Peer Review File

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Reviewer A

Comment 1: The abstract stands alone and is able to be understood without reading the entire manuscript. The introduction lays out the rationale for the study and explains its goals clearly. The term "better" in the conclusions is problematic in that is implies direct positive relationship to a specific outcome.

Reply 1: Thank you for your comments. The flexibility of stents can be evaluated by measurement of bending force and spring-back force. Lower bending force and spring-back force of stent indicates greater flexibility (1-3). We have revised the statement into "The segmented metallic Y-shaped airway stent had greater flexibility compared with wholly knitted stent in an ex vivo setting".

Changes in the text: We have modified our text. Please see page 4, line 88-89.

References:

(1) Zou Q, Xue W, Lin J, et al. Mechanical characteristics of novel polyester/NiTi wires braided composite stent for the medical application. RESULTS PHYS 2016;6:440-6.

(2) Hirdes MM, Vleggaar FP, de Beule M, et al. In vitro evaluation of the radial and axial force of self-expanding esophageal stents. ENDOSCOPY 2013;45:997-1005.

(3) Dyet JF, Watts WG, Ettles DF, et al. Mechanical properties of metallic stents: how do these properties influence the choice of stent for specific lesions? Cardiovasc Intervent Radiol 2000;23:47-54.

Comment 2: Methodology; the methodology does not provide sufficient detail that the study could be repeated. There is no clear description of the process of linking/joining the 3D portion of the stent to the knitted stents.

Reply 2: Thank you for your comments. We have added the details of stent manufacture. The stent was customized under the guidance of 3D printed airway mold. Firstly, the raw data of airway was obtained through CT scanning and 3D CT reconstruction was performed, and a 1:1 scale airway mold was printed by a 3D printer. Secondly, under the guidance of the 3D airway mold, metallic stents were woven using the airway mold as a template. The length, diameter, and angle of the stent was determined by the airway mold.

Changes in the text: We have added the details in our text. Please see page 9, line 185-199.

Comment 3: It will be curious to know why the decision was made to fit a Y stent into the LMS when a simple tubular airway stent can just fit the same in the example shown in the figure. How was the sizing of the stent done? (Example is Figure 1C)

Reply 3: Thank you for your comments. In this study, covered metallic stent was used to seal

the fistula involving the carina or distal bronchi. Tubular covered airway stent implanted into left main bronchus is prone to stent migration and obstruction of opening of lobar bronchus. Therefore, Y-shaped stent was used. The fistula was sealed and the opening of lobar bronchus was kept patent. Several previous studies have reported application of small Y-shaped stent for sealing fistula in right or left main bronchus (1-2).

The size of stent was determined according to the location and size of fistula, and the length and diameter of airway, with the aid of 3D airway mold. The design of stent was to guarantee the sealing of fistula without occluding the opening of bronchus.

Changes in the text: The reason why Y-shaped stent was used has been stated in page 16, line 339-342. The determination of stent size has been stated in page 9, line 194-199.

References:

(1) Bi Y, Li J, Wu G, et al. A small bifurcated self-expanding metallic stent for malignant bronchial fistula or severe stenosis around the upper left carina. ACTA RADIOL 2019:1286610069.

(2) Bi Y, Li J, Yu Z, et al. Metallic small y stent placement at primary right carina for bronchial disease. BMC PULM MED 2018;18.

Comment 4: The comment on tracheal carinal angle (its change during respiratory movement and malignant tumors around the carina) and its use in 3D printing for the Y stent is commendable as this may play a major factor in pressure between the stent and the bronchial wall, leading to patient discomfort and stent related complications. Clearly, this is only one aspect of all the possible geometric alterations 3D printing may address even at that location.

Reply 4: Thank you for your comments. With the 3D printed airway mold, the stent was customized to match the anatomical features of airway of specific patients. The diameter, length and angulation of stent were matched to airway anatomy. The fenestration of the stent

can match the opening of the bronchus with the aid of 3D printing.

Changes in the text: We have revised our text to elucidate the role of 3D printing. Please see page 9, line 186-199.

Comment 5: Flexibility of the Y stent as defined by the lower bending force and spring back force compared to the wholly knitted stent may be crucial in the study as this addressed airway fit and reduced airway irritation. However, it begs the question how ex vivo study was translated into in vivo testing in terms of flexibility. (Is this a typo in Figure 2A-B?).

Reply 5: Thank you for your comments. The flexibility of stent is defined as the ease of bending and deformation of the stent. In recent years, the flexibility of stent has gradually attracted attention from researchers. The flexibility of vascular stents and non-vascular stents such as biliary stents and esophageal stents has been investigated (1-5). The flexibility of stents can be evaluated by the measurement of bending force and spring-back force. Previous studies have reported that adverse events after stent implantation were related to poor flexibility and high spring-back force of the stent in the field of biliary stent and coronary stent (4, 5). The same rationale applies to Y-shaped airway stent. For Y-shaped airway stent, smaller bending force and spring-back force mean higher stent flexibility and stronger ability to adapt to dynamic changes of bronchus. After the Y-shaped airway stent is implanted, the angle of the stent may be inconsistent with the tracheal carina angle during deep inhalation and exhalation or when the airway is compressed by a tumor, and the spring-back force of the stent will act on the wall of the bronchus. The mechanical stimulation to the airway wall after airway stenting is an important factor leading to complications such as granulation hyperplasia, airway wall injury and patient intolerance. Therefore, the stent should have good flexibility to reduce the mechanical stimulation on the airway wall.

However, the quantitative characterization of flexibility of Y-shaped airway stent is complex and currently lacking. Furthermore, the comparison of flexibility of the novel stent and conventional wholly knitted stent has not been reported. Based on the previous studies of stent flexibility, we evaluated the flexibility of Y-shaped stent by the measurement of bending force and spring-back force.

Changes in the text: We have added a paragraph to introduce the definition and significance of stent flexibility. Please see page 7, line 134-148.

References:

(1) Zou Q, Xue W, Lin J, et al. Mechanical characteristics of novel polyester/NiTi wires braided composite stent for the medical application. RESULTS PHYS 2016;6:440-6.

(2) Hirdes MM, Vleggaar FP, de Beule M, et al. In vitro evaluation of the radial and axial force of self-expanding esophageal stents. ENDOSCOPY 2013;45:997-1005.

(3) Dyet JF, Watts WG, Ettles DF, et al. Mechanical properties of metallic stents: how do these properties influence the choice of stent for specific lesions? Cardiovasc

Intervent Radiol 2000;23:47-54.

(4) Gyongyosi M, Yang P, Khorsand A, et al. Longitudinal straightening effect of stents is an additional predictor for major adverse cardiac events. Austrian Wiktor Stent Study Group and European Paragon Stent Investigators. J AM COLL CARDIOL 2000;35:1580-9.

(5) Isayama H, Nakai Y, Toyokawa Y, et al. Measurement of radial and axial forces of biliary self-expandable metallic stents. GASTROINTEST ENDOSC 2009;70:37-44.

Comment 6: The connection of the three independent parts and the material used, as well as the novelty of quantitative characterization of the Y stent flexibility is impressive. Again the connection process is not well described- is this proprietary?

Reply 6: Thank you for your comments. The connecting part of the stent was woven using polytetrafluoroethylene (PTFE) thread in a mesh manner. The connecting part linked the end of main stem and branches to form "Y-shaped" stent. One of the authors of this article has a patent of the segmented stent and this has been stated in the conflicts of interest.

Changes in the text: We have added the details of stent manufacture. Please see page 9, line 190-192.

Comment 7: The standardization and statistical analysis are all appropriate. The STROBE criteria used is very commendable. For the exclusion criteria, it will be interesting to know why patients with airway stenosis were excluded from the patient population. Could be a critical challenge to this concept.

Reply 7: Thank you for your comments. Both airway stenosis and fistula can be treated with the airway stent. The aim of this study was to evaluate the feasibility of the treatment of aerodigestive fistulas involving the carina and distal bronchi with the novel stent. Therefore, we excluded patients with airway stenosis in the retrospective analysis.

Changes in the text: The inclusion and exclusion criteria have been stated. Please see page 6, line 170-174.

Comment 8:

Results:

It is understandable that the quantitative characterization of a Y stent is a first of its kind but this was very well compared to the flexibility of the segmented stent with a wholly knitted stent.

However, it will be useful to contextualize your outcomes, i.e. are the outcomes better

or worse to other series done. There is also no comparison group for stent related outcomes. This is also a small sample size but the feasibility was not addressed, especially in the few studies that addressed the use of metallic stents customized with the assistance of 3D printing technology.

Reply 8: Thank you for your comments. We have contextualized our outcomes in the discussion section and compared the outcomes with previous studies as suggested.

Changes in the text: We have revised our text as suggested. Please see page 16, line 343-345, page 17, line 353-358, page 19, line 397-400, 405-409.

Comment 9:

General comments:

This is an unusual sub-group to study. Certainly one of the more rare events that gets a stent in the airway and even more rare without stenosis or airway tumor involvement. This group seems to have a higher proportion of surgical cases that makes sense but represents perhaps a high number of surgical complications? Please comment. We would expect that these post-surgical patients to heal and do better than those patients with malignant aerodigestive fistulas.

Reply 9: Thank you for your comments. The indications of airway stenting include airway stenosis and fistula caused by benign or malignant disease. The aim of this retrospective study was to evaluate the feasibility of the treatment of aerodigestive fistulas involving the carina and distal bronchi with the novel stent. Therefore, we excluded patients with airway stenosis in the retrospective analysis.

Our institute is one of the regional medical centers. Among the 16 patients with aerodigestive fistula after esophagectomy, 4 patients underwent esophagectomy in our institute and the other patients underwent esophagectomy in other hospitals. Therefore, more patients with fistula after esophagectomy in this study does not mean higher surgical complications.

In this study, 9 of the 16 patients with fistula after esophagectomy achieved complete healing and none of the 10 malignant fistula achieved healing due to invasion of malignant tumor.

Changes in the text: The healing of fistula has been stated in the result and discussion section. Please see page 13, line 283-286 and page 17, line 353-355.

Reviewer B

In this study, the authors reviewed the outcome of 26 patients with aerodigestive fistula in whom a novel stent (covered metallic segmented Y- Y-shaped airway stent customized with 3D printing) was placed. Stent deployment was successful in all patients, Complete sealing of the fistula with no aspiration symptoms occurred in 21 (81%) of patients and the KPS score improved for the whole group from 60 to 70 ($P<0.001$). Besides, there was complete healing of the fistula in 9 patients after removal of the stent. In vitro flexibility test of the novel segmented stent compared to the conventional wholly knitted stent showed lower bending force and spring back force at different compression levels.

Median survival was 260 days with an overall reported mortality of 16 patients (61%) that were not attributed to the stent.

Complications occurred in 9 patients, (5 sputum retention, Granulation tissue in 2 patients, stent migration in 1 patient, intolerance requiring stent removal in 1 patient).

The study is interesting but will need major revision before publication:

a- Stent procedure:

Comment 1:

- Please provide a detailed description of the procedure with step by step illustration/picture of the insertion process, guidewires, loading system, etc.

Reply 1: Thank you for your comments. We have added a figure (Fig. 2) to illustrate the process of stenting procedure as suggested.

Changes in the text: The figure legend has been added. Please page 28, line 608-613.

Comment 2:

- Was rigid bronchoscopy used in the process

Reply 2: Thank you for your comments. Rigid bronchoscopy was not used in the process. Flexible bronchoscopy was used. We have revised the description of bronchoscopy.

Changes in the text: We used “flexible bronchoscopy/ bronchoscopic” instead in the stenting procedure section. Please see page 10, line 210 and line 214.

Comment 3:

- Provide a detailed description of the removal process of the stent

Reply 3: Thank you for your comments. We have added detailed description of stent removal as suggested.

Changes in the text: The description of stent removal has been added. Please see page 11, line 225-227.

b- Follow up:

Comment 4:

- How long were the patients followed? Please add the mean/median and range of duration of clinical follow up for all the patients

Reply 4: Thank you for your comments. The follow-up time of patients has been stated in the results section.

Changes in the text: Please see page 14, line 294.

Comment 5:

- Was an esophagogram performed to detect leak; if so please report the results

Reply 5: Thank you for your comments. All patients underwent esophagography after stent implantation, which has been stated in the follow-up section (page 10, line 220). The results of esophagography have been added in the results section.

Changes in the text: The results of esophagography have been added in the results section. Please see page 13, line 281-283.

c- Table 1:

Comment 6:

- Please add % to each report

Reply 6: Thank you for your comments. We have revised the table as suggested.

Changes in the text: Please see Table 1.

d- Outcome and follow up

Comment 7:

- Please revise and clarify the statement:" Airway stenting was performed at a median of 30 (IQR, 18.5-55.5) days and 117 (IQR, 35-240) days after diagnosis of fistulas for

benign aerodigestive fistulas with and without healing, respectively (P=0.017)."

Reply 7: Thank you for your comments. We have revised and clarified the statement as suggested.

Changes in the text: The statement has been revised. Please see page 14, line 288-291.

e- Flexibility of the stents:

Comment 8:

- Please place a statement under introduction about the optimal stent flexibility; A higher stent radial force can lead to mucosal ischemia and enlargement of the fistula, thus a stent that conforms to the airway anatomy with lower radial force may be better suited for aerodigestive fistula but if this stent has lower bending force it may not be optimal for removing obstruction related to external compression of the airway by a tumor.

Reply 8: Thank you for your comments. Radial force and flexibility are two important biomechanical properties of the stent. The radial force determines the ability of stent to maintain narrow lumens and external compression. The flexibility of stent is defined as the ease of bending and deformation of the stent and it determines the ability of the stent to adapt to changes in the shape of the lumen (1-5). Previous studies have reported that adverse events after stent implantation were related to poor flexibility of the stent in the field of biliary stent and coronary stent (4, 5). As regards Y-shaped stent, research on the quantitative characterization of flexibility is currently lacking, and the optimal flexibility of stent remains unclear.

Changes in the text: We have placed a statement in the introduction section. Please see page 7, line 134-line 154.

References:

(1) Zou Q, Xue W, Lin J, et al. Mechanical characteristics of novel polyester/NiTi wires braided composite stent for the medical application. RESULTS PHYS 2016;6:440-6.

(2) Hirdes MM, Vleggaar FP, de Beule M, et al. In vitro evaluation of the radial and axial force of self-expanding esophageal stents. ENDOSCOPY 2013;45:997-1005.

(3) Dyet JF, Watts WG, Ettles DF, et al. Mechanical properties of metallic stents: how do these properties influence the choice of stent for specific lesions? Cardiovasc Intervent Radiol 2000;23:47-54.

(4) Gyongyosi M, Yang P, Khorsand A, et al. Longitudinal straightening effect of stents is an additional predictor for major adverse cardiac events. Austrian Wiktor Stent Study Group and European Paragon Stent Investigators. J AM COLL CARDIOL 2000;35:1580-9.

(5) Isayama H, Nakai Y, Toyokawa Y, et al. Measurement of radial and axial forces of biliary self-expandable metallic stents. GASTROINTEST ENDOSC 2009;70:37-44.

f- Discussion:

Comment 9:

- Please compare the outcome of the novel stent to previous data published in the literature that discussed, rate of clinical improvement, aspiration, cure, recurrence, mortality, and complications.

Reply 9: Thank you for your comments. We have compared clinical improvement, cure rate and complications with previous data published in the literature in the discussion section. It is difficult to compare some outcomes of this study with those in previous studies given the differences in baseline characteristics of patient and types of stent.

Changes in the text: We have compared the outcomes with previous data. Please see page 16, line 343-345, page 17, line 353-358, page 19, line 397-400 and line 405-409.

Minor issue:

Comment 10:

g- The study will need English proofreading, the following are an example of improvements:

1- Page 4 line 72: change to:" The mortality rate of aerodigestive fistulas is high due to lethal infection and challenging treatment"

2- Page 4 line 73: change to: "and the outcome of conservative treatments is poor"

3- Page 4 line 77: remove:" which may not be completely occluded by tubular airway stents"

4- Page 6 line 127: remove:" Patient's basic anesthesia monitoring was continuously observed during the procedure."

5- Page 10 Line 215: replace effect with outcome

6- Page 10 Line 218: remove:" and it is very difficult for such patients to achieve healing because of tumor invasion"

7- Page 10 line 220: revise to: Patients with benign aerodigestive fistulas after esophagectomy have longer expected survival and thus, the aim of their treatment is complete healing of the fistula.

8- Page 11 line 223: remove:" Such stents could not only prevent the formation of granulation tissue but also suppress the ingrowth of tumors in fistulas caused by

malignant tumors. Therefore, they could be used for both malignant and benign airway fistula”

9- Page 11 line 242: remove:” and in patients with malignant tumors around the carina”

Reply 10: Thank you for your comments. We have tried our best to revise the manuscript as you suggested. We will polish the language by AME editing service to improve readability of the manuscript later.

Changes in the text: Please see page 6, line 116; page 6, line 118; page 6, line 124-125; page 10, line 209-210; page 15, line 322; page 15, line 325-326; page 15, line 328-330; page 16, line 332-336.