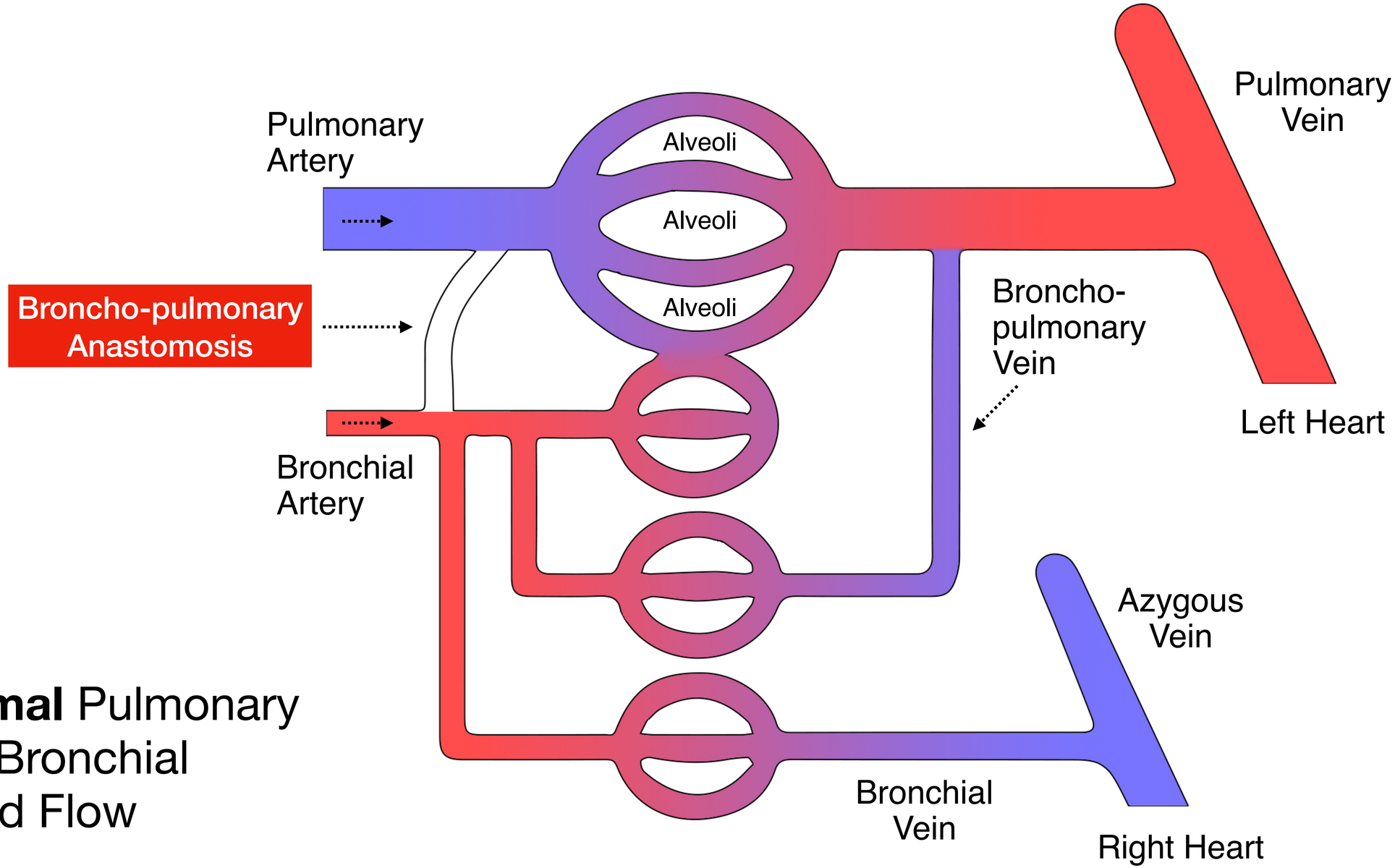
Farid Jalali MD / May 2020

In **Normal** Lung Circulation, Bronchopulmonary Anastomoses Do **Not** Have a Clinically Significant Role Unless Either Pulmonary or Bronchial Perfusion is Disturbed



Normal Pulmonary and Bronchial Blood Flow

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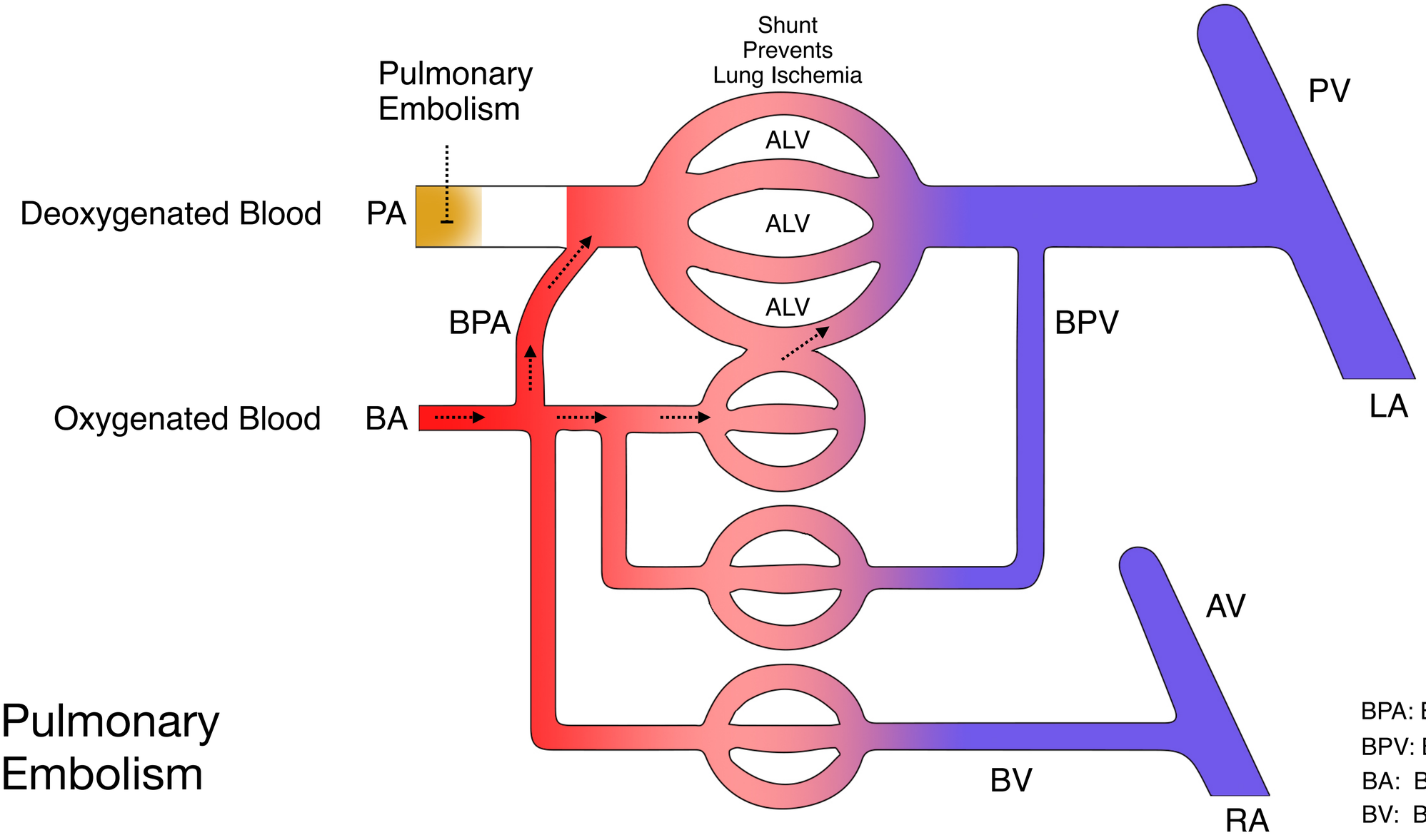
In Pulmonary Embolism, Bronchopulmonary Anastomoses (BPA) Allow **Diversion of Systemic Oxygenated Perfusion (Black Arrows)** from Bronchial to Pulmonary Circulation To **Prevent Lung Ischemia**

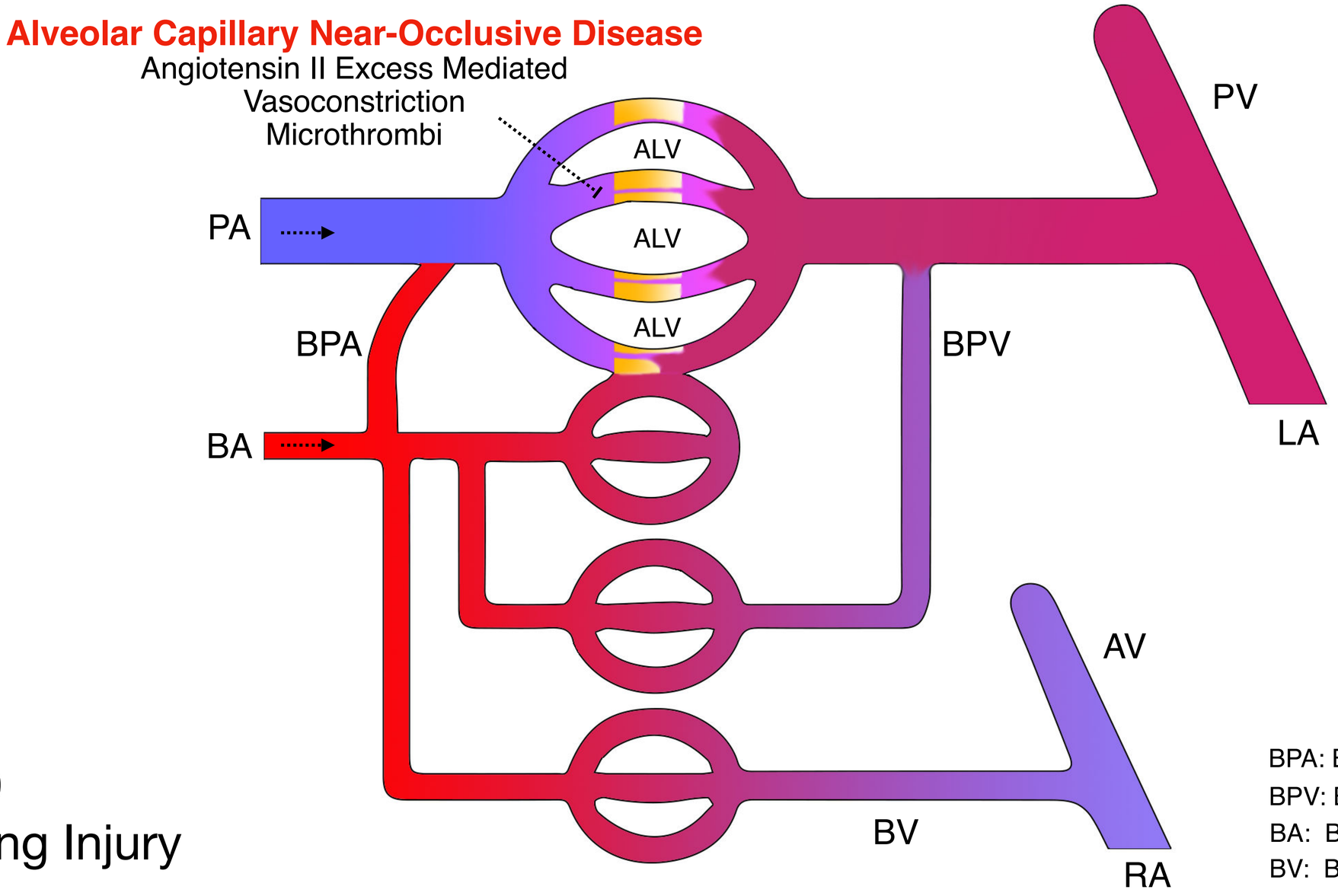


Pulmonary Embolism

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

Farid Jalali MD / May 2020

SARS-CoV-2 Action on Alveolar Capillary Endothelium Mediated by Ang II Excess Results in a Progressive **Alveolar Capillary Occlusive Disease**



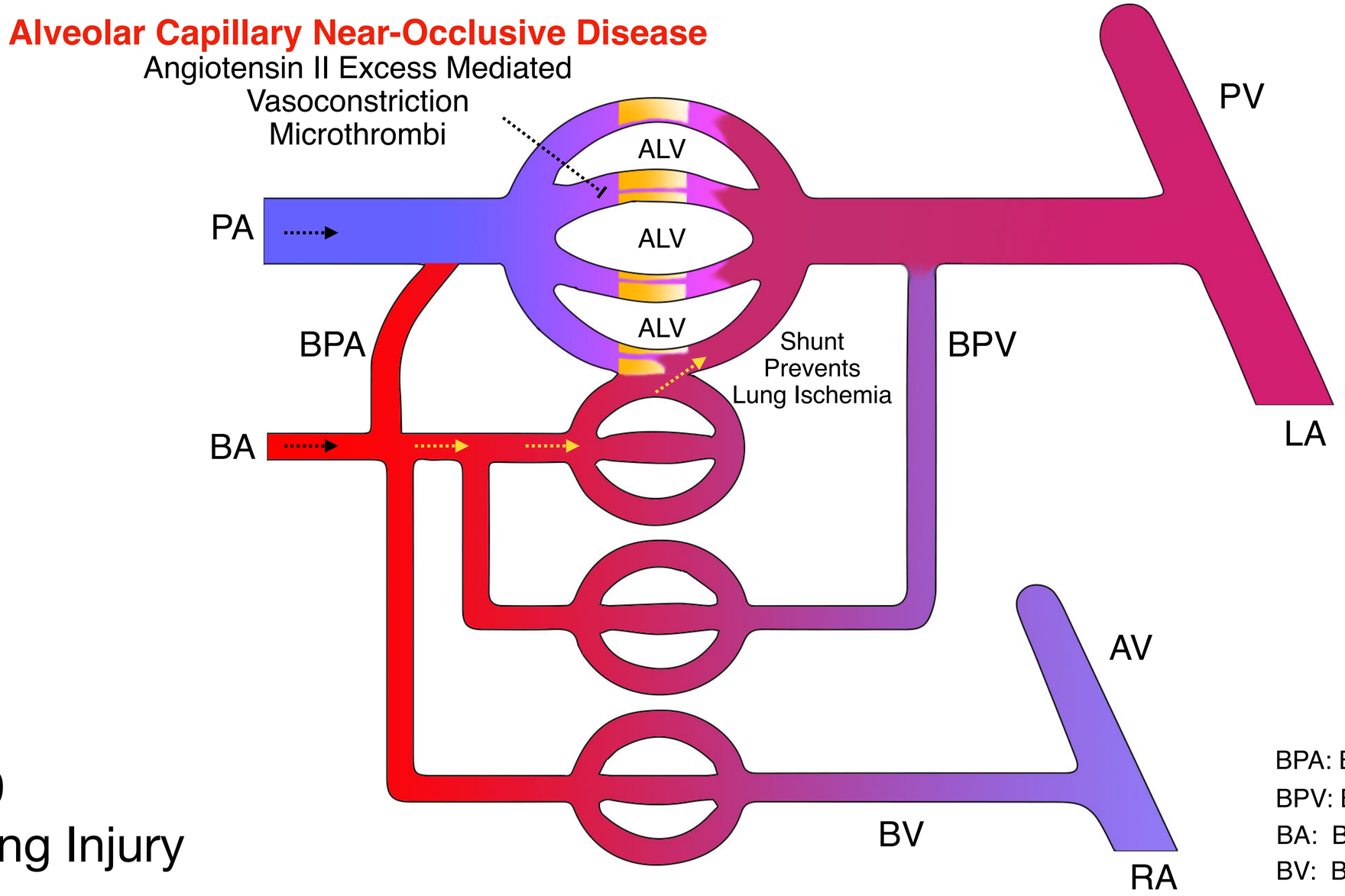
Step 1

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

Farid Jalali MD / May 2020

With Locally Impaired Pulmonary Circulation, **Bronchopulmonary Anastomoses**
Shunt Oxygenated Blood from **Bronchial** to **Pulmonary** Circulation Per **Yellow Arrows**



Step 2

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

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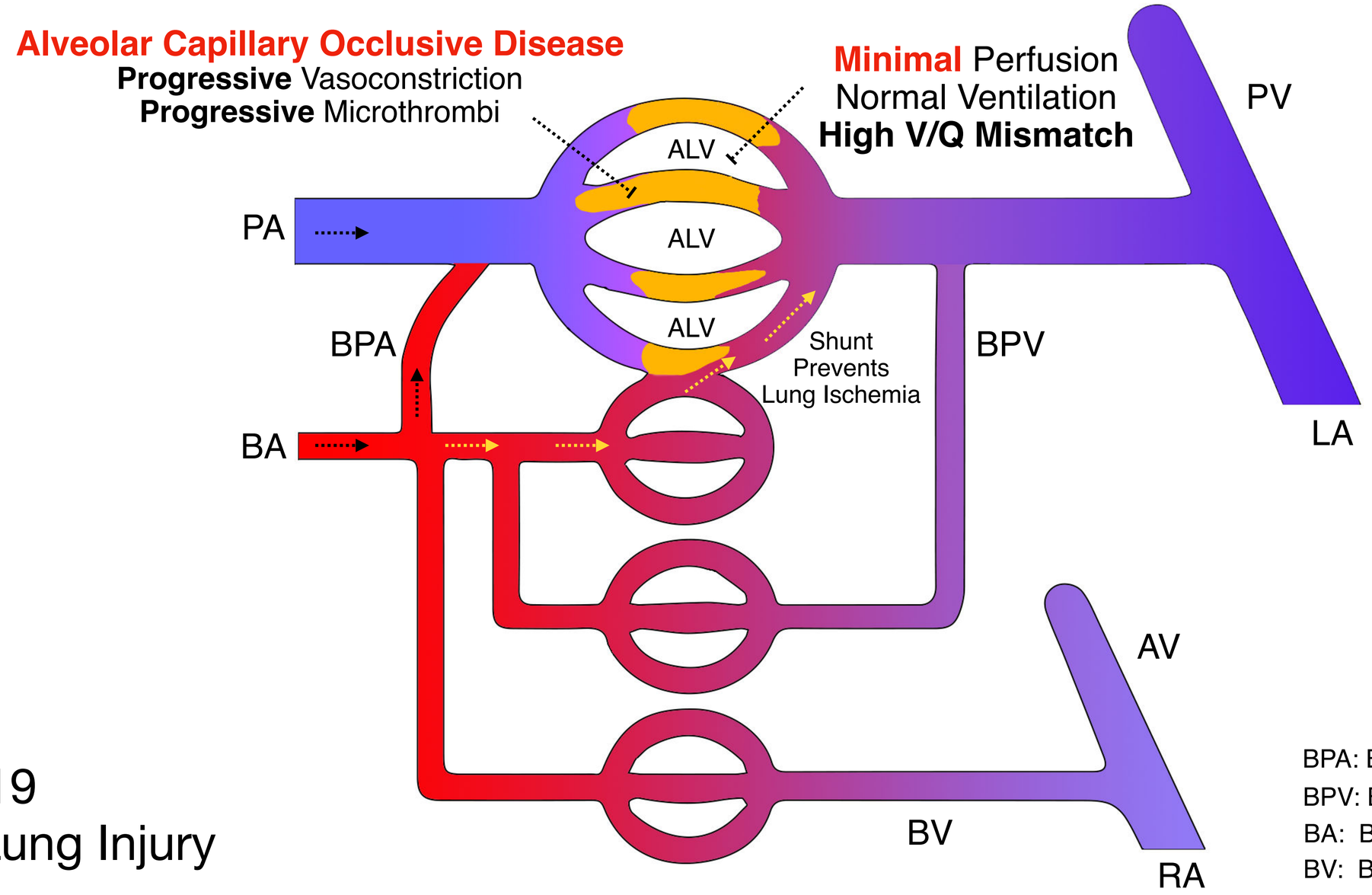
As Lung Endothelial Injury Worsens, Alveolar Capillary **Vaso-Occlusive** Disease Progresses, Resulting in Development of **Dead Space Ventilation**



Step 3

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

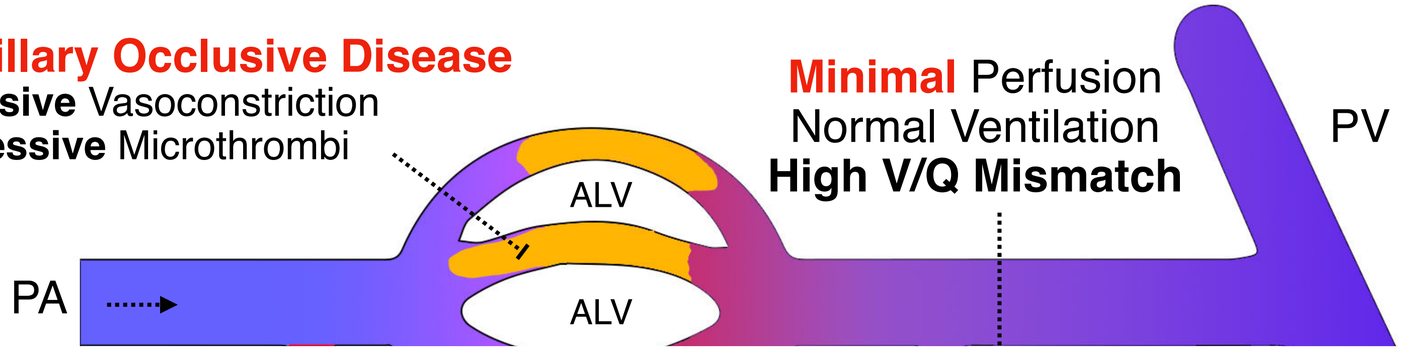
Farid Jalali MD / May 2020

As Lung Endothelial Injury Worsens, Alveolar Capillary **Vaso-Occlusive** Disease Progresses, Resulting in Development of **Dead Space Ventilation**

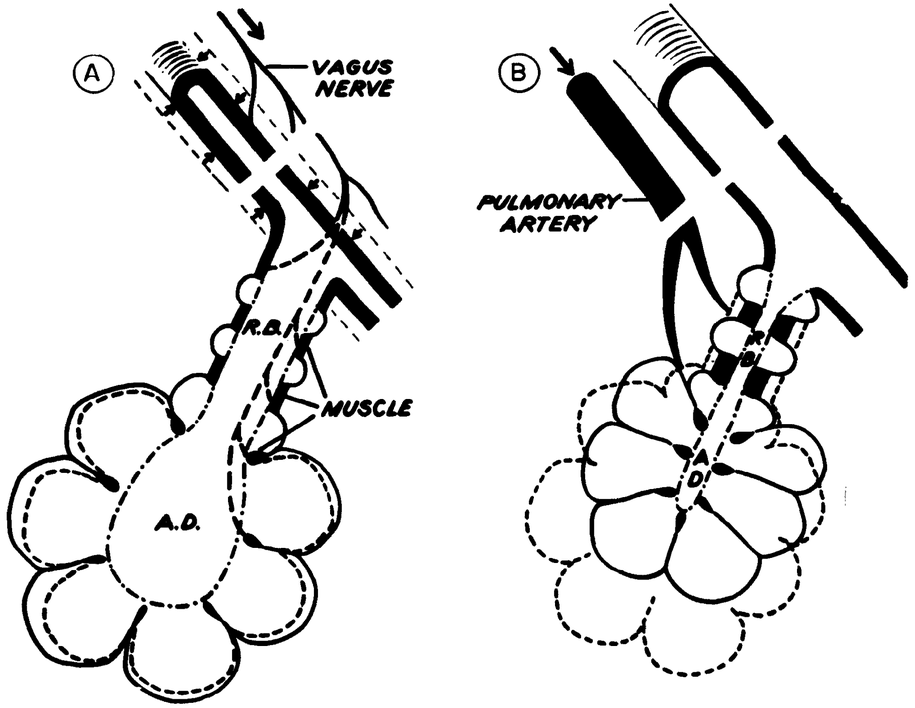
Step 4

COVID19
Acute Lung Injury

Alveolar Capillary Occlusive Disease
Progressive Vasoconstriction
Progressive Microthrombi



Minimal Perfusion
Normal Ventilation
High V/Q Mismatch



Dorsal Alveolar Hypocapnia

↓

Alveolar Duct Constriction

↓

V Redistribution To Areas with Less V/Q Mismatch

→

Ventral Alveolar Hypercapnia

↑

Alveolar Duct Dilation

↑

Preserved Overall Compliance

Protective Physiologic Response
To Avoid Overdistention of Alveoli with Poor Perfusion
To Avoid Further Injurious Capillary Vasoconstriction

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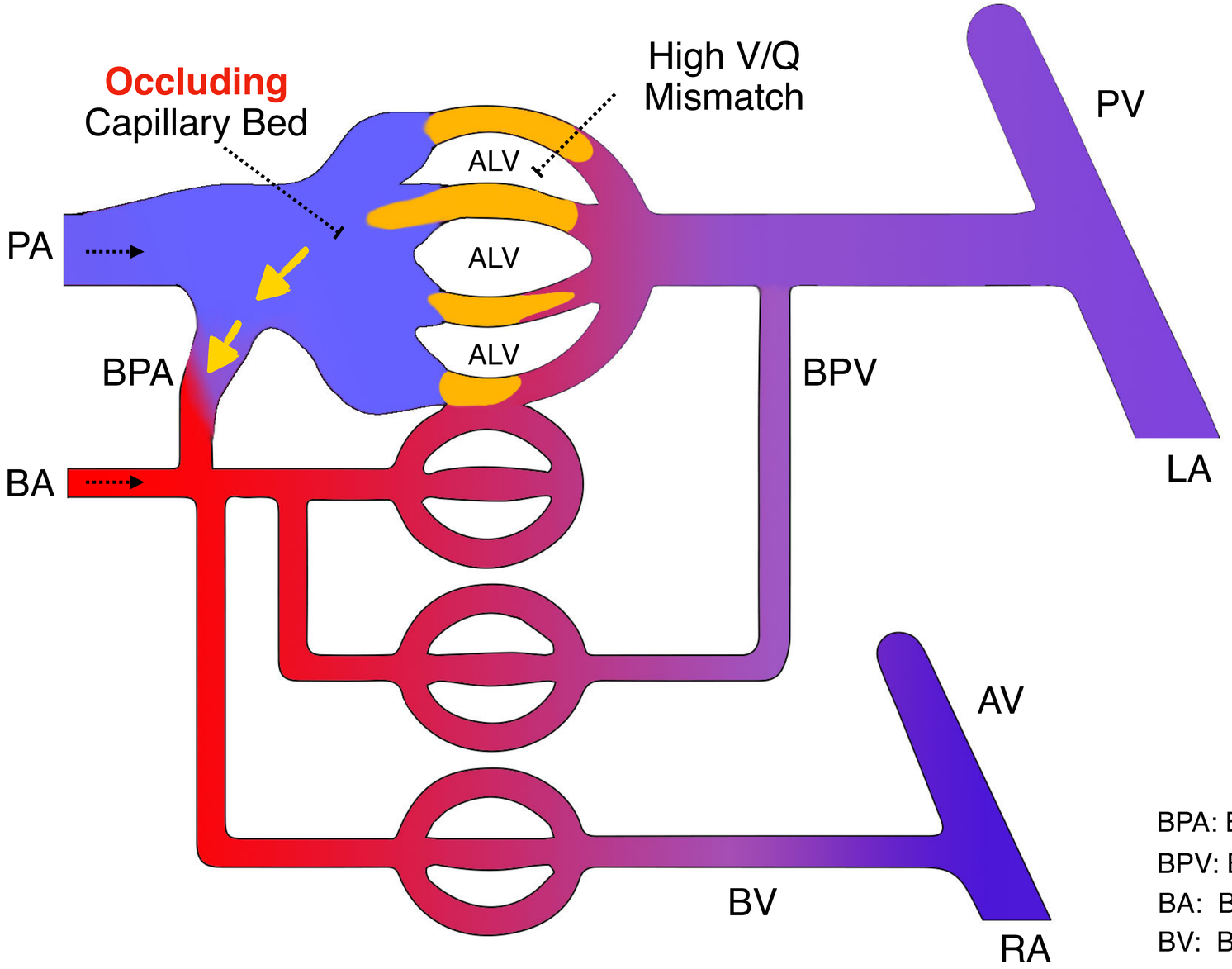
Progressive Occlusion of Alveolar Capillary Bed Results in **Backflow of Pulmonary Arteriolar Blood** across the **Bronchopulmonary Anastomoses** along **Yellow Arrows**



No Evidence of PAH due to Flow Diversion via BPA

Step 5

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

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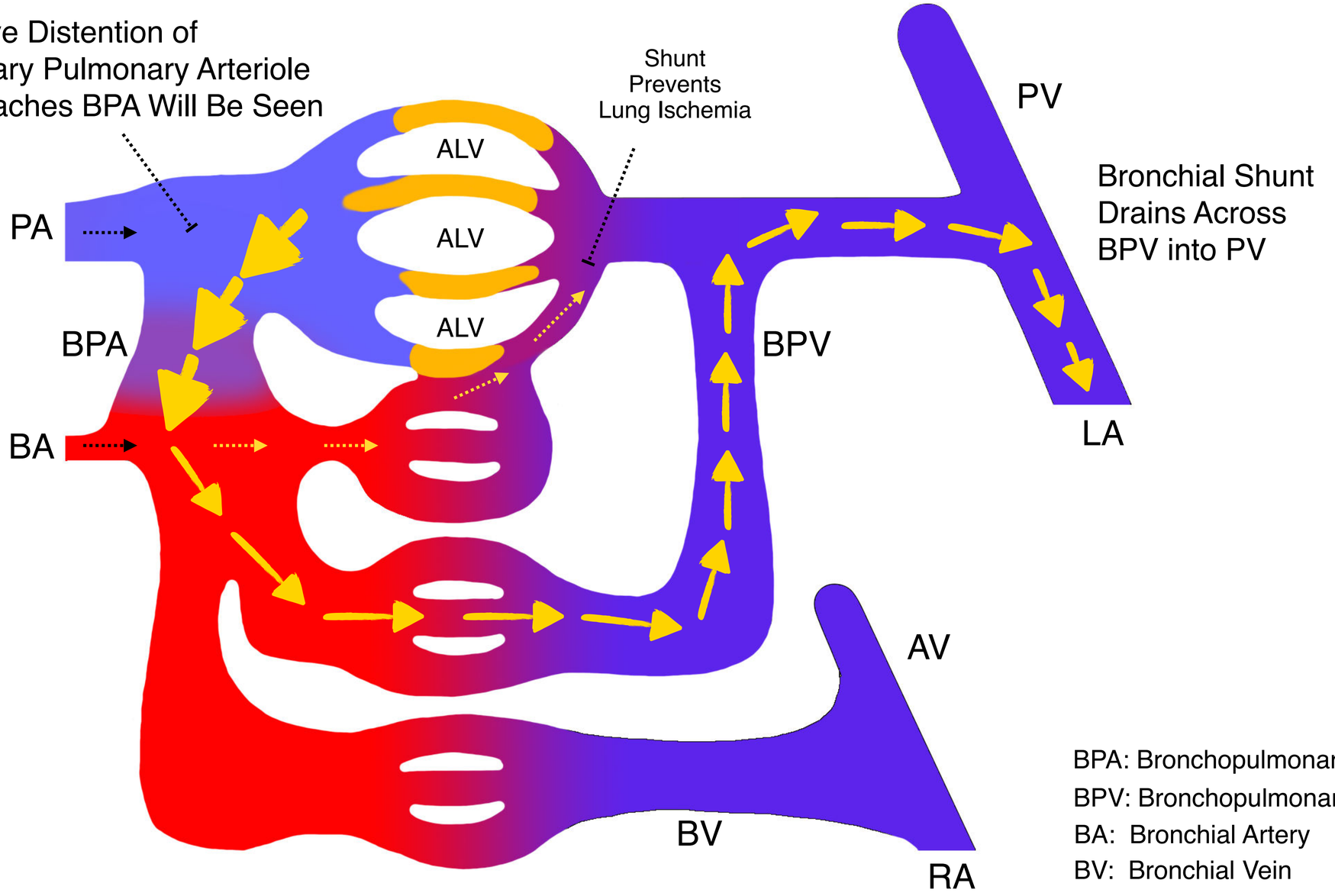
Progressive **Distention and Back Pressure Buildup** in the Direction of **Yellow Arrows**
Causing **Hyper-Perfusion** in the **Intrapulmonary Shunt** with **Low V/Q Mismatch**

Chest CTA

Progressive Distention of
Pre-Capillary Pulmonary Arteriole
Until It Reaches BPA Will Be Seen



Step 6

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

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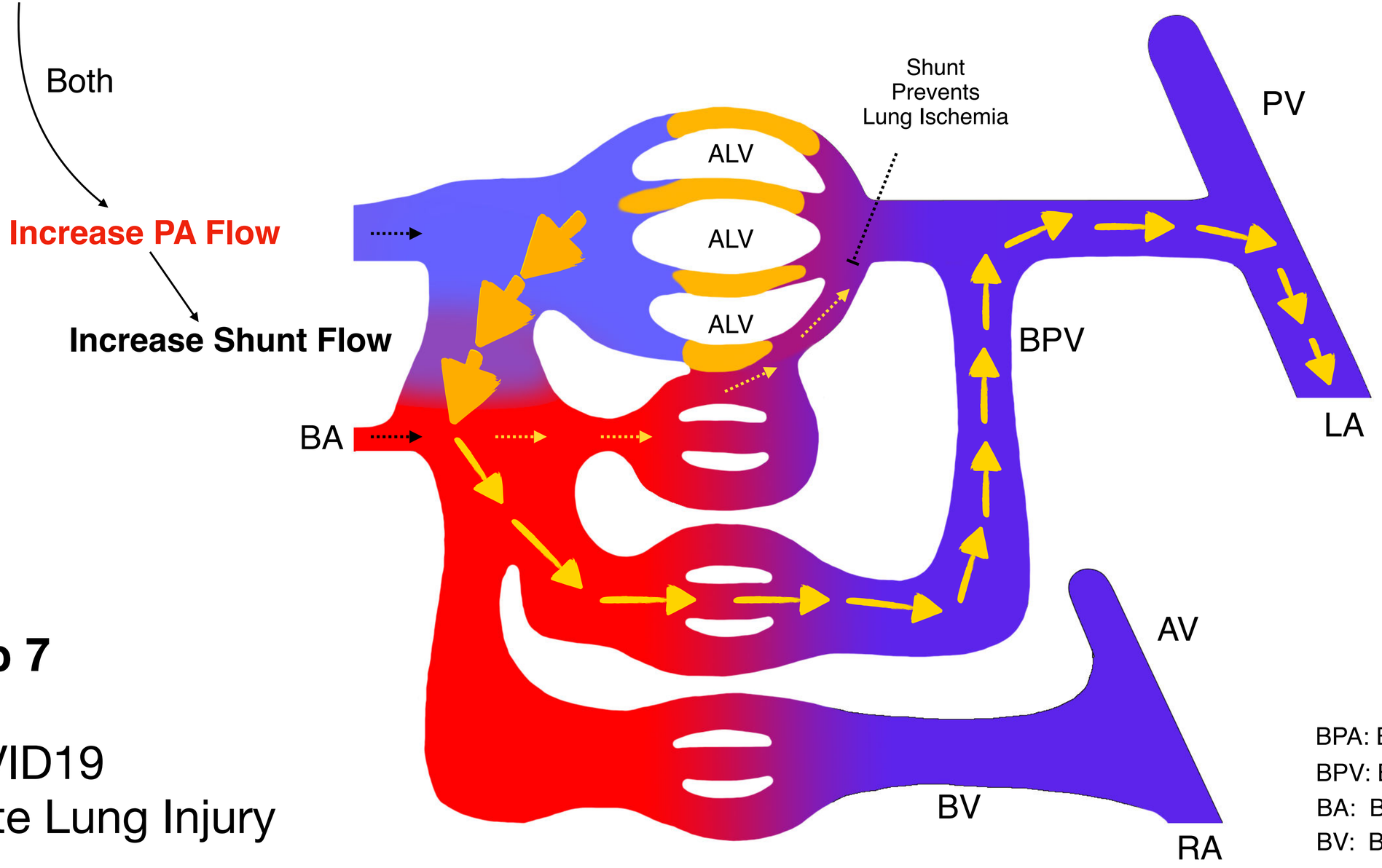
Factors That **Exacerbate** **Intrapulmonary Shunt** Physiology
Increased SVR: Valsalva, Systemic Vasoconstriction
Decreased PVR: Pulmonary Vasodilators



Step 7

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

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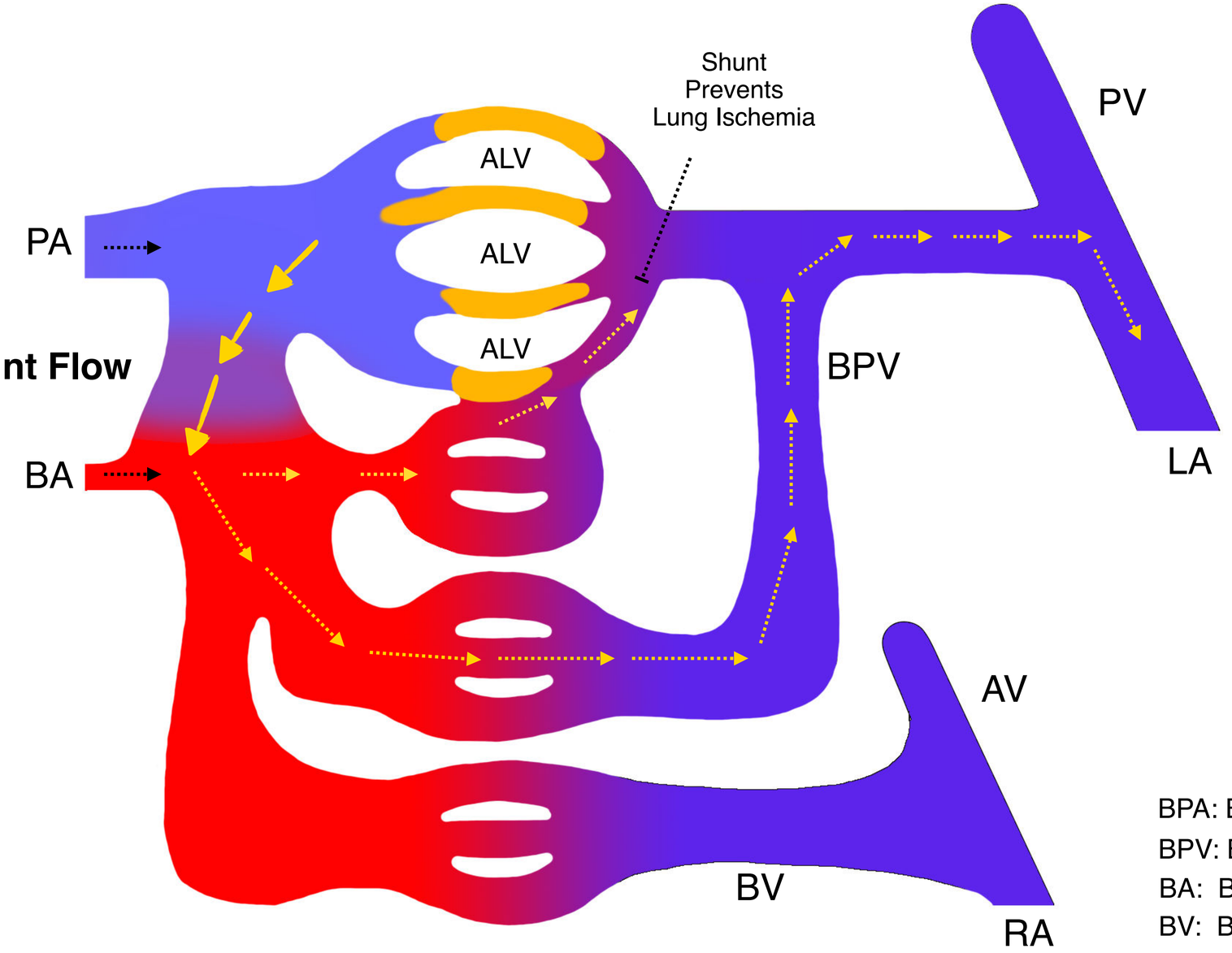
Prone Position **Improves** Dorsal-Predominant Intrapulmonary Shunt Physiology

Reduces Blood Pooling in Dorsal-Predominant Intrapulmonary Shunts By Gravity

Reduces Shunt Flow



Step 8

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

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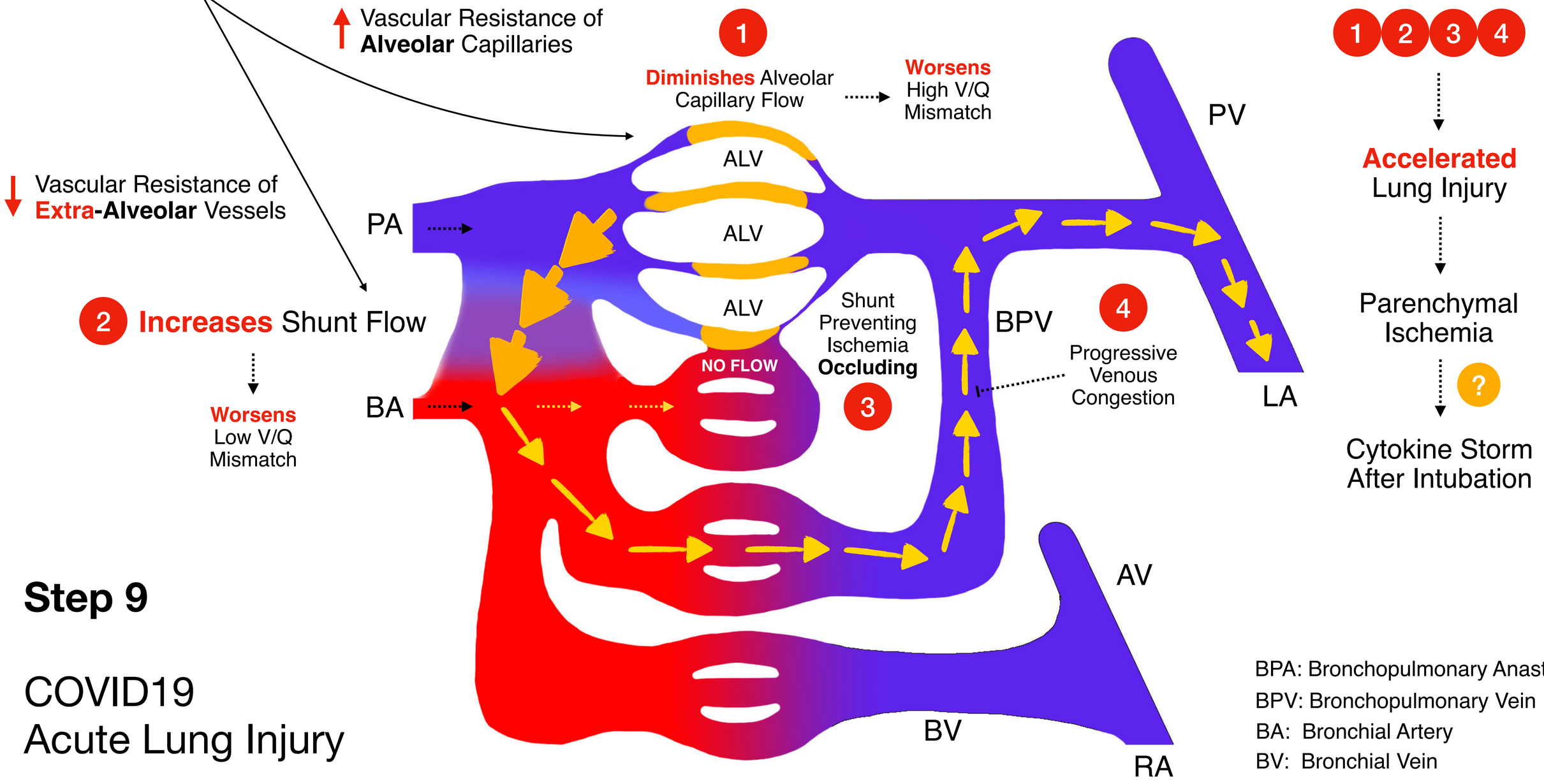
Mechanical Ventilation May Accelerate Worsening of High **and** Low V/Q Mismatch Due to Higher Lung Volume (Increased VT, Increased PEEP)



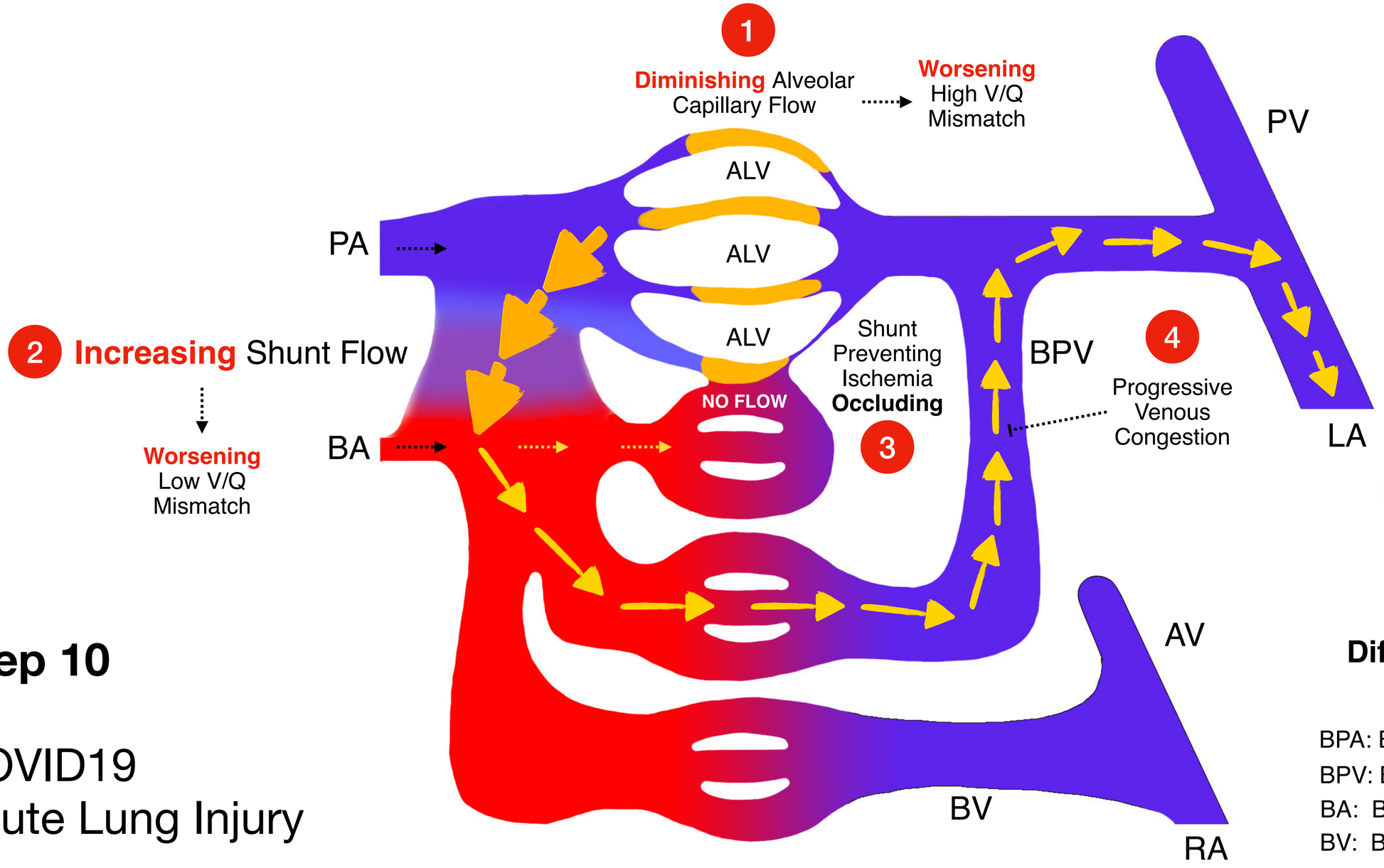
Step 9

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

Farid Jalali MD / May 2020

In **Absence** of **Endothelial Stabilization**, Proper **Anticoagulation**, And **Flow Redistribution**, Lung Injury Progresses by Worsening High **and** Low V/Q Mismatch



1 2 3 4

Progressive Lung Injury

Parenchymal Ischemia

Endothelial-Epithelial Barrier Breakdown

Diffuse Alveolar Damage

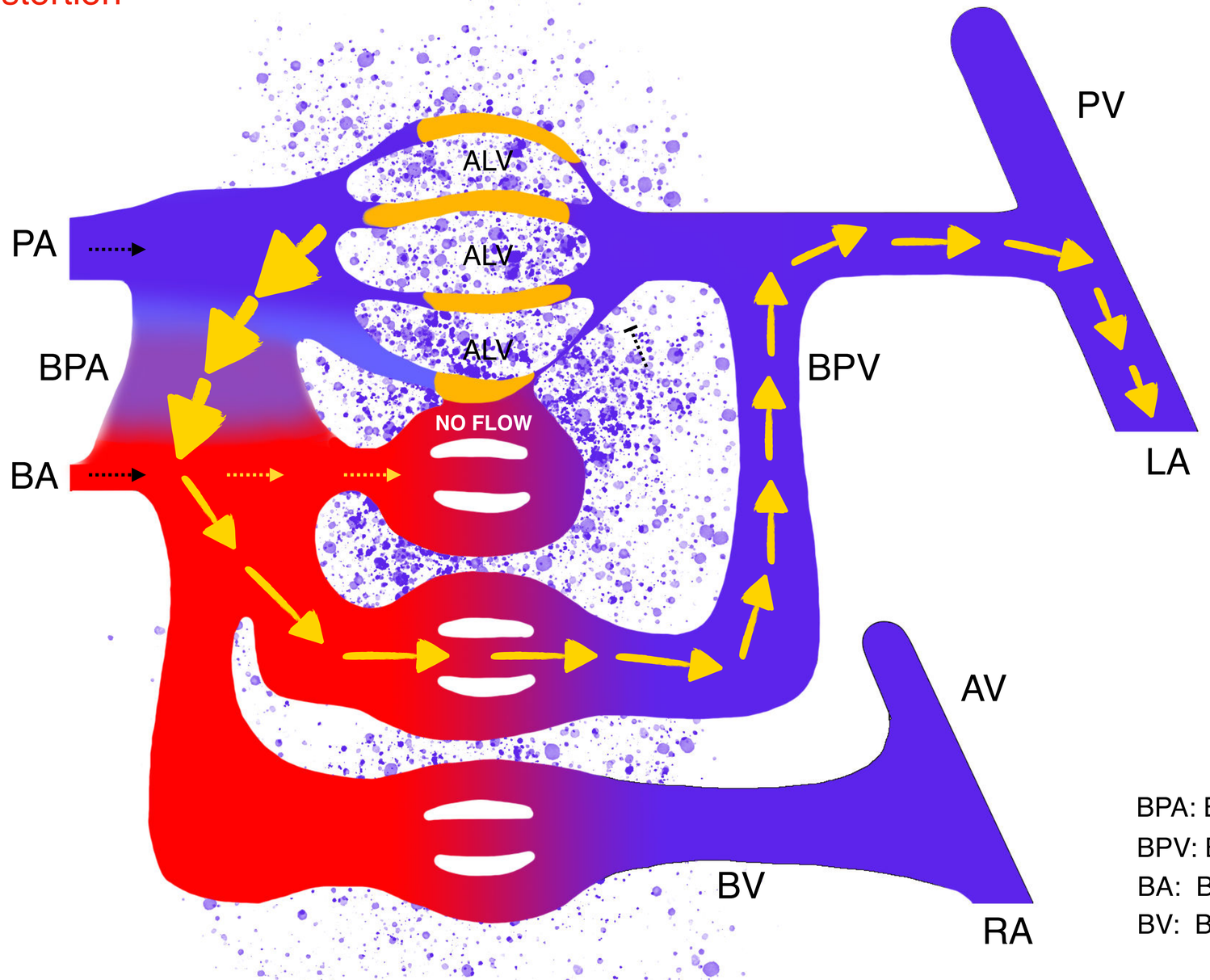
Step 10

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

Farid Jalali MD / May 2020

Late Lung Injury is Characterized by **Poor Lung Compliance**
Progressive Interstitial Edema
Progressive Alveolar Edema and Damage
Progressive Bronchial Distortion



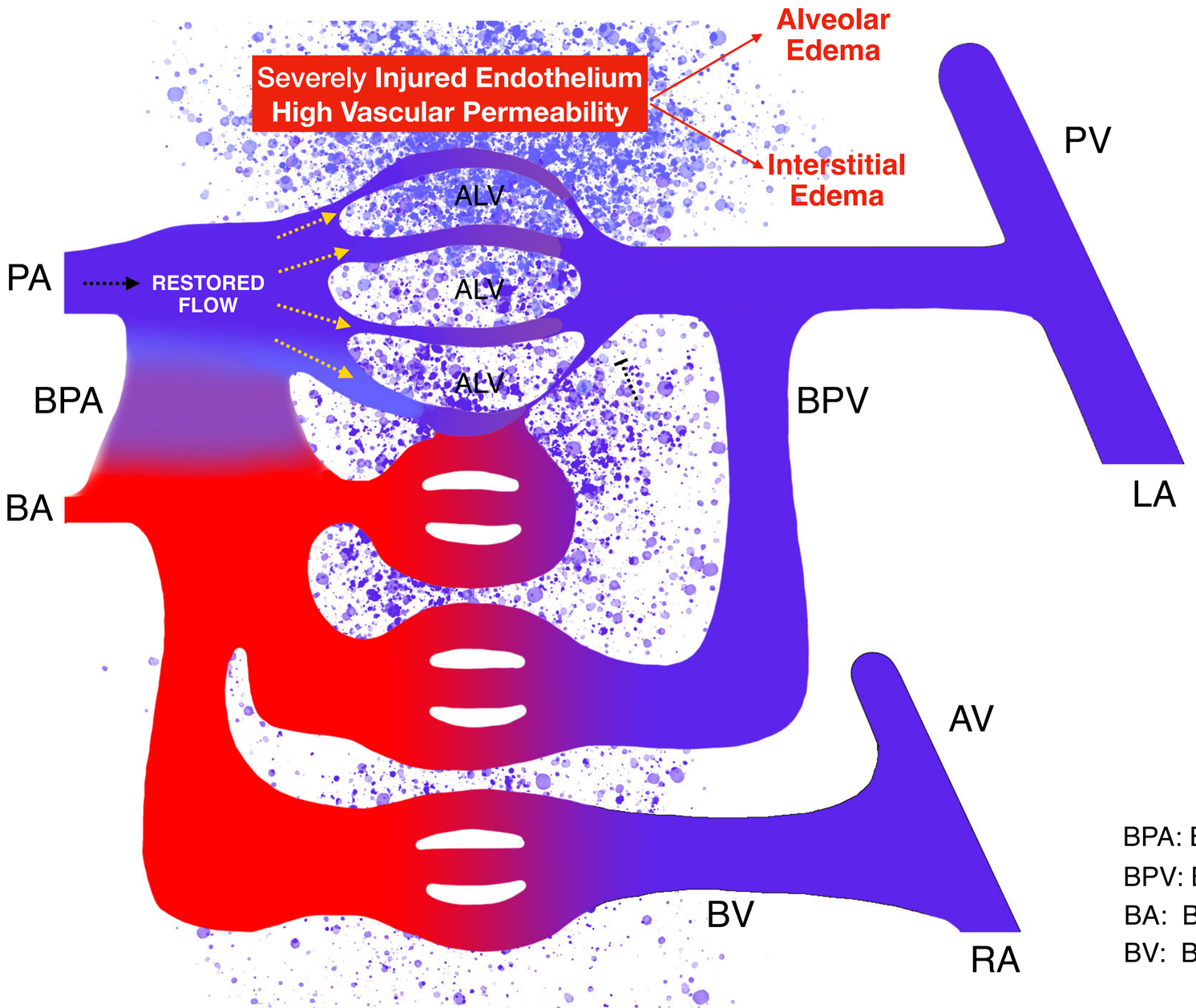
Step 11

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

Farid Jalali MD / May 2020

Significant Reperfusion Injury May Develop As Well with Microthrombi
Resolution by Anticoagulation, Thrombolytics, or via **Innate Fibrinolysis**



Step 12

COVID19
Acute Lung Injury

BPA: Bronchopulmonary Anastomosis
BPV: Bronchopulmonary Vein
BA: Bronchial Artery
BV: Bronchial Vein

Take Home Points

- Early endothelial stabilization, before hypoxia sets in, is key to prevent SARS-CoV-2 induced, excess Angiotensin II mediated, intense alveolar capillary vasoconstriction as well as the concomitant pro-inflammatory, pro-thrombotic endothelial milieu, all of which form the basis of lung injury in COVID19.

- Once hypoxia sets in, supportive care should include early and aggressive endothelial stabilization interventions, properly dosed anticoagulation to prevent lung microvascular thrombi, HFNC, and awake prone position to redistribute flow away from the forming dorsal-predominant intrapulmonary shunts.

- Alveolar capillary microvascular thrombi are not a pre-requisite for the severe lung injury in COVID19, but are a clear step in the wrong direction if allowed to be formed.

Take Home Points

- Lung's natural and physiologic protective response to SARS-CoV-2 induced alveolar capillary vasoconstriction and dead-space ventilation is characterized by alveolar hypocapnic bronchoconstriction at the level of the alveolar ducts to reduce a harmful alveolar expansion in these affected capillaries.

- Naturally, unaffected capillaries and corresponding alveoli will have a higher redistribution of ventilation, will exchange more CO2 into alveolar space, and will therefore have hypercapnic bronchodilation.

- This redistribution keeps the lung compliance preserved in the initial lung injury characterized mainly by dead-space ventilation, forming intrapulmonary shunts, without significant interstitial or alveolar edema.

Take Home Points

- Compensatory lower inspiratory volumes characterize the patient's response, associated with higher respiratory rate, and "shallow rapid breaths" without distress.

- This lower inspiratory volume is needed to prevent expansion of alveoli in the affected vasculopathic areas, as inappropriate expansion compounds the vasoconstriction in these affected alveolar capillaries.

- This will result in a compensatory tendency to develop hypocapnea on blood gas analysis, often concomitant with hypoxia as intrapulmonary shunts also begin to form as lung injury progress.

Take Home Points

- Higher lung volumes, and positive pressure ventilation, disturb the fine balance maintained physiologically in the ventilatory redistribution pattern of the COVID19 lung, between high V/Q mismatch areas (poor perfusion, compensatory reduced ventilation to protect against the vasculopathy) and the compensating lower V/Q areas that safely receive higher ventilation in return.

- Therefore, mechanical ventilation may result in worsening of dead-space ventilation by constricting alveolar capillaries in the affected vasculopathic regions, and additionally result in worsening intrapulmonary shunting (next slide) due to reduced resistance in extra-alveolar vessels with higher lung volumes.

Take Home Points

- In absence of endothelial stabilization, proper anticoagulation, and flow redistribution, lung Injury progresses to severe form by progressively worsening dead-space ventilation, resulting in intrapulmonary shunt development as described in the the diagrams.

- This advanced stage of lung injury is characterized by progressively diminished flow across the alveolar capillaries, resulting in higher flow across the formed intrapulmonary shunts, eventually culminating into progressive interstitial edema, progressive and diffuse alveolar damage, and alveolar fibrin thrombi deposition.

- Physiologically, this stage resembles “typical ARDS” where alveolar recruitment may be beneficial, but unlikely to reverse the vasculopathic disease process, inevitably resulting in high mortality. Pulmonary vasodilators and systemic vasoconstriction plausibly worsen hypoxia at this stage due to increasing flow across the intrapulmonary shunts.

Take Home Points

- Through the action of body's innate fibrinolytic system, lysis of microthrombi and reversal of flow to an area of injured endothelium may result in cycles of ischemia-reperfusion injury in the lung, mediated early on by monocytes and macrophages, and late by neutrophil activity.

- Reduction in leukocyte trafficking with corticosteroids and other therapeutics can be of value early on in the disease course to mitigate this ischemia-reperfusion injury.

- Late and sudden restoration of flow to a bed of alveolar capillaries that have had a prolonged and deep poor flow, usually in absence of proactive endothelial stabilization and proper anticoagulation, will inevitably result in a severe ischemia-reperfusion injury, significant interstitial and alveolar edema, and sudden demise.

- At this late of a stage in lung injury, ECMO may be the only solution available while pursuing lysis of microthrombi to restore alveolar capillary flow in a controlled fashion, while cardiopulmonary bypass is utilized to reduce risk of hemodynamic demise.