Peer Review File

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Reviewer A

The authors have done a credible job at sorting out the innovations in the literature with stent evolution and technology. I would suggest a main heading Evolution of airway stents, but this is nothing of great importance and would leave it to the authors discretion.

Few things need more clarification or literature references

I. A discussion with brief paragraph or as pertaining in sessions of silicone and SEMS covered and uncovered would be beneficial on 1> How much are the use of these stents around the world ? 2> What are patterns people use to prevent clogging of these silicone or SEMS stents? A discussion on how to prevent granulation or mucus formation in all kinds of stents is there any new direction or technique that has evolved or being practiced ?

Reply 1: We have made supplement according to the Reviewer's comments

Changes in the text: 1>We added some data (see Page 14, line 303-305): For the time being, among commercially available stents, Ultraflex (covered SEMS) and Dumon (silicone stent) remain the commonest type of stent used all over the world; 2>Various novel stents has evolved or being practiced to prevent granulation or mucus formation, which was discussed in this paper.

II. How much is biodegradable stents and stent customization being used despite all these research in its progress ?

Reply 2: We have made supplement according to the Reviewer's comments

Changes in the text: We added some data (see Page 9, line 194-196): Recently, a survey study has showed that amongst all available airway stents in medical applications, 7.5% of them are biodegradable stents.

III. How is stent customization onsite or by 3D printing being used ? Is it being used more around the world? Its been used in the US and Europe more now with its approval by the FDA. See reference below

Reply 3: We referred to above-mentioned references and made supplement according to the Reviewer's comments

Changes in the text: We added some data (see Page 11, line 239-247; Page 13, line 293-295): (1) First, the shape of a stent can be designed regarding the CT and bronchoscopy measures; second, a computer-aided design program is employed to construct 3D model; then a construction file containing the information of this model is generated that can be transferred to the printer; in the next step, an original customized stent is produced with the stereolithography printers; following various surface treatments including grinding, polishing, dipping in solvents or liquid polymers, and sterilization, a ultimate 3D-engineered personalized airway stent is manufactured and can be applied rapidly in clinical work (see Page 11, line 239-247). (2) As prospective as this technique may be, 3D-printed stents 3%

were seldom deployed all over the world, which might be interpreted by the high costs involved and the limited clinical experience (see Page 13, line 293-295).
Special thanks to you for your comments.

References to use or refer to :-

1. Mathew R, Hibare K, Dalar L, Roy WE. Tracheobronchial stent sizing and deployment practices airway stenting practices around the world: a survey study. J Thorac Dis. 2020;12(10):5495-5504. doi:10.21037/jtd-20-2080

2.Dutau H, Breen D, Bugalho A, et al. Current Practice of Airway Stenting in the Adult Population in Europe: A Survey of the European Association of Bronchology and Interventional Pulmonology (EABIP). Respiration 2018;95:44-54.

3. Freitag L, Gördes M, Zarogoulidis P, et al. Towards Individualized Tracheobronchial Stents: Technical, Practical and Legal Considerations. Respiration 2017;94:442-56.

4. Guibert N, Didier A, Moreno B, et al. Treatment of Post-transplant Complex Airway Stenosis with a Three-Dimensional, Computer-assisted Customized Airway Stent. Am J Respir Crit Care Med 2017;195:e31-3.

Reviewer B
Authors described the current progress of airway stents. They briefly mentioned characteristics of each stent. This manuscript was well written.

I'd like to give some minor comments (line - comment)
25; 210-211 – Authors described that future direction of stent development is 3D printing. But I think that a combination of 3D-printing method and biodegradable material is a future direction of airway stent. How do you think about on this?
Reply 1: We are in entire agreement with Reviewer.
Changes in the text: We have modified our text as advised (See Page 14, line 305-310): 3D-printed airway stents, as the vertex of scientific and technological progress, open up a new way to resolve the therapeutic impasses. Regardless of how perfect 3D-printed stent is, it is still a foreign body and side effects seem inevitable. Therefore, a combination of 3D-printing method and biodegradable material may present a promising avenue for future treatments of airway stenosis.

77 – regarding covered stent: There are many kinds of covered stent. Actually, the difference is covering materials. It would be nice if you could describe various covering materials currently using (PTFE, silicone….etc)
Reply 2: We have made supplement according to the Reviewer's comments.
Changes in the text: We added some data (see Page 4, line 89-91): Polytetrafluoroethylene, silicone, and polyurethane, as the covering materials, endow covered stents with the additional advantages of minimizing tissue ingrowth and being deployed more easily.

79 – dilating stenosis --> Do you mean "rupture"?

Reply 3: We are very sory for our vague expression. We mean “restenosis”.

Changes in the text: We have modified our text (See Page 4, line 92): “dilating stenosis” --> “restenosis”

89 – metallic stents had a higher total effective rate and lower incidence rate of complications compared with --> Please describe the details of the study in detail (What was the traditional stent used as a control? ; what were the complications and rate? etc). It's in Chinese, so I can't understand the contents.

Reply 4: We are very sory for our vague expression and have made supplement and modification according to the Reviewer’s comments.

Changes in the text: We added some data (see Page 5, line 111-117): A total of 42 patients with airway stenosis were randomly divided into the experimental group (SEMS based on nano-technology surface modification) and the control group (Ni-Ti memory alloy stents), with 21 patients in each group. Results revealed that in contrast to the control group, the lumen diameter of the airway stenosis, FVC (forced vital capacity) and FEV1 (forced expiratory volume in one second) levels in the experimental group was higher, and the incidence rate of complications significantly lower (9.52% vs. 19.05%, $P<0.05$).

172 – “class”--> classic

Reply 5: We are very sory for our incorrect writing and have made modification according to the Reviewer’s comments.

Changes in the text: We have modified our text (See Page 10, line 221): “class” --> “classic”

175 -179 – please show the detailed data [survival duration etc.]

Reply 6: We have made supplement according to the Reviewer’s comments.

Changes in the text: We added some data (see Page 10, line 224-229): The incidence of complications after stenting was found to be equal in both groups, while the RBMS group had a longer median survival compared with the CBMS group, with statistical significance (170 days vs. 123 days, $P<0.05$). Recently, a meta-analysis indicated that radioactive stents placement had a lower stent restenosis rate (13.7% vs. 37.8%, $P<0.00001$), higher 3-month survival rate (71.9% vs. 52.7%, $P=0.03$), and increased overall survival (OS) ($P<0.0001$) in comparison with normal stents placement when used to treat malignant airway stenosis, and the difference was statistically-significant

190-205 – recent important papers on 3D printing assoicated airway stent were omitted like follows. These articles should be cited.

Reply 7: We are very sory for our negligence and have cited these articles according to the Reviewer’s comments.

Changes in the text: We added some data (see Page 11-12, line 250-264): Guibert and colleagues reported the first 3D-printed application in airway stenting for a complex post-transplant airway that could not be managed by a conventional airway stent. Immediate and significant improvements in dyspnea, quality of life and pulmonary function were

observed after the operation. They then expanded the utilization of computer-aided design in other highly complex situations and obtained promising proof-of-concept outcomes that would contribute to further research on this new technique. Miyazaki et al. described their experience with a 3D printed airway model in a stenosis of the intermediate bronchus after right single-lung transplantation. A Y-shaped airway stent with the fabricated orifice to ventilate the upper lobe was accurately modified on the basis of 3D-printed technology. After the easy and successful insertion, the patient's status improved. Gildea et al. used a similar method (application of a patient-specific silicone airway stent designed from a 3D printed mold) to cope with complex airway stenosis caused by granulomatosis polyangiitis in two patients, bringing about a durable improvement of symptoms over 1-year follow-up
Special thanks to you for your comments.

- 3D-engineered personalized airway stent (custom GINA stent): introduction and performance evaluation in pigs, Respiratory Medicine and Research, 2021, 100867, https://doi.org/10.1016/j.resmer.2021.100867. (https://www.sciencedirect.com/science/article/pii/S2590041221000568)
- Application of 3D Printing for Patient-Specific Silicone Stents: 1-Year Follow-Up on 2 Patients. Respiration, 2018. 96(5): p. 488-494.
- Treatment of complex airway stenoses using patient-specific 3D-engineered stents: a proof-of-concept study. Thorax, 2019. 74(8): p. 810-813.
- Treatment of Post-transplant Complex Airway Stenosis with a Three-Dimensional, Computer-assisted Customized Airway Stent. Am J Respir Crit Care Med, 2017. 195(7): p. e31-e33.

Reviewer C

The work describe the recent advancements in the airway stenting technique. Silicone, metallic, hybrid and drug eluting stents are reviewed. Then, 3D printable stents for the upper airways are introduced and described as emerging discipline.

GENERAL COMMENTS

The work in the principle is interesting and makes a contribution. However, in my opinion is too short (only 40 references cites). A deep insight in the airways stent is expected, as this is a review. For this reason, in my opinion, a considerable revision is necessary.

In general, it is necessary to include more background and additional studies to support the review. Also, with the topic discussed by the authors, the 3D printed airways should also be improved and discussed.

Reply 1: It is really true as Reviewer suggests. We have made supplement according to the Reviewer's comments and include more background and additional studies to support the review. Additionally, 3D printed airways have also be improved and discussed.

Changes in the text: We added some data (see Page 2, line 39-41; Page 4, line 89-91; Page 9, line 194-196; Page 11, line 239-247; Page 11-12, line 250-264; Page 13-14, line 286-297; Page 14, line 302-310)

SPECIFIC COMMENTS

The 3D printable stents must include much more papers that have been published in recent years. The group of Guibert et al have extensively worked in the field and will provide additional important references for printable stents.
The discussion of the 3D printed airways, must be improved and additional studies must be considered (Malik et al, Guibert et al.).
Additional groups and papers that should be included and discussed are Melgoza et al, Dutau et al, Myiazaki et al, Gildea et al, Debiane et al, Schopf et al.).
Reply 2: We are very sory for our negligence and have referred to these articles according to the Reviewer's comments.
Changes in the text: We added some data (see Page 11, line 239-247; Page 11-12, line 250-264; Page 13-14, line 286-297; Page 14, line 302-310)

In the line 152, the commercial stent used in the work of Rodriguez-Zapater et al should be cited (ELLA stent).
Reply 3: We are very sory for our negligence and have cited this article according to the Reviewer's comments.
Changes in the text: We have modified our text (see Page 9, line 197-199)
Special thanks to you for your comments.

Reviewer D
Major Comments
The authors systematically reviewed progress in airway stents. This manuscript reports on silicone stents, metallic stents, drug-eluting stents, biodegradable stents, radioactive stents and three-dimensional printed stents. This review promotes the diffusion of knowledge about airway stents.

However, some of the work is a repetition of work that has been performed by other authors. Recently, progress in airway stent is reviewed by Nicolas Guibert et al.
(Airway stenting: Technological advancements and its role in interventional pulmonology: https://doi.org/10.1111/resp.13801).

Although radioactive stent and GINA stent are still in the animal experimental stage, the authors have made a good attempt at review these "novel" stents. My suggestion is to give more importance to new findings that are not reported in other review article.
Reply 1: It is really true as Reviewer suggests. We have made supplement and modification according to the Reviewer's comments and include new findings that are not reported in other review article.
Changes in the text: We added some data (see Page 4, line 89-100; Page 9, line 194-196; Page 11, line 239-247; Page 11-12, line 250-264; Page 13-14, line 286-297; Page 14, line 302-310)

Minor Comments
The shape of the stent is mainly explained in the text, and the figure is few. For an

inexperienced person, it may be difficult to imagine the shape without figure. You should include figures of novel stent.
Reply 2: We are in entire agreement with Reviewer. We have realized this before we performed the review. Two figures of novel stents were included in this article, however, we failed to acquire more figures because most of novel stents mainly focused on animal models, are still in their infancy, and are not authorized to use clinically.

The FDA warning on metalic stents should be further enlightened in this field. It is very good to have this point mentioned in the review.

In the selection of airway stent, necessity of general anesthesia is an important consideration. The authors describe that insertion of silicone stents requires a rigid bronchoscopy under general anesthesia. In my opinion, general anesthesia is essential for insertion of rigid bronchoscope. Soft bronchoscope can be inserted under local anesthesia or sedation. So, I recommend clarifying whether rigid bronchoscope is needed or not in each stent.
Reply 3: Considering the Reviewer's suggestion, we have made supplement in our article.
Changes in the text: We added some data (see Table 1 / Page 15-16, line 318-319)
Special thanks to you for your comments.

Reviewer E
The authors summarized novel airway stents in the papar. It was a fairly thorough literature review on newer types of stents, i.e. drug-eluting stents, radioactive stents, biodegradable stents and 3D printed stents
However, I would recommend to change the structure of the paper to make it more reader-friendly, as not every reader is an expert on airway stents. The paper listed a lot of studies, however, did not send a clear message on which type of stent had what kind of advantages over the others.
Reply 1: Special thanks to you for your detailed, valuable and helpful suggestions. We have made supplement and modification except the 1st and 2nd comment of major points. This paper aimed to pinpoint novel stents had what kind of advantages over thetraditional stents. Therefore, we did not change the primary structure of the paper.

Major points
1. For more commonly used stent, such as uncovered SEMS, covered SEMS and silicone stents, I would recommend starting by discussing the common indications of and complications from such stents and then move onto newer development in the field.
Reply 2: Please refer to "Reply 1".

2. The utilization of airway stents differs a lot in benign airway diseases and malignancies. The choice of stents are different; the complication profiles, i.e. migration rate, mucus plugging, granulation tissue formation, are different too. I would recommend to discuss benign and malignant diseases separately in each session.
Reply 3: Please refer to "Reply 1".

3. For uncovered SEMS, it was mentioned in the introduction that there was a black box warning from FDA for its use in benign airway disease. I think it would be better discussed in the session of SEMS. Following that, the authors could discuss some exceptions to the rules: such as the short term use of uncovered SEMS in TBM patients (Ernst, A., Majid, A., Feller-Kopman, D., Guerrero, J., Boiselle, P., Loring, S. H., ... & Ashiku, S. (2007). Airway stabilization with silicone stents for treating adult tracheobronchomalacia: a prospective observational study. Chest, 132(2), 609-616.). Also, in lung transplant patient population, uncovered metal stents can be used as short-term dilating stents (Ma, K. C., Li, M., Haas, A. R., Lanfranco, A. R., Moon, E. K., & DiBardino, D. M. (2020). Efficacy and safety of airway stenting to treat anastomotic complications after lung transplant: a cohort study. Journal of Thoracic Disease, 12(7), 3539.)

Reply 4: It is really true as Reviewer suggests that we should discuss some exceptions to the rules. However, it is a pity that above-mentioned two articles are related to silicone stents, and thus we did not refer to and cite these two literature.

4. For covered SEMS, the authors summarized its advantages over uncovered SEMS and silicone stents, however, could discuss a bit further in the first paragraph. For instance, less epithelialization compared with uncovered SEMS, hence easier to remove. Easier to deploy compared with silicone stents. I would recommend to give a summary then discuss in details in the following paragraphs.

Reply 5: We have made supplement according to the Reviewer's comments.

Changes in the text: We added some data (see Page 2, line 39-41): Of note, uncovered metallic stents prefer the theoretical benefit of neo-epithelialization that is instrumental in normal mucociliary clearance of secretion.

5. For covered SEMS, if the authors could also discuss about Y stents, that will be great. i.e. Sökücü, S. N., Özdemir, C., Tural Önür, S., Dalar, L., & Altın, S. (2020). Comparison of silicon and metallic bifurcated stents in patients with malignant airway lesions. The clinical respiratory journal, 14(3), 198-204. Covered Y SEMS is currently not approved in the US but has been reported elsewhere.

Reply 6: We made supplement and cited relative literature according to the Reviewer's comments.

Changes in the text: We added some data (see Page 4, line 93-100): Covered self-expanding Y-shaped stents have been introduced as a way to manage complex airway disease especially fistulization near the tracheal carina. Nevertheless, such stents have not been approved so far in the United States. Interestingly, in a latest retrospective analysis comparing long-term survival and complications amongst patients treated for malignant airway stenosis or tracheoesophageal fistula with Y-shaped silicon stents or covered self-expanding Y-stents, results indicated that symptom palliation, insertion safety, survival or complication rate were also found to be not different for the two types of stent

6. For covered SEMS, the authors mentioned its use in benign airway disease. The level of novelty is not comparable to the other stents such as drug-eluting or radioactive stents, as it currently has been frequently placed in patients with benign airway disease. I would

recommend the authors to be clearer about the novelty of those studies. Or the authors could consider to condense the paragraph.
Reply 7: We have made supplement and modification according to the Reviewer's comments.
Changes in the text: We added some data (see Page 11, line 239-247; Page 11-12, line 250-264; Page 13-14, line 286-297; Page 14, line 302-310)

7. For silicone stents, it would be helpful for the reader to know its general indications, the advantages (i.e., it is much more cost-effective than the SEMSs) and disadvantages, so that the readers understand why novel stents are needed. It is also worth to mention that there are different types of silicone stents, i.e. straight, hourglass. Each type has its own advantages and complication profile.
Reply 8: We are in entire agreement with Reviewer. A detailed description was previously given in our article (see Page 2-3, line 51-61): The clinical application of silicone stents has evolved memorably over the last few decades, beginning with the silicone T-tube designed in 1965 by Montgomery, followed by the Dumon stent, which remained safe and reliable for patients with both benign and cancer-related airway stenosis at any given moment. It should be noted that there are certain limitations with silicone stents recognized as follows: (a) Insertion of silicone stents requires a rigid bronchoscopy under general anesthesia; (b) the stent-related complications, such as migration, granuloma formation, mucus plugging, infections and restenosis, must not be neglected. Hence, over the years, various novel stents have been designed to present a promising procedure of solving the limitations that "classic" silicone and metallic stents have. Table 1 shows the details of the individual stents.

Minor points
1. In the session of 'covered stents', the authors mentioned a study using AERO stents. AERO stents are 'classic' covered SEMS. I was not quite sure what the novelty to this study is. If the authors could specify, that will be great. If no other novelty to it, I would recommend to quote this study in summary as I recommended in 'major points'.
Reply 9: Considering the Reviewer's suggestion, we would like to specify as follows. The AERO stent (Merit Medical Systems, South Jordan, UT, USA), a relatively new, fully covered SEMS , was designed to possess the advantages of both silicone stents and SEMS, and was approved in Japan in 2014. AERO stent in a small number of cases, only a few original articles have been published, and thus we cited this article to pinpoint the safety and efficacy of this relatively new AERO stent for treating malignant airway disorders.

2. For drug-eluting stents, it will be helpful to point out that the literature mainly focused on animal studies.
Reply 10: We have made supplement that "point out that the literature mainly focused on animal studies" according to the Reviewer's comments.
Changes in the text: We added some data (see Page 10, line 211-212): However, the literature mainly focused on animal trials and the sample size of related studies is small, and thus the significance of the results in clinical setting remains to be determined.

3. For 3D printed stents, the authors mentioned custom made T tubes. Since that's a slightly

different entity, I would recommend to discuss it separately.

Reply 11: Considering the Reviewer's suggestion, herein, we would like to specify as follows. Montgomery T-tube is one of the most common silicone stents. In this article, we have made supplement that how is stent customization onsite or by 3D printing being used (see Page 11, line 239-247), and on a basis of above-mentioned 3D-printed procedure, a custom-designed Montgomery T-tube was designed. Therefore, we did not make a additional and separate discussion on custom made T tubes.