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EXPERIMENTAL STUDIES

Intramural Delivery of a Specific Tyrosine Kinase Inhibitor With Biodegradable Stent Suppresses the Restenotic Changes of the Coronary Artery in Pigs In Vivo

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Objectives. **This study was designed to examine whether or not intramural delivery of ST638 (a specific tyrosine kinase inhibitor) with biodegradable stent can suppress the restenotic changes of the coronary artery in vivo.**

Background. **Clinical and animal studies demonstrated that restenosis after coronary intervention results from a combined effect of neointimal formation and geometric remodeling (decrease in total cross-sectional area). Thus, the most effective strategy to prevent the restenosis appears to inhibit both the neointimal formation and geometric remodeling by antiproliferative agent and stent, respectively. We have previously shown that ST638 markedly suppresses the restenotic changes of the porcine coronary artery when applied from the adventitial site.**

Methods. **A poly-L-lactic acid biodegradable stent was coated with either ST638 (0.8 mg) or equimolar of its inactive metabolite, ST494. A pair of these stents were implanted alternatively in the left anterior descending or circumflex coronary artery in pigs (n = 6). Three weeks after the procedure, coronary stenosis was assessed by angiography followed by histological examination.**

Results. **Coronary stenosis was significantly less at the ST638 stent site than at the ST494 stent site (47 ± 5% vs. 25 ± 4%, $p < 0.01$). Histological examination also showed that the extent of neointimal formation and that of geometric remodeling were significantly less at the ST638 stent site than at the ST494 stent site ($p < 0.05$).**

Conclusions. **These results indicate that intramural delivery of a specific tyrosine kinase inhibitor with biodegradable stent overcomes the proliferative stimuli caused by balloon injury, the stent itself, and the drug coating on the stent, resulting in the suppression of the restenotic changes of the coronary artery in vivo. This strategy might also be useful in the clinical setting in humans.**

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Percutaneous transluminal coronary angioplasty (PTCA) is a widely accepted treatment for coronary artery disease. However, the usefulness of PTCA is limited by restenosis, which occurs in 30–40% of patients within 3–6 months after the procedure (1,2). The restenosis after PTCA is currently understood as a combined process of neointimal formation and geometric remodeling in response to balloon injury (3). Therefore, the strategy to suppress both the neointimal formation by antiproliferative drugs and the geometric remodeling by stent (4,5) appears to be a reasonable approach to overcome the restenosis after PTCA.

After balloon angioplasty, a series of interactions between blood elements and the vessel wall occurs, which then promotes the migration and proliferation of smooth muscle cells within the intima (6,7). These processes are known to be induced by growth factors, such as platelet-derived growth factor (PDGF), fibroblast growth factor-2, and insulin-like growth factor-1, and by deposition of extracellular matrix components (8–12). Receptors for these growth factors have tyrosine kinase activities and phosphorylate their own tyrosine residues upon ligand binding (13). Therefore, tyrosine kinases are important transducers of a variety of extracellular signals that regulate proliferation, differentiation, and specific functions of differentiated cells (14). Indeed, we have previously shown that neointimal formation of the coronary artery induced by chronic treatment with interleukin-1 beta (IL-1β) (15) or PDGF (16), or by balloon injury (17), is markedly suppressed by ST638, a specific tyrosine kinase inhibitor, applied from the adventitial site in pigs. Since the coronary

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Abbreviations and Acronyms

EGF = epidermal growth factor
EEL = external elastic lamina
HPLC = high-performance liquid chromatography
IEL = internal elastic lamina
IL-1β = interleukin-1 beta
PDGF = platelet-derived growth factor
PLLA = poly-L-lactic acid
PTCA = percutaneous transluminal coronary angioplasty

lesions in those animal models are similar to those in human restenotic lesions, ST638 might also be effective to prevent the neointimal formation after PTCA in humans.

Synthetic polymers are more suitable than metals as a material of stent in terms of compliance and tissue responses, as well as a vehicle for intramural drug delivery (18–24). Poly-L-lactic acid (PLLA) is a biodegradable polymer that could potentially be used in many clinical situations (25–27). PLLA is suitable as a material for stent because the collapse pressure of the stents made from the polymer surpasses 300 mm Hg and its disintegrated half-life is 60–90 d, which is enough to prevent the geometric remodeling of the coronary artery after PTCA (28–30).

Methods

Materials. PLLA stents (Igaki-Tamai stent; Igaki Medical Planning) (31) were made of 120-μm PLLA thread (molecular mass ~185 kD), folded over a tubular device. The stents were loaded with 0.8 mg ST638 (α-cyano-3-ethoxy-4-hydroxy-5-phenyl-methylcinnamamide, Kaneka Co.) or equal molar ST494, as an inactive control, which is a nonactive conductor of ST638 (32). To load ST638 or ST494 steadily and smoothly, poly-ε-caprolactone, one of the biodegradable polymer, was coated on PLLA stents with these drugs (33). This coating process was performed under sterile conditions. Drug-loaded PLLA stents were then mounted on standard angioplasty balloon catheters (manufacture-specified balloon diameter, 3.0 mm). The whole implant systems were produced in a clean laboratory environment.

Animal preparation. Fourteen male domestic pigs (Nihon Crea Inc.) 2–3 months old and weighing 25–30 kg, were pretreated with aspirin (325 mg PO) daily for 5 days before the procedure, and continued throughout the experimental period. On the day of the stent implantation, the animals were sedated with ketamine hydrochloride (1.25 mg/kg IM) and were then anesthetized with sodium pentobarbital (20 mg/kg IV) (15,16). They were then intubated and ventilated with room air, and oxygen was supplemented via a positive-pressure respirator (Shinano Inc.). Arterial pH, pO_2, and pCO_2 were kept within normal ranges. Under aseptic conditions, the left carotid artery was surgically exposed, and a 10-F sheath was inserted. After systemic heparinization (10,000 U IV), angiograms of the left coronary arteries were performed with a femoral Judkins guiding catheter (10F, Medtronic Inc.). A PLLA stent loaded with either ST638 (ST638 stent) or ST494 (control stent) was implanted alternatively to the proximal segment of either the left anterior or the left circumflex coronary arteries. The coronary artery for the stenting was randomized. Arteriotomy was then repaired, the skin was closed, and the animals were allowed to recover from anesthesia.

Three weeks after the procedure, six animals again underwent coronary arteriography. They were then euthanized with a lethal dose of sodium pentobarbital and exsanguinated, and the left coronary arteries were perfusion-fixed for histological analysis. Another eight animals were sacrificed 0, 3, 7, and 21 d (two animals in each period) after the stent implantation to determine the ST638 release in vivo.

The experiment was reviewed by the Committee of the Ethics on Animal Experiment at the Kyushu University School of Medicine and was carried out under the control of the Guidelines for Animal Experiment at the Kyushu University School of Medicine and The Law (No. 105) and Notification (No. 6) of the Japanese Government.

ST638 Release from PLLA stent in vitro and its pharmacokinetics in vivo. To investigate the release of ST638 from the PLLA stent in vitro, an ST638 stent was immersed in 1 mL of fetal calf serum at room temperature for 1–21 d. Fetal calf serum was replaced daily, and the amount of ST638 released into the serum was quantified by high-performance liquid chromatography (HPLC) (15).

To determine the pharmacokinetics of ST638 in the porcine coronary artery in vivo, the coronary artery with the ST638 stent was taken out immediately after and 3, 7, and 14 d after the implantation of the ST638 stent. The amount of ST638 was quantified by HPLC and expressed as its concentration of per 1 g wet weight of the vessel.

Stent implantation in vivo. The ST638 or control stent was mounted under sterile conditions on the angioplasty catheter (diameter 3.0 mm). On the basis of the angiograms, the proximal segment with a diameter of 2.5–3.0 mm was selected in both the left anterior descending and the left circumflex coronary artery, so that the balloon-to-artery diameter ratio was approximately 1.2. An angioplasty catheter with the ST638 or control stent was then advanced to one of the two coronary segments for implantation over a standard PTCA guide wire. The balloon catheter was inflated at 8 atmospheres for 30 s two times at an interval of 2 min, and was then slowly withdrawn, leaving the stent in place. The coronary segment for stent implantation was randomized. After the angiography of the stented coronary arteries to assure the vessel patency, all equipments were removed, and the carotid artery was ligated.

Coronary angiography and hemodynamic measurements. Selective coronary angiography was performed before, immediately after, and 3 wk after the stent implantation. A preshaped Judkins catheter was inserted into the right or left carotid artery, and coronary angiography in a left oblique view was performed. Electrocardiograms in leads I, II, III, V1, and V6 were recorded. Arterial pressure was measured with a pressure transducer (Gould Inc.) connected to a Judkins

catheter. The arterial pressure, heart rate, and electrocardiograms were continuously monitored and recorded on a pen recorder (NEC San-Ei Polygraph System) throughout the procedure (15,16).

Selective coronary angiography was performed in a left anterior oblique projection that allowed a clear visualization of the stent implantation site, using the Toshiba cineangiography system (KKO-1250/CAS-CA, Toshiba Medical Inc.) (15–17). The angiograms were recorded on 35-mm cinefilm (Varicath I, VARIX) at 48 frames per second. The angle of the projection, the posture of the animal, and the distance from x-ray focus to the object and that from the object to the image intensifier were carefully kept constant during each experiment (15–17). Cineangiograms were projected on a screen using a cineprojector (ELK-35CB, Nishimoto Sangyo Inc.), and an end-diastolic frame was selected. The coronary luminal diameters were measured with a caliper (15–17). Using this technique, excellent correlations between repeated measurements (r = 0.99) and between repeated different observers (r = 0.98) were confirmed in the range of the coronary diameter from 0.98 to 5.58 mm (15–17). The coronary diameter, where either ST638 or control stent was applied, was comparable with the site just proximal to the stent implantation segment.

Histopathological study. The animals were then sacrificed with a lethal dose of sodium pentobarbital, exsanguinated, and then the heart was excised. The left coronary artery was perfused with 6% formalin at 120 mm Hg and fixed with formalin for 1 wk. For the light microscopic examination, tissue samples were embedded in paraffin, sectioned into 5-μm-thick slices, mounted on glass slides, and stained with hematoxylin-eosin and van Gieson's methods.

The intimal and medial areas were measured in photomicrographs by a computer-assisted picture analysis system (Genlocker System; Sony) (15–17). The intimal area and medial area were calculated by measuring the internal border of the vessel (lumen area), the area encircled by the internal elastic lamina (IEL area), and the area encircled by the external elastic lamina (EEL area). The degree of the neointimal formation was expressed by the intimal area/medial area ratio (I/M ratio) (15–17). The degree of the vascular remodeling was expressed by the change in the three vessel areas (lumen area, IEL area, and EEL area), which were calculated by the formula: $(A_{Tx} - A_{CONT})/A_{CONT} \times 100$ (%), where A_{Tx} and A_{CONT} are the vessel areas of the coronary segments at the treated (stent implanted) site and at the adjacent control site, respectively. The geometric remodeling was defined as the reduction of the IEL and EEL areas (15,16).

Statistical analysis. The results are expressed as mean ± SEM. Throughout the text and in the figures, n represents the number of animals examined. Multiple comparisons were made by analysis of variance for repeated examinations followed by a Scheffe's post-hoc test. Paired data were analyzed by Student's *t*-test. A p value of <0.05 was considered to be statistically significant.

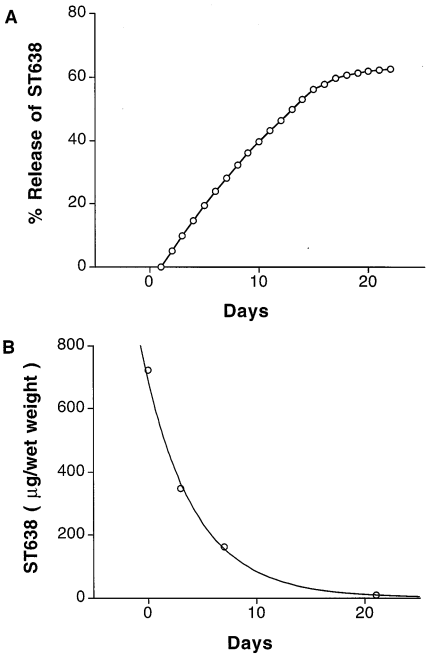


Figure 1. A, Cumulative ST638 release from PLLA stent over a 3-wk period as a percentage of the initial loaded ST638 in vitro. Each data point represents the mean of two measurements. **B,** Local concentration of ST638 in the porcine coronary arteries implanted with the ST638 stent at 0, 3, 7, and 21 d after stent implantation in vivo.

Results

ST638 release from PLLA stent in vitro and its pharmacokinetics in vivo. ST638 was released linearly into fetal calf serum from the PLLA stent for the initial 2 wk, followed by gradual release until day 21 in vitro (Fig. 1A). The concentration of ST638 in the porcine coronary artery implanted with ST638 was exponentially decreased until day 21 in vivo (Fig. 1B). The estimated local concentration of ST638 in the arterial wall at 0, 3, 7, and 21 d after the implantation was 2.0, 0.98, 0.46, 0.023 mmol/L, respectively, while regarding 1 g of wet weight of the vessel as 1 mL of fluid. The estimated local concentration of ST638 at day 0 was thus 100 times higher than that at day 21, which was equivalent to the minimal effective concentration of the inhibitor (0.025 mmol/L), which inhibits intracellular tyrosine kinases, such as tyrosine kinase of epidermal growth factor (EGF) receptor (32).

Coronary diameters and hemodynamic variables. Before the stent implantation, there was no significant difference in the coronary diameters between the coronary segments implanted with the ST638 or control stent (Table 1). However, 3 wk after the stent implantation, the diameter of the coronary segment implanted with the ST638 or control stent was significantly decreased, whereas the diameter was significantly greater at the ST638 stent site than at the ST494 stent site (Table 1). In contrast, the diameter of the untreated segment remained unchanged before and 3 wk after the stent implantation (Table 1). There was no significant difference in blood

Table 1. Coronary Diameters and Hemodynamic Variables Before and After Coronary Stenting in Pigs

		Coronary diameter (mm)				
	n	No Tx	Control Stent	ST638 Stent	mBP (mm Hg)	HR (bpm)
Before stenting	6	2.52 ± 0.12	2.66 ± 0.08	2.64 ± 0.19	115.8 ± 3.5	164.2 ± 9.0
3 weeks after stenting	6	2.53 ± 0.10	1.45 ± 0.12*	1.98 ± 0.13*†	110.8 ± 3.7	153.2 ± 7.9

Data are expressed as mean ± SEM. No Tx = untreated coronary segment; mBP = mean blood pressure; HR = heart rate. *$p < 0.01$ vs. before stenting, †$p < 0.05$ vs. control stent.

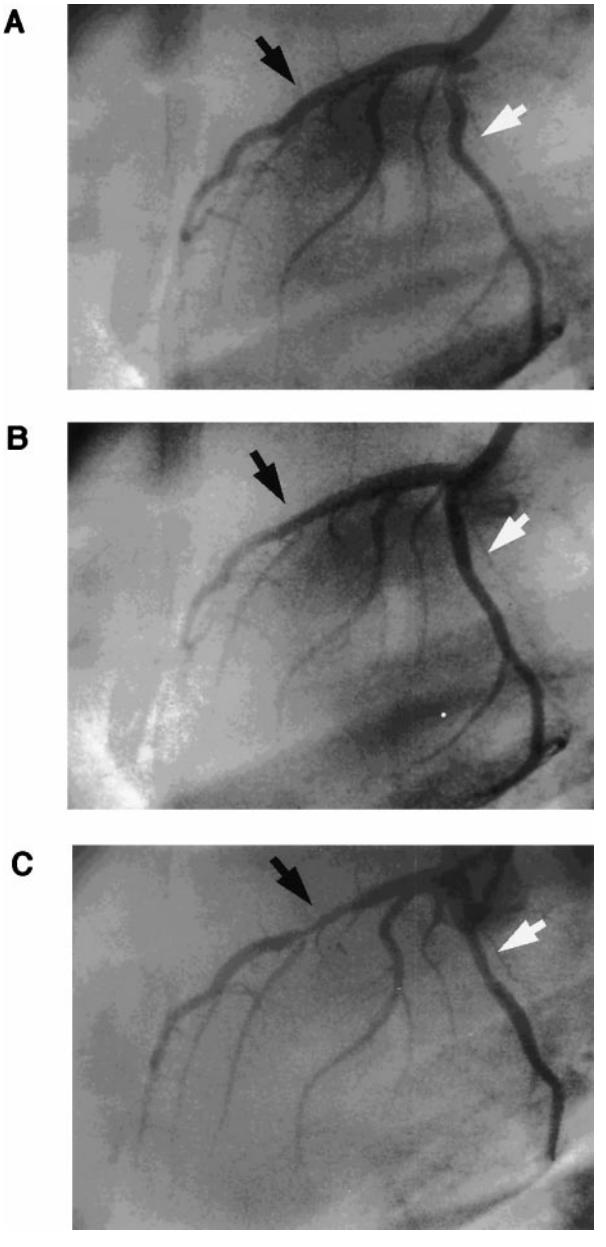
pressure or heart rate before or 3 wk after the stent implantation (Table 1).

Effects of ST638 on the development of angiographic coronary stenosis. A moderate stenotic lesion was noted at the stent site, however, the degree of the angiographic coronary stenosis was significantly less at the ST638 stent site than at the control stent site (Figs. 2 and 3).

Histological study. The balloon-to-artery ratio was comparable between the sites implanted with either the ST638 or control stent (1.2 ± 0.1 vs. 1.2 ± 0.1). Three weeks after the stent implantation, neointimal formation was noted at the stent-implanted site, where the neointima was occupied by migrated smooth muscle cells, whereas no severe inflammatory response was observed around the polymer thread (Fig. 4). The extent of the neointimal formation was significantly suppressed at the ST638 stent site compared with the control stent site (Figs. 4 and 5).

When the cross-sectional areas of the coronary artery were analyzed, the EEL and IEL areas were significantly increased at the stent-implanted sites, and the extent of the vessel enlargement was significantly greater at the ST638 stent site compared with that at the control stent site (Fig. 6).

Figure 2. Coronary angiograms in a pig. **A,** Before stent implantation; **B,** immediately after stent implantation; and **C,** 3 wk after stent implantation. The white arrow indicates the site implanted with ST638 stent, and the black arrow shows the site implanted with control stent.



Discussion

The novel findings of the present study in porcine coronary arteries were that: (1) the PLLA stent was useful in delivering a drug into the coronary arterial wall, although it caused neointimal formation and angiographic stenosis; and (2) intramural delivery of a specific tyrosine kinase inhibitor, ST638, significantly suppressed the stent-induced restenotic changes of the porcine coronary artery. To the best of our knowledge, this is the first report of a successful intramural delivery of an antiproliferative agent into the coronary artery with a biodegradable stent that resulted in the suppression of the restenotic changes of the coronary artery in vivo.

Biodegradable PLLA stent as a tool for local drug delivery. PLLA is a completely biodegradable material that can be degraded by hydrolysis, either nonenzymatically or enzymatically, and can be eliminated through carbon dioxide in the respiration (25). Schakenraad et al. (29) demonstrated that PLLA fibers cause only a mild foreign body reaction, and thus

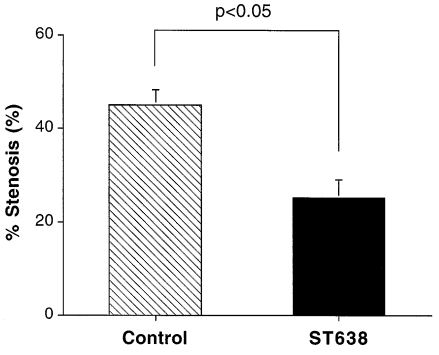


Figure 3. Angiographic coronary stenosis 3 wk after implantation with the ST638 or control stent.

have a very low inflammatory potential during the wound healing process. Several studies have investigated the potential usefulness of PLLA as a material for a bioabsorbable stent. Agrawal et al. (30) showed that PLLA provides adequate strength to the stent as the collapse pressure of the PLLA stents surpasses 300 mm Hg. Chapman et al. (18) demonstrated that the PLLA stent is endothelialized 2 wk after the implantation and remains patent without inducing any significant inflammatory or thrombotic responses for the subsequent 12 wk after the implantation in dogs in vivo. Indeed, in the present study, the EEL and IEL areas were greater at the stent sites (with either ST638 or ST494) than those at the adjacent control sites, indicating that the PLLA stent prevented the geometric remodeling.

However, Giessen et al. (34) recently reported that both biodegradable and nonbiodegradable polymers induce marked inflammatory reaction with subsequent massive neointimal formation in porcine coronary arteries. In the present study, we also noted the neointimal formation caused by PLLA stents, however, the degree of the neointimal formation was less than that reported by Giessen et al. (34) and less inflammatory response was noted. Lincoff et al. (35) recently demonstrated that low molecular mass (~80 kD) PLLA causes an intense inflammatory neointimal response, whereas high molecular mass (~321 kD) PLLA is well tolerated within the coronary artery with no evidence of associated cellular inflammation, which is consistent with our present finding.

We consider that the neointimal formation in the present study was not due to the effect of coating materials because the neointimal formation was also observed with a plain stent without any drug or with a stent with poly-ε-caprolactone alone (data not shown). This tissue reaction may be attributable to a combination of parent polymer compound, biodegradable products, and damage due to the asymmetric geometry of the stent. Moreover, these reactions might be specific to the porcine artery because none of the other animal studies have shown such a tissue reaction (18,25). Therefore, it is unclear at present whether or not similar tissue reaction is induced by a PLLA stent in the human coronary artery.

ST638 as an antiproliferative agent in vivo. ST638 potently and selectively inhibits tyrosine-specific kinase activity of the

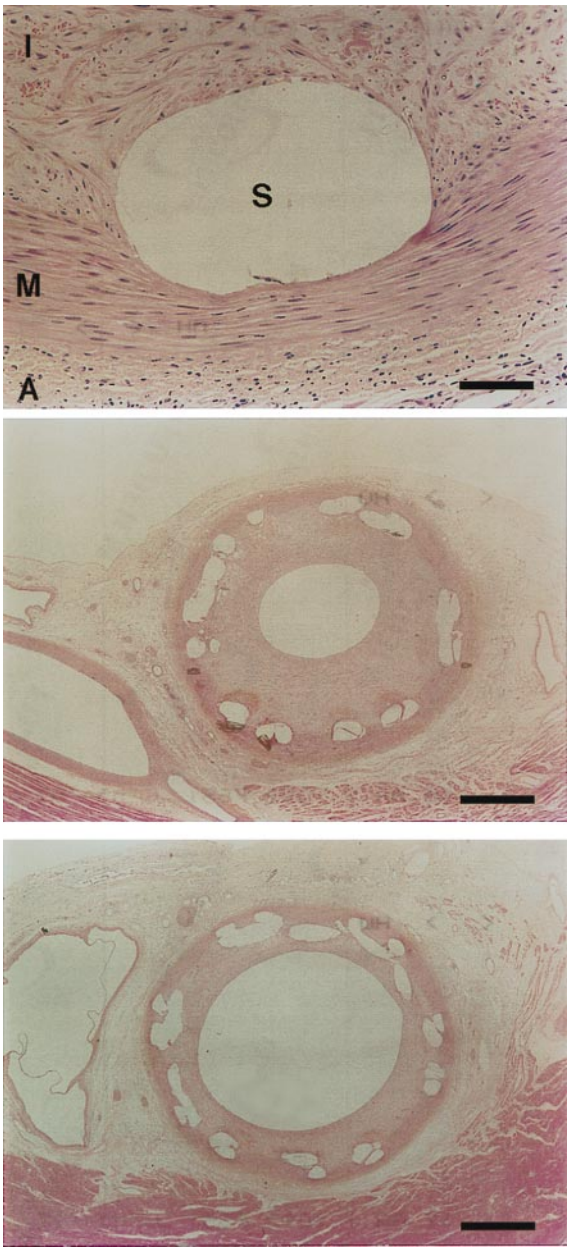


Figure 4. Photomicrograph of the stented coronary segments 3 wk after stent implantation. **A,** Neointima and media around the PLLA stent thread. **I,** Neointima; **M,** media; **A,** adventitia; **S,** stent thread (×400). **B,** A coronary segment implanted with the control stent (×40). **C,** A coronary segment implanted with the ST638 stent (×40). Calibration: 0.1 mm for **A,** and 1.0 mm for **B** and **C.**

epidermal growth factor (EGF) receptor with an IC_{50} value of 0.37 μM, and has no inhibitory effect on the enzymes of serine- and/or threonine-specific protein kinase, such as cAMP-dependent protein kinase, Ca^{2+}/phospholipid-dependent protein kinase C, casein kinase I, or casein kinase II (32). Its inhibitory effect is mediated by competing with the substrate protein for the tyrosine kinase binding site (32). We previously demonstrated that ST638 applied from the adventitial site markedly suppresses the neointimal formation and geometric

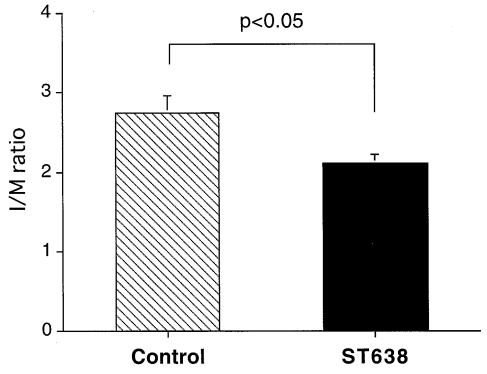
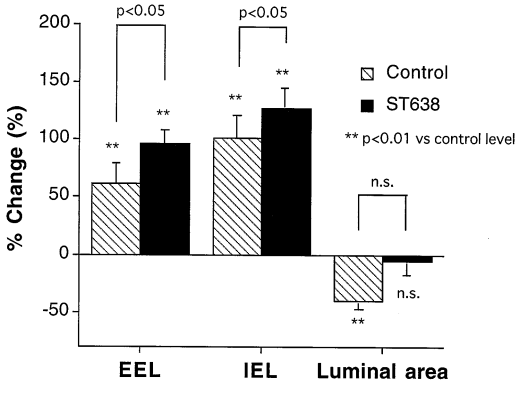


Figure 5. Intima/media ratio 3 wk after control or ST638 stent implantation.

remodeling induced by IL-1β (15), PDGF (16), and balloon injury (17) in vivo. These inhibitory effects of ST638 were indeed the result of the inhibition of tyrosine kinases because ST638 markedly suppresses the tyrosine phosphorylations induced by IL-1β (15), PDGF (16), and balloon injury (17). It is highly possible in the present study that the antiproliferative effects of ST638 overcame the proliferative stimuli caused by balloon injury, the stent itself, and the drug coating on the stent, resulting in the inhibition of the development of neointimal formation after the stent implantation in vivo. Lincoff et al. (35) recently succeeded in delivering dexamethasone into the porcine coronary artery with PLLA-coated tantalum wire stent. Although the local concentrations of dexamethasone were high enough, the steroid did not reduce the neointimal formation (35). Thus, a specific tyrosine kinase inhibitor (such as ST638) may be more useful than steroids to inhibit the neointimal formation in vivo, at least in the porcine model of stent arterial injury.

The present study demonstrated that ST638 could also prevent the geometric remodeling of the coronary artery after stenting in vivo. This result is consistent with our previous findings that ST638 applied from the adventitia inhibited the geometric remodeling induced by IL-1β (15), PDGF (16), or balloon injury (17).

Figure 6. Changes in the cross-sectional areas of porcine coronary arteries 3 wk after PLLA stent implantation. The changes in the cross-sectional areas are expressed as percent changes compared with the adjacent normal coronary segment. **Significance of the changes from control (zero) level.



Study limitations. Although the present study demonstrates the possible usefulness of a PLLA stent with a specific tyrosine kinase inhibitor to suppress the restenotic changes, several limitations could be raised. First, although local concentrations of ST638 were maintained above the effective concentration over 21 d after the stenting, neointimal formation was not completely prevented. It is conceivable that local concentrations of ST638 in the coronary artery were higher near the stent compared with the distant portion. Thus, it is necessary to develop a material that can deliver a larger amount of an antiproliferative drug and can release it for a longer period. Second, although the present study demonstrated the short-term biocompatability of our PLLA stent, the long-term biocompatability was not tested. Thus, such an examination appears to be required before the clinical use of our stent could be considered.

Summary. In summary, we were able to demonstrate that the biodegradable PLLA stent is useful in preventing geometric remodeling, although it causes neointimal formation, and that the intramural delivery of the specific tyrosine kinase inhibitor, ST638, significantly suppresses the restenotic changes after the PLLA stent implantation in the porcine coronary artery in vivo. Further studies are needed, however, to confirm the usefulness of the present strategy to use a specific tyrosine kinase inhibitor and a biodegradable stent to reduce the restenosis after successful PTCA in humans.

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