Animal study of a newly designed metal airway brachytherapy stent loaded with radioactive $^{125}$I seeds

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Abstract

Aim To evaluate dynamic tissue changes after airway stenting (AS) with a newly designed metal brachytherapy stent (BS) loaded with radioactive $^{125}$I seeds in normal rabbits.

Methods Forty-five normal New Zealand white rabbits were divided into 3 groups (group A: stent without seeds; group B: stent with 0.4 mCi active seeds; group C: stent with 0.8 mCi active seeds) and underwent AS under C-arm guidance. Then, five rabbits were killed from each group at 2, 4, and 8 weeks for further examination. Laboratory tests (including routine blood tests, liver function, kidney function, and electrolytes), gross observations, and tissue changes of Masson/hematoxylin–eosin staining, plus immunohistochemistry of α-SMA, NOX4, and TGF-β were performed at each time point.

Results All animals underwent AS successfully without procedure-related death, but one animal died at 6 weeks due to severe pulmonary infection in group C. Apart from a transient increase in white blood cells ($P < 0.05$) and a gradual increase in ROS levels ($P < 0.05$), other blood test items showed no significant changes ($P > 0.05$). The brachytherapy injury score increased with irradiation dose accumulation ($P < 0.05$), but tissue hyperplasia at the stent end in group C was less severe than that in groups A and B ($P < 0.05$). Airway lateral fibrosis was observed in all groups by histopathologic analysis; however, fibrosis in group C was more severe than that in groups A and B ($P < 0.05$).

Conclusion The brachytherapy injury score increased with irradiation dose accumulation, while granulation tissue hyperplasia at the stent end was inhibited by $^{125}$I brachytherapy within 8 weeks.

Keywords Airway stent · $^{125}$Iodine · Brachytherapy · Animal study

Abbreviations

AS Airway stenting
BS Brachytherapy stent

Introduction

Airway stenting (AS) is an important strategy to alleviate severe dyspnea caused by malignant tracheal stenosis; however, the proliferation of tumors or granulation tissue often leads to stent restenosis, with an incidence of 5–45% within 3 months (Guibert et al. 2020; Huang et al. 2018).

It is well known that external beam radiotherapy (EBRT) can significantly inhibit stent intimal hyperplasia and tumor growth, but unfortunately, 40% of patients cannot tolerate the associated complications (Rochet et al. 2012). $^{125}$I seed brachytherapy is an effective local regimen to inhibit normal cell proliferation and malignant tumors to a certain extent to prevent excessive proliferation of granulation tissue and has been applied to solid tumor treatment for many years, such prostate cancer (Nakai et al. 2020), lung cancer (Zhao et al. 2020), liver cancer (Zeng et al. 2019), and bone metastasis (Yao et al. 2021). To solve the above problems, Chinese scholars have combined radioactive $^{125}$I seeds with conventional metal airway stents to form a brachytherapy stent (BS) inspired by esophageal $^{125}$I brachytherapy stents (Qin et al. 2019) and biliary $^{125}$I brachytherapy stents (Zhou et al. 2019), which have been reported in a previous clinical study. Although a pilot study using this newly designed BS on a small sample showed its feasibility and effectiveness in patients with malignant airway obstruction (Wang et al. 2018), few studies have focused on normal tracheal dynamic
tissue changes after stenting with such newly designed metal BS. This study seeks to understand the effects of BS on the tracheal wall of normal rabbits to provide a theoretical basis for the development of new-generation stents in the future.

**Materials and methods**

**BS and grouping**

A metal self-expandable airway stent (10 mm × 20 mm) was made of nitinol wire of 0.22 mm thickness (Micro-Tech Co. Ltd., Nanjing, China). Four nitinol sheaths were attached on the stent surface to load $^{125}$I seeds (Fig. 1). The size of single $^{125}$I seeds (diameter × length) was 0.8 × 4.8 mm with a half-life of 59.6 days, and the seeds were made by Saide Biological Technology Co., Ltd., Tianjin, China. The seed released energies of 27.4–31.5 keV (γ-ray) and had an initial dose rate of 7.7 cGy/h with an irradiation distance of 17 mm. The Institutional Animal Care and Use Committee of the First Affiliated Hospital of Zhengzhou University approved this animal study (Zdyfy-2018–113). A BS loaded with four radioactive $^{125}$I seeds (Group A: 0 mCi/per seed, group B: 0.4 mCi/per seed, group C: 0.8 mCi/per seed) was tested in 45 normal New Zealand white rabbits (weight 2.5–3.0 kg, 15 animals in each group). All procedures were performed under C-arm guidance, and five rabbits from each group were killed at 2, 4, and 8 weeks for further examination.

**AS procedure**

After successful anesthesia (3% pentobarbital sodium (0.6 mL/kg) was injected intravenously), cerazine hydrochloride (0.3 mL/kg) was injected into the hip muscle 10 min before the operation. The animal was fixed in the supine position on a C-arm fluoroscopy table (Siemens Artis-zeego with flat detector C-arm CT function, Germany), and the C-arm was adjusted to the left anterior oblique position of 30°–40°. Under the guidance of X-ray fluoroscopy, a 5F KMP catheter (Cook, USA) and 0.035 inch guidewire (Cook, USA) were combined and inserted into the bronchus through the mouth. Along with the guidewire, an 8 F sheath (length 23 cm, Cook, USA) was advanced into the bronchus. The stents were inserted into the sheath and pushed into the airway using a small inner core of an 8 F sheath under real-time fluoroscopy (Fig. 1). Intraoperative C-arm CT was performed to confirm the stent position and expansion after removing the guidewire and sheath.

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Fig. 1  A The newly designed metal stent, radioactive $^{125}$I seeds (long arrow) and four nitinol sheaths on the stent surface to loaded with $^{125}$I seeds (short arrow); B 8 F sheath and stent without $^{125}$I; C–E The process of the airway stenting, along with the guidewire (C), an 8 F sheath was advanced into the bronchus (D) and then the stent were implanted into airway under fluoroscopy (E); F SPECT after brachy-therapy stent implantation (arrow); G–H granulation hyperplasia was serious at the upper stent end of group A shown on CT (arrow at figure G) and gross observation (arrow at figure H) at 8 weeks; I–J granulation hyperplasia was less than that of brachytherapy stent shown on CT (arrow at figure I) and gross observation (arrow at figure J) at 8 weeks.
Gross observation

All animals were fed as usual, and respiratory symptoms such as stridor, cough, and dyspnea were monitored every 3 days. Five animals in each group were killed after 2, 4, and 8 weeks. Tracheal tissue of the stent section was excised to observe the general trachea and the surrounding tissue morphology. In addition, it was necessary to observe the thickness of the tracheal wall and the degree of stenosis and to record granulation tissue proliferation at both stent ends.

SPECT, CT examination and brachytherapy dose

Single-photon emission computed tomography (SPECT) was performed to test the γ-ray distribution in vivo on Group B and C animals using the above anesthesia method within 3 days after stenting. CT examination was performed on all experimental animals before killing (Fig. 1). Considering that there was no local tumor modeling, to describe the cumulative γ-ray dose conveniently, 5 mm and 10 mm dose reference points were set beside the stent surface. $D_y = 34.6(\sum \Delta \phi_i) C0Teff \left[1 - e^{-(0.693/Teff) t}\right]$ ($\Delta \phi_i$ represents the constant absorbed dose, $\phi I$ represents the target absorption energy ($^{125}$I was 0.219), Teff is the physical half-life (59.6 days), and $C0$ is the radiation dose in tissues when $t = 0 \mu$Cl/g.

Serum biochemical and ROS level examination

Three milliliters of animal venous blood were collected to evaluate red blood cells (RBCs), white blood cells (WBCs), hemoglobin (Hg), aminotransferase (ALT), total bilirubin (TB), and creatinine (Cr) at 0, 1, 2, 4, and 8 weeks on an automatic biochemical analyzer. ROS levels in tissues and serum were assayed using enzyme-linked immunosorbent assay (ELISA).

Hematoxylin–eosin and Masson staining

Epithelial detachment, capillary dilatation/congestion, lymphocytic infiltration, neutrophil infiltration, submucosal glands, erythrocyte exudation and cartilage necrosis were evaluated according to histological score standards (Table 1). Fresh tracheal cross-sectional specimens were fixed with formalin and stained with hematoxylin–eosin (HE) at 2, 4, and 8 weeks. Masson staining was performed to further understand the extent of fibrosis. The peripheral diameter of the tracheal basement membrane (TBM) and total wall area (TWA) were measured by image analysis software (Pro Plus 6.0). [Masson (+) area/TBM] means were quantified and compared.

Immunohistochemistry

Tracheal cross-sectional specimens were embedded in a wax block, and the protein levels of α-SMA, TGF-β, and NOX4 were assayed at 2, 4, and 8 weeks. All data were measured by software image pro plus 6.0 (Media cybernetics, Inc., Silver Spring, MD, USA). $\alpha$-SMA (+)/TBM, NOX4 (+)/TBM and TGF-β (+)/TBM were quantified analyzed and compared.

Statistical analysis

The statistical analysis software SPSS statistics 21.0 was used for data analysis. The measurement data were expressed as the mean ± standard deviation (± SD), and the statistical software GraphPad Prism 8 was used. The three groups of measurement data were tested by the normality test and variance homogeneity test. If the data conformed to a normal distribution and homogeneity of variance, one-way ANOVA was used; if they did not conform to a normal distribution and homogeneity of variance, the rank sum test (Kruskal–Wallis method) was used. Those with uniform variance were tested by the Bonferroni method, and those with uneven variance were tested by the Mann–Whitney U method. $P < 0.05$ showed that the difference was statistically significant.

| Table 1 | Histological injury scoring criteria |
|---------|------------------------------------|
| | Scoring |
| | 0 | 1 | 2 | 3 |
| Cartilage necrosis | No | <1/3 | 1/3–2/3 | >2/3 |
| Telangiectasia and hyperemia | No | Slight | Moderate | Marked |
| Lymphocyte infiltration | No | Focal scattered | Focal dense | Dense |
| Neutrophil infiltration | No | Focal scattered | Focal dense | Dense |
| Erythrocyte exudation | No | <1/3 | 1/3–2/3 | >2/3 |
| Submucosal gland | Normal | Swelling | Atrophy | Necrosis |
Results

General results

All experimental animals successfully completed AS implantation, and there were no surgery-related deaths, implying that the technical success rate was 100%. Fourteen animals had a poor appetite but recovered within 1 week. Cough was observed in all animals during the entire follow-up time, and the frequency was higher during the first 2 weeks. One animal died due to severe lung infection with fever at 6 weeks, and the other animals successfully finished the study.

Gross observation

A large amount of viscous sputum could be seen on the surface of the stent, and there was a trend of aggravation over time in all groups. Mucosal edema and a thickening of the tracheal wall were seen in group A at all times, but the degree was lighter than that of groups B and C during the same period. Granulation tissue on both stent ends in group A was aggravated over time, and it was obviously difficult to separate the stent from the tissue at 8 weeks. Local mucosal edema increased in groups B and C over time, but granulation hyperplasia was slight, and the stent was easy to separate from the tracheal wall, even in group C at 8 weeks (Fig. 1). No local ulcers, tracheal perforation or fistula were found in any animals. Adjacent organs, such as the lung, esophagus and aorta, were normal in all animals.

SPECT examination and brachytherapy dose

Postoperative SPECT showed local γ-ray accumulation in the local tracheal wall, and there was no nuclide loss or stent displacement 3 days after AS. The cumulative doses in group B at 5 and 10 mm beside the stent were 6.72 Gy (2 weeks), 12.4 Gy (4 weeks), and 21.40 Gy (8 weeks), and 2.33 Gy (2 weeks), 4.30 Gy (4 weeks), and 7.41 Gy (8 weeks), respectively. The cumulative doses at 5 and 10 mm at group C beside the stent were 11.45 Gy (2 weeks), 24.88 Gy (4 weeks), and 42.81 Gy (8 weeks), and 4.65 Gy (2 weeks), 8.61 Gy (4 weeks), and 14.81 Gy (8 weeks), respectively (Fig. 2).

Serum biochemical and ROS level examination

After AS, WBCs showed no significant change in groups A and B at any time point, but WBCs in group C showed transient increases at 1 week and then returned to normal. Hg, ALT, TB and Cr showed no significant change in the three groups at 1, 2, 4, and 8 weeks (Table 2). The serum level of ROS increased significantly in all groups; serum ROS increased from (165.43 ± 23.56) pg/mL (2 weeks) to (872.55 ± 36.81) pg/mL (4 weeks) to (1244.71 ± 65.79) pg/mL (8 weeks) in group A, and from (1105.43 ± 59.44) pg/mL (2 weeks) to (3643.51 ± 635.14) pg/mL (4 weeks) to (4322.98 ± 803.52) pg/mL (8 weeks) in group C. The ROS in group C was higher than that of group A and B, and attained its peak level at 8 weeks. The tissue ROS level showed the same trend and reached the highest level of 6702.46 ± 744.55 pg/mL in group C at 8 weeks (Fig. 2). More details are listed in Table 3.

Hematoxylin–eosin and Masson staining

Under a light microscope, granulation tissue hyperplasia, interstitial and capillary congestion and inflammatory cells, monocytes, plasma cells, lymphocytes, and eosinophils infiltration became more aggravated in group A, and granulation hyperplasia at the upper stent end became the most obvious at 8 weeks, which was the same as gross specimen observation. Groups B and C showed that the tracheal wall and mucosa gradually thickened, and there was a large amount of inflammatory cell infiltration, including monocytes, plasma cells, lymphocytes, and eosinophils. There was obvious abnormality in submucosal new fibrous connective tissue, and the proliferation was most severe in group C, which had the highest histological scores (Table 4).

Masson staining was used to evaluate dynamic changes in typical collagen and muscle fibers. Submucosal fibroblasts also increased over time in group A but were fewer than those in groups B and C during the same period (P < 0.05) (Fig. 3). The Masson (+) area/TBM of the trachea in groups A, B and C were (183.6 ± 2.3), (220.1 ± 1.9), and (241.3 ± 1.4) µm²/µm at the 2-week evaluation; (270.2 ± 8.9), (386.4 ± 11.2), and (1036.0 ± 5.6) (µm²/µm) at the 4-week evaluation; and (360.8 ± 2.3), (758.2 ± 4.9), and (1224.8 ± 3.0) µm²/µm at the 8-week evaluation, respectively. Statistical analysis showed that there were significant differences between groups (P < 0.05) (Fig. 3).

Immunohistochemistry

α-SMA immunohistochemical staining increased significantly in all groups and reached the highest level in group C at 8 weeks (P < 0.05). The [α-SMA (+) area/TBM] in groups A, B and C were (198.3 ± 4.7), (216.4 ± 11.2), and (260.3 ± 2.9) µm²/µm at the 2-week evaluation; (231.6 ± 5.3), (280.2 ± 8.5), and (298.4 ± 6.4) µm²/µm at the 4-week evaluation; and (267.1 ± 5.6), (317.4 ± 4.8), and (460.2 ± 7.9) µm²/µm at the 8-week evaluation. Statistical analysis showed that there were significant differences between groups (P < 0.05) (Fig. 4).
Fig. 2 Tissue injury score (A), cumulative local absorption dose at different time points (B), ROS levels in blood (C) and local tissues (D) at different time points

Table 2 Blood routine and blood biochemistry changes

| Index (unit)                        | Pre-treatment | 1-week  | 2-week  | 4-week  | 8-week  |
|------------------------------------|---------------|---------|---------|---------|---------|
| Red blood cells (1012/L)           | 6.81 ± 0.52   | 7.02 ± 0.44 | 6.82 ± 0.32 | 6.61 ± 0.39 | 6.55 ± 0.40 |
| White blood cell (109/L)           | 10.22 ± 1.25  | 14.37 ± 1.57 | 10.20 ± 2.08 | 10.68 ± 2.03 | 10.52 ± 1.78 |
| Platelets (109/L)                  | 281.31 ± 70.22 | 306.6 ± 44.55 | 297.6 ± 60.14 | 285.5 ± 46.80 | 290.40 ± 34.37 |
| Hemoglobin (g/L)                   | 114.36 ± 13.41 | 115.22 ± 11.39 | 114.26 ± 10.83 | 114.01 ± 9.93 | 116.02 ± 10.52 |
| Alanine aminotransferase (U/L)     | 29.21 ± 5.66  | 28.80 ± 5.47 | 30.07 ± 5.46 | 30.82 ± 5.71 | 30.85 ± 5.53 |
| Total bilirubin (µmol/L)           | 7.53 ± 0.62   | 7.38 ± 0.59 | 7.43 ± 0.60 | 7.46 ± 0.58 | 7.53 ± 0.51 |
| Creatinine (µmol/L)                | 80.31 ± 7.60  | 82.16 ± 7.42 | 83.21 ± 7.41 | 85.22 ± 7.23 | 84.16 ± 7.70 |

Table 3 Tracheal tissue and serum ROS level

| Item                  | 2 weeks       | 4 weeks       | 8 weeks       |
|-----------------------|---------------|---------------|---------------|
|                       | Tissue        | Serum         | Tissue        | Blood        | Tissue        | Blood        |
| Group A               | 198.93 ± 11.75| 165.43 ± 23.56| 923.22 ± 41.32| 872.55 ± 36.81| 1760.40 ± 82.45| 1244.71 ± 65.79|
| Group B               | 511.40 ± 13.01| 488.39 ± 12.83| 1408.63 ± 38.30| 1338.79 ± 49.14| 2214.67 ± 229.36| 2014.67 ± 69.23|
| Group C               | 1138.20 ± 82.45| 1105.43 ± 59.44| 3920.36 ± 227.74| 3643.51 ± 635.14| 6702.46 ± 744.55| 4322.98 ± 803.52|
TGF-β increased significantly in all groups and reached the highest level in group C at 8 weeks \((P < 0.05)\). The \([\text{TGF-β} (+)/\text{area/} \text{TBM}]\) in groups A, B and C were \((201.2 \pm 3.6), (252.4 \pm 7.9), \) and \((382.1 \pm 4.7) \text{µm}^2/\mu\text{m}\) at the 2-week evaluation; \((312.6 \pm 5.5), (642.8 \pm 4.9), \) and \((1028.2 \pm 14.6) \text{µm}^2/\mu\text{m}\) at the 4-week evaluation; and \((500.8 \pm 12.4), (828.4 \pm 18.6), \) and \((1174.2 \pm 22.9) \text{µm}^2/\mu\text{m}\) at the 8-week evaluation. Statistical analysis showed that there were significant differences between groups \((P < 0.05)\).  

Nox4 increased significantly in all groups and reached its highest level in group C at 8 weeks \((P < 0.05)\). The \([\text{NOX4} (+)/\text{area/} \text{TBM}]\) in groups A, B and C were \((40.1 \pm 1.4), (57.4 \pm 6.8), \) and \((72.3 \pm 4.2) \text{µm}^2/\mu\text{m}\) at the 2-week evaluation; \((60.6 \pm 2.7), (66.2 \pm 3.8), \) and \((149.9 \pm 5.5) \text{µm}^2/\mu\text{m}\) at the 4-week evaluation; and \((79.0 \pm 1.3), (153.9 \pm 1.8), \) and \((301.2 \pm 6.9) \text{µm}^2/\mu\text{m}\) at the 8-week evaluation. Statistical analysis showed that there were significant differences between groups \((P < 0.05)\) (Fig. 4).

### Discussion

AS is the first nonsurgical strategy for malignant tracheal stenosis, but tumor ingrowth and granulation hyperplasia are both challenging issues resulting in in-stent restenosis (Neiva Machado et al. 2020). The pathophysiology of benign ingrowth is extracellular matrix (ECM) proliferation and granulation hyperplasia (Haybar et al. 2020). To prevent and inhibit this pathological change, Guo et al. (2007) and Gan et al. (2015) applied BS to normal rabbits and dogs, respectively, and verified that \(^{125}\text{I}\) seeds can inhibit normal granulation hyperplasia through cell cycle arrest and apoptosis to alleviate benign stenosis. However, these studies did not involve the study of signaling pathways. Considering the close relationship between radiotherapy and ROS found in a previous study (Kawamura et al. 2018), this study focused on ROS, α-SMA, TGF-β and NOX4.

The technical success rate of AS was 100%. During the follow-up time, 14 animals had poor appetite within the first week, while the other experimental animals were normal, implying that BS is a safe treatment with little effect on the entire body. WBC levels in Group C showed transient elevation within 1 week. A reasonable explanation may be that these animals underwent initial experiments, and operator inexperience possibly led to long-term operation, resulting in more damage.

### Table 4 Histogram score at different time

| Group            | 2-week | 4-week | 8-week |
|------------------|--------|--------|--------|
| Group A (control)| 4.2±0.7| 6.1±0.4| 8.9±0.5|
| Group B (0.4 mCi/seed) | 7.1±0.6| 8.7±0.2| 11.4±0.8|
| Group C (0.8 mCi/seed) | 9.2±0.3| 12.4±0.8| 14.6±0.9|
As irradiation damage occurred, seed activity was the key factor. The HE and Masson staining of group A showed a trend toward increased damage and fibrosis, which was weaker than that of groups B and C. The results suggest that metal stent and 125I seed brachytherapy can both cause damage; however, stent lateral support force was the main reason stimulating mucosal granulation tissue proliferation at an early stage. As time progressed, the local cumulative irradiation dose increased, which means more brachytherapy damage. Wang et al. (2017) investigated a newly designed covered tracheal BS on healthy Beagle dogs. Pathological changes were mainly found in the mucosal and submucosal layers, and irradiation injury also increased with the extension of time. Jiao et al. (2021) investigated a novel ureteral BS in normal Beagle dogs and found that epithelial cell proliferation was lighter in the high-dose group (0.8 mCi group) than in the low-dose group (0.4 mCi group), but the fibrosis of the former group was more serious. The above result is consistent with the present study.

The traditional view is that the death mode of tumor cells induced by irradiation is via direct and indirect effects, in which the direct effect of radiation is damage to the DNA structure, and the indirect effect is the hydroxyl radical (HO\(^\cdot\)), superoxide anion (O\(_2\)\(^{−}\))\(\cdot\)H\(_2\)O\(_2\), and other reactive oxygen species (ROS) produced by ionizing water molecules by radiation through a complex chain reaction of physics, chemistry and biology, which will eventually lead to damage (Byun et al. 2018). Myofibroblasts can be derived from interstitial intrinsic fibroblast activation and have the dual characteristics of being fibroblasts and smooth muscle cells. ROS are released during the phenotypic transformation from fibroblasts to myofibroblasts and play an important role in controlling extracellular matrix (ECM) protein deposition. This study found that the levels of ROS in local tissue and peripheral blood gradually increased after BS implantation, which is also an important reason for irradiation injury to local tracheal tissue. According to the different biological characteristics of normal tissues and their different reactivity to ionizing radiation, the trachea belongs to late response tissues, which means that the selection of 125I activity should be carefully considered to decrease brachytherapy at late stage. This study showed that the maximal cumulative dose was 42.81 Gy at 5 mm beside the BS at 8 weeks; however, there was no perforation or ulcer formation in the mucosa, indicating that this dose is safe and feasible for tracheal brachytherapy.

TGF-β and NOX4 play important roles in maintaining normal tissue growth balance (Amini et al. 2020), though they are not or are only marginally expressed in normal tracheal tissue. TGF-β is also a powerful inducer of ECM synthesis and deposition, and it is one of the key molecules of tissue fibrosis (Zi 2019). After tracheal stenting, the
tissue stress response and the expression of TGF-β and NOX4 increased with a certain dose–effect relationship in our study, suggesting that this is a positive feedback mechanism that continuously generates ECM and propels fibrosis.

Hanley et al. (2018) and Barman and Fulton (2017) et al., confirmed that NOX4 can be involved in cancer-associated and vascular remodeling-associated fibroblasts, respectively. NADPH oxidase is a good source of ROS in human fibroblasts (Reis et al. 2020); when it is activated, ROS are subsequently produced. Then, increased ROS can activate TGF-β/Smad signaling, promote potential TGF-β conversion to the active form, and enhance the phosphorylation of ALK5 and Smad2/3 (Liu and Desai 2015). Therefore, activated TGF-β/ROS signaling promotes ECM remodeling by fibroblasts. The potential protein molecule interaction network is shown in Fig. 5 after referring to published literature (Al-Azzam et al. 2020; He et al. 2016).

This study had the following shortcomings: (1) only the influence of benign hyperplasia was considered because of the lack of a tumor model; (2) the BS as a noncovered stent induces severe granulation hyperplasia, which will lower the evaluated function of 125I brachytherapy; (3) the follow-up time was limited to only 8 weeks, and the long-term influence of the BS on the trachea was not evaluated; (4) only the proteins of ROS, α-SMA, TGF-β and NOX4 were described, while other macromolecules such as RNA, DNA and other proteins in signaling pathways were not investigated.

In conclusion, brachytherapy injury after BS implantation increased with irradiation dose accumulation, while granulation tissue hyperplasia at the stent end was inhibited by 125I brachytherapy within 8 weeks. Clinical studies will be required to test its use in humans, in the future.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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