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*Original Article*

# Late neointimal proliferation following implantation of stents for relief of pulmonary arterial stenosis

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**Abstract** On the assumption that the diameter of the reference vessel might determine the thickness of neointimal coverage of stents placed in the pulmonary arteries, we analyzed the angiograms of 28 lesions in 17 patients who underwent follow-up cardiac catheterization. Excluding 2 lesions where late stenosis was determined mainly by recoil of greater than 30%, we investigated the neointimal thickness of 26 lesions in 16 patients. Several factors that might contribute to late re-stenosis were also analyzed. Age and body weight at implantation ranged from 0.8 to 20 years, with a median of 6 years, and from 6.8 to 77.5 kg, with a median of 17.6 kg. Follow-up interval was from 6 to 15 months, with a median of 6 months.

There was a significant increase in diameter, as well as a reduction in pressure gradient, immediately after the implantation of stents. Although there was no significant difference between the achieved diameter and the diameter of the stent at follow-up, the diameter of the lesion at follow-up was significantly smaller than the diameter achieved by stenting. The increase in the pressure gradient at follow-up was slightly greater in 4 lesions where the late reduction in diameter was greater than 30% than in the 18 lesions where this was less than 30% ($p = 0.05$). The diameter of the reference vessel, and the diameter by stenting correlated with the late reduction in diameter. All lesions with diameter reduced greater than 30% had a reference diameter of less than 6.1 mm, and a diameter achieved by stenting of less than 6.5 mm. Late loss in luminal diameter directly correlated with the thickness of the neointimal coverage. In conclusion, close observation should be mandatory following implantation of stents in small pulmonary arteries.

Keywords: Late loss; stent; pulmonary artery stenosis

Implantation of stents is now an option for treatment of various stenotic lesions in the great vessels.[1–8] Although neointimal covering of the surface of the stent may lead to some degree of late luminal narrowing, 1–2 mm of neointimal growth is usually regarded as insignificant.[3,7,9,10] In this study, we investigated the neointimal thickness on stents implanted in the pulmonary arteries, on the assumption that the diameter of the reference vessel may determine its extent, as in the coronary artery.[11–13]

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## Subjects and methods

We analyzed angiograms of 28 lesions in 17 patients who underwent follow-up cardiac catheterization 6 months or more after implantation of stents. Age and body weight at implantation ranged from 0.8 to 20 years, with a median of 6 years, and from 6.8 to 77.5 kg, with a median of 17.6 kg, while follow-up interval was 6–15 months, with a median of 6 months. Underlying heart diseases included 11 patients with tetralogy of Fallot, 6 with accompanying pulmonary atresia, 4 with univentricular physiology, produced by tricuspid atresia, double inlet right ventricle, double outlet right ventricle, and hypoplastic left heart syndrome, one each complete, and corrected transposition with ventricular septal defect and pulmonary atresia. Lesions were located in the left pulmonary artery in

13 cases, the right pulmonary artery in 14, and the pulmonary trunk in one. On the right side, 5 lesions were distal to the first branch, while the others involved the pulmonary trunk. Surgical procedures included angioplasty with or without insertion of a patch in 22, and 1 valved pericardial roll. Five lesions were native. Palmaz P308, 188, or 128 stents were implanted for central lesions, and P106, or P205 were implanted in lesions involving the distal right pulmonary artery. Implantation was performed using techniques described extensively by other authors,[1–3,7,8] while the balloon was inflated to 10–12 atmospheres using a 20 ml inflator. Predilation was performed in only 2 lesions where a long sheath could not be passed across the stenosis. Aspirin or dipyridamole was given until follow-up angiography.

Under intubated general anesthesia, routine cardiac catheterization was performed. Prior to implantation, we measured the minimal diameter of the lesion, the diameter of the reference vessel on the left or right anterior and cranial angiogram for the left or right pulmonary artery, and on the lateral projection for the pulmonary trunk. The achieved diameter represented the diameter after implantation of the stent. On follow-up angiogram, we measured the minimal diameter, the internal diameter of the stent strut, and the thickness of the separation between the narrowest lumen and the stent strut, this latter value being regarded as the neointimal coverage on the stent. Magnification was corrected using a grid positioned similarly to the patient. Stenosis ratio, acute gain, achieved ratio, recoil, and late loss were calculated as follows:

- Stenosis ratio (%) = minimal diameter of the lesion × 100/diameter of the reference vessel.
- Acute gain (%) = (achieved diameter − minimal diameter) × 100/minimal diameter.
- Achieved ratio (%) = (diameter of the reference vessel − achieved diameter) × 100/diameter of the reference vessel.
- Recoil (%) = (achieved diameter − diameter of the stent at follow-up) × 100/achieved diameter.
- Late loss (%) = (achieved diameter − minimal diameter at follow-up) × 100/achieved diameter.

After excluding 2 lesions where late luminal loss was largely due to recoil, we analyzed factors that contributed to subsequent luminal narrowing in 26 lesions.

Written informed consent for implantation of stents and cardiac catheterization was obtained from the patient and/or their parents.

Data were expressed as mean ± standard deviation. Statistical comparisons were done by chi-square, Welch's t-test, and linear regression function test using StatView 5.0 software (SAS Institute, Cary, NC, USA). A p-value less than 0.05 was considered statistically significant.

## Results

The minimal diameter of the lesions, the achieved diameter, and the diameter of the stent, and lesion at follow-up ranged from 1.5–7.8 (4.4 ± 1.7) mm, 4.2–13.0 (8.2 ± 2.2) mm, 4.0–13.0 (7.9 ± 2.0) mm, and 2.4–13.0 (6.9 ± 2.6) mm, respectively. There was a significant increase in the diameter, as well as a reduction in the pressure gradient, immediately after implantation of stents. Although there was no significant difference between the diameter achieved and that of the stent, the minimal diameter of the lesion at follow-up was significantly smaller than the diameter achieved by stenting. There was no significant change in the pressure gradient at follow-up (Fig. 1).

Late luminal narrowing ranged from −2% to 63%, while the recoil ratio ranged around ±10%, except for 2 lesions (closed circle in Fig. 2, left) that recoiled 32% and 43% each on follow-up (Fig. 2, left). In this particular patient, the proximal portion of 2 stents that were implanted simultaneously at the bifurcation in a Y-shape, recoiled in the follow-up.

Although the increase in pressure gradient at follow-up was slightly larger in 4 lesions where the late narrowing was greater than 30% (11 ± 4 mmHg) than in 18 lesions where the late narrowing was less than 30% (5 ± 11) mmHg ($p = 0.05$), we did not find a significant correlation between late narrowing and any increase in pressure gradient.

There was no significant correlation between late narrowing and either age at implantation, weight at implantation, follow-up interval, achieved ratio, or the stenosis ratio. Lesions in the left pulmonary artery showed a significantly greater late narrowing than did these in the right pulmonary artery. The diameter of the reference vessel and the achieved diameter both correlated with late narrowing (Table 1, Fig. 2, right).

Table 1.

| Analyzed factors | p | Remarks |
|---|---|---|
| Age at implantation | ns | |
| Weight at implantation | ns | |
| Follow-up interval | ns | |
| Acute gain | ns | |
| Achieved ratio | ns | |
| Laterality of the lesion | 0.04 | left > right |
| Stenosis ratio | ns | |
| Lesion diameter | ns | |
| Diameter of the reference vessel | 0.02 | $r = -0.46$ |
| Achieved diameter | 0.004 | $r = -0.55$ |

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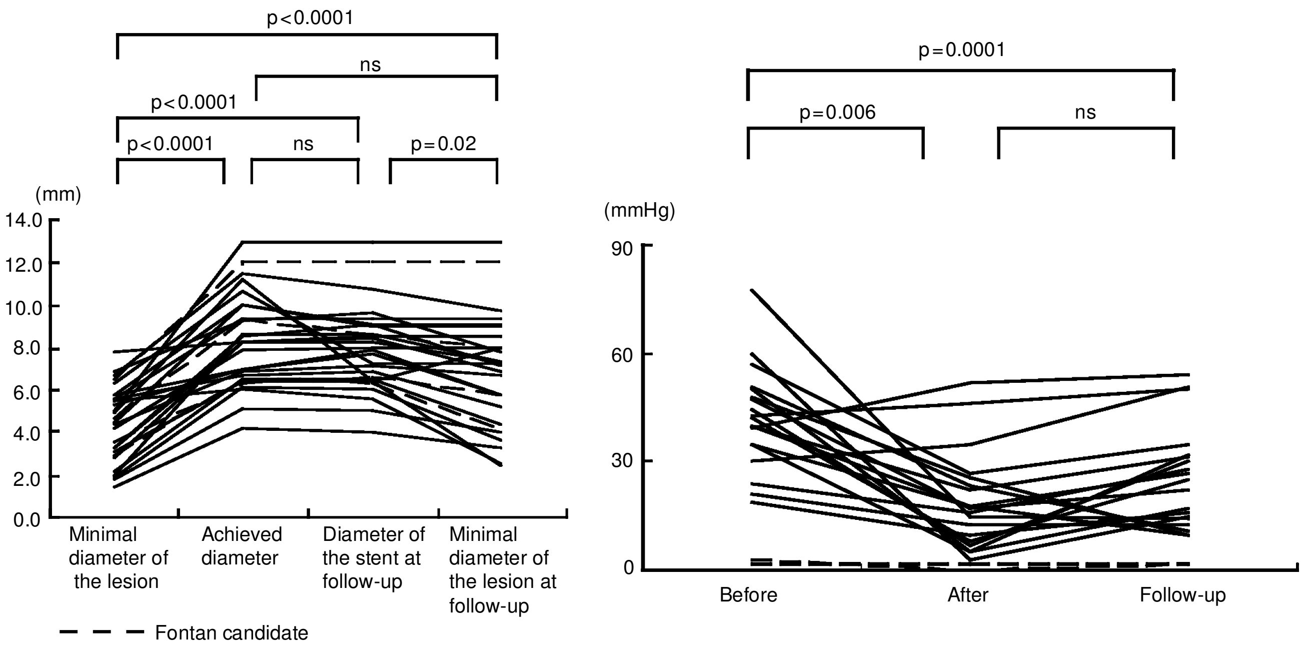


**Figure 1.**
*Changes in the minimal diameter of the lesion, the achieved diameter, the diameter of the stent at follow-up, and the minimal diameter of the lesion at follow-up (left), and pressure gradient before, after, and at follow-up after implantation of stents (right).*

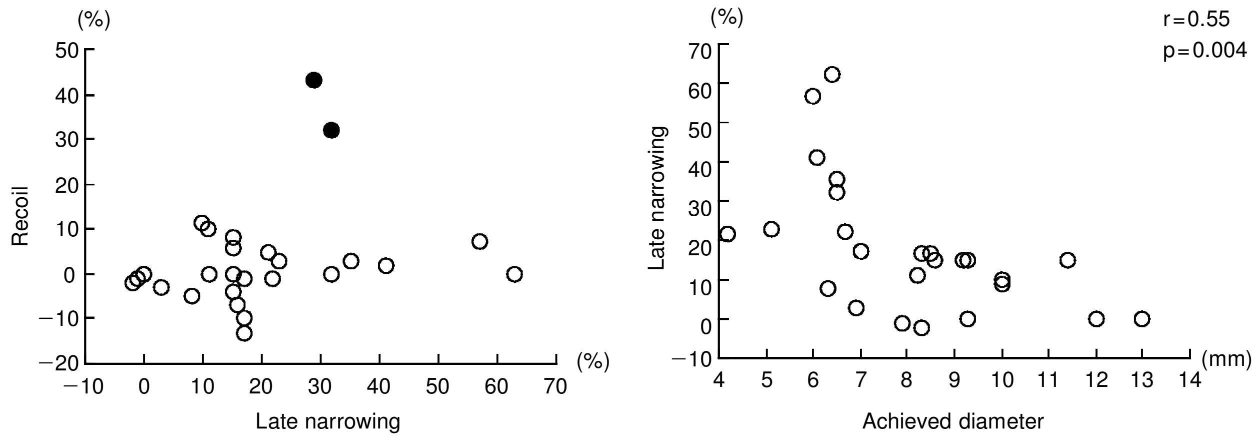


**Figure 2.**
*Distribution of late luminal narrowing and the recoil (left), and relationship between late narrowing and the achieved diameter (right). Two lesions (closed circle in Fig. 2, left) recoiled 32 and 43% each on follow-up.*

Total thickness of neointimal coverage also correlated well with both late narrowing, and the diameter achieved by stenting (Fig. 3, left and right).

We performed redilation of 5 lesions in 3 patients (cases 2, 8, 15), because of excessive neointimal proliferation and/or increase in pressure gradient. Neointimal coverage was most marked at the distal stent in 1, focal at the site of previous stenosis in 1, and diffuse in 3.

## Discussion

Currently implantation of stents is considered a useful strategy for treating pulmonary stenosis, even in infants or small children.[14–16] Early studies demonstrated that, in the intermediate term, neointimal proliferation on the stent strut rarely produced a significant increase in the pressure gradient. A small number of patients, nonetheless, required redilation of the stent because of in-stent re-stenosis.[3,7,9,10]

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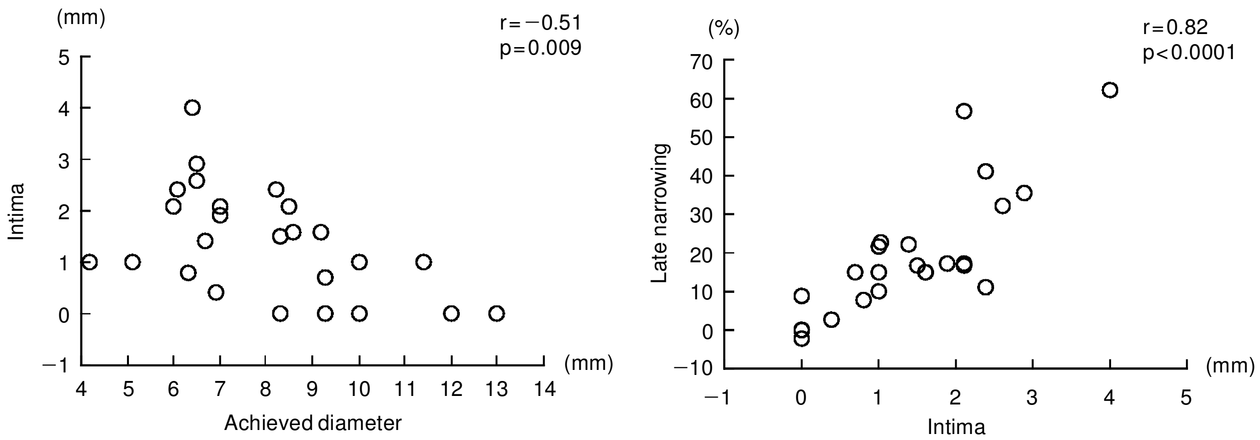


**Figure 3.**
*Relationship between thickness of neointima and the achieved diameter (left), and between late narrowing and thickness of neointima (right).*

Diabetes, multiple stents, and smaller final minimal diameters were reported as strong predictors of re-stenosis after placement of coronary stents in adults. A minimal diameter less than 3 mm at the end of the procedure increased the risk of re-stenosis.[11–13] There is a paucity of data, however, regarding the extent to which the diameter of the reference vessel itself influences subsequent neointimal proliferation. As reported previously, implantation of stents was highly effective in the present study. Furthermore, there was no significant increase in pressure gradient at follow-up. But, there was a significant decrease in the minimal diameter of the lesion at follow-up, with late luminal loss ranging 2–63%. Late loss was significantly greater in lesions involving the left pulmonary artery than in the right. The diameter of the reference vessel itself, and the diameter achieved by stenting, negatively correlated with late luminal narrowing. As these diameters were smaller in the left than in the right pulmonary artery, we believe the difference in the late narrowing was determined by the diameter of the vessels themselves. All lesions with narrowing of greater than 30% had diameters of the reference vessels less than 6.1 mm, and diameters produced by stenting of less than 6.5 mm. As the late narrowing directly correlated with the thickness of the neointimal coverage, excluding the lesions with large stent recoil, we believe that pulmonary arterial stenosis of this degree is at high risk of excessive intimal proliferation. In 2 stents, implanted at the bifurcation in a Y-shape simultaneously, recoil exceeded 30%. Although we could not determine the precise mechanism of such recoil, we believe that the proximal portion, where only small lengths of the 2 stents contacted each other, might have less radial strength.

Although the increase in pressure gradient at follow-up was slightly larger in lesions where narrowing was greater than 30% compared to those with less narrowing, we did not find significant correlation between late narrowing and an increase in pressure gradient. Excluding 4 patients with Fontan physiology, where the pressure gradient may not directly reflect the severity of stenosis because of the low pressure circulation, 10 of 13 patients had multiple lesions. As pressure gradients depend on the volume of flow of blood through the lesion, disproportionate narrowing in these circumstances may cause the discrepancy between the narrowing observed and the increase in pressure gradient.

Fogelman et al.[7] reported 3 patterns of ingrowth; proximal or distal ingrowth where the implant was larger than the diameter of the adjacent vessel, focal ingrowth at the site of previous stenosis, and diffuse ingrowth. Although all these patterns were identified in our study, we could not clarify the factors that determined the various patterns. Fogelman et al.[7] also reported that over-dilation of the stent may promote intimal proliferation at its edge. We did not find any correlation between the achieved ratio and late narrowing. There should be limits, however, to the diameter to which a stent can be dilated, particularly in small vessels. Consequently, medical treatment to prevent excessive ingrowth of intima[17,18] might be necessary for such lesions.

The small number of our patients had limited our interpretation. Thus, we could not clarify any relationship between previous surgical methods and late intimal growth because of the great variety of techniques and materials used in a relatively small number of patients. As the degree of intimal proliferation may depend on the design of the stent, patterns of intimal proliferation should be investigated using novel stents.[13,19,20]

In conclusion, close observation should be mandatory following implantation of stents in small

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pulmonary arteries. Early redilation might occasionally be required for such lesions.

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