Differences in the Regulation of Vascular Resistance in Guinea Pigs with Right and Left Heart Failure

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SUMMARY We investigated neurogenic, non-neurogenic, and structural contributions to vascular resistance in hindquarters in five groups of guinea pigs after heart failure produced by (1) constriction of the pulmonary artery (RHF), (2) constriction of the ascending aorta (LHF_A), and (3) constriction of the descending thoracic aorta (LHF_D); (4) after left ventricular hypertrophy produced by mild constriction of the ascending aorta (LVH); and (5) after sham surgery. Pressure-flow curves were used to assess vascular resistance in the isolated, perfused hindquarters. In RHF and LHF_D, vascular resistance tended to increase and for different reasons. In the LHF_A group, sympathectomy produced the greatest vasodilation. Therefore, neurogenic influences predominated. The high neurogenic tone may have been related to reduced arterial pulse pressure (P < 0.05) and reflexes arising in arterial baroreceptors. In contrast, the LHF_D group had increased arterial pressure and pulse pressure (P < 0.05) and normal neurogenic vasoconstriction. However, non-neurogenic vasoconstriction was increased probably as a result of increased vascular responsiveness to constrictor stimuli. In the RHF group, papaverine produced the greatest vasodilation (P < 0.05). Therefore, non-neurogenic influences predominated. This was attributed to both increased vascular responsiveness and to altered humoral stimuli. Similar maximal vasodilation indicated that structural factors contributed equally to vascular resistance in all the groups. These results indicate differences in the regulation of vascular resistance in anesthetized, guinea pig models of right and left heart failure.

THE RELATIVE importance of neurogenic, humoral, vascular reactive, and structural contributions to vascular resistance in heart failure has not been established. Some investigators have suggested that the neurogenic contribution is predominant.1,4 Others have reported observations that detract from this concept. In one study, for example, the reflex vasoconstrictor response to carotid occlusion was less in dogs with right heart failure than in normal dogs.5 In two other studies reported from our own laboratory, the neurogenic influence, as estimated from the vasodilator response to sympathectomy, was not abnormally increased in hamsters with cardiomyopathy4 or in dogs with right heart failure.7 These observations have led us to consider the possibility that various types of heart failure might differ with regard to the relative importance of the factors regulating vascular resistance. Theoretical considerations would appear to support this possibility. Mechanoreceptors in the right and left atria may mediate different compensatory changes. Brennan et al.6 have suggested that mechanoreceptors in the right atrium modulate plasma levels of renin. Brennan et al.6 and Johnson et al.8 have suggested that receptors in the left atrium modulate plasma levels of antidiuretic hormone. Mason and Led-some10 and Mark et al.11 have suggested that receptors in the left atrium and left ventricle, respectively, modulate reflex control of vascular resistances. Thus, in left and right heart failure, which could stress different populations of mechanoreceptors, the factors contributing to vascular resistance might be different.

The intent of this study was to investigate the relative importance of neurogenic, non-neurogenic, and structural influences on vascular resistance in hindquarters of guinea pigs with left and right heart failure.

Methods

PREPARATIVE SURGERY

Anesthesia was induced in fasting male guinea pigs, 700–900 g, with halothane (Fluothane, Ayerst) and maintained with intravenously administered sodium pentobarbital (Nembutal, Abbott), 15 mg/kg. Succinylcholine (Squibb), 1 mg, was administered intraperitoneally to establish neuromuscular blockage and facilitate control of respiration. Ventilation through a tracheal cannula inserted at the midneck was controlled with a rodent respirator (Harvard Apparatus). Room air and 100% oxygen at 2 liters/min were mixed in a wide mouth plastic bottle; this mixture (approximately 40% O_2) was drawn into the inspiratory port of the respirator through an extension tube and was intended to maintain the blood PaO_2 near 100 mm Hg or above. We maintained tidal volume at 3 ml and rate at 60/min. Every 30 minutes, we closed the inspiratory port for three breaths to hyperinflame the lungs and minimize atelectasis.

The great vessels were exposed through an incision in the left 4th intercostal space. Each guinea pig was subjected to one of the following procedures: (1) right heart

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failure mortality was in the heart failure groups: (1) nine died acutely and 13 died later in RHF; (2) seven died acutely and 21 died later in LHF A; and (3) four pigs survived and underwent study 30 days after the initial surgery.

The bands were constructed by inserting a short (4.1-6.3 mm) length of 24-gauge copper wire and a 10-cm length of 4-0 silk suture through the lumen of a short piece of polyethylene tubing (PE 50) the same length as the copper wire. The bands were formed by bending the plastic-enclosed copper wire and suture around a precisely machined stainless steel rod, 2.0, 1.8, or 1.3 mm in diameter. The bands were inserted over the aorta or pulmonary artery by gently squeezing the vessel with small forceps and using the suture to pull the band into place. The two ends of the copper wire were apposed by firmly tying a square knot at the vessel surface with the two ends of the suture. This established a reproducible decrease in lumen area ranging from approximately 75% in the LHF D and LVH groups to 80-85% in the RHF and LHF A groups. The constriction was quantified in two ways. First, at the expected site of banding. Cross-sectional area was calculated from the measurement. The percent reduction in cross-sectional area was estimated by using the internal diameter of the band to obtain the postbanding cross-sectional area. Second, at the time of death, normal vessel size was estimated from the diameter of probes that could be inserted into the vessel lumen 1 mm upstream and downstream to the constriction; these values were averaged. The constricted vessel size was estimated from the diameter of the largest probe that could fit through the vessel lumen at the point of constriction.

To assess the effects of constriction of vessels on cardiac output and other variables and estimate the severity of the hemodynamic stress, determinations were carried out immediately after the surgical preparations of two or three guinea pigs in the RHF, LHFD, and sham groups. Cardiac output was determined by an indicator-dilution technique. Systemic arterial and central venous pressures also were measured in these guinea pigs.

After surgery, the guinea pigs were caged individually, given water ad libitum, and fed identical rations until the studies were performed 30 days later.

A total of 97 guinea pigs underwent surgical preparations. Twenty died during surgery as a result of perforation of vessels and uncontrollable bleeding. Thirty-nine died in the postoperative period, most in the 1st week. The greatest mortality was in the heart failure groups: (1) nine died acutely during surgery and five died later in LHF A; (2) seven died acutely and 21 died later in LHF D; and (3) four died acutely and 13 died later in RHF. Thirty-eight guinea pigs survived and underwent study 30 days after the initial surgery.

STUDIES

Guinea pigs were anesthetized and ventilated as described above. A cannula was inserted into the right carotid artery and connected to a strain gauge pressure transducer (Statham P23AA) for measurement of systemic arterial blood pressure. This and other variables were recorded on a direct-writing oscillograph (Beckman, type RS). Heart rate was counted from the phasic pressure record. The distal abdominal aorta just above the bifurcation was cannulated with polyethylene tubing (PE 90); both hindquarters were perfused at constant flow with heparinized arterial blood obtained from the proximal segment of the divided aorta using a Holter model RL 175 roller pump (Extracorporeal Medical Specialties). Flow was maintained at 3.5 ml/min except as noted. Perfusion pressure was monitored with a pressure transducer (Statham P23AA). With constant flow, changes in perfusion pressure indicated changes in hindquarter vascular resistance. Perfusion pressure decreased to 5-12 mg Hg when the pump was stopped, and backflow of blood from the distal transected aorta was not detected, thus indicating that collateral flow to the hindquarters was negligible.

In each guinea pig we determined hindquarter vascular resistance before and after sympathetic denervation to assess the neurogenic component and again after the administration of a potent pharmacological vasodilator stimulus, papaverine, to assess the non-neurogenic component. After maximal dilation, the remaining resistance was ascribed to the structural determinants of vascular resistance. In addition, we determined vasconstrictor responses to norepinephrine, angiotensin, and the electrical stimulation of lumbar sympathetic nerves in order to characterize vascular reactivity to neural and humoral stimuli.

To assess vascular resistance in the hindquarters, arterial flow was varied (2, 3.5, and 5 ml/min) and perfusion pressure was monitored to obtain pressure-flow curves. These flow rates were chosen arbitrarily because preliminary experiments indicated they could be achieved without appreciable change in systemic arterial pressure and they resulted in perfusion pressures that were approximately in the range of normal systemic arterial pressures (Fig. 1). Pressure-flow curves were obtained for the innervated hindquarters, for the denervated hindquarters after cutting both the right and left lumbar sympathetic chains at the level of the 2nd to 4th lumbar vertebrae (Fig. 1), and again during the intra-arterial administration of papaverine, 0.37 mg/min, to the hindquarters. This dose of papaverine produced almost maximal vasodilation, since increasing the dose to 0.74 mg/min produced only a very small additional decrease in perfusion pressure.

Vasoconstrictor responses to adrenergic and nonadrenergic stimuli were observed also. The responses to constrictor stimuli were obtained after sympathectomy and before the administration of papaverine. We injected I-norepinephrine bitartrate (Levophed, Winthrop) and 5-Val-angiotensin II amide (Hypertensin, Ciba) into the perfusion tubing upstream from the pump in 5-40 μl of saline; injection of these volumes of saline alone had small, reproducible effects that were similar in all the groups and, therefore, of no consequence in the compari-
aorta for determination of blood gases and hematocrit. These determinations confirmed that ventilation was maintained at an adequate level and that hematocrits were normal in all the groups.

ANALYSES OF TISSUES

At the termination of studies, the guinea pigs were killed by rapidly dislocating the cervical vertebrae. Hearts and lungs were taken for determination of organ weights. The atri, pulmonary artery, and aorta were trimmed away along the atroventricular (AV) groove. The free wall of the right ventricle was excised, blotted, and weighed leaving the interventricular septum and left ventricular free wall to be blotted and weighed separately as a unit. The lungs were taken in toto; the bronchi and major vessels were trimmed away proximal to the first branches of the main stem bronchi; the lungs were lightly blotted, and weighed.

Statistical analyses were performed by analysis of variance and Tukey's test.13 Responses to constrictor stimuli were compared by analysis of variance and a parallel line bioassay.14

Results

Acute constriction of the pulmonary artery, ascending aorta, and descending aorta produced 29%, 25%, and 19% lower cardiac outputs, respectively, without significantly lowering systemic arterial pressure or raising central venous pressure, in comparison to the cardiac output and other variables immediately after sham surgery (Table 1).

All guinea pigs tended to lose a small amount of weight after surgery. The groups had comparable total body weights at the time of the study (Table 2). In comparison to the sham group, 30 days after surgery significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2). Significant increases in the weights of the right ventricles, mottling on the surface of the livers which correlated with histological evidence of hepatic congestion, and, in three of the guinea pigs, ascites, indicated right heart failure in one group (RHF, Table 2).

Vascular resistance tended to be increased (P > 0.05) in the hindquarters of the RHF group and also in the hindquarters of the LHF group (Fig. 2). Hindquarter

### Table 1: Hemodynamic Observations Immediately after Acute Constriction of Vessels

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>n</th>
<th>Cardiac output (ml/min per kg)</th>
<th>MAP (mm Hg)</th>
<th>CVP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>2</td>
<td>93 ± 2</td>
<td>93 ± 13</td>
<td>5</td>
</tr>
<tr>
<td>Constriction of pulmonary artery (85 ± 3%)</td>
<td>2</td>
<td>66 ± 3</td>
<td>93 ± 3</td>
<td>4 ± 0.5</td>
</tr>
<tr>
<td>Constriction of ascending aorta (81 ± 1%)</td>
<td>3</td>
<td>69 ± 4</td>
<td>107 ± 7</td>
<td>4 ± 0.6</td>
</tr>
<tr>
<td>Constriction of descending aorta (74 ± 4%)</td>
<td>3</td>
<td>76 ± 10</td>
<td>90 ± 9</td>
<td>7 ± 3.2</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; CVP = central venous pressure.

Values are means ± SE. The three groups with constriction of vessels correspond to the RHF, LHF_a, and LHF_b groups, respectively, in Table 2. The average level of vessel constriction, decrease in lumen area, is given in parentheses for these guinea pigs. The CVP was measured in only one of the two sham guinea pigs.
Table 2  Evidence of Cardiac Hypertrophy and Heart Failure

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>n</th>
<th>Final total body weight (kg)</th>
<th>Tissue weights (g/kg body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left ventricle</td>
</tr>
<tr>
<td>Sham operation</td>
<td>8</td>
<td>0.88 ± 0.063</td>
<td>1.69 ± 0.08</td>
</tr>
<tr>
<td>LHFₐ, 85% constriction of ascending aorta</td>
<td>8</td>
<td>0.79 ± 0.025</td>
<td>2.63 ± 0.15*</td>
</tr>
<tr>
<td>RHF, 85% constriction of main pulmonary artery</td>
<td>7</td>
<td>0.78 ± 0.018</td>
<td>1.56 ± 0.09</td>
</tr>
<tr>
<td>LHFₐ, 75% constriction of descending aorta</td>
<td>7</td>
<td>0.77 ± 0.025</td>
<td>2.63 ± 0.12*</td>
</tr>
<tr>
<td>LVH, 75% constriction of ascending aorta</td>
<td>8</td>
<td>0.82 ± 0.025</td>
<td>2.13 ± 0.08</td>
</tr>
</tbody>
</table>

Values are means ± SE. LHF = left heart failure; RHF = right heart failure; LVH = left ventricular hypertrophy.

* P < 0.01 indicates that means of the sham group and another group differed significantly. These comparisons were performed by analysis of variance and Tukey’s test.

vascular resistance in the other groups (LHFₐ and LVH) differed very little from that in the sham group. Arterial pulse pressure (systolic minus diastolic) was decreased (P < 0.05) in one group (LHFₐ); mean systemic arterial pressure and arterial pulse pressure were increased (P < 0.05) in one group (LHFₐ) (Fig. 3). The five groups did not differ with respect to heart rates; the average heart rates ranged from 204 to 239 beats/min during the experimental protocols.

The groups did not differ statistically with respect to blood gases at the termination of the experiments (Table 3). However, there was considerable variability in Po₂ and values less than 100 mm Hg occurred in the sham group (69 mm Hg), the LVH group (41, 61, and 77 mm Hg) and the RHF group (70 and 74 mm Hg). All other values for Po₂ were greater than 100 mm Hg. The RHF group also tended to have higher pH values and lower Pco₂ values; however, these were not significantly different from corresponding values in the other groups (Table 3).

Figure 2  Before sympathectomy, a tendency (P > 0.05) toward a higher vascular resistance, indicated by a shift of the pressure-flow curve in the direction of the pressure axis, was observed in guinea pigs with right heart failure produced by constriction of the main pulmonary artery (RHF) (△) and in guinea pigs with left heart failure produced by constriction of the ascending aorta (LHFₐ) (△). Lower, more normal vascular resistance was observed in guinea pigs with left heart failure produced by constriction of the descending thoracic aorta (LHFₐ) (O), in guinea pigs with left ventricular hypertrophy produced by mild constriction of the ascending aorta (LVH) (O), and in sham-operated guinea pigs (O). The symbols at the left indicate average perfusion pressure when perfusion pumps were stopped. Values are means ± SE. The number of guinea pigs in a group is indicated in Table 2.

Figure 3  The vasodilator responses to sympathectomy in the different groups were normalized by averaging the decreases in perfusion pressure at three levels of arterial perfusion, 2, 3.5, and 5 ml/min, in each guinea pig as described in Figure 1, and dividing by the number of guinea pigs in each group. The vasodilator response to sympathectomy, i.e., the neurogenic contribution to hindquarter vascular resistance, was increased in the group with left heart failure (LHFₐ, *P < 0.05) and was normal in the other groups including the group with right heart failure. The asterisk at the top indicates that the mean systemic arterial pressures (MAP) or arterial pulse pressures in the LHFₐ and LHFₐ groups differed from the corresponding values in the sham group (P < 0.05). The bar indicates that the two variables in the LHFₐ group differed from those in the LHFₐ group (P < 0.05). Abbreviations are further identified in Figure 2.
### Table 3 Blood Gases

<table>
<thead>
<tr>
<th>Group</th>
<th>Po_2</th>
<th>Pco_2</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>138 ± 27</td>
<td>40 ± 4</td>
<td>7.44 ± 0.03</td>
</tr>
<tr>
<td>LHF_A</td>
<td>248 ± 44</td>
<td>42 ± 5</td>
<td>7.37 ± 0.02</td>
</tr>
<tr>
<td>RHF</td>
<td>127 ± 19</td>
<td>29 ± 2</td>
<td>7.48 ± 0.05</td>
</tr>
<tr>
<td>LHFD</td>
<td>255 ± 62</td>
<td>39 ± 7</td>
<td>7.38 ± 0.05</td>
</tr>
<tr>
<td>LVH</td>
<td>129 ± 25</td>
<td>52 ± 6</td>
<td>7.34 ± 0.03</td>
</tr>
</tbody>
</table>

### A. Data on blood gases

#### B. Analysis of variance on the data on blood gases

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>MS</th>
<th>F</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between groups</td>
<td>4</td>
<td>25,795</td>
<td>3.391</td>
<td>4</td>
<td>3.017</td>
<td>4</td>
</tr>
<tr>
<td>Within groups</td>
<td>26</td>
<td>7,606</td>
<td>31</td>
<td>27</td>
<td>0.009</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td></td>
<td></td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

df = degrees of freedom; MS = mean square; F = the F ratio.

Note that the critical differences required to achieve statistically significant differences between groups with a P < 0.05 are not exceeded for any of the variables in part A. These critical differences, calculated by Tukey's test, are 162 mm Hg for Po_2, 24 mm Hg for Pco_2, and 0.18 units for pH.

### NEUROGENIC FACTORS

The vasodilator responses to sympathectomy were greater (P < 0.05) in the LHF_A group than in the other groups (Fig. 3).

### NON-NEUROGENIC FACTORS

After sympathectomy, the vasodilator responses to papaverine were greater (P < 0.05) in the RHF group than in the two groups with left heart failure, and also greater in the RHF group than in the sham group and the group with left ventricular hypertrophy alone (Fig. 4). The vasodilator responses to papaverine also were greater in the LHF_A and LHFD groups than in the sham group, but only the difference between the LHFD and sham groups achieved significance (P < 0.01) (Fig. 4).

### STRUCTURAL FACTORS

The maximal vasodilation produced by papaverine was similar in all the groups (Fig. 5).

### VASOCONSTRICTOR RESPONSES

The increases in hindquarter perfusion pressure produced by norepinephrine and electrical stimulation of the lumbar sympathetic chains were augmented similarly in the RHF and LHFD groups. The augmentation was not consistent in the LHF_A group and not detected in the guinea pigs with left ventricular hypertrophy alone (Fig. 6 and Tables 4 and 5). The responses to angiotensin over-
These results suggested that the regulation of hindquarter vascular resistance beds differed in right and left heart failure. Maintenance almost exclusively by non-neurogenic factors. In the group LHFA, baseline hindquarter vascular resistance was maintained primarily by neurogenic mechanisms. In the group RHF, vascular resistance was maintained almost exclusively by non-neurogenic factors. These results suggested that the regulation of hindquarter resistance beds differed in right and left heart failure.

Discussion

In the one group of guinea pigs with left heart failure, LHFA, baseline hindquarter vascular resistance was maintained primarily by neurogenic mechanisms. In the group with right heart failure, RHF, vascular resistance was maintained almost exclusively by non-neurogenic factors. These results suggested that the regulation of hindquarter resistance beds differed in right and left heart failure.

We considered the possibility that structural changes accounted for these differences. None was detected (Fig. 5). The maximal vasodilation evoked by papaverine, which would have been limited by structural changes in vascular and perivascular tissues, was similar in all the experimental animal models used in these studies.

We also considered the possibility that debility (weakness, illness) might have accounted for the differences among the groups with heart failure. If this had occurred it should have been reflected by a decrease in the total body weights of the guinea pigs. The groups did not differ statistically with respect to total body weights. Therefore, the results cannot be ascribed to a deterioration of guinea pigs in any of the groups.

Although blood gases did not differ significantly between the various groups, variability was observed, making it necessary to consider the possible contribution of altered blood gases to the results. Six guinea pigs had P02 values less than 100 mg Hg. None of the P02 values was less than 30 mm Hg, which is reported to be the degree of hypoxemia necessary to influence vascular resistance directly and inhibit responses to constrictor stimuli in limb vasculature. Furthermore, the guinea pigs with low

![Figure 6](http://circres.ahajournals.org/)

**Figure 6** These are the vascular responses to constrictor stimuli in the five groups of guinea pigs. Values are means ± SE. The responses are increases in hindquarter perfusion pressures (mm Hg) induced with close intra-anerial injections of drugs into the constantly perfused hindquarters (3.5 ml/min) and with electrical stimulation of the lumbar sympathetic chains. Responses in the sham group were compared with responses in the other groups by analysis of variance and a parallel line bioassay (Table 4 and 5). The responses to constrictor stimuli were augmented in the RHF and LHFA groups with heart failure, but the response to angiotensin was selectively augmented in the RHF group. Abbreviations as in Figure 2.

Table 4 Analysis of Variance of the Data in Figure 6

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Sympathetic nerve stimulation</th>
<th>Norepinephrine</th>
<th>Angiotensin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>MS</td>
<td>F</td>
</tr>
<tr>
<td>Groups</td>
<td>4</td>
<td>1,220.4</td>
<td>22.4</td>
</tr>
<tr>
<td>Regression</td>
<td>1</td>
<td>11,676.9</td>
<td>214.0</td>
</tr>
<tr>
<td>Parallelism</td>
<td>4</td>
<td>130.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Linearity</td>
<td>10</td>
<td>29.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Error</td>
<td>132</td>
<td>54.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Total</td>
<td>151</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis of variance was calculated by computer using the program of McArthur et al.14 df = degrees of freedom and MS = mean square. F values were calculated using the error MS as divisor. Significant F values for regression and nonsignificant F values for parallelism and linearity indicate that (1) the slopes of dose-response curves were significant statistically; (2) the dose-response curves of different groups did not deviate from parallelism, that is, the slopes of dose-response curves for the individual groups were similar; and (3) the dose-response curves of individual groups were linear. Linearity was not tested in the case of responses to angiotensin since only two doses of the drug were used.

Table 5 Relative Potencies of Norepinephrine, Sympathetic Nerve Stimulation, and Angiotensin in Guinea Pigs with Right and Left Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>RHF</th>
<th>LHFA</th>
<th>LHFa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>2.91*</td>
<td>1.46*</td>
<td>2.14*</td>
</tr>
<tr>
<td>(2.03-4.33)</td>
<td>(1.05-2.06)</td>
<td>(1.51-3.12)</td>
<td></td>
</tr>
<tr>
<td>Sympathetic nerve stimulation</td>
<td>3.20*</td>
<td>1.71*</td>
<td>2.20*</td>
</tr>
<tr>
<td>(2.25-4.75)</td>
<td>(1.24-2.42)</td>
<td>(1.57-3.19)</td>
<td></td>
</tr>
<tr>
<td>Angiotensin</td>
<td>15.07*</td>
<td>1.81</td>
<td>2.68*</td>
</tr>
<tr>
<td>(5.92-54.67)</td>
<td>(0.82-4.34)</td>
<td>(1.18-6.96)</td>
<td></td>
</tr>
</tbody>
</table>

These values were calculated from the data in Figure 6 and the analysis of variance in Table 3. Relative potency is the ratio of the stimulus that produced a certain response in the sham group to the stimulus that was required to produce the same response in one of the heart failure groups. For example, a relative potency of 15 for angiotensin in the RHF group means that, in order to produce a given response, 15 times more angiotensin was required in the sham guinea pigs than in the RHF guinea pigs. * The responses to norepinephrine, sympathetic nerve stimulation, and angiotensin were augmented significantly (P < 0.05) if the 95% confidence limits of the ratio (in parentheses) did not overlap the value 1.0. † In the RHF group, the fact that the lower 95% confidence limit of the relative potency for angiotensin did not overlap the lower 95% confidence limits of the relative potencies for norepinephrine and sympathetic nerve stimulation means that the responses to angiotensin were augmented more (P < 0.05) than the responses to adrenergic stimuli.
Po2 values had vasodilator responses to sympathectomy and papaverine and responses to constrictor stimuli that were typical of the other guinea pigs with Po2 values greater than 100 mm Hg in their respective groups. Thus, moderately low Po2 values in the six guinea pigs probably did not alter the results.

The pH values in the RHF group tended to be higher and the PCO2 values tended to be lower than in the other groups. The differences were not statistically significant (Table 3) and we do not believe these trends altered the major conclusions of the study. On the basis of previous work, there appear to be offsetting effects of increased pH on large and small resistance vessels18 and on muscle and cutaneous beds. Therefore, we cannot predict what influence a slightly higher pH value might have had in the perfused hindquarters of the RHF group. In three RHF guinea pigs without hypocapnia and alkalosis, responses were comparable to the RHF group means. Furthermore, including or excluding the data from two sham guinea pigs and four RHF guinea pigs with hypocapnia and alkalosis did not alter the differences between the groups. Rather than detracting from the conclusions, these considerations support the conclusions and the likelihood that blood gases had little overall influence on the results.

Finally, we considered the possibility that the acute hemodynamic alterations induced by vessel constriction could have differed and accounted for the chronic differences in vascular regulation. Acutely the constriction of vessels in the heart failure groups produced approximately the same levels of cardiac output, and the same reductions compared to the cardiac outputs in the sham group. Moreover, the acute representatives of the RHF, LHFA, and LHFD groups did not differ with respect to systemic arterial pressure or central venous pressure immediately after surgery. These observations indicated that the differences in vascular regulation in the RHF, LHFA, and LHFD groups were not the result of initial differences in the cardiac output, arterial pressure, and central venous pressure. Therefore, the differences in vascular regulation are attributed to differences in the chronic compensatory adjustments to constriction of the pulmonary artery, ascending aorta, and descending thoracic aorta.

The experimental models of heart failure used in the present studies were similar to those used in a separate study of the parasympathetic innervation of the failing heart.28 Also, the group with left heart failure produced by constriction of the ascending aorta, LHFA, was analogous to the experimental guinea pig models reported by Ger
tier,21 Schwartz and Lee,22 and Spann and co-workers.23 The weights of the left ventricles plus septum and the weights of right ventricles were almost identical to those reported for a guinea pig model of left heart failure by Spann et al.20 In agreement with Spann and co-workers,23 our preparations with left heart failure also exhibited modest right ventricular enlargement. There was no evidence of mottling on the liver surfaces or ascites in our groups with left heart failure, therefore, they did not appear to have signs or symptoms of right heart failure. Furthermore, the right ventricular weights of our two groups with left heart failure, LHFA and LHFD, were increased only by 36% and 40%, respectively, compared to the sham values (P > 0.1), whereas the right ventricular weight of our group with right heart failure, RHF, was increased by an average of 132% (P < 0.01).

NEUROGENIC MECHANISMS

In this study, constriction of vessels was intended to affect different groups of mechanoreceptors in the cardio-pulmonary and arterial systems. Constriction of the pulmonary artery (RHF) would be expected to activate mechanoreceptors upstream in the right ventricle, right atrium, and connecting veins. Constriction of the ascending aorta (LHFA) would be expected to activate mechanoreceptors upstream in the left ventricle, the left atrium, the connecting pulmonary vasculature, and possibly some of the receptors further upstream in the right heart chambers although to a much more limited degree than in the RHF group. Constriction of the descending thoracic aorta (LHFD) would be expected to activate receptors in the carotid artery and aortic arch as well as the other receptors further upstream mentioned above.

The results permitted only limited conclusions about the cause of the increased sympathetic vascular tone in the LHFD group. Activation of receptors upstream to the pulmonary artery, such as occurred in the RHF group, probably did not trigger neurogenic vasoconstriction since this was not observed in the RHF group. Distention of the left atrium and left ventricle probably did not trigger the neurogenic vasoconstriction since a lesser degree of ascending aortic constriction and left heart pressure overload in the LVH group was not associated with intermediate changes which might have been expected if distention of the left heart chambers had been responsible for the high sympathetic vasmotor tone. Furthermore, Mason and Ledsome,10 Mark et al.,11 Mancia and Donald,24 and Koike et al.25 have reported that cardiopulmonary receptors mediate reflex inhibition of sympathetic vasmotor tone rather than neurogenic vasoconstriction. However, we did not observe in any group a level of neurogenic vascular tone that was lower than in the sham group.

The increased neurogenic vascular tone in the LHFA group most likely resulted from the decreased arterial pulse pressure and the resultant decrease in the baroreceptor inhibition of the vasoconstrictor signals. In contrast, constriction of the descending aorta in the LFH group and the significant increases in systemic arterial pressure that probably decreased vasoconstrictor tone via the arterial baroreceptor reflex was not associated with increased neurogenic vascular tone.

The presence of a mild constrictor band on the ascending aorta in the one group (LVH) was not associated with an increase in neurogenic vascular tone, therefore the band alone did not account for our observations.

One of the goals of this study was to assess the status of postganglionic sympathetic nerve terminals in guinea pigs with heart failure. This was done by comparing the constrictor responses to norepinephrine and sympathetic nerve stimulation in each group. No statistically significant differences were observed (Fig. 6 and Table 5). Thus, no functional alterations were detected. This is in accord with other recent reports from this laboratory.8,13 In the absence of selectively greater responses to sympathetic nerve
stimulation than to norepinephrine in the LHF_A group, it is difficult to ascribe the neurogenic vasoconstriction to functional alterations in terminal sympathetic nerves.\textsuperscript{5,2,4} On the basis of these considerations, we infer that any change in sympathetic vascular tone in heart failure (LHF_A) may have resulted from the activation of arterial baroreceptor reflexes and increased central vasomotor discharge.

**NON-NEUROGENIC MECHANISMS**

The vasodilator responses to papaverine indicated that non-neurogenic factors had a greater influence on hindquarter vascular resistance in the RHF group than in the LHF_B and LHF_A group. Non-neurogenic factors also had a greater influence on vascular resistance in the LHF_B than in the sham group (Fig. 4). Since structural changes were not detected, we attributed the non-neurogenic control to altered vascular responsiveness in the LHF_B group and to altered vascular responsiveness, and possibly also to a selective change in humoral factors in the RHF group.

Increased responsiveness to vasoactive stimuli, particularly in the RHF and LHF_B groups, was indicated by the parallel shifts to the left in the dose-response curves for norepinephrine, sympathetic nerve stimulation, and angiotensin (Table 4 and Fig. 6). The parallelism of the dose-response curves suggested that reactive functional changes and not structural changes accounted for the increased vascular responsiveness.\textsuperscript{26-27} However, it was necessary to consider the role of the initial hindquarter vascular resistance when interpreting the responses to constrictor stimuli. The initial resistances after sympathectomy and before constrictor responses were tested were 10.7 ± 1.0 mm Hg per ml/min (x ± se units) at a flow rate of 3.5 ml/min in LHF_A. 11.1 ± 0.8 units in LHF_B, and 14.7 ± 1.7 units in RHF, compared to 8.9 ± 0.9 units in LVH (P > 0.1) and 8.7 ± 1.2 units in sham (P > 0.1). An analysis of the linear correlation (r value and the slope of the regression) between the initial perfusion pressures and the responses to constrictor stimuli indicated that the higher initial vascular resistances could have accounted for 9-12% of the increased responsiveness in the LHF_B group and 14-16% of the increased responsiveness in the RHF group. Thus, it appeared that the slightly higher initial resistances in the heart failure groups contributed minimally to the augmented responses to constrictor stimuli. This is consistent with previous work from other laboratories.\textsuperscript{56-59}

Again it should be emphasized that the unimpaired maximal vasodilation (Fig. 5) in the LHF_B and RHF groups plus the parallel shifts in dose-response curves for constrictor agents\textsuperscript{56} provide evidence that structural changes did not occur and, therefore, could not explain increases in vascular responsiveness to the agonists. Furthermore, if the only vascular alteration in RHF were a structural change, it would be predicted that all vasoconstrictors should produce the same shift in the dose-response relationship. Angiotensin was affected selectively more than norepinephrine and sympathetic nerve stimulation, clearly implicating a mechanism other than a structural change.

Altered vascular reactivity may have accounted for most of the increased response to papaverine in the LHF_B group. Two considerations supported this conclusion. Responses to adrenergic and nonadrenergic stimuli were altered similarly. In addition, the responses to vasoconstrictor and vasodilator stimuli were greater in the LHF_B than in the LHF_A group. Thus, in the LHF_B and LHF_A groups, the level of non-neurogenic vascular tone appeared to follow the same pattern of change as the alterations in vascular reactivity.

Altered vascular reactivity cannot totally explain the increased response to papaverine in the RHF group. Adrenergic constrictor responses were similar to those in the LHF_B group, whereas the vasodilator response to papaverine was significantly greater than in the LHF_B group. Therefore, additional factor(s) beside altered vascular reactivity may have contributed. We speculate that this additional non-neurogenic influence in the RHF group was a humoral factor.

Angiotensin II may not have contributed to the high non-neurogenic vascular tone in the RHF group. The vasoconstrictor responses to injections of angiotensin II were increased selectively in the RHF group by a factor of 15 compared to 1.8- to 2.7-fold increases in adrenergic responses. Of the several possible explanations for selective alterations in reactivity to angiotensin II, the most attractive is a greater availability of angiotensin II receptors as a result of low circulating levels of angiotensin II.\textsuperscript{59-61} Differences in receptor binding\textsuperscript{56,59} and in the metabolism of the injected angiotensin II\textsuperscript{41} also could explain these results, however.

Further studies of the renin-angiotensin system and the contribution of angiotensin to vascular resistance in these models of heart failure, particularly the model of right heart failure, will be required before the role of this peptide hormone in vascular control is settled. However, the results strongly suggest that the role of angiotensin in vascular control could be quite different in established right and left heart failure.

The foregoing considerations suggested that hindquarter vascular resistance in right heart failure may have been maintained by humoral factors, by increased vascular responsiveness to humoral stimuli, or by a combination of both mechanisms. The relative importance of catecholamines,\textsuperscript{56} vasopressin,\textsuperscript{37} and possibly other vasoactive hormones\textsuperscript{56} in the maintenance of vascular resistance in right heart failure as well as the role of these hormones in other models of heart failure will require extensive further study.

The present studies have demonstrated differences in the regulation of baseline hindquarter vascular resistance in anesthetized guinea pigs with established right and left heart failure. Neurogenic influences predominated in one (LHF_A), but not in a second (LHF_B) model of left heart failure. Non-neurogenic influences contributed significantly to vascular resistance in the LHF_A group. This was ascribed to alterations in vascular reactivity. Non-neurogenic influences predominated in a model of right heart failure; the non-neurogenic vasoconstriction was ascribed to both changes in vascular reactivity and humoral factors. The contributions of the renin-angiotensin system and other vasoactive hormones to the increased non-neurogenic vascular tone in right heart failure will need to be
investigated further. Structural factors did not contribute abnormally to vascular resistance in any of the heart failure models employed in these studies.

Before the present observations of chronic compensatory events in the hindlimb of resting anesthetized guinea pigs can be extrapolated to other models of heart failure, other regional beds, acute stages of heart failure, and stressful circumstances such as exercise, additional studies will be required. However, under the conditions of this study, the different experimental models of heart failure clearly had different mechanisms regulating hindquarter vascular resistance.

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