This multivariable analysis, which included all 9,238 eligible participants, yielded very similar results to those reported in our recent article (Table 1).

Finally, we appreciate Dr. Liu and Dr. Zhou's comment on our definition of menopause. We used the mean age at menopause in U.S. women (51 yr) to define menopause. Indeed, average estradiol levels dropped markedly after age 50 years among women included in our analysis. In a secondary analysis, we did not find a significant interaction between menopause (as defined here) and serum estradiol on asthma in participating women. Given the comments by Dr. Liu and Dr. Zhou, we repeated the secondary analysis redefining menopause as not having had a menstrual period for at least a year ([age when interviewed/examined] – [self-reported age at the last menstrual period] $\geqslant$1 yr) or self-report of having had a hysterectomy in which both ovaries were removed. Using this alternative definition, we also found no significant interaction between menopause and serum estradiol on current asthma.

Large longitudinal studies with precise information on menopausal status should help better understand the relation between sex hormones and current asthma in adults. ■

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Early Disruption of VEGF Receptor Signaling and the Risk for Adult Emphysema

To the Editor:

We read with interest two recent letters to the editor that describe the remarkable effects of the combination of SU5416, an inhibitor of VEGFR2 signaling, with chronic hypoxia on pulmonary circulation in adult rats (1, 2). Over time, this exposure causes marked elevations of pulmonary artery pressure, with right ventricular hypertrophy, striking hypertensive remodeling of the pulmonary arteries, and, most interestingly, obstructive intimal lesions that resemble the extreme histopathology of severe human pulmonary artery hypertension (PAH). These findings are consistent with the original description of this rodent PAH model (3), which greatly stimulated the field because of the presence of the unique feature of obliterative vascular disease, which is generally missing from other animal models of PAH.

Interestingly, one of the letters convincingly noted the additional finding of enlarged distal airspaces in this model, which supports the concept that the combination of SU5416 with chronic hypoxia causes histologic features of emphysema in addition to PAH (1, 3). This striking association of impaired vascular structure and function with the development of emphysema supports the unique opportunities of using this model to investigate fundamental mechanisms through which paracrine vascular signals modulate airspace structure and that disruption of "angiocrine signals" could contribute to the pathobiology of emphysema. Thus, the presence of emphysema-like changes may provide unique opportunities to use the SU-hypoxia model to further understand the pathogenesis and treatment of chronic lung diseases in adults, such as emphysema and chronic obstructive pulmonary disease, as well as severe PAH.

As suggested in the letter from Bogaard and colleagues (1), however, findings of airspace enlargement may not be consistently observed between the different reports involving the SU-hypoxia model to study PAH in adult rats. The authors question the degree of changes in lung airspace size and that such an effect may be milder than reported by Kojonazarov and colleagues (2).

How to best reconcile these differences is uncertain; however, one clear message from published data emerges regarding the important role of the developmental timing of disrupted VEGF signaling (4–6). Intrauterine treatment of fetal sheep with a VEGF-specific aptamer not only causes striking pulmonary hypertension (PH) and vascular remodeling but further reduces vascular and airspace growth and causes severe neonatal PH at birth (4). Similarly, hemodynamic pulmonary vascular stress *in utero* causes sustained PH but also inhibits angiogenesis and decreases distal airspace growth before birth (4). Perinatal disruption of VEGF signaling also has long-lasting implications regarding the risk for emphysema in adult life. Importantly, SU5416 injection on the first day of life is sufficient to cause PH and alveolar simplification in 3-week-old rats and also leads to sustained abnormalities of lung alveolar structure that persist into adulthood (3–4 mo of age) with reduced pulmonary vascular density and increased right ventricular hypertrophy (6) (Figure 1). These changes are linked to the critical role of developmental timing of lung vascular injury on early (infant) and late (adult) lung structure, which are independent of hypoxia.

Thus, despite controversies on the impact of SU5416 with or without chronic hypoxia in the adult lung, strong data remain that support the concept of developmental origins of lung disease, in which early disruption of angiogenesis (by early disruption of VEGF receptor signaling or other critical pathways) not only impairs alveolar growth throughout infancy but also can extend into adult life, which likely increases

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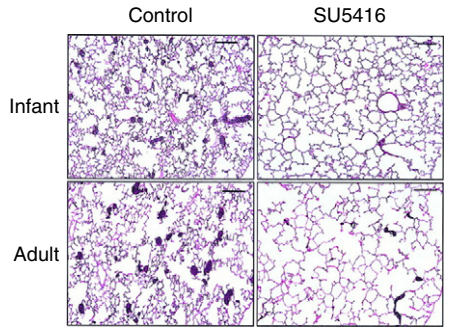

Figure 1. Effects of neonatal SU5416 treatment on lung histology in infant and adult rats. Lung histology of infant rats treated with a single dose of SU5416 on the first day of life showed alveolar simplification and decreased pulmonary arteries, which appear brown in color because of barium infusion. This pattern of reduced alveolar number and vessel density persisted into adulthood. Rats in this study were maintained in room air at Denver's altitude (5,280 ft above sea level) and not exposed to hypoxia. Scale bars, 100 μm. Reprinted by permission from Reference 6.

susceptibility for chronic lung disease, especially with a late secondary injury such as tobacco smoke, pollution, vaping, or other insult. ■

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The Adult Sprague-Dawley Sugen-Hypoxia Rat Is Still "the One:" A Model of Group 1 Pulmonary Hypertension: Reply to Le Cras and Abman

From the Authors:

Kojonazarov and colleagues recently reported severe emphysema in the SU5416/hypoxia (SuHx) rat model of pulmonary hypertension (PH) (1). The authors found that adult male Wistar Kyoto (WKY) rats had an increased air-to-tissue ratio as judged by nongated *in vivo* microcomputed tomography, and an increased mean linear intercept (MLI) as a surrogate for emphysema (1, 2). Le Cras and Abman now respond to Kojonazarov and colleagues' report by underlining the "important role of the developmental timing of disrupted VEGF signaling." They cite earlier studies conducted on ovine fetuses that showed that VEGF inhibition caused vascular remodeling, a reduction in vascular and airway growth, and neonatal PH at birth (3).

Although the VEGFR inhibitor SU5416 is known to induce emphysema in rats housed in room air at Denver altitude (1,609 m altitude) (4, 5), we contended in our response letter (6) that, at least in male Sprague-Dawley (SD) rats, the combination of VEGFR inhibition and hypoxia does not lead to any biologically relevant emphysema or other significant parenchymal lung disease (7) but rather to pulmonary arterial hypertension (PAH) due to severe angioproliferative remodeling (7, 8). A similar degree of PH without apparent alveolar simplification was seen when VEGF blockade was administered *in utero* to fetal or neonatal sheep (3). *In utero*, P_{O_2} is approximately 19 mm Hg in the fetal pulmonary artery and 34 mm Hg in the umbilical vein (maximum systemic oxygenation), which represent hypoxemic/hypoxic values for newborns after postnatal cardiopulmonary adaptation. Thus, it may not be surprising that VEGF blockade *in utero* causes

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