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ORIGINAL ARTICLE

Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations

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Abstract

Rationale: Clinical and epidemiologic data in coronavirus disease (COVID-19) have accrued rapidly since the outbreak, but few address the underlying pathophysiology.

Objectives: To ascertain the physiologic, hematologic, and imaging basis of lung injury in severe COVID-19 pneumonia.

Methods: Clinical, physiologic, and laboratory data were collated. Radiologic (computed tomography (CT) pulmonary angiography [$n = 39$] and dual-energy CT [DECT, $n = 20$]) studies were evaluated: observers quantified CT patterns (including the extent of abnormal lung and the presence and extent of dilated peripheral vessels) and perfusion defects on DECT. Coagulation status was assessed using thromboelastography.

Measurements and Results: In 39 consecutive patients (male: female, 32:7; mean age, 53 ± 10 yr [range, 29–79 yr]; Black and minority ethnic, $n = 25$ [64%]), there was a significant vascular perfusion abnormality and increased physiologic dead space (dynamic compliance, 33.7 ± 14.7 ml/cm H_2O; Murray lung injury score, 3.14 ± 0.53; mean ventilatory ratios, 2.6 ± 0.8) with evidence of hypercoagulability and fibrinolytic "shutdown". The mean CT extent (±SD) of normally aerated lung, ground-glass opacification, and dense parenchymal opacification were 23.5 ± 16.7%, 36.3 ± 24.7%, and 42.7 ± 27.1%, respectively. Dilated peripheral vessels were present in 21/33 (63.6%) patients with at least two assessable lobes (including 10/21 [47.6%] with no evidence of acute pulmonary emboli). Perfusion defects on DECT (assessable in 18/20 [90%]) were present in all patients (wedge-shaped, $n = 3$; mottled, $n = 9$; mixed pattern, $n = 6$).

Conclusions: Physiologic, hematologic, and imaging data show not only the presence of a hypercoagulable phenotype in severe COVID-19 pneumonia but also markedly impaired pulmonary perfusion likely caused by pulmonary angiopathy and thrombosis.

Keywords: novel coronavirus disease 2019; acute respiratory distress syndrome; pulmonary perfusion; thoracic imaging; mechanical ventilation

BACKGROUND

- COVID-19, caused by SARS-CoV-2, was classified a pandemic by the WHO in March 2020 with respiratory failure is the dominant cause of death. However, it has been stated that respiratory physiology in COVID-19 differs from "conventional" ARDS.
- Emerging evidence suggests that **activation of inflammatory** and **coagulation cascades** (termed "immunothrombosis") in COVID-19 pneumonia together with elevated levels of IL-6, D-dimer, LDH, and ferritin on admission are linked with higher mortality.
- The other major issue in COVID-19 is the fundamental role of **endothelial injury** and **disrupted vasoregulation**. Indeed, the latter has been proposed as a key component in early COVID-19–related ARDS.
- Accordingly, we examined a cohort of mechanically ventilated patients with severe COVID-19 pneumonia abnormalities focusing on:
  - **Physiologic data**
  - **Imaging** findings on CTPA
  - **Lung perfusion** as demonstrated by DECT pulmonary blood volume "maps"
  - **Hematologic tests** evidence of hypercoagulability and impaired fibrinolysis.

METHOD

STUDY DESIGN AND PARTICIPANT

- Study Design: Retrospective, observational study (study was approved by Research Ethic Committee)
- Participants:
  - 39 consecutive mechanically ventilated patient
  - Patient was transferred from referral site to the institution between 17 March to 10 April 2020 (for further management/ECMO)
  - Inclusion criteria:
    - Laboratory-confirmed positive for COVID-19
    - Patient were mechanically ventilated or on ECMO with active COVID-19-induced respiratory failure
    - Had undergone CTPA and where feasible, DECT pulmonary blood volume "maps"

DATA COLLECTION

- Demographic, clinical, laboratory and treatment data were extracted from electronic medical records and a point-of-care database.
- Respiratory physiology measurement are presented as on admission and shortly before CT-scan imaging.
- All data were reviewed and collated by investigating physicians (B.V.P. and D.J.A.)

LABORATORY PROCEDURES

- SARS-CoV-2 infection was confirmed on real-time PCR assay
- Routine blood investigation:
  - Complete blood count
  - Coagulation profile* [assess using thromboelastography (TEG 6; Haemonetics)]
  - Serum biochemical test (including RFT and LFT, LDH and electrolytes)
  - Myocardial enzymes
  - Serum ferritin
- The frequency of investigations and further tests were determined by the treating physician.

CT IMAGE ACQUISITION AND INTERPRETATION

All patients were scanned in a dedicated COVID-19 CT suite using a second-generation dual-source CT system (Somatom Definition Flash; Siemens Healthineers).

The incidence of venous thrombosis was confirmed by review of reports of lower and upper limb compression ultrasound and/or CT venography where available.

Two observers (A.D. and S.R.D., both thoracic radiologists of 14 and 24 years experience, respectively), reviewed all available CT studies by consensus, blinded to clinical data.

The overall extent of abnormal lung and the percentage of aerated, GGO, and DPO as a component of abnormal lung were visually quantified.

The presence of peripheral dilated (branching and tortuous) vessels in the lung not obscured by DPO was recorded.

In 20 of 39 (51%) cases, CTPA studies were acquired using the DECT technique; in those, 18/20 had assessable lobes.

Pulmonary blood volume images acquired using DECT were reviewed by two thoracic radiologists (C.R. and S.P.G.P.; 14 and 30 years experience, respectively).

The evaluation for the presence/absence of perfusion defects and, when present, categorized as wedge-shaped, mottled, or mixed based on appearances described in chronic thromboembolic disease.

STATISTICAL ANALYSIS

- Descriptive statistic – summarize the data; results are reported as medians and interquartile ranges or means and SD
- Categorical variables – summarize as counts and percentages.
- Statistical analyses were performed using GraphPad Prism v8.4 (GraphPad Software).
  - Normality for continuous variables was tested with the D'Agostino and Pearson normality test.
  - Two-tailed t test, Mann-Whitney U test, or Kruskal-Wallis test with Dunn's multicomparison was used to compare differences between groups where appropriate.
  - Correlation performed using Spearman correlation coefficient and nonlinear least squares regression fitting.

RESULTS

1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTIC OF PATIENTS

Table 1. Clinical and Laboratory Characterization

Demographics and Clinical Characteristics	Number (%), Median (Range), or Mean (±SD)
Age	52.5 (29–79)
Sex, M	32 (82)
Sex, F	7 (18)
White	14 (36)
Black and minority ethnic	25 (64)
BMI, kg/m^2	31.3 (±6.1)
BMI > 30 kg/m^2	22 (57)
Diabetes mellitus	8 (21)
Hypertension	15 (39)
Asthma	3 (8)
Hyperlipidemia	2 (5)

- Mean duration of symptoms was 8.2 +- 3.5 days
- Mean time between hospital admission and endotracheal intubation was 1.3 +- 2.0 days
- Mean number of days of mechanical ventilation prior to transfer was 3.2 +-3.1 days
- From admission, all patient received at least prophylactic dose of LMWH or UH for patient on ECMO or RRT

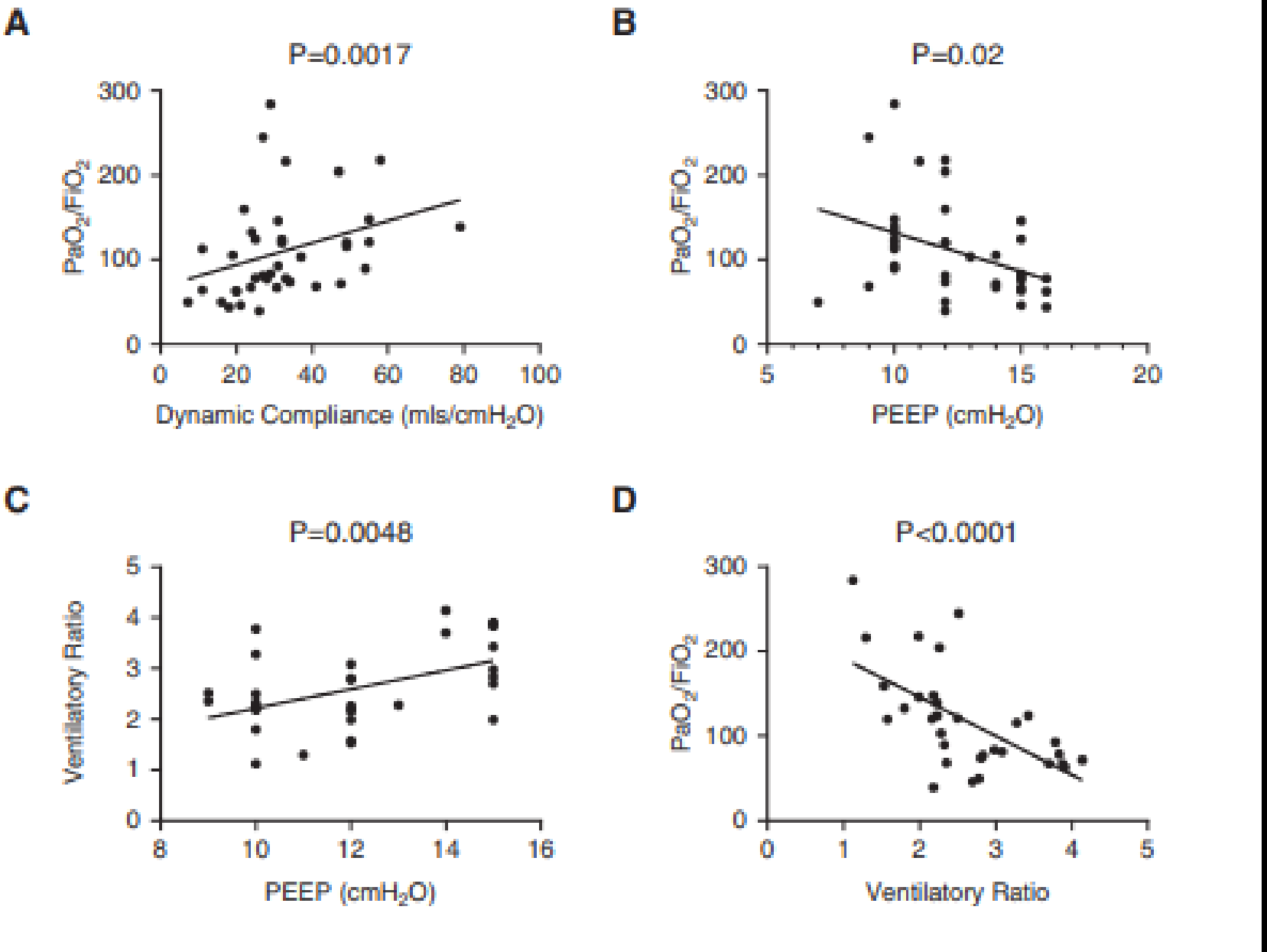
Table 1. Clinical and Laboratory Characterization

Demographics and Clinical Characteristics	Number (%), Median (Range), or Mean (±SD)
Physiologic characteristics (on admission)	
Pa_{O_2}/Fi_{O_2}	114.9 (±74.2)
Pa_{CO2}, mm Hg	63.6 (±20.6)
Minute ventilation, L/min	11.7 (±2.2)
Dynamic compliance, ml/cm H_2O	33.7 (±14.7)
Positive end-expiratory pressure, cm H_2O	12.3 (±2.4)
Murray lung injury score	3.14 (±0.53)
Ventilatory ratio	2.6 (±0.8)
Admission sequential organ failure score	8.0 (±2.5)
Admission APACHE II score	18.7 (±5.0)
Respiratory ECMO survival prediction score	3.4 (±1.9)
Laboratory tests on admission (normal values)	
White cell count, $\times 10^9$/L (3.6–11.0)	10.6 (±4.4)
Neutrophils, $\times 10^9$/L (1.8–7.5)	9.3 (±4.3)
Lymphocytes, $\times 10^9$/L (1.0–4.0)	0.76 (±0.4)
Creatinine, µmol/L (45–110)	172 (±141)
CRP, mg/L (<3)	305 (±101)
Ferritin, ng/ml (18–270)	987 (552–1,425)
Lactate dehydrogenase, U/L (<250)	996 (773–1,270)
Platelets, 10^9/L (146–360)	272 (±77)
Fibrinogen, g/L (1.5–4.5)	6.6 (±1.9)
Antithrombin 3, IU/dl (70–140)	70.6 (±23.7)
APTT, s (26–36)	38.8 (±13.1)
PT, s (10–12.5)	14.1 (±2.1)
D-dimer, ng/ml (208–318)	6,440 (±10,434)
High-sensitivity troponin, ng/L (<14)	143 (±262)
Brain natriuretic peptide, ng/L (<100)	186 (±274)

Definition of abbreviations: APACHE = The Acute Physiology and Chronic Health Evaluation; APTT = activated partial thromboplastin time; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; PT = prothrombin time.

2. PHYSIOLOGIC AND LABORATORY FINDINGS

- ARDS severity on admission was graded as moderate to severe:
  - $Pa0_2/Fl0_2$
  - Dynamic respiratory system compliance (Crs)
  - Murray lung injury score


A
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300
200
100
0
PaO_2/FiO_2
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20
40
60
80
100
Dynamic Compliance (mls/cmH_2O)
B
P=0.02
300
200
100
0
PaO_2/FiO_2
5
10
15
20
PEEP (cmH_2O)
C
P=0.0048
5
4
3
2
1
0
Ventilatory Ratio
8
10
12
14
16
PEEP (cmH_2O)
D
P<0.0001
300
200
100
0
PaO_2/FiO_2
0
1
2
3
4
5
Ventilatory Ratio

3. CTPA AND DECT FINDINGS

Computed Tomography Findings	All (*N* = 39)
Aerated lung, %	23.5 (±16.7)
Ground-glass opacity, %	36.3 (±24.7)
Dense parenchymal opacification, %	42.7 (±27.1)

- CTPA was performed in 39 patients whereby 20/39 patient (51%) underwent DECT [technical limitation (i.e., body mass index >35 or an inability to armraise)].
- 18 patient were on ECMO at the time of CT.
- Median interval between intubation and CT was 6 days (0-18 days).

% Extent of normal lung aeration

21.1 +- 10.8 %

Crs: positively correlated(P = 0.0499)

Increasing severity of injury (assessed by Murray lung injury score): negatively correlated (P = 0.02)

No correlation with Pa02/FI02 or ventilator ratio

%GGO

36.3 +- 24.7%

Crs: positively correlated(P = 0.0028)

Increasing severity of injury (assessed by Murray lung injury score): negatively correlated (P = 0.095)

No correlation with Pa02/FI02 or ventilator ratio

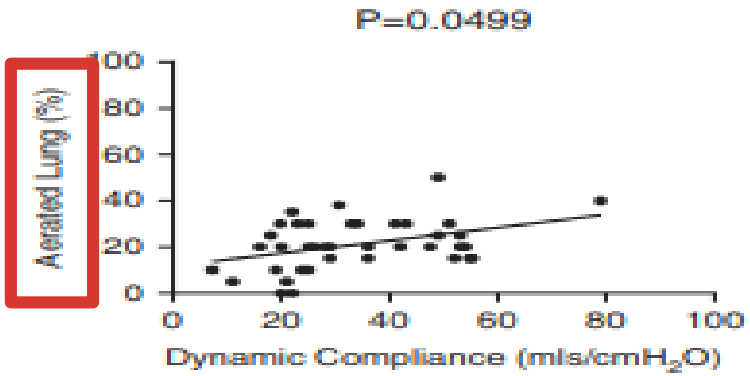
%DPO

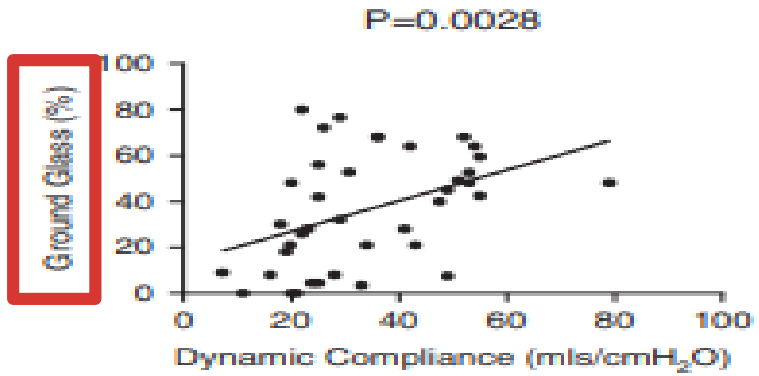
42.7 +- 27.1%

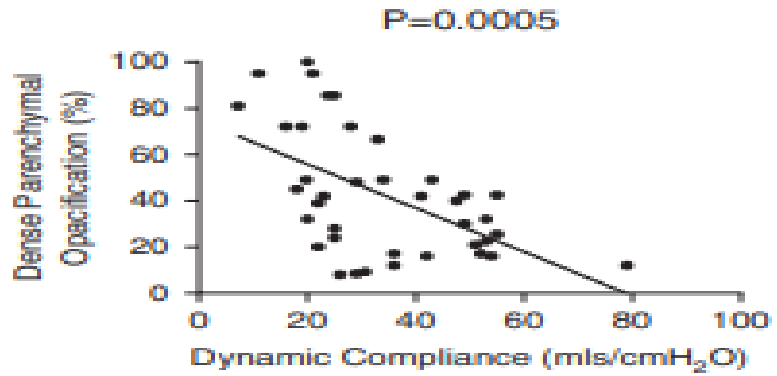
Crs: negatively correlated(P = 00005)

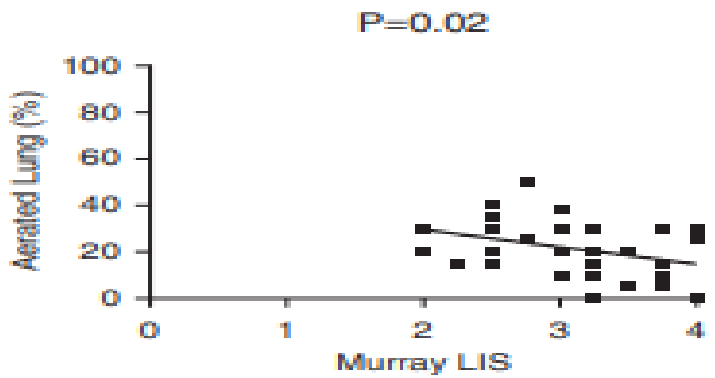
Increasing severity of injury (assessed by Murray lung injury score): positively correlated (P = 0.03)

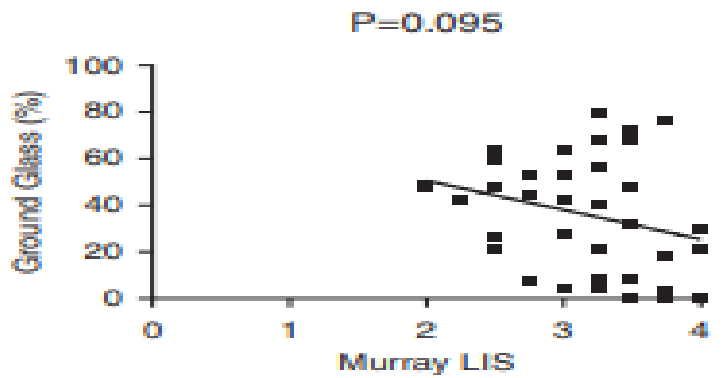
No correlation with Pa02/FI02 or ventilator ratio

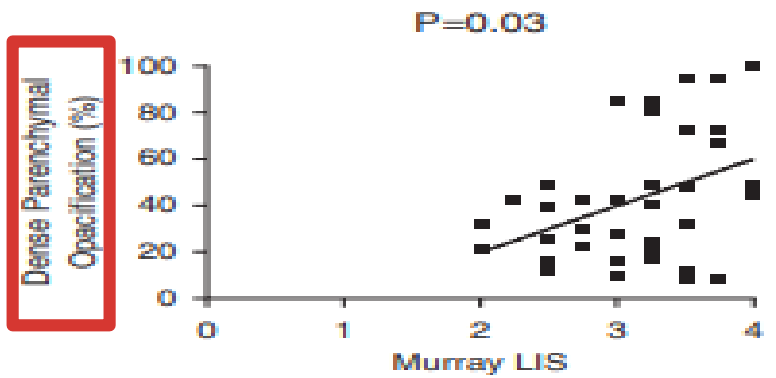










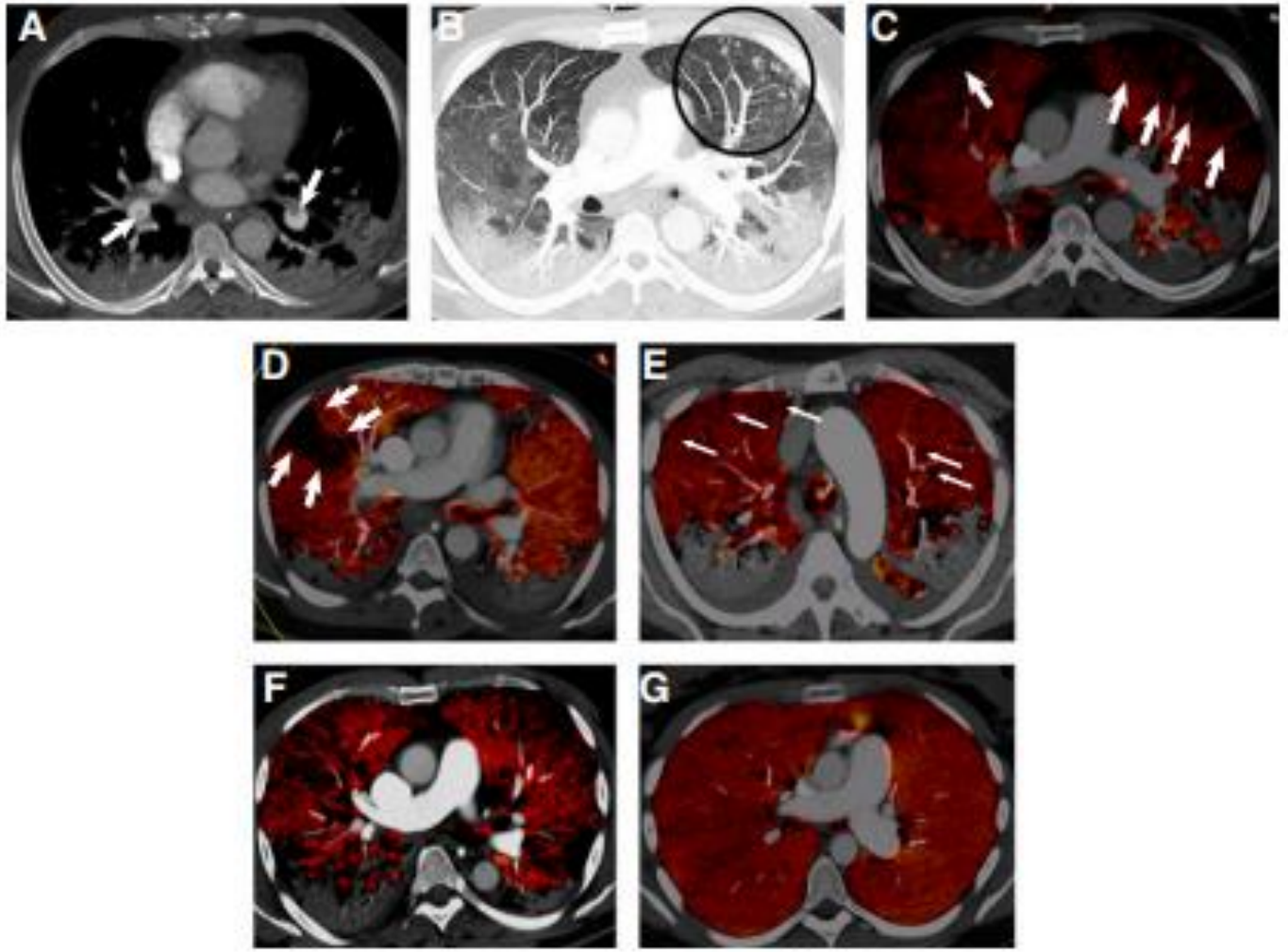


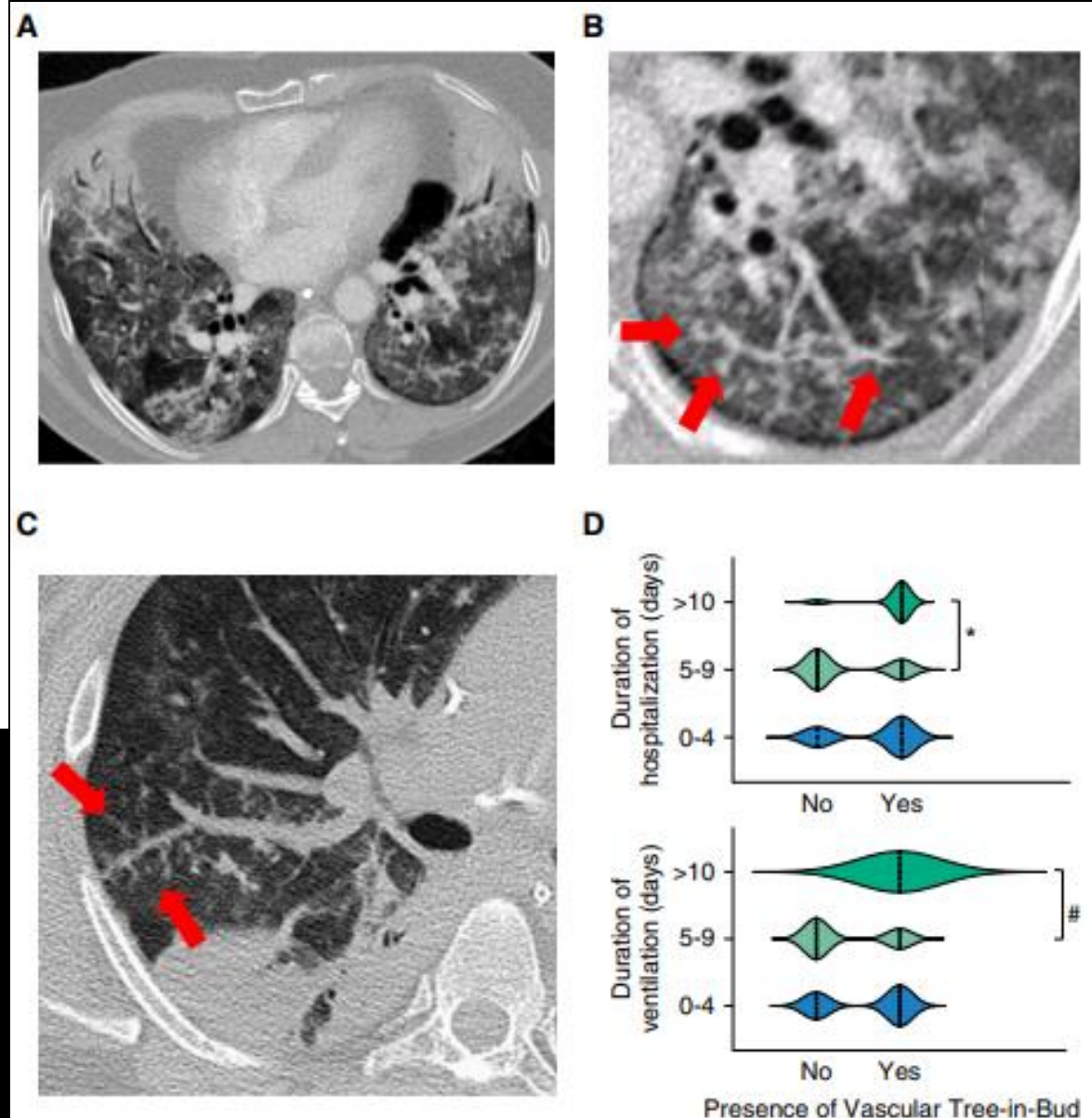
VASCULAR PERFUSION ABNORMALITIES ON CTPA AND DECT FINDINGS

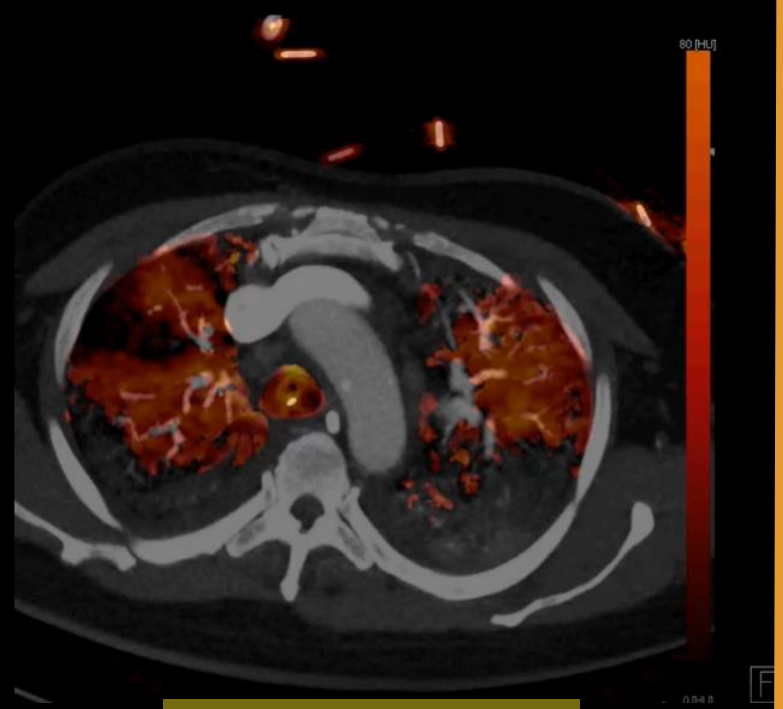
	Number of Patients	Proportion (%)
Pulmonary embolism	15	15/39 (38.5)
Dilated peripheral vessels	21	21/33* (63.6)
1–5 segments	14	14/21 (66.7)
6–10 segments	7	7/21(33.3)
>10 segments	0	0/21 (0)
Dilated peripheral vessels without PE	10	10/21 (47.6)
Perfusion defect present	18	18/18† (100)
1–5 segments	14	14/18 (77.8)
6–10 segments	4	4/18 (22.2)
>10 segments	0	0/18
Perfusion defects without PE	8	8/18 (44.4)
DECT perfusion defect morphology		
Wedge shaped	3	3/18 (16.7)
Mottled	9	9/18 (50)
Mixed pattern	6	6/18 (33.3)
Deep venous thrombosis	4	4/22‡ (18.2)

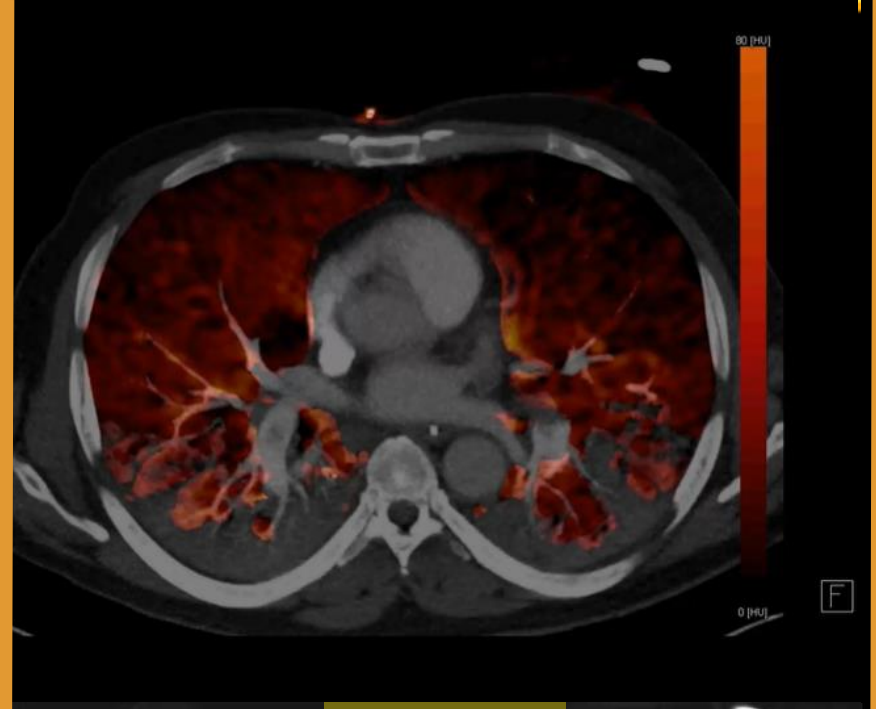
Definition of abbreviations: COVID-19 = coronavirus disease; DECT = dual-energy computed tomography; PE = pulmonary embolism.
*Of 39 patients, 33 had at least two assessable lobes not obscured by dense collapse or consolidation.
†Of 20 patients, 18 had at least two assessable lobes on pulmonary blood volume color maps.
‡Twenty-two patients underwent peripheral limb ultrasound or computed tomography venography.

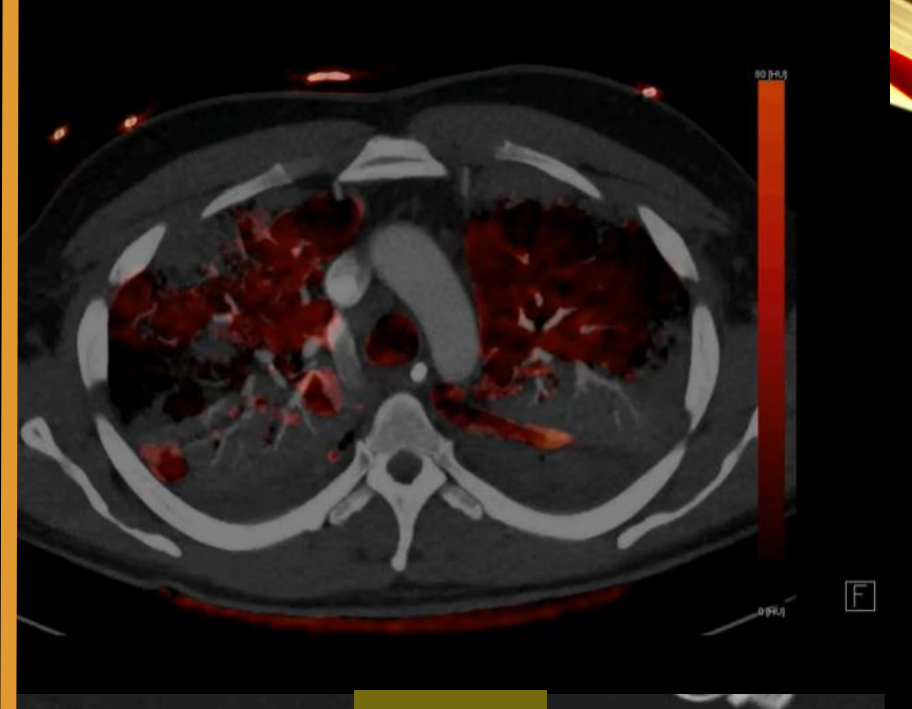
- Prevalence of dilated peripheral vessels increased significantly with increasing duration of hospitalization and length of ventilation
  - P = 0.013 with Kruskal-Wallis
  - Dunn's multicomparison P = 0.0127


A
B
C
D
E
F
G

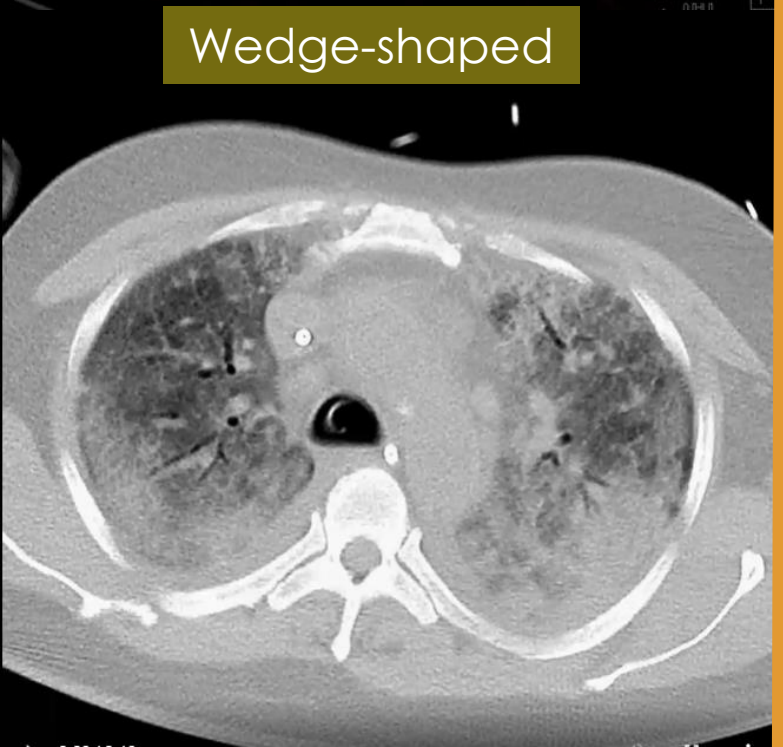

A
B
C
D
Duration of hospitalization (days)
>10
5-9
0-4
No
Yes
*
Duration of ventilation (days)
>10
5-9
0-4
No
Yes
#
Presence of Vascular Tree-in-Bud



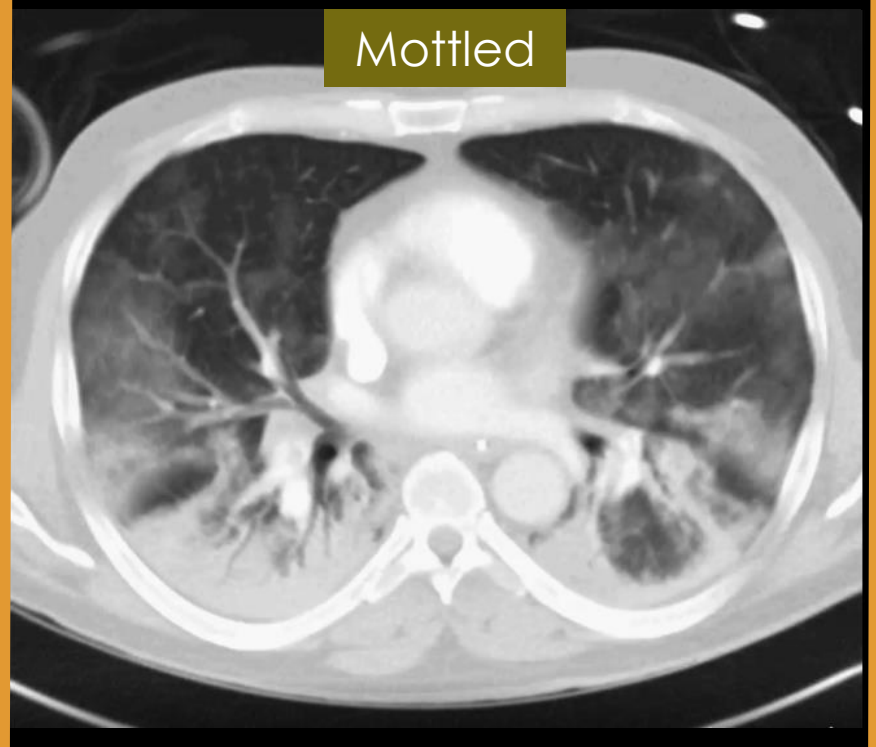




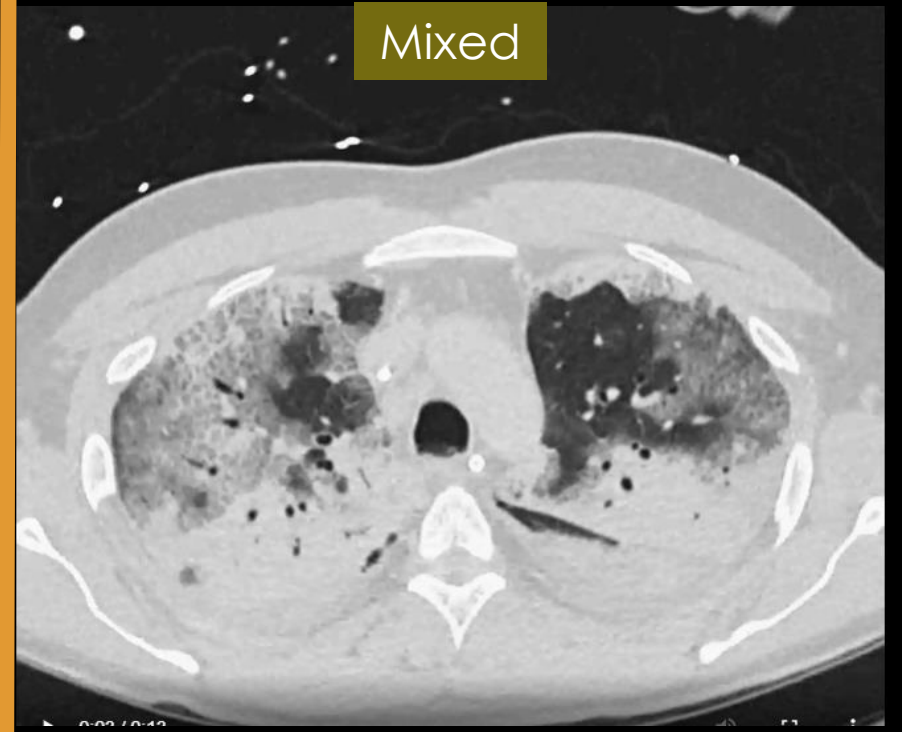
Wedge-shaped



Mottled



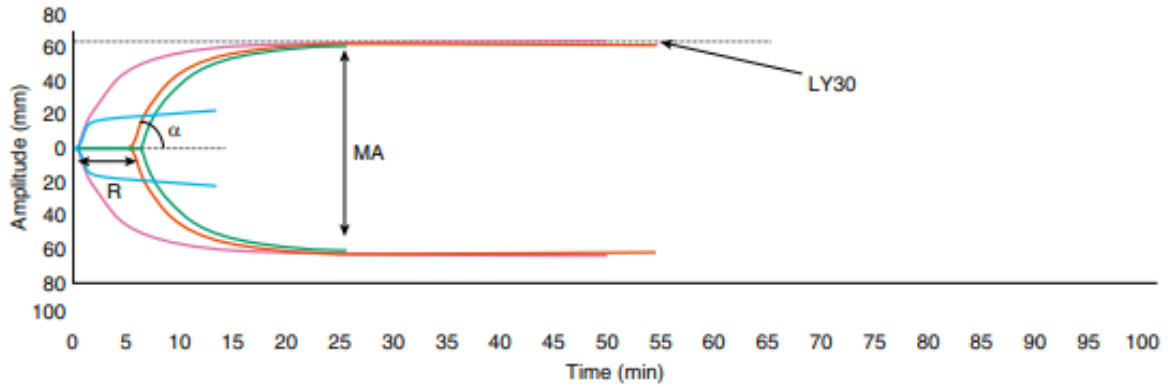
Mixed



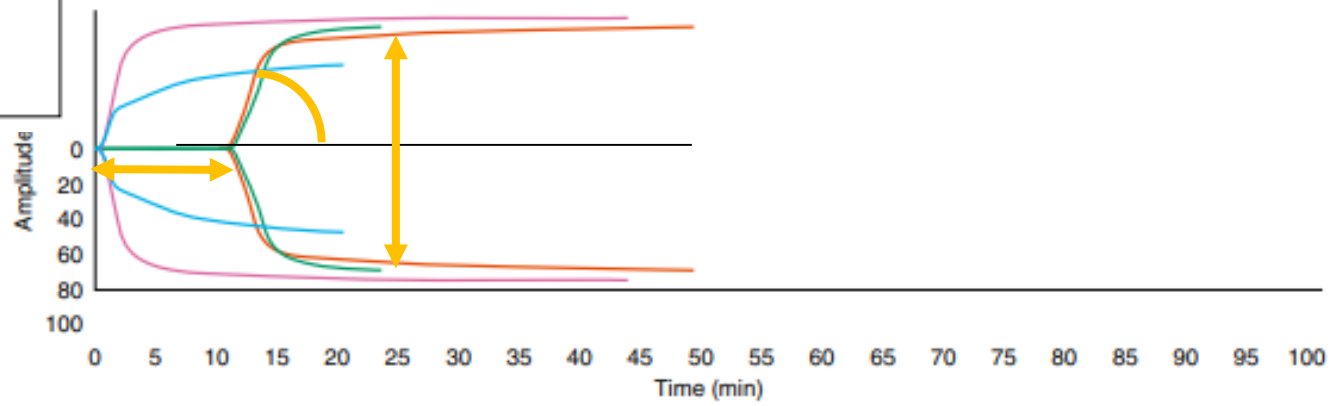
4. COAGULATION ABNORMALITIES

- TEG data from the citrated kaolin heparinase channel showed **hypercoagulability** characterized by **raised maximal amplitude (MA)** and **absent fibrinolysis**
  - MA represents the maximal clot strength as determined by platelet number and function (80% of MA contribution is from platelets and the other 20% from fibrinogen).
    - 21/39 (54%) patients had MA above the normal reference range (52–69 mm)
  - Significantly raised functional fibrinogen levels suggesting a strong contribution of platelets and fibrin to clot strength.
    - 29/39(74%) had functional fibrinogen levels higher than the normal reference range (15–32 mm).
  - All patients showed absent fibrinolysis as evident by LY30 of 0% across the whole cohort.

B



	TEG–ACT (sec)	R (min)	K (min)	ANGLE (deg)	A10 (mm)	MA (mm)	LY30 (%)
CK		5.4 4.6 – 9.1	1.1 0.8 – 2.1	74.5 63 – 78		62.6 52 – 69	0.1 0.0 – 2.6
CRT	97.3 82 – 152	0.5 0.3 – 1.1	1.0 0.8 – 2.7	77.0 60 – 78	58. 1 44 – 67	63.1 52 – 70	0.0 0.0 – 2.2
CKH		6.2 4.3 – 8.3	1.2 0.8 – 1.9	73.3 64 – 77		61.5 52 – 69	
CFF					22.2 15 – 30	23.0 15 – 32	



	TEG–ACT (sec)	R (min)	K (min)	ANGLE (deg)	A10 (mm)	MA (mm)	LY30 (%)
CK		11.0 4.6 – 9.1	1.2 0.8 – 2.1	77.5 63 – 78		62.7 52 – 69	0.0 0..0 – 2.6
CRT	106.6 82 –152	0.6 0.3 –1.1	0.7 0.8 –2.7	81.6 60 –78	72.4 44 –67	73.4 52 – 70	0.0 0.0 – 2.2
CKH		11.3 4.3 – 8.3	1.3 0.8 – 1.9	75.7 64 – 77		70.6 52.69	
CFF					43.2 15 – 30	48.5 15 – 32	

DISCUSSION

- Mechanically ventilated patients with severe COVID-19 pneumonia present with hypercapnic respiratory failure and a relatively preserved respiratory system compliance initially, reflecting **increased pulmonary dead space** and a predominant **defect in pulmonary perfusion.**

- The current study is the first to systematically evaluate the combined physiologic, hematologic, and morphologic abnormalities in patients with COVID-19 pneumonia. Our observations point to an **increased physiologic dead space**, **hypercoagulability** (with absent fibrinolysis), and imaging signs of **major vascular involvement.**

- Accordingly, and in light of emerging pathologic evidence of major vascular involvement we suggest that our results support the **presence of a widespread pulmonary angiopathy** in severe COVID-19 pneumonia.

PHYSIOLOGY

- Physiology of COVID-19-induced ARDS stemmed from the proposal by Gattinoni and colleagues of two broad (but almost certainly overlapping) phenotypes:
  - "Type L" with high lung compliance and limited ground-glass opacification on CT; responsive to lower PEEP
  - "Type H" with low lung compliance and more extensive disease on CT; potentially benefitting from higher PEEP

- Our data also confirm **considerable overlap in phenotypes,** with all patients showing a significant (>50% of lung volume) combination of GGO and DPO, presumably related to the progression of disease. Our study shows higher Murray lung injury score showing lower percentage aeration/GGO but greater DPO.

- Moreover, the association between **higher PEEP** (lower PaO2/FiO2) and **worsening hypoxemia** and **greater physiological dead space fraction** (higher ventilatory ratio) all point to **disproportionate vascular dysregulation.**

IMAGING

- From our study, the possible pathophysiological explanation for this increased physiological dead space are:
  - **Frequent presence of dilated, branching, and/or tortuous vessels in the peripheral lung**
  - **Perfusion defects on DECT.**
- It has been previously suggested that vessel enlargement in COVID-19 pneumonia might be a marker of increased blood flow. However, we do not subscribe to this explanation but instead suspect that the vascular tree-in-bud pattern in COVID-19 likely is a manifestation of **pulmonary thrombotic angiopathy.**
- Support for this comes from postmortem data. In one of previous studies, features of diffuse alveolar damage were present in all cases, but COVID-19 lungs were distinguished by the presence of **widespread microthromboses and striking new vessel growth**; the latter was termed "intussusceptive angiogenesis" and linked with increasing hospitalization.
- Intriguingly, albeit in a small number, we also found a linkage between the vascular tree-in-bud pattern and duration of both hospitalization and ventilation before CT. Thus, it is tempting to speculate that the **vascular tree-in-bud pattern in COVID-19 pneumonia may be an important CT marker of immunothrombosis and angiogenesis.**

- The DECT scanning technique, although lacking a routine role in the imaging of lung disease, has certainly attracted attention as an alternative means of assessing pulmonary perfusion in acute and chronic thromboembolic disease.

- **Abnormalities of perfusion were seen in all patients** with assessable lobes, irrespective of whether this was in dependent or nondependent areas of the lung.

- SARS-CoV-2 might, through direct endothelial infection, lead to significant **pulmonary microvascular endothelial injury** with associated viremia.

- Interestingly, SARS-CoV-1 has been shown to induce **pulmonary cellular necrosis**, and the pathobiological processes leading to **immunothrombosis** (endothelial injury, vascular inflammation, and thrombotic microangiopathy) might then serve to explain our observation of **dilated peripheral vessels and perfusion defects on imaging.**

PE AND DVT

- The issue of deep venous thrombosis (DVT) and acute PE in COVID-19 pneumonia merits brief consideration. PE was present on CT in 15 of 39 patients in our study.

- Thus, it might conceivably be argued that the dilated peripheral vessels in our patients were simply being rendered visible on CT by embolic material from upper- or lower-limb DVT.

- However, against this, DVT was recorded in only 4 of 22 patients undergoing lower-limb compression ultrasound or CT venography, and **only 1 patient with PE had DVT.**

- We suggest that in COVID-19 there may be dual pathologies at play, namely, **acute PE from DVT and a widespread pulmonary angiopathy.**

HEMATOLOGICAL

- We regard the hematological tests in our patients as important and complementary, serving to confirm **hypercoagulability** (as evidenced by raised MA, functional fibrinogen levels), and **absent fibrinolysis** given the LY30 of 0% in all patients.

- Impaired fibrinolysis is regarded as a predictor of first and recurrent PE. Although use of TEG outside cardiac surgery and liver disease is limited, there is emerging evidence from several studies for a role for **viscoelastic tests in assessing the bleeding and thrombotic risk** in critically ill patients with infection/inflammation.

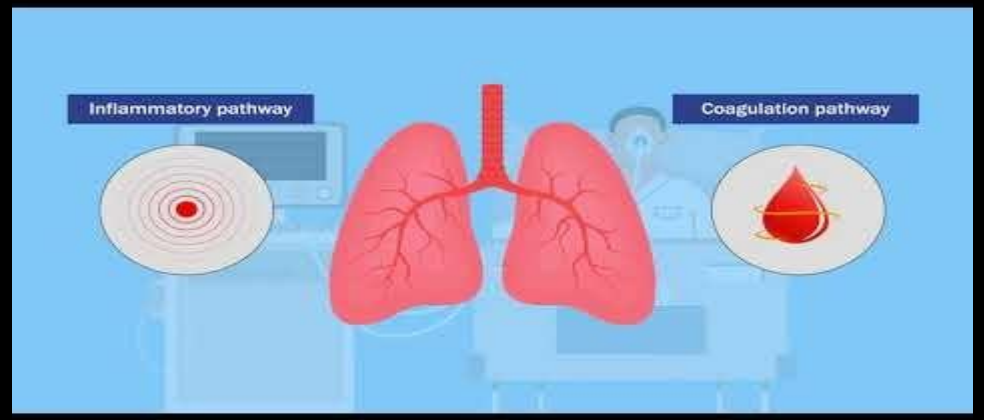
- Furthermore, hypercoagulability as evidence by **TEG** has been shown to be **predictive of thrombosis** in patients with trauma and in the general population.

CONCLUSION

- We propose that our observations not only provide important noninvasive evidence of pulmonary vascular involvement through imaging but also add to the understanding of clinicophysiological phenotypes and pathobiology of COVID-19 pneumonia/ARDS.

- Our observations on CTPA and DECT, coupled with the physiologic and hematologic features, point to major pulmonary vascular involvement in severe COVID-19 pneumonia. Further validation of these imaging markers is clearly warranted, but in light of the emerging pathologic evidence of angiopathy, we believe our findings have implications for further pathobiologic and therapeutic studies.

- https://www.youtube.com/watch?v=kcm3anfhjJM



- Supplementary videos available at:
  - https://www.atsjournals.org/doi/suppl/10.1164/rccm.202004-1412OC

…THANK YOU…