Treatment of complex airway stenoses using patient-specific 3D-engineered stents: a proof-of-concept study

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ABSTRACT

Anatomically complex airway stenosis (ACAS) represents a challenging situation in which commercially available stents often result in migration or granulation tissue reaction due to poor congruence. This proof-of-concept clinical trial investigated the feasibility and safety of computer-assisted designed (CAD) and manufactured personalised three-dimensional (3D) stents in patients with ACAS from various origins. After CAD of a virtual stent from a CT scan, a mould is manufactured using a 3D computer numerical control machine, from which a medical-grade silicone stent is made. Complication rate, dyspnoea, quality of life and respiratory function were followed after implantation. The congruence of the stent was assessed peroperatively and at 1 week postimplantation (CT scan). The stent could be implanted in all 10 patients. The 3-month complication rate was 40%, including one benign mucus plugging, one stent removal due to intense cough and two stent migrations. 9 of 10 stents showed great congruence within the airways, and 8 of 10 induced significant improvement in dyspnoea, quality of life and respiratory function. These promising outcomes in highly complex situations support further investigation on the subject, including technological improvements.

Trial registration number NCT02889029.

INTRODUCTION

Airway stenting allows for rapid and dramatic clinical improvement in most cases of central airway obstruction.[1] However, the limited diversity of shapes in commercially available devices constitutes a major limitation for the relief of anatomically complex airway stenosis (ACAS) cases. The main consequences of the lack of congruence are both migration and tissue reactions. Thus, we hypothesised that patient-specific stents may potentially overcome ACAS situations.

METHODS

Patients

After informed consent, patients with non-malignant and symptomatic (grade II or worse dyspnoea according to the New York Heart Association [NYHA] scale, recurring retention infections) ACAS were included in this prospective proof-of-concept clinical trial. 'Anatomically complex stenosis' was defined either as a stenosis in which the anatomy was too complex to allow the use of commercialised stents or when these devices had previously failed (due to migration, granulation tissue reaction or other complications of anatomical origin leading to stent removal). Patients in an emergency setting (SpO_2 <90% (peripheral oxygen saturation), peak expiratory flow rate [PEFR] <20%, acute respiratory distress) or with malignant obstruction were excluded.

Manufacturing and implantation of the stent

Thanks to a computer-assisted modelling of the airways from a chest CT scan performed during forced inspiration, the stenosis is virtually relieved and a virtual stent and corresponding mould are designed. The numerical data are then entered in a three-dimensional (3D) computer numerical control machine to manufacture the mould in Ertacetal. Next, the implant is manufactured using a medical-grade silicone injection. It is then sterilised and placed into the patient under rigid bronchoscopy. The thickness of the stent, ranging from 0.8 mm to 2 mm, is chosen depending on the radial force needed, which takes into account both the airway segment involved and the indication (figure 1).

Complications, dyspnoea (NYHA scale), quality of life (VQ11 questionnaire, a COPD-specific quality of life questionnaire) and respiratory function were monitored (before, on day 7 and at 3 months postimplantation). The stent congruence was assessed both peroperatively (flexible bronchoscopy) and on day 7 postimplantation (CT scan). If any new symptoms arose that were worrisome for a complication, spirometry and flexible bronchoscopy were performed.

Statistics

We planned to enrol 10 patients for this feasibility, proof-of-concept study; its primary objective was the safety of patient-specific stents. The per cent of procedures with no complications at 3 months was chosen as the primary judgement criterion, and we anticipated a 50% overall complication rate. The per cent of procedures with encouraging anatomical congruence (defined as a distance less than 0.5 mm between the stent wall and the airway over the whole surface of the stent on the postoperative CT scan) and the per cent of patients with clinical, functional and quality of life improvements after 7 days and 3 months postplacement were other secondary judgement criteria.

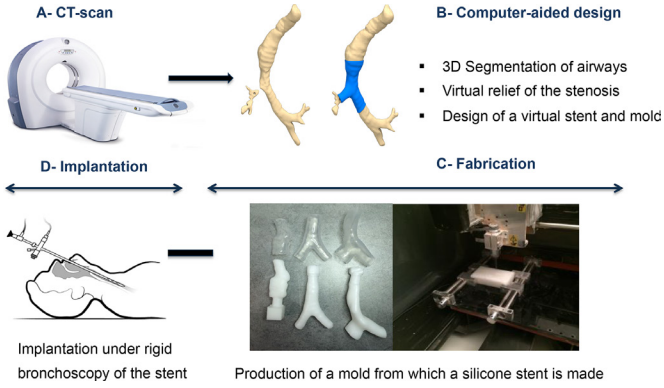


Figure 1 Conception and fabrication of the patient-specific stent. (A) CT scan acquisition in forced inspiration. (B) Computer-aided design (VGStudio MAX V.3.0 software) of a virtual stent and mould (AnatomikModeling). (C) Manufacturing of a mould in Ertacetal (Roland DG MDX 40A) and fabrication of the customised airway stent (Sebbin) by injection of medical-grade silicone (non-sterile test prototypes). (D) Implantation of the stent under rigid bronchoscopy and general anaesthesia. 3D, three-dimensional.

RESULTS

The main results are summarised in figure 2. Ten patients were included between October 2016 and July 2018, seven of whom were previously treated using conventional stents that failed, and the remaining three had post-transplant airway stenoses for which conventional devices were not suitable (patients 1–3).

Feasibility and safety (primary objective)

Patient-specific stents were inserted without peroperative complications in all patients. The complication rate at 3 months was 40% (4 of 10: 1 mucus plugging, 2 migrations and 1 removal for cough), and three required stent removal. An additional mucus plugging event occurred in a patient at 4 months. One patient developed a distal stenosis at 4 months at the lobar level (beyond the distal extremity of the stent) that required balloon bronchoplasty. None of the complications seen were life-threatening (figure 2). Of note, the three cases in which a complication led to stent removal had previously experienced the same complications (Y stent removal for intense cough in patient 6, and multiple stent migrations in patients 9 and 10) with conventional airway stents before participating in this study.

Congruence

In nine out of ten patients treated (90%), the stent showed great congruence. One stent showed poor congruence on both peroperative flexible bronchoscopy and CT scan controls (patient 7). The results for three patients are shown in figure 3.

Efficacy

Eight out of ten (80%) patients experienced improvements in dyspnoea (>1 NYHA point gain), quality of life (>10% VQ11 (COPD-specific quality of life questionnaire) score increase) and functionality (>10% FEV_1 or PEFR flow increase) (figure 2).

Focus on post-transplant ACAS (patients 1–4)

Conventional airway stents were not suitable due to complex anatomy in patients 1–3 and previously failed in patient 4 (stent migration). All four patients treated for post-transplant ACAS had clinical and functional improvements on day 7 and 3 months postimplantation (figure 2). One[2] developed more distal stenosis after 4 months, beyond the lowermost level of the stent (patient 1). The second stent (patient 2) is still in place after 23 months, and the patient has refused a device removal due to the lack of symptoms. The third stent (patient 3) had to be removed after 4 months due to mucus plugging and was not replaced because no residual stenosis was present at this time. The last stent (patient 4) was placed 3 months ago, showing perfect congruence and functional improvement on day 7 and 3 months postimplantation. However, flexible bronchoscopy was required for mucus plugging removal on day 9 (figure 3A).

Focus on ACAS following thoracic surgeries (patients 5 and 6)

Patient 5 was treated for complete obstruction of the bronchus intermedius/carina anastomosis after sleeve right upper lobectomy, which resulted in respiratory distress requiring mechanical ventilation. A Y stent allowed for a rapid ventilator weaning but subsequently induced intense granulation tissue reactions due to poor congruence, before being replaced by a patient-specific stent (figure 3B). The patient-specific stent led to perfect congruence and dramatic clinical improvement. Patient 6 had previously received 11 conventional devices of various shapes to treat an ACAS due to tracheal ring rupture acquired as a complication of aortic surgery. All of them had to be removed and replaced after short delays (1 day to 4 months) due to migration and/or granulation tissue reaction. A 3D stent was implanted 21 months ago and showed exquisite congruence, leading to durable efficacy (figure 3C).

Focus on tracheobronchomalacia (patient 7)

A stent was placed for a severe tracheobronchomalacia (TBM) for which surgical tracheoplasty[3] was excluded due to poor general and respiratory conditions (patient 7). The patient-specific stent demonstrated suboptimal congruence and was removed after 2 months for recurrent cough.

Focus on post-tracheotomy ACAS (patients 8–10)

Three patients were treated for post-tracheotomy ACAS after failure of commercially available devices (multiple migrations for patients 9 and 10, and iterative mucus plugging and intense cough for patient 8). The PEFR in patient 8 has improved from 30% to 90% and she is asymptomatic 6 months after implantation. Two other stents migrated, despite good congruence (patients 9 and 10); one out of both could be efficiently replaced and subsequently removed after 6 months (patient 10).

DISCUSSION

The ideal stent, in particular for ACAS management, should (1) be easy to place and remove; (2) be rigid enough to lift the compression but maintain flexibility to mimic the physiology of the airways; and (3) be the most suitable as possible to the patient's anatomy to prevent migration, facilitate mucus clearance and avoid granulation tissue reaction. If such a stent does not yet exist, we hypothesised that CT-derived patient-specific implants would address the third point and lead to improved tolerance and lower complication rates.

Our proof-of-concept study clearly demonstrated the feasibility of the use of personalised stents and showed promising results in difficult clinical situations. The 3-month complication rate (40%) appears to be higher than what is usually reported with conventional airway stents.[1 4] However, this is expected because of the complexity of the patient population for which conventional devices had to be removed due to severe complications (7 of 10) or were otherwise not suitable (3 of 10). No

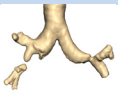
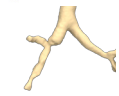
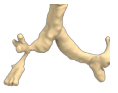
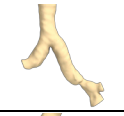
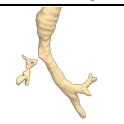
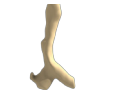
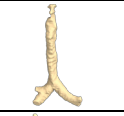
Indication	Pretreatment 3D segmentation	Virtual stent	TAT	Pre-treatment clinical status	Day 7 clinical functional status	Day 7 CT	3 months clinical functional status	Complications (last control when still in place)
1) Post transplant VBIS			39	NYHA 3 Infections VQ11 22 FEV1 75%	NYHA 1 VQ11 11 FEV1 105%	Good congruence	NYHA 1 VQ11 NA FEV1 85%	More distal stenosis, at 4 months: Stent removal and dilatation
2) Post transplant RMB malacia and stenosis			87	NYHA 3 Infections VQ11 27 FEV1 65%	NYHA 2 VQ11 15 FEV1 70%	Perfect congruence	NYHA 1 VQ11 11 FEV1 102%	None. Still in place (23 months)
3) Post transplant BI malacia and stenosis			40	NYHA 3 Infections VQ11 51 FEV1 84%	NYHA 1 VQ11 NA FEV1 100%	Perfect congruence	NYHA 1 VQ11 36 FEV1 100%	Mucus plugging. Removed after 4 months, no residual stenosis, FEV1 100%
4) Post transplant LMB stenosis			65	NYHA 2 Infections VQ11 19/55 PEFR 40% FEV1 76%	NYHA 1 VQ11 19/55 PEFR 70% FEV1 82%	Perfect congruence	NYHA 1 VQ11 NA PEFR 69% FEV1 73%	Mucus plugging at day 9 (3 months)
5) Post sleeve lobectomy BI occlusion			29	NYHA 4 Infections Intense granulation VQ11 52 FEV1 30%	NYHA 2 VQ11 31 FEV1 40%	Perfect congruence	NYHA 2 VQ11 31 FEV1 35%	None. Still in place (5 months)
6) Localized malacia (cartilage ring rupture)			73	NYHA 3 Cough Granulation Migrations VQ11 23 FEV1 66% PEFR 49%	NYHA 1 VQ11 15 FEV1 92% PEFR 81%	Perfect congruence	NYHA 1 VQ11 16 FEV 75% PEFR 88%	None. Still in place (18 months)
7) Severe TBM			60	NYHA 3 Intense cough VQ11 40 FEV1 97%	NYHA 1 Cough VQ11 NA FEV1 94%	Imperfect congruence	NA	Removed after 2 months (cough)
8) Post tracheotomy complex stenosis			39	NYHA 3 VQ11 44 FEV1 63% PEFR 30%	NYHA 2 VQ11 20 FEV1 82% PEFR 50%	Perfect congruence	no dyspnea VQ11 12 FEV1 91% PEFR 90%	None Still in place (6 months)
9) Post tracheotomy complex stenosis			109	NYHA 2 cough migration X3 VQ11 38 FEV1 82% PEFR 47%	NYHA 2 VQ11 FEV1 88% PEFR 53%	Good congruence	NA	Migration 2 months
10) Post tracheotomy complex stenosis			41	NYHA 3 cough retention migration X3 FEV1 94% PEFR 72%	NA	NA (Good endoscopic congruence)	NYHA 1 FEV1 106% PEFR 85%	Migration day 7. Replaced. Removed after 6 months, no residual stenosis.

Figure 2 Main indications and outcomes on day 7 and 3 months. FEV_1 variations are presented for stenoses involving the bronchial level (PEFR is also reported for patient 4 for whom FEV_1 remained stable within time); PEFR and FEV_1 variations are presented for tracheal stenoses. 3D, three-dimensional; BI, bronchus intermedius; LMB, left main bronchus; NA, not applicable; NYHA, New York Heart Association dyspnoea classification; PEFR, peak expiratory flow rate; RMB, right main bronchus; TAT, turnaround time (time between inclusion and stent implantation, in days); TBM, tracheobronchomalacia; VBIS, vanishing bronchus intermedius syndrome. VQ11: COPD-specific quality of life questionnaire

unexpected complications have been observed. No complications have been life-threatening. Only three patients required stent removal, and each of these patients had previously suffered the same complications with conventional devices. Our relatively short follow-up does not allow for reliable exploration of potential long-term complications; thus, longer monitoring will be needed in future efficacy studies.

Furthermore, the pitfalls and limitations encountered are potentially addressable by further technological improvements.

Failure to acquire a baseline CT in forced inspiration may explain the poor congruence observed in one case of TBM. *Four-dimensional dynamic CT scan* can take into account the changes in airway volumes during respiration (particularly in TBM cases) and may overcome this pitfall.[5 6]

For both migration cases, no airway bifurcation or significant distortion clearly predicted durable stability. *Reinforcement* rings or patient-specific structures in predefined areas may reduce migration risks in such cases. The customisation could thus not be limited to the shape but also to the wall of a same stent, with radial force being preferentially applied to the stenotic portion. In the meantime, extremities and non-supporting areas can be maintained smoother and thinner to decrease mucosal aggression.

The major limitation of this new approach is its turnaround time (time between patient inclusion and stent implantation, with a median of 50 days in this study, with approximately 30 days for fabrication, including 15 days of sterilisation). Even if the delay of the process can be reduced to approximately 10 days (by using shorter sterilisation processes and with the instalment of dedicated software in the hospital allowing cloud-based

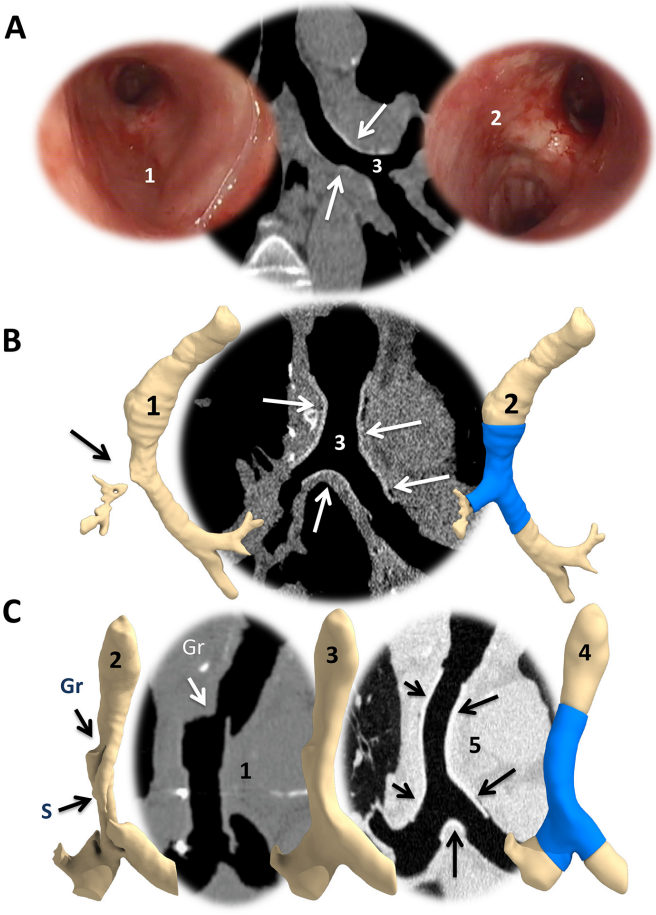


Figure 3 Examples of airway stenting in various indications: (A) Patient 4: bronchoscopic view of the upper (1) and lower (2) extremities of a customised stent implanted for a post-transplant ACAS of the left main bronchus; (3) 7-day CT scan showing perfect congruence between the device and the airways. (B) Patient 5: (1) pretreatment three-dimensional segmentation of the airways; (2) design of the virtual stent after stenosis virtual relief; (3) 7-day outcomes showing a perfect congruence of the stent within the airways on CT scan. (C) Patient 6: (1) pretreatment CT scan showing a previous commercially available stent that migrated and induced a dramatic granulation tissue reaction at its upper extremity (Gr); (2) three-dimensional segmentation of the airways with stent in place; (3 and 4) design of the virtual stent after virtual relief of the stent and stenosis; (5) 7-day outcomes showing a perfect congruence of the stent within the airways on CT scan. ACAS, anatomically complex airway stenosis.

data transfer), this technique cannot cover emergency situations. Over-riding the intermediary step of moulding and direct 3D printing of the silicone stent from the 3D model would considerably decrease the turnaround time. However, to the best of our knowledge, no 3D printer can yet print in medical-grade silicone (or any other flexible and biocompatible material). Beyond this technical barrier, there are also legal considerations that may delay the clinical adoption of 3D printing as the biocompatibility of the silicone, the sterilisation process and other production steps have to be rigorously validated.[7–9]

Finally, the question of the systematic removal of a temporary stent which is no longer necessary (ie, transient stenting after transplantation) but does not induce any symptoms (patient 2 for example) paves the way towards the development of stents that are both personalised and *biodegradable*.[10]

In conclusion, this proof-of-concept study demonstrates promising outcomes using patient-specific stents and strongly indicates the need to further assess this approach in less selected populations, as well as further research and development into technological improvements.

Contributors NG: principal investigator of the work, conception and design of the work, computer-aided design of the stents, stent implantation, acquisition and interpretation of data, drafting the manuscript. AD: conception and design of the work, interpretation of data, revising the manuscript, approved the final version of the manuscript. BM: computer-aided design of the stents, manufacturing moulds, approved the final version of the manuscript. BL: conception and design of the work, statistical analysis of data, approved the final version of the manuscript. PL: computer-aided design of the stents, manufacturing moulds, approved the final version of the manuscript. GP: conception and design of the work, stent implantation, acquisition and interpretation of data, approved the final version of the manuscript. LM: acquisition and interpretation of data, approved the final version of the manuscript. MM: interpretation of data, approved the final version of the manuscript. JM: conception and design of the work, acquisition and interpretation of data, revising the manuscript, approved the final version of the manuscript. CH: conception and design of the work, computer-aided design of the stents, implantation of stents, acquisition and interpretation of data, approved the final version of the manuscript.

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Competing interests BM and PL are employees of AnatomikModeling.

Patient consent for publication Not required.

Ethics approval Our study was approved by local ethical instances (CPP) and by the National Agency of Medical Devices (ANSM).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All individual de-identified participant data will be shared, as well as study protocol, statistical analysis plan, informed consent form, clinical study report and analytical code, to any researcher who provides a methodologically sound proposal to achieve aims in the approved proposal. Proposals should be directed to guibert.n@chu-toulouse.fr. To gain access, data requestors will need to sign a data access agreement. Data are available immediately and indefinitely.

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