Intramyocardial Injection of Fibroblast Growth Factor-2 Plus Heparin Suppresses Cardiac Failure Progression in Rats With Hypertensive Heart Disease

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SUMMARY

A reduction of coronary flow reserve has been reported in patients with hypertensive heart disease (HHD), which suggests that myocardial ischemia may contribute to the progression to cardiac failure in HHD. Therefore, we evaluated whether fibroblast growth factor (FGF)-2 and/or heparin, which induce angiogenesis, may affect cardiac function in the setting of HHD.

We used Dahl salt sensitive (DS) rats as an HHD model. Direct intramyocardial injection of 100 µg of FGF-2 plus 1.28 µg of heparin ($n=6$), 100 µg of FGF-2 ($n=6$), 1.28 µg of heparin ($n=6$) or saline ($n=6$) were performed in 9-week-old rats. Echocardiography was performed to evaluate cardiac function at 9, 11, and 13 weeks of age. Plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) concentrations were measured at 8 and 13 weeks of age. DS rats were killed 4 weeks after myocardial injection (at 13 weeks of age), and myocardial capillary density was assessed by von Willebrand factor staining. Injection of FGF-2 plus heparin significantly decreased left ventricular end-diastolic diameter ($P<0.0001$) and left ventricular end-systolic diameter ($P<0.0001$), significantly improved the reduction of left ventricular fractional shortening ($P=0.0005$), significantly decreased plasma ANP ($P<0.0001$) and BNP ($P=0.016$) concentrations, and significantly increased myocardial capillary density ($P=0.0002$) compared with injection of saline.

These findings indicate that intramyocardial injection of FGF-2 plus heparin suppresses the progression of cardiac failure in DS rats. FGF-2 plus heparin administration may be a new therapeutic strategy for the treatment of HHD. (Int Heart J 2005; 46: 289-301)

Key words: Heart failure, Fibroblast growth factor-2, Hypertensive heart disease, Angiogenesis, Dahl salt sensitive rat

SUSTAINED hypertension induces left ventricular hypertrophy1) and disturbs the coronary circulation.2-4) Hypertensive heart disease (HHD) has been shown to

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progress to heart failure in the end stage. As an etiology of heart failure, hypertension ranks second to coronary artery disease. Left ventricular hypertrophy represents an adaptive response of the heart to volume and/or pressure overload, which preserves left ventricular chamber function.

In the setting of arterial hypertension, left ventricular hypertrophy is a strong predictor of cardiovascular morbidity and mortality. Cardiovascular risk in patients with hypertensive left ventricular hypertrophy has been attributed to several pathophysiologic factors, including impairment in coronary structure and vasodilator capacity, which may explain the increased prevalence of myocardial ischemia, arrhythmias, and sudden death in this population. Several factors are involved in reducing coronary flow reserve in hypertensive patients. The decline in coronary flow reserve is caused by a reduction in the size of the microcirculatory bed that is induced by vascular changes in the intramyocardial coronary arteries, increased coronary arteriolar tone, inadequate angiogenesis, endothelial dysfunction, and extravascular compression. HHD can progress to cause diastolic dysfunction and finally, overt heart failure. Coronary flow reserve alterations may be a determinant of myocardial diastolic dysfunction or diastolic impairment that should be taken into account as possibly contributing to coronary flow reductions.

Dahl salt sensitive (DS) rats fed an 8% NaCl (high-salt) diet from 6 weeks of age develop concentric left ventricular hypertrophy at 11 weeks of age, followed by marked left ventricular dilation between 15 and 20 weeks of age. During the latter stage, the DS rats show forced breathing with global left ventricular hypokinesis. Severe pulmonary congestion appears in all DS rats by 17 weeks of age, and these rats die within 1 week of these symptoms appearing. The DS rat fed a high-salt diet is a useful model in which the transition from compensatory hypertrophy to decompensatory dilation of the left ventricle is easily and consistently manifested. In humans, the compensatory phase is relatively longer than the decompensatory phase. Therefore, it is important that the progression of HHD be suppressed in the compensatory phase.

Fibroblast growth factor (FGF)-2 contains 146 amino acids and is a pluripotent mitogen that stimulates migration and proliferation of a variety of cell types including fibroblasts, macrophages, vascular smooth muscle cells, and vascular endothelial cells. FGF-2 induces angiogenesis under ischemic conditions, resulting in a beneficial response, and is a heparin-binding protein that binds to heparan sulfate on vascular endothelial cell surfaces. This interaction has been demonstrated to be important for FGF-2 receptor binding and biologic activity. Heparin prolongs the half-life of the FGF-2 protein and facilitates its binding to FGF-2 receptors, stimulating cell proliferation and migration.
Accordingly, we evaluated whether intramyocardial administration of FGF-2 and/or heparin changes cardiac function by inducing angiogenesis in a rat model of HHD.

**METHODS**

**Animal models:** We used male DS (strain DIS/Eis) rats at 6 weeks of age. These rats were individually housed in an air-conditioned room with an automated 12 h/12 h light/dark cycle. All rats were fed an 8% NaCl diet beginning at 6 weeks of age. The diet and tap water were given *ad libitum* throughout the experiment. Blood pressure and heart rate were measured at 9, 11, and 13 weeks of age with a tail-cuff system (LE5001, Panlab, Barcelona, Spain) without the use of anesthesia. Blood pressure and heart rate were measured ten times in each rat, and the average was presented. Body weight was also measured at 9, 11, and 13 weeks of age. All experimental procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

**Echocardiography:** Echocardiography was performed just before myocardial injection (9 weeks of age), and 2 weeks (11 weeks of age) and 4 weeks (13 weeks of age) after myocardial injection. Rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (20 mg/kg, Dainippon Pharmaceutical, Osaka, Japan). An 11-MHz transducer (LA39; GE Medical Systems, Tokyo), known to give good resolution in the assessment of small-animal hearts, was used. The probe was placed at approximately the fourth intercostal space. M-mode echocardiograms at the papillary muscle level were acquired, guided by two-dimensional long-axis images, and were recorded at a paper speed of 50 mm/sec on an image printer (UP-890MD, Sony Corporation, Tokyo). All measurements were made in a blinded manner. Left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), diastolic interventricular septal thickness (IVSTd), and diastolic posterior wall thickness (PWTd) were measured by the leading-edge method recommended by the American Society of Echocardiography for at least three consecutive cardiac cycles. Left ventricular fractional shortening (FS) was calculated as a percentage from the LVDd and LVDs.

**Treatment with FGF-2, heparin, and saline:** At 9 weeks of age, the rats were anesthetized with an intraperitoneal injection of ketamine hydrochloride (130 mg/kg, Sankyo, Tokyo) and intubated endotracheally for artificial ventilation with a rodent respirator (KN-55, Natsume Seisakusho, Tokyo). The rats were randomized to one of four groups: (1) FGF-2 plus heparin injection group (F+H group: *n* = 6), 100 µg of FGF-2 (Kaken Pharmaceutical, Tokyo) plus 1.28 µg of sodium heparin (Sigma Chemical, St. Louis, MO), (2) FGF-2 injection group (F
group: \( n = 6 \), 100 \( \mu \text{g} \) of FGF-2, (3) heparin injection group (H group: \( n = 6 \), 1.28 \( \mu \text{g} \) of heparin, or (4) vehicle (saline) injection group (V group: \( n = 6 \)). The appropriate solutions were brought to a heparin concentration of 1.4 \( \mu \text{M} \). We used a heparin concentration of 1.4 \( \mu \text{M} \) because a high concentration of heparin (10 \( \mu \text{M} \)) was reported to inhibit FGF-2 receptor binding in cells under all conditions.\(^{22}\)

After thoracotomy at the left intercostal space, rats were electrocardiographically monitored during myocardial injection of agents. A single injection was made in the left anterolateral wall of the heart using a 0.5 mL syringe and a 29-gauge needle. Care was taken to deliver the injection to the subepicardial layer of the myocardium, as confirmed by the presence of a bleb beneath the epicardium when the syringe had been emptied. The chest was then closed and the rat was allowed to recover.

**Immunohistochemical staining and histologic assessment:** After echocardiography, we weighed the rats at 13 weeks of age prior to sacrifice and removal of the heart, which was then fixed in 10% buffered formalin by perfusion fixation at a pressure of 100 mm Hg. The heart was weighed and histologic sections were cut. The sections were stained for von Willebrand factor (DakoCytomation, Kyoto, Japan) to identify endothelial cells and thus permit counting of blood vessels. Three serial sections at the center of the injected area of myocardium were analyzed. All vessels in each section were counted by two investigators blinded to other data and the values expressed as vessels/mm\(^2\). Fibrotic areas in the sections were evaluated by Masson’s trichrome staining. The area of fibrosis was measured using a Scion Image analyzer (Scion Corporation, Frederick, MD) by two investigators blinded to other data. The ratio of the fibrotic area to the total tissue area was calculated.

**Laboratory analysis:** Plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) concentrations were measured in rats at 8 and 13 weeks of age. For the measurement of plasma ANP and BNP concentrations, we obtained blood samples from the cervical vein of conscious rats using a 5 mL syringe with a 23-gauge needle in 8 and 13 week old animals. These blood samples, which were mixed with EDTA-2Na and aprotinin, were separated by centrifugation at 3000 rpm for 15 minutes at 4\(^\circ\)C and stored at -80\(^\circ\)C until the time of assay. Plasma ANP and BNP concentrations were determined by radioimmunoassay [\( \alpha \)-ANF (Rat) RIA kit and BNP-32 (Rat) RIA kit, Peninsula Lab., San Carlos, CA].

**Statistical analysis:** Echocardiographic data, quantitative histologic data, and serum chemistry data for each group were analyzed by one-way analysis of variance. When statistically significant effects were found, the Bonferroni test was performed to determine the differences between groups. A \( P \) value < 0.05 was considered significant. All data are presented as the mean \( \pm \) SEM.
RESULTS

Echocardiography: To compare cardiac function after intramyocardial injection among the groups, we measured LVDd, LVDs, IVSTd, and PWTd by echocardiography. As shown in Table I, the LVDd, LVDs, and FS in 9-week-old rats were similar among all groups. At 11 weeks of age, the LVDd and LVDs of the F+H group were significantly smaller than those of the H and V groups. At 13 weeks of age, the LVDd and LVDs of the F+H group were significantly smaller than those of the other three groups (Table I & Figure 1). Based on these results, we conclude that the intramyocardial injection of FGF-2 plus heparin inhibited the left ventricular dilation of the rats.

In contrast, FS at 9 and 11 weeks of age were similar among all of the groups. The FS of the F+H group was significantly higher than that of the H and V groups in 13-week-old rats. The FS of the F group was similar to that of the F+H group at 13 weeks of age. However, it did not significantly differ from those of the H and V groups. Although FS of the H and V groups deteriorated further at 13 weeks of age, that of the F+H group did not worsen. The IVSTd and PWTd were similar among all groups at 9, 11, and 13 weeks of age (Table I).

Table I. Echocardiographic Findings at 9, 11, and 13 Weeks of Age

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (weeks of age)</th>
<th>LVDd (mm)</th>
<th>LVDs (mm)</th>
<th>FS (%)</th>
<th>IVSTd (mm)</th>
<th>PWTd (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F+H</td>
<td>9</td>
<td>6.52 ± 0.04</td>
<td>2.75 ± 0.02</td>
<td>57.8 ± 0.33</td>
<td>1.93 ± 0.01</td>
<td>1.93 ± 0.01</td>
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<tr>
<td></td>
<td>11</td>
<td>6.60 ± 0.02***</td>
<td>3.05 ± 0.04†</td>
<td>53.9 ± 0.67</td>
<td>2.42 ± 0.02</td>
<td>2.40 ± 0.02</td>
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<tr>
<td></td>
<td>13</td>
<td>6.92 ± 0.10*</td>
<td>3.20 ± 0.06‡</td>
<td>53.8 ± 0.38**</td>
<td>2.41 ± 0.02</td>
<td>2.41 ± 0.02</td>
</tr>
<tr>
<td>F</td>
<td>9</td>
<td>6.49 ± 0.04</td>
<td>2.76 ± 0.03</td>
<td>57.6 ± 0.41</td>
<td>1.96 ± 0.01</td>
<td>1.96 ± 0.01</td>
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<td>6.78 ± 0.01</td>
<td>3.18 ± 0.03</td>
<td>53.2 ± 0.31</td>
<td>2.41 ± 0.01</td>
<td>2.40 ± 0.01</td>
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<td>13</td>
<td>7.45 ± 0.01</td>
<td>3.66 ± 0.05</td>
<td>50.8 ± 0.65</td>
<td>2.39 ± 0.01</td>
<td>2.40 ± 0.00</td>
</tr>
<tr>
<td>H</td>
<td>9</td>
<td>6.49 ± 0.08</td>
<td>2.80 ± 0.04</td>
<td>56.8 ± 0.61</td>
<td>1.93 ± 0.01</td>
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<td>11</td>
<td>6.97 ± 0.10</td>
<td>3.26 ± 0.06</td>
<td>53.3 ± 0.23</td>
<td>2.41 ± 0.01</td>
<td>2.41 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>7.60 ± 0.06</td>
<td>4.00 ± 0.04</td>
<td>47.4 ± 0.35</td>
<td>2.40 ± 0.00</td>
<td>2.40 ± 0.00</td>
</tr>
<tr>
<td>V</td>
<td>9</td>
<td>6.47 ± 0.03</td>
<td>2.76 ± 0.03</td>
<td>57.3 ± 0.47</td>
<td>1.91 ± 0.01</td>
<td>1.91 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>6.96 ± 0.12</td>
<td>3.22 ± 0.06</td>
<td>53.8 ± 0.44</td>
<td>2.40 ± 0.01</td>
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<td>13</td>
<td>7.62 ± 0.06</td>
<td>4.01 ± 0.19</td>
<td>47.4 ± 2.20</td>
<td>2.42 ± 0.01</td>
<td>2.42 ± 0.01</td>
</tr>
</tbody>
</table>

*P < 0.0001 for F+H group versus F, H and V groups, **P = 0.0013 and P = 0.0005 for F+H group versus H and V groups, respectively, ***P = 0.0034 and P = 0.0016 for F+H group versus H and V groups, respectively. †P = 0.0059 and P = 0.011 for F+H group versus H and V groups, respectively, ‡P = 0.0073 for F+H group versus F group, §P < 0.0001 for F+H group versus H and V groups. Mean ± SEM values were calculated from 6 rats in each group. LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; FS = fractional shortening; IVSTd = diastolic interventricular septal thickness; PWTd = diastolic posterior wall thickness; F+H = injection of FGF-2 plus heparin; F = injection of FGF-2; H = injection of heparin; V = injection of saline.
Plasma ANP and BNP concentrations: We examined whether the plasma ANP and BNP concentrations of the rats in all of the groups were influenced by the injection of FGF-2 and/or heparin at 13 weeks of age. The plasma ANP concentration in 8-week-old rats did not differ significantly among the different groups. However, the plasma ANP concentration of the F+H group was significantly lower than those of the other three groups at 13 weeks of age (Figure 2). The plasma BNP concentration did not differ significantly among groups in 8-week-old rats. In 13-week-old rats, the plasma BNP concentration in the F+H group was significantly lower than that in the V group (Figure 2). Moreover, the plasma BNP concentration in the F+H group tended to be lower compared with that in the H group ($P = 0.09$).

Immunohistochemistry: Immunohistochemical staining of hearts for von Willebrand factor was performed in each group at 4 weeks after injection (13 weeks of age) (Figure 3) and the stained capillaries were counted. As shown in Figure 4, the number of capillaries in the F+H group was significantly higher than the other three groups. The number of capillaries in the F group tended to be higher compared with those in the H and V groups ($P = 0.052$ and $P = 0.081$, respectively).

FGF-2 is a pluripotent mitogen that stimulates the migration and proliferation of fibroblasts. We therefore measured the fibrotic area stained with Masson’s trichrome method, and calculated the area relative to that of myocardium. The myocardial fibrosis was hardly observed in all rats. Consequently, this ratio did not significantly differ between the four groups at 13 weeks of age (data not shown).
Figure 2. Changes in the plasma ANP and BNP concentrations. *$P < 0.0001$ versus the other groups, **$P = 0.016$ for F+H group versus V group. Bars represent mean ± SEM of measurements in 6 rats of each group. ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; F+H = injection of FGF-2 plus heparin; F = injection of FGF-2; H = injection of heparin; V = injection of saline.

Figure 3. Representative immunohistochemical staining for von Willebrand factor in 13-week-old rats ($\times$ 200). The arrows show the factor positive capillaries. F+H = injection of FGF-2 plus heparin; F = injection of FGF-2; H = injection of heparin; V = injection of saline.
Heart and body weights: As shown in Table II, the body weight of the F+H group was significantly higher than in the other three groups at 13 weeks of age. The heart weights of the F+H and F groups were significantly lower than that of the V group. Furthermore, the ratio of heart-to-body weight in the F+H group was significantly lower than in the other three groups.

Table II. Heart Weight (mg), Body Weight (g) and Heart-to-body Weight (mg/g) Ratio at 13 Weeks of Age

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart weight (mg)</th>
<th>Body weight (g)</th>
<th>Heart-to-body weight ratio (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F+H</td>
<td>1332.5 ± 42.9</td>
<td>340.0 ± 5.56</td>
<td>3.92 ± 0.087</td>
</tr>
<tr>
<td>F</td>
<td>1242.5 ± 43.7</td>
<td>280.5 ± 8.17*</td>
<td>4.43 ± 0.128***</td>
</tr>
<tr>
<td>H</td>
<td>1410.8 ± 30.5</td>
<td>293.5 ± 6.74*</td>
<td>4.82 ± 0.178†</td>
</tr>
<tr>
<td>V</td>
<td>1450.5 ± 26.8‡</td>
<td>302.5 ± 7.19**</td>
<td>4.82 ± 0.241†</td>
</tr>
</tbody>
</table>

*P < 0.0001 for F+H group versus F and H groups, **P = 0.0004 for F+H group versus V group, ***P = 0.019 for F+H group versus F group, †P = 0.0003 for F+H group versus H and V groups, ‡P = 0.028 for F+H group versus V group. Mean ± SEM values were calculated from 6 rats in each group. F+H = injection of FGF-2 plus heparin; F = injection of FGF-2; H = injection of heparin; V = injection of saline.
Blood pressure and heart rate: The tail-cuff system was used to measure blood pressure and heart rate in conscious rats at 9, 11, and 13 weeks of age. As shown in Figure 5, both systolic blood pressure and diastolic blood pressure were similar between all groups at 9, 11, and 13 weeks of age. Furthermore, the heart rate did not significantly differ between the groups at 9, 11, and 13 weeks of age. Therefore, the administration of FGF-2 and/or heparin did not affect either blood pressure or heart rate.

**DISCUSSION**

This study demonstrates that the intramyocardial injection of FGF-2 plus heparin significantly decreases LVDd and LVDs, and significantly attenuates the reduction of FS compared with the injection of vehicle in our animal HHD model. The injection of FGF-2 plus heparin also significantly lowers plasma ANP and BNP concentrations compared with the injection of vehicle. Furthermore, the injection of FGF-2 plus heparin significantly increased the body weight and significantly decreased the heart weight of rats with HHD. As a result, the injection of FGF-2 plus heparin led to a significant decrease in the heart-to-body weight.
ratio of HHD rats compared with the other groups, which indicates that the left ventricular hypertrophy was suppressed by the injection of FGF-2 plus heparin.

The injection of FGF-2 plus heparin significantly increased the number of capillaries compared with the other groups. These findings indicate that remodeling and deterioration of cardiac function in HHD rats were suppressed by the intramyocardial injection of FGF-2 plus heparin.

In contrast, LVDs, and FS tended to improve by the injection of FGF-2 alone. The heart-to-body weight ratio also tended to decrease with the injection of FGF-2 alone. The number of capillaries tended to increase with the injection of FGF-2 alone. The difference between the results of the injection of FGF-2 plus heparin and of FGF-2 alone may be explained by the findings that heparin prolongs the half-life of the FGF-2 protein\(^{19}\) and facilitates its binding to FGF-2 receptors.\(^{19,20,22}\)

A microvascular disorder exists in the myocardium in the setting of HHD, which is caused by sustained hypertension. The decrease in coronary flow reserve is caused by a reduction in the microcirculatory bed.\(^2\)\(^-\)\(^4\) We therefore hypothesized that angiogenesis in the myocardium induced by FGF-2 plus heparin can suppress the deterioration in cardiac function in HHD, and confirmed that the increases in LVDd and LVDs and the reduction in FS were significantly suppressed by the intramyocardial injection of FGF-2 plus heparin.

Myocardial FGF-2 expression is upregulated by ischemia.\(^{17}\) FGF-2, in turn, upregulates the expression of vascular endothelial growth factor (VEGF).\(^{23}\) FGF-2 and VEGF enhance endothelium-dependent vascular smooth muscle relaxation through stimulation of nitric oxide release.\(^{24,25}\) FGF-2 and VEGF improve perfusion in the coronary microcirculation and increase regional blood flow by endothelium-dependent relaxation.\(^{24-27}\) In a clinical trial of direct myocardial injection of the gene encoding VEGF-165 as the sole therapy for myocardial ischemia, sestamibi perfusion imaging showed improved perfusion of the inferior wall in spite of a limited area (anterolateral wall) of injection.\(^{28}\) In the present study, we identified the presence of local angiogenesis with intramyocardial injection of FGF-2 plus heparin or FGF-2 alone.

How could intramyocardial injection of FGF-2 confined to the anterolateral wall improve global left ventricular dysfunction? It may be due to the interaction between FGF-2 and the other effects. FGF-2 can affect nitric oxide release\(^{24}\) and has an antiapoptosis effect.\(^{29}\) We believe that autocrine and paracrine effects of nitric oxide\(^{30}\) induced by FGF-2 contributed to the improvement in global left ventricular dysfunction. With long-term inhibition of nitric oxide synthase in the rat, the left ventricular chamber geometry changes, normalizing systolic wall stress, and decreasing myocardial passive stiffness. This allows for greater muscle strain for a given diastolic stress or preload.\(^{31}\) Upregulation of vascular con-
nstitutive nitric oxide synthase activity has a protective cardiovascular homeostatic role in the setting of hypertension. Moreover, it has been reported that FGF-2 attenuates myocardial ischemic stunning in the mouse independent of alterations in intracellular calcium by stimulating nitric oxide production.

Concerning our manner of administration of FGF-2, if FGF-2 will be injected into other locations such as subcutaneous or skeletal muscle, a higher concentration of FGF-2 is needed in order to affect the myocardium than is needed when injected directly into the intramyocardium. A high concentration of FGF-2 will cause local and systemic adverse effects in that case. Accordingly, we injected FGF-2 directly into the myocardium.

FGF-2 binds to heparan sulfate proteoglycans on the endothelial cell surface. Together with heparin and heparan sulfate, FGF-2 binds to its receptors with a high affinity. We found that a single intramyocardial injection of FGF-2 alone can promote angiogenesis. Moreover, the microvascular density significantly increased with the injection of FGF-2 plus heparin compared with FGF-2 alone. FGF-2 protein has a relatively short biologic half-life. Heparin may exert angiogenic effects by binding to growth factors, including FGF-2 and VEGF. This action would be independent of the anticoagulant action of heparin. In an ovine model of left ventricular hypertrophy, heparin administration during left ventricular hypertension increased the expression of heparin-binding angiogenic factors FGF-2 and VEGF in the left ventricle and ameliorated the decreases in left ventricular perfusion capacity and capillary density. Angiogenesis did not occur with the injection of heparin alone because the concentration of heparin (1.4 µM) used in this study was lower than that of previous reports. A high concentration of heparin (10 µM) was reported to inhibit FGF-2 receptor binding in cells.

ANP and BNP are neurohumoral factors which are secreted from heart and act as cardiac hormones. The plasma BNP concentration is increased in many hypertensive patients with left ventricular hypertrophy. The increase in the plasma BNP concentration seems to be related to left ventricular hypertrophy or the cardiac overload associated with left ventricular hypertrophy. ANP is released by ventricular myocytes only in the presence of left ventricular hypertrophy in rats. The plasma ANP concentration is also increased in patients with essential hypertensive and left ventricular hypertrophy. In this study, blood pressure, IVSTd, and PWTd were similar in all of the groups. Although the mechanism cannot be determined, FGF-2 plus heparin may have a beneficial effect in the setting of HHD, because the injection of FGF-2 plus heparin significantly decreased plasma ANP and BNP concentrations compared with the injection of vehicle alone.
Conclusion: Our findings indicate that a single intramyocardial injection of FGF-2 plus heparin suppresses progression of cardiac dysfunction in a rat model of HHD. These results suggest the possibility of a new therapeutic approach using FGF-2 plus heparin for HHD.

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