Remodeling of lung interstitium but not resistance vessels in canine pacing-induced heart failure

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Departments of 1Physiology and 2Pathology, University of South Alabama, Mobile, Alabama 36688; 3Department of Physiology, University of Bergen, Bergen, Norway; and 4Department of Medicine, University of California, San Diego, La Jolla, California 92103

TOWNSLEY, Mary I., Kenneth S. Snell, Claire L. Ivey, Donald E. Culberson, Da Chang Liu, Rolf K. Reed, and Odile Mathieu-Costello. Remodeling of lung interstitium but not resistance vessels in canine pacing-induced heart failure. J. Appl. Physiol. 87(5): 1823–1830, 1999.—We previously reported that pacing-induced heart failure in dogs results in an enhancement of pulmonary vascular reactivity. In the present study we hypothesized that enhanced matrix deposition and structural remodeling of lung resistance microvessels would underlie these functional changes. Using biochemical measures, we found no difference in the normalized lung content of hyaluronan, uronic acid, and collagen between control dogs and dogs paced for 1 mo, although lung dry weight and noncollagen protein content increased significantly in the paced group (P < 0.05). From separate Formalin-fixed lung lobes, 5-µm frozen sections were prepared and stained with Masson's trichrome, and vascular structure was evaluated using standard morphometric techniques. When perivascular fluid cuffs were excluded from the measure of wall thickness, collagen and media volume fractions in any size range did not differ between paced and control groups. Similarly, in the paced group, medial thickness in <400-µm arterial or venular microvessels did not vary significantly from that in the controls. In contrast, the relationship of interstitial fluid pressure to lung water was significantly shifted to the right in the paced group, such that normal tissue pressures were observed, despite the increased water content. We conclude that although 1 mo of pacing-induced heart failure results in altered interstitial function, the attendant pulmonary hypertension and/or hormonal responses are insufficient to induce medial hypertrophy or other remodeling of the extra-alveolar microvasculature.

WE PREVIOUSLY REPORTED that the reactivity of the pulmonary vasculature to ANG II and norepinephrine is enhanced and total pulmonary vascular compliance is reduced in dogs after 1 mo of rapid ventricular pacing to produce congestive heart failure and chronic pulmonary venous hypertension (30, 35). However, whether these functional adaptations are correlated with altered deposition of matrix in the pulmonary vasculature and lung parenchyma and/or to medial hypertrophy is not clear. Each of the major constituents of interstitial matrix, i.e., collagens and the glycosaminoglycans, including hyaluronan and proteoglycans, could play a role, since they are known to be determinants of structural integrity (32). Vascular matrix deposition and structural alterations in the vascular wall have been important targets for study in pulmonary arterial hypertension. For example, vascular collagen synthesis has been shown to be increased in various forms of chronic pulmonary hypertension (5, 19, 33). Furthermore, in rat models of pulmonary arterial hypertension induced by chronic hypoxia or monocrotaline, increased matrix synthesis is accompanied by medial hypertrophy in the arterial resistance network after as little as 10–14 days (20, 21, 37). Whether pulmonary hypertension associated with the pacing model of heart failure results in similar vascular remodeling has clear clinical relevance, pertaining not only to potential early changes in pulmonary structure and/or function in patients with heart failure or mitral stenosis, but also to those with relatively short-term supraventricular tachycardia (8, 11, 28).

Thus the goal of the present study was, first, to evaluate the lung content of each of these interstitial matrix components and, second, to determine whether there was concurrent structural remodeling in the pulmonary resistance vasculature. Finally, because collagen and the glycosaminoglycans are also important determinants of tissue water content and interstitial fluid pressure (32), a third goal was to determine whether there was significant interstitial remodeling that might impact on transcapillary fluid exchange.

METHODS

Rapid ventricular pacing model. Heart worm-negative, conditioned mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg iv). Under sterile operating conditions, a bipolar pacing electrode (Medtronic) was introduced into the right ventricle via the right jugular vein. A small subcutaneous pocket was created anterior to the first rib for insertion of the pacemaker generator (custom SX-5985 or 8329, Medtronic), with the lead tunneled subcutaneously to the pocket and attached to the generator. After the skin incisions were closed, anesthesia was discontinued. During the recovery phase, the implanted pacemaker was not active. Cefazolin in sodium (1 g im) was given at the completion of the surgical procedure. The dogs were maintained on the antibiotic orally (500 mg twice daily) for 5 days postoperatively. After recovery from surgery (1-2 days), the generator was set to deliver 240–245 impulses/min (1, 30, 34, 35) by means of an external programmer (model 9710, Medtronic). Pacing was maintained for ~1 mo or until left ventricular shortening fraction (LVSF), measured via echocardiography in sinus rhythm, had fallen to ~50% of the baseline prepace value.

Isolation of lung lobes. Paced animals (n = 10) and unpaced controls (n = 6) were anesthetized to a surgical plane of anesthesia for the terminal experiment with pentobarbital sodium (~15 mg/kg iv in the paced group vs. 30 mg/kg iv in controls), supplemented with intravenous α-chloralose as needed, then intubated and mechanically ventilated with room air. Subsequently, 10,000 U of heparin were adminis-
were measured colorimetrically as uronic acid after reactions of tissue hydrolysate with 0.025 M sodium tetraborate in sulfuric acid and 0.125% carbazole. For measurements of lung collagen, separate aliquots of freeze-dried tissue were hydrolyzed in 6 N HCl for 16 h at 125°C. The analysis of collagen in the hydrolysate was based on a colorimetric reaction with perchloric acid and p-dimethylaminobenzaldehyde to detect hydroxyproline, then collagen mass was calculated with the assumption of a content of 0.91 µmol hydroxyprolyl per 1.0 mg collagen (26). Total noncollagen proteins were measured in separate aliquots of freeze-dried tissue. 1 ml of 0.2 N NaOH was added to 10 mg of freeze-dried tissue and incubated at 60°C overnight. Protein concentration in the resultant clear solution was measured using the Bradford assay (Bio-Rad). As a negative control, 10 mg of collagen were similarly hydrolyzed, but no protein was detected in the assay. The mass of matrix components in tissue was normalized per gram of dry tissue weight and per milligram of total noncollagen protein in control and paced groups.

Morphometry. Initially, fixed lobes were embedded in gelatin and then sectioned into 1-cm slabs with a random starting orientation. Point counting and the Cavalieri method were used to define the total lung volume as well as the volume fractions for coarse and fine lung parenchyma (22). For this purpose, coarse parenchyma was arbitrarily defined as vessels or airways with an external diameter > 2 mm, so that, by subtraction, the remainder of the lung volume was composed of fine parenchyma. Next, the fractionator technique was used to choose four to seven tissue cubes at random for subsequent processing (9, 22). Four to six 5-µm frozen sections were cut from each block and transferred to glass slides for processing. Intervening sections were discarded. Sections were stained with Masson's trichrome to highlight smooth muscle and collagen fibers and examined using light microscopy. Images were captured with an on-line color videocamera. Vessels to be analyzed were chosen using systematic random sampling; each section was examined from a rotating start point, and then one arterial and one venous vessel in each size bin (see below) were analyzed until all size bins were filled or until the slide had been completely surveyed. For each vessel examined, the intersection of a grid on the image film was used to choose points at random. Volume and perimeter and the short-axis lumen diameter were determined. At each of four positions around the circumference of the vessel determined by the intersection of the grid lines with the intimal surface, total wall thickness (including adventitial fluid cuff) was measured as long as the adventitial border could be defined along that vector (Fig. 1). Next, the portion of the wall occupied by collagen, media + intima, and fluid cuff was determined, starting at each of these same four points, and volume fractions for each component were estimated by linear integration. In this analysis the length ratio (e.g., media + intima vs. total wall) reflects the volume ratio for that component (9). Medial thickness could then be calculated by multiplying the wall thickness by the length (or volume) fraction for media + intima in each vessel. When vessels were obviously cut along the longitudinal axis or were obviously tangential sections, wall thickness measurements were only made along the short axis. Volume fractions derived from the length measurements for collagen, media + intima, and cuff are not affected by tangential planes of section, since all are reported as fractions of the total wall thickness. For each lobe, this information was collected in size bins according to the short-axis lumen diameter by using bin ranges of 21–50, 51–100, 101–200, 201–400, and > 401 µm. Furthermore, each vessel was categorized according to its relationship to the adjacent airways (i.e., bronchi, bronchi-
Fig. 1. Schematic illustration of morphometric measurements. First, short-axis diameter was measured. Then, wall thickness (arrow labeled "wall") was measured at right angles to lumen surface at 4 points around vessel wall, marked by intersection of wall with grid crosshairs. Next, length of total wall from intimal to adventitial surface (arrow labeled T) along crosshair and length occupied by media (arrow labeled M), collagen, and fluid cuff were measured. Volume fractions were then calculated by linear integration, since volume fraction is equivalent to length fraction (9, 22). Thickness of media + intima layer was calculated as product of total wall thickness and length fraction for media + intima.

Matrix content in canine lung after pacing-induced heart failure. Total lung volumes determined via the Cavalieri technique were not different in right caudal lobes between control and paced animals (171 ± 15 and 166 ± 23 ml, respectively). However, the fraction of that volume occupied by coarse parenchyma (i.e., structures ≥ 2 mm diameter) was significantly lower in the paced group (0.095 ± 0.004) than in controls (0.122 ± 0.010, P < 0.05). Representative micrographs comparing arterioles and venules in lobes from control and paced dogs (Fig. 2) suggest that little structural alteration occurred in the lung microvasculature after 1 mo of pacing-induced heart failure.

This was confirmed by the morphometric data. Table 2 shows the general characteristics of the data collected in each size bin. Measurements were collected in vessels up to ~800 µm diameter, although the numbers of vessels available through all sections examined per lobe decreased progressively as short-axis lumen diameter rose above 200 µm in both groups. The high wall thickness (141.4 ± 63.7 µm) for 101- to 200-µm arteries in the control group is due to the inclusion of two vessels with large cuffs. Without these two vessels, wall thickness in the remaining 15 arteries in this bin averaged 53.0 ± 27.8 µm. Average medial thickness was not significantly impacted by the inclusion or exclusion of these two vessels in this bin. As shown in Fig. 3, the volume fractions for collagen, media (including, terminal bronchioles, or parenchymal septal vessels), the latter allowed separation of information within each size bin into bins for arterial vs. venular vessels. Data were accumulated for one arterial and one venular vessel in each size bin until all bins were filled for that slide or until the slide had been completely examined. Tissues and sections were evaluated in a blinded fashion with respect to experimental group until all measurements were completed.

Statistical analysis. Analytic data are reported as means ± SE. Comparisons of data between groups were accomplished by means of ANOVA. P < 0.05 was considered significant.

RESULTS

We previously reported measures of LVSF and hemodynamics in these animals as part of a larger study (35). However, for reference, LVSF was 27.4 ± 3.7% in the present control group and 11.7 ± 1.9% in the paced dogs (P < 0.05). Left ventricular end-diastolic pressure rose from 2.8 ± 0.6 mmHg in controls to 45.3 ± 6.5 mmHg after pacing (P < 0.05). The latter was measured in sinus rhythm under anesthesia during the terminal experiment. On histological evaluation, widespread inflammation was observed in the lung from one control dog; this state had not been evident at the macroscopic level. The inflammation was evidenced by the presence of substantial numbers of eosinophils and monocyteic cells in the alveolar spaces. There was no such evidence of a pulmonary cellular infiltrate in other control or paced dogs. As a result, this one animal was not included in any means or in any statistical analysis. However, structural changes in this one lobe are addressed in the DISCUSSION.

Lung matrix content. The results of the biochemical measures for hyaluronan, uronic acid, and collagen in lung are shown in Table 1. Lung blood-free dry weight and TTW were increased significantly in paced animals, in agreement with our earlier reports (34, 35). Similarly, lung protein content increased significantly in the paced group. This finding is not likely due to increased vascular or extravasated blood content in lung in the paced group, inasmuch as the residual blood content was not different from control. The content of lung hyaluronan, uronic acid, and collagen (normalized per gram of dry weight) did not change after 1 mo of pacing-induced heart failure. When normalized for total noncollagen proteins, lung uronic acid fell in the paced group (P < 0.05). Neither hyaluronan nor collagen was significantly different from control when normalized in this fashion.

Table 1. Matrix content in canine lung after pacing-induced heart failure

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<tr>
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<th>Control (n = 5)</th>
<th>Pace (n = 7)</th>
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<tr>
<td>Lobar blood-free dry wt, g</td>
<td>3.3 ± 0.4</td>
<td>5.8 ± 0.6*</td>
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<tr>
<td>Lobar residual blood, ml/g dry wt</td>
<td>2.5 ± 0.2</td>
<td>1.7 ± 0.4</td>
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<tr>
<td>Total protein, mg/g dry wt</td>
<td>341.2 ± 31.0</td>
<td>455.6 ± 26.9*</td>
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<td>Hyaluronan</td>
<td>mg/g dry wt</td>
<td>0.62 ± 0.08</td>
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<td></td>
<td>µg/mg protein</td>
<td>1.90 ± 0.36</td>
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<tr>
<td>Uronic acid</td>
<td>mg/g dry wt</td>
<td>11.1 ± 0.5</td>
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<tr>
<td></td>
<td>µg/mg protein</td>
<td>33.5 ± 3.0</td>
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<tr>
<td>Collagen</td>
<td>mg/g dry wt</td>
<td>163.7 ± 11.4</td>
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<tr>
<td></td>
<td>µg/mg protein</td>
<td>0.50 ± 0.07</td>
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<tr>
<td>TTW, g/g dry wt</td>
<td>3.74 ± 0.06</td>
<td>4.61 ± 0.12*</td>
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Values are means ± SE; n, number of lobes. TTW, total tissue water. Measure of total protein excluded collagen (see METHODS). *P < 0.05 vs. control.
ing intima), and fluid cuff were remarkably similar in the two groups. Medial (including intima) thickness and the ratio of media (including intima) to the lumen perimeter for each size bin are shown in Fig. 4. Although the media in arteries and veins >200 µm tended to be thicker in the paced group, this was significant only for arteries ≥401 µm. The tendency toward larger ratios of media + intima to lumen perimeter, although not statistically significant, does suggest a larger degree of vascular tone in the paced group, reflective of the increased resistance seen at the whole lobe level (30, 35). Finally, occluded microvessels suggestive of rarefaction were extremely rare and then seen only in septal corner vessels. No such vessels were observed in the control group, and only two were found in all sections of lung examined from paced animals.

Changes in the Pt vs. EVLW relationship. In contrast to the morphometric analysis, the shift in the relationship between Pt and EVLW (Fig. 5) was suggestive of significant interstitial remodeling. In the paced group the average Pt was normal, i.e., subatmospheric, despite the elevation in baseline EVLW. In fact, in one paced lobe with a baseline EVLW of 5.43 ml/g, Pt was −6.5 cmH₂O. In both groups, when further hydration was induced, Pt increased similarly to near 0 cmH₂O. Although EVLW does reflect cell water in addition to interstitial water, the increment in EVLW with hydrostatic and colloid osmotic pressure-induced hydration should reflect an increment in interstitial fluid volume. Thus one can infer that lung interstitial compliance (i.e., the change in interstitial volume induced by a given increment in interstitial fluid volume, shown by the slope of the Pt vs. EVLW relationship) is similar in both groups.

DISCUSSION
During congestive heart failure, the pulmonary vasculature is chronically exposed to high Pt at rest, with further increases up to 37 mmHg during exercise (13, 31). In an experimental model of heart failure induced by rapid ventricular pacing in dogs, we found similar
pulmonary venous hypertension, accompanied by an almost threefold increase in pulmonary vascular resistance, an 
50% fall in pulmonary vascular compliance, and significant pulmonary edema compared with controls (30, 34, 35). The hemodynamic changes seen in the paced group are not likely due to the pulmonary edema per se, since Michel et al. (23) found that acute formation of substantial interstitial edema does not compress pulmonary vessels. This left open the possibility that vascular structure was directly modified. In addition to the alterations in hemodynamics in lobes from paced dogs, we found significant enhancements in the pulmonary vasoconstrictor responses to ANG II (30) and norepinephrine (35). The enhanced response to norepinephrine was maintained at high Pv. Because pressor responses in normal lung are attenuated when P v is acutely elevated (3, 12), this observation was also suggestive of structural modification. Our working hypothesis has been that, as a consequence of the chronic venous hypertension and/or the endocrine sequelae to heart failure, the lung vasculature and interstitium are remodeled in an adaptive response.

<table>
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<th>Table 2. Demographics of morphometric measurements in the lung microvasculature</th>
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<tr>
<td>Size Bin</td>
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<tr>
<td>21–50 µm</td>
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<tr>
<td>Control</td>
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<td>Pace</td>
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<td>51–100 µm</td>
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<td>101–200 µm</td>
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<td>201–400 µm</td>
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<tr>
<td>≥401 µm</td>
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<tr>
<td>Control</td>
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<tr>
<td>Pace</td>
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Values are means ± SE. Numbers in parentheses represent number of arteries and veins for which long axis could be measured in each bin. *P < 0.05 vs. arteries within the same group.

Fig. 3. Volume fractions for media + intima, collagen, and fluid cuff grouped into bins according to lumen short-axis diameter for pulmonary microvessels in control and paced dogs. †P < 0.05 vs. artery in same group.

Fig. 4. Thickness of media + intima layer and ratio of this thickness to lumen perimeter of vessel in each size bin for control and paced groups. *P < 0.05 vs. control for same vessel type; †P < 0.05 vs. artery in same group.
Thickening of the media vascular wall collagen volume fraction in any size bin. can be evidenced by our previous observation that lung uronic acid content increases acutely in the overhydrated canine lung within 3 h (36). Similarly, we found no pacing-induced changes in the vascular wall collagen volume fraction in any size bin. Thickening of the media + intima layer was observed in the largest extra-alveolar arteries evaluated in the paced group (≥401 µm short-axis diameter), although it was not evident in smaller pulmonary arteries or veins. One could argue that this failure to detect marked changes in vascular structure was due to the fact that the lung lobes were not fixed at constant vascular pressure. However, because medial thickness was calculated on the basis of the medial volume fraction rather than any direct measure of medial thickness, this concern is not likely to be problematic. Furthermore, the interdependence of lung tissue helps prevent collapse of extra-alveolar vessels as the lung is distended. The fact that the long-to-short axis ratio was low further supports this notion. Finally, one could argue that the small numbers of vessels and/or animals preclude our ability to detect any differences between the two groups. However, these stereological techniques are quite powerful (9). Indeed, the coefficient of variation within any one size bin for any one dog generally remained <10%. Furthermore, we did find significant thickening of the endothelial and epithelial cell layers in the alveolocapillary barrier, as well as interstitial thickening, within 1 mo of pacing (34). These differences were detected using similar stereological methods with n = 3–4 in each group.

In the one control lung that was found to be inflamed and thus was not included in the overall means, extra-alveolar vessels up to 50 µm lumen diameter showed wall and medial thicknesses 1.5–2 standard deviations higher than in the remaining control lobes. The glycosaminoglycan content and dry weight in this one lobe were also 1.5–2 standard deviations higher than in the remainder of the control group. This inflammation-induced remodeling is reminiscent of that reported by Cottrill et al. (6), where unilateral pulmonary vein banding resulted in no medial hypertrophy. Yoshikawa et al. (40) found that alveolar and interstitial eosinophilia, induced by infection with Toxocara canis, resulted in significant vascular remodeling in the rat lung. These observations and our own present work suggest that, in the absence of an inflammatory response, the extra-alveolar vasculature is relatively resistant to structural remodeling induced by pulmonary venous hypertension per se. This notion is supported by the study of Labourene et al. (16). They reported that 6 wk of pulmonary vein banding resulted in no medial hypertrophy or altered matrix deposition in pulmonary arteries, despite significant pulmonary arterial hypertension and right ventricular hypertrophy. Mild intimal thickening and an increase in fractional collagen content were found in large pulmonary veins, although again no medial hypertrophy was observed. Jones and Reid (14) suggested that the pattern of structural changes in pulmonary hypertension is dependent on the initial target of injury. Because the baseline pulmonary microvascular permeability remains normal in the pacing model of venous hypertension (30, 34, 35), the lack of any initiating endothelial injury and/or the lack of an attendant inflammatory response may contribute to the apparent protracted time course for remodeling of the resistance vasculature. That finite structural changes induced by rapid ventricular pacing and heart failure are slow to occur in the pulmonary vasculature would help explain the rapid recovery of patients with clinical signs of heart failure secondary to short-term supraventricular tachycardia (2) and in dogs with pacing-induced heart failure (39). The absence of significant medial hypertrophy in small pulmonary resistance microvessels after 1 mo of pacing in the dog suggests that alterations in vascular smooth muscle function at the level of the receptors and/or second-messenger signaling must explain the heightened pulmonary vasoconstrictor responses we observe in paced

![Graph](image-url)
dogs (30, 35) rather than any change in smooth muscle mass per se.

In contrast, we did find evidence for adaptations in interstitial function. Normally, when fluid filters across the capillary endothelium, the volume added into the interstitium alters the transcapillary balance of Starling forces: $P_I$ and lymph flow are increased, while the interstitial colloid osmotic pressure falls (32). Together, these safety factors are readjustments that reduce transcapillary fluid filtration, thus counteracting a moderate increase in capillary pressure. When the lung hydrates to the point that $P_I$ increases to zero, the interstitium reaches a highly compliant state, and further increases in interstitial fluid volume do not alter $P_I$ (17), i.e., the $P_I$ component of the safety factor is lost. Consistent with our earlier findings (30, 34, 35), baseline EVLW was significantly elevated in the paced group. In contrast to the predicted effect, $P_I$ in this group remained subatmospheric, with an average value not different from that in the normally hydrated control lobes. The similarity between the slopes of the $P_I$ vs. EVLW relationship implies that interstitial compliance (i.e., the change in $P_I$ induced by an increment in interstitial fluid volume) remained normal. These data suggest that matrix deposition in the interstitium may have increased to maintain the interstitial concentration of matrix components, thus allowing tissue pressure to remain normal in the face of increased hydration. Although global measures of collagen and hyaluronan were not increased in the paced group (compared with control) when normalized for dry weight or total protein, the fact that lobar dry weight and protein content increased leaves open the possibility of compartmentalized changes that might impact interstitial function. This will remain a focus for further study. One could argue that since we measured $P_I$ in sheaths not far from the hilum, an extrapolation to perivascular $P_I$ in the septal region where fluid exchange occurs is tenuous. However, Bhattacharya et al. (4) used micropuncture to show that there was a positive gradient in $P_I$ from the septal region to the hilum in isolated canine lung lobes, such that fluid flow toward the hilum was facilitated. Their baseline measures of $P_I$ at the hilum were similar to those reported here ($-1.8 \text{ cmH}_2\text{O}$), although different techniques were used. Furthermore, perihilar and septal $P_I$ increased similarly in their study with edema formation. Finally, interstitial remodeling has been observed in the heart after the development of chronic right heart failure in the dog (18). In this model, myocardial edema was associated with interstitial fibrosis, collagen deposition, and an increase in $P_I$. These authors hypothesized that matrix deposition was in response to an initial increase in interstitial water content, although the signaling mechanism is unclear. This notion is similar to one we posed earlier (36), when we observed a significant increase in uronic acid content in the canine lung after 3 h of saline-loading-induced fluid filtration. Although the mechanism linking edema formation and matrix deposition is not well understood, the significance of such adaptive remodeling in the lung interstitium is clear.

With retention of normal interstitial compliance, the lung would regain a safety factor against further edema formation. This would be important in the face of acute increments in pulmonary vascular pressure, such as those imposed by exercise (13, 31).

In conclusion, we can find no evidence for vascular structural remodeling in < 400-μm pulmonary arteries or veins after 1 mo of pacing-induced heart failure. In contrast, interstitial remodeling does occur, conferring a measure of protection against further edema formation in these hypertensive lungs. This latter adaptation thus adds to the protection resulting from the increased resistance of the capillary endothelial barrier to injury in this model (30, 34). Together, these findings suggest that early adaptations to chronic pulmonary venous hypertension are primarily directed at limiting fluid accumulation in the lung parenchyma. These are important adaptations, allowing a measure of protection against further increments in lung water.

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