a part of routine care for our center. We used the same innovative surgical approach as the previous protocol (NCT01331863, clinicaltrials.gov identifier) published by our group. Seven new patients with a therapeutic impasse have been added to the study since March 13, 2019. Our principal objectives are to include prospectively new patients with end-stage tracheobronchial diseases (TRITON 01 study); to compare airway transplantation using stented cryopreserved aortic allografts to standard therapy in patients with a major thyroid cancer invading the trachea (TRITON 02 study); to decipher the mechanisms of \textit{de novo} cartilage regeneration and immunoregulation within transplanted aortic matrices; to optimize \textit{de novo} cartilage regeneration using \textit{in vitro} preconditioning of cryopreserved aortic allografts or \textit{in vivo} local injection of mesenchymal stem cells; and finally to test new types of bioengineered and/or 3D printed aortic grafts with a commercial potential for a wider dissemination.

\textbf{Keywords:} Trachea; bronchi; surgery; transplantation; tissue regeneration

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