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主論文
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# Basic Fibroblast Growth Factor Attenuates Left Ventricular Remodeling Following Surgical Ventricular Restoration in a Rat Ischemic Cardiomyopathy Model

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**Keywords:**

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**Abstract**

*Objective* Although surgical ventricular restoration for ischemic cardiomyopathy is expected as an alternative or bridge to heart transplantation, post-operative remodeling of left ventricle (LV) needs to be addressed. This study aimed to examine the effect of basic fibroblast growth factor (bFGF), which induces angiogenesis and tissue regeneration in ischemic myocardium, to prevent remodeling after surgical ventricular restoration (SVR) using a rat ischemic cardiomyopahy model.

*Methods* Four weeks after coronary artery ligation, rats were divided into two groups: rats treated with SVR alone (SVR; n = 21), and rats treated with SVR and local sustained-release of bFGF using gelatin hydrogel sheet (SVR + bFGF; n = 22). Cardiac function was assessed by serial echocardiography and cardiac catheterization. Cardiac tissue sections were histologically examined for vascular density and fibrosis.

*Results* Higher systolic function and lower LV end-diastolic pressure (LVEDP) were observed in rats treated with SVR+bFGF (SVR vs SVR+bFGF; Ees: 0.22 ± 0.11 vs 0.33 ± 0.22 mmHg/μL, $p = 0.0328$; LVEDP: 12.7 ± 7.0 vs 8.5 ± 4.3 mmHg, $p = 0.0230$). LV area tended to be lower in rats treated with SVR+bFGF compared to rats treated with SVR alone (left ventricular end-diastolic area: 0.66 ± 0.07 vs 0.62 ± 0.07 $cm^2$, $p = 0.071$). Vascular density tended to be higher in rats treated with SVR+bFGF than those without bFGF (23.3 ± 8.1 vs 28.8 ± 9.5 / $mm^2$, $p = 0.0509$).

*Conclusions* BFGF induced angiogenesis and attenuates remodeling after SVR which secured the efficacy of SVR in a rat ischemic cardiomyopathy model. (250 words)

## Introduction

Surgical ventricular restoration (SVR) has been widely performed as a treatment for end-stage ischemic cardiomyopathy (ICM), as an alternative or a bridge to heart transplantation. Several groups have reported excellent early and/or late results[1-3]. However, it is also reported in some cases that the treated left ventricle (LV) dilates again and congestive heart failure recurs during the follow up period after surgery[4, 5]. Thus, it is indispensable to prevent LV remodeling after SVR.

Because of limited adequate animal experimental models, most of studies on SVR are retrospective assessments of clinical cases. To overcome this limitation, we have previously established an experimental SVR model of rat[6], and reported that the LV remodeling after SVR was attenuated by systemic administration of renin-angiotensin system (RAS) inhibitors such as angiotensin-converting-enzyme inhibitor, angiotensin II Receptor blocker and atrial natriuretic peptide which worked on inhibiting myocardial fibrosis and myocardial hypertrophy of remote intact and contractile myocardium[7-9].

Basic fibroblast growth factor (bFGF) is one of potent angiogenic cytokines which induce endothelial and smooth muscle cell proliferation and elicit angiogenesis and arteriogenesis through the migration and proliferation of endothelial cells, vascular tube formation and linkage to the extant vascular network[10, 11]. We have reported several basic and clinical studies applying angiogenic effects of bFGF for wound healing[12, 13] or ischemic limb[14, 15], and reported that local sustained release of bFGF using gelatin hydrogel improved LV function and attenuated LV remodeling of chronic MI heart by inducing angiogenesis in border-zone (peri-infarct) myocardium using rat

and canine models[16, 17].

In the present study, we hypothesized that local sustained-release of bFGF induces angiogenesis in border-zone myocardium adjacent to the suture line of SVR and attenuates LV remodeling after SVR in a rat ICM model.

## Methods

This study was performed in accordance with the guidelines for animal experiments of Kyoto University, which conforms to Japanese law and the *Guide for the Care and Use of Laboratory Animals*.

### *Preparation of bFGF-incorporated Gelatin Hydrogel Sheet*

Gelatin with an isoelectric point value of 4.9 was isolated from bovine bone collagen by means of an alkaline process using $Ca(OH)_2$ (Nitta Gelatin Co., Osaka, Japan). Human recombinant bFGF with an isoelectric point value of 9.6 was generously gifted from Kaken Pharmaceutical Co. (Tokyo, Japan). Gelatin hydrogel sheets were prepared according to a method described previously[16, 18]. Sheets were freeze-dried and cut in elliptical shape (20 × 15 mm) and impregnated with phosphate buffered saline (PBS) containing 100 μg of bFGF at 4 °C for 12 hours to prepare bFGF-incorporated gelatin hydrogel sheets. All experimental procedures were conducted under sterile conditions.

### *Rat Ischemic Cardiomyopathy (ICM) Model*

Myocardial infarction (MI) was induced in male Sprague-Dawley rats (7 weeks of age) by proximal ligation of the left anterior descending coronary artery (LAD) as described

previously[6]. Ninety-two out of 99 rats survived at four weeks after ligation (survival rate: 92.9 %). The infarct size and cardiac function were evaluated by echocardiography. Animals less than 10 % of akinetic lesion were excluded from this study. Animals with atrophy of anterior papillary muscle were also excluded because of potential papillary muscle dysfunction and mitral regurgitation. Thirty-five rats were excluded according to the exclusion criteria.

***Experimental Groups***

Four weeks after the MI induction surgery, ICM model rats were randomized into two groups and undergone SVR. Fifty out of 57 rats survived after SVR (survival rate: 87.7 %). In SVR group, rats were undergone SVR surgery (described below) followed by a placement of gelatin hydrogel sheet incorporated with PBS covering the suture line of SVR. In SVR+bFGF group, rats were undergone SVR surgery followed by a placement of bFGF-incorporated gelatin hydrogel sheet. Twenty-one out of 24 rats in SVR group (survival rate: 87.5 %) and 22 out of 26 rats in SVR+bFGF group (survival rate: 84.6 %) were survived until 4 weeks after the placement. All survived rats after 4 weeks of observation after SVR surgery were included in the present study (n=21 for SVR group, n=22 for SVR+bFGF group, respectively).

***Procedure of Surgical Ventricular Restoration (SVR)***

An ICM model rats were undergone general anesthesia with isoflurane and others on a volume-cycled ventilator for small animals (Rodent Ventilator, model 683, Harvard Apparatus, Holliston, MA). The heart was exposed by dissecting the adhering pericardium after left anterior thoracotomy, and the infarct area was plicated by 5-0

polypropylene U-stay and over and over sutures. A gelatin hydrogel sheet incorporated with PBS or bFGF covering the plicated potion and the suture line was placed immediately after the SVR surgery. The pericardium was closed as far as possible. Echocardiography after SVR procedure showed reduced LV volume caused by the plication and exclusion of infarct area (Figure 1).

***Echocardiography***

By echocardiography, LV dimension and systolic function were assessed just before and two days after the SVR surgery and followed up weekly until 4 weeks after the surgery. Images were recorded using a 10- to 12-MHz phased-array transducer (Model 21380A with HP SONOS 5500 imaging system, Agilent Technologies, Andover, MA). LV end-diastolic and end-systolic area (LVEDA and LVESA, respectively), FAC and the percentage of akinetic endocardial length to the whole LV endocardial circumference (AL) were measured and calculated from 2-dimensional B-mode tracings from the short-axis view of the left ventricle at the papillary muscle level. FAC was calculated as (LVEDA-LVESA) / LVEDA. All measurements were performed in a blind fashion according to the guidelines of the American Society for Echocardiology, and averaged over 3 consecutive cardiac cycles.

***Cardiac Catheterization***

After the final echocardiographic assessment, all rats underwent cardiac catheterization as previously described[19]. In brief, a 2-Fr micromanometer-tipped catheter (Millar Instruments Inc., Houston, TX) was inserted via the right carotid artery into the left ventricle, and a 3-Fr occlusion balloon catheter (Applied Medical Resources, Rancho

Santa Margarita, CA) was inserted into the inferior vena cava (IVC) through the right or left femoral vein. Two-dimensional echocardiography was simultaneously performed to determine the end-diastolic and end-systolic diameter of LV (LVDd and LVDs, respectively). During caval occlusion, LV pressure waveforms and echocardiographic M-mode tracings were recorded simultaneously. Then, the LV maximum time-varying elastance (Ees, in millimeters of mercury per microliter) and the time-constant of isovolumic relaxation (Tau "τ", in milliseconds = pressure at peak of -dP/dt) were calculated as an index of global systolic and diastolic function, respectively. LV end-diastolic pressure (LVEDP) was also measured simultaneously. We could not perform pressure-volume loop analyses because we could quantify temporary LV volume at end-systole and end-diastole (not continuously) with our system. All data were acquired under stable hemodynamic conditions.

***Histological Assessments***

After hemodynamic measurements were completed, all rats were euthanized with an overdose of isoflurane inhalation. The hearts were removed and fixed with 10% buffered formaldehyde. The specimens were sliced into 2-mm-thickness sections at the base of papillary muscles along the short axis and were paraffin-embedded.

The sections were stained with anti-smooth-muscle-actin (SMA) antibody to visualize and quantify the vessel number. The number of the vessels which are positive for antigen per unit area were counted in two random fields of the border zone. The average number of the vessels was used for assessment of vascular density.

The sections were also stained with Picrosirius red, a collagen-specific dye, to determine the degree of myocardial fibrosis. In each section, 20 separate parts of the LV

remote area from the plication site were scanned under microscopy (magnification ×200), and the images were analyzed using the IPlab imaging system software (Version 3.71 for Windows; Scanalytics Inc, Rockville, MD). The myocardial fibrosis ratio was automatically measured and calculated as the mean ratio of Picrosirius red-positive area.

### *Statistical Analysis*

All data are described as mean ± standard deviation. All data were analyzed by unpaired Student *t*-test or 2-way analysis of valiance with simple main effect test. All of the statistical analysis was performed using a computer software (JMP Pro 14.0.0, SAS Institute Inc., Cary, NC). A $p$ value < 0.05 was considered statistically significant.

## Results

### *Echocardiography*

The two-dimensional echocardiography data are summarized in Table 1. The extent of akinetic region and systolic function before treatment was comparable in SVR and SVR+bFGF groups (SVR vs SVR+bFGF; AL: 17.2 ± 2.6 vs 17.6 ± 2.1 %, $p$ = 0.567 / FAC: 34.5 ± 5.5 vs 33.7 ± 6.9 %, $p$ = 0.642). LVEDA at 2 days after SVR decreased in both groups indicating successful reduction of LV area (0.70 ± 0.08 $cm^2$ to 0.47 ± 0.06 $cm^2$ in SVR group; 0.70 ± 0.05 $cm^2$ to 0.45 ± 0.07 $cm^2$ in SVR+bFGF group). FAC at 2 days after SVR increased in both groups indicating an advantageous effect of LV area reduction on LV systolic function (from 34.5 ± 5.5 to 54.3 ± 7.9 % in SVR group and from 33.7 ± 6.9 to 56.4 ± 6.0 % in SVR+bFGF group).

During 2 days to 4 weeks after SVR, LVEDA increased after SVR operation

in both groups. The value at four weeks after SVR operation tended to be smaller in SVR+ bFGF group than in SVR group (SVR vs SVR+bFGF; 0.66 ± 0.07 vs 0.62 ± 0.07 $cm^2$, $p$ = 0.071). FAC decreased after SVR operation in both groups, and the value at four weeks after SVR operation tended to be higher in SVR+ bFGF group than that in SVR group without statistical significance (36.7 ± 4.6 vs 40.4 ± 5.8 %, $p$ = 0.057).

***Cardiac Catheterization***

We performed cardiac catheterization at 4 weeks after SVR (Figure 2). Ees was significantly higher in SVR+bFGF group compared to that in SVR group (SVR vs SVR+bFGF; 0.22 ± 0.11 vs 0.33 ± 0.22 mmHg/μL, p = 0.0328). Tau was significantly lower in SVR+bFGF group compared to that in SVR group (15.9 ± 2.4 vs 14.4 ± 1.8 ms, $p$ = 0.0205). LVEDP was significantly lower in SVR+bFGF group compared to that in SVR group (12.7 ± 7.0 vs 8.5 ± 4.3 mmHg, $p$ = 0.0230).

***Histological Assessments***

Vascular density evaluated by anti-SMA immunostaining tended to be higher in SVR+bFGF group compared to that in SVR group at border zone (SVR vs SVR+bFGF; 23.3 ± 8.1 vs 28.8 ± 9.5 / $mm^2$, $p$ = 0.0509) (Figure 3). Picrosirius red staining showed that myocardial fibrosis in remote zone was not statistically different between both groups (5.7 ± 1.7 vs 5.3 ± 2.2 %, $p$ = 0.545) (Figure 4).

**Discussion**

From echocardiographic data, although LV remodeling after SVR occurred in both

groups, smaller tendency of LV area was observed in SVR+bFGF group than in SVR group. Cardiac catheterization data showed that SVR+bFGF group had higher systolic and diastolic function, and lower LVEDP than those in SVR group at four weeks after SVR which indicates attenuation of LV remodeling after bFGF treatment concomitant with SVR. Histological assessment suggested that angiogenesis might have been induced in border zone of SVR+bFGF group. However, myocardial fibrosis in remote area was not affected by the bFGF therapy. These findings might suggest that local sustained-release of bFGF induced angiogenesis in border zone, consequently attenuated LV remodeling after SVR.

Since middle of 90's, numerous clinical studies on SVR for ischemic cardiomyopathy have been reported[2, 4, 20] . Although the early and late outcomes of SVR were mostly acceptable, continuous LV remodeling[21] and recurrence of congestive heart failure were often observed in late follow-up after SVR[4, 5, 22, 23]. Several modifications and new techniques of surgical procedure such as septal anterior ventricular exclusion (SAVE) operation and overlapping procedure, which aimed to make elliptical (not spherical) shape of LV, were developed[2, 5]. Simultaneously, the importance of concomitant procedure, such as revascularization for ischemic myocardium[24] or valvular reconstruction for mitral regurgitation, have been pointed out[25]. Even though intense researches have been conducted, continued LV remodeling and recurrence of heart failure after SVR still remain as unsolved problems.

As French and Kramer summarized in their review articles[26-28], mechanisms of post-infarct LV remodeling include three major components: "infarct expansion" in infarct area, "non-ischemic infarct extension" in border zone, and "hypertrophy and dilatation of non-infarcted myocardium". The mechanisms of LV remodeling after SVR

can be explained by similar theory. The border zone myocardium adjacent to the suture line is extended because of increased stress and stretch force due to juxtaposition between the fixed plication site and the remote contractile myocardium. The present results showed that local sustained-release of bFGF induced attenuated LV remodeling after SVR procedure. Angiogenesis might contribute to increase blood supply in border zone myocardium considerably subjected to mechanical stress caused by bending and stretching between the fixed plication site and the contractile non-infarcted myocardium.

We could not confirm the attenuation of fibrosis by the bFGF treatment after SVR surgery. It is previously reported that chronic myocardial hibernation occurs after ischemia-reperfusion or reduced blood flow[29] and that the functional recovery after revascularization is small after severe myocardial damage which indicates that the increase of blood flow could improve LV function when the reduced cardiac function was attributed by the myocardial hibernation related to chronic low blood perfusion [16, 30, 31]. It would be possible that bFGF treatment in the present study might have promoted angiogenesis and developed collateral blood flow which may have contributed to the improvement of cardiac function through the recovery from myocardial hibernation even though the fibrotic lesion was not attenuated by the bFGF treatment.

The present study holds some limitations. This model differs from clinical cases in some features: (1) it is carried out without cardiopulmonary bypass, (2) the infarct area does not include ventricular septum, (3) the SVR procedure is similar to “linear closure”, and the infarct myocardium is not excised but only plicated, (4) concomitant procedures such as CABG or mitral valve repair are not considered, (5) pharmacokinetics *in vivo* would be different between rats and large animals or human

considering the difference of the thickness of ventricular wall, and (6) biological and histological mechanisms of the bFGF treatment should be further investigated. Although the rat model would fairly recapitulate cardiac physiology after clinical SVR, large animal experiments similar to clinical SVRs would be desirable and should be investigated in the future.

In conclusion, local sustained-release of bFGF attenuated LV remodeling and re-deterioration after SVR in a rat ischemic cardiomyopathy model. Concomitant bFGF therapy would be beneficial to improve the results of SVR procedure.

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**Conflict of interest statement**

The authors have declared that no conflict of interest exists.

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**Legends for Figures and Table**

Figure 1. Echocardiogram of pre-/post-SVR (end-diastolic phase)

The short-axis view of the left ventricle at mid papillary muscle level. A: pre-SVR, B: post-SVR. The white arrow points to a papillary muscle. The black arrow points to the infracted scar. The anterior papillary muscle is not included in the infarct area or the plication site. The asterisk indicates a gelatin sheet.

Figure 2. Hemodynamic data of cardiac catheterization

Ees = left ventricular maximum time-varying elastance, Tau = time-constant of isovolumic relaxation, LVEDP = left ventricular end-diastolic pressure

Ees and tau are an index of grobal systolic and diastolic function of left ventricle, respectively.

Figure 3. Vascular density in border zone (anti-αSMA staining)

A: Illustration of border zone and remote zone of LV after myocardial infacrtion (Masson's trichrome stain). B: Representative anti-αSMA staining (brown). C: Quantification of vascular density. Scale bars = 100 μm.

Figure 4. Myocardial fibrosis in remote area (Sirius-red staining)

A: Representative picrosirius red staining (red indicates fibrosis). B: Quantification of the percentage of fibrosis. Scale bars = 50 μm.

Table 1. Echocardiographic data

SVR = surgical ventricular restoration, bFGF = basic fibroblast growth factor, AL = percentage of akinetic endocardial length to the whole LV endocardial circumference, LVEDA = left ventricular end-diastolic area, FAC = fractional

area change, pre = pre-SVR, 2days = 2days after SVR, 4wks = 4 weeks after SVR.

Table 1: Echocardiographic data

| Group | SVR (n = 21) | SVR + bFGF (n = 22) | *p*-value |
|---|---|---|---|
| **AL** (%) | | | |
| pre | 17.2 ± 2.6 | 17.6 ± 2.1 | 0.567 |
| **LVEDA** ($cm^2$) | | | |
| pre | 0.70 ± 0.08 | 0.70 ± 0.05 | 0.924 |
| 2 days | 0.47 ± 0.06 | 0.45 ± 0.07 | 0.380 |
| 4 wks | 0.66 ± 0.07 | 0.62 ± 0.07 | 0.071 |
| **FAC** (%) | | | |
| pre | 34.5 ± 5.5 | 33.7 ± 6.9 | 0.642 |
| 2 days | 54.3 ± 7.9 | 56.4 ± 6.0 | 0.267 |
| 4 wks | 36.7 ± 4.6 | 40.4 ± 5.8 | 0.057 |

FIGURE 1.

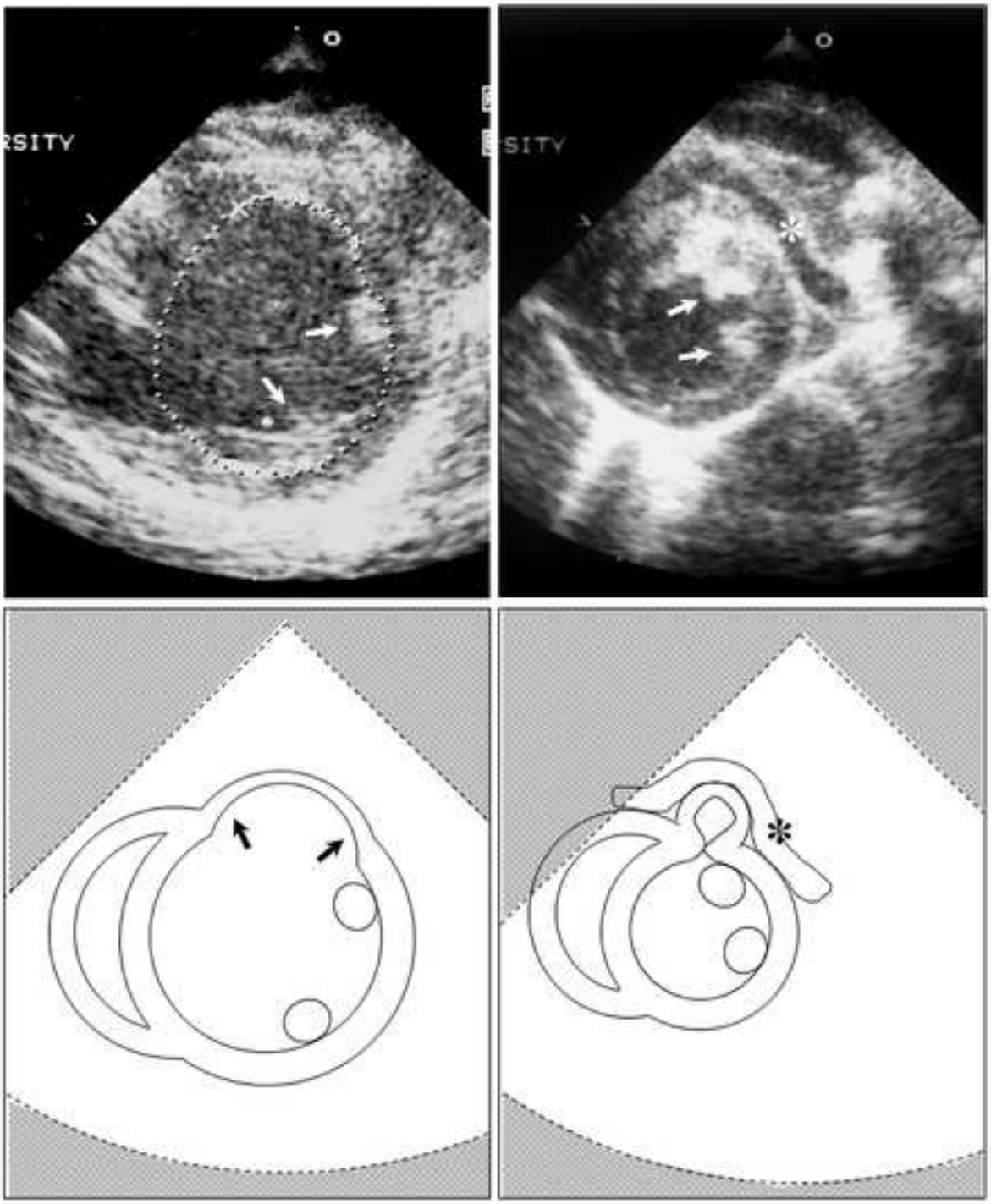

Figure 2

Click here to access/download;Figure;Figure 2.TIF

**FIGURE 2.**

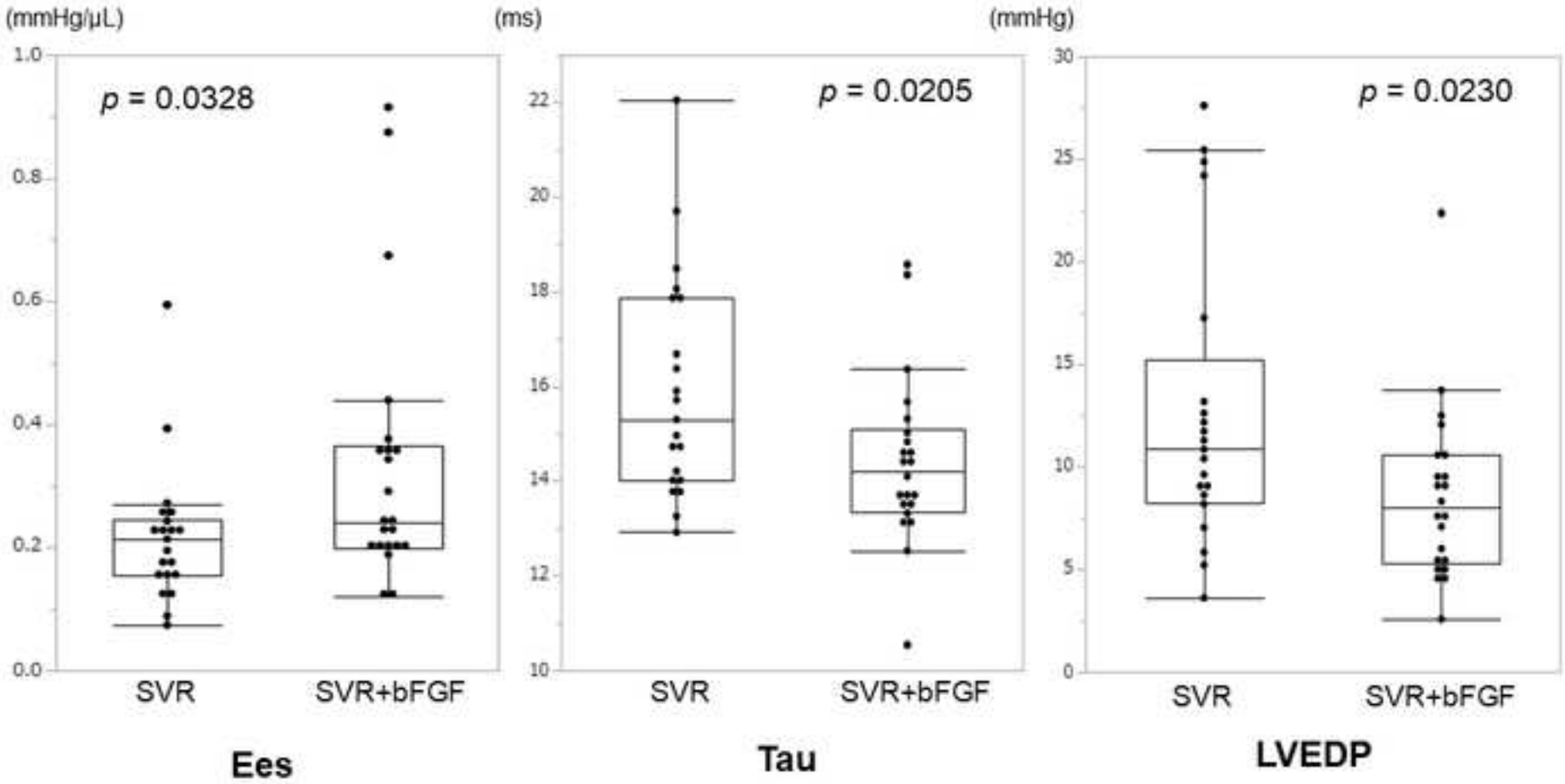

FIGURE 3.

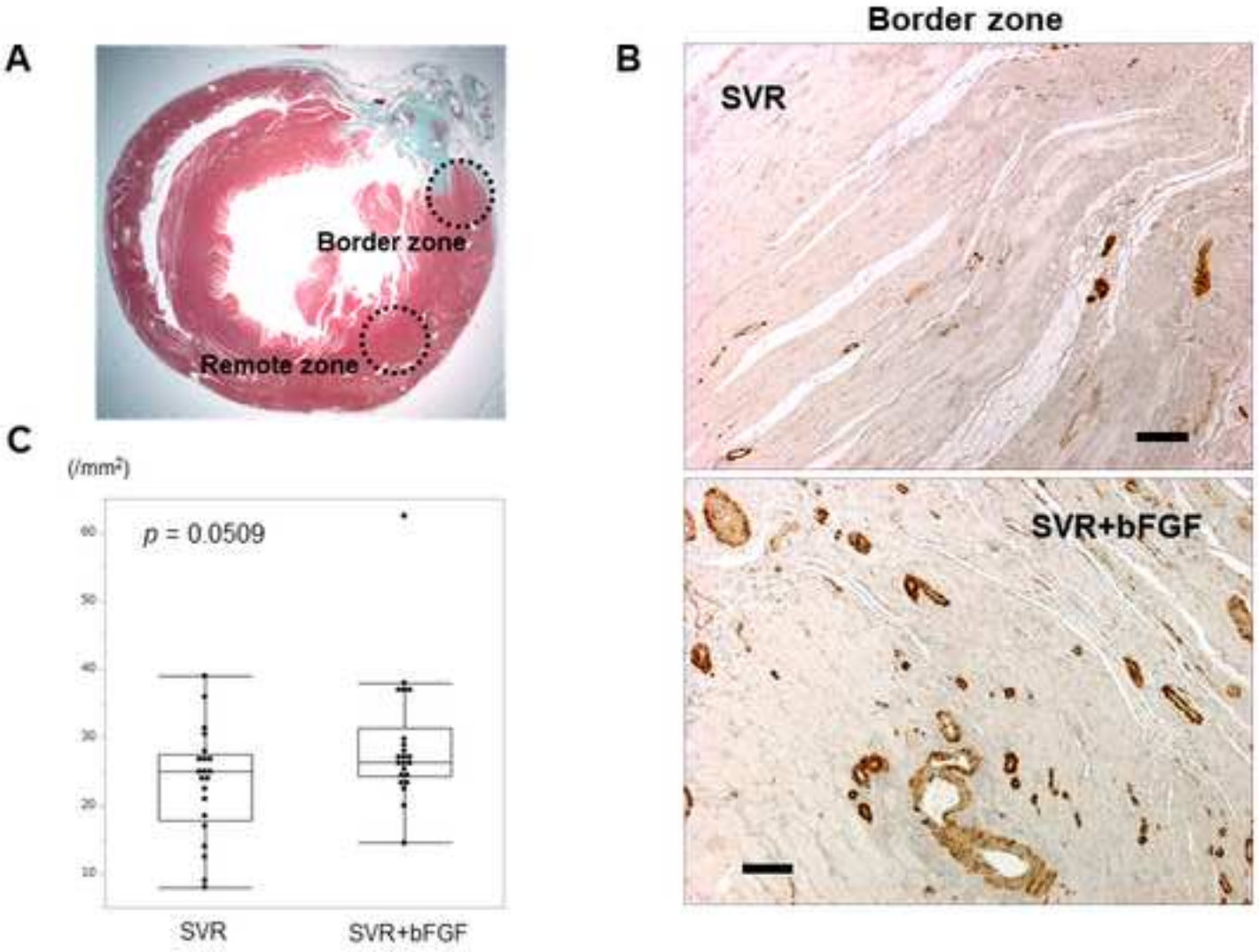

FIGURE 4.