Heparin Prevents Pulmonary Artery Remodeling in Postobstructive Pulmonary Arteriopathy in Dogs

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Patients with proximal pulmonary artery obstruction from chronic, organized pulmonary emboli develop hypertensive changes in both the patent and obstructed pulmonary arterial beds. We have found that these postobstructive changes can be reproduced in a canine model by chronic ligation of the left pulmonary artery. In this model, the right (patent) lung remains normal, while the obstructed left lung develops medial hypertrophy, intimal proliferation, and, in some cases, plexiform lesions. We have also found that these hypertensive-like changes (postobstructive pulmonary arteriopathy [PPA]) occur in the absence of distal thrombosis, hypoxemia, or elevated pressure, while their occurrence is temporally related to the development of significant bronchial collateral vessels with precapillary bronchopulmonary anastomoses.

It has been previously found that heparin can suppress vascular smooth muscle cell proliferation in vitro and in vivo, both in a dry air injury model in rat carotid artery and in hypoxic pulmonary hypertension models. Our purpose was to examine the effect of heparin on pulmonary arterial smooth muscle cell proliferation in a nonhypoxic model of pulmonary vascular remodeling.

Six adult dogs of mixed breeds were premedicated and sedated before being intubated and placed on mechanical ventilation with a Harvard Apparatus Animal Respirator, after which general anesthesia was maintained with Halothane. A thermodilution pulmonary artery catheter and a femoral artery catheter were placed. A left lateral thoracotomy was performed in the fourth intercostal space under sterile conditions, and the left pulmonary artery was ligated. Hemodynamic measurements were made, and arterial blood gases were measured at baseline and after ligation. The incision was closed after ligation. The animals received IM penicillin and streptomycin for 10 days postoperatively. Heparin (Elkins-Sinn, Inc) therapy was started on the second postoperative day at a dose of 300 units/kg administered subcutaneously twice a day. The animals were exercised daily throughout the 6-week postoperative period. The partial thromboplastin time (PTT) was measured midway through the postoperative period at 1 hour after a heparin dose, 4 hours later, and just before the next dose.

At the end of 6 weeks, a repeated left lateral thoracotomy was performed in the fifth intercostal space after placement of arterial and pulmonary artery catheters. Similar hemodynamic measurements were made. The animals were then sacrificed. The heart and lungs were removed in a block and fixed by tracheal instillation of formalin from a height of 30 cm. Sections from the upper and lower lobes of each lung...
were prepared for histologic processing and stained with hematoxylin and eosin and elastic stains.

The presence of PPA was determined by the mean muscle area (MMA) ratio, which is [(total vessel area − luminal area)/total vessel area]. Areas were determined by planimetry on elastic stained slides of 30-100-μ diameter vessels. Multiple measurements were made in each lobe. An analysis of variance was used to test the differences between the left and right lung MMA ratios.

As we found previously, the mean pulmonary artery pressure rose only slightly, from 15 ± 1.5 mm Hg to 16.4 ± 2 mm Hg (p = 0.0466). The PaO₂ remained normal throughout (86 ± 4 mm Hg at baseline; 95 ± 10 mm Hg at 6 weeks). The normal PTT in dogs is 12 seconds. The mean PTT was slightly elevated 1 and 4 hours after a dose of heparin (14.7 ± 1.2 s and 15.1 ± 1.1 s) but returned to the normal value of 12.1 ± 0.9 s just before the next dose. Thus, the animals had a minimal elevation of the PTT but not in the antithrombotic range (1.5 N).

In contrast to the animals we studied previously, who had undergone only left pulmonary artery ligation, the MMA ratio was not significantly different in the left and right lungs in these animals who received heparin after pulmonary artery ligation (486 ± 0.0295 vs. 513 ± 0.033; p = 0.362.)

We conclude that heparin appears to inhibit the development of PPA which is a nonhypoxic model of pulmonary vascular remodeling. With the data mentioned earlier, this finding suggests that heparin may be a common regulator of pulmonary vascular smooth muscle growth. It also suggests that endothelial cell injury, allowing derepression of heparin-mediated endothelial cell control over smooth muscle cell growth, may occur in this model.

REFERENCES

Hypoxia and the Pulmonary Microvasculature*

Physiology and Pathophysiology

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Our interest in the effect of hypoxia on the pulmonary microcirculation was its use as a tool to answer the question: what is the origin of the vascular smooth muscle (VSM) of the pulmonary arterioles in adult pulmonary hypertension? Although "true" pulmonary arterioles are not present in the adult mammalian lung, traces of VSM persist even in the aged lung arterioles. We wished to distinguish between possible recall or activation of VSM and the de novo formation of VSM and believed that hypoxic challenge was an appropriate tool. With 10% O₂ in nitrogen or ¼ atm exposure, we found rapid changes in the prealaevolar (acinar) arterioles of less than 30 μ diameter. Blebs developed between the endothelium and its basal lamina, and edema occurred in the arteriolar wall connective tissue. These were present after 1 h of hypoxia (Fig 1); 5% O₂ produced similar changes after only 15 min. Fibroblasts, normally present in the arteriolar wall at the intercept with the alveolar wall, tripled in number by 24 h, migrated subendothelialy, and during the next 24-48 h developed a basal lamina, myofibrils, lost their rich endomyselar reticular connective tissue, and completed their transformation into typical VSM by 3-4 days. The endothelium of these muscularized vessels appeared normal after 48 h. These changes of subendothelial blebbing, wall edema, and increased number of fibroblasts were not present in the capillary bed, small venules, or proximal small arteries. The number of platelets per arteriolar cross-section increased by 24 h and peaked at 48 h, with an occasional platelet adherent to the endothelium.

The rapid onset of these sequential changes in a limited segment of the pulmonary microvasculature with hypoxia suggested an anatomic cascade triggered by a biochemical sequence. We thought an endothelium-derived arachidonic acid (AA) release could initiate such a cascade of events. Therefore, in the anesthetized rat we infused mepacrine IV and recorded pressure from the pulmonary artery prior to and during 10% O₂ challenge. This was effective in blocking the acute rise in pulmonary pressure. In parallel experiments with mepacrine blockade of hypoxic response, AA, and PGF₂₅ each produced an increase in pulmonary artery pressure, indicating persistent vasoactive response. Blockage of hypoxic pulmonary hypertension by mepacrine for up to 4 h markedly reduced the immediate anatomic changes in the arteriolar wall seen during hypoxia when examined by light microscopy.

Further review of EMs now shows an accumulation of platelets at the endothelium, with the presence of membrane bound densely staining bodies, circular in section, and without the characteristic structure of Weibel-Palade bodies. They accumulate rapidly and are profuse at 1 h of 10% oxygen, persist at 24 h, and begin to disappear at 48 h.

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