

# Vascular morphology of Alveolar Capillary Dysplasia Revisited: Report of a Case, Literature Review and a Morphometric Approach to Assess Cases of Atypical Clinical Presentation

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*<sup>3</sup>INSERM U1256 Nutrition, génétique, exposition aux risques environnementaux*

**SOFFOET Septembre 2018**

# Case presentation: lung histopathology

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## Lung histopathological features

- misplaced vein accompanying artery and bronchiole
- thickened mesenchyme septa
- muscularized arterioles
- capillaries not in contact with alveoli
- hypertrophy of media of small arteries

**Alveolar Capillary Dysplasia Associated With Misalignment of Pulmonary Veins  
(ICD-9 Code 516.64) ACDMPV, Popler et al. CHEST 2012; 142: 774–80**

*Congenital Alveolar Capillary Dysplasia—An Unusual Cause  
of Respiratory Distress in the Newborn*

CHRISTINE G. JANNEY, M.D., FREDERIC B. ASKIN, M.D., AND CHARLES KUHN, III, M.D.

Am J Clin Pathol 1981;76:722–727.

State of the Art

Am J Respir Crit Care Med 2011,184: 172–79,

**Alveolar Capillary Dysplasia**

Naomi B. Bishop<sup>1</sup>, Pawel Stankiewicz<sup>2</sup>, and Robin H. Steinhorn<sup>3</sup>

*J. Paediatr. Child Health* (2002) 38, 397–400

**Incidence of alveolar capillary dysplasia in  
severe idiopathic persistent pulmonary hypertension  
of the newborn**

J TIBBALLS<sup>1</sup> and CW CHOW<sup>2</sup>

# Alveolar capillary dysplasia with misalignment of the pulmonary veins: clinical, histological, and genetic aspects

**Evelien Slot<sup>1,2</sup>, Gabriëla Edel<sup>1</sup>, Ernest Cutz<sup>3</sup>, Arno van Heijst<sup>4</sup>, Martin Post<sup>5</sup>, Marco Schnater<sup>1</sup>, René Wijnen<sup>1</sup>, Dick Tibboel<sup>1</sup>, Robbert Rottier<sup>1</sup> and Annelies de Klein<sup>2</sup>**

<sup>1</sup>Department of Pediatric Surgery, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, The Netherlands; <sup>2</sup>Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands; <sup>3</sup>Division of Pathology, Department of Paediatric Laboratory Medicine, Hospital for Sick Children, Toronto, ON, Canada; <sup>4</sup>Department of Neonatology, Radboud University Medical Center –Amalia Children's Hospital, Nijmegen, The Netherlands; <sup>5</sup>Department of Translational Medicine, Hospital for Sick Children, Toronto, ON, Canada

Pulmonary Circulation 2018; 8(3) 1–8

## Infants with Atypical Presentations of Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins Who Underwent Bilateral Lung Transplantation

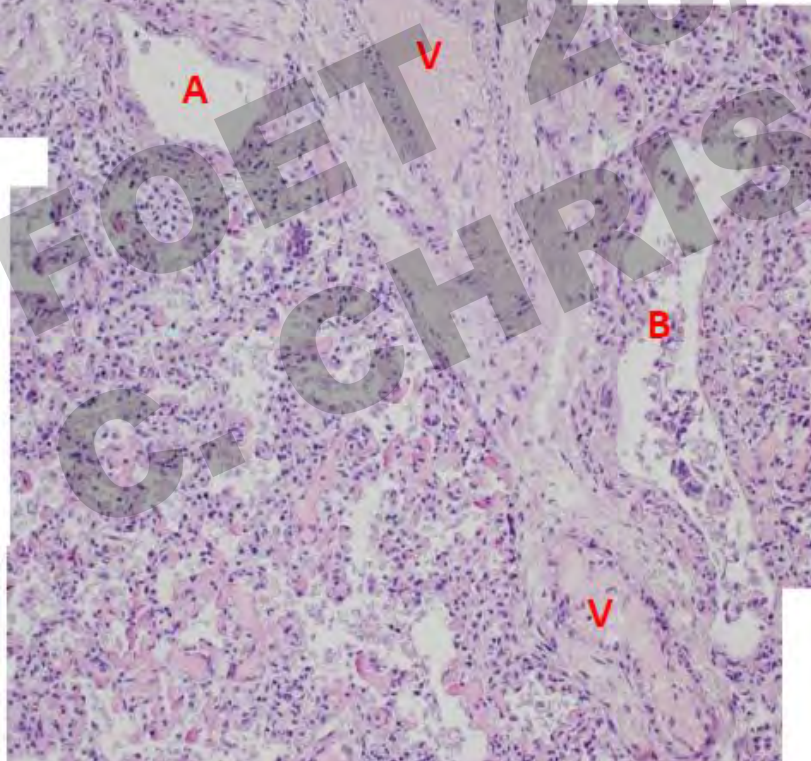
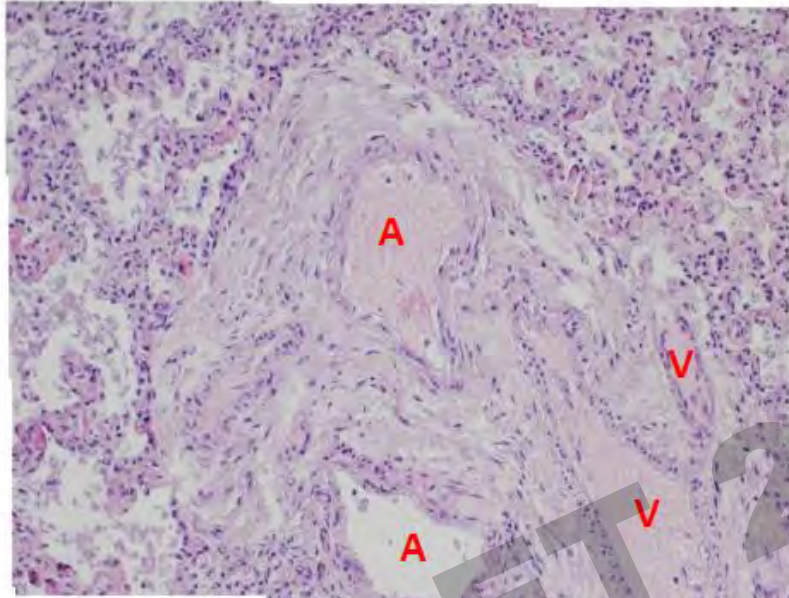
Christopher T. Towe, MD<sup>1</sup>, Frances V. White, MD<sup>2</sup>, R. Mark Grady, MD<sup>3</sup>, Stuart C. Sweet, MD, PhD<sup>3</sup>, Pirooz Eghtesady, MD, PhD<sup>4</sup>, Daniel J. Wegner, MS<sup>3</sup>, Partha Sen, PhD<sup>5</sup>, Przemyslaw Szafranski, PhD<sup>5</sup>, Pawel Stankiewicz, PhD<sup>5</sup>, Aaron Hamvas, MD<sup>6</sup>, F. Sessions Cole, MD<sup>3</sup>, and Jennifer A. Wambach, MD, MS<sup>3</sup>

J Pediatr 2018;194:158-64

## Histopathological features

- **misplaced vein accompanying artery and bronchiole**
- **thickened mesenchyme septa**
- **muscularized arterioles**
- **capillaries not in contact with alveoli**
- **hypertrophy of media of small arteries**

## Abnormally situated vein accompanies artery and bronchiole (1)

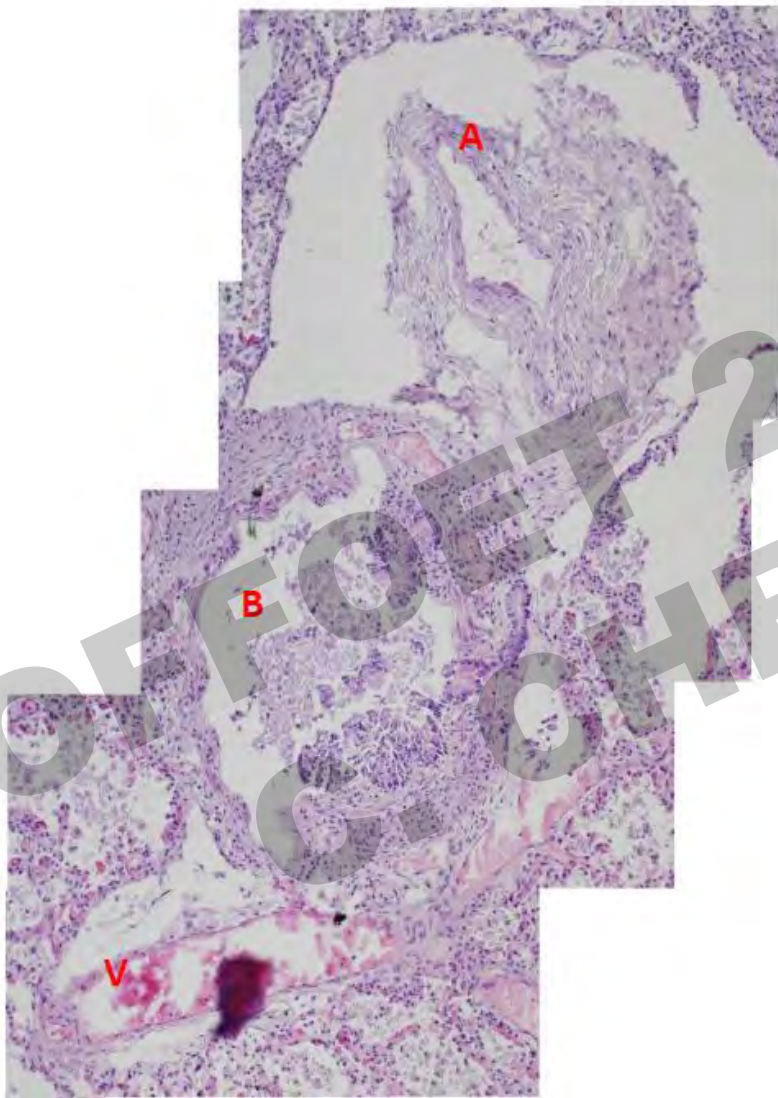


■ A = artery

■ B = bronchiole

■ V = vein

## Abnormally situated vein accompanies artery and bronchiole (2)



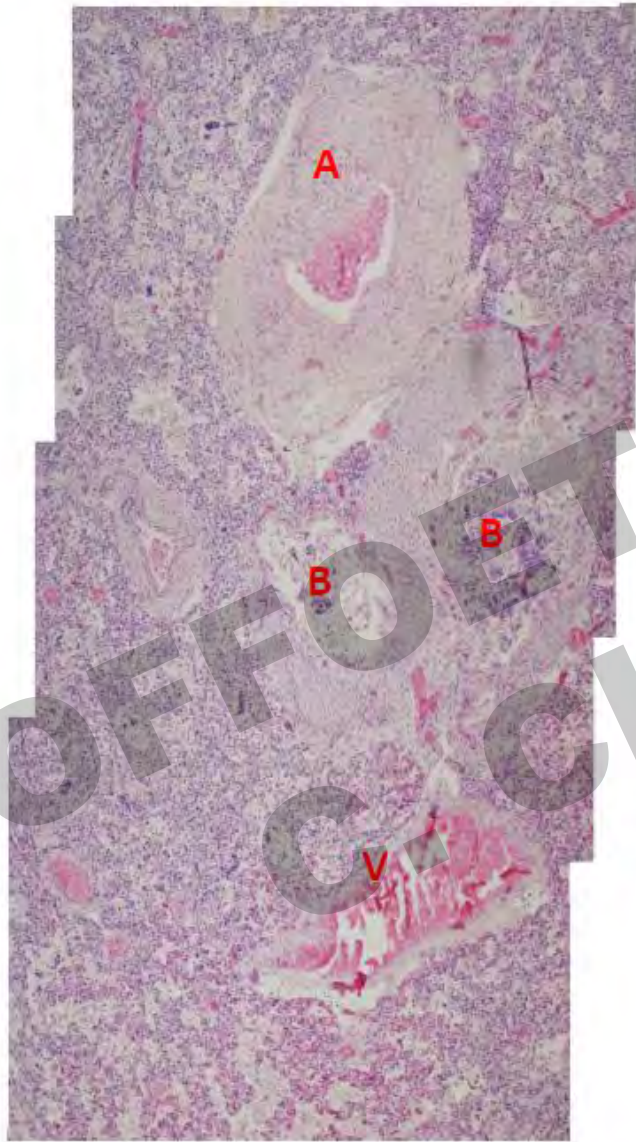
■ A = artery

■ B = bronchiole

■ V = vein



### Abnormally situated vein accompanies artery and bronchiole (3)

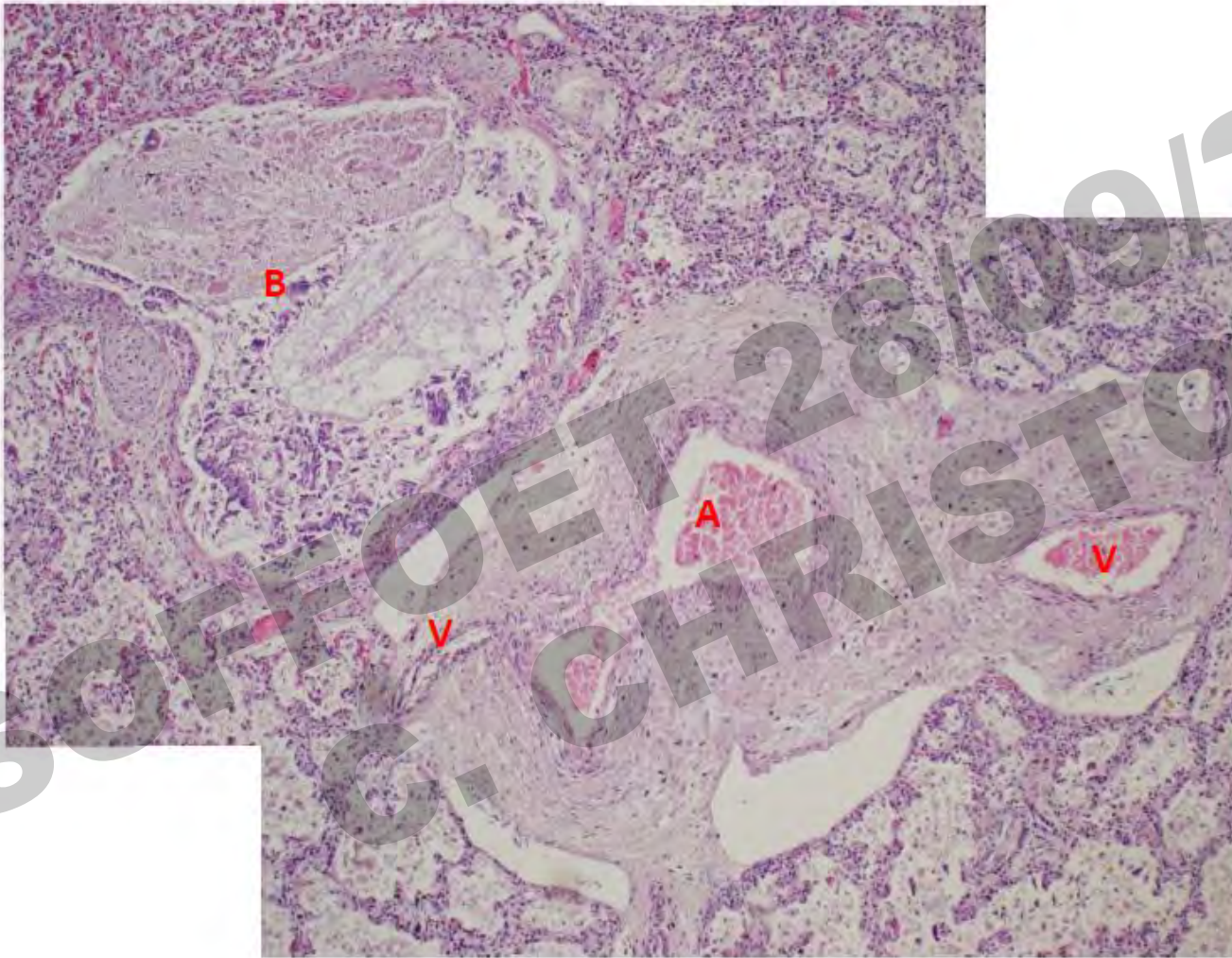


▪ A = artery

▪ B = bronchiole

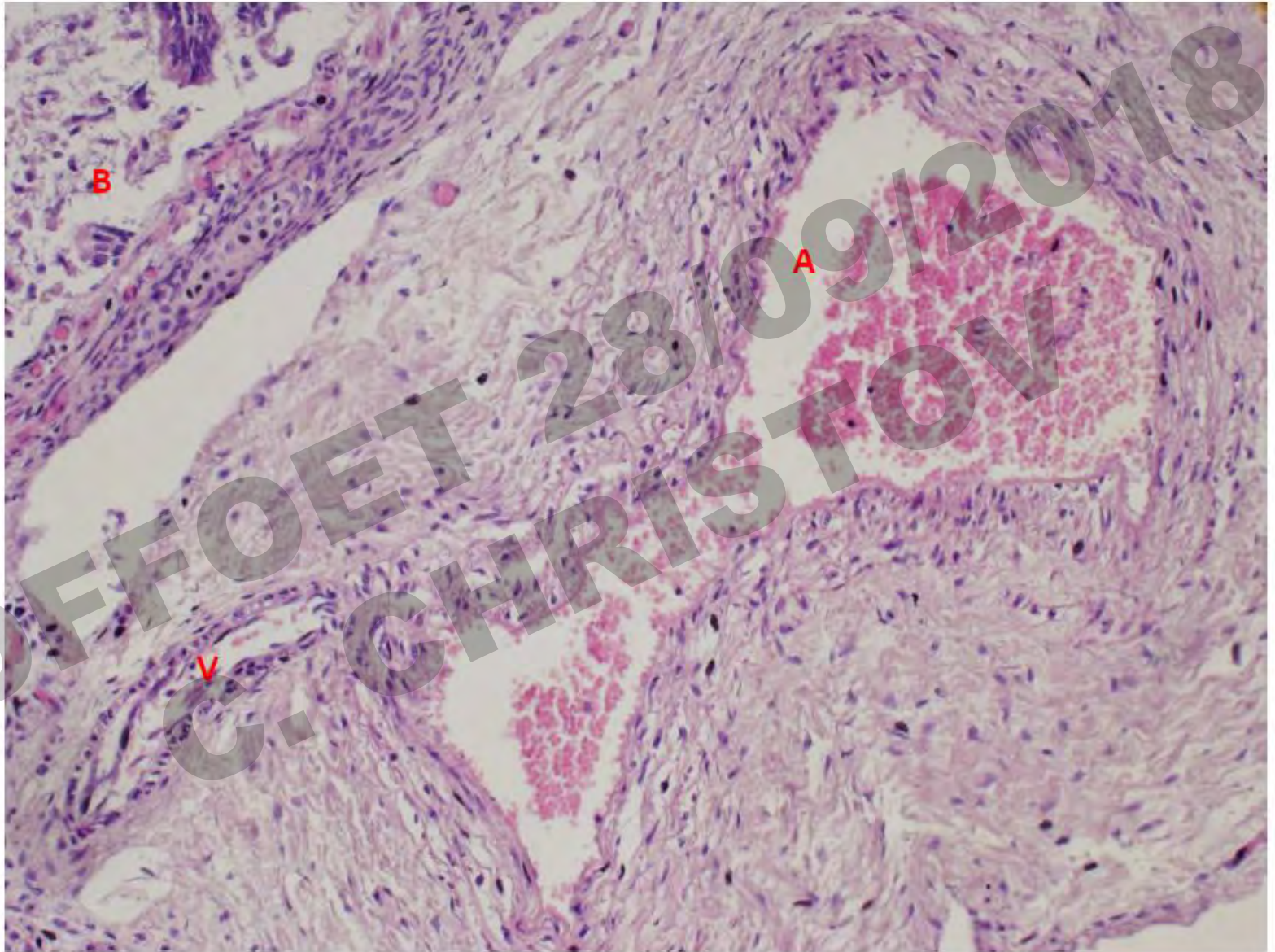
▪ V = vein

## Abnormally situated vein accompanies artery and bronchiole (4)

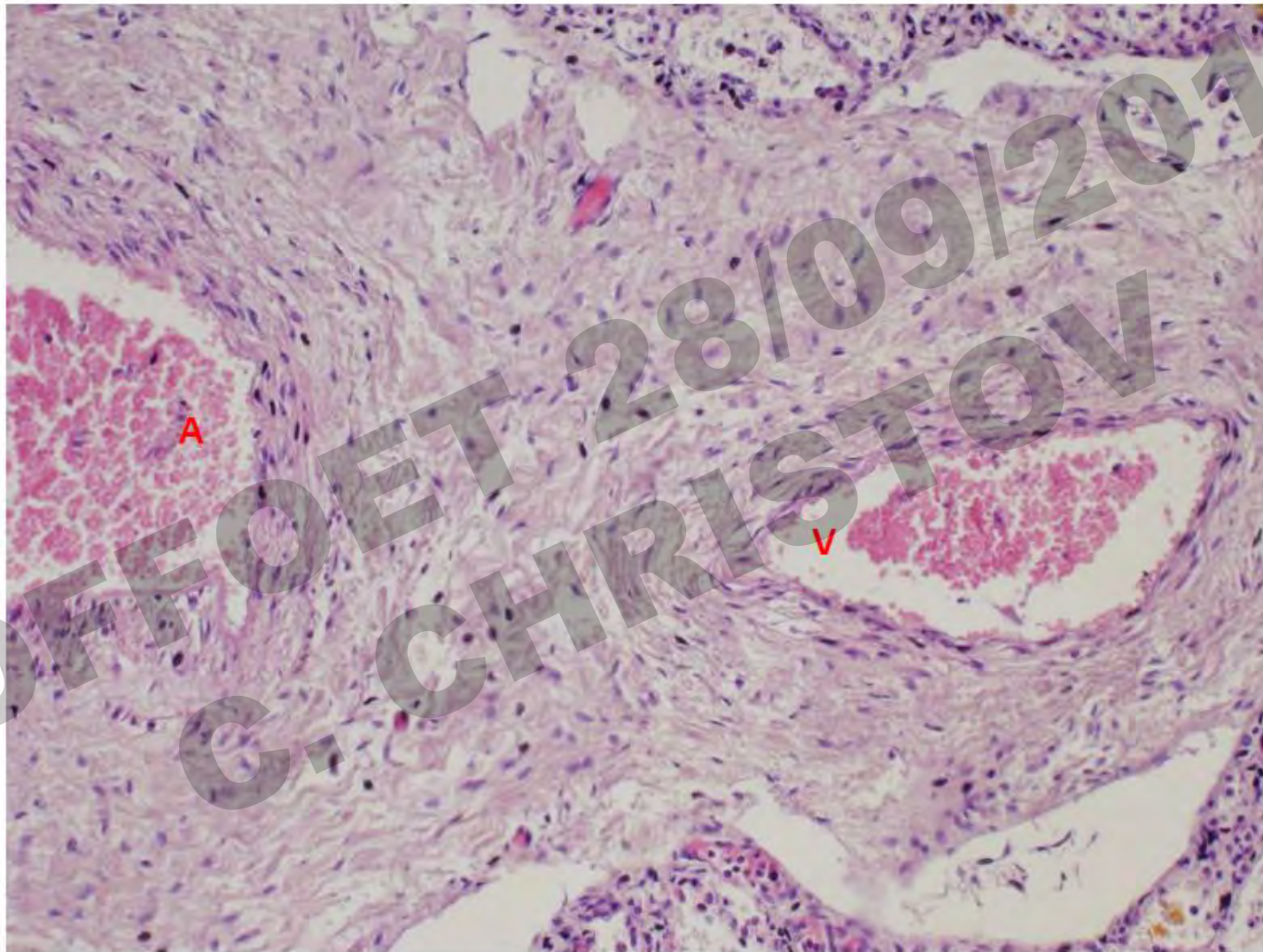


- A = artery
- B = bronchiole
- V = vein

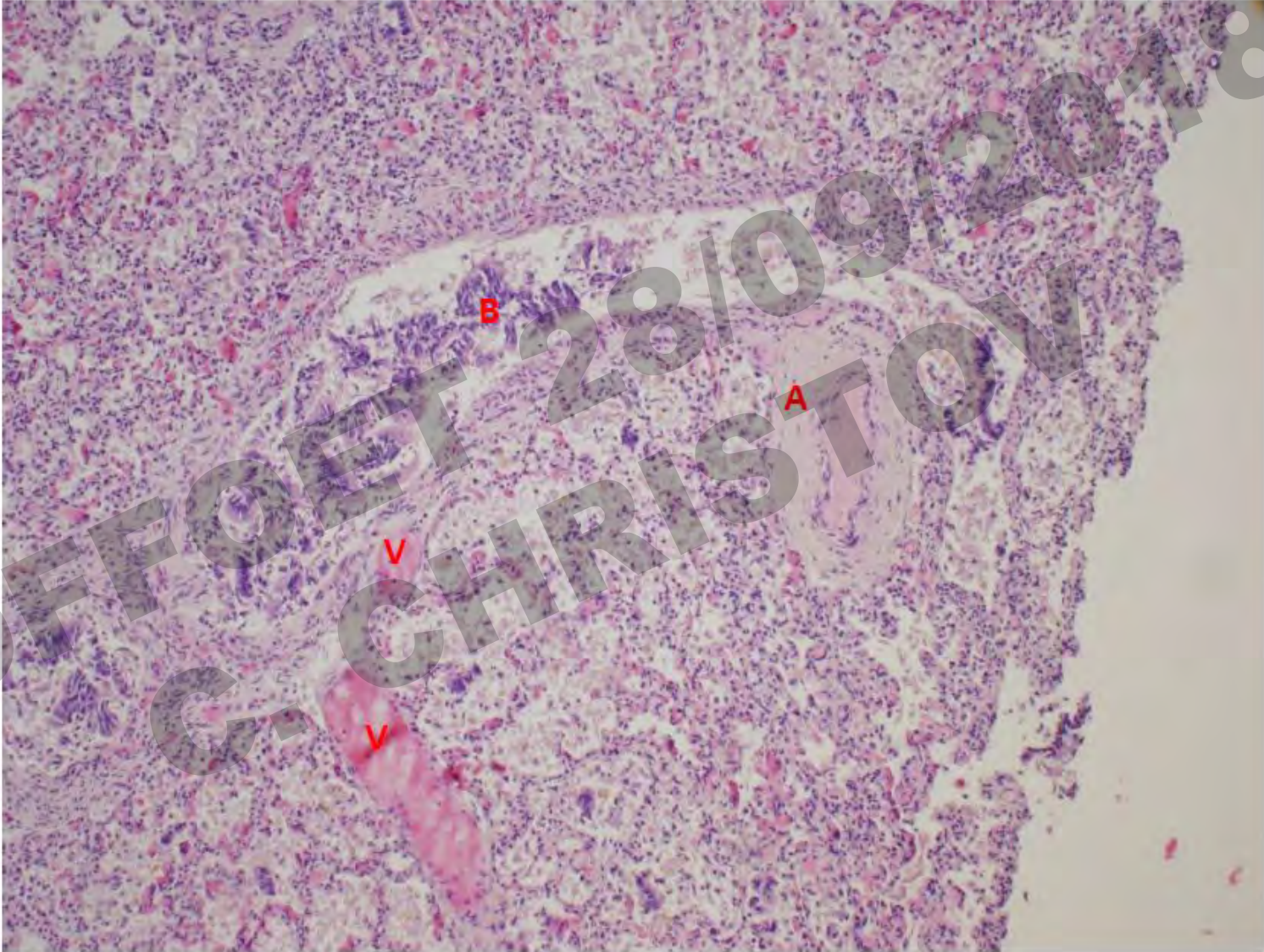
Abnormally situated vein accompanies artery and bronchiole (4): detail



Abnormally situated vein accompanies artery and bronchiole (4): detail



Abnormally situated vein accompanies artery and bronchiole (5)

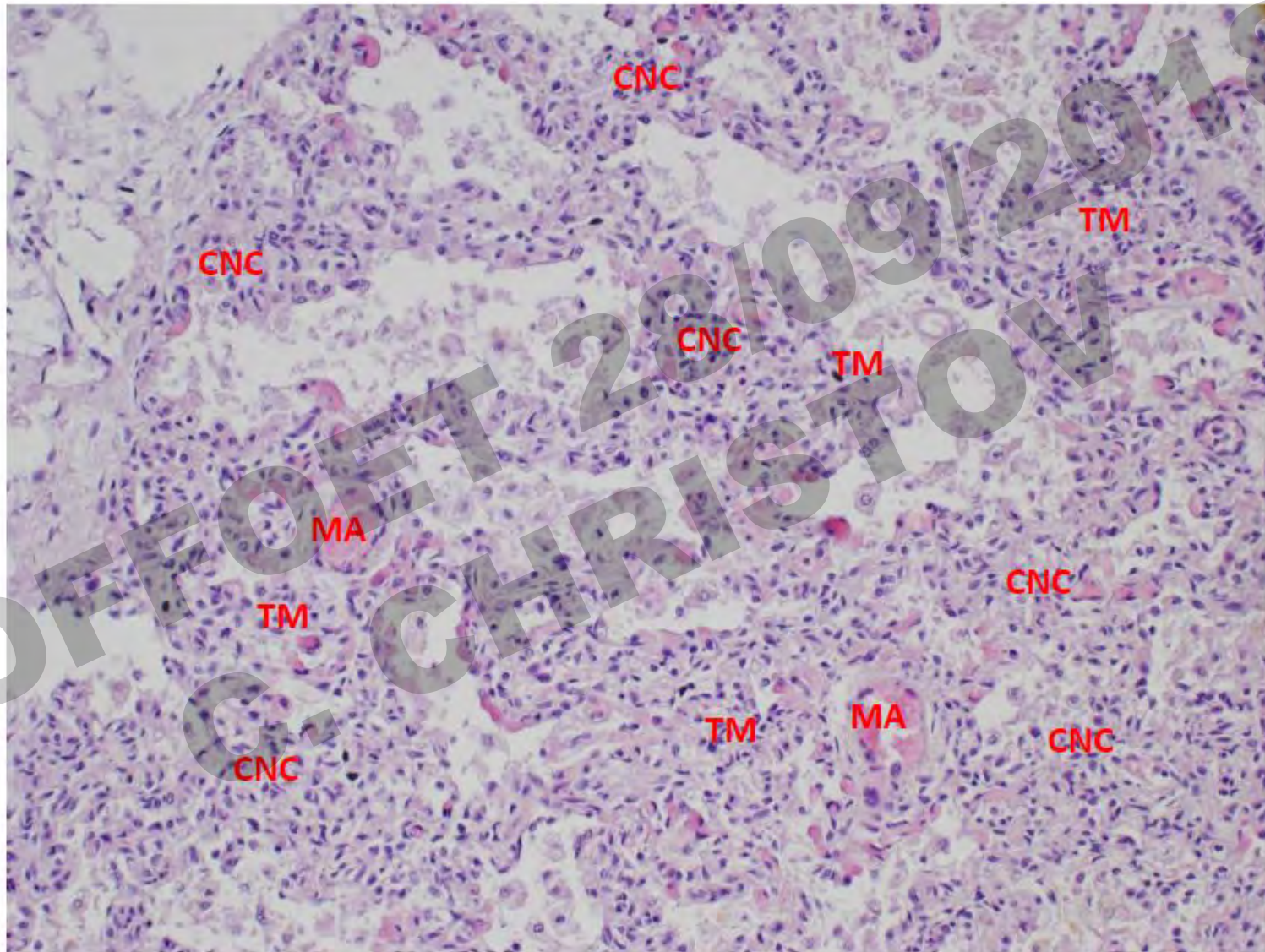


## Histopathological features

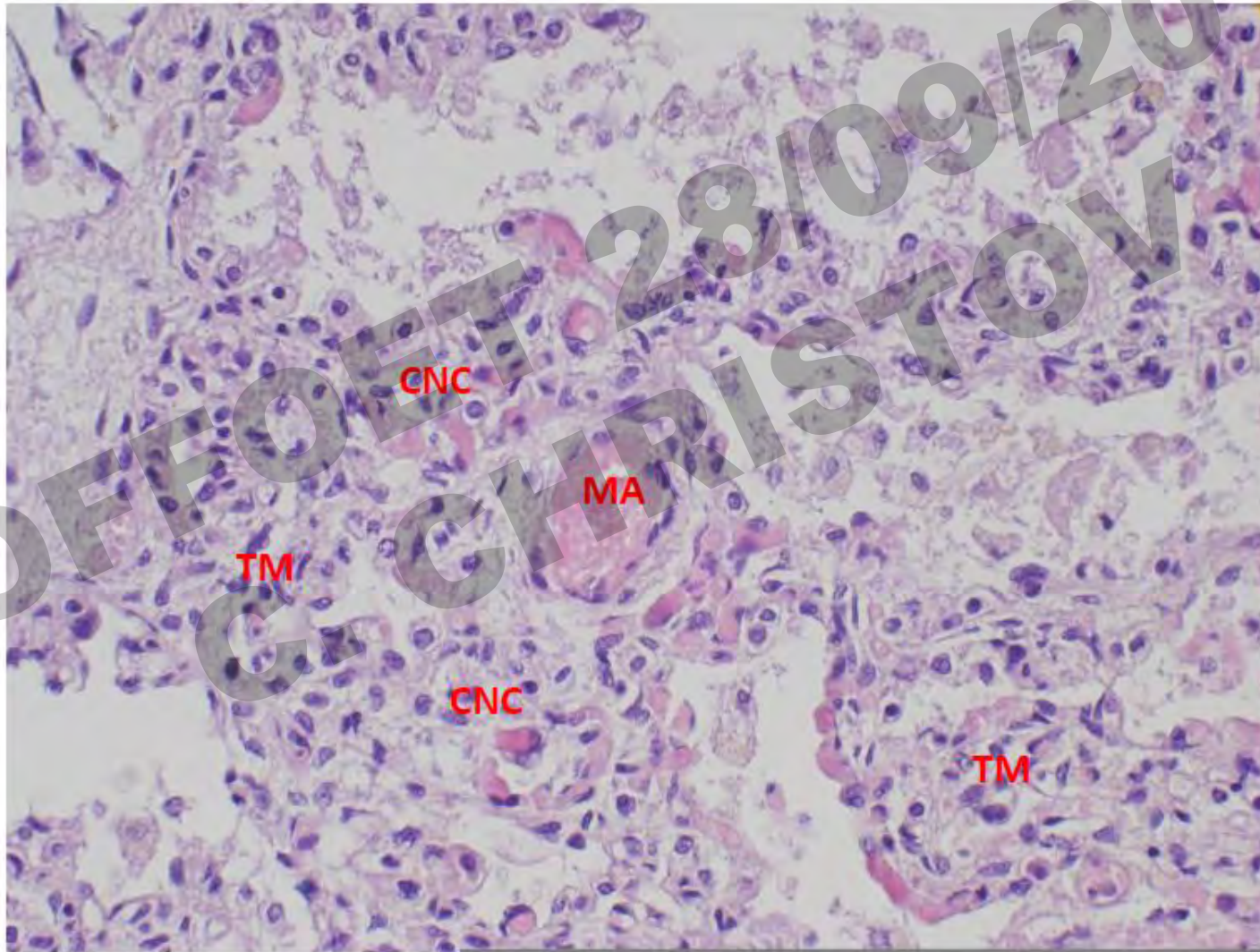
- misplaced vein accompanying artery and bronchiole
- thickened mesenchyme septa
- muscularized arterioles
- capillaries not in contact with alveoli\*
- hypertrophy of media of small arteries

\*with alveolar spaces, non apposed, non juxtaposed, not forming an air/blood barrier

Thickened mesenchyme (TM) in septa, muscularized arterioles (MA),  
capillaries not in contact with air spaces (CNC) (1)



Thickened mesenchyme (TM) in septa, muscularized arterioles (MA),  
capillaries not in contact with air spaces (CNC) (2)

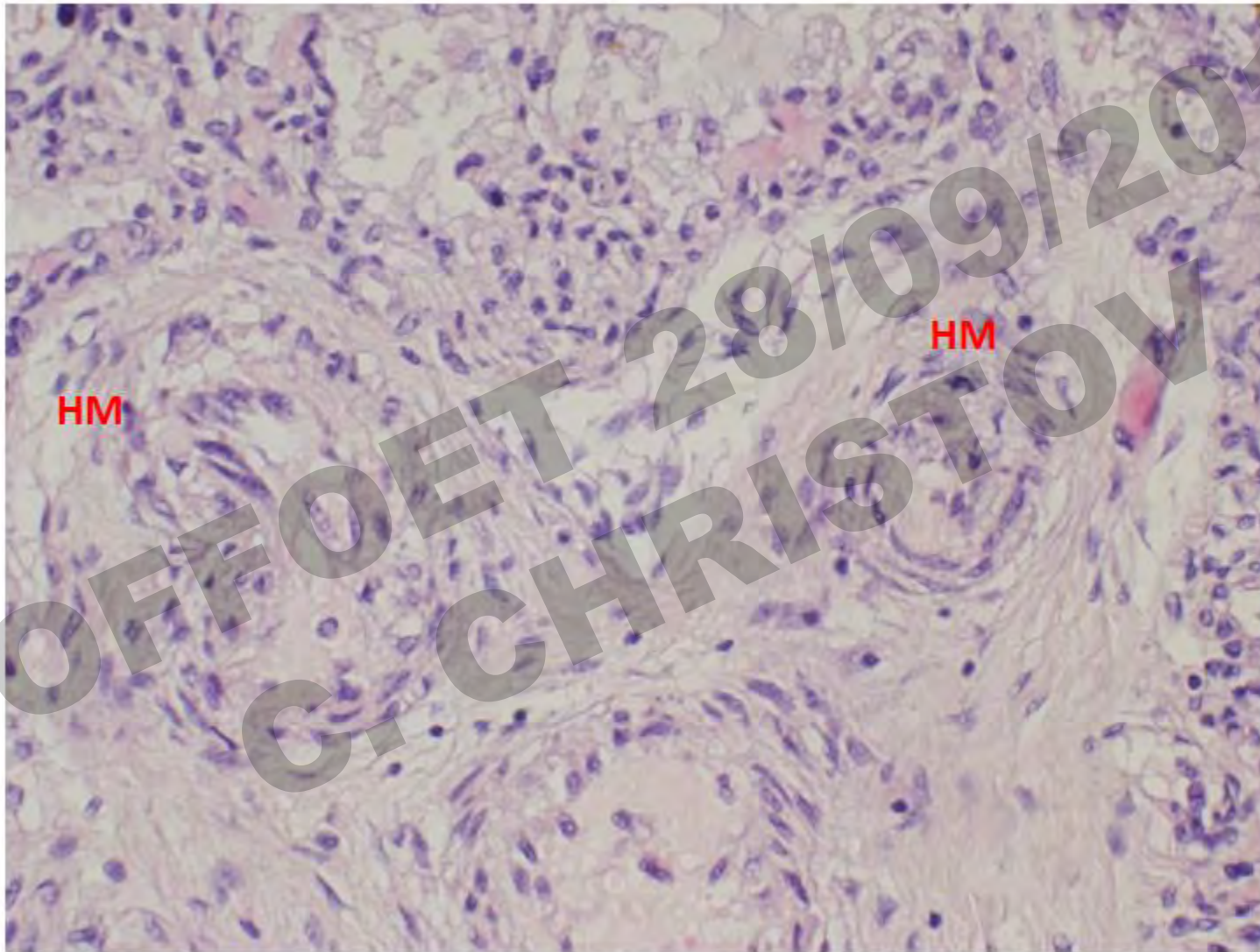




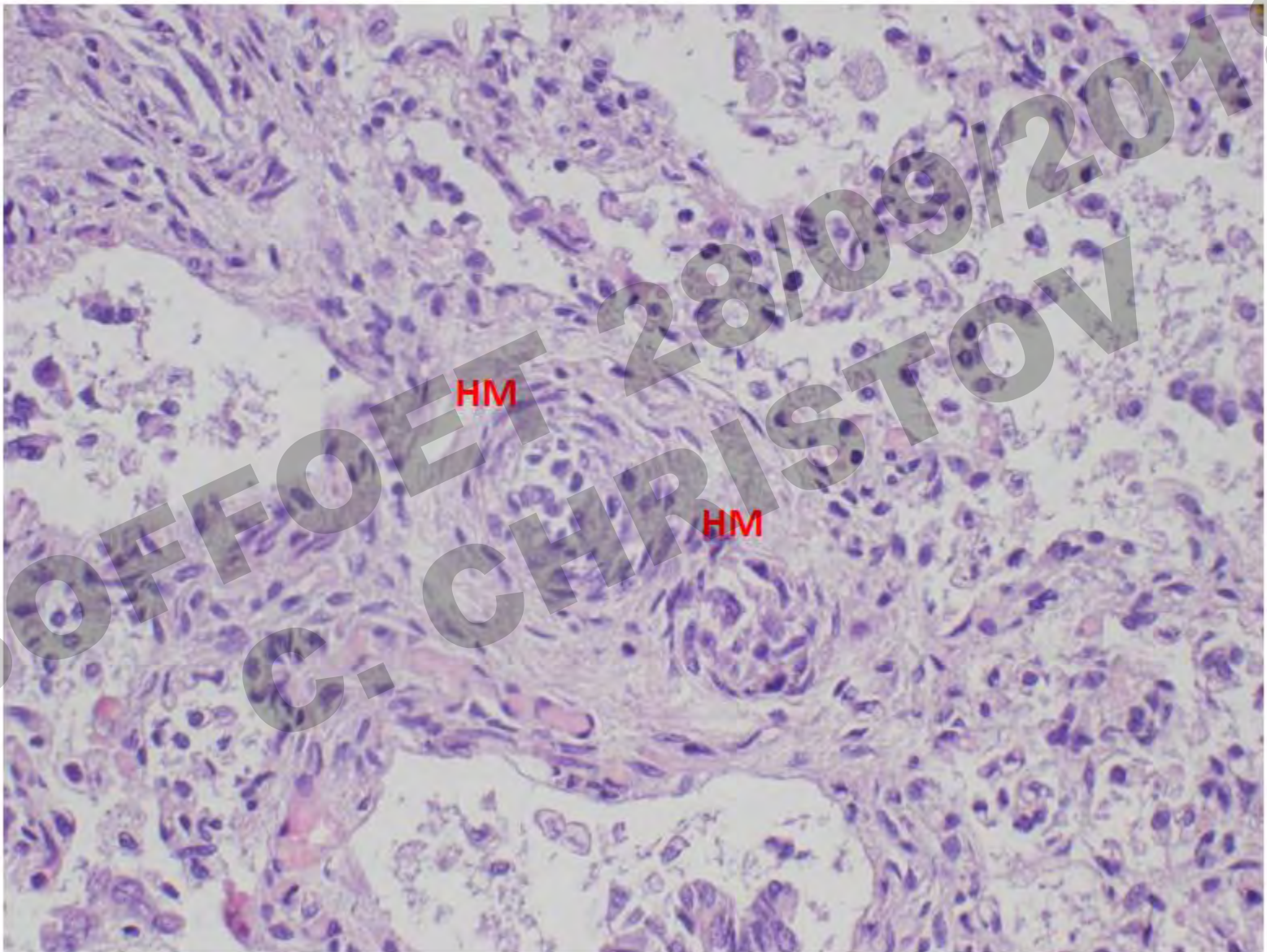
## Histopathological features

- **misplaced vein accompanying artery and bronchiole**
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- **capillaries not in contact with alveoli**
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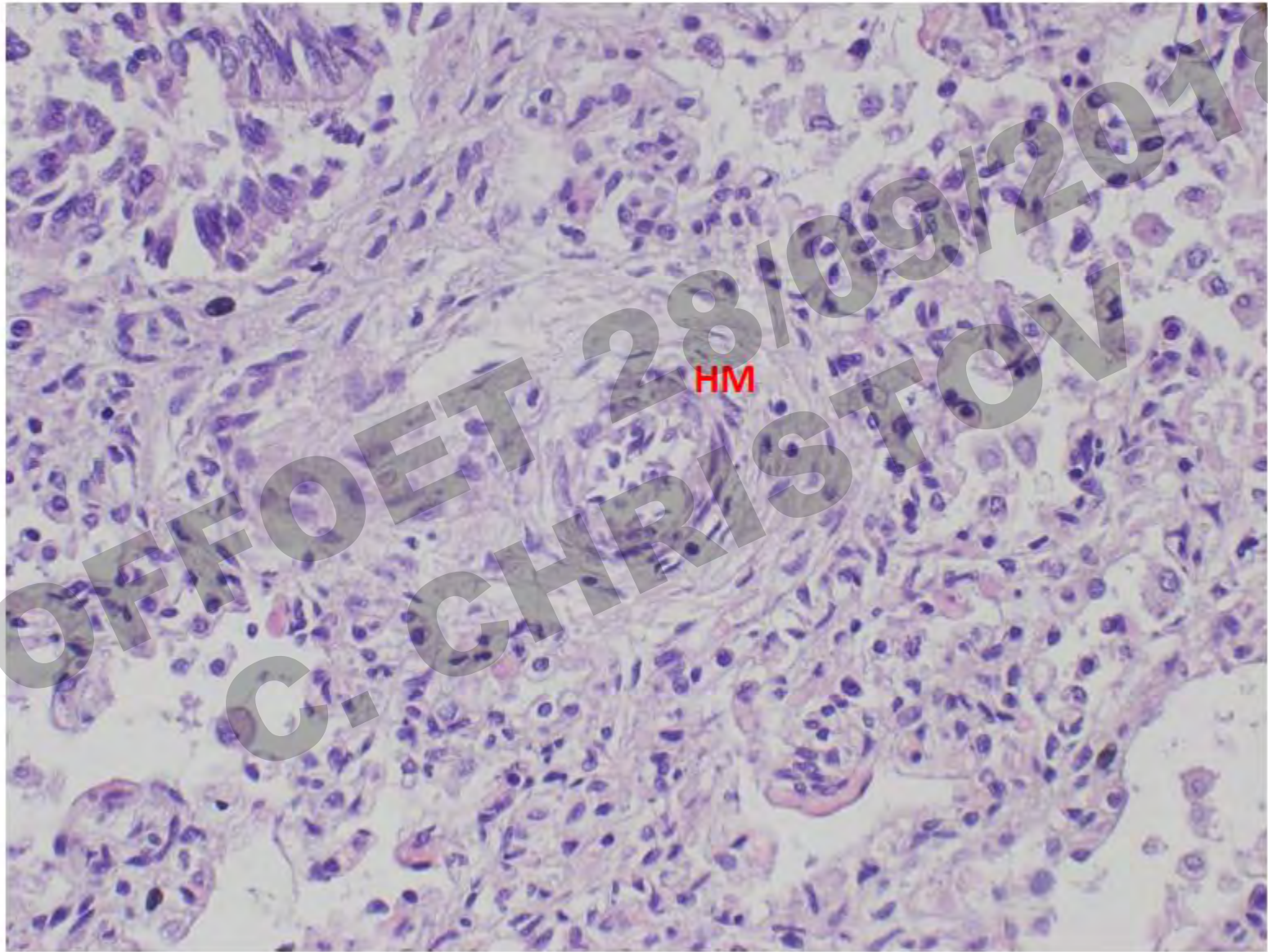
## Hypertrophy of media of small arteries (HM) (1)



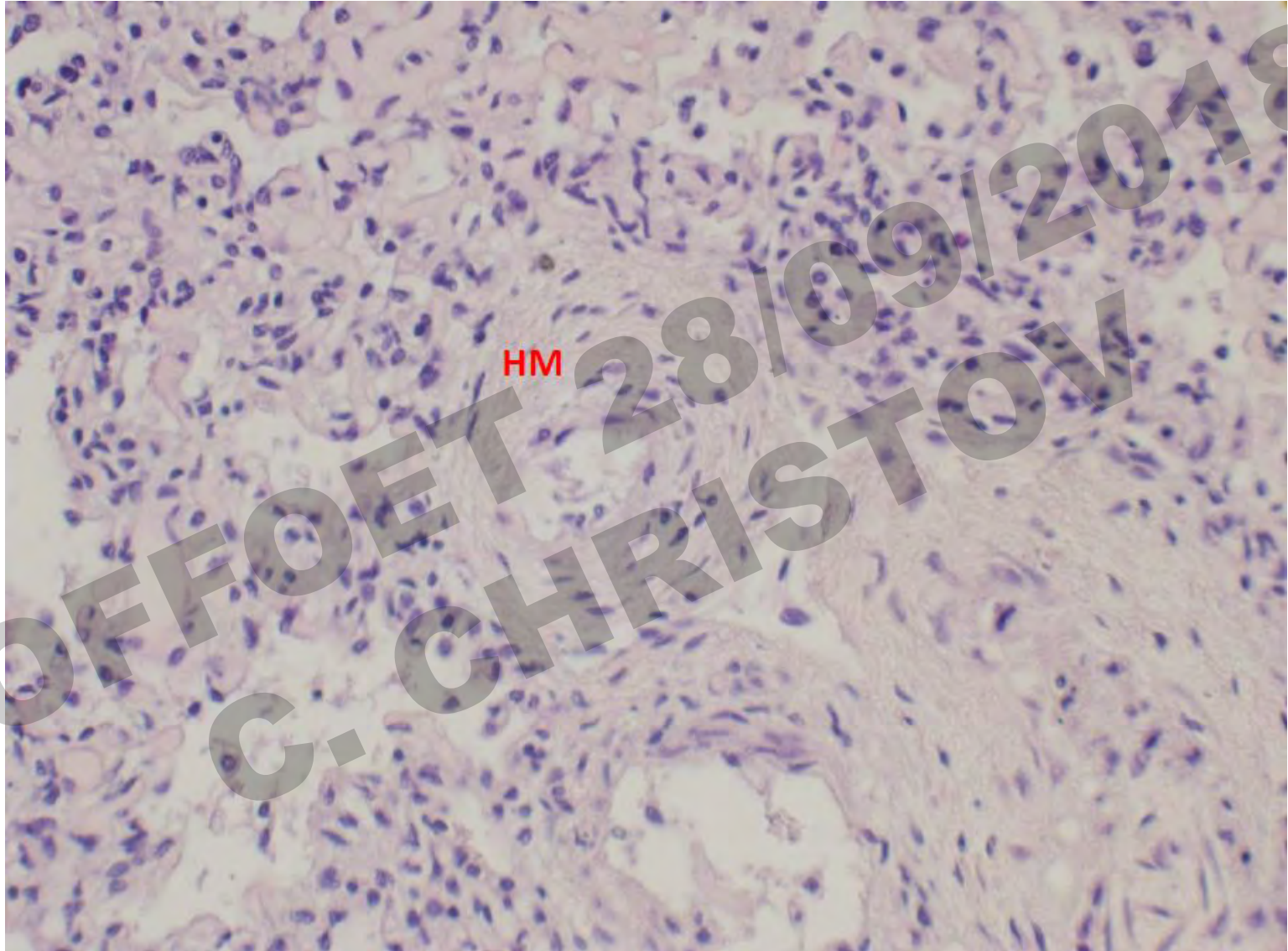
## Hypertrophy of media of small arteries (HM) (2)



### Hypertrophy of media of small arteries (HM) (3)



## Hypertrophy of media of small arteries (HM) (4)



# Physiopathology & Hemodynamics

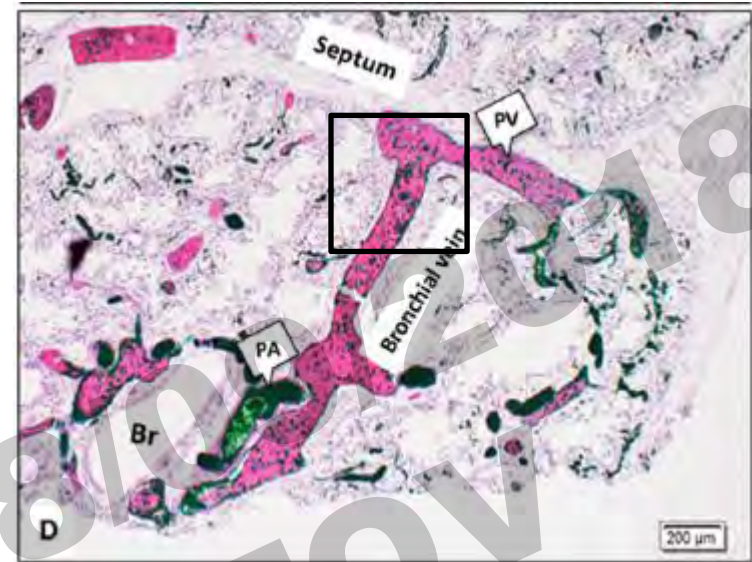
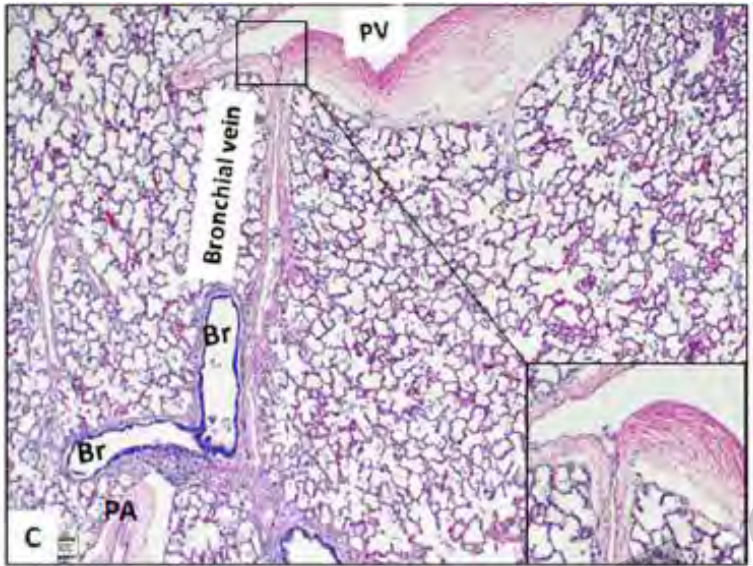
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# Physiopathology

- early disturbance of lung development
  - embryonic
  - pseudoglandular phase
  - continues in canalicular and saccular phases
- reduction of the lung capillary bed is the primary event
  - pulmonary right to left shunt
  - pulmonary artery → bronchial artery
  - bronchial vein → pulmonary vein
  - medial hypertrophy arterial walls
  - muscularization of the wall of small arteries

*“Misplaced” pulmonary veins are likely dilated bronchial veins draining in pulmonary veins*

## Shunts (1): bronchial vein pulmonary vein



## Shunts (2): bronchial artery pulmonary artery

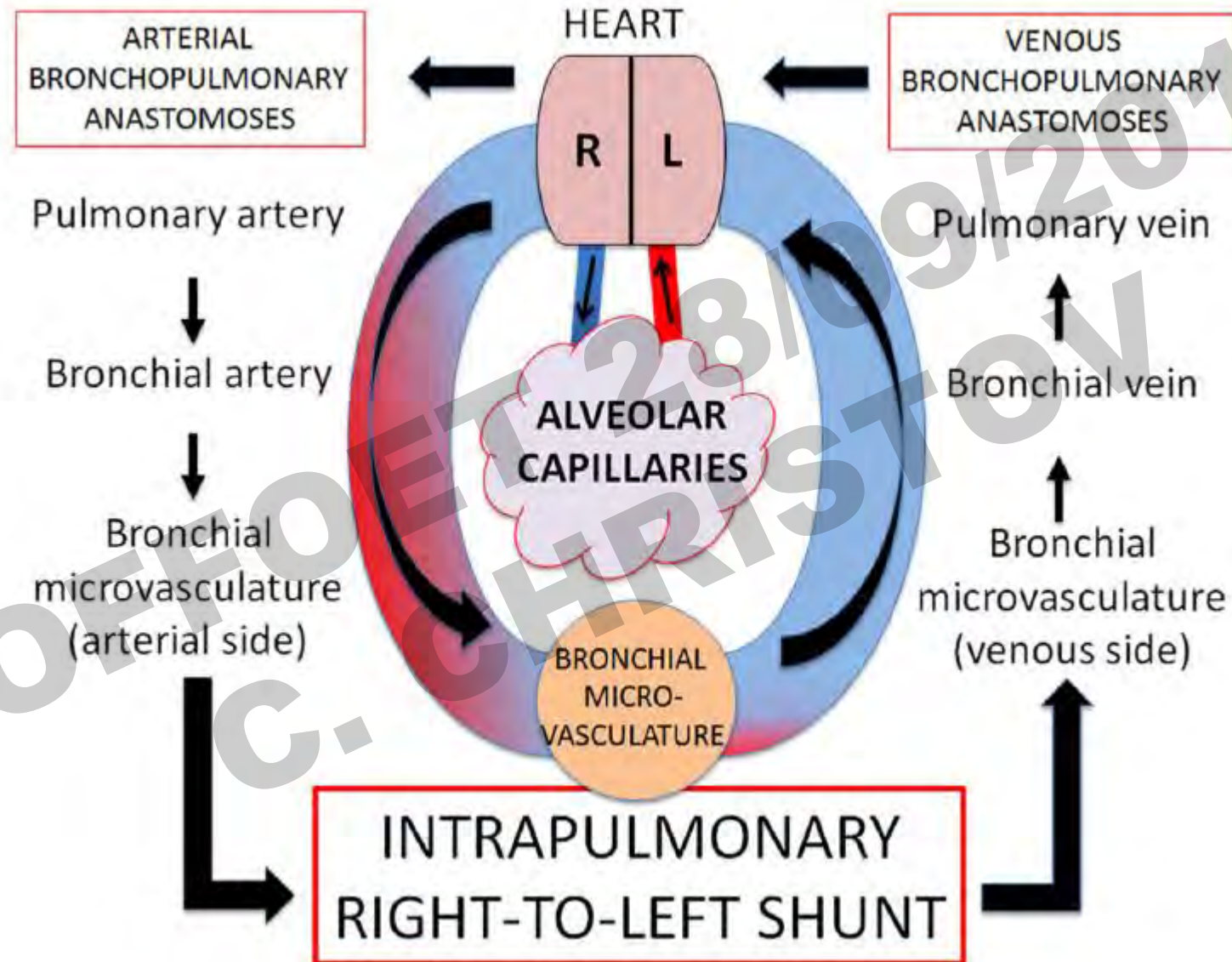


*Galambos et al. Thorax. 2015;70:84-5.*

*Galambos et al. J Pediatr. 2014;164:192-5.*



## Shunts (2): general scheme



# Epidemiology

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# Epidemiology

- 200 cases (probably an underestimate)
- mature term infants normal weight and Apgar scores 95%
- male infants 60%
- familial cases on record
- associated anomalies
- diagnosis: autopsy is the gold standard

## Summary 40 cases: male (60%), term gestation (96%)

Table 1

Clinical and pathological features of the reported cases of alveolar capillary dysplasia

Features	Percent
Male	60
Term gestation	96
Family history	12
Respiratory distress	100
Onset of the disease: at 24 h of age	52
at 2–6 weeks of age	14
Associated anomalies:	
Gastrointestinal tract anomalies	40
Genitourinary system anomalies	32
Cardiovascular system anomalies	16
Phocomelia	8
Diaphragmatic hernia	4
Diagnosis at autopsy	97
Diagnosis by biopsy	9
Diffuse involvement of the lung	85
Focal involvement	15
Mortality	100

*Al-Hathlol et al. Early Human Development 2000; 57: 85 –94*

## Summary 40 cases: family history (12%)

Table 1

Clinical and pathological features of the reported cases of alveolar capillary dysplasia

Features	Percent
Male	60
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Diffuse involvement of the lung	85
Focal involvement	15
Mortality	100

*Al-Hathlol et al. Early Human Development 2000; 57: 85 –94*

## Summary 40 cases: diagnosis at autopsy: 97%

Table 1

Clinical and pathological features of the reported cases of alveolar capillary dysplasia

Features	Percent
Male	60
Term gestation	96
Family history	12
Respiratory distress	100
Onset of the disease: at 24 h of age	52
at 2–6 weeks of age	14
Associated anomalies:	
Gastrointestinal tract anomalies	40
Genitourinary system anomalies	32
Cardiovascular system anomalies	16
Phocomelia	8
Diaphragmatic hernia	4
<u>Diagnosis at autopsy</u>	<u>97</u>
Diagnosis by biopsy	9
Diffuse involvement of the lung	85
Focal involvement	15
Mortality	100

*Some studies claim a 85% successful biopsy lung biopsy rate (Eulmesekian et al. J Perinat Med 2005; 33: 347–52.)*

## Summary 40 cases: GIT (40%), GUS (32%), CV (16%)

Table 1

Clinical and pathological features of the reported cases of alveolar capillary dysplasia

Features	Percent
Male	60
Term gestation	96
Family history	12
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*Al-Hathlol et al. Early Human Development 2000; 57: 85 –94*

**TABLE 2. EXTRAPULMONARY ANOMALIES ASSOCIATED WITH ALVEOLAR CAPILLARY DYSPLASIA WITH MISALIGNMENT OF THE PULMONARY VEINS**

System	Examples (References)
Gastrointestinal	<p>Intestinal malrotation (10, 14–16, 30, 34, 46, 63)</p> <p>Esophageal atresia (14)</p> <p>Tracheoesophageal fistula (14, 15)</p> <p>Anal atresia (14, 51)</p> <p>Absent gallbladder (10, 14, 29, 34)</p> <p>Postpyloric ectasy of the small intestine (34, 64)</p> <p>Omphalocele (23)</p> <p>Duodenal stenosis (14, 21, 34, 63)</p> <p>Meckel diverticulum (34, 59)</p> <p>Arteriovenous malformation of the liver (cavernous hemangioma) (10, 20)</p> <p>Volvulus of the small bowel (34, 63)</p> <p>Total absence or decreased number of ganglionic cells of the colon (10, 14, 15, 39, 63)</p> <p>Redundant colon (14, 15, 34, 63)</p> <p>Imperforate anus (10, 14, 20, 34)</p> <p>Annular pancreas (14, 30, 34)</p> <p>Asplenia (14, 22, 34, 43)</p>
Urogenital	<p>Bilateral ureteropelvic junction obstruction with hydronephrosis (9, 10, 34)</p> <p>Bilateral hydronephrosis, posterior urethral valves (10, 15, 34, 63)</p> <p>Bladder hypertrophy (10)</p> <p>Hydroureter (10)</p> <p>Stenosis of the distal ureters with hydronephrosis (34, 37, 65)</p> <p>Bicornuate uterus (8, 34, 63, 66)</p> <p>Cryptorchidism (9, 15, 34)</p>
Cardiovascular	<p>Hypoplastic left heart syndrome, left outflow tract stenosis (10, 34, 40, 44)</p> <p>Bicuspid aortic valve (21, 40)</p> <p>Patent ductus arteriosus (43, 44)</p> <p>Atrial septal defect (10, 43, 44)</p> <p>Atrioventricular septal defect, quadricuspid pulmonary valve (40)</p> <p>Pulmonary valvular and subvalvular stenosis (43)</p> <p>Malfomed mitral and tricuspid valves (10, 59)</p> <p>Retrosophageal subclavian artery (34, 63)</p> <p>Continuation of the left superior vena cava with the coronary sinus (18, 34)</p> <p>Absent right umbilical artery (34)</p> <p>Cor triatriatum, nonobstructive (10, 34, 43, 46)</p>

## Associated anomalies

***Bishop et al. Am J Respir Crit Care Med. 2011; 184: 172-9.***



## Typical cases

- onset respiratory distress syndrome: birth-48h
- survival:  $\approx$  4 weeks

## Typical case presentation

- disease-free interval <24h, < 48h
- rapid onset respiratory distress syndrome
- hypoxia, hypoxemia, acidosis
- pulmonary arterial hypertension (PAH)
- death within weeks

*Slot et al. Pulmonary Circulation 2018; 8: 2045894018795143*

# 18 typical and 2 atypical cases

Table I. Phenotypic data on 23 study subjects with ACD

Subject	Gestational age	Birth weight (g)	Sex	Age at respiratory distress	Suspected diagnosis of ACD <sup>‡</sup>	Expired	Associated anomaly <sup>†</sup>
1	Term	‡	F	Birth	Yes at 6 d	22 d	Yes
2	40 wk	‡	F	22 d	Yes at 26 d	27 d	No
3	‡	‡	M	12 h	No	40 d	Yes
4	38 3/7 wk	4270	F	24 h	Yes at 5 d	7 d	Yes
5	38 6/7 wk	3017	M	12 h	No	22 d	Yes
6	39 wk	LGA	M	1 h	Yes at 7 d	10 d	Yes
7	38 wk	3295	M	Birth	No	4 d	Yes
8	40 wk	‡	M	20 min	Yes at 14 d (biopsy)	17 d	Yes
9	Term	3600	F	10 h	No	2 d	Yes
10	39 wk	‡	M	2 h	Yes at 19 d (biopsy)	22 d	Yes
11	Term	3850	F	Birth	No	5 d	Yes
12	Term	‡	F	<12 h	No	9 d	Yes
13	32 wk	‡	M	Birth	No	10 d	Yes
14	36 4/7 wk	3120	F	Birth	No	33 d	No
15	Term	‡	M	12 h	Yes at age unknown	12 d	No
16	41 wk	2790	F	20 h	No	19 d	No
17	Term	2900	M	20 h	Yes at 15 d (biopsy)	21 d	Yes
18	Term	3595	F	9 d	No	30 d	Yes
19*	N/A	N/A	F	N/A	No	N/A	N/A
20	Term	‡	M	Birth	Yes at birth	87 d	Yes
21	Term	3460	F	24 h	Yes at birth	113 d	Yes
22	38 wk	3267	F	Birth	No	14 d	Limited autopsy, N/A
23	Term	‡	F	?	No	16 d	Yes
24	Term	2435	M	?	No	?	Yes

## **“Atypical” cases:**

- **onset respiratory distress syndrome: 5-28 weeks**
- **survival: 12-250 weeks**

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## Onset: 12-28 weeks; survival: 28-250 weeks

Ages at presentation	EGA (wk)	Sex	Family history	Neonatal symptom	Histology	FOXF1 sequencing	Outcome	Authors
5 weeks	Term	Female	Male sibling with ACDMPV	Cyanosis and respiratory distress after birth, episode of tachypnea and lethargy, discharge home at 10 days	Capillaries of alveolar septa did not reach alveolar epithelium, muscularization of peripheral arterial branches, misalignment of the pulmonary veins, dilated lymphatics	NR	Death at 5 weeks	Abdallah et al <sup>7</sup>
4 weeks	NR	NR	NR	None	Alveolar capillary dysplasia	NR	Death during hospital course	Michalsky et al <sup>5</sup>
7 weeks	Term	Female	NR	None	Malalignment of pulmonary veins, paucity of alveolar capillaries, prominent muscularization of arterioles, thickening of alveolar septa, widened interstitium	NR	<u>Death at 4 months</u>	Shankar et al <sup>8</sup>
7 months	Term	Female	NR	Cyanotic episode after birth, received 0.1 L/min oxygen for 1 days, mild pulmonary hypertension on echocardiogram	Small pulmonary lobules, few normally positioned capillaries, muscularized small arterioles, misalignment of the pulmonary veins, patchy lymphatic dilation	NR	<u>Death at 7-8 months</u>	Ahmed et al <sup>4</sup>
3 months	Term	Male	Negative	None	Misalignment of the pulmonary veins, thick alveolar walls with poor alveolar capillary development, several normal alveolar walls	c.899Tdel p.L300Rfs*79 <i>de novo</i>	Alive at 38 months per manuscript, <u>alive at 62 months of age*</u>	Ito et al <sup>9</sup>

***Towe et al. J Pediatr. 2018; 194: 158-164.***

## Onset: 12-28 weeks; survival: 60-80 weeks

Patients	EGA (wks)	Age at presentation	Age at transplantation (mo)
1	Term	<u>3 months</u> (109 days)	4
2	Term	Birth	<u>20</u>
3	36	2 months (71 days)	5
4	34	2 months (67 days)	5
5	34	3 months (92 days)	9
6	Term	7 months (212 days)	<u>15</u>

*Towe et al. J Pediatr. 2018; 194: 158-64.*

## Onset: 12-28 weeks; survival: 120-190 weeks

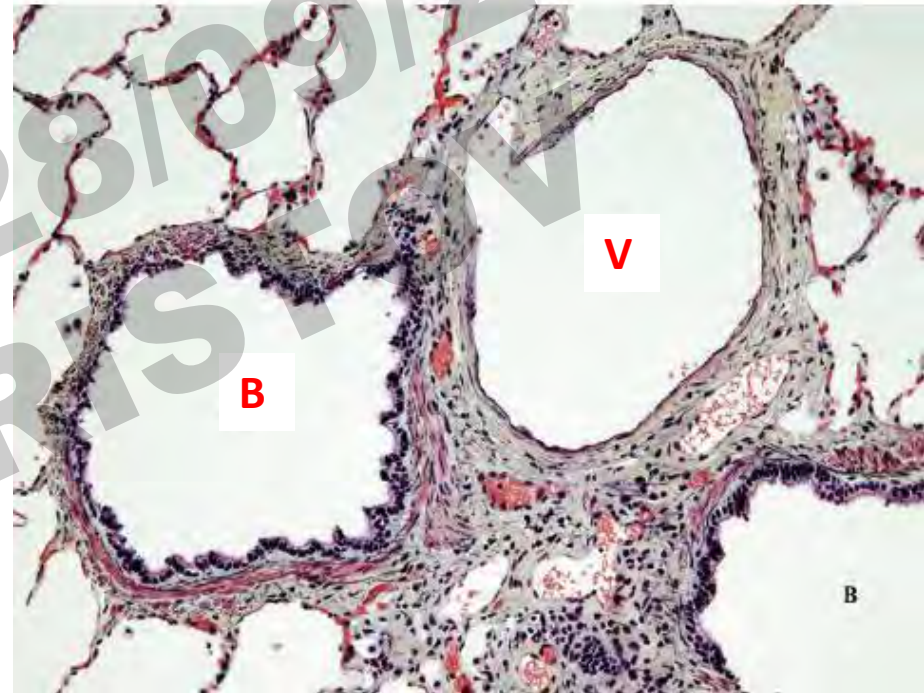
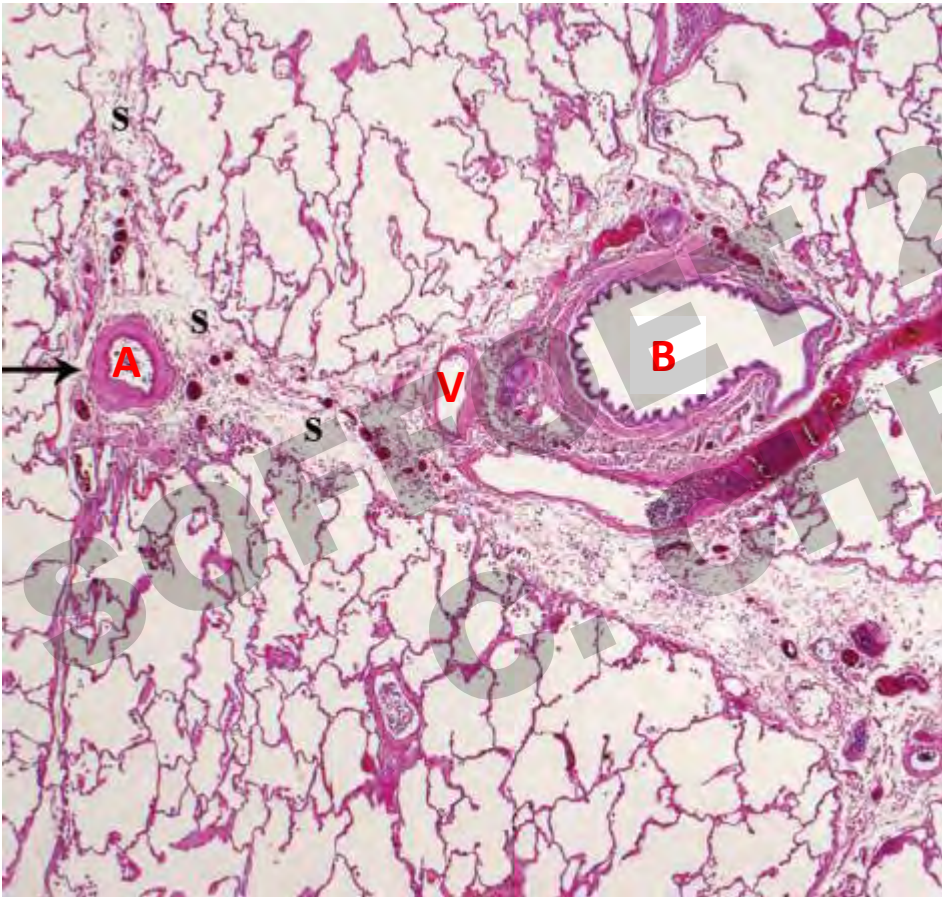
Final classification	Capillary apposition	Capillary density	PAH preacinar	PAH acinar	MPV	ICC	Type 2 cell hyperplasia	Alveolar density	Outcome (age at last f/up or death)
CAD	5	6	3	4	2	0	1	2-3	DoD
CAD	5 (focal 2)	5 (focal 2)	2-3	3-4	1	2	2	4	<u>Alive (4 years)</u>
CAD	5	5	2	3	0	4	2	2-4	DoD (1 month)
CAD	5-6	5-6	1-2	1-2	0	2	2	2-4	DoD
CAD	5-6	5-6	2	3	0	1	1	1-2	DoD (6 months)
CAD	5	5	2	2	2	3	2	2-4	<u>AwD (2.5 years)</u>

*Melly et al. Histopathology 2008, 53, 450-7.*

## CASE REPORT

# Misplaced pulmonary arteries in an adult patient with pulmonary hypertension

<sup>1</sup>G B MARSHALL, MD, FRCP(C), <sup>1</sup>C I S SILVA, MD, PhD, <sup>2</sup>J C ENGLISH, MD, FRCP(C), <sup>3</sup>R D LEVY, MD, FRCP(C) and <sup>1</sup>N L MÜLLER, MD, PhD, FRCP(C)



- A = artery
- B = bronchiole
- V = vein



## Comparison

	Typical cases	Atypical cases n ≈ 14
Onset	0 -48 hours	5-28 weeks
Survival	4 weeks	12-250 weeks

# **“Atypical” cases: histopathological hallmarks?**

- **patchy distribution of lesions**
- **capillary network abnormalities**

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# “Atypical” cases: histopathological hallmarks?

- **patchy distribution of lesions**
- capillary network abnormalities

## Patchy distribution of lesions

- often stated
- poorly documented
- atypical cases with diffuse distribution on record
- only one detailed study

*Histopathology* 1995, 27, 192-194

CASE REPORT

### **Misalignment of lung vessels and alveolar capillary dysplasia**

J.OLDENBURG, H.J.H.VAN DER PAL, L.S.SCHREVEL, A.P.R.BLOK &  
C.A.WAGENVOORT\*.

*Departments of Pathology, Academic Medical Centre, Amsterdam, and \*Erasmus University, Rotterdam, The Netherlands*

- 24 areas x 2 mm<sup>2</sup> from both lungs
- % muscularized arterioles
- % arteries associated with veins
- % misplaced veins
- A (n=9) mild, B (n=15) severe

CASE REPORT **n = 1**

## Misalignment of lung vessels and alveolar capillary dysplasia

J.OLDENBURG, H.J.H.VAN DER PAL, L.S.SCHREVEL, A.P.R.BLOK & C.A.WAGENVOORT\*.

*Departments of Pathology, Academic Medical Centre, Amsterdam, and \*Erasmus University, Rotterdam, The Netherlands*

Group	Alveolar capillary dysplasia	Average number per mm <sup>2</sup>		Percentage	
		Arteries	Veins	Arteries associated with veins	Misaligned veins
A	Mild	5.2	5.9	39	32
B	Severe	5.1	10.1	92	47

# “Atypical” cases: histopathological hallmarks?

- patchy distribution of lesions
- capillary network abnormalities
  - capillary density ↑↑↑
  - capillary juxtaposition ↑↑↑

## Capillary apposition and density in the diagnosis of alveolar capillary dysplasia **n = 6**

L Melly, N J Sebire,<sup>1</sup> M Malone<sup>1</sup> & A G Nicholson<sup>2</sup>

*Departments of Histopathology, Royal Free Hospital, <sup>1</sup>Great Ormond Street Hospital and <sup>2</sup>Royal Brompton Hospital, London, UK*

**Table 1.** Histological parameters scored in a semiquantitative fashion

---

Misalignment of veins: present (2), probably present (1), absent (0)

---

Septal development: normal/abnormal

---

Presence of clear cells in interstitium [0 (absent)–6 (abundant)]

---

Presence of type 2 cell hyperplasia [0 (absent)–6 (marked)]

---

Evidence of PAH in preacinar arteries [0 (absent)–6 (marked)]

---

Evidence of PAH in intra-acinar arteries [0 (absent)–6 (marked)]

---

Capillary density [0 (absent)–6 (normal)]

---

Capillary apposition [0 (absent)–6 (normal)]

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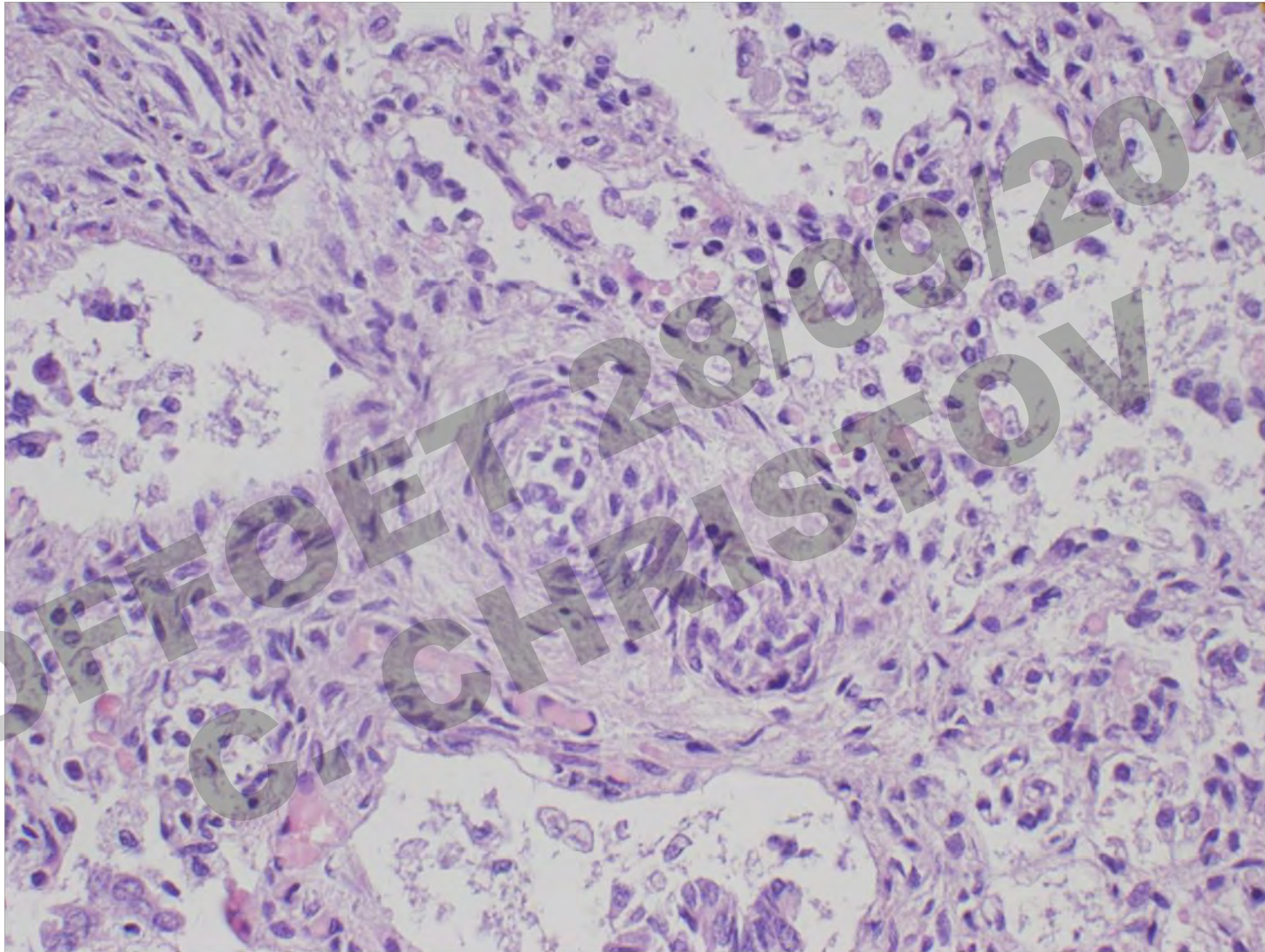
## Higher capillary density and more capillary forming an air/blood barrier may be crucial for longer survival

Final classification	Capillary apposition	Capillary density	PAH preacinar	PAH acinar	MPV	ICC	Type 2 cell hyperplasia	Alveolar density	Outcome (age at last f/up or death)
CAD	5	6	3	4	2	0	1	2-3	DoD
CAD	5 (focal 2)	5 (focal 2)	2-3	3-4	1	2	2	4	Alive (4 years)
CAD	5	5	2	3	0	4	2	2-4	DoD (1 month)
CAD	5-6	5-6	1-2	1-2	0	2	2	2-4	DoD
CAD	5-6	5-6	2	3	0	1	1	1-2	DoD (6 months)
CAD	5	5	2	2	2	3	2	2-4	AwD (2.5 years)

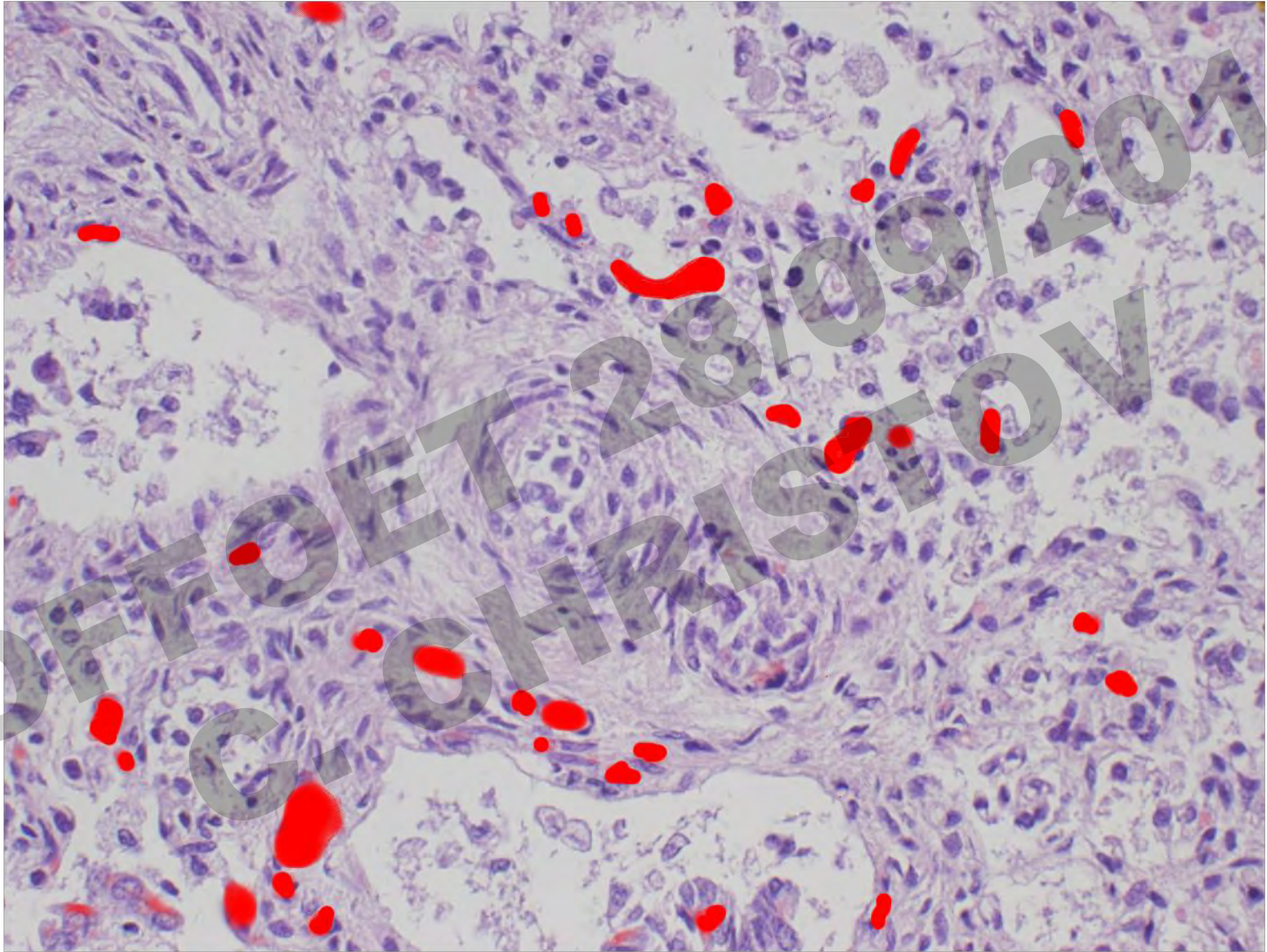
## A proposed study

- **N cases (10 – 20 ???)**
- **an endothelial cell immunohistochemical marker (CD34?)**
- **measure capillary density and % of apposed capillaries**
- **correlate with age of onset and survival**

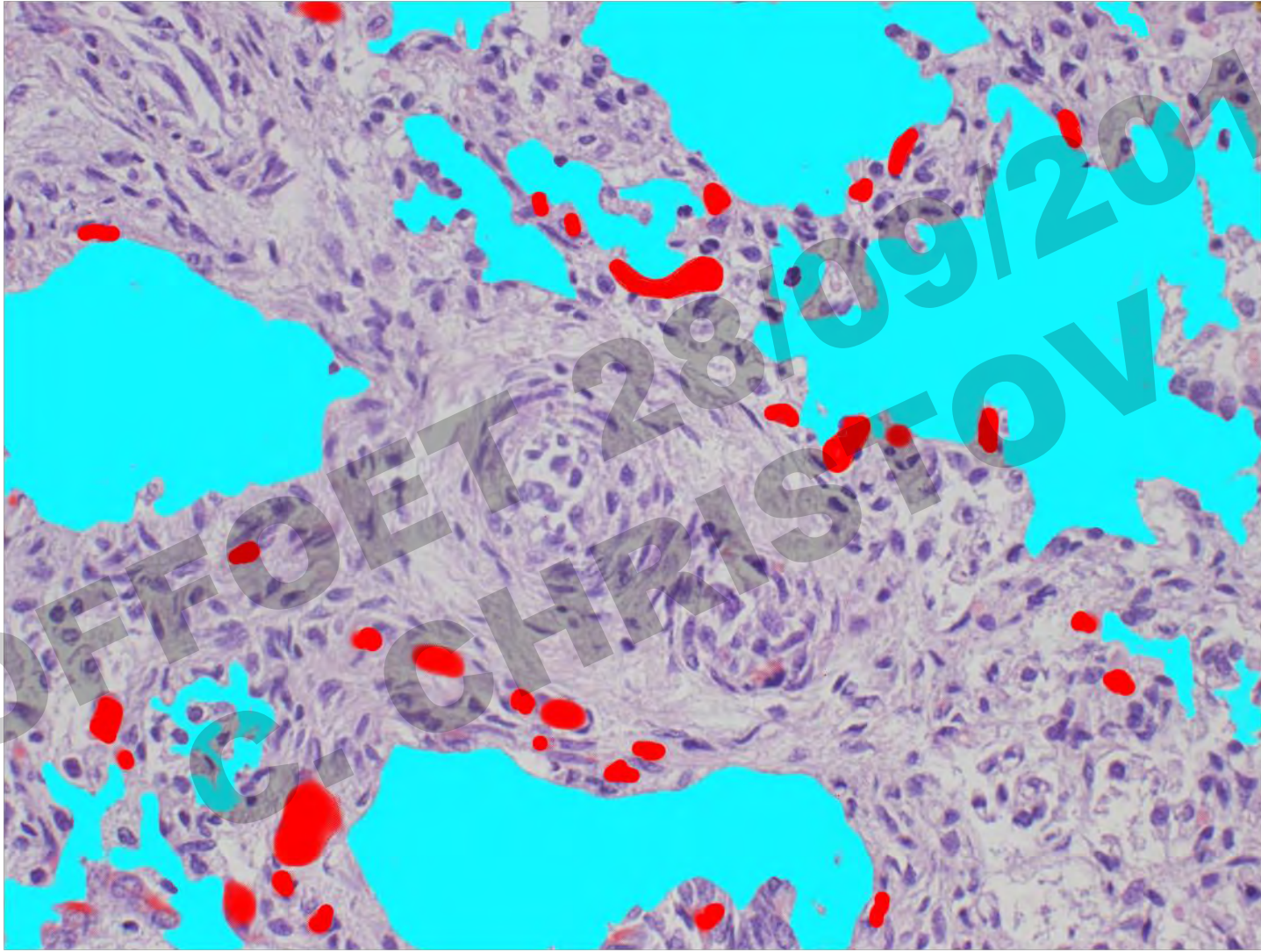
# Image



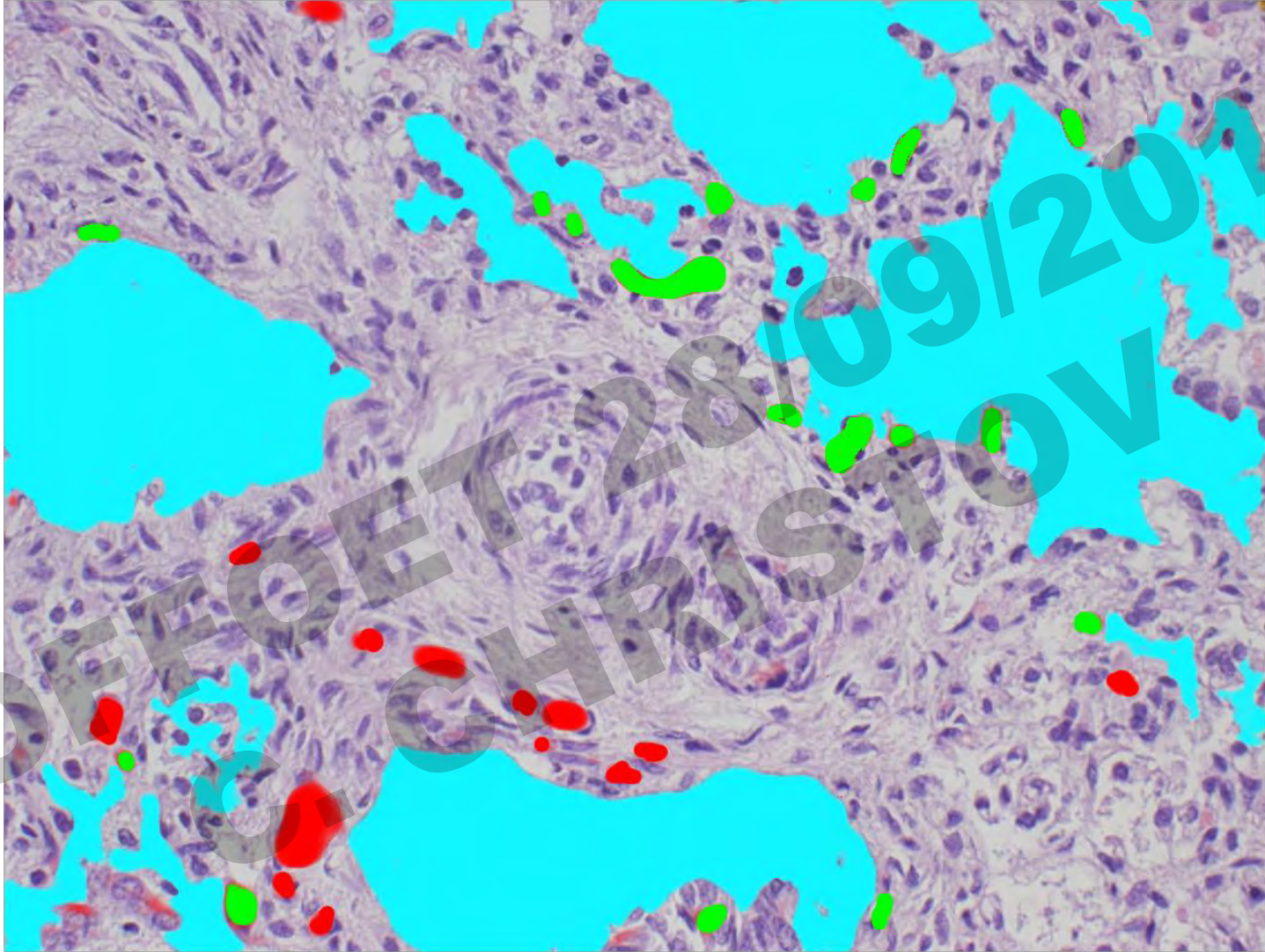
## Segment capillaries



## Segment air spaces



# Identify apposed capillaries potentially participating in gas exchanges



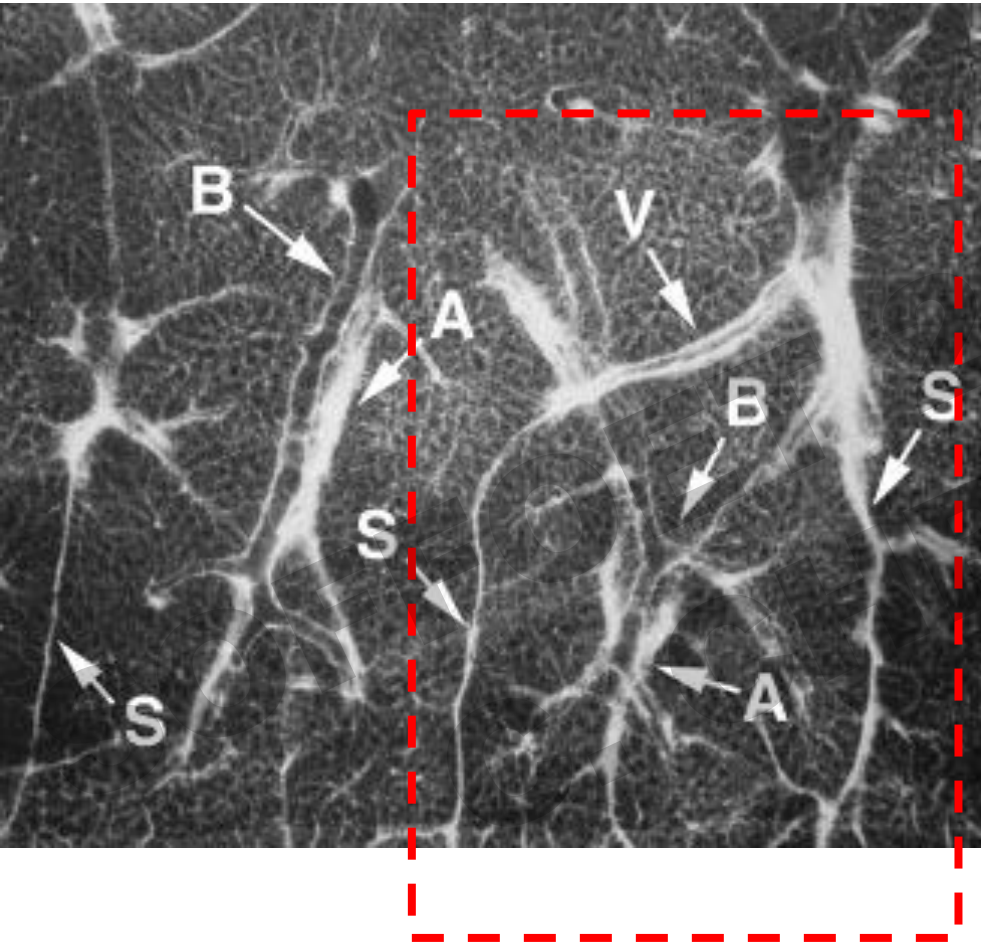
17: 50%, in this example

# **Anatomical note (1)**

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C. CHRISTOV

# CT: secondary pulmonary lobule

Webb WR. Thin-Section CT of the Secondary Pulmonary Lobule: Anatomy and the Image. The 2004 Fleischner Lecture. *Radiology* 2006; 239: 322-38.



- B = bronchiole
- A = arteriole
- V = vein
- S = septum

bronchiole + arteriole  
in central position

vein  
in delimiting septa



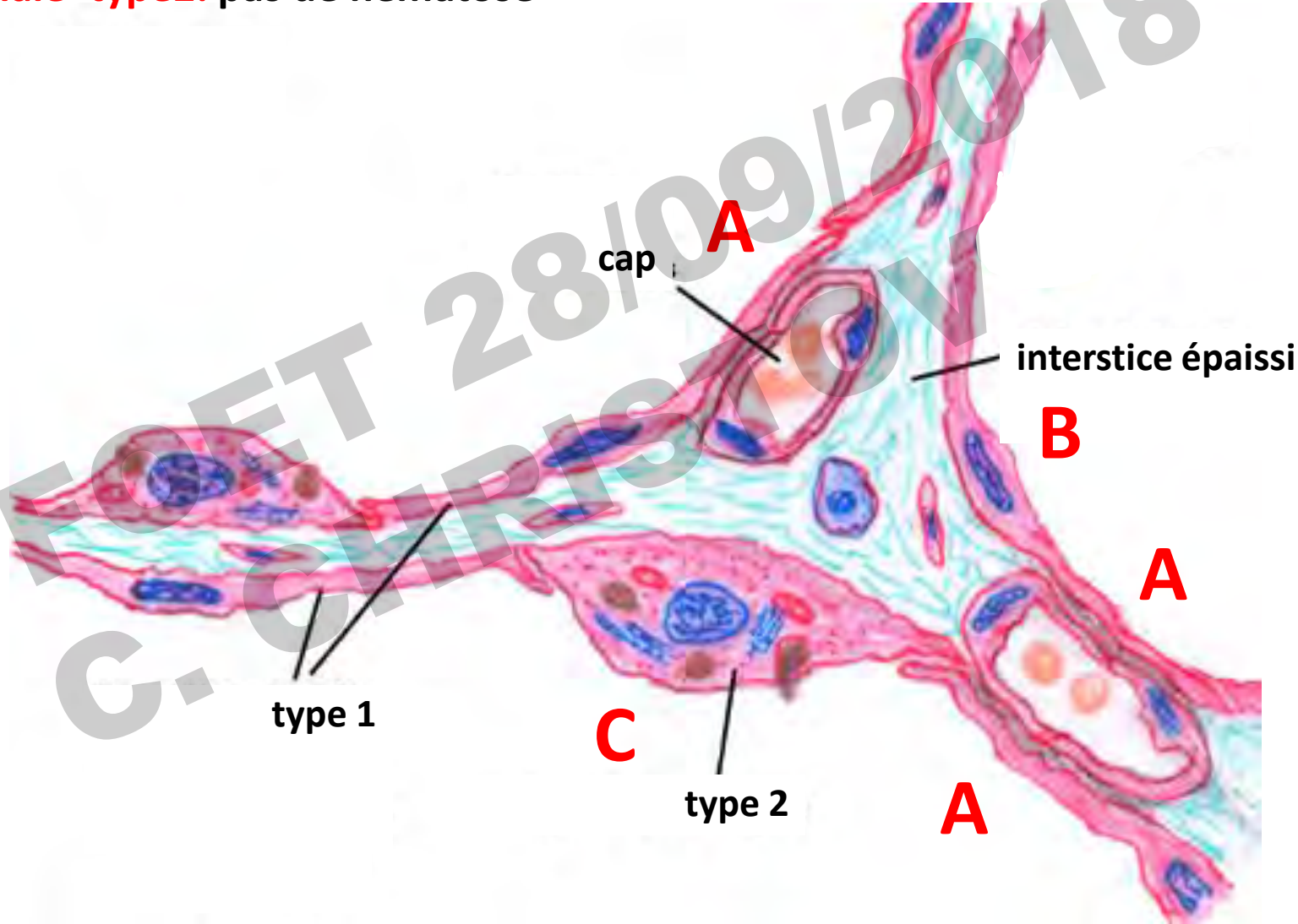
# **Anatomical note (2): the blood/air barrier**

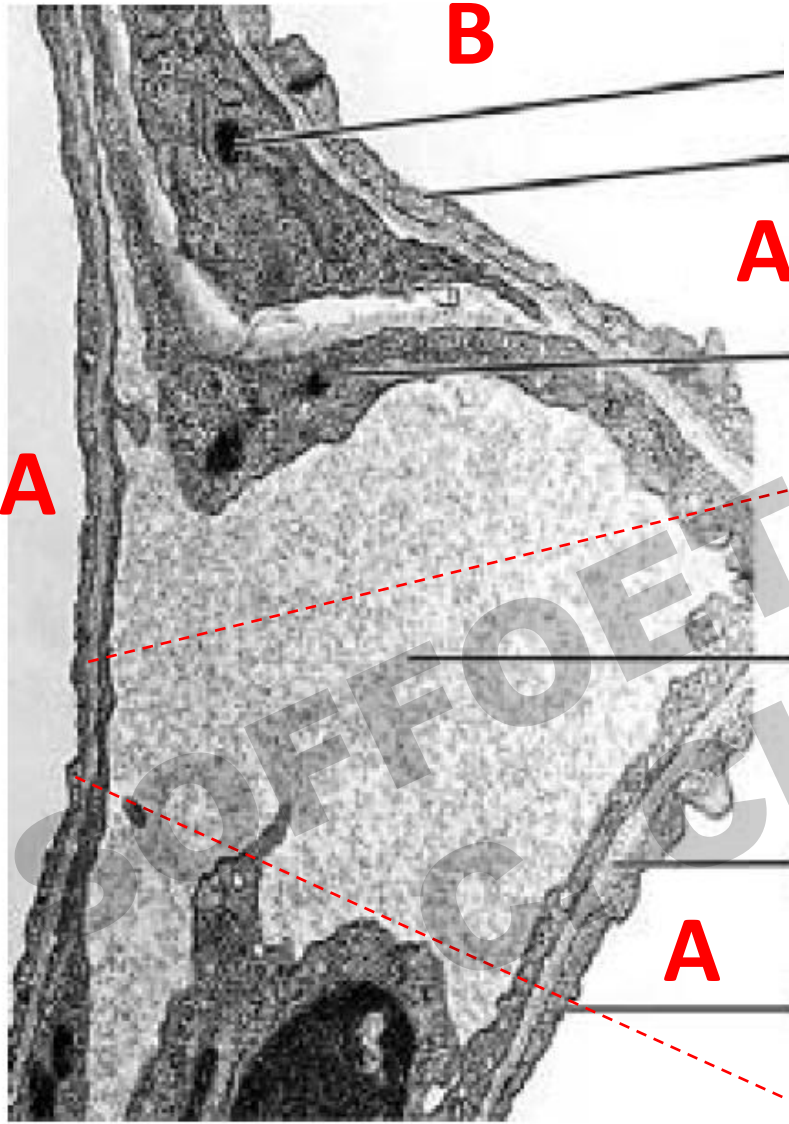
SOFFOET 28/09/2018  
C. CHRISTOV

**A = c. endothéliale+type1: lame basale commune, hématose**

**B = c. endothéliale+type1: interstice interposé, pas de hématose**

**C = c. endothéliale+type2: pas de hématose**





fibroblaste  
interstitiel

type 1

cellule  
endothéliale

capillaire

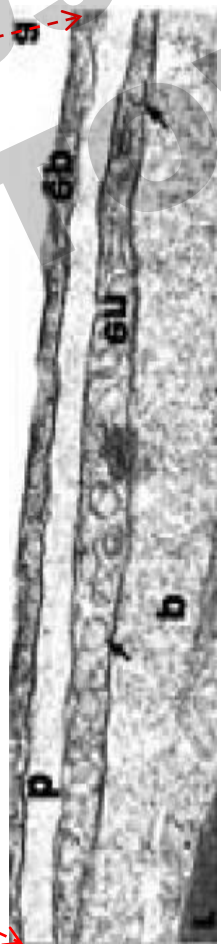
capillaire

type1

**A = c. endothéliale+type1:  
lame basale commune, hématoze**

**B = c. endothéliale+type1:  
interstice interposé, pas de hématoze**

< 0.5 μm

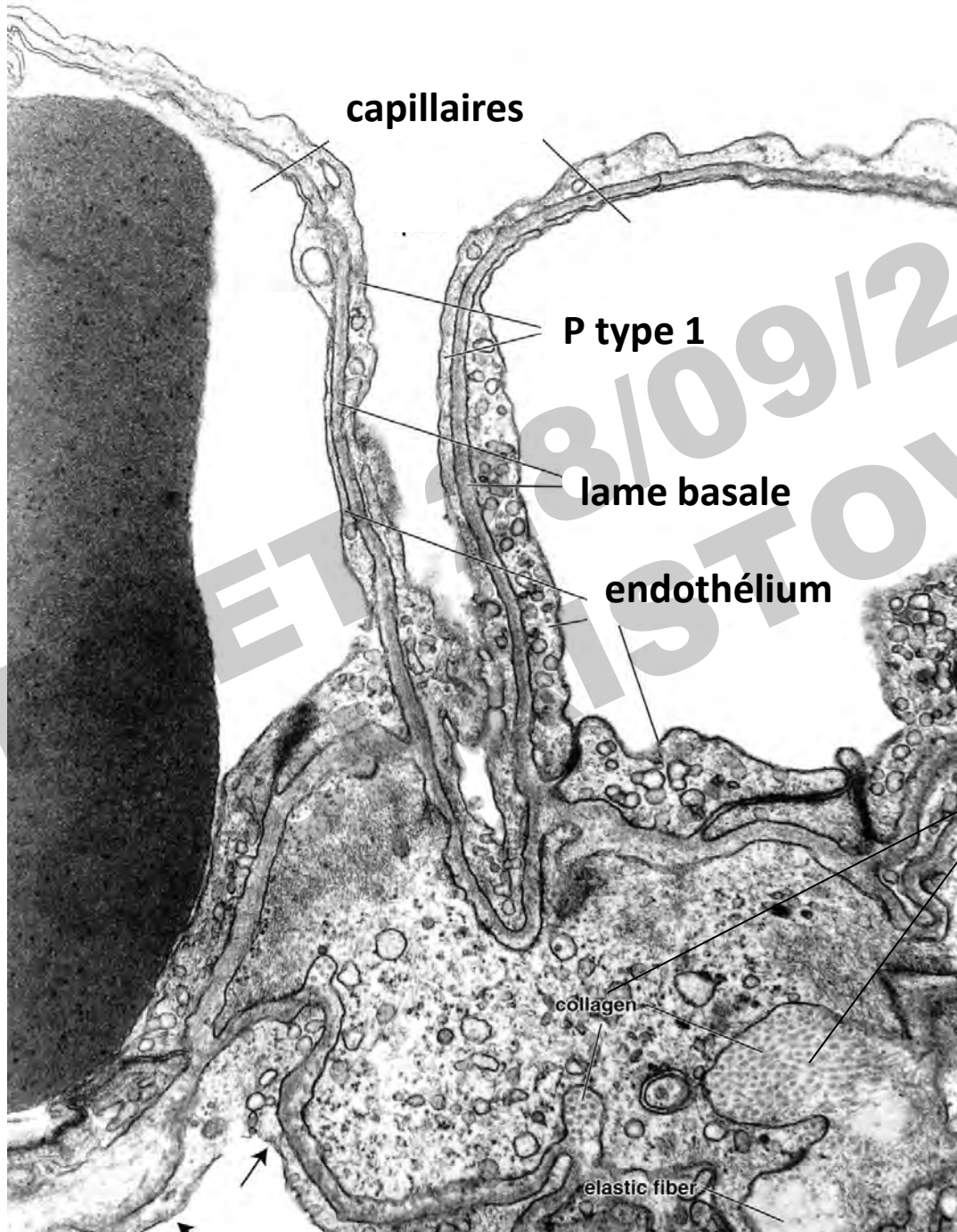


**A**

**B**

**A**

**A**



capillaires

P type 1

lame basale

endothélium

interstice:  
collagène,  
fibres élastiques

collagen

elastic fiber

SOFT ET 8/09/2018 HISTOV

## La barrière air/sang a 3 composantes qui permettent l'hématose



1 voile du pneumocyte 1

2 lame basale commune

3 cytoplasme de la cellule endothéliale

*Elle peut être très mince: 0.2  $\mu\text{m}$ ,  
solidité grâce aux fibres de collagène I*

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