Remodeling of left circumflex coronary arterial tree in pacing-induced heart failure

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Huo Y, Kassab GS. Remodeling of left circumflex coronary arterial tree in pacing-induced heart failure. J Appl Physiol 119: 404–411, 2015. First published July 9, 2015; doi:10.1152/japplphysiol.00262.2015.—Congestive heart failure (CHF) is a very serious heart disease that manifests an imbalance between left ventricle supply and demand. Although the mechanical demand of the failing heart has been well characterized, the systematic remodeling of the entire coronary arterial tree that constitutes the supply of the myocardium is lacking. We hypothesize that the well-known increase in ventricle wall stress during CHF causes coronary vascular rarefaction to increase the vascular flow resistance, which in turn compromises the perfusion of the heart. Morphometric (diameters, length, and numbers) data of the swine left circumflex (LCx) arterial tree were measured in both CHF (n = 6) and control (n = 6) groups, from which a computer reconstruction of the entire LCx tree was implemented down to the capillary level based on these morphometric measurements. The blood flow and wall shear stress (WSS) were determined in each vessel of the reconstructed LCx arterial tree in both experimental and control groups. A computer reconstruction of the entire LCx arterial tree was implemented down to the capillary level based on these morphometric measurements. The blood flow and wall shear stress (WSS) were determined in each vessel of the reconstructed LCx arterial tree of CHF animals. This study enhances our knowledge of coronary arterial tree remodeling in heart failure, which provides a deeper understanding of the deterioration of supply-demand relation in left ventricle.

Conflict of Interest: The authors declare no competing financial interests.

MATERIALS AND METHODS

Experimental Methods

Animal preparation. Studies were performed in 12 Yorkshire pigs (6 pacing-induced CHF and 6 sham control animals with weight of 66 ± 4 and 64 ± 6 kg, respectively). All animal experiments were performed in accordance with national and local ethical guidelines, including the Institute of Laboratory Animal Research Guide, Public Health Service policy, Animal Welfare Act, and Indiana University-Purdue University, Indianapolis polices regarding the use of animals in research. This study was reviewed and approved by the Institutional Animal Care and Use Committee.

Surgical anesthesia was induced with TKX (telazol 500 mg, ketamine 250 mg, xylazine 250 mg) and maintained with 2% isoflurane. The animal was intubated and ventilated with room air and oxygen by a respiratory pump. At left thoracotomy, an epicardial unipolar lead was placed 1.0 cm below the atrioventricular groove in the lateral wall of the LV. The power generator (Spectrax 5985; Medtronic) was inserted into a subcutaneous pocket in the abdomen. The chest was closed, and the animal was allowed to recover from the surgery for 1 wk. Ventricle pacing was then initiated at 210–220 beats/min for 1 wk, and 190–220 beats/min for additional 2–3 wk, depending on the status of the heart (16, 18).

After 3–4 wk of pacing, the CHF and sham control animals were anesthetized, intubated, and ventilated with room air. A midline sternotomy was performed. The heart was arrested with a bolus injection of KCl through the jugular vein. The heart was then excised with the aorta clamped to keep air bubbles out of the coronary arteries and placed in saline while the right coronary artery, left anterior descending and LCx arteries were cannulated and perfused by cardioplegic solution. The pressure changes at the inlet of coronary arterial trees were imposed with a pressure regulator, according to selected loading and unloading ramps and monitored by a pressure sensor (Summit Disposable Pressure Transducer, Baxter Healthcare;
error of ±2% at full scale), while the flows were measured with a flow probe (Transonic Systems, relative error of ±2% at full scale).

We measured an ~15% drop of mean blood pressure in Yorkshire pigs after 3–4 wk of pacing, in agreement with a previous study (4). Therefore, the LCx vasculature was perfused with silicone elastomer and Cab-O-Sil and then allowed to solidify in a specific period of time at a static pressure of 100 mmHg for control and 85 mmHg for CHF pigs, similar to previous studies (8, 11, 17). The LCx cast was dissected to identify the atrial branches that were tied a suture before corrosion of the myocardium. The two atria were cut away from the cast heart at the level of the atroventricular valves. The right ventricular (RV) free wall, LV free wall, and septum were excised and weighed.

Histological and cast measurements of LCx branches. The morphometric data on coronary arterioles of diameters < 40 μm were measured from histological specimens, while the data on coronary arterial vessels of diameters > 40 μm were obtained from casts. Briefly, 12 plugs of myocardial tissue were removed from LV free wall of three CHF pigs and 12 plugs from LV wall of three control pigs (at regions corresponding to those in the CHF hearts). Each plug was −4 × 4 mm² in cross section and extended transmurally from epicardium to endocardium. Each plug was completely sectioned transmurally into 60- to 80-μm thickness. Each section was dehydrated with alcohol and cleared with methyl salicylate to render transparent myocardium and visible microvasculature. After removal of tissue plugs, the same hearts were digested with a 30% KOH solution for several days. The digested tissue was washed away with soap and water. The veins were carefully pruned away, leaving the LCx and its branches intact with clusters of capillaries. The morphometric measurements from histological specimens and casts of swine hearts were identical to those described previously (15).

Reconstruction of the entire LCx arterial tree. We implemented a computer reconstruction of entire LCx arterial tree from morphometric measurements. Briefly, a two-step approach was employed in the reconstruction of the entire LCx arterial tree down to the capillary level. The cast data were reconstructed one bifurcation at a time. The simulated growth of a broken terminal cast vessel >40 μm entailed the search of intact bifurcations (for which mother and the two daughter vessels were measured from the cast data) with mother diameter closest (smallest difference) to the terminal vessel. Once such a bifurcation was found, it was “pasted” to the broken vessel. A search was then made for each of the two daughter vessels of the “pasted” bifurcation and so on. This process was repeated until the tree was reconstructed down to ~40 μm. On the other hand, the growth of a broken or terminal cast vessel ≤40 μm entailed the search of intact subtrees (for which a subtree was determined from the histological data) with the inlet diameter closest (smallest difference) to the terminal vessel. The selected subtree was then pasted to the cut vessel. The above process was repeated until the entire LCx arterial tree had terminal vessels with diameters ≤8 μm.

We assigned the diameter-defined Strahler system in the reconstructed entire LCx arterial tree, similar to a previous study (11). A vessel segment between two nodes of bifurcation is defined as a segment. Since each segment is assigned an order number in the diameter-defined Strahler system, one or more segments of the same order in series are considered as a single element of that order. It should be noted that the digital morphometric model of coronary arterial tree is different from that reported in Kassab et al. (15) because the assignment of orders was done automatically after the entire tree was reconstructed.

Flow Simulation

After the branching pattern and vascular geometry of LCx arterial tree were generated, a steady-state flow analysis was performed. Briefly, the governing equations are that \( Z(0) = 128 \mu L D^4 + Z(L) \), the conservation of mass at each junction, \( Q_{mother} = \sum Q_{daughters} \), and the continuous pressure at each junction, \( P(0)_{mother} = P(0)_{daughters} \), where \( L, D, \) and \( Q \) are the length, diameter, and flow rate of the vessel segment, respectively; \( Z(0) \) and \( Z(L) \) are the resistance at the entrance and exit of the vessel, respectively; \( P(0) \) and \( P(L) \) are the pressures at the entrance and exit of the vessels, respectively; and \( \mu \) is the blood viscosity as a function of vessel diameter (29). The pressure at the inlet of control LCx arterial tree was set as 100 mmHg. The pressure at the inlet of CHF LCx arterial tree, however, was set as 85 mmHg because the in vivo measured mean arterial pressure had a 15% drop after 3–4 wk of pacing. The resistance at each outlet of LCx arterial tree was taken as \( 128 \mu \text{capillary} L_{\text{capillary}}/\pi D^4_{\text{capillary}} \), where \( D_{\text{capillary}} \) and \( L_{\text{capillary}} \) refer to the diameter, length, and viscosity, respectively, in the first capillary segments to mimic the distal resistance. The solution of method is similar to a previous study (10).

Data Analysis

The morphometric and hemodynamic data were expressed as means ± SD. The diameter, length, flow rate, flow velocity, and WSS of vessel segments and elements were summarized in each order of the diameter-defined Strahler system. The relative error of these parameters were expressed as (CHF value − control value)/control value × 100 in each order of LCx arterial tree.

These data were further classified in four regimes: 1) epicardial (orders 9–11, which mainly exit in the epicardium); 2) transmural (orders 5–8, which perforate the myocardium); 3) perfusion subnetworks (orders 1–4, which are in all sheets of myocardium to provide local coronary perfusion); and 4) the first capillary vessels (order 0). ANOVA (SigmaStat 3.5) was used to detect differences between CHF and control. A \( P \) value < 0.05 was indicative of a significant difference between the two populations.

RESULTS

The heart weights were 300 ± 57 and 263 ± 21 g (\( P \) value = 0.38) for CHF and control groups, respectively. The ratios of RV/(LV + septum) were 0.41 ± 0.10 in CHF group and 0.31 ± 0.09 in control group (\( P \) value < 0.05). The RV mass of CHF increased significantly, while the LV mass remained relatively unchanged, which was consistent with previous studies (22, 43).
The postmortem measurements also showed approximately twofold increase of LV volume of CHF ($P$ value < 0.05).

The accumulative length of a representative LCx main trunk was 85 mm in CHF and 82 mm in control, where the main trunk begins at the root (the most proximal vessel of the tree) and is defined by the path corresponding to the largest vessel at each bifurcation/trifurcation down to the first capillary vessels. There were a total of 17 and 21 primary branches arising from the LCx main trunk in CHF and control, respectively.

Figure 1 shows good agreement ($R^2 = 0.99$) and the computed values were within ±1 SD of the measurements) between experimental and computational pressure-flow relations. The flow rates in CHF were statistically different from those in control, as pressure was varied from 40 to 180 mmHg. The measured vascular flow resistances were 2.1 ± 0.15 and 1.2 ± 0.11 mmHg-min·ml⁻¹ ($P$ value < 0.05) for the LCx arterial trees of CHF and control groups, respectively.

Tables 1 and 2 list the number, diameter, and length of vessel segments and elements as well as the segment-to-element number ratio in each order for the LCx arterial trees of CHF and control groups, respectively. There were 11 total orders from the root to the first capillaries of these trees. Figure 2, A and B, shows the relative error of diameter and length in vessel segments of each order of the LCx arterial trees. The CHF reduced the vessel diameter by ~10% in the first capillary segments. The vessel length remained unchanged in the first capillary segments, but decreased (>12%) in perfusion subnetwork of CHF group. There was a significant increase of both vessel diameter and length in transmural and epicardial subnetworks of the CHF group.

Figure 3A shows the relationship between mean segment flow (average of flow rates in all segments of each order) and mean segment pressure (average of inlet pressure + outlet pressure/2 in all segments of each order) for LCx arterial trees of CHF and control swine. The vascular flow resistance in each order increased significantly in the perfusion subnetwork of the CHF group, as shown in Fig. 3B. Figure 4, A and B, shows the relative error of flow rate and WSS in vessel segments in each order of the LCx arterial trees. The flow velocity had similar a variation trend to the WSS. There was a statistical difference of these parameters between CHF and control in all orders, except for those with marked $P$ values in Figs. 3 and 4.

**DISCUSSION**

We obtained the most systematic reconstruction of the entire LCx arterial tree along with a network analysis of blood flow in pacing-induced CHF. We report two major findings, includ-

### Table 1. Diameter and length of vessel segments and elements and S/E in each order for the left circumflex arterial trees of congestive heart failure group

<table>
<thead>
<tr>
<th>Order</th>
<th>Segment No.</th>
<th>Diameter, μm</th>
<th>Length, μm</th>
<th>Element No.</th>
<th>Diameter, μm</th>
<th>Length, μm</th>
<th>S/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>547,289</td>
<td>6.3 ± 1.2</td>
<td>45 ± 37</td>
<td>547,289</td>
<td>6.3 ± 1.2</td>
<td>45 ± 37</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>288,717</td>
<td>9.0 ± 0.6</td>
<td>54 ± 42</td>
<td>172,295</td>
<td>9.0 ± 0.6</td>
<td>91 ± 70</td>
<td>1.68 ± 0.91</td>
</tr>
<tr>
<td>2</td>
<td>148,397</td>
<td>12.4 ± 1.3</td>
<td>67 ± 48</td>
<td>89,447</td>
<td>12.2 ± 1.1</td>
<td>111 ± 89</td>
<td>1.66 ± 0.95</td>
</tr>
<tr>
<td>3</td>
<td>55,613</td>
<td>17.7 ± 1.7</td>
<td>69 ± 45</td>
<td>32,180</td>
<td>17.6 ± 1.3</td>
<td>119 ± 85</td>
<td>1.73 ± 0.85</td>
</tr>
<tr>
<td>4</td>
<td>41,110</td>
<td>28.1 ± 5.9</td>
<td>100 ± 114</td>
<td>15,961</td>
<td>27.2 ± 3.9</td>
<td>259 ± 223</td>
<td>2.58 ± 1.48</td>
</tr>
<tr>
<td>5</td>
<td>8,903</td>
<td>72.7 ± 18.9</td>
<td>503 ± 545</td>
<td>4,758</td>
<td>69.1 ± 14.0</td>
<td>941 ± 974</td>
<td>1.87 ± 1.03</td>
</tr>
<tr>
<td>6</td>
<td>2,945</td>
<td>155.2 ± 27.5</td>
<td>748 ± 675</td>
<td>1,211</td>
<td>147.3 ± 19.2</td>
<td>1,818 ± 1,651</td>
<td>2.43 ± 1.59</td>
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<tr>
<td>7</td>
<td>932</td>
<td>265.7 ± 35.2</td>
<td>935 ± 703</td>
<td>298</td>
<td>258.1 ± 23.3</td>
<td>2,923 ± 1,748</td>
<td>3.13 ± 2.09</td>
</tr>
<tr>
<td>8</td>
<td>493</td>
<td>428.1 ± 62.8</td>
<td>1,188 ± 883</td>
<td>122</td>
<td>421.1 ± 39.5</td>
<td>4,800 ± 3,167</td>
<td>4.04 ± 2.93</td>
</tr>
<tr>
<td>9</td>
<td>92</td>
<td>843.6 ± 200.3</td>
<td>1,521 ± 1,080</td>
<td>27</td>
<td>863.1 ± 190.9</td>
<td>5,181 ± 4,111</td>
<td>3.41 ± 2.82</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>1,429 ± 575.9</td>
<td>3,090 ± 5,097</td>
<td>16</td>
<td>1,545 ± 283.7</td>
<td>14,350 ± 19,850</td>
<td>4.50 ± 4.80</td>
</tr>
<tr>
<td>11</td>
<td>14</td>
<td>3,167 ± 247.5</td>
<td>5,388 ± 4,676</td>
<td>1</td>
<td>3,167</td>
<td>75,420</td>
<td>14</td>
</tr>
</tbody>
</table>

Values are means ± SD, averaged over vessel segments/elements or elements in each order of diameter-defined Strahler system. S/E, segment-to-element number ratio.

### Table 2. Diameter and length of vessel segments and elements and S/E in each order for the left circumflex arterial trees of control group

<table>
<thead>
<tr>
<th>Order</th>
<th>Segment No.</th>
<th>Diameter, μm</th>
<th>Length, μm</th>
<th>Element No.</th>
<th>Diameter, μm</th>
<th>Length, μm</th>
<th>S/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,029,000</td>
<td>6.9 ± 1.0</td>
<td>45 ± 31</td>
<td>1,029,000</td>
<td>6.9 ± 1.0</td>
<td>45 ± 31</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>569,310</td>
<td>9.1 ± 0.7</td>
<td>69 ± 39</td>
<td>368,917</td>
<td>9.0 ± 0.6</td>
<td>106 ± 53</td>
<td>1.54 ± 0.70</td>
</tr>
<tr>
<td>2</td>
<td>265,073</td>
<td>12.5 ± 1.4</td>
<td>82 ± 33</td>
<td>156,260</td>
<td>12.4 ± 1.2</td>
<td>139 ± 65</td>
<td>1.70 ± 0.90</td>
</tr>
<tr>
<td>3</td>
<td>126,936</td>
<td>17.5 ± 1.7</td>
<td>78 ± 58</td>
<td>59,416</td>
<td>17.5 ± 1.3</td>
<td>167 ± 119</td>
<td>2.14 ± 1.05</td>
</tr>
<tr>
<td>4</td>
<td>44,743</td>
<td>26.7 ± 3.1</td>
<td>120 ± 102</td>
<td>19,528</td>
<td>26.2 ± 1.8</td>
<td>274 ± 204</td>
<td>2.29 ± 1.16</td>
</tr>
<tr>
<td>5</td>
<td>15,721</td>
<td>42.5 ± 6.9</td>
<td>231 ± 191</td>
<td>7,914</td>
<td>41.9 ± 5.1</td>
<td>458 ± 386</td>
<td>2.00 ± 1.00</td>
</tr>
<tr>
<td>6</td>
<td>4,566</td>
<td>79.5 ± 15.3</td>
<td>364 ± 337</td>
<td>2,320</td>
<td>77.2 ± 10.9</td>
<td>716 ± 575</td>
<td>2.00 ± 1.01</td>
</tr>
<tr>
<td>7</td>
<td>1,687</td>
<td>164.8 ± 38.3</td>
<td>552 ± 465</td>
<td>654</td>
<td>156.6 ± 24.0</td>
<td>1,424 ± 1,095</td>
<td>2.58 ± 1.41</td>
</tr>
<tr>
<td>8</td>
<td>543</td>
<td>346.6 ± 58.9</td>
<td>788 ± 685</td>
<td>173</td>
<td>333.4 ± 41.9</td>
<td>2,473 ± 1,833</td>
<td>3.14 ± 2.12</td>
</tr>
<tr>
<td>9</td>
<td>300</td>
<td>591.8 ± 120.4</td>
<td>1,229 ± 1,407</td>
<td>79</td>
<td>574.9 ± 90.9</td>
<td>4,667 ± 3,917</td>
<td>3.80 ± 2.75</td>
</tr>
<tr>
<td>10</td>
<td>76</td>
<td>1,193 ± 191.5</td>
<td>2,316 ± 1,881</td>
<td>13</td>
<td>1,182 ± 152.1</td>
<td>13,540 ± 10,150</td>
<td>5.85 ± 4.05</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>2,206 ± 458.7</td>
<td>3,531 ± 3,546</td>
<td>3</td>
<td>2,219 ± 199.5</td>
<td>51,790 ± 5,490</td>
<td>14.7 ± 1.2</td>
</tr>
</tbody>
</table>

Values are means ± SD, averaged over vessel segments/elements or elements in each order of diameter-defined Strahler system.
CHF increased the vascular flow resistance by \( \sim 75\% \) due to a significant decrease of vessel number \((\sim 45\%)\) of the LCx arterial tree after 3–4 wk of pacing; and 2) the structural remodeling preserved the flow rate per vessel in CHF, but significantly changed the WSS in vessel segments of each order. These findings are discussed as follows.

**Structural and Functional Coronary Remodeling**

Spinale et al. (38, 40) showed a 13% reduction in capillary density within LV subendocardium and \( >50\% \) reduction of myocardial blood flow at basal state, rapid pacing, and maximal vasodilation in the chronic atrial pacing hearts. Helmer et al. (6) indicated that the LV free wall received less blood flow with an increased flow resistance than the septum during 21–28 days of ventricular pacing. We found that the 3- to 4-wk ventricular pacing increased the vascular flow resistance by \( \sim 100\% \) in an open heart procedure in situ perfused by non-pulsatile cardioplegia (16, 18). The ex vivo measurements indicated \( \sim 75\% \) increase in vascular flow resistance of the LV free wall (i.e., \( 1.2 \pm 0.11 \) mmHg-min-ml\(^{-1}\) in control vs. \( 2.1 \pm 0.15 \) mmHg-min-ml\(^{-1}\) in CHF, while the computational results were within \( \pm 1 \) SD of the measurements), which was less than the in situ change likely because of the substantial lack of vasomotor tone in the ex vivo measurement. Despite the significantly decreased coronary flow reserve in CHF (34, 37, 38, 40, 44), the endothelium-dependent vasodilation still occurred after 3–5 wk of rapid pacing (32). The preserved endothelium-dependent tone may be a potential reason for the disparity between ex vivo and in situ measurements.

Since the LV free wall was mainly perfused through the LCx artery, we performed the reconstruction of the entire LCx arterial trees of CHF and control groups. The total vessel number significantly decreased by \( \sim 45\% \) in the LCx arterial tree of CHF (Table 1 vs. Table 2). Since small arterioles were the major site of vascular resistance (7, 13, 42), the decrease in vessel number increased the flow resistance in CHF, given the fewer paths for blood flow. The change in capillary diameter was consistent with the measurements by Spinale et al. (40).
The approximately twofold increase of LV lumen volume without change in LV wall mass suggests a significant increase in ventricle wall stress. We have shown that the interplay of cavity-induced extracellular pressure and shortening-induced intramyocyte pressure exerts extravascular forces on coronary blood vessels (1), which can affect the circumferential stress and WSS (2, 28, 30). Hence, the increased ventricle wall stress is likely the culprit for the decreased vascularity and dimension of capillaries by impacting the balance of circumferential stress and WSS in coronary vessel wall as per the uniform circumferential stress and WSS hypotheses for the regulation of vascular remodeling and angiogenesis (14, 21, 28, 30). There are likely other possible mechanisms for the structural remodeling in the LCx arterial tree of CHF, e.g., myocardial ischemia (33, 34, 37, 38), abnormalities of cardiac calcium regulation (3, 25), and myocyte and extracellular matrix remodeling (39, 45), which still required further investigations.

Our laboratory has recently carried out continuous measurements of pressure and flow velocity in the coronary arterial tree by telemetry in pacing-induced CHF (4). There was a decrease of mean aortic pressure (from 100 to 64 mmHg), but an increase of coronary flow velocity during the first 2 wk of rapid pacing. Endothelial dysfunction correlated with CHF and increased vessel wall thickness (h) (27). The circumferential stress is proportional to \( (P-D)/h \), while WSS \( \approx U/D \), where \( U \) is flow velocity. The decrease in pressure and the increase in flow velocity and vessel wall thickness required the increased diameter to maintain circumferential stress (21) and WSS (14) in epicardial coronary arteries of CHF hearts, as shown in Fig. 2A. Moreover, the enlarged LV surface increased the length of epicardial coronary arteries of CHF hearts. The change ratio of vessel length in epicardial subnetwork in Fig. 2B agrees with that of changes in LV surface of CHF hearts (46).

On the other hand, the vascular rarefaction altered the remodeling of vessel connections in the LCx arterial tree of CHF, e.g., a small vessel skipped a middle vessel and connected to a large vessel because of regression of the middle vessel. The remodeling of vessel connections in CHF stemmed from orders 4 and 5 that marked the hemodynamic transition from the perfusion to transmural subnetworks, such that it resulted in a significant increase of vessel diameter and length in the transmural subnetwork compared with the control, as shown in Fig. 2.
Although the flow rate at the inlet of LCx arterial tree was reduced by CHF (Fig. 1), it was distributed through fewer channels, such that the flow rate in a given vessel of each order was relatively unchanged (Fig. 4A). Although the flow per capillary was also unchanged in CHF, there was a significant decrease (\(-11\%\)) of coefficient of variation (i.e., coefficient of variation = SD/mean) of the flow rate in the first capillary segments such that the flow heterogeneity was reduced in the LV free wall (7). The observed decrease of flow heterogeneity in CHF can be attributed to a decrease in work heterogeneity in that state, as described in a previous study (5).

The structural remodeling of the LCx arterial tree in CHF increased WSS and flow velocity in vessel segments of orders 0–2, but significantly reduced them in higher orders (Fig. 4B). Since WSS \(\propto \frac{\sqrt{Q}}{D^2}\), a 10% decrease of diameter increased WSS by 33%. The decrease of vessel diameter in orders 0–2 and the increase of vessel diameter in higher orders were the main reasons for the change of WSS, given the relatively unchanged flow rate in these vessels. Moreover, despite the uniform WSS hypothesis for vascular remodeling (14), the gradual increase of LV wall stress with pacing, as well as the curvilinear change (i.e., the progressive decrease within the first 2 wk and reversion to baseline thereafter) of aortic pressure (4) led to the WSS distribution in the LCx arterial tree in Fig. 4B. The increase of WSS in orders 0–2 could be an attempt to negate the rarefication of arterioles and capillaries in the LCx arterial tree.

**Critique of Study**

Although there was good agreement between experimental and computational results (Fig. 1), a number of assumptions were used in the hemodynamic analysis such as the steady-state flow analysis, ad hoc resistance boundary condition at each outlet of the arterial tree without considering the realistic capillary network and venous trees, and rigid wall boundary condition in the absence of vascular tone. The arterial circuit should be extended to the entire coronary vasculature, including the full capillary network and venous trees. The three-dimensional reconstruction of coronary vasculature (7), cou-
plied with a pulsatile model (9), contractile myocardial model (19), and vascular tone model (12), should be used to explore the diastolic/systolic dysfunctions during different periods of pacing-induced CHF. The reversal of CHF after termination of rapid pacing also required investigation.

Significance of Study

We showed a very significant decrease of number of blood vessels throughout the coronary arterial tree as well as a significant change of some of the vessel diameters and lengths in the LCx arterial tree after 3–4 wk of ventricular pacing. The structural remodeling resulted in a significant increase of vascular flow resistance, as well as altered WSS and flow velocity in vessels of the LCx arterial tree in CHF. The present study may provide new insight into targeted angiogenesis in the coronary arterial tree to enhance perfusion.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: Y.H. and G.S.K. conception and design of research; Y.H. and G.S.K. performed experiments; Y.H. and G.S.K. analyzed data; Y.H. and G.S.K. drafted manuscript; Y.H. and G.S.K. edited and revised manuscript; Y.H. and G.S.K. approved final version of manuscript.

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