Circulation Reports
Circ Rep 2020; 2: 682–690
doi:10.1253/circrep.CR-20-0095

Efficacy of Super Slow Inflation as Lesion Preparation for Drug-Coated Balloons in Femoropopliteal Lesions

Makoto Sugihara, MD, PhD; Kaori Mine, MD; Makito Futami, MD, PhD;
Yuta Kato, MD, PhD; Tadaaki Arimura, MD, PhD; Masaya Yano, MD, PhD;
Yosuke Takamiya, MD, PhD; Takashi Kuwano, MD, PhD; Shin-ichiro Miura, MD, PhD

Background: Drug-coated balloon strategies in endovascular therapy often result in severe dissection, so lesion preparation must be improved. We evaluated the efficacy of a gradual inflation method, termed "super slow inflation" (SSI), in preparing lesions to avoid severe dissections.

Methods and Results: The association between balloon pressure and the dilatation of a model constricted vessel, as well as the load applied to the balloon surface, were determined using a burst leak detector for a quick inflation (QI; 1 atm/s) protocol and SSI (1 atm/20 s). A retrospective, single-center, non-randomized study evaluated differences in vessel dissection patterns after balloon angioplasty depending on inflation method in 81 consecutive patients (mean [±SD] age 74.6±9.2 years; 54 males) who underwent balloon angioplasty for de novo femoropopliteal lesions between January 2017 and March 2019. In the constricted vessel model, vessel dilatation increased gradually using SSI, with the maximum dilatation load being approximately 100 g lower for the SSI than QI protocol. In patients, the rate of severe vessel dissection was significantly lower in the SSI than non-SSI group (17.6% vs. 55.2%, respectively; P<0.001). Multivariate regression analysis revealed that SSI was an independent factor preventing severe dissection (odds ratio 0.18; 95% confidence interval 0.06–0.53; P=0.002).

Conclusions: SSI is a gentle and effective method for the preparation of femoropopliteal lesions to reduce the incidence of severe angiographic dissection when using drug-coated balloons.

Key Words: Angioplasty; Balloon; Endovascular therapy; Peripheral artery disease

Self-expanding nitinol stents have improved the durability of revascularization in the femoropopliteal segment. Recently, some studies reported superior results with stents over balloon angioplasty for lesions of short to intermediate length in the femoropopliteal artery, with 1-year patency rates ranging from 63% to 83%,[1,2] and long-term patency rates of 49–60%.[3,4] However, the medium-term patency of standard balloon angioplasty or bare nitinol stents in Trans-Atlantic Inter-Society Consensus (TASC) II C or D lesions has not been demonstrated sufficiently.[2]

Although recent studies have reported the efficacy of drug-coated balloons (DCBs) in femoropopliteal lesions as a long-term treatment option, some cases required bail-out stenting due to severe dissection during lesion preparation.[5,6] Because provisional stents are not covered by the national health insurance in Japan, DCB and metallic stents cannot be used simultaneously. This system differs from that in other countries. Fully covered stents are not considered standard care. The frequency of restenosis following stenting in long superficial femoral artery lesions has been reported to be up to 50%.[7–9] The pattern of restenosis for fully covered stents is either diffuse in-stent restenosis or in-stent occlusion, which are a challenge to treat.[7] In contrast, using DCBs may result in favorable clinical outcomes in patients with severe TASC C and D femoropopliteal artery disease and be the optimal long-term therapeutic option for patients with claudication.[10] However, even though DCBs exhibit promising primary patency rates after 1 year, the implantation of provisional stents remains necessary following DCB treatment in a substantial number of patients with complex lesions.[11–13] Because DCB therapy is associated with elastic recoil or the development of flow-limiting dissections, the quality of lesion preparation with non-coated normal balloons must be improved.

Some methods of lesion preparation have been proposed

Received August 20, 2020; accepted August 20, 2020; J-STAGE Advance Publication released online October 16, 2020 Time for primary review: 1 day

Department of Cardiology, Fukuoka University School of Medicine, Fukuoka (M.S., K.M., M.F., Y.K., T.A., M.Y., Y.T., T.K., S.M.); Department of Cardiology, Fukuoka University Nishijin Hospital, Fukuoka (S.M.), Japan

S.M. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Shin-ichiro Miura, MD, Department of Cardiology, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. E-mail: miuras@cis.fukuoka-u.ac.jp

ISSN-2434-0790

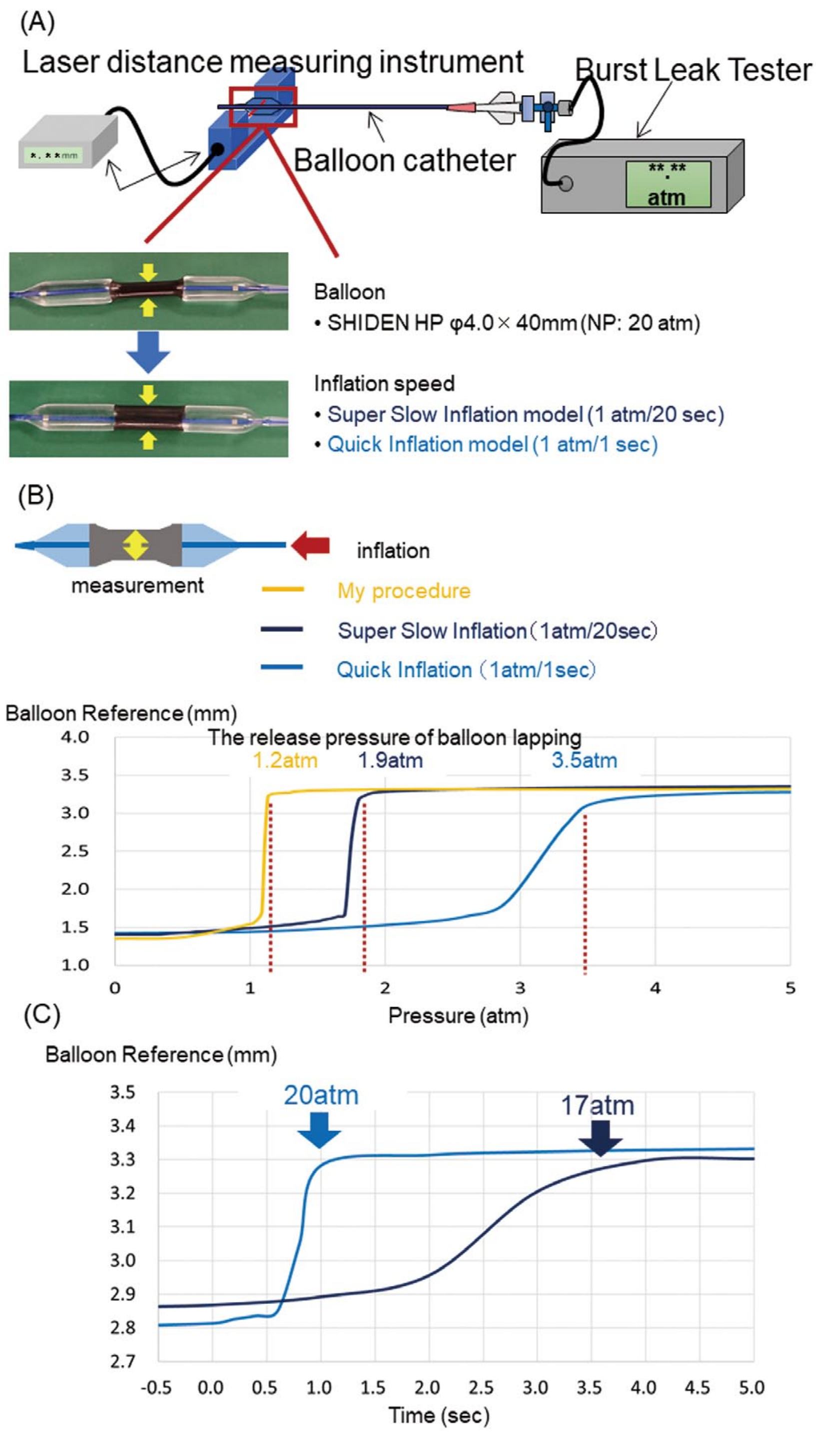

Figure 1. (**A**) Experimental set-up to compare the quick inflation (QI; 1 atm/s) and super slow inflation (SSI; 1 atm/20 s) protocols in a model of vessel constriction. The model was created using a laser distance measuring instrument, the Hydraulic Burst-leak Tester (Crescent Design, San Diego, CA, USA), and 4.0-mm×40-mm high-pressure balloon (SHIDEN HP; KANEKA Medics, Osaka, Japan). NP, nominal pressure. (**B**) The pressure to start dilatation of folded balloon was lower for manual slow inflation and the SSI protocol than the QI protocol. (**C**) The diameter of the balloon after inflation under the SSI protocol increased gradually, and the maximum dilatation pressure with the SSI protocol (17 atm) was lower than with the QI protocol (20 atm).

in Japan. Recent studies investigated the efficacy of using a long balloon and prolonged inflation time (>3 min) to prevent severe dissection.[14,15] The fracture mechanics during expansion of a plaque consist of an elastic phase and a plastic phase. The principles of yield strength, defined as the stress at which a predetermined amount of permanent deformation occurs, and ultimate tensile strength, which is the maximum stress that a material can withstand while being stretched or pulled, apply.[16]

Thus, we hypothesized that gradual balloon inflation using a super slow inflation (SSI) protocol may reduce the incidence of severe dissection because of a gentle and equal dilatation with minimal force. Therefore, in this study we compared a quick inflation (QI) protocol with the SSI protocol in a model of a constricted vessel model, and investigated the efficacy of angioplasty with SSI in femoropopliteal lesions to reduce the incidence of severe angiographic dissection.

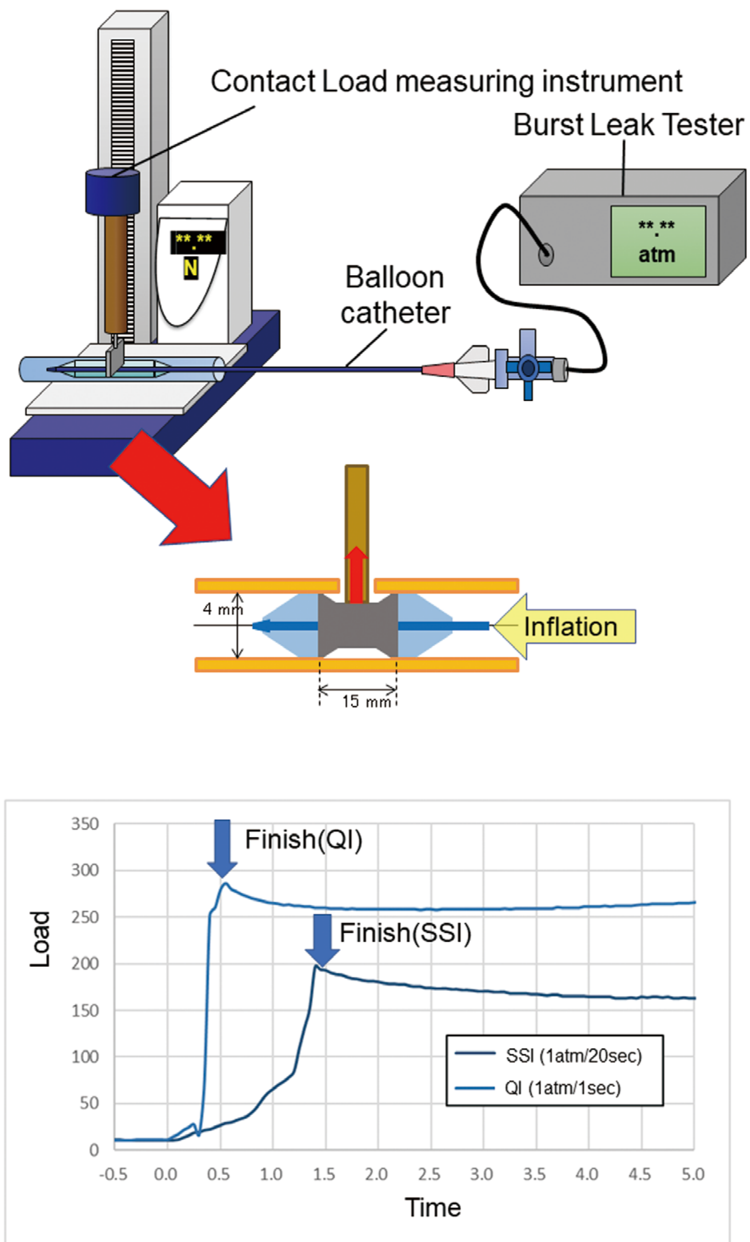

Figure 2. Diagram showing the set-up for measuring the load applied to the balloon surface using a contact load measuring instrument (STROGRAPH; TOYO Seiki Seisakusyo, Tokyo, Japan) for the quick inflation (QI; 1 atm/s) and super slow inflation (SSI; 1 atm/20 s) protocols. The load applied was lower for the SSI than QI protocol.

Methods

Experimental Study

The experimental study was performed using a constriction vessel model (Hydraulic Burst-leak Tester; Crescent Design, San Diego, CA, USA) and 4.0-mm×40-mm high-pressure balloon (SHIDEN HP; KANEKA Medics, Osaka, Japan; see **Figure 1**). The association between balloon pressure and expansion of the model constricted vessel was measured using a laser and compared between the QI (1 atm/s) and SSI (1 atm/20 s) protocols (**Figure 1A**). The load applied to the balloon surface was also measured for both protocols using a contact load measuring instrument (STROGRAPH; TOYO Seiki Seisakusyo, Tokyo, Japan; see **Figure 2**).

Clinical Study

A retrospective, single-center, non-randomized study was performed to evaluate differences in vessel dissection patterns after balloon angioplasty depending on inflation method. This study was performed using data from 81 consecutive patients (mean [±SD] age 74.6±9.2 years; 54 males) with symptomatic peripheral arterial disease who underwent balloon angioplasty for de novo femoropopliteal lesions between January 2017 and March 2019. Patients with in-stent restenosis and acute limb ischemia were excluded from the analysis. The SSI protocol was used in 30 patients (mean [±SD] age 72.9±9.4 years; 24 males), whereas a conventional inflation method was used in 51 patients (mean [±SD] age 75.1±8.6 years; 30 males). Baseline patient and lesion characteristics are summarized in **Table 1**.

Table 1. Baseline Patient and Lesion Characteristics Overall and in the SSI (1 atm/20 s) and Non-SSI Groups Separately

	Overall	SSI	Non-SSI	P value
Patient characteristics				
No. patients	81	30	51	
Age (years)	74.6±9.2	72.9±9.4	75.1±8.6	0.40
Male sex	66.7 (54)	80.0 (24)	58.8 (30)	0.06
BMI (kg/m²)	22.0±3.5	22.7±3.5	21.6±3.4	0.26
Hypertension	88.9 (72)	86.7 (26)	90.2 (46)	0.72
Dyslipidemia	69.1 (56)	80.0 (24)	62.7 (32)	0.14
Diabetes	66.7 (54)	60.0 (18)	70.6 (36)	0.34
CKD	46.9 (42)	50.0 (15)	45.1 (23)	0.82
Hemodialysis	18.5 (15)	20.0 (6)	17.6 (9)	0.78
Prior PCI	34.6 (28)	30.0 (9)	37.3 (19)	0.63
OMI	9.9 (8)	13.3 (4)	7.8 (4)	0.46
Prior CVD	22.2 (18)	23.3 (7)	21.6 (11)	1.00
Heart failure	12.4 (10)	10.0 (3)	13.7 (7)	0.74
Past or current smoker	69.1 (56)	73.3 (22)	67.7 (34)	0.62
Aspirin	81.5 (66)	83.3 (25)	80.4 (41)	0.76
Thienopyridine	64.2 (52)	66.7 (20)	62.7 (32)	0.81
Cilostazol	34.6 (28)	30.0 (9)	37.3 (19)	0.63
DOAC	7.4 (6)	10.0 (3)	5.9 (3)	0.69
ARB/ACEI	59.3 (48)	63.3 (19)	56.9 (29)	0.64
Statin	61.7 (50)	73.3 (22)	54.9 (28)	0.16
Insulin	16.1 (13)	16.7 (5)	15.7 (8)	1.00
CLTI	42.0 (38)	36.4 (12)	44.1 (26)	0.51
ABI	0.50±0.30	0.54±0.28	0.47±0.32	0.27
Lesion characteristics				
No. lesions	92	34	58	
TASC II classification				0.11
A	20.7 (19)	14.7 (5)	24.1 (14)	
B	23.9 (22)	38.2 (13)	15.5 (9)	
C	25.0 (23)	20.6 (7)	27.6 (16)	
D	30.4 (28)	26.5 (9)	32.8 (19)	
TASC high (TASC C/D)	55.4 (51)	47.1 (16)	60.3 (35)	0.28
RVD (mm)				
QVA	4.58±0.91	4.50±0.99	4.62±0.86	0.54
IVUS	4.98±0.78	5.09±0.79	4.91±0.78	0.38
Lesion length (mm)	179.2±97.3	165.4±89.3	187.3±101.6	0.30
CTO	57.6 (53)	61.8 (21)	55.2 (32)	0.52
PACSS grade				0.47
0	28.2 (26)	29.4 (10)	27.6 (16)	
1	7.6 (7)	2.9 (1)	10.3 (6)	
2	11.9 (11)	17.6 (6)	8.6 (5)	
3	13.0 (12)	8.8 (3)	15.5 (9)	
4	39.1 (36)	41.2 (14)	37.9 (22)	
Severe calcification (PACSS 3/4)	52.2 (48)	50.0 (17)	53.4 (31)	0.83

Continuous data are presented as the mean ± SD. Categorical data are presented as the percentage (number). ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CLTI, chronic limb-threatening ischemia; CTO, chronic total occlusion; CVD, cerebrovascular disease; DOAC, direct oral anticoagulants; IVUS, intravascular ultrasound; PACSS, Peripheral Arterial Calcium Scoring System; PCI, percutaneous coronary intervention; OMI, old myocardial infarction; QVA, quantitative vessel angiography; RVD, reference vessel diameter; SSI, super slow inflation; TASC, Trans-Atlantic Inter-Society Consensus.

The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Fukuoka University (No. 2018M087). All patients provided written informed consent for endovascular therapy (EVT) and were given the opportunity to opt-out via the Fukuoka University Hospital website.

Procedures

A 4.5- or 6.0-Fr guiding sheath was inserted via the ipsi- or contralateral common femoral artery. Unfractionated heparin (5,000 units) was injected via the sheath. After the lesion was crossed successfully, balloon pressure was maintained at 1–2 atm until the balloon was filled with contrast

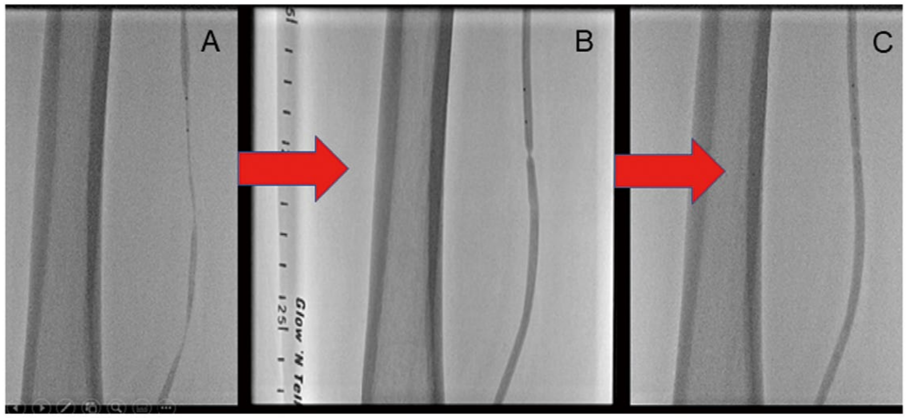

Figure 3. (**A**) A Balloon is kept maintained at a pressure of 1–2 atm until the balloon is filled with contrast from edge to edge. (**B**) After the balloon surface is attached to the vessel wall, the pressure is increased gently and gradually. (**C**) The balloon is dilated gradually depending on changes in balloon indentation seen on the monitor.

from edge to edge. The balloon was equally dilated from edge to edge, leaving harder plaque in the lesion. After the surface of the balloon attached to the vessel wall, pressure was increased slowly and gradually. Balloon dilation was gradual depending on image of balloon indentation seen on the monitor. The residual stenosis was dilated gradually with minimum load. After balloon indentation disappeared, the balloon was dilated to the optimal diameter at a rate of 1 atm every 3 s (**Figure 3**). If there was any residual stenosis and/or flow-limiting dissection after balloon dilation, further balloon dilation was performed and/or a self-expanding stent was placed at the discretion of the operator.

Angiogram Evaluations and Definitions

All angiograms were evaluated independently by 2 experienced operators for procedural success, grading of vessel dissection, and complications. All lesions within the femoropopliteal segment were characterized according to the TASC II classification.[17] Calcification in the femoropopliteal segment was assessed using unsubtracted angiography. The degree of lesion calcification was categorized according to the Peripheral Arterial Calcium Scoring System (PACSS) as follows: Grade 0, no visible calcification at the site of the target lesion; Grade 1, unilateral calcification <5 cm; Grade 2, unilateral calcification >5 cm; Grade 3, bilateral calcification <5 cm; and Grade 4, bilateral calcification >5 cm.[18]

Vessel dissection patterns after balloon angioplasty were classified according to the National Heart, Lung, and Blood Institute (NHLBI) classification system as follows: Type A, dissection with minor radiolucent areas; Type B, linear dissection; Type C, dissection with contrast outside the lumen; Type D, spiral dissection; Type E, persistent filling defects; and Type F, total occlusion without distal antegrade flow. Severe dissection was defined as Type C or higher, as reported previously.[19] In the present study, if multiple dissection patterns were observed in a single lesion, the more severe pattern was used in analyses.

Primary patency was assessed clinically based on patient symptoms and examinations, including the Rutherford classification and ankle-brachial index (ABI). If the symptoms and ABI were worsened, patients underwent duplex ultrasound assessment. Restenosis was defined as a peak systolic velocity ratio of 2.4 on duplex ultrasonography, which was considered to indicate >50% narrowing.

Statistical Analysis

Statistical analyses were performed using Excel 2016 (Microsoft, Washington, USA) and EZR ver. 1.41 (Saitama Medical Center, Jichi Medical University, Tochigi, Japan) which is a graphical user interface for R ver. 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Continuous variables are presented as the mean±SD and were compared between groups using t-tests. Categorical variables were compared between the groups using Chi-squared analysis or Fisher's exact test. Multivariate analysis was performed by logistic regression analysis for independent variables that were related to severe dissection. Two-tailed $P<0.05$ was considered significant.

Baseline characteristics of atherosclerotic risk factors, lesion characteristics, and the procedural methods were prescreened using univariate logistic regression analysis to identify independent predictors of severe dissection. The lesion characteristics evaluated herein are based on those reported previously,[15,19] and procedural methods were entered into a multivariate logistic regression analysis. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Results

Experimental Results

The extent of dilation of a model constricted vessel was measured using laser distance measuring instrument for the QI (1 atm/s) and SSI (1 atm/20 s) protocols. The pressure to start dilatation of folded balloon of manual slow inflation and the SSI protocol was 1.7 atm lower than that for the QI protocol (**Figure 1B**). The extent of dilation with the SSI protocol increased gradually, with the maximum dilatation

Table 2. Procedure Characteristics and Results for Lesions Overall and in the SSI (1 atm/20 s) and Non-SSI Groups Separately

	Overall (n=92)	SSI (n=34)	Non-SSI (n=58)	P value
Balloon diameter (mm)	4.79±0.72	4.79±0.73	4.79±0.72	0.99
Maximum balloon diameter (mm)	4.93±0.74	4.89±0.78	4.95±0.72	0.70
Balloon to vessel diameter ratio	0.97±0.14	0.94±0.15	0.99±0.13	0.19
Maximum inflation pressure (atm)	12.8±5.0	14.7±5.1	11.7±4.7	0.004
Inflation time (s)	214±126	342±64	139±86	<0.001
Use of high-pressure balloon	41.3 (38)	64.7 (22)	27.6 (16)	<0.001
Use of scoring balloon	6.5 (6)	0	10.3 (6)	0.08
Use of IVUS	66.3 (61)	70.6 (24)	63.8 (37)	0.64
Dissection type				<0.001
None	16.3 (15)	35.3 (12)	5.2 (3)	
A	25.0 (23)	32.4 (11)	20.7 (12)	
B	17.4 (16)	14.7 (5)	19.0 (11)	
C	18.5 (17)	2.9 (1)	27.6 (16)	
D	20.7 (19)	14.7 (5)	24.1 (14)	
E	2.2 (2)	0	3.4 (2)	
F	0	0	0	
Severe dissection (C–F)	41.3 (38)	17.6 (6)	55.2 (32)	<0.001
Final device				
Drug-coated stent	28.3 (26)	11.8 (4)	37.9 (22)	<0.001
Drug-coated balloon	19.6 (18)	50.0 (17)	1.7 (1)	<0.001
POBA	21.7 (20)	29.4 (10)	17.2 (10)	
Stentless	41.3 (38)	79.4 (27)	18.9 (11)	
ABI after the procedure	0.95±0.16	0.98±0.17	0.93±0.16	0.23

Continuous data are presented as the mean ± SD; categorical data are given as the percentage (number). IVUS, intravascular ultrasound; POBA, plain old balloon angioplasty; SSI, super slow inflation.

Table 3. Results of Univariate and Multivariate Analysis for Factors Associated With Severe Dissection

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Male sex	0.93 (0.33–2.62)	1.00		
Hypertension	1.59 (0.31–10.6)	0.72		
Diabetes	1.16 (0.41–3.33)	0.81		
Dyslipidemia	1.96 (0.69–6.17)	0.23		
CKD	0.75 (0.28–1.99)	0.65		
Hemodialysis	0.60 (0.15–2.2)	0.57		
CLTI	0.98 (0.39–2.46)	1.00		
CTO	1.59 (0.63–4.08)	0.30	1.92 (0.70–5.30)	0.21
Small vessel (RVD <4 mm)	0.62 (0.22–1.67)	0.37		
Long lesion (length >150 mm)	1.59 (0.63–4.01)	0.29	0.99 (0.35–2.76)	0.99
PACSS Grade4	1.15 (0.45–2.9)	0.83		
Balloon to vessel diameter ratio >0.9	2.72 (0.98–8.2)	0.04	1.92 (0.67–5.46)	0.22
Use of high-pressure balloon	0.47 (0.18–1.19)	0.09	0.78 (0.27–2.23)	0.65
SSI	0.16 (0.05–0.49)	<0.001	0.18 (0.06–0.53)	0.002

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

pressure for the same balloon expansion being lower with the SSI than QI protocol (17 vs. 20 atm, respectively; **Figure 1C**). The load applied to the balloon surface was also determined using a contact load measuring instrument for both the SSI and QI protocols models. The load applied to the balloon surface was approximately 100 g lower for the SSI than QI protocol (**Figure 2**).

Clinical Outcomes

As indicated in **Table 1**, there were no significant differences in patient and lesion characteristics, including medications, between the SSI and non-SSI groups. However, the maximum inflation pressure was significantly (P=0.004) higher and inflation time was significantly (P<0.001) longer in the SSI than non-SSI group (**Table 2**). The use of a high-pressure balloon was also significantly (P<0.001) higher in

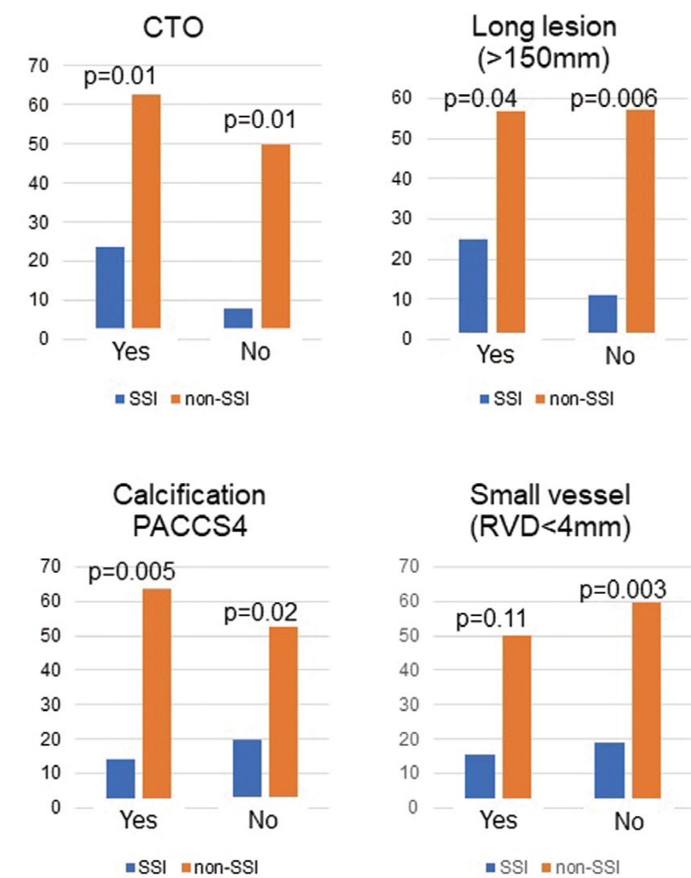

Figure 4. Incidence of severe dissection (%) in different types of lesions prepared using the super slow inflation (SSI; 1 atm/20 s) and non-SSI protocols. CTO, chronic total occlusion; PACCS4, Peripheral Arterial Calcium Scoring System Grade 4; RVD, reference vessel diameter.

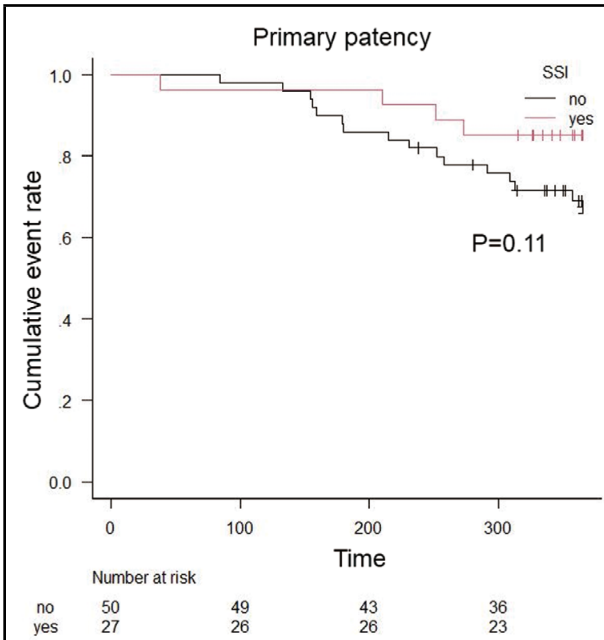

Figure 5. Kaplan-Meier estimates of primary patency demonstrated no significant differences between the super slow inflation (SSI; 1 atm/20 s) and non-SSI groups.

the SSI group.

In terms the final device used, the rate of use of drug-eluting stents (DES) was significantly higher in the non-SSI than SSI group (37.9% vs. 11.8%, respectively; P<0.001). In contrast, the rate of DCB use was higher in the SSI than non-SSI group (50.0% vs. 1.7%, respectively; P<0.001). The rate of severe vessel dissection was significantly lower in the SSI than non-SSI group (17.6% vs. 55.2%, respectively; P<0.001). In terms of clinical outcomes, the ABI improved significantly after the procedure in both groups.

The results of logistic regression analyses to determine factors associated with severe dissection are given in **Table 3**. Univariate regression analysis demonstrated that a balloon to vessel diameter ratio >0.9 (OR 2.72; 95% CI 0.98–8.20; P=0.043) and SSI (OR 0.16; 95% CI 0.05–0.49; P<0.001) were significantly associated with the absence of severe dissection. Multivariate regression analysis demonstrated that SSI was an independent factor preventing severe dissection (OR 0.18; 95% CI 0.06–0.53; P=0.002).

In additional analyses taking into account lesion characteristics, the efficacy of the SSI procedure was demonstrated for complex lesions, namely those with chronic total occlusion (CTO), long (>150 mm) lesions, and those with calcification (PACSS Grade 4). In small vessels (reference vessel diameter <4 mm), the SSI procedure was not associated with a significant reduction in the occurrence of severe dissection (OR 0.19; 95% CI 0.02–1.34; P=0.11; **Figure 4**).

Primary patency over a 12-month period was 85.2% in the SSI group and 68.0% in the non-SSI group. Kaplan-

Meier estimates of primary patency did not differ significantly between the SSI and non-SSI groups (P=0.11; **Figure 5**).

Discussion

The main findings of this study are that the SSI protocol can dilate plaques using lower force and that this method is associated with a lower risk of severe dissection. To the best of our knowledge, there are no studies reporting on experimental evaluations of the dilatation process and the clinical efficacy of the SSI protocol.

In the experimental study, we demonstrated that the pressure to start dilatation of folded balloon was approximately 2 atm (**Figure 1B**). With the SSI protocol, it is important to wait until the relief of balloon lapping. By waiting, equal dilatation from edge to edge of the balloon is attained. The SSI protocol dilated the model constricted vessel gradually and with lower load than the QI protocol (**Figure 1C**). To obtain good dilatation of vessels, some dissection is necessary. The distribution of soft plaque and minimal dissection of hard plaque are key to achieving better results of lesion preparation. Based on the assumption that dissection will occur when a balloon presses against the plaque surface, redistribution of the plaque at the start, using equal balloon dilatation with minimum pressure, is the most important aspect of the SSI protocol. The possibility of equal and gradual dilatation of the plaque was demonstrated by the experimental study. In our clinical experience, most lesions were dilated at approximately 2atm.; this means that the plaque is dilated equally with minimum load when a balloon comes in contact with the plaque first.

With regard to the process of plaque dilatation, the yield or tensile strength of the plaque are not known. If the dilatation strength is small, the plaque will recoil; if the dilatation strength is excessive, the plaque will be greatly dissected. However, we can determine whether a plaque is softer or harder by observing the SSI process. Gradual inflation is important at the beginning of balloon dilatation in the SSI protocol, and the balloon must be dilated to the optimal extent after indentation disappears so that optimal dilatation is obtained. In the present study, the rate of use of high-pressure balloons was higher in the SSI group. Although there were no significant differences in maximum balloon diameter, maximum inflation pressure was higher in the SSI group. This means that the lesions may be dilated by optimal balloon diameter with enough pressure using high-pressure balloons. Generally, a balloon begins to elongate and twist when the dilatation pressure is beyond a nominal pressure, because the balloon mechanics consist of radial and circumferential strength. This phenomenon was tends to be seen with semicompliant balloons rather than high-pressure balloons and means that unequal force will be applied to the plaque. High-pressure balloons may apply enough force equally because the nominal pressure of the balloon is relatively high. Although a benefit of using high-pressure balloons for lesion preparation with the SSI protocol was not demonstrated by logistic regression analysis, the SSI protocol may become more effective by using high-pressure balloons from the point of view of equal and optimal dilatation.

In fact, the present study found that lesion preparation with the SSI protocol produced better results in the clinical setting than conventional balloon angioplasty. Fujihara et al reported that dissection grades above type C were observed in 42% of cases, and smaller vessel diameter and/or longer lesions were related to a high incidence of dissection.[19] Horie et al reported on the angiographic outcomes of balloon angioplasty with inflation times >3 min and demonstrated that higher success rates were achieved by preventing severe dissection.[15] Because gradual and gentle inflation takes a long time, total inflation time is also quite long with the SSI protocol. Gradual, gentle, and long inflation times would reduce long dissections and enable the balloon to fix the flap on the vessel wall even if dissection occurs.[20,21] Plaques that can be spread at low pressure are already compressed evenly, preventing longitudinal extension of the dissection when hard plaques are dilated. This is why the total length of dissections is shorter and dissection grades are reduced. Compared with previous studies, the lesions in this study included complex lesions, such as long lesions, small vessels, and CTO lesions, but the incidence of severe dissection in the SSI group was lower. Although statistically significant differences were not demonstrated between SSI and non-SSI groups for small vessels, a trend in favor of SSI was seen. This SSI protocol may be effective for any lesion.

The results of the present study indicate that the SSI protocol may be effective for avoiding unwanted dissection; it does not require any special devices and can be performed in an easy, safe, and inexpensive manner. The SSI protocol as a form of lesion preparation may lead to increased treatment options.

Study Limitations

This study has several important limitations. First, the study was a non-randomized, retrospective, single-center analysis with a small sample size. Second, selection bias regarding balloon selection and the inflation method could not be eliminated. Final devices were chosen at the discretion of the operator depending on patient characteristics, the severity of vessel dissection, and lumen area after predilatation. Third, this study did not demonstrate statistically significant differences in primary patency, although the primary patency rate was relatively high in the SSI group. Finally, this study lacked independent angiographic core laboratory adjudication.

Conclusions

SSI is a gentle and effective method for the preparation of femoropopliteal lesions that can reduce the incidence of severe angiographic dissection in the DCB era.

Acknowledgements

None.

Sources of Funding

This study did not receive any specific funding.

Disclosures

S.M. is a member of *Circulation Reports*' Editorial Team. S.M. has received remunerations from Daiichi Sankyo, Takeda Pharmaceutical, Boehringer Ingelheim, Otsuka Pharmaceutical, and Bayer Yakuhin; research funding from Daiichi Sankyo, Takeda Pharmaceutical, Astellas Pharma, and Bayer Yakuhin; and scholarship funds from Alfresa Corporation. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Ethics Committee of Fukuoka University (No. 2018M087).

Data Availability

The data analysis file and all annotated data files are available from J-STAGE data.

References

1. Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med* 2006; **354:** 1879–1888.
2. Soga Y, Iida O, Hirano K, Yokoi H, Nanto S, Nobuyoshi M. Mid-term clinical outcome and predictors of vessel patency after femoropopliteal stenting with self-expandable nitinol stent. *J Vasc Surg* 2010; **52:** 608–615.
3. Iida O, Takahara M, Soga Y, Suzuki K, Hirano K, Kawasaki D, et al. Shared and differential factors influencing restenosis following endovascular therapy between TASC (Trans-Atlantic Inter-Society Consensus) II class A to C and D lesions in the femoropopliteal artery. *Am J Coll Cardiol Cardiovasc Interv* 2014; **7:** 792–798.
4. Rocha-Singh KJ, Bosiers M, Schultz G, Jaff MR, Metha M, Matsumura JS, et al. A single stent strategy in patients with lifestyle limiting claudication: 3-year results from the Durability II trial. *Catheter Cardiovasc Interv* 2015; **86:** 164–170.
5. Laird JA, Schneider PA, Jaff MR, Brodmann M, Zeller T, Metzger DC, et al. Long-term clinical effectiveness of a drug-coated balloon for the treatment of femoropopliteal lesions. *Circ Cardiovasc Interv* 2019; **12:** e007702.
6. Thieme M, Von Bilderling P, Paetzel C, Karnabatidis D, Delgado JP, Lichtenberg M, et al. The 24-month results of the Lutonix Global SFA Registry. *Am J Coll Cardiol Cardiovasc Interv* 2017; **10:** 1682–1690.
7. Bosiers M, Deloose K, Callaert J, Moreels N, Keirse K, Peeters P, et al. Results of the Protege EverFlex 200-mm-long nitinol stent (ev3) in TASC C and D femoropopliteal lesions. *J Vasc Surg* 2011; **54:** 1042–1050.
8. Armstrong EJ, Saeed H, Alvandi B, Singh S, Singh GD, Yeo KK, et al. Nitinol self-expanding stents vs. balloon angioplasty for very long femoropopliteal lesions. *J Endovasc Ther* 2014; **21:** 34–43.
9. Tosaka A, Soga Y, Iida O, Ishihara T, Hirano K, Suzuki K, et al. Classification and clinical impact of restenosis after femoropopliteal stenting. *Am J Coll Cardiol* 2012; **59:** 16–23.
10. Micari A, Vadalà G, Castriota F, Liso A, Grattoni C, Russo P, et al. 1-Year results of PCBs for long SFA lesions. *Am J Coll Cardiol Cardiovasc Interv* 2016; **9:** 950–956.
11. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med* 2015; **373:** 145–153.
12. Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari J, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation* 2015; **131:** 495–502.
13. Bausback Y, Wittig T, Schmidt A, Zeller T, Scheinert D, Peeters P, et al. Drug-eluting stent versus drug-coated balloon revascularization in patients with femoropopliteal arterial disease. *Am J Coll Cardiol* 2019; **73:** 667–679.
14. Tan M, Urasawa K, Koshida R, Haraguchi T, Kitani S, Igarashi K, et al. Comparison of angiographic dissection patterns caused by long vs short balloons during balloon angioplasty of chronic femoropopliteal occlusions. *J Endovasc Ther* 2018; **25:** 192–200.
15. Horie K, Tanaka A, Taguri M, Kato S, Inoue N. Impact of prolonged inflation times during plain balloon angioplasty on angiographic dissection in femoropopliteal lesions. *J Endovasc Ther* 2018; **25:** 683–691.
16. Courtney TH. Overview of mechanical behavior, permanent deformation. *Mechanical Behavior of Materials* 2005; **chapter1.3:** 6–13.
17. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007; **33**(Suppl 1)**:** S1–S75.
18. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: Prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv* 2014; **83:** E212–E220.
19. Rogers JH, Lasala JM. Coronary artery dissection and perforation complicating percutaneous coronary intervention. *J Invasive Cardiol* 2004; **16:** 493–499.
20. Palazzo AM, Gustafson GM, Santilli E, Kemp HG Jr. Unusually long inflation times during percutaneous transluminal coronary angioplasty. *Catheter Cardiovasc Diagn* 1988; **14:** 154–158.
21. Sievert H, Ensslen R, Merle H, Milde H, Scherer D, Schulze R, et al. Long term dilatation after unsuccessful percutaneous transluminal coronary angioplasty. *Dtsch Med Wochenschr* 1994; **119:** 1458–1461 (in German).