Hemodynamic Stresses Induce Endothelial Dysfunction and Remodeling of Pulmonary Artery in Experimental Compensated Heart Failure

Ahmed Ben Driss, MD; Corinne Devaux, MS; Daniel Henrion, PhD; Micheline Duriez, MS; Christian Thuillez, MD, PhD; Bernard I. Levy, MD, PhD; Jean-Baptiste Michel, MD, PhD

Background—We hypothesized that, in compensated heart failure (HF), hemodynamic perturbations and their consequences exist in pulmonary artery (PA) despite the absence of any perturbation in thoracic aorta (TA).

Methods and Results—The left coronary artery was ligated in 20 male Wistar rats with compensated HF. Four months after ligation, these rats were compared with 20 sham-operated control rats. Blood pressure, velocity, viscosity, luminal diameter, and wall tensile and shear stresses were determined in PA and TA. Arterial rings were mounted in a myograph for ex vivo study. Endothelial nitric oxide synthase (eNOS) mRNA expression was determined in lung and aorta. Sections of PA and TA were used for histomorphometric study. In PA from rats with compensated HF, (1) blood pressure and wall tensile stress increased, whereas blood velocity and wall shear stress decreased; (2) contractions to KCl were not altered, but maximal contraction to phenylephrine and EC50 decreased; (3) endothelium-dependent relaxation to acetylcholine and basal NO activity were blunted, whereas endothelium-independent relaxation was preserved; (4) eNOS mRNA levels and eNOS transcription in lung nuclei decreased; and (5) medial cross-sectional area, thickness, smooth muscle cell number, elastin, and collagen contents increased. Conversely, no such changes were found in TA from rats with compensated HF.

Conclusions—In compensated HF induced by small myocardial infarction, hemodynamics, vascular wall function, and structure are altered in PA but preserved in TA. These results indicate that the pulmonary vascular bed is an early target of regional circulatory alterations in HF. (Circulation. 2000;101:2764-2770.)

Key Words: stress ■ endothelium ■ remodeling ■ vasculature ■ heart failure ■ arteries

Left ventricular failure due to infarction has hemodynamic consequences both to pulmonary circulation upstream and aortic circulation downstream. Nevertheless, for the same cardiac output, hemodynamic changes differ between pulmonary artery and thoracic aorta; blood pressure increases upstream to failing left ventricle and tends to decrease downstream. The pulmonary artery and thoracic aorta differ both structurally and functionally. The pulmonary arterial bed is a capacitave vascular system in which small changes in pressure induce large changes in dimensions. Ontkean et al showed that endothelial dysfunction was present in both pulmonary artery and aorta at a decompensated stage of chronic heart failure. Huang et al showed decreased expression of angiotensin-converting enzyme, a protein mainly expressed by endothelial cells, in lung. Sakai et al showed an increase in endothelin expression in lung without change in kidney.

Nevertheless, to the best of our knowledge, no information is available about the functional and structural status of pulmonary artery versus thoracic aorta in the early compensated stage of heart failure (HF). At this stage, pulmonary artery and thoracic aorta are submitted to different local hemodynamics. Therefore, we examined differential effects of mechanical factors on structure and function of large arteries by studying in the same animal pulmonary circulation and thoracic aorta.

We used the model of left ventricular myocardial infarction of small size, in which cardiac output was not detectably perturbed at rest, and demonstrated that pulmonary hypertension precedes any change in aortic hemodynamics and may be responsible for pulmonary endothelial dysfunction and wall remodeling.

Methods

Experimental Design
Male Wistar rats (IffaCredo, Lyon, France) that weighed 225±25 g were used. Left ventricular infarction was produced by ligation of the left descending anterior coronary artery. In sham operations, the heart was manipulated in the same way. Four months after the surgical procedure, rats were anesthetized for hemodynamic study. Only rats with compensated HF...
(ie, with normal cardiac index at rest ≥20 mL/min per 100 g) were included in the study. These rats (20 of 40 operated) underwent the pharmacological and histomorphometric study described below (sham-operated rats, n = 20; compensated HF rats, n = 20).

The present investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996), Bethesda, Md.

**Hemodynamic Study**

Four months after undergoing surgical coronary artery ligation, rats were anesthetized with pentobarbital (50 mg/kg IP), intubated, and ventilated. Thoracic aorta and pulmonary artery blood velocity and diameter were measured in vivo in closed chest by use of an echocardiographic apparatus with a 10-MHz frequency probe (Esaote AU 4 Idea). Thoracic aortic lumen diameter was measured in a bidimensional longitudinal parasternal view 5 mm beyond insertion of the aortic valve. Pulmonary artery lumen diameter was measured in a bidimensional axial parasternal view 5 mm beyond the insertion of the pulmonary valve. Mean blood velocity was measured with a pulsed Doppler coupled with an echocardiographic in the thoracic aorta and pulmonary artery at the same levels of measurement as for diameters.

As described elsewhere, a microtip catheter was introduced into the right carotid artery and advanced into the ascending aorta. A left thoracotomy was performed, and the pulmonary artery was dissected free. Another microtip catheter was placed in the pulmonary artery to record simultaneously aortic and pulmonary arterial pressures. The system was allowed to stabilize for 5 minutes. Left thoracotomy did not modify aortic pressure. All parameters were calculated on a beat-to-beat basis for 30 seconds and averaged. Aortic blood then was collected to measure blood viscosity.

Pulse pressures were calculated as the difference between systolic and diastolic blood pressures. Blood flow was calculated as the product of blood velocity and arterial lumen cross-sectional area. Cardiac output was calculated as the product of aortic integral time velocity, aortic cross-sectional area, and heart rate. Wall tension (in dynes per centimeter) was calculated as the product of arterial blood pressure and luminal radius; wall-tensile stress (in dynes per centimeter squared) was the ratio of wall tension to arterial wall thickness (measured later in histological sections). Wall shear stress (in dynes per centimeter squared) was determined from arterial viscosity \( \mu \), blood flow \( Q \), and luminal radius \( r \) as \( \tau = (4\mu Q)/(\pi r^3) \).

**Infarct-Size Determination**

Animals received a lethal dose of pentobarbital, and heart, lungs, and aorta were removed. Heart and ventricles were weighed. The left ventricle was opened with an incision along the septum from base to apex. Myocardial infarction size was measured.

**Viscosity Measurement**

Whole-blood viscosity was measured at 37°C with a Brookfield model LVT cone-plate viscosimeter at different shear rates; plasma viscosity was measured at 37°C with Ostwald capillary viscosimeters.

**Pharmacological Study**

Rings of aorta and pulmonary artery 3 mm in length were mounted in an organ bath. After determination of maximum response to \( K^+ \) \((60 \text{ mmol/L}) \), cumulative concentration–response curves to phenylephrine \( (10^{-7} \text{ to } 10^{-2} \text{ mol/L}) \) and acetylcholine \( (10^{-7} \text{ to } 10^{-2} \text{ mol/L}) \) were established. Basal nitric oxide (NO) production was assessed by adding \( N^3 \)-nitro-l-arginine methyl ester (L-NAME; 10 \( \mu \text{mol/L} \)) to rings precontracted with phenylephrine \( (10\% \text{ maximum}) \). Maximum arterial dilation was obtained with sodium nitroprusside (SNP; 10 \( g \text{ of GAPDH} \)) was performed at 52°C for 2 days. Probes used were 10 \( \mu \text{g} \) of the plasmid-containing insert of eNOS cDNA or 10 \( \mu \text{g} \) of GAPDH cDNA. Bluescript KS plasmid and pgEM plasmid were used as controls. After hybridization was complete, blots were washed and exposed to Kodak Biomax MS film with an intensifying screen at −80°C for 15 to 21 days. Relative intensity of eNOS band was determined as ratio of eNOS to GAPDH intensity.

**Morphological Study**

Thoracic aorta and pulmonary artery were fixed in situ under mean arterial blood pressure by a perfusion of 10% formaldehyde for 30 minutes. Segments of these 2 vessels, 0.5 to 1 cm in length, were then removed, dehydrated, and embedded in paraffin. Longitudinal and transverse sections (5 \( \mu \text{m} \) thick) were stained with Sirius red for collagen fibers, orcein for elastin, and neutral red for nuclei. Slides were analyzed in an automatic-image analyzer.

**Statistical Analysis**

Results are expressed as mean ± SE. The experimental design allowed us to use 1-way and 2-way ANOVA to show differences due to compensated HF and interaction between compensated HF and arterial localization of the measurement (pulmonary versus aortic parameters). Differences between groups were evaluated with Scheffé’s \( F \) test.

<table>
<thead>
<tr>
<th>TABLE 1. Body and Heart Weights</th>
<th>Sham</th>
<th>Compensated HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, g</td>
<td>533±5</td>
<td>532±11</td>
</tr>
<tr>
<td>Heart/BW, mg/g</td>
<td>2.19±0.04</td>
<td>2.63±0.11†</td>
</tr>
<tr>
<td>Left ventricle/BW, mg/g</td>
<td>1.64±0.02</td>
<td>1.86±0.04‡</td>
</tr>
<tr>
<td>Right ventricle/BW, mg/g</td>
<td>0.55±0.03</td>
<td>0.77±0.08*</td>
</tr>
</tbody>
</table>

Values are mean ± SE; BW indicates body weight.

*\( P < 0.02 \); †\( P < 0.01 \); ‡\( P < 0.001 \) vs sham-operated control group.
Cardiac and Hemodynamic Characteristics

Infarct size averaged 27±2% of the left ventricle in rats with compensated HF. Cardiac index was similar in compensated HF and in sham-operated controls (23±6 versus 22±6 mL/min per 100 g, respectively; P=NS). Left ventricular infarction was associated with right ventricular hypertrophy (40±14%; P<0.02) and pulmonary hypertension (38±7%; P<0.01) without change in aortic blood pressure (Tables 1 and 2). Blood viscosity was similar in rats with compensated HF and controls (0.026±0.001 versus 0.027±0.001 poise, respectively).

Pulmonary arterial diameter, wall tension, and tensile stress increased, whereas blood velocity and wall shear stress decreased in rats with compensated HF (Table 2). No hemodynamic changes were found in thoracic aorta. A powerful statistical interaction occurred between compensated HF and the pulmonary arterial site for measurement of arterial diameter (F=16; P<0.001), blood velocity (F=9; P<0.01), and wall shear stress (F=14; P<0.001).

Pharmacological Studies

Pulmonary Artery

Maximal contraction to KCl of pulmonary artery rings from rats with compensated HF was similar to controls (1.8±0.5 versus 1.9±0.3 mN/mg, respectively). Concentration-response curves to phenylephrine obtained in pulmonary artery rings from rats with compensated HF were signif-

### TABLE 2. Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Site</th>
<th>ANOVA</th>
<th>Site Effect</th>
<th>Interaction</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model Effect</td>
<td>Site Effect</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>139±5</td>
<td>F=0.6</td>
<td>F=769</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>140±5</td>
<td>NS</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>114±4</td>
<td>F=0.6</td>
<td>F=980</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>115±4</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>122±4</td>
<td>F=0.6</td>
<td>F=970</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>123±4</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Mean blood velocity, cm/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>27±2</td>
<td>F=1</td>
<td>F=0.4</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>30±2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>3.0±0.1</td>
<td>F=12</td>
<td>F=0.2</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>2.9±0.1</td>
<td>P&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Flow, mL/min</td>
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<td></td>
</tr>
<tr>
<td>Shim</td>
<td>115±5</td>
<td>F=1.7</td>
<td>F=0.06</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>123±7</td>
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<td>NS</td>
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<tr>
<td>Systolic wall tension, 10^3 dyne/cm</td>
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<td></td>
</tr>
<tr>
<td>Shim</td>
<td>27.9±1.1</td>
<td>F=1.5</td>
<td>F=653</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>28.3±1.2</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Diastolic wall tension, 10^3 dyne/cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>22.8±0.9</td>
<td>F=0.7</td>
<td>F=730</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>23.0±1.1</td>
<td>NS</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Mean wall tension, 10^4 dyne/cm</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>24.5±0.9</td>
<td>F=1</td>
<td>F=730</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>24.8±1.1</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Tensile stress, 10^6 dyne/cm²</td>
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<td></td>
<td></td>
</tr>
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<td>2.5±0.1</td>
<td>F=0.6</td>
<td>F=309</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>2.4±0.1</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Shear stress, dyne/cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shim</td>
<td>21±2</td>
<td>F=4</td>
<td>F=0.5</td>
</tr>
<tr>
<td>Compensated HF</td>
<td>22±1</td>
<td>P=0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SE.

*R*=P<0.05, †P<0.01, ‡P<0.001 vs sham-operated control group.
significantly desensitized compared with control curves; maximal contraction response and EC_{50} were decreased (1.6 ± 0.1 mN/mg, \textit{P}<0.01, and 3.2 ± 0.6 versus 5.7 ± 0.8 \times 10^{-8} \text{mol/L}, \textit{P}<0.05), respectively, in rats with compensated HF (Figure 1A).

Maximal relaxation to acetylcholine was reduced in rats with compensated HF (49 ± 8 versus 74 ± 7\% in controls; \textit{P}<0.05). EC_{50} for relaxation was \approx-4-fold greater in rats with compensated HF (116 ± 42 versus 27 ± 7 \times 10^{-8} \text{mol/L} in controls; \textit{P}<0.05; Figure 2A). Antagonism of basal NO activity to induce pulmonary-ring contraction by L-NAME was significantly reduced in rats with compensated HF (0.56 ± 0.10 versus 1.28 ± 0.31 mN/mg in controls; \textit{P}<0.05). Endothelium-independent relaxation to SNP was not significantly different between the 2 groups of rats (91 ± 2\% in HF versus 94 ± 6\% in controls).

**Thoracic Aorta**

Maximal contraction to KCl (3.1 ± 0.3 in HF versus 2.6 ± 0.4 mN/mg in controls) as well as the concentration-response curves to phenylephrine (Figure 1B), and the response to L-NAME (1.75 ± 0.4 versus 1.8 ± 0.3 in HF versus controls, respectively) of thoracic aorta rings obtained from rats with compensated HF and from controls were similar.

Concentration-response curves to acetylcholine and the endothelium-independent relaxation to SNP (92 ± 8 in HF versus 87 ± 5\% in controls, NS) were similar in the 2 groups of rats (Figure 2B).

**eNOS mRNA Expression**

Because eNOS expression has been shown to be dependent on shear stress,^{13,14} we used eNOS mRNA expression as a marker of endothelial dysfunction. Two-way ANOVA showed that eNOS mRNA levels evaluated by comparative RT-PCR were significantly higher in lung than aorta (\textit{F}=580; \textit{P}<0.001). A significant interaction occurred between the site of analysis (lung or aorta) and compensated HF (\textit{F}=13; \textit{P}<0.001); eNOS mRNA levels did not differ in the aorta (\textit{F}=0.2; \textit{P}=NS) but significantly differed in the lung (\textit{F}=13; \textit{P}<0.01; Figure 3A). These results were confirmed by run-on assay, which showed significantly decreased in vitro transcription of eNOS by lung nuclei from rats with compensated HF (n=5; t=4.9, \textit{P}<0.05) (Figure 3B).

**Histomorphometry**

Pulmonary hypertension secondary to myocardial infarction induced an increase in medial cross-sectional area, thickness,
arterial pulse pressure was similar in compensated HF and increased in rats with compensated HF, whereas pulmonary values. Nevertheless, mean pulmonary arterial pressure was and wall shear stress decreased in comparison with control
diameter, and wall tension increased, whereas blood velocity
artery. Therefore, pulmonary arterial blood pressure, lumen
affected in the aorta but were modified in the pulmonary
compensated HF, when cardiac output is not yet modified at
rest, hemodynamic perturbations with consequences on arte-
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irine was modified in pulmonary artery but not in aortic rings
provides evidence for this hypothesis and confirms previous
data.14

smooth -muscle number, elastin, and collagen contents in
the pulmonary artery of rats with compensated HF. Smooth
muscle cell nuclear size and elastin/collagen ratio remained
similar to controls (Table 3). Compensated HF did not affect
medial wall constituents of thoracic aorta (Table 3).

A powerful statistical interaction occurred between com-
penated HF and the pulmonary arterial site for analysis of
medial cross-sectional area (F=7, P<0.01), elastin and
collagen contents (F=8, P<0.01, and F=8, P<0.01, re-
spectively) and number of smooth muscle cell nuclei (F=9;
P<0.01).

![Graph showing eNOS/GAPDH mRNA levels in aorta and lung.](https://example.com/graph)

Figure 3. Comparison of endothelial eNOS expression in lung and aorta. eNOS mRNA levels were not modified by compen-
sated HF in aorta but were significantly decreased in lung (A).

Discussion

The objective of the present study was to show that, in
compensated HF, when cardiac output is not yet modified at
rest, hemodynamic perturbations with consequences on arte-
rinal wall function and structure may exist in the pulmonary
artery when aortic hemodynamics and wall structure remain
unmodified.

In the compensated HF group, hemodynamics were not
affected in the aorta but were modified in the pulmonary
artery. Therefore, pulmonary arterial blood pressure, lumen
diameter, and wall tension increased, whereas blood velocity
and wall shear stress decreased in comparison with control
values. Nevertheless, mean pulmonary arterial pressure was
increased in rats with compensated HF, whereas pulmonary
arterial pulse pressure was similar in compensated HF and
control groups. Indeed, because in each rat blood flow was
identical in aorta and pulmonary artery, the observed decrease
in pulmonary-wall shear stress and a part of the increase in
pulmonary-wall tensile stress were most likely due to changes
in pulmonary artery luminal dimensions. Because of low
stiffness (or high compliance) of the pulmonary arterial
vasculature, small changes in blood pressure induce large
increases in pulmonary arterial dimensions.1 This influences
shear stress but also amplifies the increase in tensile stress by
means of application of the law of Laplace. Therefore,
pressure-dependent and dimension-dependent early changes
in mechanical stresses observed in pulmonary circulation
could modify local expression and activity of autacoid factors
such NO or the intracellular signaling response to these
factors. Differences in alterations of vasomotor tone and
vascular structure between pulmonary artery and thoracic
aorta in rats with compensated HF could be a consequence of
local hemodynamically induced changes in wall shear and
tensile stresses.

Changes in resistance vessels have been reported previ-
ously.13 Because our present study was aimed at investigating
the effect of changes in mechanical stresses on the structure
of large arteries, we have no data concerning behavior of
systemic and pulmonary resistance vessels and skeletal
muscles.

Given that the maximal response to KCl was unchanged
and the response to phenylephrine decreased, we suggest that
the intrinsic contractility of pulmonary artery is not affected,
whereas the sensitivity and maximal response to exogenous
α1-adrenergic stimuli are reduced in compensated HF. Spec-
ific local changes in hemodynamics and wall structure could
modify signals within the target cells in response to catechol-
amines. The fact that the dose-response curve to phenyleph-
irine was modified in pulmonary artery but not in aortic rings
provides evidence for this hypothesis and confirms previous
data.14

Pulmonary artery endothelial function was blunted in rats
with compensated HF. The same results were reported in rats
with decompensated HF.2 Unchanged relaxation to SNP in
rats with compensated HF suggests that the ability of smooth
muscle to respond to NO was preserved. Thus, the defect in
NO activity reported in the pulmonary artery of rats with
compensated HF could be due in part to diminished NO
production or release by endothelial cells. Basal NO activity
was assessed by measuring the increase in force that occurred
when arterial rings were exposed to L-NAME. Decreased
response to L-NAME in the pulmonary artery rings from rats
with compensated HF suggests that basal NO activity was
reduced under these experimental conditions. Similar results
were reported at a decompensated stage.2,15

One physiologically important stimulus for the release of
NO is the value of shear stress.10,16 Therefore, we measured
eNOS expression as a possible marker of hemodynamically
induced endothelial dysfunction. We showed that eNOS
mRNA levels were similar between controls and compen-
sated HF in aorta and significantly different in lung. This last
result was confirmed by run-on assay, which showed a
decrease in transcription in the lung in compensated HF.
Previous studies performed to explore endothelial dysfunc-
Previous studies reported an impairment in endothelial function in thoracic aorta of rats with myocardial infarction-induced HF.\textsuperscript{2,15,17} However, in these studies, congestive HF was due to large myocardial infarction and resulted in a marked alteration in aortic hemodynamics. Differences in results between these studies and the present one thus are probably due to a smaller infarct size in the present investigation, which permitted the coexistence of preserved aortic hemodynamics with an altered pulmonary artery circulation.

In parallel with the alteration in vasoreactivity, arterial wall remodeling was assessed in thoracic aorta and pulmonary artery. The main findings are absence of thoracic aorta remodeling and expansive pulmonary artery remodeling in

\begin{table}
\centering
\caption{Histomorphometric Parameters}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\multicolumn{2}{|c|}{Site} & \multicolumn{3}{c|}{ANOVA} \\
\hline
 & Thoracic Aorta & Pulmonary Artery & Model Effect & Site Effect & Interaction \\
\hline
Media CSA, 10\textsuperscript{3} \(\mu \text{m}^2\) & & & & & \\
Sham & 499±20 & 257±23 & F=5 & F=81 & F=8 \\
Compensated HF & 486±16 & 359±22\textsuperscript{†} & P<0.05 & P<0.001 & P<0.01 \\
\hline
Media wall thickness, \(\mu \text{m}\) & & & & & \\
Sham & 106±3 & 64±4 & F=4 & F=97 & F=3 \\
Compensated HF & 107±3 & 78±4\textsuperscript{*} & P<0.05 & P<0.001 & NS \\
\hline
Elastin content, % & & & & & \\
Sham & 21±1 & 15±1 & F=1.6 & F=15 & F=3.6 \\
Compensated HF & 20±1 & 18±1\textsuperscript{*} & NS & P<0.001 & NS \\
\hline
Elastin content per CSA, 10\textsuperscript{3} \(\mu \text{m}^2\) & & & & & \\
Sham & 107±8 & 39±4 & F=2 & F=61 & F=7 \\
Compensated HF & 100±7 & 65±5\textsuperscript{†} & NS & P<0.001 & P<0.02 \\
\hline
Collagen content, % & & & & & \\
Sham & 13±1 & 15±1 & F=1.6 & F=5.6 & F=0.05 \\
Compensated HF & 14±1 & 16±1 & NS & P<0.05 & NS \\
\hline
Collagen content per CSA, 10\textsuperscript{3} \(\mu \text{m}^2\) & & & & & \\
Sham & 68±5 & 35±3 & F=6 & F=22 & F=8 \\
Compensated HF & 66±3 & 58±6\textsuperscript{†} & P<0.02 & P<0.001 & P<0.01 \\
\hline
Elastin/collagen & & & & & \\
Sham & 1.75±0.15 & 1.09±0.12 & F=0.4 & F=17 & F=2 \\
Compensated HF & 1.51±0.09 & 1.19±0.09 & NS & P<0.001 & NS \\
\hline
No. of SMC nuclei per CSA & & & & & \\
Sham & 202±122 & 1181±80 & F=0.9 & F=15 & F=9 \\
Compensated HF & 1777±119 & 1662±138\textsuperscript{*} & NS & P<0.001 & P<0.01 \\
\hline
SMC nuclei size, \(\mu \text{m}^2\) & & & & & \\
Sham & 8.7±0.5 & 7.5±0.5 & F=0.7 & F=1 & F=1.6 \\
Compensated HF & 7.6±0.3 & 7.8±0.7 & NS & NS & NS \\
\hline
\end{tabular}
\end{table}

*\(P<0.05\), †\(P<0.01\) vs sham-operated control group.

Values are mean±SE. CSA indicates cross-sectional area; SMC, smooth muscle cell.

\textsuperscript{17} Previous studies reported an impairment in endothelial function in thoracic aorta of rats with myocardial infarction-induced HF.\textsuperscript{2,15,17} While these studies did not detect any significant decrease in eNOS mRNA expression in aorta of myocardial infarcted rats, and Varin et al\textsuperscript{18} recently reported a decrease in eNOS mRNA expression in the skeletal muscle in decompensated HF. Nevertheless, because we used lung tissue to evaluate eNOS expression, cellular sources other than endothelium could contribute to this difference in eNOS expression. Therefore, in the present study, a decrease in wall shear stress might alter endothelium-dependent vasodilation. Pulmonary hypertension induced by left ventricular infarction was associated with a significant increase in pulmonary artery luminal diameter that contributed to reduced pulmonary artery wall shear stress and increased tensile stress. These 2 factors may lead to the endothelial dysfunction observed in the present study. The inactivation of NO by superoxide anions could also participate in endothelial dysfunction.\textsuperscript{17}
rats with compensated HF. Therefore, differential hemodynamic stresses and strains are probably one of the main determinants of differential remodeling between pulmonary artery and aorta in compensated HF.

In conclusion, in compensated HF induced by left ventricular infarction, (1) hemodynamics, vasomoticricity, and vascular wall structure are altered in the pulmonary artery but remain unmodified in the thoracic aorta and (2) pulmonary alterations may be related to chronic decrease in shear stress and increase in tensile stress. These results indicate that the pulmonary circulation may be one of the first regional targets of hemodynamic changes in compensated HF.

Acknowledgments
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