Effects of Chronic Heparin Administration on Coronary Vascular Adaptation to Hypertension and Ventricular Hypertrophy in Sheep

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Background—Hypertension decreases myocardial perfusion capacity in adults for several reasons, including insufficient coronary angiogenesis with left ventricular (LV) hypertrophy, arteriolar hypertrophy, and altered vasomotion. Heparin influences growth factors that promote angiogenesis and vasodilation and inhibit arteriolar wall thickening.

Methods and Results—Adult sheep were given heparin 200 U/kg body wt SC twice daily throughout 6 weeks of LV and coronary hypertension from a progressively constricted ascending aortic band (n = 14). They were compared with untreated sheep with (n = 13) and without (n = 13) aortic stenosis. After 6 weeks, maximum myocardial perfusion was measured during adenosine infusion in the conscious state by the microsphere method. Sheep with aortic stenosis had less maximum coronary flow per gram, less conductance reserve, and thicker arteriolar walls in the LV and nonhypertrophied right ventricle. Capillary density decreased in the LV endomyocardium and remained unchanged in the right ventricle. Heparin-treated sheep had significant partial normalization of coronary conductance reserve and maximum perfusion in both ventricles and capillary density in the LV endomyocardium. Arteriolar wall thickness was unchanged. Compared with untreated sheep with aortic stenosis, in heparin-treated sheep LV FGF-2 protein increased 2-fold, whereas FGF-2 mRNA remained unchanged. VEGF mRNA and protein increased 3-fold and 1.4-fold, respectively, whereas TGF-β1 mRNA declined 3-fold.

Conclusions—Heparin administration during LV hypertension increases heparin-binding angiogenic factors FGF-2 and VEGF in the LV and ameliorates decreases in LV perfusion capacity and capillary density. (Circulation. 1999;100:981-987.)

Key Words: heparin □ angiogenesis □ growth substances □ hypertrophy □ hypertension □ microcirculation

A nonnal myocardial perfusion capacity, intermittent ischemia, and secondary fibrosis occur with hypertension in adults and may contribute to its adverse consequences, including heart failure, arrhythmias, and sudden death. The limitation in coronary perfusion capacity in adults is due to left ventricular (LV) hypertrophy without proportionate microvascular growth and effects of hypertension on coronary structure and vasomotion.1–4 In contrast to adults, at a young age, hypertension results in coronary angiogenesis that is proportionate to LV hypertrophy and less impairment of coronary conductance and myocardial function.1–3 Developmentally regulated changes in heparin-binding and modifiable growth factors (eg, fibroblast growth factor [FGF]-2 and vascular endothelial growth factor [VEGF]) mediate perinatal physiological coronary angiogenesis and arterial adaptations to increasing pressure and may be responsible for the advantageous coronary adaptations exhibited with hypertension by the young.5–8 Methods to promote coronary angiogenesis into ischemic myocardium by administration of FGF-2 or VEGF are receiving much attention.8 Methods to modulate coronary arterial wall thickening by inhibition of vascular smooth muscle transforming growth factor [TGF]-β1 and FGF-2 are also being investigated.9 Heparins may be useful to modify endogenous growth factors to favorably affect angiogenesis, vasodilation, and arterial smooth muscle proliferation processes that contribute to myocardial perfusion abnormalities with hypertension and ventricular hypertrophy. Heparin interacts with multiple heparin-binding growth factors and receptors that modulate angiogenesis, including FGF-2, VEGF, TGF-β1, and others in ways that promote angiogenesis.8–15 Heparin increases cardi-
ac16 and coronary17 FGF-2 and accelerates coronary angiogenesis.8 In addition, heparin inhibits arterial thickening with hypertension18 and injury through interactions with FGF-2 and TGF-β.8,9,19 Heparin lowers vascular resistance with hypertension14,18 through interactions with several factors14,15 that probably include FGF-2 and VEGF.5,20

The purpose of this investigation was to determine whether heparin can modulate coronary angiogenesis and vascular responses with hypertension. Coronary microvascular density, arterial wall thickening, and conductance were measured in the hypertrophied LV and in the nonhypertrophied right ventricle (RV). Findings were correlated with changes in FGF-2, VEGF, and TGF-β.

Methods

Aortic Stenosis/Heparin Treatment Model

Studies were performed in 3 groups of Suffolk and Hampshire 2-year-old adult nonpregnant ewes: the experimental group (n = 13) had aortic stenosis but were not treated with heparin. The second group (n = 14) had aortic stenosis but were not treated with heparin. The third group (n = 13) received thoracotomy and instrumentation but did not receive aortic stenosis or heparin.

The model of progressive ascending aortic stenosis has been described in detail.1,2 Procedures followed were according to institutional guidelines. Under general anesthesia through a thoracotomy, the ascending aorta distal to the coronary arteries was encircled with an adjustable occluder. Catheters were placed in the aorta, LV, left atrium, and hemiazygos vein. Sham sheep underwent similar aortic dissection but did not receive an occluder. After recovery, the aortic occluder was inflated to induce an LV-to-aortic systolic pressure peak-to-peak pressure gradient of 30 mm Hg. The pressure gradient was increased 10 mm Hg weekly to 60 to 80 mm Hg. All animals received penicillin and streptomycin intramuscularly twice daily.

Heparin-treated aortic stenosis sheep received whole heparin 200 U/kg body wt SC twice daily (Hepar, Kabi Vitrum). This particular heparin induces angiogenesis and inhibits vascular smooth muscle proliferation (personal communication, Dr Carl Magnus Svahn, Kabi Vitrum, Stockholm, Sweden). Preliminary studies in 4 animals indicated that this dose increased partial thromboplastin time by 2±0.4-fold.

Coronary Physiology Measurements

After 6 weeks, with the sheep conscious, LV and aortic pressures were measured as previously described.2 Coronary blood flow and conductance and cardiac output were measured by the radioactive microsphere technique at baseline and during maximal coronary vasodilation induced with infusion of adenosine (4 μmol·kg body wt·min⁻¹) as previously described.1,7 All animals received heparin 5000 U IV before measurements. Mean coronary inflow pressure was measured as the integrated mean of LV systolic and aortic diastolic pressures. Diastolic perfusion pressure was calculated from the difference of mean diastolic pressures in aorta and LV. Mean coronary conductance was calculated as the ratio of mean coronary flow and inflow pressure. Coronary conductance reserve was calculated as the increase in mean conductance from baseline to maximum with adenosine infusion.

Coronary Microvascular Morphometric Measurements

Coronary capillary density was measured by use of 2 different histological and morphometric techniques in 2 separate laboratories. Postarteriolar capillary density was evaluated by the alkaline phosphatase staining method. The sheep were sedated with ketamine or thiopental, and the heart was arrested in diastole with KCl. Frozen sections 10 μm thick were prepared, fixed in acetone, and stained by the indoxyl tetrazolium method as previously described.7 Capillaries per mm² were counted in 10 to 20 cross-sectional fields of LV endomyocardium and midwall and RV.21

Independent analyses were performed on separate sheep with silver stain and glutaraldehyde perfusion fixation as previously described.4 Samples were dehydrated in ethanol, embedded in historesin, sectioned 1 μm thick, and stained by the silver methenamine method for basement membrane. Microvessel density and morphometrics were measured with an image analyzer as previously described.3,4 In the midwall of each ventricle, arteriolar external and lumen axes, distribution of arterioles of different sizes, and the wall thickness in arterioles of various external sizes were measured in 300 to 400 arterioles. The group identity of the slide was unknown to the investigators during both morphometric analyses.

Protein Isolation and Analysis

Heparin-binding growth factors were purified from frozen LV with standard protein isolation techniques and heparin affinity chromatography.21 Total protein concentration in the elution was determined by Pierce Coomassie assay.

ELISA was used to measure LV FGF-2 protein by use of a kit (R&D Systems). Samples in triplicate from each individual were measured together on multiwell plates. The assay was repeated. Similar ELISA assays for human VEGF and TGF-β had no cross-reactivity with sheep.

Western immunoblotting was used to measure VEGF protein. LV protein, recombinant VEGF (Santa Cruz Biotechnology), and molecular-weight protein standards (Bio Rad) were size-fractionated with SDS-PAGE (Bio-Rad Laboratories) according to the manufacturer’s recommendation. The proteins were electrophoretically trans-

<table>
<thead>
<tr>
<th>TABLE 1. Hemodynamic Data</th>
<th>Cardiac Index, ml·min⁻¹·kg⁻¹</th>
<th>LV Peak Pressure, mm Hg</th>
<th>LV End-Diastolic Pressure, mm Hg</th>
<th>Aortic Peak Pressure, mm Hg</th>
<th>Aortic Diastolic Pressure, mm Hg</th>
<th>Pressure Gradient, mm Hg</th>
<th>Coronary Mean Pressure, mm Hg</th>
<th>Diastolic Perfusion Pressure, mm Hg</th>
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<tr>
<td>Group</td>
<td>Heart Rate, bpm</td>
<td>130±21</td>
<td>121±5</td>
<td>8±1</td>
<td>121±6</td>
<td>91±4</td>
<td>0±1</td>
<td>104±5</td>
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<td>Sham</td>
<td>100±9</td>
<td>130±21</td>
<td>121±5</td>
<td>8±1</td>
<td>121±6</td>
<td>91±4</td>
<td>0±1</td>
<td>104±5</td>
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<td>119±19</td>
<td>188±9*</td>
<td>18±3*</td>
<td>121±8</td>
<td>92±4</td>
<td>65±5*</td>
<td>126±8</td>
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<tr>
<td>LWH+Heparin</td>
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<td>114±21</td>
<td>189±7*</td>
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<td>110±4</td>
<td>84±4</td>
<td>73±6*</td>
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<td>Adenosine</td>
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<td>191±26</td>
<td>98±4</td>
<td>9±2</td>
<td>92±4</td>
<td>40±5</td>
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<tr>
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<td>212±25</td>
<td>193±11*</td>
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<td>79±4</td>
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<td>200±12*</td>
<td>11±4</td>
<td>78±6</td>
<td>46±3</td>
<td>122±10*</td>
<td>103±6*</td>
</tr>
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</table>

Abbreviations as in Figure 1. *P<0.05 aortic stenosis.
ferred to PVDF membrane (Millipore) in a wet-transfer device (BioRad) according to the manufacturer’s instructions. Western blotting was done with primary antibody to VEGF (rabbit anti-human VEGF, Genentech) and Vectastain ABC-AP Kit (Vector Laboratories) according to the manufacturer’s instructions.

RNA Extraction and Analysis
Total RNA was extracted from the LV by the acid guanidinium thiocyanate–phenol-chloroform method, and Northern blot analysis was performed as previously described. The blots were hybridized with the following CDNAAs labeled with [32P]dCTP by the random priming method: (1) a 500-bp fragment of human FGF-2 (R&D Systems), (2) a 930-bp fragment of human VEGF (Genentech), (3) a 1.4-kb fragment encoding human TGF-β1 (Drs Bradley Arrick and Rik Derynck, Dartmouth Medical School, Hanover, NH), and (4) a 0.8-kb fragment of human GAPDH (Dr Constance Brinckerhoff, Dartmouth Medical School, Hanover, NH). Autoradiograms in the linear range were quantified by densitometry (Adobe Photoshop and Silverscreen or NIH Image). The data for each individual were normalized to the density of the corresponding signal for GAPDH.

Statistical Analysis
Results are expressed as mean±SEM. Statistical analysis of the effects of heparin on the responses to hypertension was done by multivariate ANOVA. The relationships of coronary conductance and capillary density to LV FGF-2, VEGF, and TGF-β1 were assessed by simple regression analysis. It is recognized that these relationships are biologically complex and interrelated and may not be linear.

Results
LV Hypertrophy and Hemodynamics
Aortic stenosis increased the ratio of LV to body weight by 42% in both untreated and heparin-treated sheep over sham sheep (2.7±0.1 versus 1.9±0.1, P<0.01). No RV hypertrophy occurred.

Hemodynamic data are shown in Table 1. The severity of LV hypertension was similar in heparin-treated and untreated sheep with aortic stenosis. Heparin-treated sheep had a statistically insignificant decrease in aortic pressure. Hemodynamic factors that may influence coronary flow were similar in heparin-treated and untreated aortic stenosis sheep.

Myocardial Perfusion
At rest, LV perfusion was similar in all groups (data not shown). Maximum coronary flow and conductance data are shown in Figures 1 and 2, respectively. LV coronary conductance reserve decreased with aortic stenosis. Heparin administration increased LV coronary conductance reserve 72% and maximum myocardial perfusion 38% over untreated sheep with aortic stenosis, but conductance remained less than in sham sheep.

RV coronary conductance reserve also decreased with aortic stenosis but was 59% greater in heparin-treated than untreated sheep. In heparin-treated sheep, maximum perfusion of both ventricles was similar to that in sham sheep.

Arteriolar Wall Thickness and Lumen Size
Morphometric data of arteriolar wall thickness and size in the LV are shown in Table 2 and Figure 3. Similar findings were present in the RV. Arteriolar relative wall thickness increased and mean lumen diameter decreased with aortic stenosis and were unaffected by heparin. The frequency distribution of arterioles of different sizes was similar in all groups (data not shown).

Microvascular Density
Capillary density data from 2 independent techniques are shown in Table 2. Capillary density decreased in the LV.
endothelial cell proliferation with aortic stenosis. Heparin ameliorated these effects; LV endomyocardial capillary density with the alkaline phosphatase and silver stain techniques was 17% (P=0.06) and 26% higher (P=0.05), respectively, in heparin-treated sheep than in untreated aortic stenosis sheep. In the LV midwall and RV, no changes in capillary or arteriolar density were evident.

LV FGF-2

Data of LV FGF-2 protein levels are shown in Figure 4. The effects of aortic stenosis and heparin were significant and opposing. Untreated sheep with aortic stenosis had 71% less LV FGF-2 protein than sham sheep. Heparin-treated sheep had 2-fold greater LV FGF-2 protein than untreated sheep with aortic stenosis, but it remained 31% less than in sham sheep. The increase in LV FGF-2 protein in heparin-treated sheep was not associated with a detectable change in FGF-2 mRNA (Figure 5). In individual untreated and treated sheep with aortic stenosis, LV FGF-2 protein level correlated with LV endomyocardial capillary density (alkaline phosphatase method, P<0.001, R²=0.88), maximum perfusion (P<0.001, R²=0.91), and coronary reserve (P<0.001, R²=0.85).

LV VEGF

Data on LV VEGF mRNA and protein levels are shown in Figures 5 and 6, respectively. Levels of VEGF mRNAs in the LV were similar in untreated aortic stenosis sheep and sham sheep. Heparin-treated sheep had 3-fold more VEGF mRNA than untreated aortic stenosis sheep. VEGF₁₆₅ protein was 51% greater in heparin-treated than untreated sheep with aortic stenosis and 213% greater than in sham sheep (effect of heparin, P=0.06). In sheep with aortic stenosis, LV VEGF₁₆₅ RNA correlated with LV endomyocardial capillary density (P=0.006, R²=0.74), maximum perfusion (P=0.004, R²=0.78), and coronary reserve (P=0.001, R²=0.84).

LV TGF-β₁

Untreated sheep with aortic stenosis had a trend toward a mild increase in LV TGF-β₁ mRNA compared with sham sheep (Figure 5). In contrast, TGF-β₁ mRNA decreased 66% in heparin-treated sheep from the level in untreated aortic stenosis sheep. The level of LV TGF-β₁ RNA has a negative relationship with LV endomyocardial capillary density (P=0.007, R²=0.6), maximum perfusion (P=0.008, R²=0.66), and coronary reserve (P=0.037, R²=0.54) in sheep with stenosis.

Discussion

This study demonstrates that administration of heparin to young adult sheep during development of LV hypertension and hypertrophy partially ameliorates the decrement in LV capillary density. These findings were seen with 2 independent methods in 2 sets of animals. The increase in capillary density in heparin-treated sheep most likely was from promotion of angiogenesis, although decreased rarefaction is
possible. This is consistent with previous studies demonstrating angiogenic effects of heparin\textsuperscript{10} that can accelerate coronary collateral growth.\textsuperscript{8} The changes occurred in the LV endomyocardium, where hypertrophy with hypertension occurs most intensely, and capillary density is most greatly influenced by alterations in angiogenesis.\textsuperscript{1,3,6,7} The increase in maximal flow and improved flow distribution with less myocardium per capillary can increase maximal myocardial oxygenation.\textsuperscript{3}

A second result shown here is that the increase in LV capillaries with heparin correlates with increases in LV FGF-2 and VEGF and decreased TGF-\textbeta\textsubscript{1} mRNA. Previous studies have demonstrated that heparin increases the amount and angiogenic effect of FGF-2 and VEGF. Heparin increases FGF-2 by impeding its degradation and by releasing FGF from extracellular heparan sulfate–binding sites.\textsuperscript{8,10} In vitro, heparin increases coronary FGF-2 and FGF receptor-1 content and FGF-2 release.\textsuperscript{16,17} In addition, heparin can substitute for heparan sulfate as a required factor for FGF-2 receptor binding and may separately bind FGF to cells and facilitate internalization.\textsuperscript{8,11} VEGF also requires heparins for binding to cell receptors, and addition of exogenous heparin releases VEGF from extracellular heparin-like binding sites and increases its half-life and binding to endothelial receptors.\textsuperscript{8,12,13} Secondary interactions may contribute; FGF-2 upregulates VEGF mRNA.\textsuperscript{8,23} Therefore, a heparin-mediated increase in FGF-2 protein may increase VEGF mRNA. Together, VEGF and FGF-2 synergistically accelerate angiogenesis.\textsuperscript{8,24} Both FGF and VEGF promote coronary angiogenesis in several species, including humans.\textsuperscript{8} In sheep, age-associated changes in cardiac FGF-2 and VEGF levels correlate with coronary angiogenesis with pressure-overload hypertrophy.\textsuperscript{5} In lambs, administration of protamine, which binds and reduces the amount of vascular heparins and inhibits FGF-2 and VEGF receptor binding,\textsuperscript{8,10} impedes age-associated coronary angiogenesis.\textsuperscript{6,7}

TGF-\textbeta\textsubscript{1} has complex interactions with growth factors, angiogenesis, and vascular smooth muscle.\textsuperscript{25} In vivo, pericyte TGF-\textbeta\textsubscript{1} inhibits angiogenesis.\textsuperscript{25} Vascular hypertrophy and fibrosis with hypertension are mediated in part by TGF-\textbeta\textsubscript{1}.\textsuperscript{26} Heparin modifies TGF-\textbeta\textsubscript{1} metabolism.\textsuperscript{9} In addition, down-regulation of TGF-\textbeta\textsubscript{1} with heparin could result from changes in FGF-2 (or other factors), modifying TGF-\textbeta\textsubscript{1} expression.\textsuperscript{25}

These studies suggest that in this model, heparin may promote LV coronary capillary angiogenesis, at least in part, through actions that increase the amount of LV FGF-2 and VEGF and reducing TGF-\textbeta\textsubscript{1}. To the best of our knowledge, the effects observed here of heparin on cardiac FGF-2 and on VEGF and TGF-\textbeta\textsubscript{1} mRNA in vivo are novel.

The coronary angiogenic effects of heparin seen in this study may involve effects of heparin on angiogenic processes\textsuperscript{8} not examined here. These include heparin facilitation of

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**Figure 5.** A, Data from Northern blot analyses of LV for FGF-2, VEGF, and TGF-\textbeta\textsubscript{1} referenced to amount of GAPDH in each sample and shown as percentage of mean for Sham sheep. VEGFa refers to upper VEGF band, with a size corresponding to VEGF\textsubscript{165,30} VEGFb refers to adjacent lower VEGF bands, with sizes corresponding to VEGF\textsubscript{165} and VEGF\textsubscript{121,30} Numbers of tested animals in each group are in white print at bottom of each bar. *Effect of heparin, \textit{P} ≤ 0.001. **Effect of heparin, \textit{P} ≤ 0.001. B, Representative blots hybridized sequentially with probes for FGF-2, VEGF, and GAPDH (control) and blots hybridized with probes for TGF-\textbeta\textsubscript{1} and GAPDH. Positions of ribosomal RNAs (rRNA) in blots are shown along right side for size markers. Heparin increased LV VEGF mRNA, decreased TGF-\textbeta\textsubscript{1} mRNA, and did not change FGF-2 mRNA. Abbreviations as in Figure 1.

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**Figure 6.** A, Densitometry data from Western blot analyses for VEGF. Numbers of animals tested are shown at bottom of each bar. B, Representative Western blot of LV heparin-binding (HB) protein isolated by heparin affinity chromatography with 1.1 mol/L NaCl elution, non–heparin-binding (NHB) proteins, and recombinant human VEGF protein as controls (right lane). Positions of molecular weight standards are shown. Abbreviations as in Figure 1.
FGF and VEGF receptor binding,\textsuperscript{11,12} upregulation of nitric oxide,\textsuperscript{8,15} and interference with inhibition of angiogenesis. Heparin blocks inactivation of FGF-2, VEGF, and TGF-β\textsubscript{1} by α\textsubscript{2}-macroglobulin,\textsuperscript{6} interferes with endothelin and thrombospondin (which inhibit angiogenesis and promote vascular smooth muscle proliferation),\textsuperscript{8,14,15} and strongly binds angiostatin and endostatin, powerful inhibitors of angiogenesis.

A third observation of this study is that heparin appears to ameliorate the adverse effects of hypertension on coronary conductance and maximum perfusion. Coronary arteriolar wall thickness increased and lumen diameter and coronary conductance decreased in both ventricles with ascending aortic stenosis. This is consistent with well-described changes with hypertension of arterial wall thickening, lumen narrowing, abnormal endothelium, and abnormal vasomotion.\textsuperscript{1,4} In heparin-treated sheep, the decrement in coronary conductance with hypertension was less in both ventricles, implying an effect of heparin treatment on direct hypertension-induced changes in coronary vascular structure or vasomotion, separate from ventricular hypertrophy.

Heparin partially reverses pulmonary arterial thickening with hypertension in rats,\textsuperscript{18} perhaps through effects on FGF-2, thrombospondin, platelet-derived growth factor, TGF-β\textsubscript{1}, endothelin, and nitric oxide.\textsuperscript{8,9,14,15,19} Morphometric analysis in this study does not demonstrate changes in arteriolar structure that provide a basis for the ameliorating effect of heparin treatment on coronary conductance. The magnitude of heparin effects on coronary conductance was moderate and anticipated associated changes in coronary lumen size exponentially smaller and within the SDs of the data. However, no tendency for a decrease in coronary wall thickness in heparin-treated animals was observed.

Alternatively, heparin effects on coronary conductance could be from effects on hypertension-induced abnormalities in the coronary endothelium and vasomotion. Many heparin-modifiable factors, including FGF and VEGF, influence vasomotion.\textsuperscript{8,14,15,19,20} Heparin administration lowers systemic\textsuperscript{14} and pulmonary\textsuperscript{15} hypertension by regulating vascular nitric oxide, endothelin,\textsuperscript{14,15} and possibly other substances. Supportive effects of heparin on endothelial integrity,\textsuperscript{2,22} mediated by heparin-induced changes in vascular FGF\textsuperscript{28,17,20,28} and VEGF,\textsuperscript{29} may ameliorate the adverse effects of baro-trauma and improve arterial conductance.\textsuperscript{20,27,28} These effects were not directly examined in this study.

Important effects of the heparin type, dose schedule, amount, route, duration, and timing of onset of treatment were not addressed in this study. Although heparin administration after development of pulmonary hypertension does partially reverse vascular changes,\textsuperscript{18} it is unknown whether heparin would reverse changes in coronary conductance or induce coronary angiogenesis if given after hypertension is established. The persistence of effects is not clear; over longer time periods, the effects of heparin could lessen. Alternative routes of administration and types of heparin may circumvent anticoagulant effects and other disadvantages with subcutaneous heparin administration.

In conclusion, in this model, administration of heparin during LV hypertension appears to modulate the heparin-binding angiogenic factors FGF-2, VEGF, and TGF-β\textsubscript{1} in the LV and ameliorates decrease in LV perfusion capacity and capillary density. To the best of our knowledge, this represents a novel in vivo model for therapeutic coronary angiogenesis through pharmacological manipulation of endogenous regulators of angiogenesis.

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References


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