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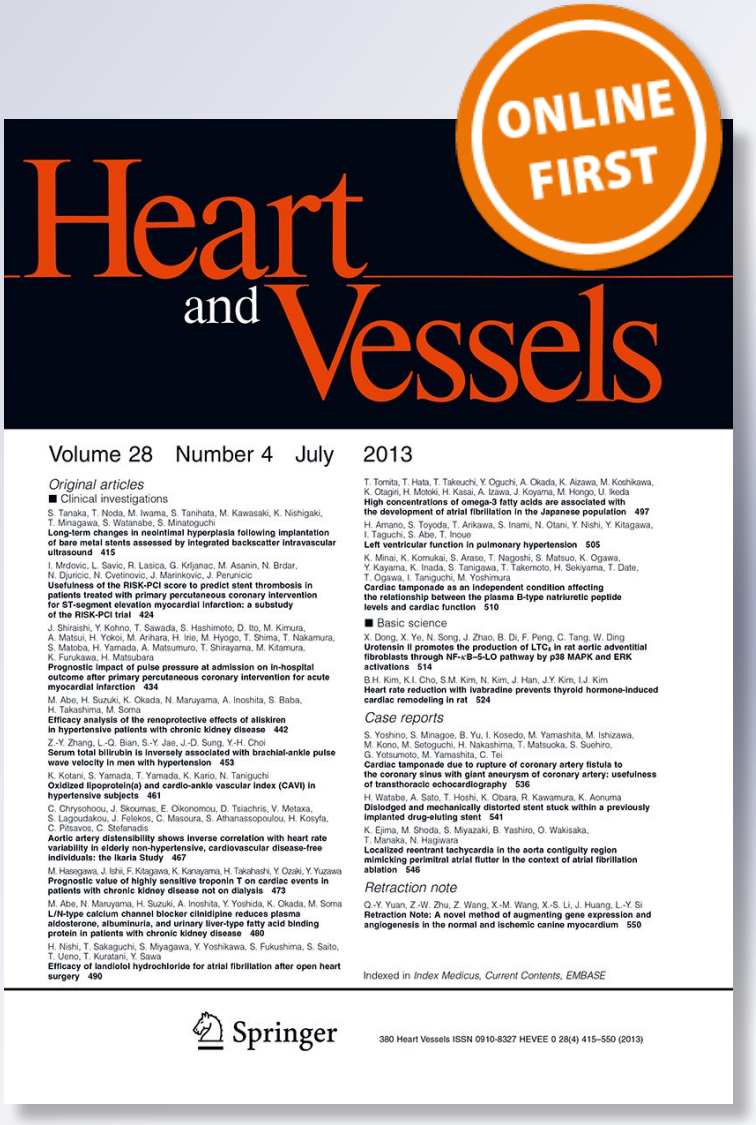

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ORIGINAL ARTICLE

Stent unzipping using an ultra-high-pressure balloon: in vitro and animal experiments

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Abstract As a child grows, limitations to the maximum dilatable stent diameter (MDD) will result in stenosis associated with size mismatch. If an implanted stent can be intentionally fractured along its length, a process called "unzipping," it may eventually be redilated to adult vessel size. Few studies have addressed how a stent can be unzipped using an ultra-high-pressure balloon (UHB) with the smallest balloon diameter. Eleven commercially available stents, three Liberté stents (LS), six genesis renal stents (GS), and two express vascular SD stents (ES), were tested for in vitro unzipping. In addition, using eight stents, we investigated whether a balloon that had unzipped the stent in vitro would work similarly in the vessel of a pig. Finally, we assessed the histological influence of the unzipped stent on the surrounding tissue. In a bench test, LS, GS, and ES were consistently unzipped by a balloon whose diameter was ≥ 1.5, 2.18, and 1.66 times that of MDD, respectively. In animal experiments, LS, GS, and ES were predictably unzipped with balloons of 1.50, 1.81, and 1.66 times the MDD, respectively. After unzipping, the unzipped strut did not damage the surrounding tissue histologically. Use of a UHB enabled unzipping of the stent with a balloon diameter less than two times the MDD enables implantation of a larger stent in the unzipped small stent by incremental steps.

Keywords Stents · Fracture · Ultra-high-pressure balloon

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Introduction

Stenting for vascular stenosis associated with congenital heart diseases has become a standard treatment option since the first report in 1991 [1]. In the mid-1990s, several studies proved that redilation of a vessel segment with a stent and stent-in-stent deployment for further support was successful and safe. The innovation of premounted small-diameter stents delivered through a small introducer sheath enables delivery of stents to small vessels. The evolving interventional equipment has also led to decreases in the complication rate when performing cardiac catheterization in pediatric patients [2]. However, the maximum dilatable stent diameter (MDD) of such stents coupled with somatic growth may eventually result in stenosis associated with size mismatch. Intentional fracture of a maximally dilated balloon-expandable stent, termed as "unzipping," may solve such size mismatch in pediatric patients.

Despite a few experimental and preliminary clinical studies of such unzipping, information on optimal technical conditions for success remains limited.

In this study, we determined the smallest balloon diameter that could unzip several types of small-diameter stents, commonly used for pediatric vascular stenosis in Japan. In addition, we assessed the damage to the adjacent vessel wall during unzipping.

Materials and methods

In vitro bench tests

Eleven commercially available coronary and peripheral stents, three Liberté stents (LS), six genesis renal stents (GS), and two express vascular SD stents (ES), of various

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diameters and lengths were tested in vitro. All stents were made of stainless steel; and although LS and GS have a closed cell, ES has a semi-open cell configuration. The stent diameter ranged from 4 to 6 mm while the MDD ranged from 5.5 to 7.5 mm (Table 1).

Stent dilations were performed with the balloon angioplasty catheter provided for the premounted stents. Inflations were performed according to the manufacturers' recommended nominal pressure. After inflation to nominal pressure, serial dilations were performed with 1 mm increments up to 10 mm, and then up to 12 mm in balloon size until the stent was fractured. The endpoint of balloon dilation was defined as having met either one of the following: (1) complete dilatation of the balloon to 12 mm without any waist, (2) napkin-ring formation (extreme foreshortening without increase in stent diameter) without fracture, or (3) complete occurrence of the first stent strut fracture. Once the stents were unzipped, all the stents were dilated using the same UHB up-to 20 atm until complete longitudinal unzipping of the stent.

Animal experiments

Eight stents of various diameters and lengths were implanted in two piglets with a body weight of 45 and 47 kg. Because the vessel diameters of the superior mesenteric artery (SMA) and the descending aorta (dAo) ranged from 2.2 to 2.9 mm and 5.9 to 7.4 mm, respectively, LS, which required the smallest percentage increase in balloon diameter over the MDD for unzipping in vitro, was implanted in the SMA; the other stents were implanted in the dAo. The stents implanted in the dAo were remounted on a balloon whose diameter was 2 mm smaller than the balloon that could unzip the stent in vitro. After implantation, the stent was further dilated using Conquest® balloons 8–10 mm (median, 10 mm) in diameter and 2 cm in length until complete longitudinal unzipping. The study protocol was approved by the review board of CIMIC Pharma Science (Approval No. 16K1030N).

Histological study

Macroscopic and microscopic analyses were performed for stents after staining with hematoxylin and eosin, elastic Van Gieson, and Azan. The degree of superficial vascular

Table 1 Vessel injury score

Injury score	Description of injury
0	Internal elastic lamina intact; endothelium typically denuded; media compressed but not lacerated
1	Internal elastic lamina lacerated; media typically compressed but not lacerated
2	Internal elastic lamina lacerated; media visibly lacerated; external elastic lamina intact and not compressed
3	External elastic lamina lacerated; typically large lacerations of media extending through external elastic lamina; coil wires sometimes residing in adventitia

Table 2 Results of the bench test

Stent	Stent profile	MDD	UHB profile	% of MDD	Unzip	Pressure for unzip
LS	4 mm/20 mm	6	8 mm/20 mm	122	×	–
LS	*4 mm/20 mm*	*6*	*9 mm/20 mm*	*150*	○	*11*
LS	4 mm/16 mm	6	12 mm/20 mm	200	○	19
GS	6 mm/18 mm	7.5	10 mm/20 mm	133	×	–
GS	6 mm/18 mm	7.5	12 mm/20 mm	160	×	–
GS	4 mm/15 mm	5.5	9 mm/20 mm	163	×	–
GS	4 mm/15 mm	5.5	10 mm/20 mm	181	△	18
GS	*4 mm/15 mm*	*5.5*	*12 mm/20 mm*	*218*	○	*6*
GS	6 mm/18 mm	7.5	9 + 12 mm/20 mm	231	○	12
ES	4 mm/19 mm	6	9 mm/20 mm	150	△	19
ES	*4 mm/19 mm*	*6*	*10 mm/20 mm*	*167*	○	*9*

Italicized indicates the smallest percentage increase in diameter of the balloon over the MDD of each stent that could unzip the stent

LS Liberté stent, *GS* genesis renal stent, *ES* express vascular SD stent, *SMA* superior mesenteric artery, *dAo* descending aorta, *MDD* maximally dilatable stent diameter, *UHB* ultra-high-pressure balloon, ○ completely unzipped, △ partially unzipped, × could not unzip

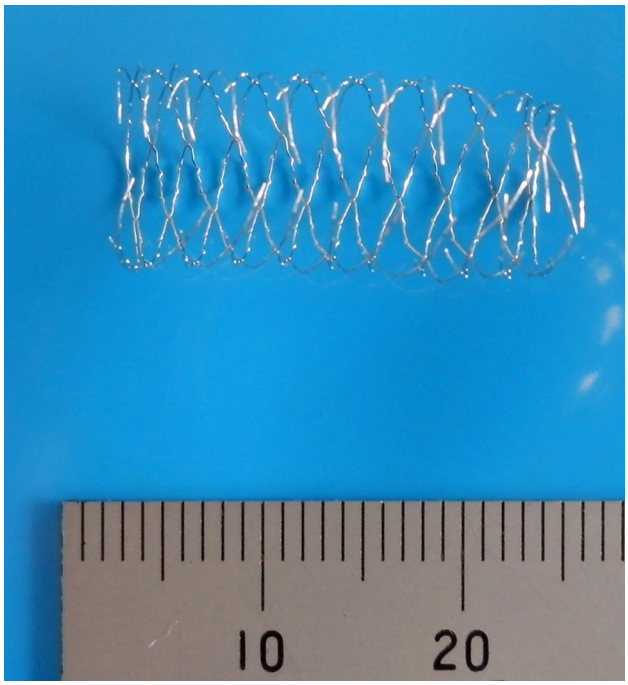

Fig. 1 Liberté stent (LS; 4 mm/24 mm) unzipped by a Conquest balloon 9 mm/20 mm

damage was gathered for all specimens using the scale created by Schwartz et al. [3] (Table 1). For example, intact internal elastic lamia in contact with stent strut was defined as zero.

We investigated whether a balloon that unzipped the stent in vitro might work similarly in the vessel of a pig, and assessed the resulting histological damage to the surrounding tissue.

Results

Bench test

Table 2 shows the bench test results. LS, GS, and ES were consistently unzipped by a balloon whose diameter was greater than or equal to 1.5, 2.18, and 1.66 times the MDD, respectively. GS tended to require a larger balloon diameter for unzipping than did the other kinds of stent. No stent could be unzipped with a balloon diameter ≤ 1.4 times MDD. To unzip the GS 6 mm/18 mm, a double balloon technique using two Conquest balloons of 9 and 12 mm (assumed 231% of MDD) were required. The pressure required for unzip ranged from 6 to 19 (median, 12) atm. Figure 1a shows an unzipped LS stent 4 mm/20 mm using a Conquest 9 mm/20 mm at 11 atm.

Animal experiments

Table 3 shows the results of the animal study. Two stents were implanted in the SMA and six in the descending aorta. Predictably, LS, GS, and ES were unzipped with a balloon ≥ 1.5, 1.81, and 1.66 times the MDD, respectively. No stents could be completely unzipped with balloons less than or equal to 1.4 times the MDD, as we observed in the bench test. The smallest percentage increase in balloon diameter over the MDD that could unzip the stent in the animal experiments tended to be lower than in the bench test. The pressure for unzipping ranged from 12 to 18 (median 16) atm, which tended to be higher than in the bench test. The morphology of all unzipped stents showed minimal shortening with organized fractures (Fig. 2). Angiography of all stents after stent unzipping did not show any vascular wall damage, such as dissection, aneurysm formation, or contrast leak (Fig. 3). Microscopic findings for all implanted tissues showed no evidence of

Table 3 Result of the animal experiments

Stent	Target vessel	Stent profile	Balloon size for remount	UHP balloon profile	% of MDD	Unzip	Pressure for unzip	Vessel injury score
LS	SMA	4 mm/24 mm	–	8 mm/20 mm	133	△	12	–
LS	*SMA*	*4 mm/24 mm*	–	*9 mm/20 mm*	*150*	○	*15*	*1*
GS	*dAo*	*4 mm/18 mm*	*8 mm/20 mm*	*10 mm/20 mm*	*181*	○	*16*	*0*
GS	*dAo*	*4 mm/15 mm*	*8 mm/20 mm*	*10 mm/20 mm*	*181*	○	*18*	*0*
ES	*dAo*	*4 mm/19 mm*	*8 mm/20 mm*	*10 mm/20 mm*	*166*	○	*12*	*0*
ES	*dAo*	*4 mm/19 mm*	*8 mm/20 mm*	*10 mm/20 mm*	*166*	○	*16*	*0*
ES	*dAo*	*5 mm/19 mm*	*8 mm/20 mm*	*10 mm/20 mm*	*166*	○	*14*	*0*
ES	*dAo*	*5 mm/19 mm*	*8 mm/20 mm*	*10 mm/20 mm*	*166*	○	*16*	*0*

Italicized indicates the smallest percentage increase in diameter of the balloon over the MDD of each stent that could unzip the stent

LS Liberté stent, *GS* genesis renal stent, *ES* express vascular SD stent, *SMA* superior mesenteric artery, *dAo* descending aorta, *MDD* maximally dilatable stent diameter, *UHB* ultra-high-pressure balloon, ○ completely unzipped, △ partially unzipped, × could not unzip

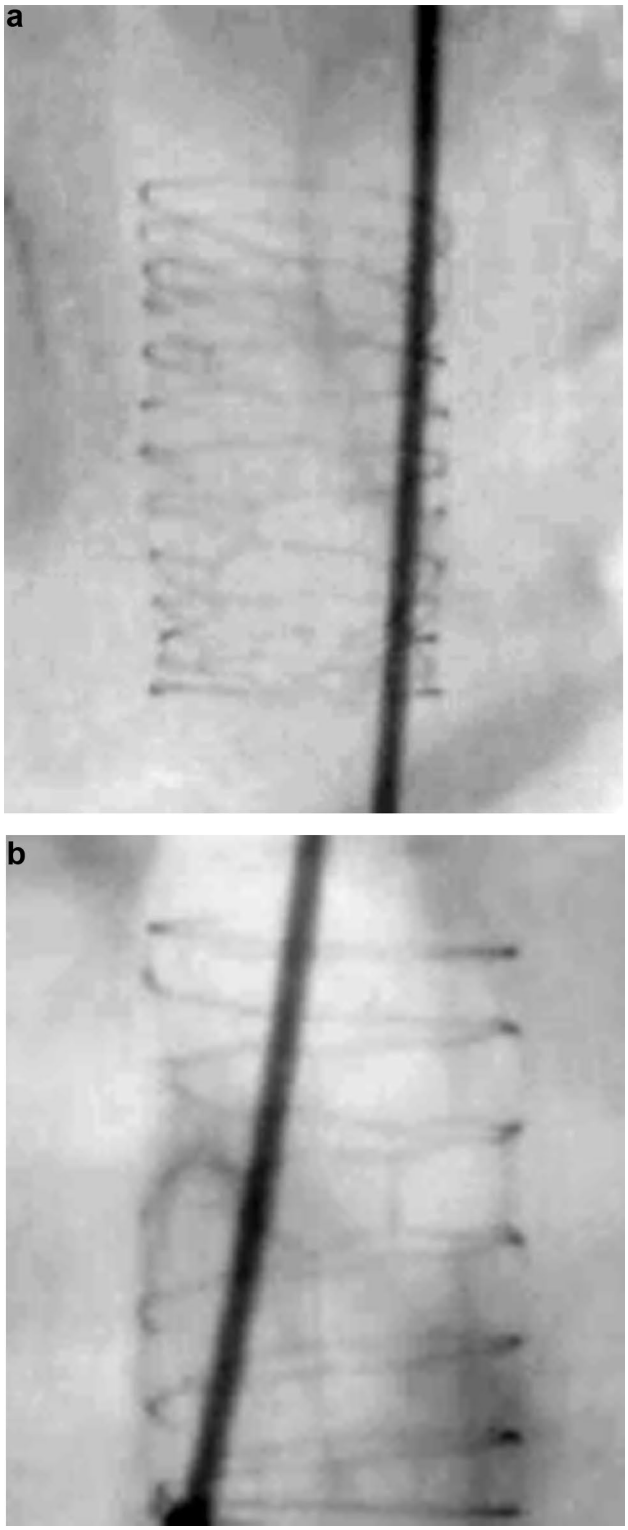

Fig. 2 **a** Unzipped express vascular stent. **b** Unzipped genesis renal stent

damage of the media by the unzipped strut in the surrounding tissue (Fig. 4).

Discussion

There are only a few publications on the clinical or experimental aspects of unzipping small stents [4, 5]. Our present data expand the technical considerations and ideas about future clinical applications.

Our principal finding confirms that small-diameter, stainless-steel stents can be consistently unzipped reproducibly by the smallest diameter balloon. Fracture was achieved by UHBs using a balloon diameter of 1.5–2.18 of the MDD of the stent. The successful unzipping of closed-cell coronary stents with the smallest diameter was noteworthy.

The lack of medial damage to the surrounding tissue by the unzipped stent, an important observation by Sathanandam et al. [6], was confirmed in our study. According to their study, coronary and renal stents unzipped at twice their nominal diameters, although GS could be widened by a balloon up to 2.5 times the nominal diameter of the stent with 42% shortening in length before becoming unzipped. In our study, once MDD was achieved, LS, GS, and ES would be unzipped by a UHB with a diameter of 133–181% of the MDD. LS and ES may be given slight preference over GS for future unzipping.

In this study, stents were unzipped using smaller diameter balloons than those used in Sathanandam's vivo report [6]. Two reasons have been proposed to account for this fact. (1) The recent report [6] has shown that unzipping with fewer balloon inflations resulted in unzipping stents at smaller balloon diameters. The number of balloon inflations in this study was fewer than that in their report. (2) In their report [6], stents were dilated with 1 mm increments in balloon diameter until 6 mm, followed by 2 mm increments until the stents unzipped, whereas in our study, stents were dilated with 1 mm increments up to 10 mm and then up to 12 mm until the stents unzipped. The difference in the method with respect to serial dilation between our study and their report [6] might affect the balloon diameter needed for unzipping the stent.

Although there was no significant damage to the arterial wall in our healthy piglets, we still need to determine whether co-existing chronic conditions render the vessel more susceptible to damage. In addition, whether arteries and veins differ with respect to potential damage remains undetermined. According to Sathanandam's vivo report [6], the degree of vessel wall injury caused by unzipped vessels in piglets was shown to be higher in the systemic artery than in systemic veins. However, the fact that vessels with unzipped stents were equal in vessel wall injury score to controls of similar vessels after dilation with an UHB shows that the risk of perforation was low. As Sathanandam's study [6] points out, all vessel injury following unzip were associated with overdilation to the adjacent normal vessel diameter to a greater extent. Limiting the balloon diameter to not

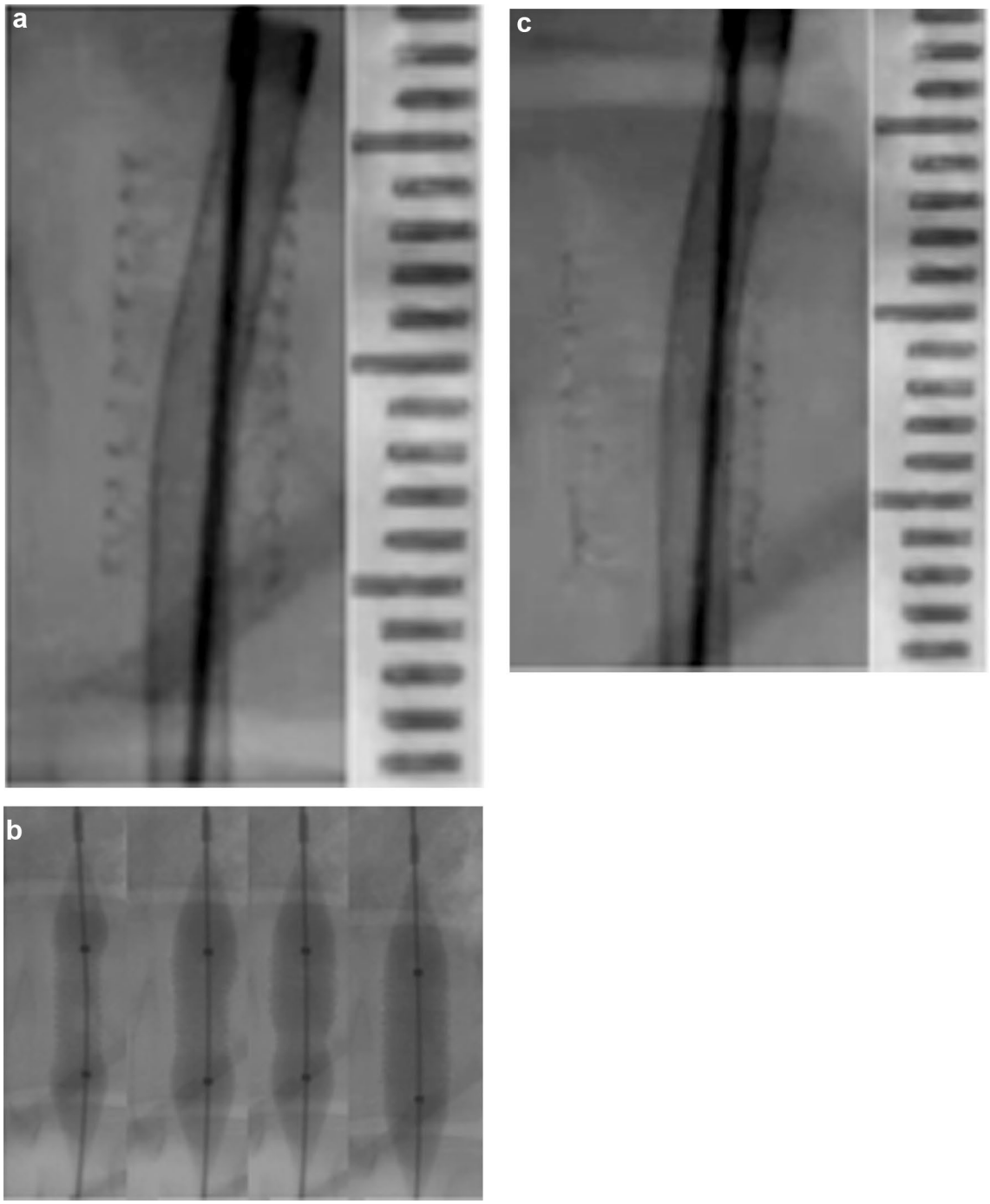

Fig. 3 **a** Express vascular (ES) stent 4 mm/19 mm remounted on PowerFlex P3 8 mm/20 mm. **b** ES stent dilated by Conquest 10 mm/20 mm and unzipped sequentially. **c** ES stent completely unzipped at 12 atm

larger than the adjacent normal vessel diameter may avoid vessel wall injury associated with unzipping. In case of vessel perforation, the implantation of a covered stent over the unzipped stents might be effective. However, at this point, the efficacy of vessel wall perforation by implantation of covered stents over unzipped stents is uncertain. Further investigation on how to avoid and bail-out vessel perforation by unzipped stents is required.

In addition, the stent morphology after unzipping is important for considering potential vessel wall perforation. Factors which may determine organized or disorganized unzipping remain unclear. For example, GS were unzipped with disorganized fracture in Sathanandam's study [6], while

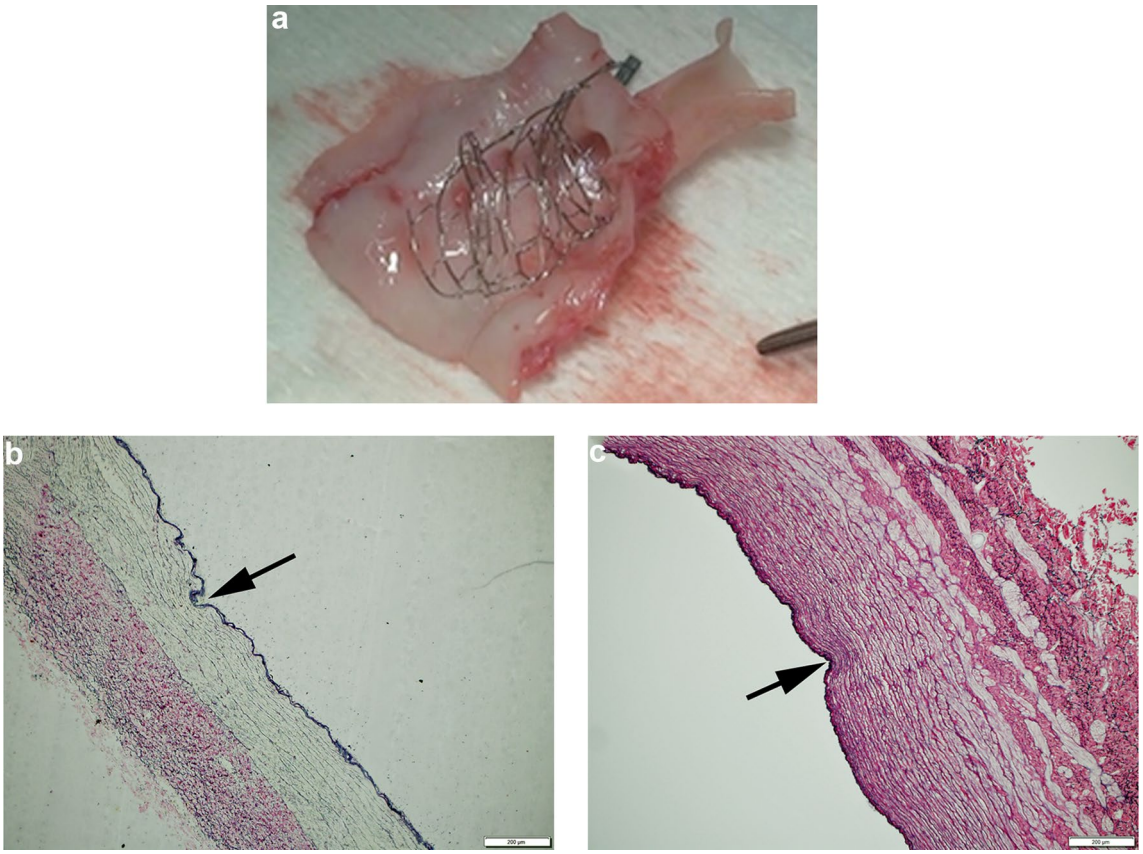

Fig. 4 **a** Unzipped genesis renal (GS) stent (4 mm/18 mm) in the descending aorta (dAo). **b** Histological tissue specimen of superior mesenteric artery (SMA) after elastic Van Gieson (EVG) staining. SMA with Liberté stent showing injury to the internal elastic lamina scored as 1 (black arrow). **c** Histological tissue specimen of dAo after EVG staining. The express vascular stent that was unzipped in dAo with no vessel wall injury scored as 0 (black arrow)

they unzipped with organized fracture in this study. It can be presumed that the difference in stent profile between Genesis biliary stents and GS has resulted in the variation in stent morphology after unzipping between our study and their report. Genesis biliary stent diameter used in their study ranged from 4 to 7 mm, whereas GS diameter used in this study ranged from 4 to 6 mm.

Several investigators have proposed technical enhancements, for example a breakable stent [7], an open-ring stent [8], or a bioresorbable stent [9], for application in infants and neonates to overcome size mismatch following somatic growth. However, practical clinical experience is limited; furthermore, we must find practical safe solutions that will avoid multiple surgery for existing cases of size mismatch. We believe intentional stent unzipping may be a new treatment strategy for carefully selected cases of acquired stenosis.

Limitations

The number of animals was small, which limits the statistical power of the study and our ability to generalize our findings. Observations were acute and in healthy animals, while we may encounter chronic changes in the diseased vessel. The chronic influence on the surrounding vessel wall by unzipped struts remains a potential problem. Stents were unzipped only in the systemic arteries, which have different morphology and properties than veins. Consequently, we cannot apply our outcome in the animal experiment to these vessels. These novel procedures require further evaluation both experimentally and clinically to identify the factors determining their effectiveness and safety.

Conclusion

The use of UHBs enabled the unzipping of stents with a balloon diameter less than twice the MDD. The ratio of smallest balloon diameter that could unzip the stent to MDD varied

with the type of stent. These techniques make it possible to incrementally deploy larger stents in unzipped small stents. Further investigation on how to avoid and bail-out vessel perforation by unzipped stents is required.

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Compliance with ethical standards

Conflict of interest The author received a research grant from Miyata Cardiac Research Promotion Foundation.

Ethical approval All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice where the studies were conducted.

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