Stroke and COVID-19: Is COVID a Vascular Endothelial Disease

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Disclosures

- Research and consultant support: Canon, Stryker, Penumbra, Medtronic, Jacobs Institute
- Founding member: Neurovascular Diagnostics
- Stockholder: Blockade Medical

Questions to consider

- Why are some young patients getting strokes and blood clots?
- Why are their different lung phenotypes? Is there a problem with air getting to the lungs, or a problem of blood getting to the lungs, or both?
- Why do some pts have very compliant lungs with hypoxia (Gattinoni type L)?
- Why are some pts getting extubated and seeming to improve only to die from cardiac arrest?
- Why are some patients being discharged home and then coming back very sick later?

- Can we challenge our current thinking to imaging this is a vascular disease with an infectious etiology? And might that explain all of this?

UBNS Virtual Visiting Professor GR

- Link: https://buffalo.zoom.us/j/99187628667?pwd=SGhBRUZrTFdIekQ4bVNzN3M0c25udz09

COVID 19 NYC and Neurosurgery: A Perspective

UB UNIVERSITY AT BUFFALO
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Chairman, Department of Neurosurgery
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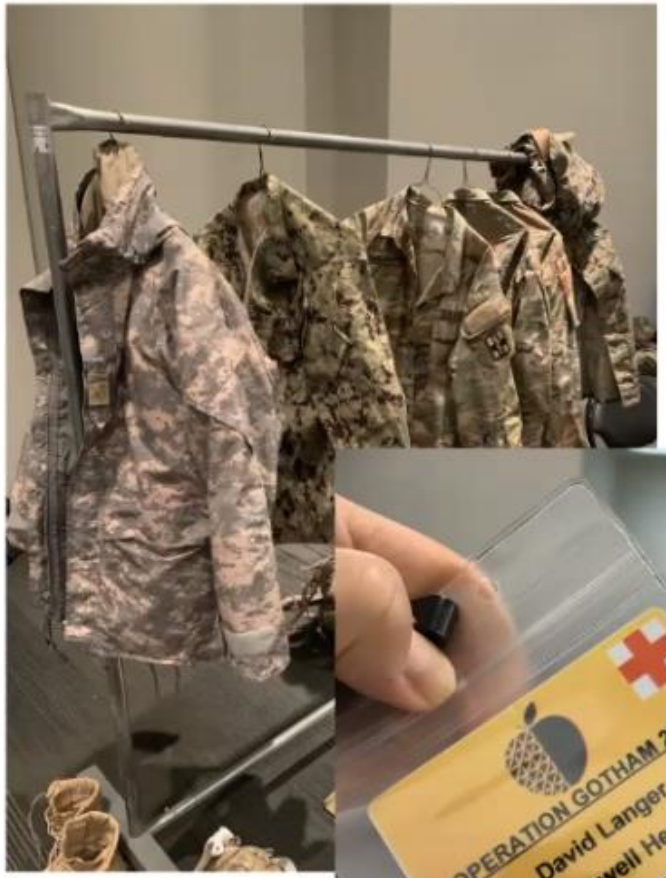

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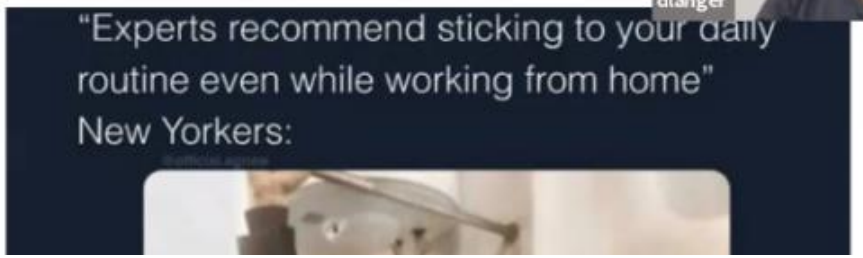

Neurological Manifestations

1. Onset symptoms
2. Encephalopathy
3. Encephalitis
4. Demyelinating disease
5. Seizures
6. Stroke

Managing CNS dysfunction

1. Extremely challenging
2. Imaging
3. Exposure
4. Lack of therapeutics
5. Multi organ failure

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Project Structure: preliminary opportunities across domains

Clinic Workflows	Patient Education	Research	Inpatient/ Surgical Journey	Training/ Education	Communication/ Administrative
Furthering our telehealth strategy & workflow	Designing in-office educational experience	Research projects	Surgical clearances available through cloud	Innovator in the virtual conference space	Overall communication channels and meeting frequency (Teams)
All providers working at 'top of license'	Continuing to build out our YouTube channel	Enhancing clinical trials	Improved document sharing with external providers	Optimizing weekly case conferences/ tumor board	Work from home opportunities & policies
Designing the in-person pre-op visit	Leveraging Playback	Coordinating with the Medical School	Virtual rounding & billing	Creating a virtual summer internship (brainterns)	Trading up obsolete technologies (e.g., scan/fax)
Improved access to translation services	Content creation across multiple languages & abilities		Surgical video/remote surgical management		Revenue/billable opportunities
Imaging upload capabilities	Right content at the right time for each patient		Inpatient consult billing		
Redesign physical office to align with strategy	VR / Surgical Theater				

Enabler: Technology & Digital Communication

3/21

COVID-19 Dashboard | Leadership Only | testing | TAT & Pending Tests | Banner Update

Coronavirus COVID-19 Readiness Dashboard

Lenox Hill Hospital - Command Center

Lenox Hill Hospital Northwell Health

If you need access to this page: Contact - Juan Rada @ Jrada@northwell.edu

COVID-19 # 51

CAP # 9

PUI # 28

House Census 250

ED Census 29

ER Holds 7

COVID-19 Rooms Availability

COVID-19 Units

08EA	07EA	08LA	07LA	07WO	07UR		08WO		04LA	ED	Other Floors
0801-01	0701-01◆	0819-02	0719-02	0731-01	7601-01Ⓑ	7615-01	0831-01	0846-01	0419-01	ED	04UR 4601 02
0802-01	0702-01	0820-01	0720-02Ⓑ	0732-01	7601-02	7615-02	0832-01	0849-01Ⓑ	0419-02	ED	06UR 6622 01
0803-01◆	0703-01◆	0820-02	0722-01Ⓑ	0733-01	7602-01Ⓑ	7616-02	0833-01	0849-02	0420-01	ED	
0804-01◆	0704-01◆	0822-01Ⓑ	0722-02	0734-01Ⓑ	7602-02	7617-02	0834-01Ⓑ	ⓘ0851-01	0420-02	ED	
0805-01	0705-01◆	0822-02	0723-01	0734-02	7603-02	7618-01	0834-02	ⓘ0853-01	0421-01	ED	
ⓘ0806-01◆	ⓘ0706-01◆	0823-01	0723-02	0735-01	7604-01Ⓑ	7618-02	0835-01	ⓘ0855-01	0421-02	ED	
ⓘ0807-01	ⓘ0707-01◆	0823-02Ⓑ	0725-01Ⓑ	0736-01Ⓑ	7604-02	7619-01Ⓑ	0837-01Ⓑ		0422-01Ⓑ	ERHO-13	
ⓘ0808-01◆	ⓘ0708-01◆	0825-01	0725-02	0736-02	7605-01Ⓑ	7619-02	0837-02		0422-02	ERHO-30	
0809-01◆	0709-01◆	0825-02	0726-01Ⓑ	0740-01	7605-02Ⓑ	7620-01	0838-01		0423-01Ⓑ		
0810-01	0710-01	0826-01Ⓑ	0726-02	0740-02Ⓑ	7606-01	7620-02	0838-02		0423-02		
0811-01◆	0711-01◆	0826-02Ⓑ	0727-01Ⓑ	0741-01	7608-01	7621-01Ⓑ	0840-01Ⓑ		0424-01Ⓑ		
0812-01◆	0712-01◆	0827-01	0727-02Ⓑ	0741-02	7610-01	7621-02	0840-02		0424-02		
		0827-02Ⓑ	0728-01Ⓑ	0742-02	7611-01	7622-01	0841-01		0425-01Ⓑ		
		0828-01	0728-02	0745-02	7611-02	7623-01	0841-02		0425-02		
		0828-02Ⓑ	ⓘ0729-01	0749-02	7612-02		0844-01		0426-01		
		ⓘ0829-01		ⓘ0751-01	7613-02		0844-02		0426-02		
				ⓘ0753-01	7614-01Ⓑ		0845-01Ⓑ		ⓘ0427-01		
				ⓘ0755-01	7614-02		0845-02		ⓘ0428-01		

Color Key
- COVID-19
- R/O COVID-19
- Occupied
- Empty/Other
- CAP
- IsoBlocked

ⓘ Negative Pressure Rooms
Ⓑ IsoBlocked
◆ Mechanical Vent

dlanger

4/11

Coronavirus COVID-19 Readiness Dashboard

Lenox Hill Hospital - Command Center

Lenox Hill Hospital Northwell Health

COVID-19 303

CAP # 32

PUI # 18

IP Census 408

ED Census 6

ER Holds 4

Level of Care: ICU

ICU

COVID									Non-COVID		
05EA	07EA	08EA	09EA	05LA	07LA	08LA	09LA	05UR	11UR	02UA	10LA
CCUN-01◆	0701-01◆	0801-01	0901-01◆	0519-01◆	0719-01◆	0819-01◆	0920-01◆	5611-01	1113-01	2733-03	10LA-05
CCUN-02	0702-01	0802-01◆	0902-01◆	0519-02	0719-02◆	0819-02◆	0920-02◆		1113-02	2735-03	10LA-06
CCUN-03	0703-01◆	0803-01◆	0903-01◆	0520-01◆	0720-01	0820-01◆	0922-02◆		1113-03	2737-03@	10LA-07
CCUN-04◆	0704-01	0804-01	0904-01◆	0520-02	0720-02◆	0820-02◆	0923-01◆		1113-04	2739-03	10LA-08
CCUN-05◆	0705-01	0805-01◆	0905-01◆	0522-01	0722-01◆	0822-01◆	0923-02		1113-05	2741-03◆	10LA-09
CCUN-06◆	0706-01◆ⓘ	0806-01ⓘ	0906-01◆ⓘ	0522-02◆	0722-02◆	0823-01◆	0926-02◆		1118-01◆	2741-04Ⓑ	10LA-10
CCUN-07◆	0707-01◆ⓘ	0807-01ⓘ	0907-01◆ⓘ	0523-01◆	0723-02◆	0823-02	0929-01ⓘ		1199-93	2743-03	10LA-11
CCUN-08◆	0708-01◆ⓘ	0808-01◆ⓘ	0908-01ⓘ	0525-02◆	0725-01◆	0825-01◆			1199-94	2743-04	10LA-12
CCUN-09◆	0709-01	0809-01◆	0909-01◆		0725-02◆	0827-02			1199-99		10LA-13
CCUN-10◆	0710-01◆	0810-01◆	0910-01◆		0726-02◆						10LA-14
CCUN-11	0711-01◆	0811-01◆	0911-01		0727-02◆						10LA-15
CCUN-12◆	0712-01◆	0812-01◆	0912-01		0729-01ⓘ						10LA-16

Trends

NYC Data Available

ICU 4

Tele 30

Regional 29

CAP 12

Only Covid Units

Color Key
- COVID-19
- Empty/Other
- IsoBlocked
- Occupied
- R/O COVID-19

ⓘ Negative Pressure
Ⓑ IsoBlocked
◆ Mechanical Vent
@ Assigned

Questions - Jrada@northwell.edu

Lenox Hill Hospital + tableau Team

dlanger

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal *has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.*

Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

- Oxley, Mocco et al.
- 5 COVID-19+ cases of LVO in age < 50 patients
- Mean NIHSS 17 at presentation

Oxley, T. J., Mocco, J.Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med, 382*(20), e60. doi:10.1056/NEJMc2009787

Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age — yr	33	37	39	44	49
Sex	Female	Male	Male	Male	Male
Medical history and risk factors for stroke†	None	None	Hyperlipidemia, hypertension	Undiagnosed diabetes	Mild stroke, diabetes
Medications	None	None	None	None	Aspirin (81 mg), atorvastatin (80 mg)
NIHSS score‡					
On admission	19	13	16	23	13
At 24 hr	17	11	4	19	11
At last follow-up	13 (on day 14)	5 (on day 10)	NA; intubated and sedated, with multiorgan failure	19 (on day 12)	7 (on day 4)
Outcome status	Discharged to rehabilitation facility	Discharged home	Intensive care unit	Stroke unit	Discharged to rehabilitation facility
Time to presentation — hr	28	16	8	2	8
Signs and symptoms of stroke	Hemiplegia on left side, facial droop, gaze preference, homonymous hemianopia, dysarthria, sensory deficit	Reduced level of consciousness, dysphasia, hemiplegia on right side, dysarthria, sensory deficit	Reduced level of consciousness, gaze preference to the right, left homonymous hemianopia, hemiplegia on left side, ataxia	Reduced level of consciousness, global dysphasia, hemiplegia on right side, gaze preference	Reduced level of consciousness, hemiplegia on left side, dysarthria, facial weakness
Vascular territory	Right internal carotid artery	Left middle cerebral artery	Right posterior cerebral artery	Left middle cerebral artery	Right middle cerebral artery
Imaging for diagnosis	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP
Treatment for stroke	Apixaban (5 mg twice daily)	Clot retrieval, apixaban (5 mg twice daily)	Clot retrieval, aspirin (81 mg daily)	Intravenous t-PA, clot retrieval, hemicraniectomy, aspirin (81 mg daily)	Clot retrieval, stent, aspirin (325 mg daily), clopidogrel (75 mg daily)
Covid-19 symptoms	Cough, headache, chills	No symptoms; recently exposed to family member with PCR-positive Covid-19	None	Lethargy	Fever, cough, lethargy
White-cell count — per mm^3	7800	9900	5500	9000	4900
Platelet count — per mm^3	427,000	299,000	135,000	372,000	255,000
Prothrombin time — sec	13.3	13.4	14.4	12.8	15.2
Activated partial-thromboplastin time — sec	25.0	42.7	27.7	26.9	37.0
Fibrinogen — mg/dl	501	370	739	443	531
D-dimer — ng/ml	460	52	2230	13,800	1750
Ferritin — ng/ml	7	136	1564	987	596

* Reference ranges are as follows: platelet count, 150,000 to 450,000 per cubic millimeter; prothrombin time, 12.3 to 14.9 seconds; activated partial-thromboplastin time, 25.4 to 34.9 seconds; fibrinogen, 175 to 450 mg per deciliter; D-dimer, 0 to 500 ng per milliliter; and ferritin, 30 to 400 ng per milliliter. CT denotes computed tomography, CTA CT angiography, CTP CT perfusion, MRI magnetic resonance imaging, NA not applicable, PCR polymerase chain reaction, and t-PA tissue plasminogen activator.
† The patients were screened for smoking, hypertension, hyperlipidemia, diabetes, atrial fibrillation, congestive heart failure, illicit drug use, and neck trauma.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher numbers indicating more severe stroke.

Oxley, T. J., Mocco, J., Majidi, S., Kellner, C. P., Shoirah, H., Singh, I. P., . . . Fifi, J. T. (2020). Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med, 382*(20), e60. doi:10.1056/NEJMc2009787

Prospective Acute Ischemic Stroke Outcomes After Endovascular Therapy: A Real-World Experience

Sabareesh K. Natarajan[1,3], Yuval Karmon[1,3], Kenneth V. Snyder[1,3], Hajime Ohta[1,3], Erik F. Hauck[1,3], L. Nelson Hopkins[1,2,3], Adnan H. Siddiqui[1,2,3], Elad I. Levy[1,2,3]

■ OBJECTIVE: **To report results of endovascular therapy for acute ischemic stroke (AIS) in patients who were not candidates for intravenous thrombolysis (IVT) or in whom IVT failed.**

■ METHODS: **Prospectively collected data for patients treated between January 2006 and June 2009 were analyzed retrospectively. After careful patient and therapy selection, 213 AIS patients with a mean NIHSS score of 14.2 at presentation underwent intervention. End points analyzed were Thrombolysis in Myocardial Infarction (TIMI) 2/3 reperfusion, symptomatic intracranial hemorrhage (SICH) rates, and 90-day outcomes (modified Rankin Scale [mRS] and mortality). Multivariate binary logistic regression analysis was used to assess independent predictors of end points.**

■ RESULTS: **Of 189 patients with anterior circulation occlusions, 135 were treated within 0–8 hours, 33 were treated after 8 or more hours, and 21 were treated after wake-up stroke (WUS). Among 24 patients treated with posterior circulation occlusions, 4 had WUS. After treatment, 72.3% patients had TIMI 2/3 reperfusion; SICH rate was 8.7%; at 90 days, 36.6% recovered to mRS 2 or less. SICH rate was higher in patients with anterior circulation strokes who received treatment 8 or more hours after symptom onset (odds ratio [OR] = 3.8) and patients with WUS (OR = 4.9). In patients treated within 8 hours of onset of symptoms of anterior circulation stroke, SICH rate was only 6.7%. There was no difference in outcomes in patients with WUS compared with patients treated less than 8 hours after stroke onset.**

■ CONCLUSIONS: **This is the first and largest prospective study to the authors' knowledge that shows endovascular therapy for AIS patients in a real-world setting. High recanalization rates with low SICH rates were achieved using careful patient and therapy selection.**

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ORIGINAL ARTICLE

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Jeffrey L. Saver, M.D., Mayank Goyal, M.D., Alain Bonafe, M.D., Hans-Christoph Diener, M.D., Ph.D., Elad I. Levy, M.D., Vitor M. Pereira, M.D., Gregory W. Albers, M.D., Christophe Cognard, M.D., David J. Cohen, M.D., Werner Hacke, M.D., Ph.D., Olav Jansen, M.D., Ph.D., Tudor G. Jovin, M.D., Heinrich P. Mattle, M.D., Raul G. Nogueira, M.D., Adnan H. Siddiqui, M.D., Ph.D., Dileep R. Yavagal, M.D., Blaise W. Baxter, M.D., Thomas G. Devlin, M.D., Ph.D., Demetrius K. Lopes, M.D., Vivek K. Reddy, M.D., Richard du Mesnil de Rochemont, M.D., Oliver C. Singer, M.D., and Reza Jahan, M.D., for the SWIFT PRIME Investigators*

SWIFT PRIME

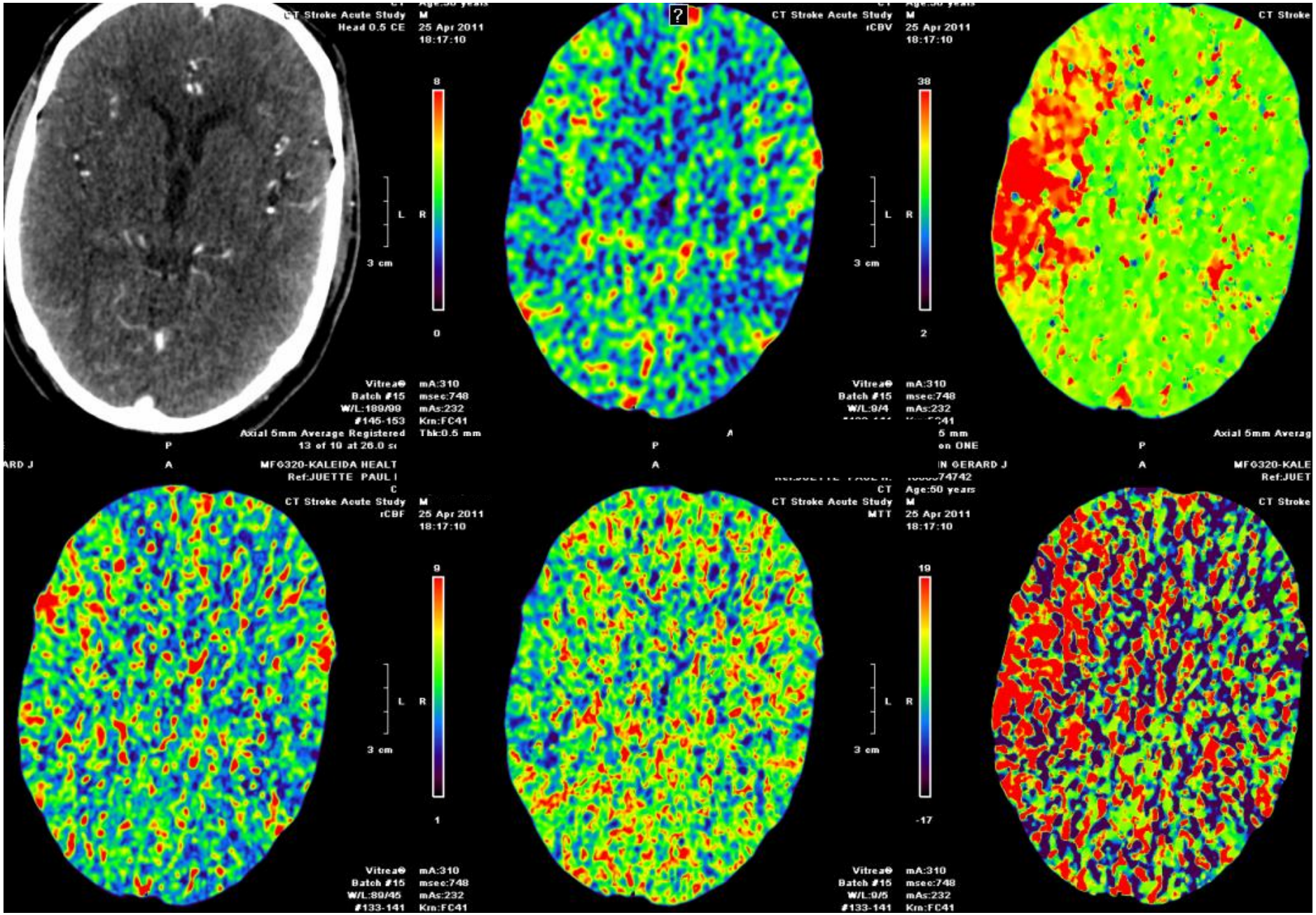
Medtronic- US

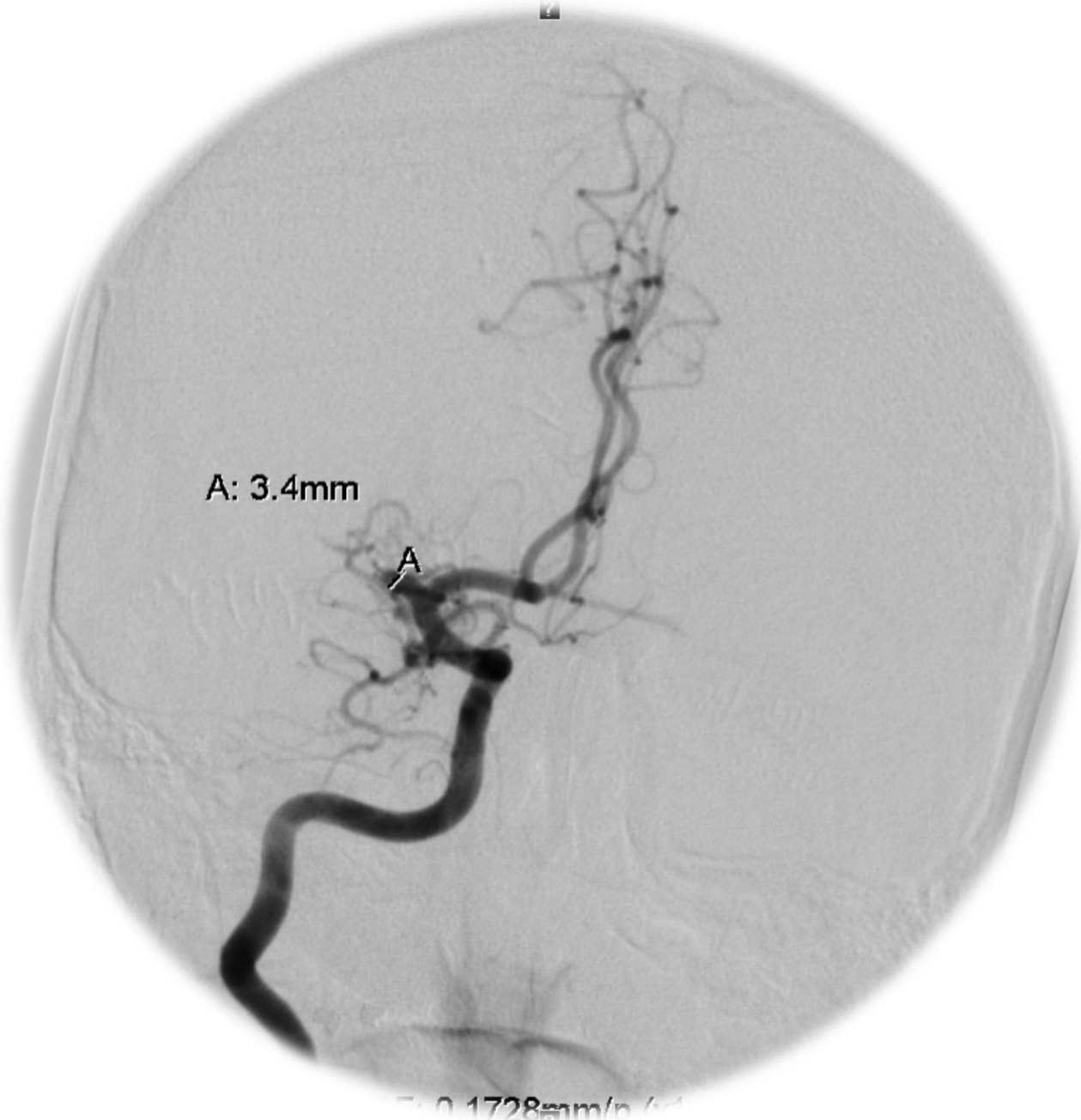
- Proximal anterior circulation occlusion
- Randomized patients who received IV-tPA to undergo endovascular therapy with Solitaire or continue receiving IV-tPA alone

- RESULTS:
- Endovascular showed improvement in mRS at 90 days
  - **60.2% vs 35.5% , P<0.001**
- No significant differences in mortality or the occurrence of symptomatic ICH
- **NNT = 4**

2.2.3. Mechanical Thrombectomy Eligibility–Vessel Imaging (Continued)	COR	LOE	New, Revised, or Unchanged
5. It may be reasonable to incorporate collateral flow status into clinical decision-making in some candidates to determine eligibility for mechanical thrombectomy.	**IIb**	**C-LD**	Recommendation revised from 2015 Endovascular.
Several studies, including secondary analyses from MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands) and IMS (Interventional Management of Stroke) III, provide data supporting the role of collateral assessments in identifying patients likely or unlikely to benefit from mechanical thrombectomy.[103,104] The ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), using multiphase CTA to select patients with moderate to good collateral circulation for mechanical thrombectomy up to 12 hours from onset, was stopped early for efficacy.[105] Acquisition of advanced imaging should not delay door–to–groin puncture times.			See Tables XXIV and XXV in online Data Supplement 1.

2.2.4. Mechanical Thrombectomy Eligibility–Multimodal Imaging	COR	LOE	New, Revised, or Unchanged
1. When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window.	**I**	**A**	New recommendation.
The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical-core mismatch (a combination of age-adjusted NIHSS score and age-adjusted core infarct size on CTP or DW-MRI) as an eligibility criterion to select patients with large anterior circulation vessel occlusion for mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in functional outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33% [95% CI, 21–44]; posterior probability of superiority >0.999).[51] The DEFUSE 3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67 [95% CI, 1.60–4.48]; $P<0.0001$).[52] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice.[51,52]			See Table XVII in online Data Supplement 1.


CT Stroke Acute Study
Head 0.5 CE
25 Apr 2011
18:17:10
8
0
3 cm
Vitrea
Batch #15
W/L:189/89
#145-153
Axial 5mm Average Registered
13 of 10 at 26.0
mA:310
msec:748
mAs:232
Krn:FC41
Thk:0.5 mm
CT Stroke Acute Study
rCBV
25 Apr 2011
18:17:10
38
2
3 cm
W/L:9/4
CT Stroke
Axial 5mm Averag
MF0320-KALE
Ref:JUET
CT Stroke Acute Study
rCBF
25 Apr 2011
18:17:10
9
1
3 cm
W/L:89/45
CT Stroke Acute Study
MTT
25 Apr 2011
18:17:10
Age:50 years
19
-17
3 cm
W/L:9/5
CT Stroke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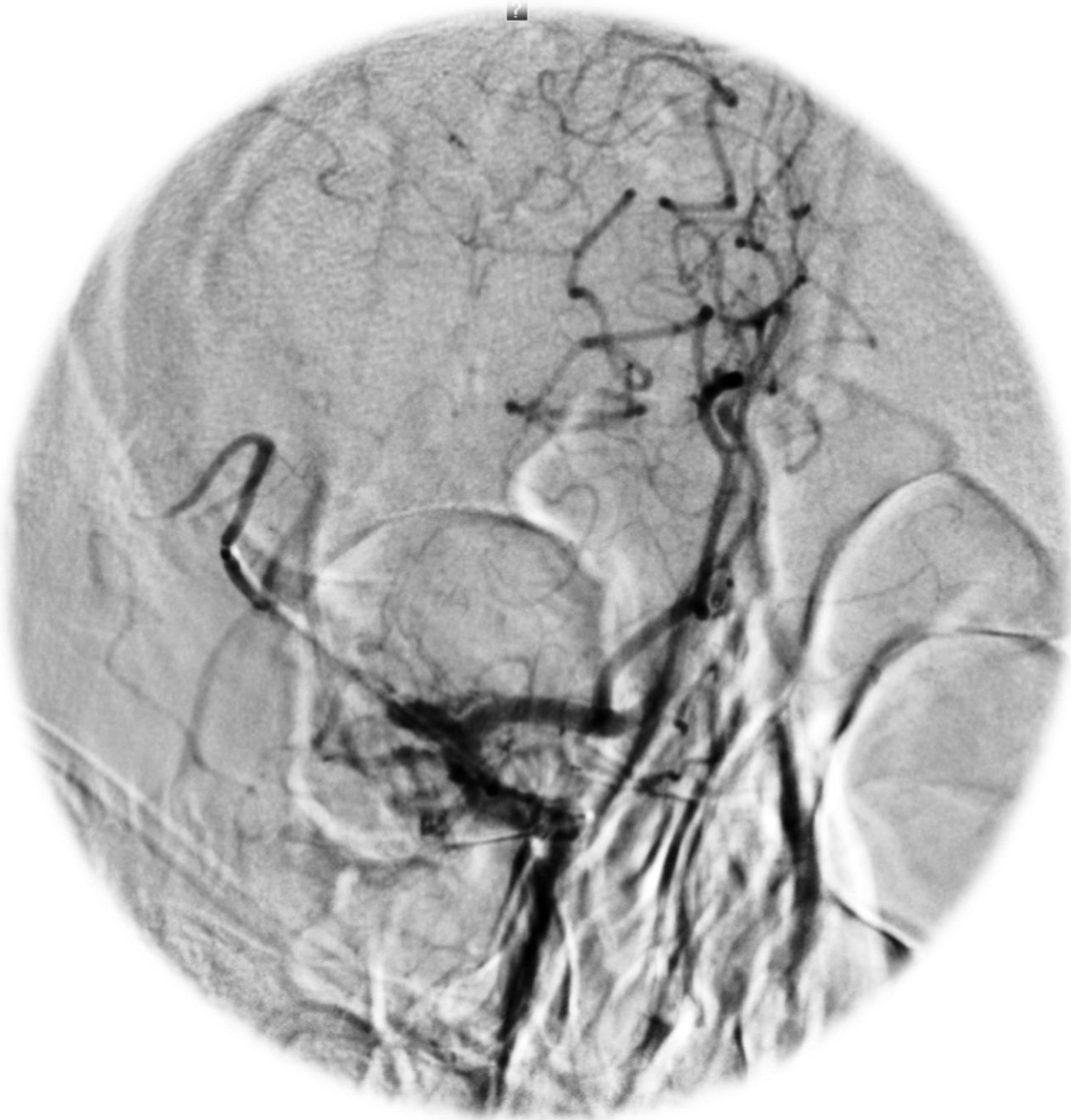
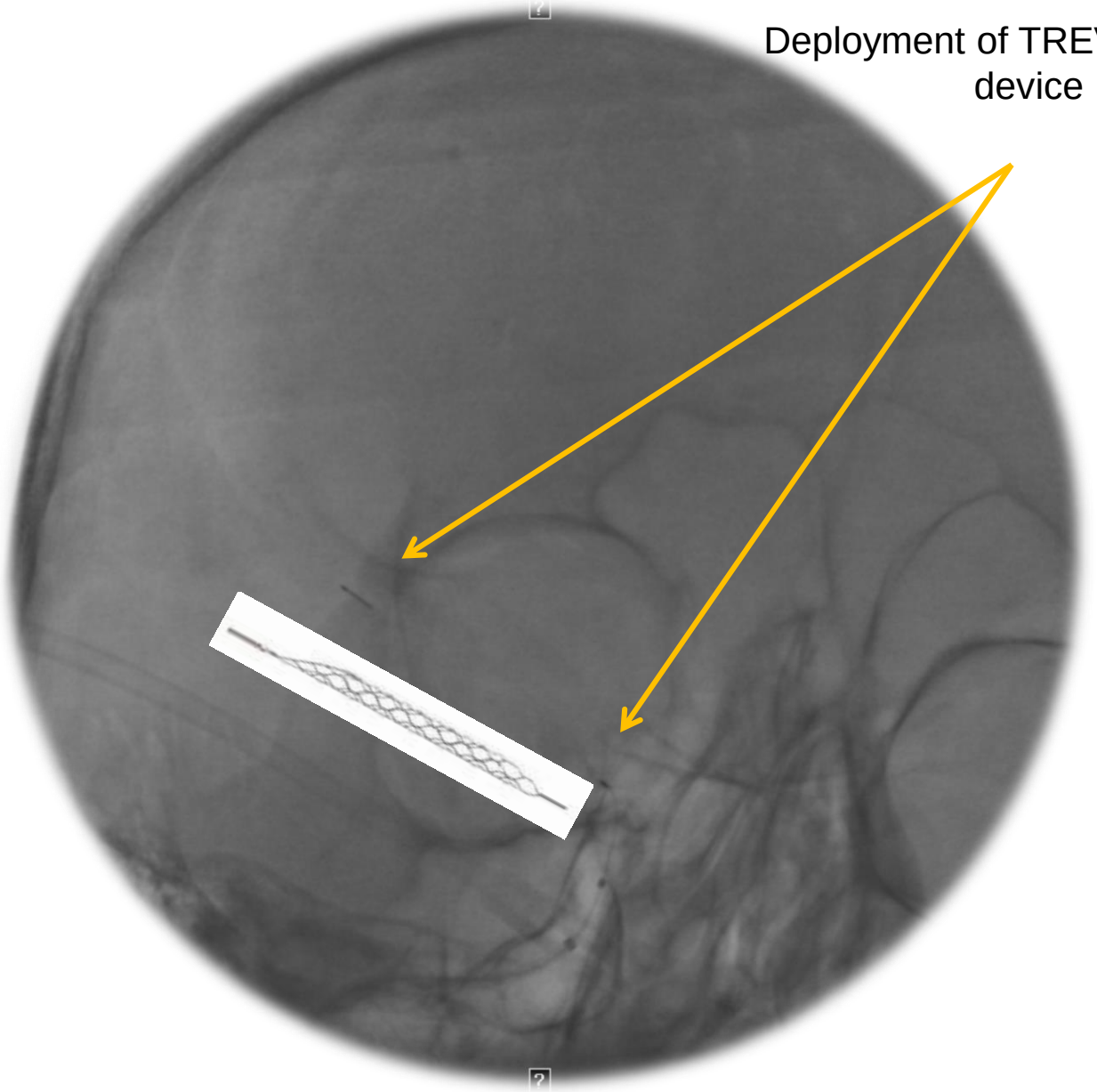
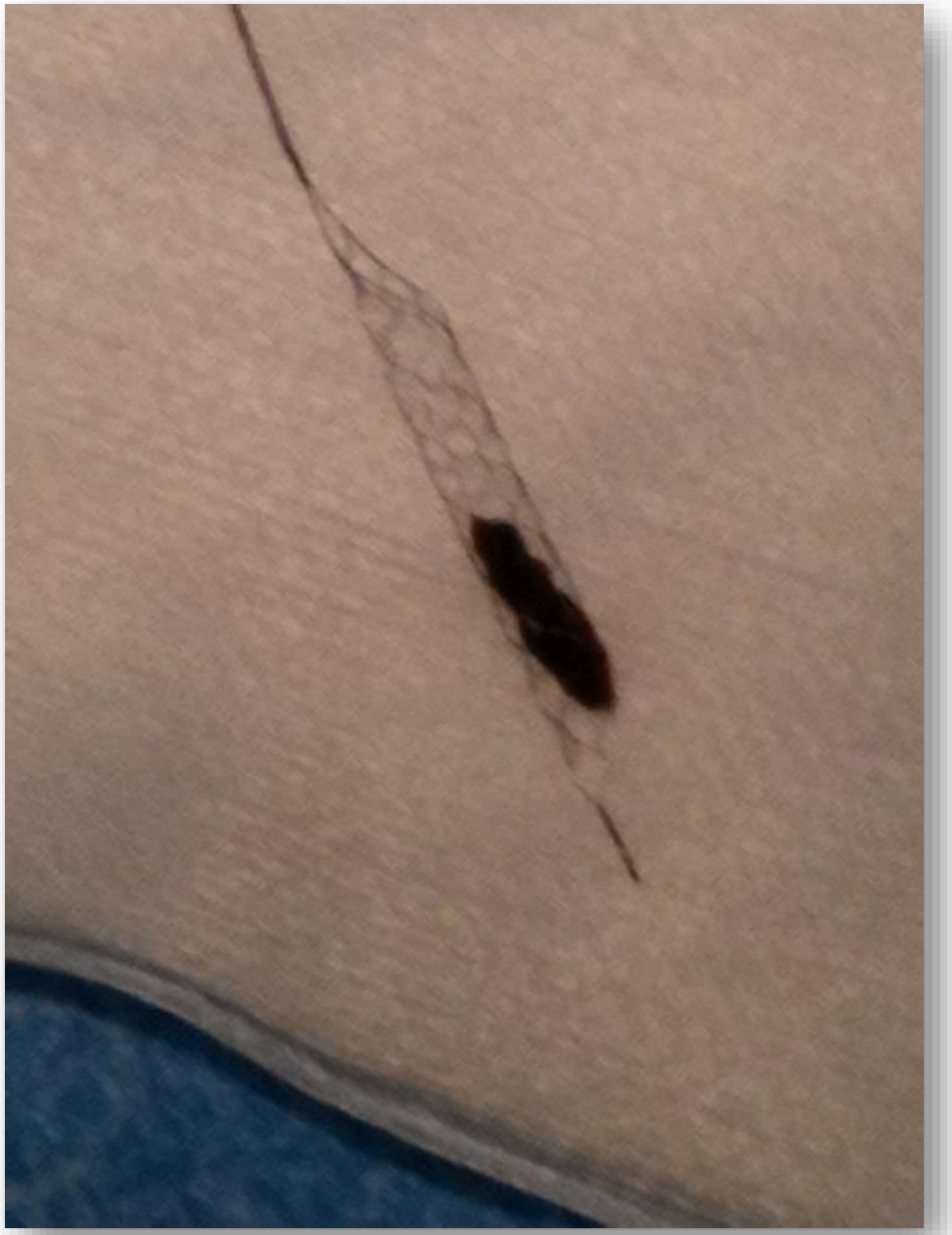
A

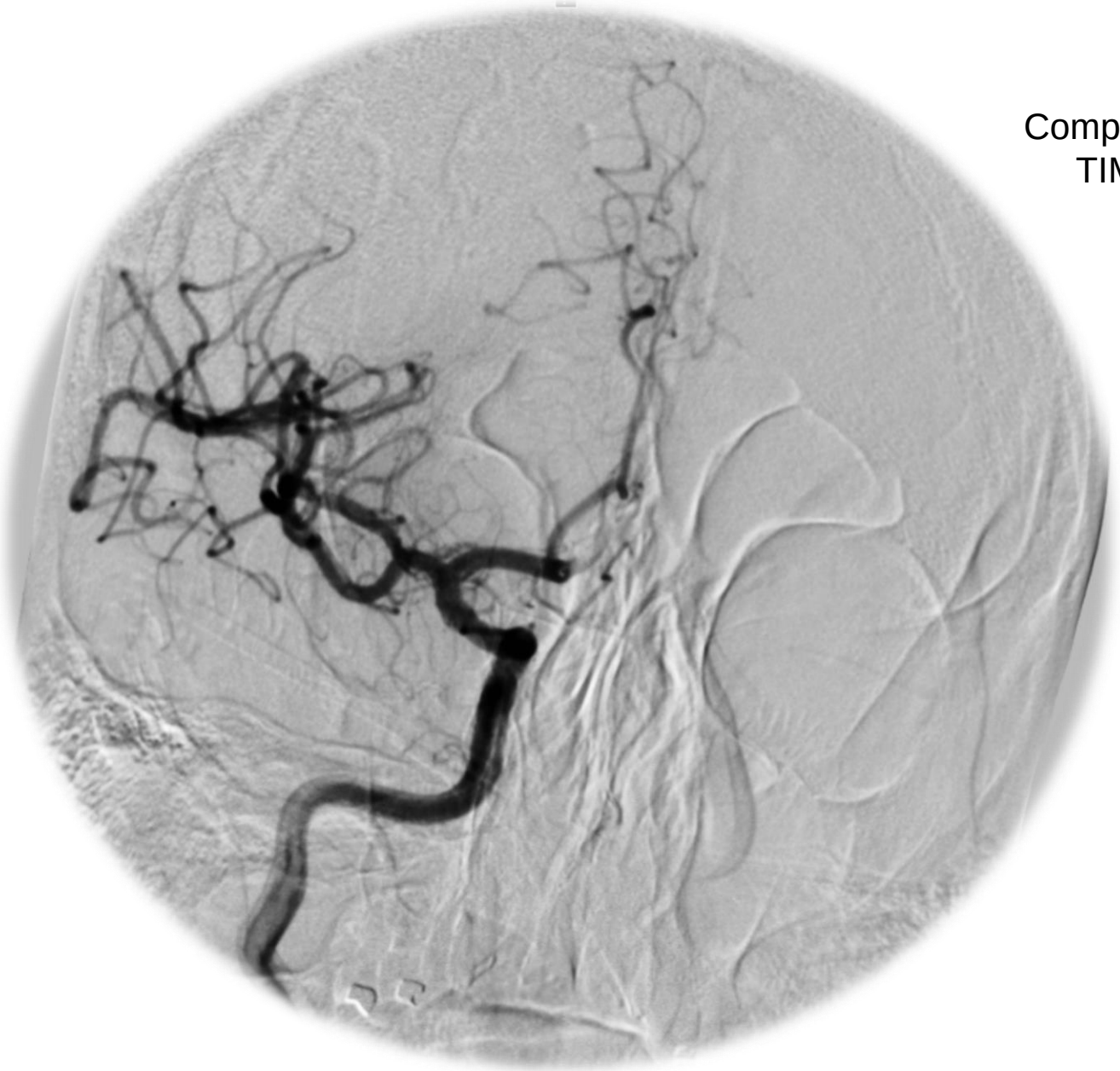



Deployment of TREVO retrieval device



1st pull of the microcatheter with the retrieval device

Total intervention time ~20 min

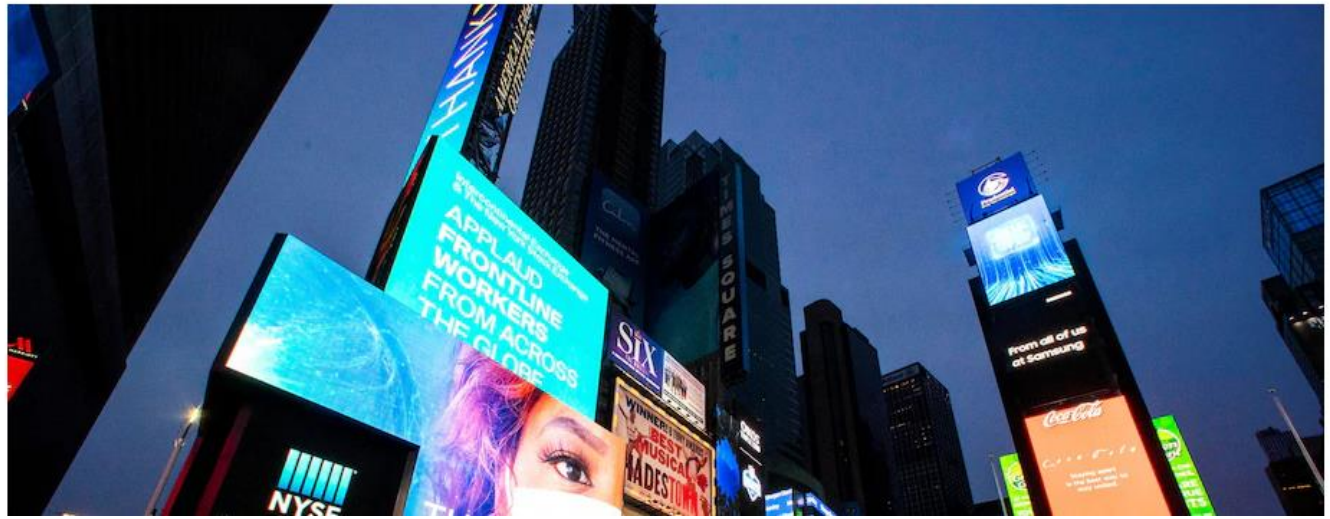


Complete recanalization
TIMI-3 after 1 pull

Health

Young and middle-aged people, barely sick with covid-19, are dying of strokes

Doctors sound alarm about patients in their 30s and 40s left debilitated or dead. Some didn't even know they were infected.



As Oxley, an interventional neurologist, began the procedure to remove the clot, he observed something he had never seen before. On the monitors, the brain typically shows up as a tangle of black squiggles — "like a can of spaghetti," he said — that provide a map of blood vessels. A clot shows up as a blank spot. As he used a needlelike device to pull out the clot, he saw new clots forming in real-time around it.

"This is crazy," he remembers telling his boss.

Many doctors expressed worry that as the New York City Fire Department was picking up four times as many people who died at home as normal during the peak of infection that some of the dead had suffered sudden strokes. The truth may never be known because few autopsies were conducted.

COVID and LVO in young patients?

- NE AHA/ASA – not consistent, some with increased hemorrhagic strokes from normal rates
- NYS stroke consortium – not consistent

- Function of local prevalence?
  - NYC (25-30% prevalence)
  - Mt Sinai ~2500 pts/day

Where are all the stokes?

Stroke Ahead of Print…this week.

EDITORIAL

The Curious Case of the Missing Strokes During the COVID-19 Pandemic

Diana Aguiar de Sousa, MD, MSc; Else Charlotte Sandset, MD, PhD; Mitchell S. V. Elkind, MD, MS

- Two registries recently published…One from China (280 centers) and the other from Barcelona Spain
- China
  - 40% drop in stroke admissions during pandemic surge
  - Proportion of thrombectomy cases same
- Barcelona
  - 23% reduction in admissions
  - 330% increase in emergency medical calls
  - They report no changes in in hospital metrics (door to need times, door to groin puncture, proportion of patients undergoing thrombectomy, neurologic and functional outcomes)

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Collateral Effect of Covid-19 on Stroke Evaluation in the United States

- Kansagra, Goyal et al.
- RAPID software platform (iSchemaView)
- 231,753 patients who underwent imaging processed with RAPID software in 856 hospitals in the United States from July 1, 2019 through April 27, 2020

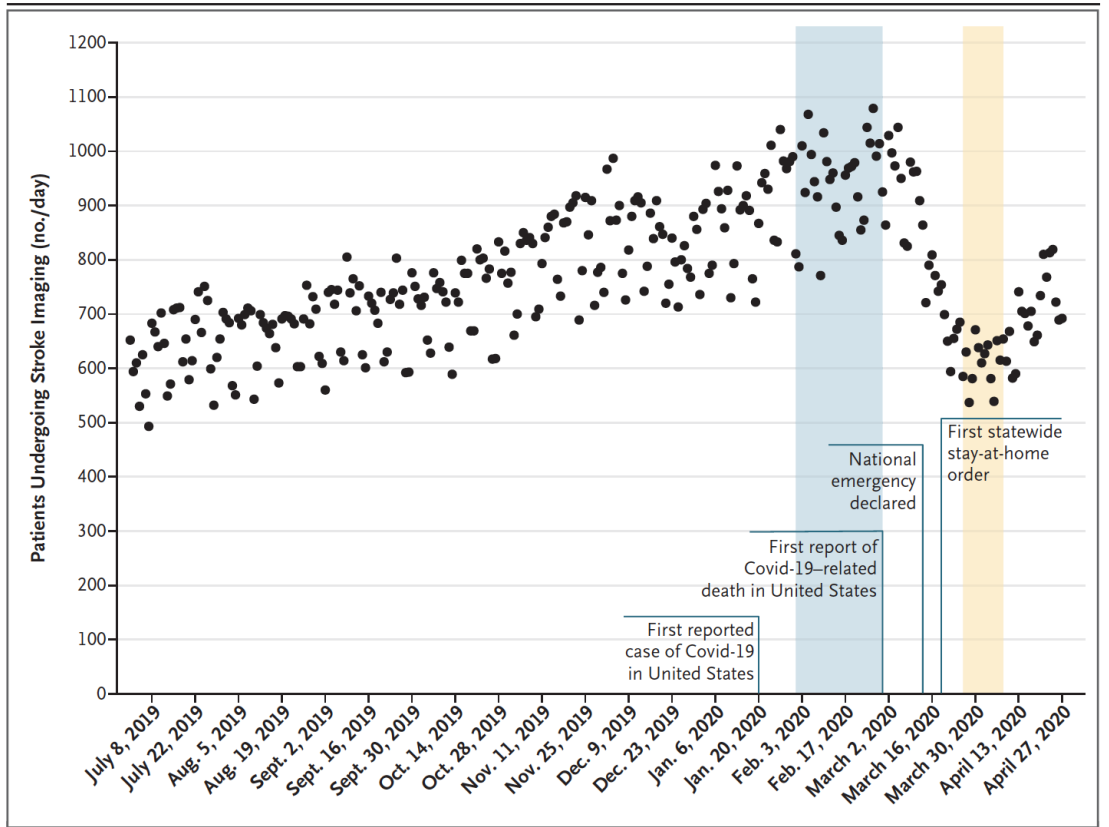


Figure 1. Daily Counts of Unique Patients Who Underwent Neuroimaging for Stroke in the United States, July 2019 through April 2020.

All the neuroimaging tests were processed with RAPID software. Each dot represents a daily count of patients. Shaded regions correspond to the prepandemic (blue) and early-pandemic (yellow) epochs. The increase in the number of patients who underwent imaging from July 2019 to March 2020 reflects an increase in the number of hospitals that were using RAPID software.

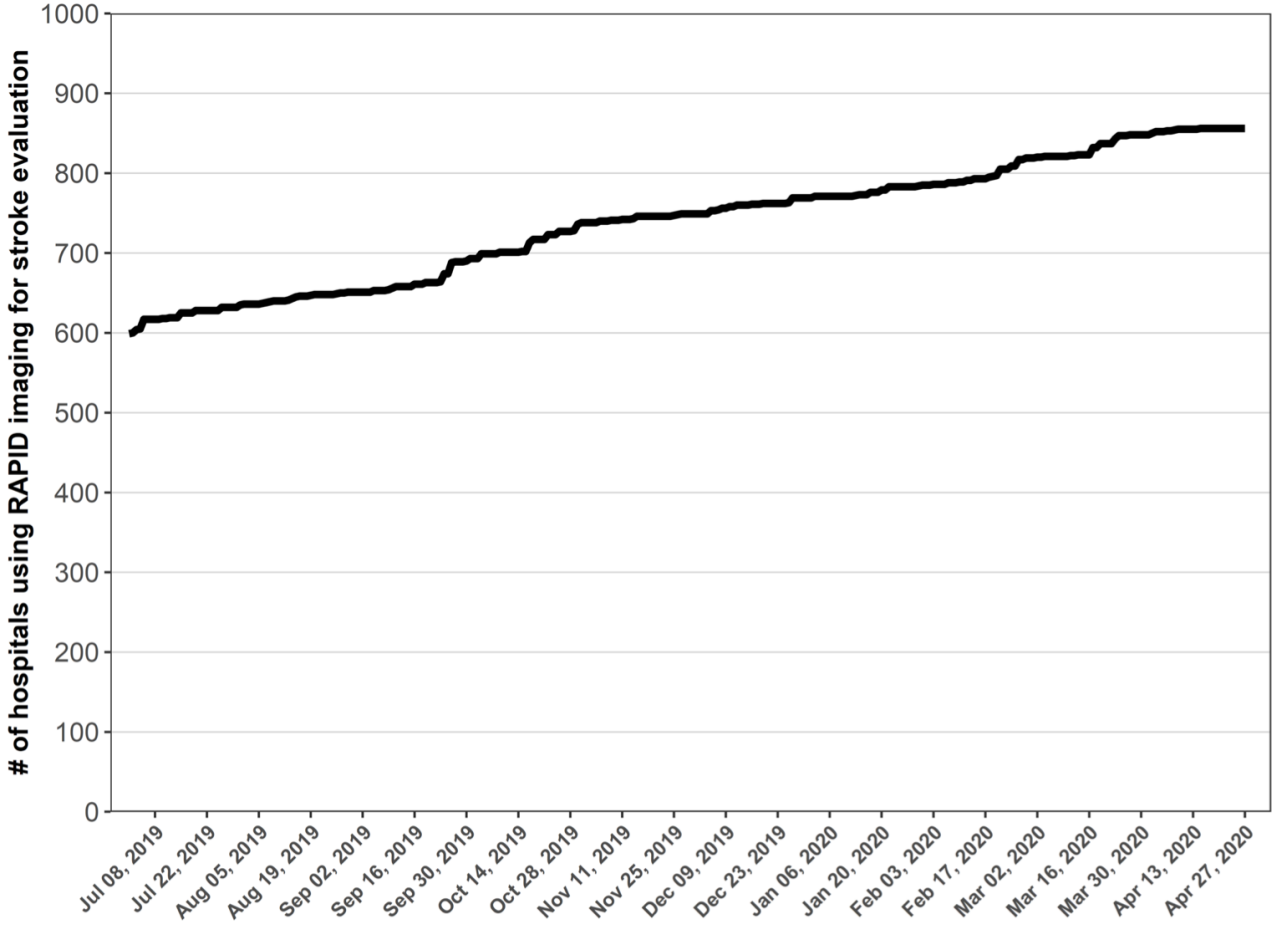


Figure S2. Number of RAPID-connected hospitals in the United States.

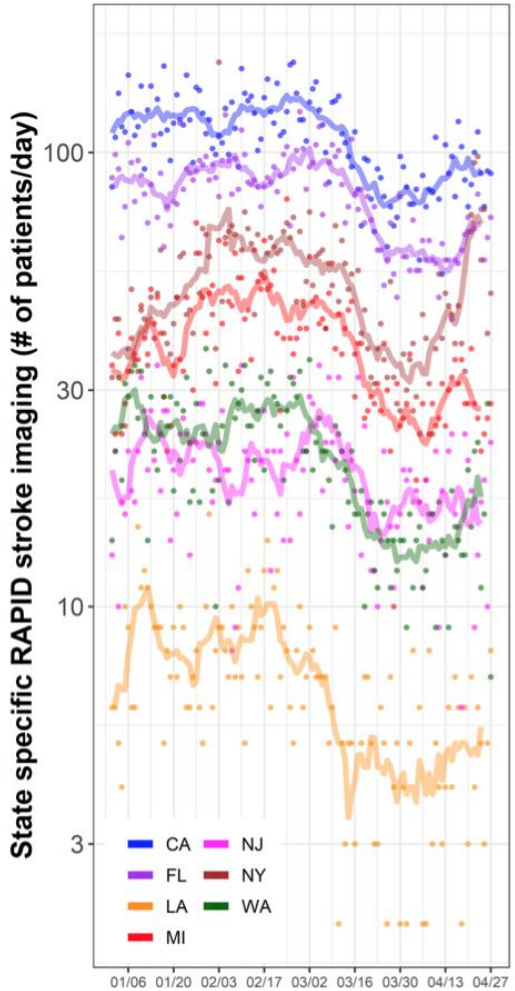


Figure S3. Patients evaluated daily with RAPID software in selected states. Trendlines are generated using a 1-week moving average of underlying daily counts.

Leading Opinion

International Journal of Stroke
WSO

COVID-19 and stroke—A global World Stroke Organization perspective

Hugh S Markus[1] and Michael Brainin[2]

International Journal of Stroke
0(0) 1–4

DOI: 10.1177/1747493020923472
journals.sagepub.com/home/wso
SAGE

Abstract

The COVID-19 pandemic affecting all parts of the world is having huge implications for stroke care. Not only do stroke patients appear to be more susceptible to severe infection, but the pandemic is having major implications on how we deliver stroke care, while ensuing safety of both our patients and health care professionals. COVID-19 infection itself has also been described as a risk factor for stroke. The World Stroke Organization has been monitoring the impact of the pandemic globally, and has identified an initial marked fall in stroke presentations as well as a widespread impact on stroke services. The pandemic is changing the way we deliver care, and has highlighted the enormous potential of telemedicine in stroke care.

Keywords

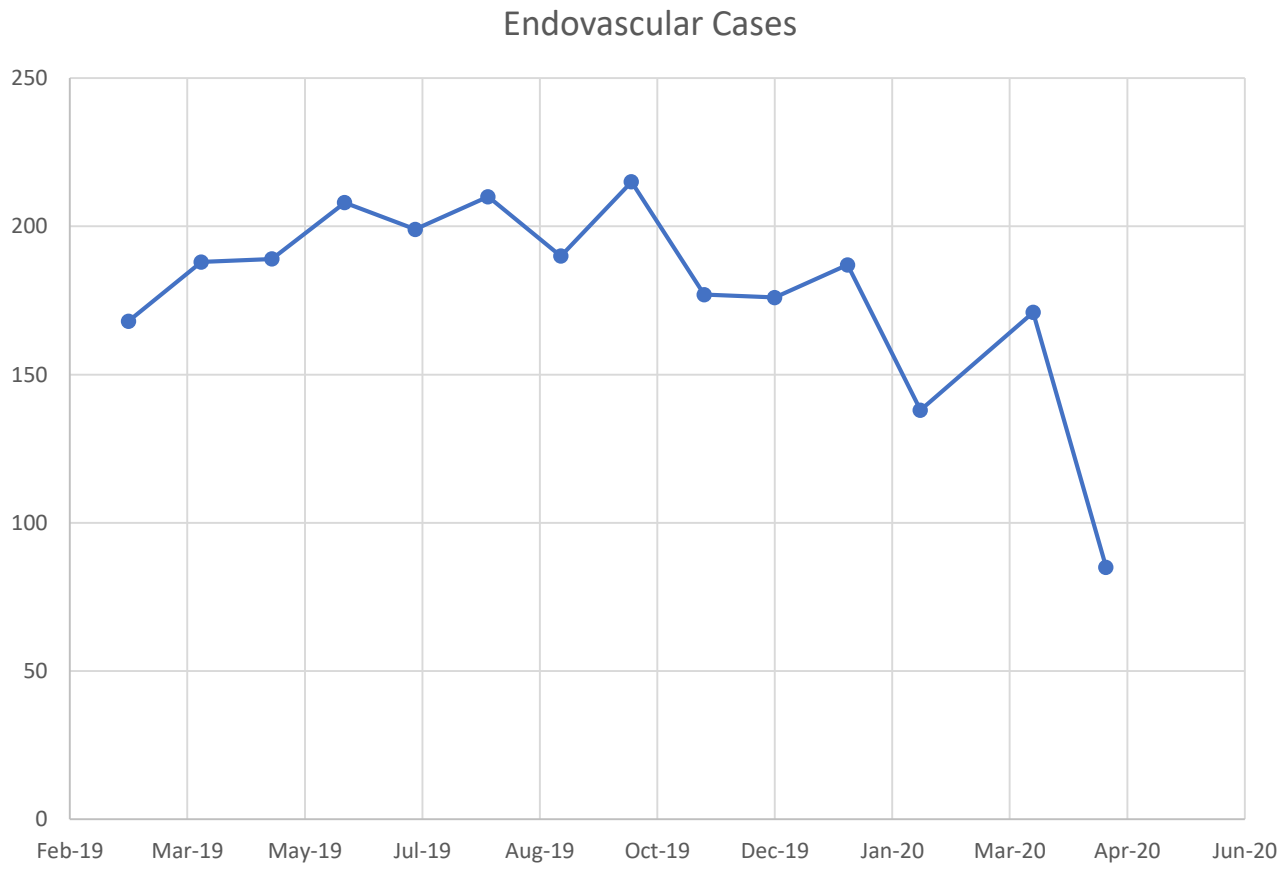
COVID-19, stroke, pandemic, World Stroke Organization, Intensive Care Unit, healthcare systems

Received: 14 April 2020; accepted: 14 April 2020

- WSO monitoring stroke numbers worldwide
  - Decreased presentations
    - Patients afraid to come to hospital with milder symptoms
    - Nonurgent cases
    - Delayed presentations, including intervention times
- Sharp reduction number of acute stroke admissions
  - Chile, Colombia, Iran, Greece, UK, Belgium, and Italy
    - Reductions in some countries 50-80%

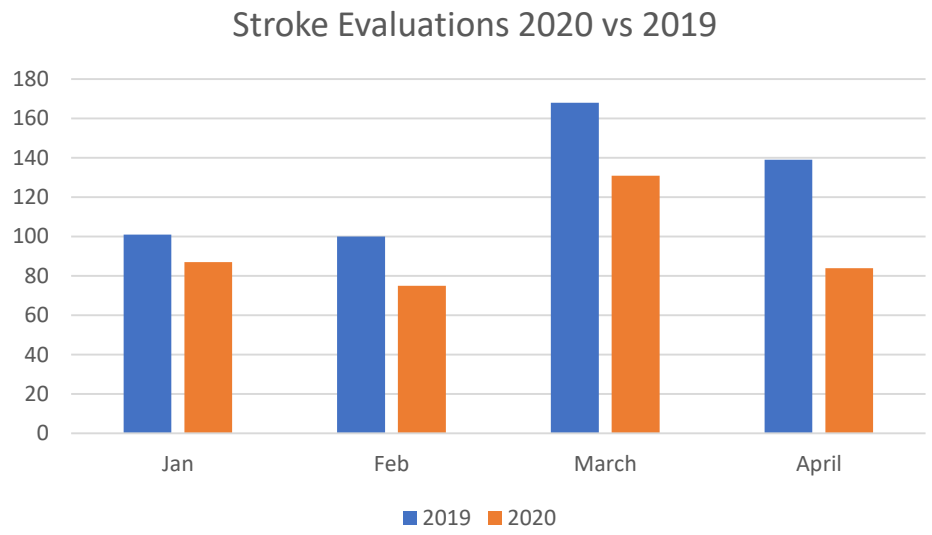
Neuroendovascular Service March 2019 – April 2020

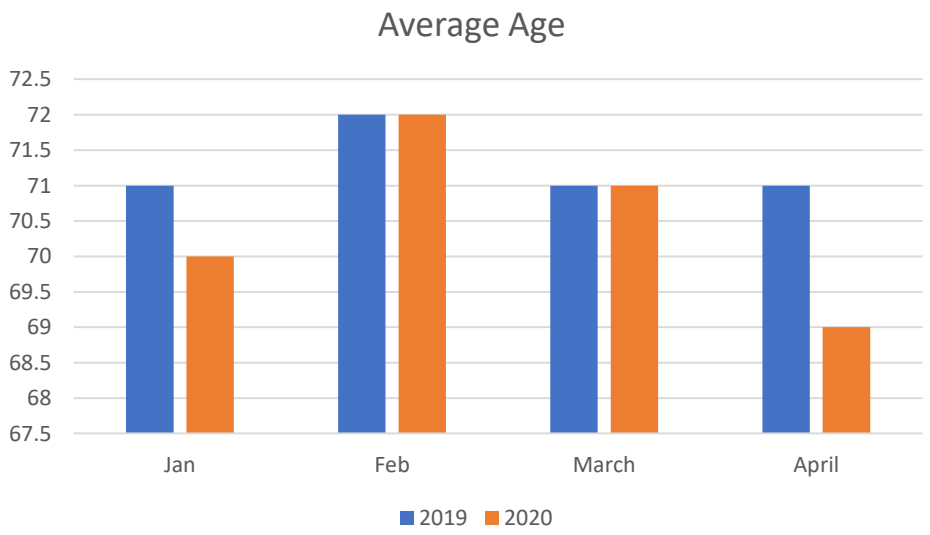
- Total cases: 2245 (average 187/month)
- Diagnostic Total: 1353 (average 113/month)
- Intervention Total: 892 (average 74/month)

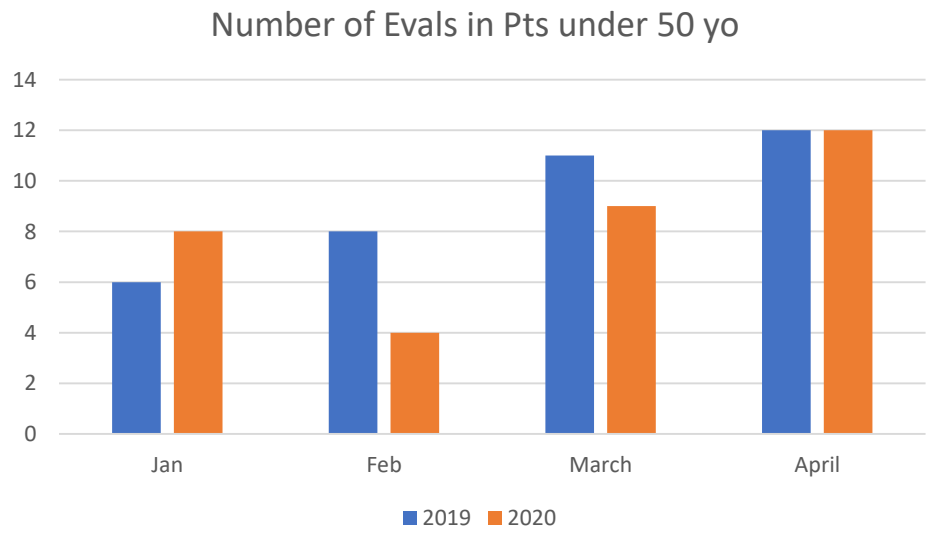


All Stroke Evals

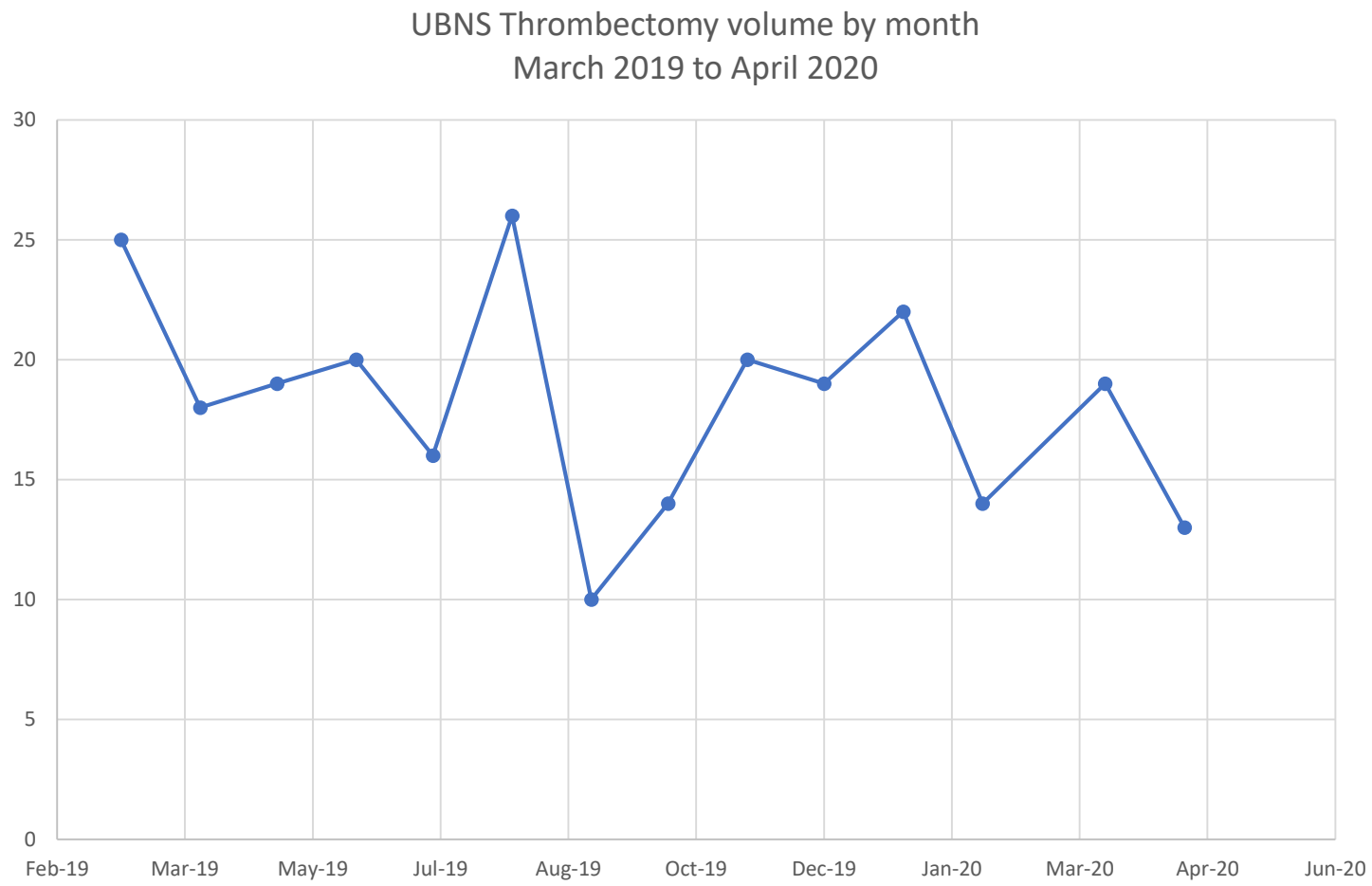
Currently reviewed severity of NIHSS at presentation







Month	Thrombectomy volume
Mar-19	25
Apr-19	18
May-19	19
Jun-19	20
Jul-19	16
Aug-19	26
Sep-19	10
Oct-19	14
Nov-19	20
Dec-19	19
Jan-20	22
Feb-20	14
Mar-20	19
Apr-20	13



Where are all the stokes?

- Strict stay at home orders and fear of going to hospital
- Mild strokes are staying at home? (no sign difference in NIHSS presentation)
- Increased social isolation
  - Young are less apt to isolate and they are coming in when identified?
  - Significant increase in mortality unexplained by COVID19 alone (Excess mortality rate)
- Massive increase in emergency calls hampered normal stroke pathway (not at comprehensive centers)
- Misdiagnosis
- Stroke numbers may actually have reduced (multifactorial)

UBNS COVID publications

- Pandey AS, Ringer AJ, Rai AT, Kan P, Jabbour P, Siddiqui AH, Levy EI, Snyder KV, Riina H, Tanweer O, Levitt MR, Kim LJ, Veznedaroglu E, Binning MJ, Arthur AS, Mocco J, Schirmer C, Thompson BG, Langer D; Endovascular Neurosurgery Research Group (ENRG); Minimizing SARS-CoV-2 Exposure when Performing Surgical Interventions During the COVID-19 Pandemic. *J Neurointerv Surg* (epub May 20, 2020 DOI 10.1136/neurintsurg-2020-016161). PMID 32434798 Free article https://jnis.bmj.com/content/early/2020/05/19/neurintsurg-2020-016161.long
- Pandey AS, Ringer AJ, Rai A, Kan PT, Jabbour PM, Siddiqui A, Levy E, Snyder KV, Riina HA,Tanweer O, Levitt MR, Kim LJ, Veznedaroglu E, Binning M, Arthur AS, Mocco J, Schirmer CM, Thompson BG, Langer D;Endovascular Neurosurgery Research Group (ENRG): Letter: Considerations for Performing Emergent Neurointerventional Procedures in a COVID-19 Environment. *Neurosurgery* (epub May 2, 2020 DOI 10.1093/neuros/nyaa173) PMID 32358606 Free article https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa173/5828027
- Fraser JF, Arthur A, Chen M, Levitt M, Mocco J, Albuquerque F, Ansari SA, Dabus G, Jayaraman MV, Mack WJ, Milburn JM, Mokin M, Narayanan S, Puri AS, Siddiqui AH, Tsai JP, Klucznik RP: Society of NeuroInterventional Surgery Recommendations for the Care of Emergent Neurointerventional Patients in the Setting of COVID-19. *SNIS Neuro News* (epub April 3, 2020). https://www.snisonline.org/wp-content/uploads/2020/03/SNIS-COVID-Stroke-Protocol.pdf

Treatment of Acute Ischemic Stroke due to Large Vessel Occlusion With COVID-19

Experience From Paris

Simon Escalard, Benjamin Maïer, Hocine Redjem, François Delvoye, Solène Hébert, Stanislas Smajda, Gabriele Ciccio, Jean-Philippe Desilles, Mikael Mazighi, Raphael Blanc, Michel Piotin

Originally published 29 May 2020 | Stroke. ;0

Jump to

Abstract

Footnotes

Abstract

Background and Purpose:

Higher rates of strokes have been observed in patients with coronavirus disease 2019 (COVID-19), but data regarding the outcomes of COVID-19 patients suffering from acute ischemic stroke due to large vessel occlusion (LVO) are lacking. We report our initial experience in the treatment of acute ischemic stroke with LVO in patients with COVID-19.

Methods:

All consecutive patients with COVID-19 with acute ischemic stroke due to LVO treated in our institution during the 6 first weeks of the COVID-19 outbreak were included. Baseline clinical and radiological findings, treatment, and short-term outcomes are reported.

Results:

We identified 10 patients with confirmed COVID-19 treated for an acute ischemic stroke due to LVO. Eight were men, with a median age of 59.5 years. Seven had none or mild symptoms of COVID-19 at stroke onset. Median time from COVID-19 symptoms to stroke onset was 6 days. All patients had brain imaging within 3 hours from symptoms onset. Five patients had multi-territory LVO. Five received intravenous alteplase. All patients had mechanical thrombectomy. Nine patients achieved successful recanalization (mTICI2B-3), none experienced early neurological improvement, 4 had early cerebral reocclusion, and a total of 6 patients (60%) died in the hospital.

Conclusions:

Best medical care including early intravenous thrombolysis, and successful and prompt recanalization achieved with mechanical thrombectomy, resulted in poor outcomes in patients with COVID-19. Although our results require further confirmation, a different pharmacological approach (antiplatelet or other) should be investigated to take in account inflammatory and coagulation disorders associated with COVID-19.

Stroke

BRIEF REPORT

Clinical Characteristics and Outcomes of COVID-19 Patients With a History of Stroke in Wuhan, China

Chuan Qin, MD, PhD*; Luoqi Zhou, MD*; Ziwei Hu, MD; Sheng Yang, MD; Shuoqi Zhang, MD, PhD; Man Chen, MD; Haihan Yu, MD; Dai-Shi Tian, MD, PhD; Wei Wang, MD, PhD

BACKGROUND AND PURPOSE: Information on stroke survivors infected with coronavirus disease 2019 (COVID-19) is limited. The aim of this study was to describe specific clinical characteristics and outcomes of patients with COVID-19 with a history of stroke.

METHODS: All the confirmed cases of COVID-19 at Tongji Hospital from January 27 to March 5, 2020, were included in our cohort study. Clinical data were analyzed and compared between patients with and without a history of stroke.

RESULTS: Of the included 1875 patients with COVID-19, 50 patients had a history of stroke. The COVID-19 patients with medical history of stroke were older with more comorbidities, had higher neutrophil count, and lower lymphocyte and platelet counts than those without history of stroke. The levels of D-dimers, cardiac troponin I, NT-pro-brain natriuretic peptide, and interleukin-6 were also markedly higher in patients with history of stroke. Stroke survivors who underwent COVID-19 developed more acute respiratory distress syndrome and received more noninvasive mechanical ventilation. Data from propensity-matched analysis indicated a higher proportion of patients with COVD-19 with a history of stroke were admitted to the intensive care unit requiring mechanical ventilation and were more likely to be held in the unit or die, compared with non-stroke history COVID-19 patients.

CONCLUSIONS: Patients with COVID-19 with a history of stroke had more severe clinical symptoms and poorer outcomes compared with those without a history of stroke.

Key Words: cardiovascular disease ■ comorbidity ■ COVID-19 ■ platelet count ■ troponin I

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c], M.S. Arbous[d], D.A.M.P.J. Gommers[e], K.M. Kant[f], F.H.J. Kaptein[a], J. van Paassen[d], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[e,1]

[a] Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands
[b] Department of Haematology, Erasmus University Medical Center, Rotterdam, the Netherlands
[c] Department of Anesthesiology and Critical Care, Amphia Hospital Breda and Oosterhout the Netherlands and TIAS/Tilburg University, Tilburg, the Netherlands
[d] Department of Intensive Care Medicine, Leiden University Medical Center, Leiden, the Netherlands
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[f] Department of Intensive Care, Amphia Hospital, Breda, the Netherlands

ABSTRACT

Introduction: COVID-19 may predispose to both venous and arterial thromboembolism due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation. Reports on the incidence of thrombotic complications are however not available.
Methods: We evaluated the incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism in all COVID-19 patients admitted to the ICU of 2 Dutch university hospitals and 1 Dutch teaching hospital.
Results: We studied 184 ICU patients with proven COVID-19 pneumonia of whom 23 died (13%), 22 were discharged alive (12%) and 139 (76%) were still on the ICU on April 5th 2020. All patients received at least standard doses thromboprophylaxis. The cumulative incidence of the composite outcome was 31% (95%CI 20-41), of which CTPA and/or ultrasonography confirmed VTE in 27% (95%CI 17-37%) and arterial thrombotic events in 3.7% (95%CI 0-8.2%). PE was the most frequent thrombotic complication (n = 25, 81%). Age (adjusted hazard ratio (aHR) 1.05/per year, 95%CI 1.004-1.01) and coagulopathy, defined as spontaneous prolongation of the prothrombin time > 3 s or activated partial thromboplastin time > 5 s (aHR 4.1, 95%CI 1.9-9.1), were independent predictors of thrombotic complications.
Conclusion: The 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high. Our findings reinforce the recommendation to strictly apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU, and are strongly suggestive of increasing the prophylaxis towards high-prophylactic doses, even in the absence of randomized evidence.

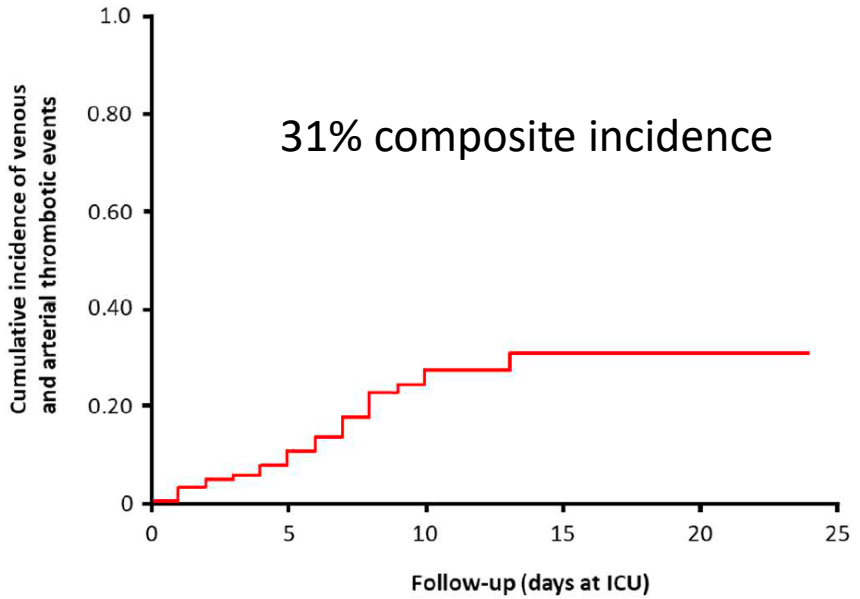


Fig. 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.

- Acute pulmonary embolism (PE)
- Deep-vein thrombosis (DVT)
- Ischemic stroke
- Myocardial infarction
- Systemic arterial embolism

Klok, F. A., Kruip, M., van der Meer, N. J. M., Arbous, M. S., Gommers, D., Kant, K. M., . . . Endeman, H. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. doi:10.1016/j.thromres.2020.04.013
Klok, F. A., Kruip, M., van der Meer, N. J. M., Arbous, M. S., Gommers, D., Kant, K. M., . . . Endeman, H. (2020). Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. doi:10.1016/j.thromres.2020.04.041

What does this all mean?

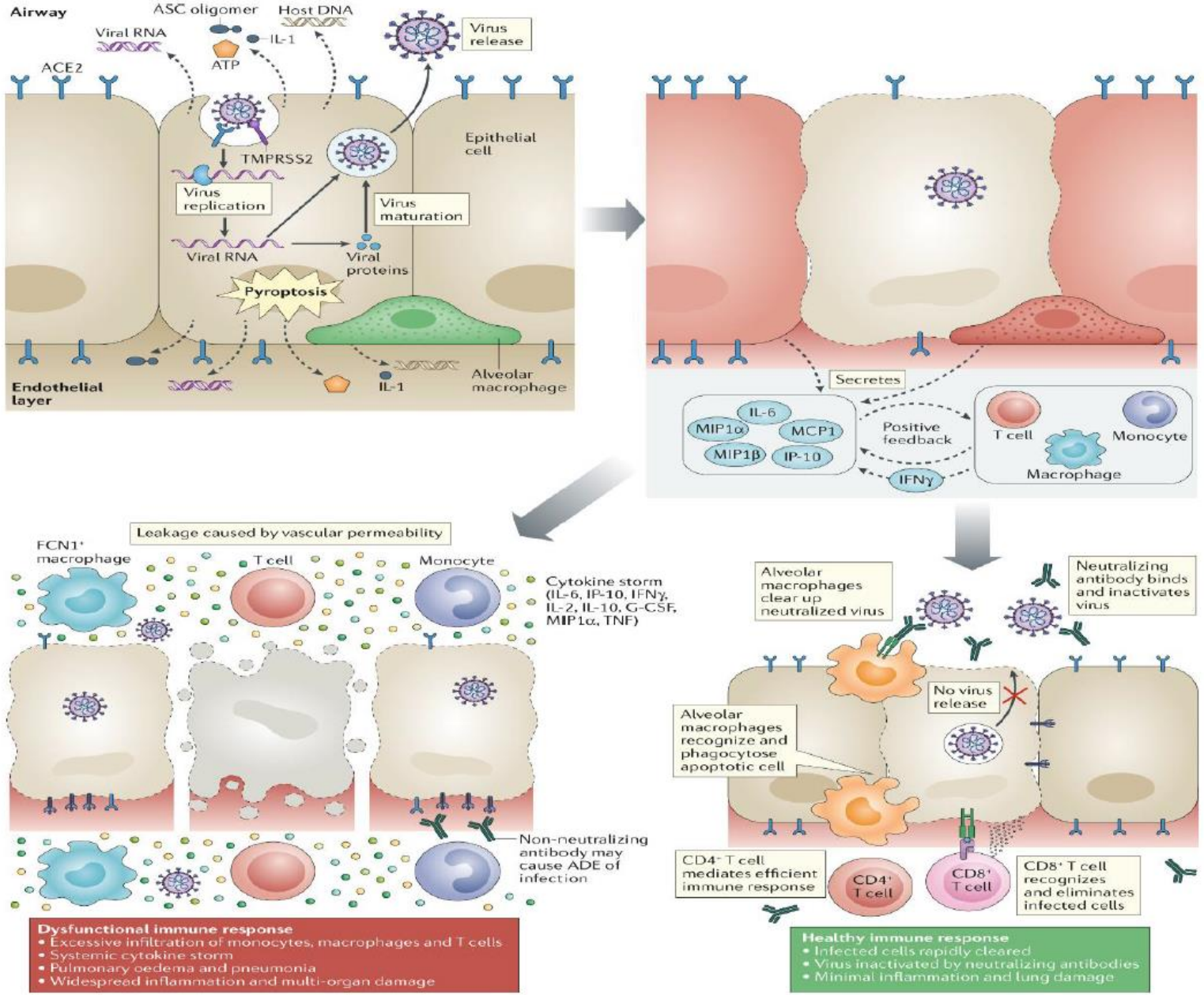
- Increased LVO in young?
  - Unclear
  - May need higher local prevalence/higher case numbers to identify
- Behavior of clot during thrombectomy suggests something further related to underlying etiology
- Systemic Thrombotic complications in severe COVID pts

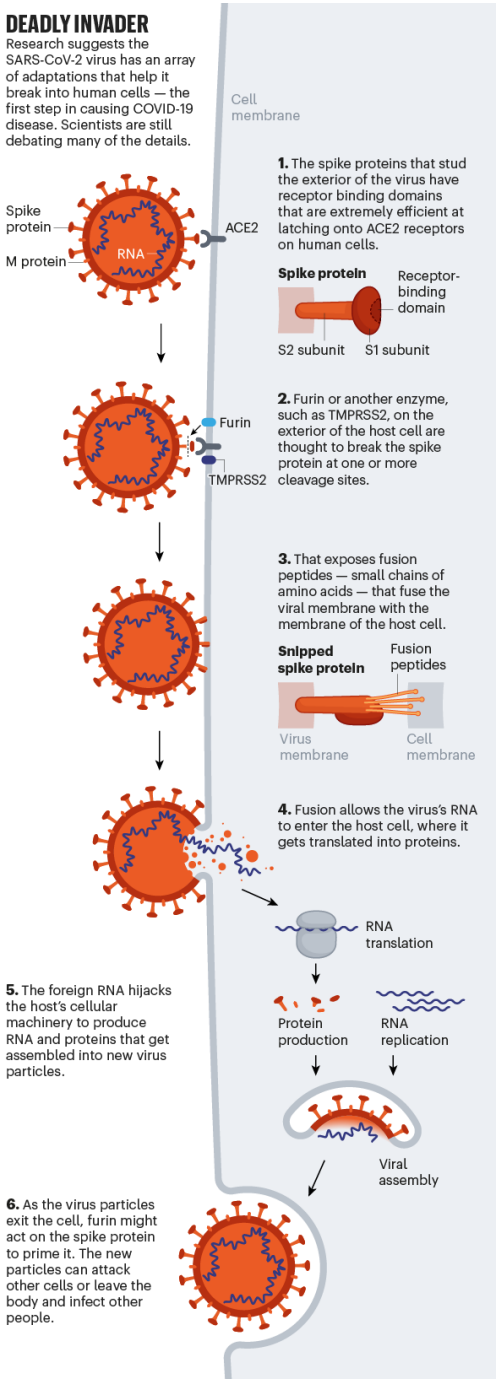
Is COVID-19 a vascular endothelial disease?

Dr Sanjay Sethi

Mini Grand rounds

5/27/20





Spike protein Ab

Furin, TMPRSS2 (Camostat-Denmark),

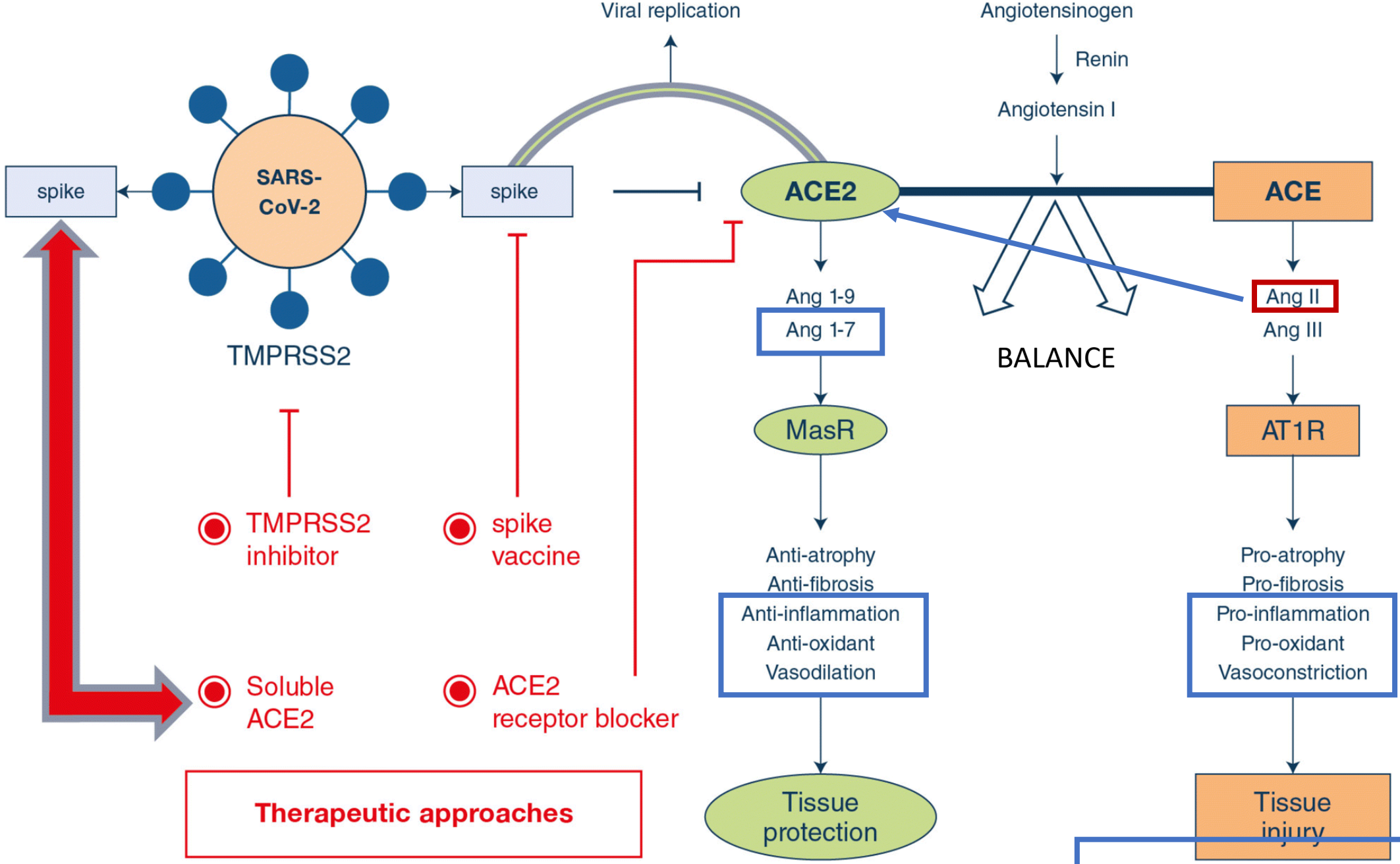
Cathepsin L (endosomes – respiratory and GI, **not endothelium)**

Lopinavir/Ritonavir – Inh viral proteases
Remdesivir – inh viral replicase

How virus invades

- ACE-2 receptor for is found in airway and alveolar epithelium, lung parenchyma, enterocytes of the small intestine, kidney cells, arterial smooth muscle, and **arterial and venous endothelium**.
- T cells directly infected (doesn't replicate)
- Binds via spike-protein
  - Similar as SARS virus, 10-20x more affinity for binding

Hess, D. C., Eldahshan, W., & Rutkowski, E. (2020). COVID-19-Related Stroke. *Transl Stroke Res, 11*(3), 322-325. doi:10.1007/s12975-020-00818-9
www.nature.com/articles/d41586-020-01315-7
Tang, X., Wu, C., Li, X., Song, Y., Yao, X., Wu, X., . . . Lu, J. (2020). On the origin and continuing evolution of SARS-CoV-2. National Science Review. doi:10.1093/nsr/nwaa036



Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med, 46*(4), 586-590. doi:10.1007/s00134-020-05985-9

AT II (elevated with loss of ACE2R) stimulates ROS

Published in final edited form as:
World J Hypertens. 2012 August 23; 2(4): 34–44. doi:10.5494/wjh.v2.i4.34.

Oxidative stress-mediated effects of angiotensin II in the cardiovascular system

Hairuo Wen,
Department of Cell Biology and Molecular Medicine, UMDNJ-New Jersey Medical School, Newark, NJ 07103, United States

Judith K Gwathmey, and
Gwathmey Inc., Cambridge, MA 02138, United States

School of Optometry, Massachusetts College of Pharmacy and Health Sciences, Wor
01608, United States

Ang II and oxidative stress

Oxidative stress describes an imbalance state while the production of ROS, including superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydoxyl radicals (OH), exceeds antioxidant defenses. There are several enzyme systems contributing to the formation of ROS, including NAD(P)H oxidase, xanthine oxidase and mitochondrial electron leakage from electron transport chain. ROS are normally generated as a natural byproduct of oxygen metabolism and play important roles in cell signaling. However, ROS levels can be increased dramatically under oxidative stress conditions, such as heart failure, ischemia-reperfusion and aging.

NAD(P)H oxidase, which has seven NOX isoforms, is a membrane-bound, heteromeric enzyme complex distributed throughout the endothelial cells, VSM cells[52] and cardiac myocytes[53]. NAD(P)H oxidase-generated ROS was initially recognized as a major source for vasculature ROS[54] and later for cardiac ROS as well[53]. Previous studies have demonstrated that the Ang II can double the vascular oxidants (ROS) production *in vivo* in a NAD(P)H-dependent manner[55]. It is well accepted that AT_1R activation stimulates NAD(P)H oxidase. Using intracellular NAD(P)H and NADH as electron donors, the activated NAD(P)H oxidase will catalyze the conversion of extracellular molecular oxygen

ACE2 pathway and Increased AT1,7 are endothelial protective and reduce ROS

Format: Abstract Send to

Am J Physiol Heart Circ Physiol. 2008 Oct;295(4):H1377-84. doi: 10.1152/ajpheart.00331.2008. Epub 2008 Jul 25.

Angiotensin converting enzyme-2 confers endothelial protection and attenuates atherosclerosis.

Lovren F[1], Pan Y, Quan A, Teoh H, Wang G, Shukla PC, Levitt KS, Oudit GY, Al-Omran M, Stewart DJ, Slutsky AS, Peterson MD, Backx PH, Penninger JM, Verma S.

Author information

Abstract

The endothelium plays a central role in the maintenance of vascular homeostasis. One of the main effectors of endothelial dysfunction is ANG II, and pharmacological approaches to limit ANG II bioactivity remain the cornerstone of cardiovascular therapeutics. Angiotensin converting enzyme-2 (ACE2) has been identified as a critical negative modulator of ANG II bioactivity, counterbalancing the effects of ACE in determining net tissue ANG II levels; however, the role of ACE2 in the vasculature remains unknown. In the present study, we hypothesized that ACE2 is a novel target to limit endothelial dysfunction and atherosclerosis. To this aim, we performed in vitro gain and loss of function experiments in endothelial cells and evaluated in vivo angiogenesis and atherosclerosis in apolipoprotein E-knockout mice treated with AdACE2. ACE2-deficient mice exhibited impaired endothelium-dependent relaxation. Overexpression of ACE2 in human endothelial cells stimulated endothelial cell migration and tube formation, and limited monocyte and cellular adhesion molecule expression; effects that were reversed in ACE2 gene silenced and endothelial cells isolated from ACE2-deficient animals. ACE2 attenuated ANG II-induced reactive oxygen species production in part through decreasing the expression of p22phox. The effects of ACE2 on endothelial activation were attenuated by pharmacological blockade of ANG-(1-

apolipoprotein E-knockout mice These data indicate that ACE2, in an ANG-(1-7)-dependent fashion, functions to improve endothelial homeostasis via a mechanism that may involve attenuation of NADPHox-induced reactive oxygen species production. ACE2-based treatment approaches may be a novel approach to limit aberrant vascular responses and atherothrombosis.

PMID: 18660448 DOI: 10.1152/ajpheart.00331.2008

[Indexed for MEDLINE] Free full text

Inflamm Res. 2015 Apr;64(3-4):253-60. doi: 10.1007/s00011-015-0805-1. Epub 2015 Feb 27.

ACE2 and Ang-(1-7) protect endothelial cell function and prevent early atherosclerosis by inhibiting inflammatory response.

Zhang YH[1], Zhang YH, Dong XF, Hao QQ, Zhou XM, Yu QT, Li SY, Chen X, Tengbeh AF, Dong B, Zhang Y.

Author information

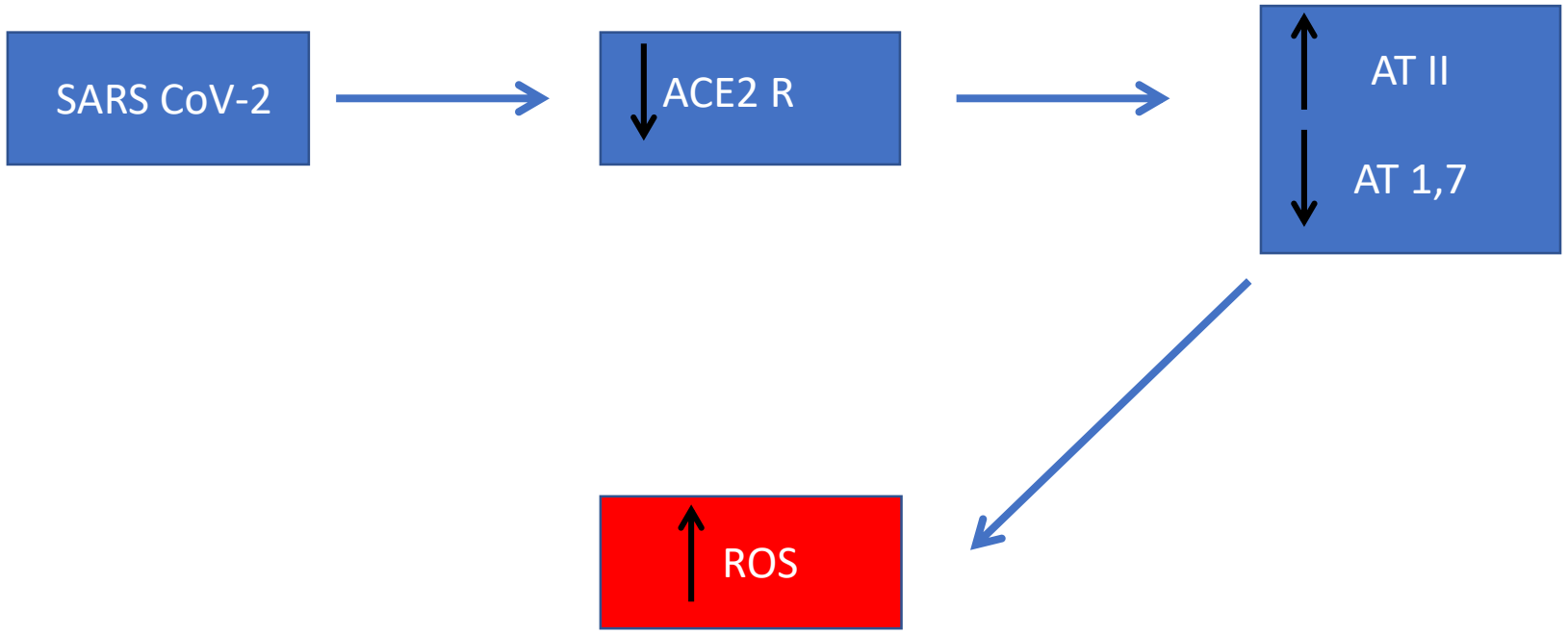
Abstract

BACKGROUND: Angiotensin-converting enzyme 2 (ACE2) is a counter-regulator against ACE by converting angiotensin II (Ang-II) to Ang-(1-7), but the effect of ACE2 and Ang-(1-7) on endothelial cell function and atherosclerotic evolution is unknown. We hypothesized that ACE2 overexpression and Ang-(1-7) may protect endothelial cell function by counterregulation of angiotensin II signaling and inhibition of inflammatory response.

METHODS: We used a recombinant adenovirus vector to locally overexpress ACE2 gene (Ad-ACE2) in human endothelial cells in vitro and in apoE-deficient mice in vivo. The Ang II-induced MCP-1, VCAM-1 and E-selectin expression, endothelial cell migration and adhesion of human monocytic cells (U-937) to HUVECs by ACE2 gene transfer were evaluated in vitro. Accelerated atherosclerosis was studied in vivo, and atherosclerosis was induced in apoE-deficient mice which were divided randomly into four groups that received respectively a ACE2 gene transfer, Ad-ACE2, Ad-EGFP, Ad-ACE2 + A779, an Ang-(1-7) receptor antagonist, control group. After a gene transfer for 4 weeks, atherosclerotic pathology was evaluated.

RESULTS: ACE2 gene transfer not only promoted HUVECs migration, inhibited adhesion of monocyte to HUVECs and decreased Ang II-induced MCP-1, VCAM-1 and E-selectin protein production in vitro, but also decreased the level of MCP-1, VCAM-1 and interleukin 6 and inhibit atherosclerotic plaque evolution in vivo. Further, administration of A779 increased the level of MCP-1, VCAM-1 and interleukin 6 in vivo and led to further advancements in atherosclerotic extent.

A779 is a AT1,7 inh


SARS CoV-2
ACE2 R
AT II
AT 1,7
ROS

COVID associated Increased Neutrophils…ROS

Asian Pacific Journal of Allergy and Immunology

APJAI

REVIEW ARTICLE

Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic

Eakachai Prompetchara,[1,2,3] Chutitorn Ketloy,[1,2] Tanapat Palaga[4,5]

Based on hospitalized patient data, the majority of COVID-19 cases (about 80%) presented with asymptomatic or with mild symptoms while the remainder are severe or critical.[2,4] It seems that the severity and fatality rate of COVID-19 are milder than that of SARS and MERS. With similar clinical presentations as SARS and MERS, the most common symptoms of COVID-19 are fever, fatigue, and respiratory symptoms,

Innate Immune Responses to SARS-CoV-2 Infection: Gaining Insight from Strategies used by SARS-CoV and MERS-CoV

Currently, only limited information is available on the host innate immune status of SARS-CoV-2 infected patients. In one report where 99 cases in Wuhan were investigated, increased total neutrophils (38%), reduced total lymphocytes (35%),

APJAI *Asian Pac J Allergy Immunol 2020;38:1-9 DOI 10.12932/AP-200220-0772*

increased serum IL-6 (52%) and increased c-reactive protein (84%) were observed.[25] In a separate report also from Wuhan, it revealed that in 41 patients, increased total neutrophils, decreased total lymphocytes in patients of ICU vs. non-ICU care were found to be statistically different. Increased neutrophils

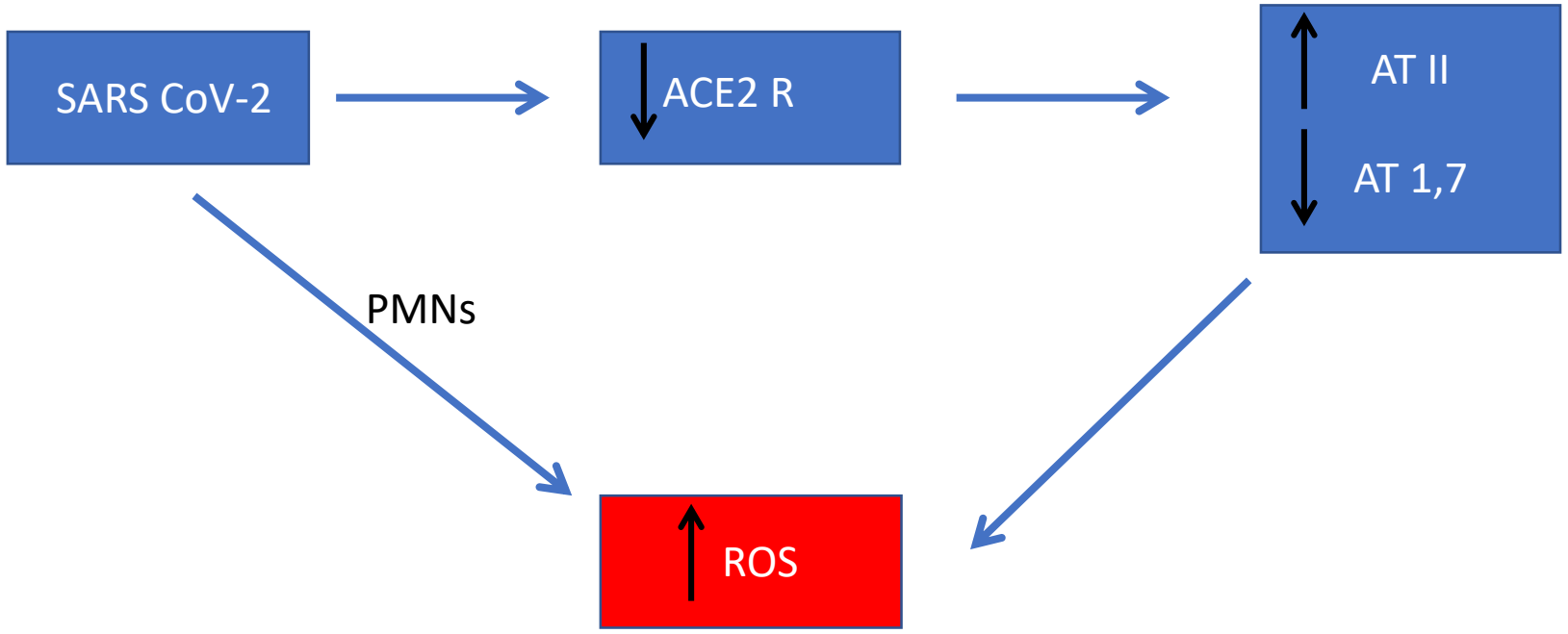
T cells, a key feature in SARS-CoV-mediated pathogenesis.[27] Whether SARS-CoV-2 infects any immune cells are still unknown. Only minimal percentages of monocytes/macrophages in the lung expressed ACE2.[26] If ACE2 is minimally expressed in the potential target immune cells, it is possible that other re-

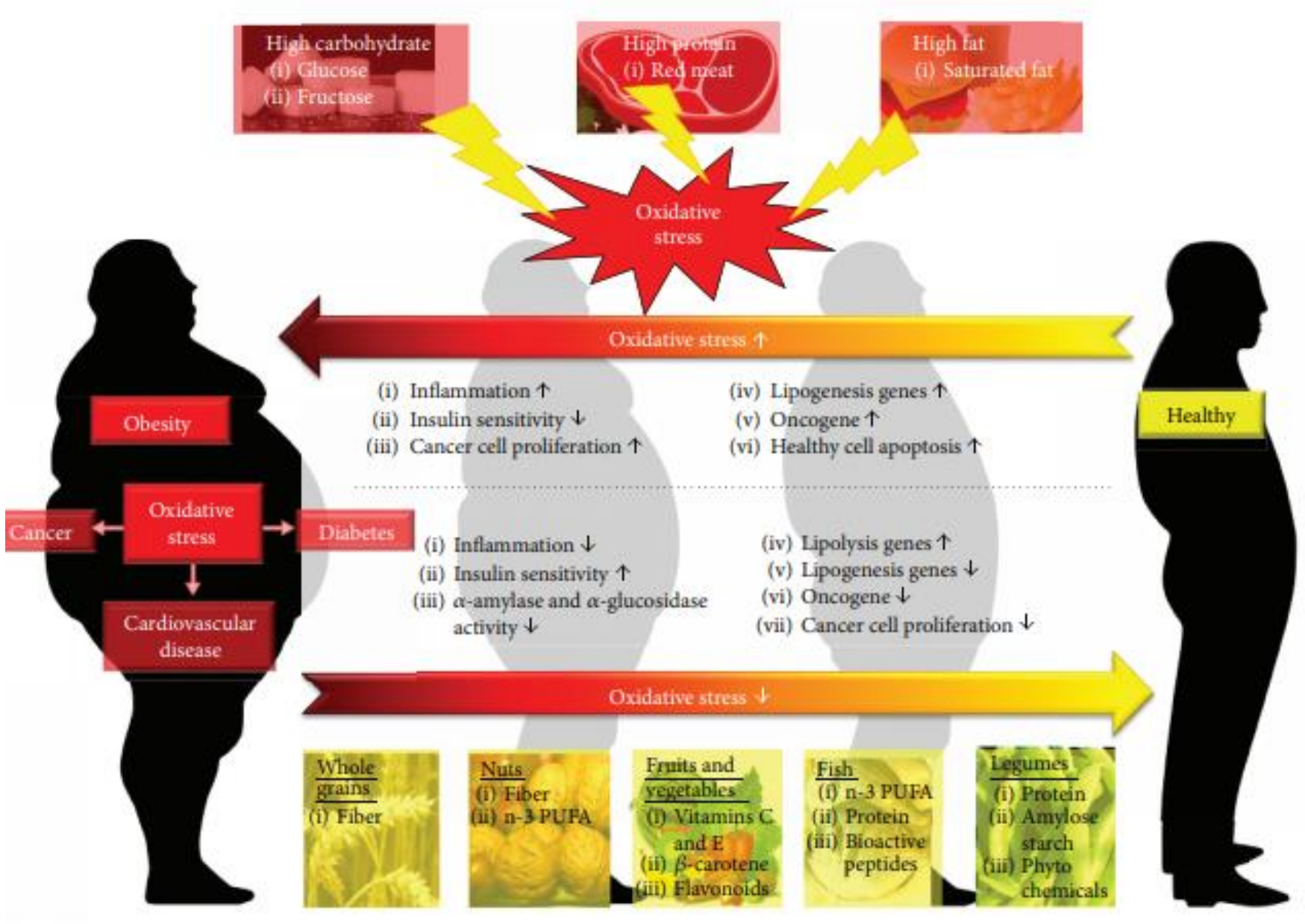
Neutrophils to the ROScue: Mechanisms of NADPH Oxidase Activation and Bacterial Resistance

Giang T. Nguyen[1], Erin R. Green[2] and Joan Mecsas[1,2*]

[1]Graduate Program in Immunology, Sackler School of Graduate Biomedical Sciences, Tufts University, Boston, MA, United States

[2]Department of Molecular Biology and Microbiology, Tufts University School of Medicine, Boston, MA, United States


SARS CoV-2
ACE2 R
AT II
AT 1,7
PMNs
ROS



Review Article: Nutrients and Oxidative Stress: Friend or Foe? Tan et al. Oxidative Medicine and Cellular Longevity 2018

Symptoms associated with coronavirus disease 2019 (COVID-19)[1]

Symptoms that may be seen in patients with COVID-19
▪ Fever
▪ Cough
▪ Dyspnea (new or worsening over baseline)
▪ Anosmia or other smell abnormalities
▪ Ageusia or other taste abnormalities
▪ Sore throat
▪ Myalgias
▪ Chills/rigors
▪ Headache
▪ Rhinorrhea
▪ Nausea/vomiting
▪ Diarrhea
▪ Fatigue
▪ Confusion
▪ Chest pain or pressure

Research

JAMA | Original Investigation

Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area

Safiya Richardson, MD, MPH; Jamie S. Hirsch, MD, MA, MSB; Mangala Narasimhan, DO; James M. Crawford, MD, PhD; Thomas McGinn, MD, MPH; Karina W. Davidson, PhD, MASc; and the Northwell COVID-19 Research Consortium

- Only 1/3 had Fever
- Similar to general Population:
  - Asthma (9%)
  - COPD (5%)
  - OSA (3%)
- Higher than general population:
  - HTN (57%)
  - CAD (11%)
  - CHF (7%)
  - BMI > 30 (42%)

McIntosh et al. Coronavirus disease 2019 (COVID-19): Clinical features and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on May 30, 2020.)

Pathophysiol Haemost Thromb. 2002 Sep-Dec;32(5-6):359-60.

Oxidative stress in endothelial cell dysfunction and thrombosis.

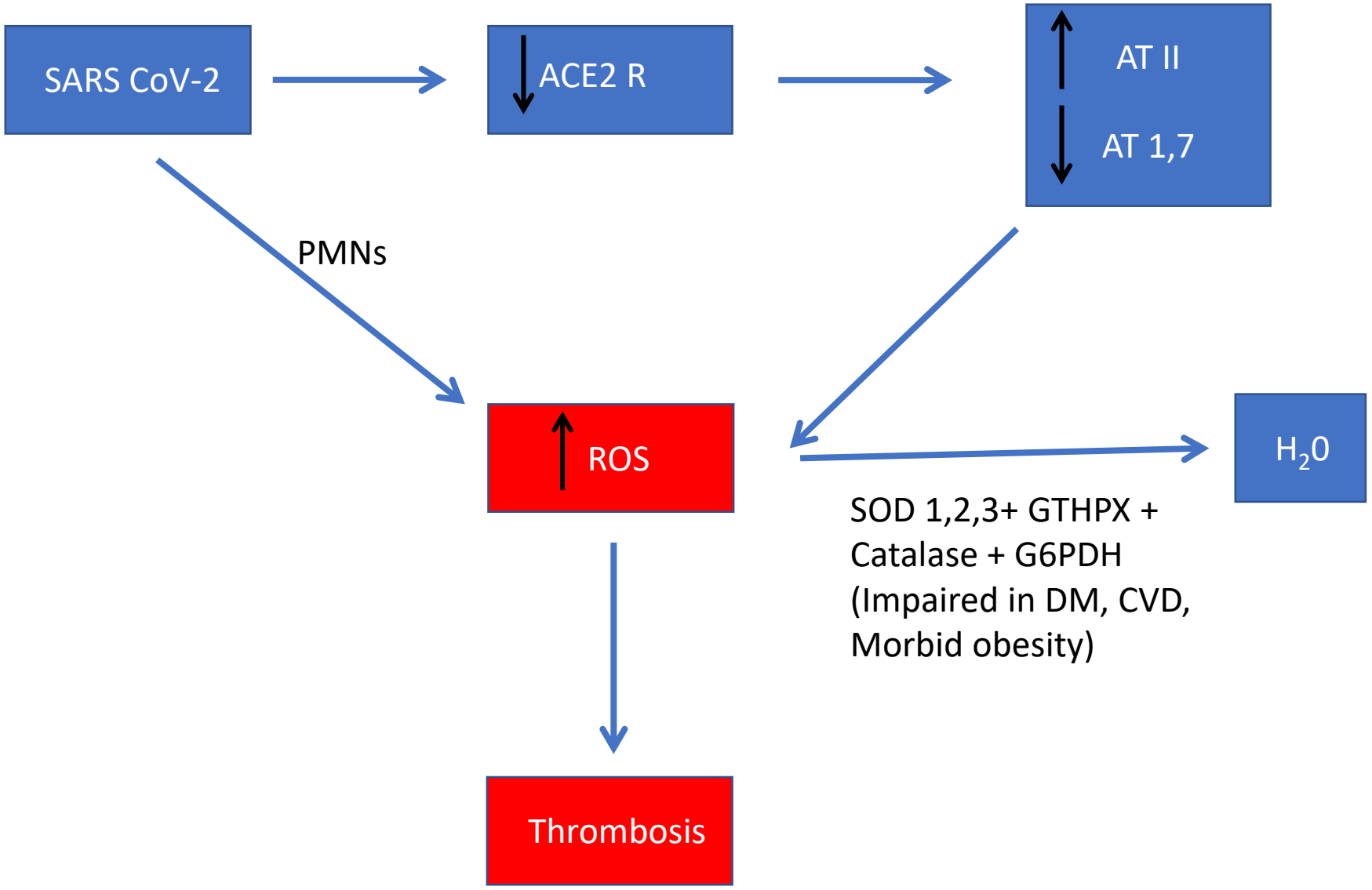
Loscalzo J[1].

Author information

Abstract

Endothelial dysfunction (ECD) is the earliest phenotypic change in the vasculature following exposure to atherothrombotic risk factors. ECD is associated with decreased synthesis and increased oxidative inactivation of nitric oxide (NO). Critical antioxidant enzymes essential for eliminating reactive oxygen species that can inactivate NO include the superoxide dismutases, the glutathione peroxidases, catalase, and glucose-6-phosphate dehydrogenase. Deficiencies of these enzymes increase oxidative stress and NO inactivation and, as such, can either lead to ECD or account for the underlying mechanism of ECD associated with a given atherothrombotic risk factor. Selected antioxidants improve intracellular redox state and reverse ECD by improving the bioavailability of NO. These observations provide mechanistic insights into the molecular basis of ECD in vascular disease and its treatment.

- Endothelial dysfunction from oxygen radical, associated with decreased synthesis and increased oxidative inactivation of NO.
- Critical antioxidant enzymes essential for eliminating reactive oxygen species that can inactive NO include superoxide dismutases (SOD), Glutathione peroxidases, catalase, and Glucose-6-phosphate dehydrogenase.
- NO is critical to normal endothelial function. It is how AT 1,7 works!
- Connects oxidative stress, endothelial damage, NO, and thrombosis.


SARS CoV-2
ACE2 R
AT II
AT 1,7
PMNs
ROS
H_20
SOD 1,2,3+ GTHPX +
Catalase + G6PDH
(Impaired in DM, CVD,
Morbid obesity)
Thrombosis

Journal List › Elsevier Public Health Emergency Collection › PMC7156948

THROMBOSIS RESEARCH

Elsevier

Thromb Res. 2020 Apr 15 PMCID: PMC7156948
doi: 10.1016/j.thromres.2020.04.014 [Epub ahead of print] PMID: 32305740

Elsevier Public Health Emergency Collection

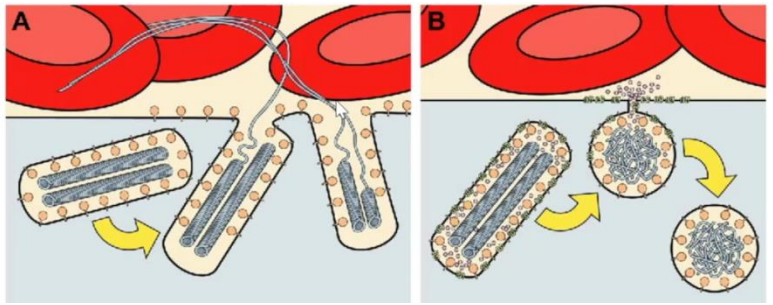
Severe COVID-19 infection associated with endothelial activation

Robert Escher,[a] Neal Breakey,[a,*] and Bernhard Lämmle[b,c,d]

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Mounting evidence supports the strong prognostic importance of D-dimers and the impact of coagulopathy in COVID-19 patients [1,2,3]. We would like to emphasize the significance of anticoagulation in severe COVID-19 disease, by adding our observation of highly pathological data on anti-phospholipid-antibodies, von Willebrand Factor (VWF) and Factor VIII. We observed a 72-year-old previously healthy male patient admitted to our hospital 6 days after the onset of respiratory

- 72 yo, healthy, 6 days out ARDS, ARI, ALOC, sent to ICU.
- D-Dimer – increases…some sort of coagulation problem
- Massive elevation of VWF (Ag 555%, VWF activity 520%) associated with increased Factor VIII (activity 369%)
- VWF is release if there is damage to the endothelium…it is subendothelial…but can get into the circulation with damage and it is a pro coagulant.
- VWF binds to Factor VIII in lumen of blood vessels
- Suggests blood clots mediated by very high VWF levels and/or Factor VIII
- IgM positive, IgG were negative (indicating an acute phase)
- Release of VWF from Weibel-Palade bodies (only found in endothelial cell)



	Day 6	Day 21	Day 24	Day 29
D Dimer	0.69	20.63	6.26	1.94

Open access peer-reviewed chapter

Endothelial Cell von Willebrand Factor Secretion in Health and Cardiovascular Disease

By Luiza Rusu and Richard D. Minshall

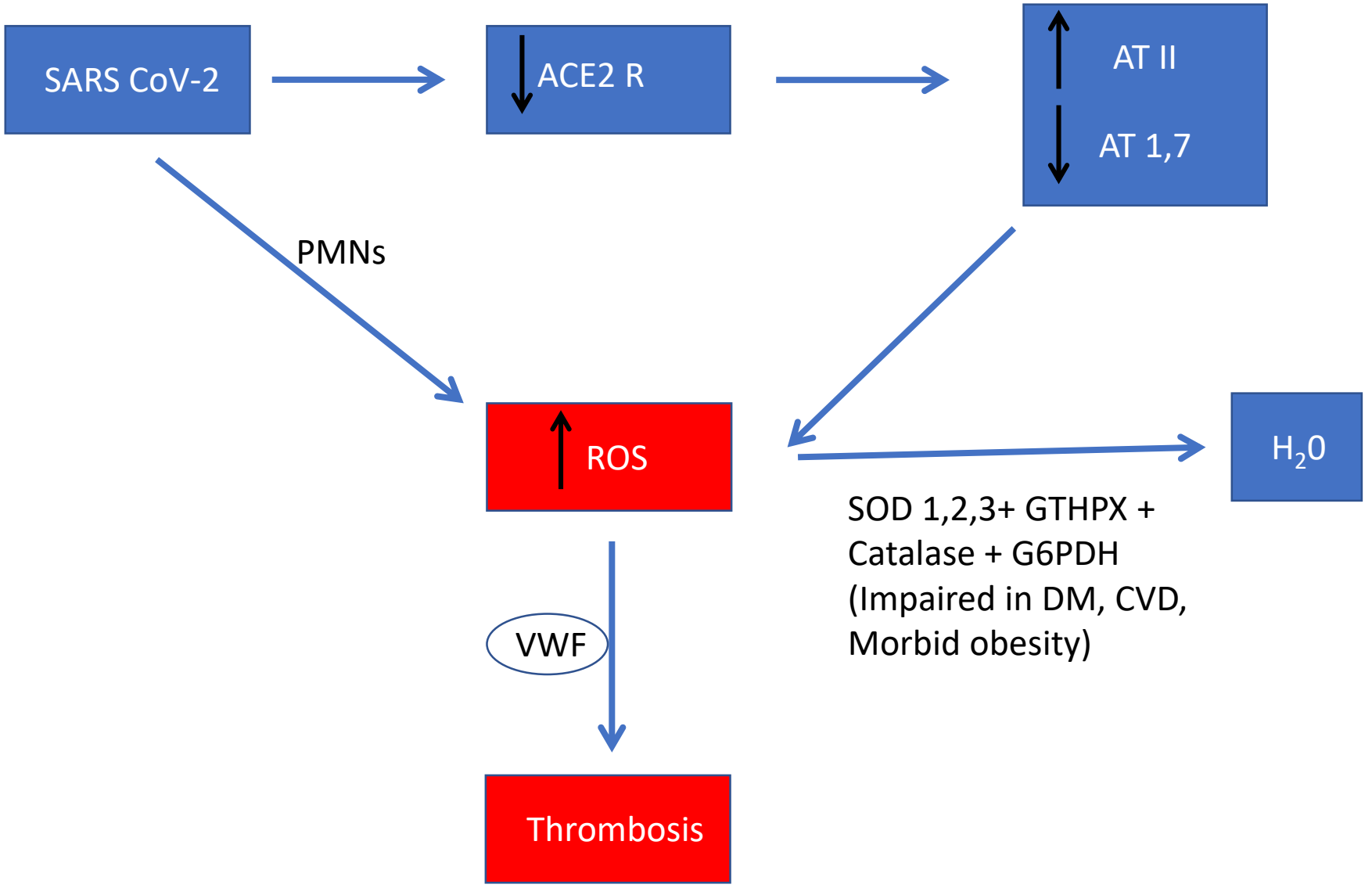
Submitted: May 8th 2017 Reviewed: January 15th 2018 Published: October 24th 2018
DOI: 10.5772/intechopen.74029

The main function of von Willebrand factor (vWF) is to initiate platelet adhesion upon vascular injury. The hallmark of acute and chronical inflammation is the widespread activation of endothelial cells which provokes excessive vWF secretion from the endothelial cell storage pool. The level of vWF in blood not only reflects the state of endothelial activation early on in the pathogenesis, but also predicts disease outcome. Elevation in the blood level of vWF occurs either by pathologic increase in the rate of basal vWF secretion or by increased evoked vWF release from dysfunctional/activated endothelial cells (ECs). The increase in plasma vWF is predictive of prothrombotic complications and multi-organ system failure associated with reduced survival in the context of severe inflammatory response syndrome, type II diabetes mellitus, stroke and other inflammatory cardiovascular disease states. This chapter focuses on the role of high circulating vWF levels in thrombotic and inflammatory disease while paying attention to the emerging vWF-related drug development strategies.

VWF is a surrogate marker of endothelial cell dysfunction

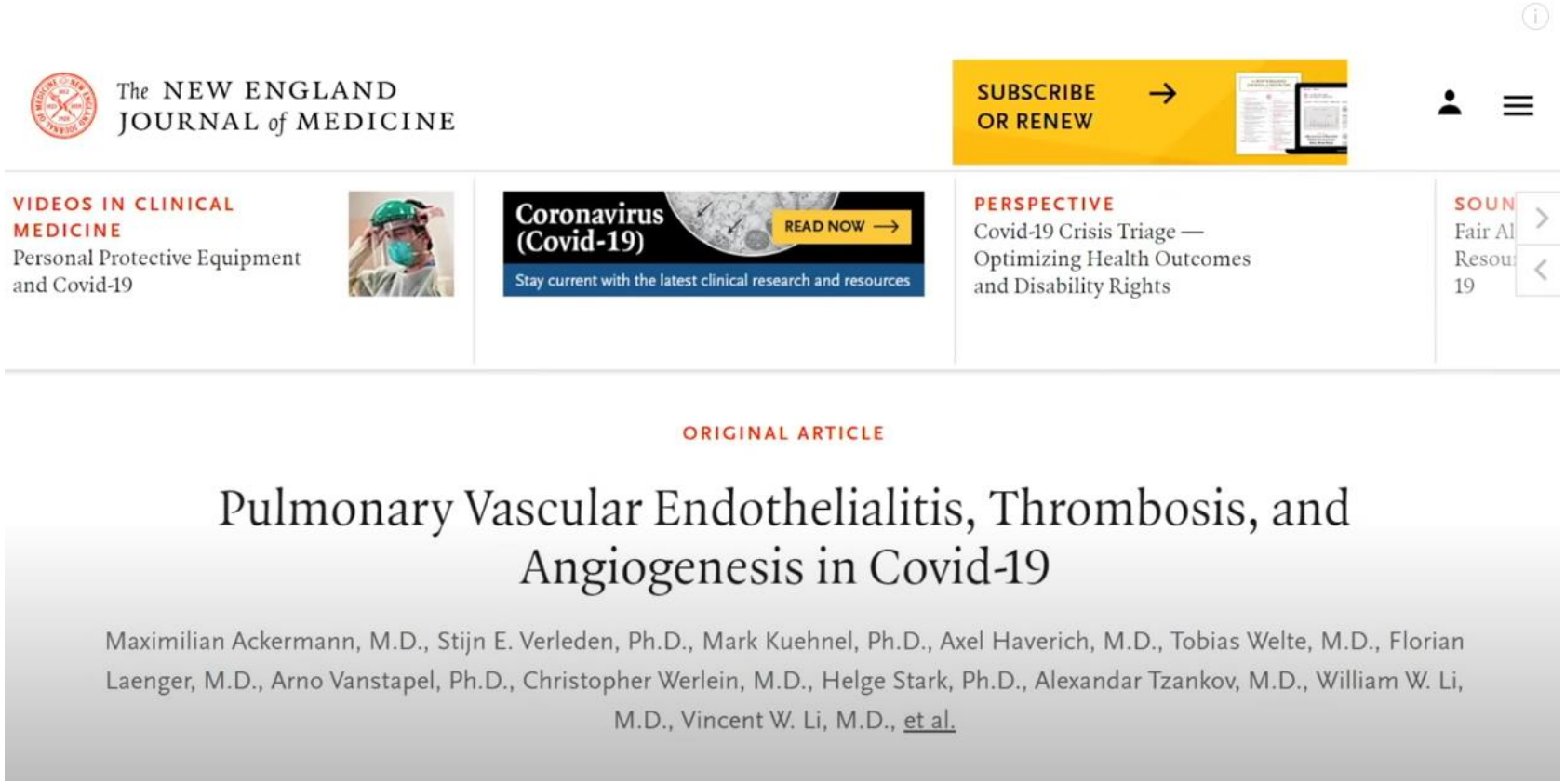
Highly multimeric form is not seen in health serum but in various pathologic settings

ADAMTS13 cleaves and cuts up VWF (Zn containing enzyme)…to reduce its effectiveness.


SARS CoV-2
ACE2 R
AT II
AT 1,7
PMNs
ROS
H_20
SOD 1,2,3+ GTHPX +
Catalase + G6PDH
(Impaired in DM, CVD,
Morbid obesity)
VWF
Thrombosis

COVID is a Endothelial disease- Hypothesis

- Virus enters in lungs but becomes systemic in blood
- Binds to ACE2 R in endothelium throughout the body
- Oxidative stress becomes the link
  - PMNs increase ROS.
  - Loss of ACE2R Decreases AT 1,7 and increases in AT II further increasing ROS
- ROS damages endothelial and subendothelial tissue
  - VWF is released
  - Procoagulant and as well as increases viscosity
- Microvascular thrombosis in multiple end organs and increased thrombotic events (PE, MI, Stroke)
- DM, CVD, morbid obesity…all share loss of protective pathways for removal of ROS.
  - loss of compensatory mechanism (decreased SOD and GTHPX)…may be relying on renin-angiotensin system which making these pts vulnerable!
- Inherent Differences in VWF in O blood type



- 5/21/20: 7 lungs during autopsy compared to 7 ARDS H1N1 and uninfected age matched control lungs
- Seven color immunohistochemical analysis, micro CT, SEM, corrosion casting, direct multiplexed measurement of gene expression
- Uniquely, the lungs from pts with COVID19 showed distinctive vascular features consisting of **severe endothelial injury** associated with the presence of intracellular virus and disrupted cell membranes.
- Histology of pulmonary vessels showed **widespread thrombosis with microangiopathy**.
- **Alveolar capillary microthrombi** were 9 times as prevalent in COVID pt than with influenza (P<0.001).
- COVID pt lungs, **New vessel growth** (intussusceptive angiogenesis) was 2.7 times higher than influenza (P<0.001).

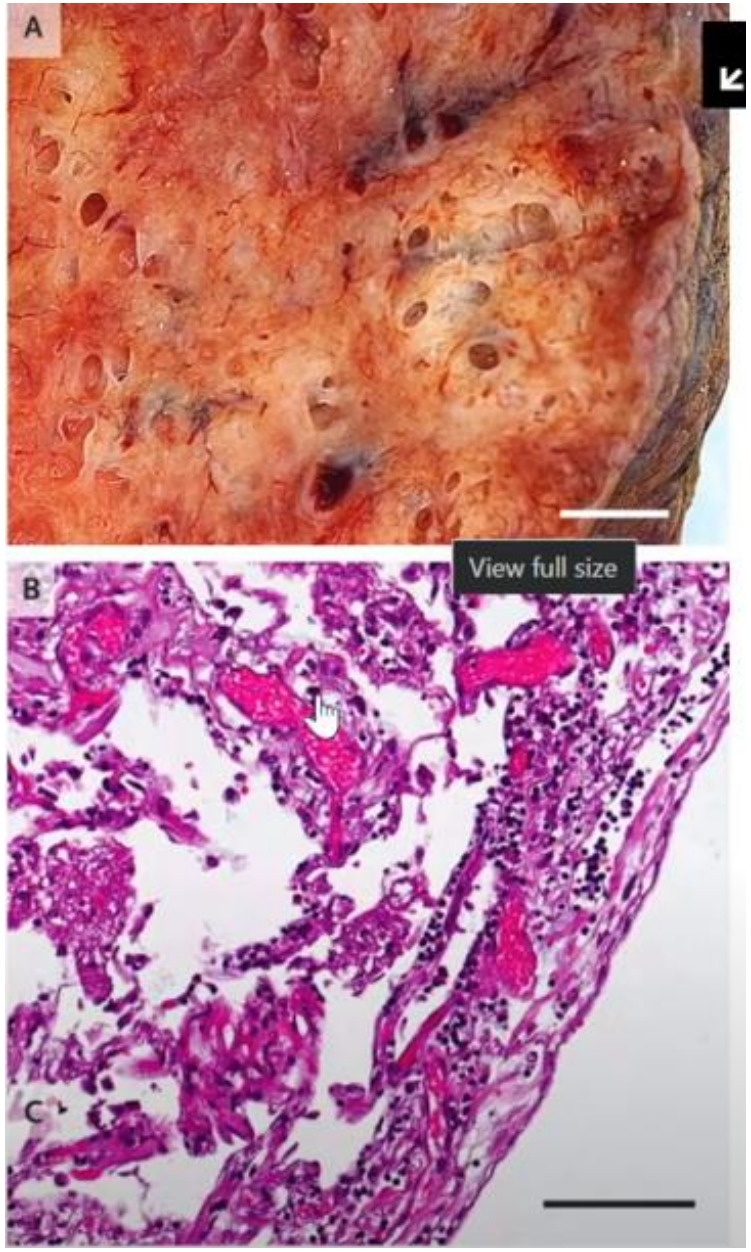
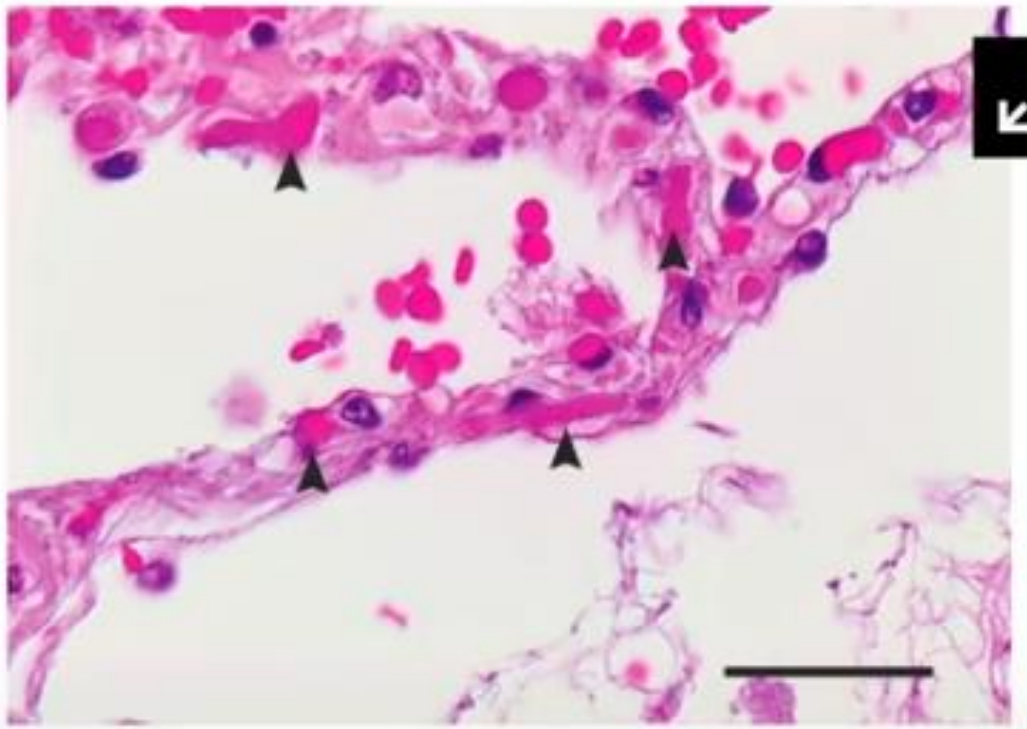


Figure 2.



Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.

Fig 1. Lymphocytic infiltration
Fig 2. many capillaries filled with blood clot (arrows) preventing oxygen exchange, walls are relatively fine (Happy Hypoxic, low O2 sats).

NEJM paper

- SEM found viral particles in endothelial space
- Greater number of ACE2 + endothelial cells in lungs of COVID pts and significant changes in endothelial morphology compared to influenza.
- COVID pts endothelial cells showed **disruption of intercellular junctions, cell swelling, and loss of contact with basal membrane**.

- NOTE: VWF is subendothelial release can occur with loss of BM contact

Endothelial cell infection and endotheliitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood.[1,2]

SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells.[3] Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus is currently unknown. Intriguingly, SARS-CoV-2

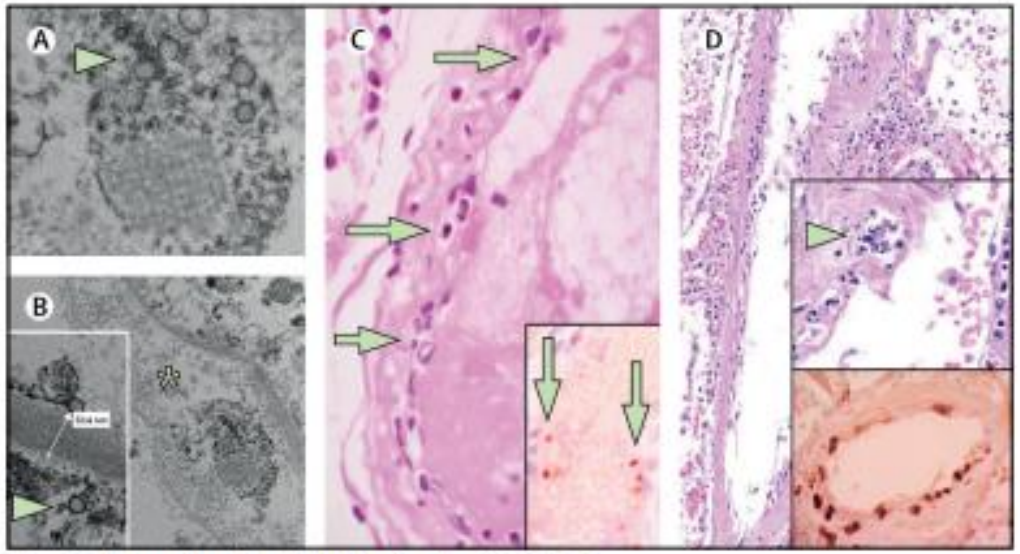


Figure: **Pathology of endothelial cell dysfunction in COVID-19**

(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with dense circular surface and lucid centre. The asterisk in panel B marks peritubular space consistent with capillary containing viral particles. The inset in panel B shows the glomerular basement membrane with endothelial cell and a viral particle (arrow; about 150 nm in diameter). (C) Small bowel resection specimen of patient 3, stained with haematoxylin and eosin. Arrows point to dominant mononuclear cell infiltrates within the intima along the lumen of many vessels. The inset of panel C shows an immunohistochemical staining of caspase 3 in small bowel specimens from serial section of tissue described in panel D. Staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections, indicating that apoptosis is induced in a substantial proportion of these cells. (D) Post-mortem lung specimen stained with haematoxylin and eosin showed thickened lung septa, including a large arterial vessel with mononuclear and neutrophilic infiltration (arrow in upper inset). The lower inset shows an immunohistochemical staining of caspase 3 on the same lung specimen; these staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections. COVID-19=coronavirus disease 2019.

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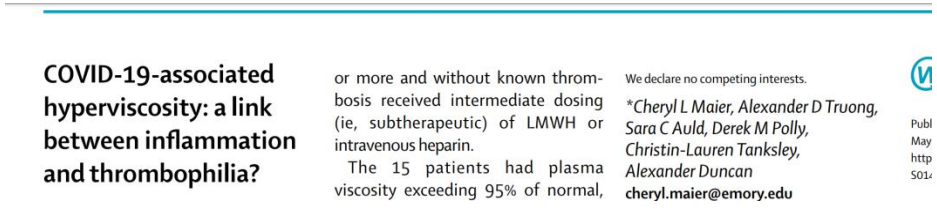
S0140-6736(20)30937-5

SUMMARY: Stroke and COVID-19

- COVID stroke patients seem to have tenacious clots with poor prognosis. May need aggressive IA/IV and surgical methods to revascularize.
- Stroke mechanism unknown but may be independent of hypercoagulable markers, or related to combo of hypercoagulable state and direct endothelial damage (endotheliitis)
- Interventions targeting the endothelium may prove helpful in treating COVID-19
  - NAC (Sloan, antioxidant, breaks disulfide bonds, anticoagulant)
  - AT 1,7 (used in pre eclampsia)
  - Aggressive Anticoagulation
    - Improved outcomes
    - Failures may be related to hyperviscosity



COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia?

or more and without known thrombosis received intermediate dosing (ie, subtherapeutic) of LMWH or intravenous heparin.

The 15 patients had plasma viscosity exceeding 95% of normal,

We declare no competing interests.

*Cheryl L Maier, Alexander D Truong, Sara C Auld, Derek M Polly, Christin-Lauren Tanksley, Alexander Duncan
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Treatment Options

Anticoagulation

NAC

AT1,7

AT 1,7 as a treatment option! And why ARBS might help.

Am J Physiol Regul Integr Comp Physiol. 2020 Jan 1;318(1):R148-R155. doi: 10.1152/ajpregu.00221.2019. Epub 2019 Oct 2.

Local angiotensin-(1-7) administration improves microvascular endothelial function in women who have had preeclampsia.

Stanhewicz AE[1], Alexander LM[1].

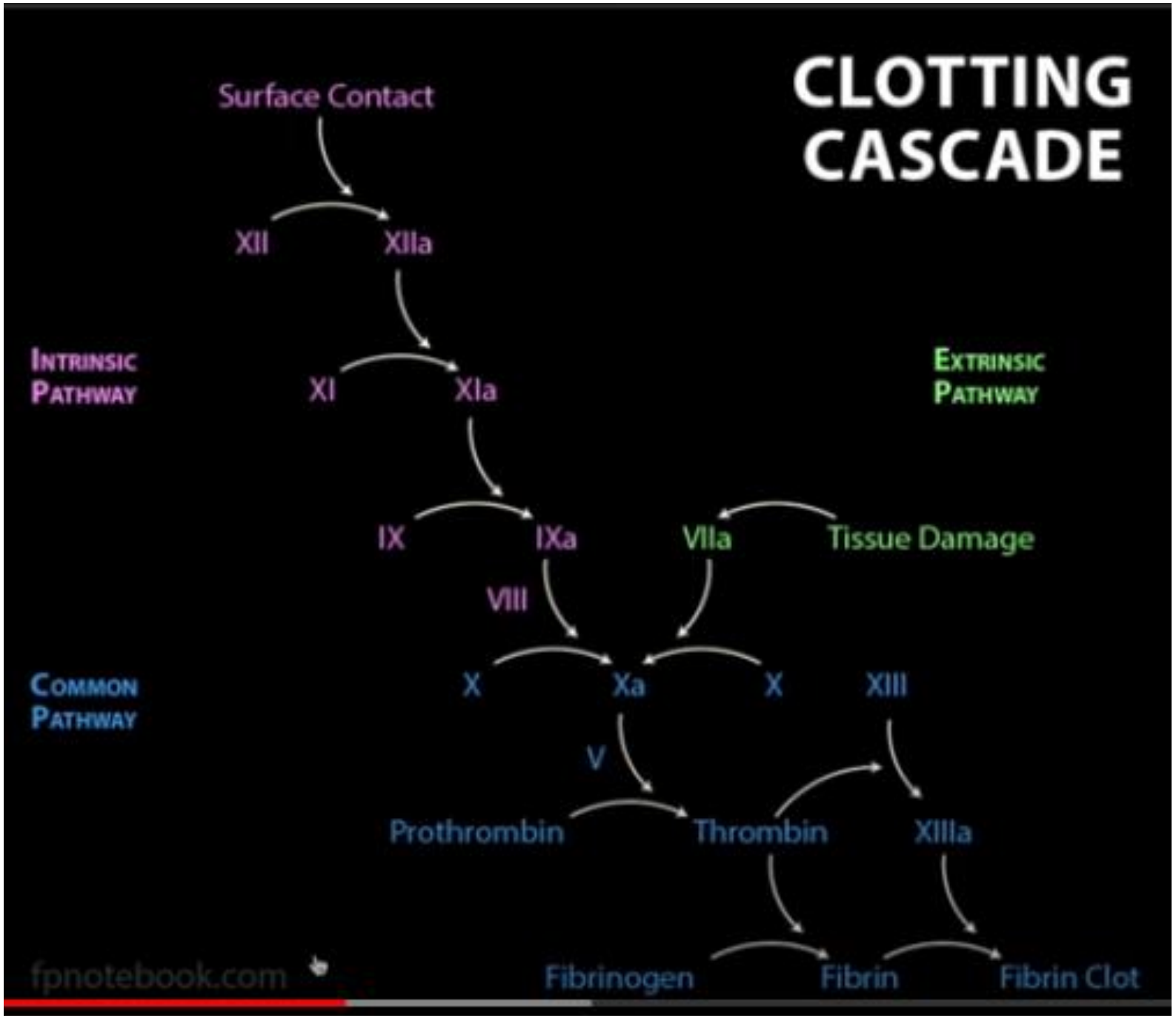
Author information

Abstract

Despite remission of clinical symptoms postpartum, women who have had preeclampsia demonstrate microvascular endothelial dysfunction, mediated in part by increased sensitivity to angiotensin II (ANG II). Angiotensin-(1-7) [Ang-(1-7)] is an endogenous inhibitor of the actions of ANG II and plausible druggable target in women who had preeclampsia. We therefore examined the therapeutic potential of Ang-(1-7) in the microvasculature of women with a history of preeclampsia (PrEC; n = 13) and parity-matched healthy control women (HC; n = 13) hypothesizing that administration of Ang-(1-7) would increase endothelium-dependent dilation and nitric oxide (NO)-dependent dilation and decrease ANG II-mediated constriction in PrEC. Using the cutaneous microcirculation, we assessed endothelium-dependent vasodilator function in response to graded infusion of acetylcholine (ACh; 10^{-7} to 10^{2} mmol/L) in control sites and sites treated with 15 mmol/L N^{G}-nitro-l-arginine methyl ester (l-NAME; NO-synthase inhibitor), 100 µmol/L Ang-(1-7), or 15 mmol/L l-NAME + 100 µmol/L Ang-(1-7). Vasoconstrictor function was measured in response to ANG II (10^{-20}-10^{-4} mol/L) in control sites and sites treated with 100 µmol/L Ang-(1-7). PrEC had reduced endothelium-dependent dilation (P < 0.001) and NO-dependent dilation (P = 0.04 vs. HC). Ang-(1-7) coinfusion augmented endothelium-dependent dilation (P < 0.01) and NO-dependent dilation (P = 0.03) in PrEC but had no effect in HC. PrEC demonstrated augmented vasoconstrictor responses to ANG II (P < 0.01 vs. HC), which was attenuated by coinfusion of Ang-(1-7) (P < 0.001). Ang-(1-7) increased endothelium-dependent vasodilation via NO synthase-mediated pathways and attenuated ANG II-mediated constriction in women who have had preeclampsia, suggesting that Ang-(1-7) may be a viable therapeutic target for improved microvascular function in women who have had a preeclamptic pregnancy.

10:12 / 19:56

Treat with AT 1,7!!!!


CLOTTING CASCADE
Surface Contact
XII
XIIa
INTRINSIC PATHWAY
XI
XIa
EXTRINSIC PATHWAY
IX
IXa
VIIa
Tissue Damage
VIII
COMMON PATHWAY
X
Xa
X
XIII
V
Prothrombin
Thrombin
XIIIa
fpnotebook.com
Fibrinogen
Fibrin
Fibrin Clot

J Thromb Haemost. 2020 May;18(5):1094-1099. doi: 10.1111/jth.14817. Epub 2020 Apr 27.

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy.

Tang N[1], Bai H[1], Chen X[1], Gong J[1], Li D[2], Sun Z[1].

Author information

Abstract

BACKGROUND: A relatively high mortality of severe coronavirus disease 2019 (COVID-19) is worrying, and the application of heparin in COVID-19 has been recommended by some expert consensus because of the risk of disseminated intravascular coagulation and venous thromboembolism. However, its efficacy remains to be validated.

METHODS: Coagulation results, medications, and outcomes of consecutive patients being classified as having severe COVID-19 in Tongji hospital were retrospectively analyzed. The 28-day mortality between heparin users and nonusers were compared, as was a different risk of coagulopathy, which was stratified by the sepsis-induced coagulopathy (SIC) score or D-dimer result.

RESULTS: There were 449 patients with severe COVID-19 enrolled into the study, 99 of them received heparin (mainly with low molecular weight heparin) for 7 days or longer. D-dimer, prothrombin time, and age were positively, and platelet count was negatively, correlated with 28-day mortality in multivariate analysis. No difference in 28-day mortality was found between heparin users and nonusers (30.3% vs 29.7%, P = .910). But the 28-day mortality of heparin users was lower than nonusers in patients with SIC score ≥4 (40.0% vs 64.2%, P = .029), or D-dimer >6-fold of upper limit of normal (32.8% vs 52.4%, P = .017).

CONCLUSIONS: Anticoagulant therapy mainly with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.

- All comers no difference in mortality
- SIC (sepsis induce coagulopathy) score of 4 or more (suggests severe case, and increased risk for DIC/coagulopathies) and d-dimer >6 fold of upper limit of normal, Mortality rates statistically significantly difference (32.8% vs 52.4% (P = 0.017)) if receiving heparin gtt (mainly LMWH for 7 days or longer).

Journal Pre-proof

Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19

Ishan Paranjpe, BS, Valentin Fuster, MD, PhD, Anuradha Lala, MD, Adam Russak, MD, Benjamin S. Glicksberg, PhD, Matthew A. Levin, MD, Alexander W. Charney, MD, PhD, Jagat Narula, MD, PhD, Zahi A. Fayad, PhD, Emilia Bagiella, PhD, Shan Zhao, MD, PhD, Girish N. Nadkarni, MD, MPH

PII: S0735-1097(20)35218-9

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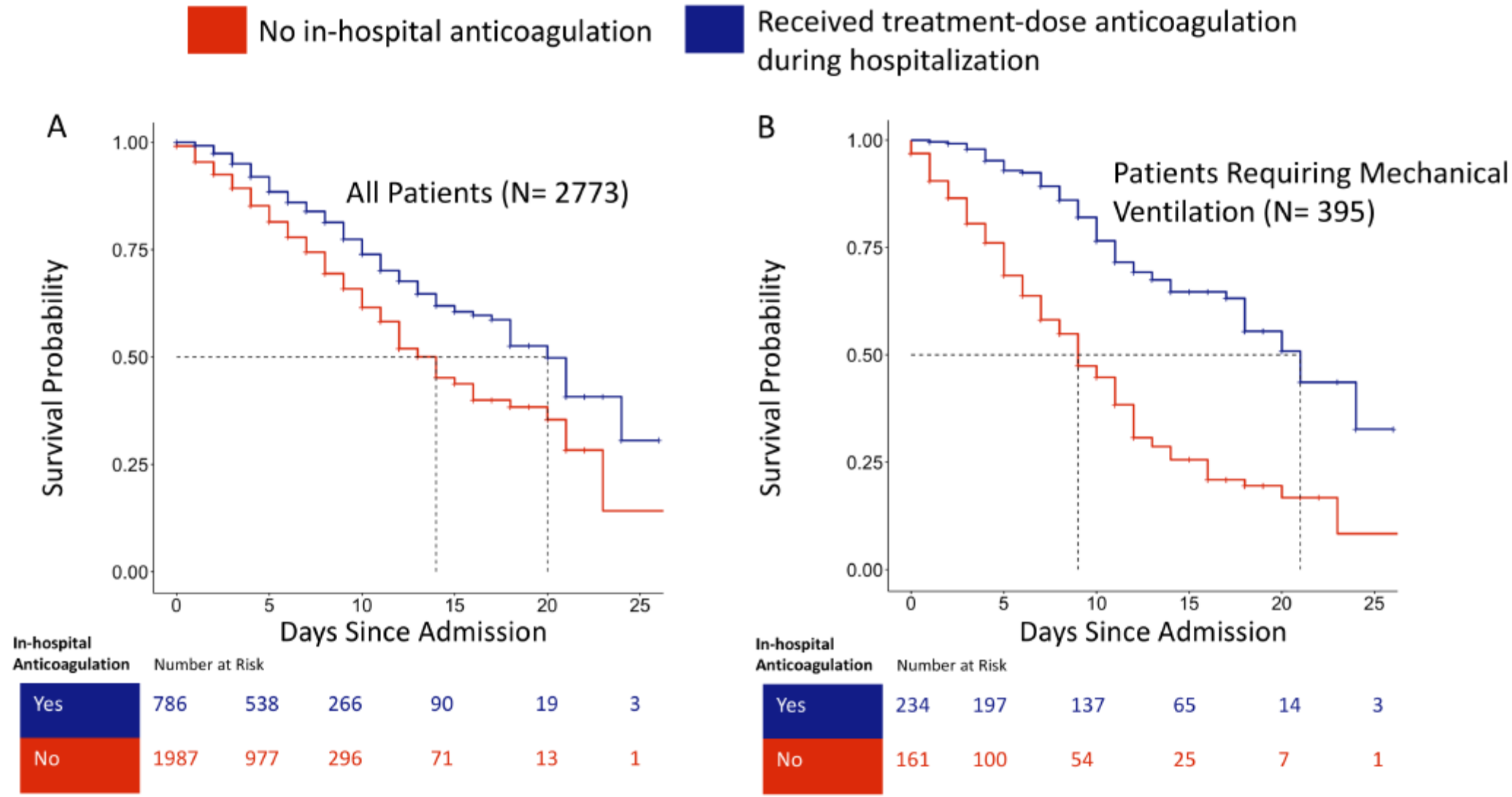
Reference: JAC 27327

To appear in: *Journal of the American College of Cardiology*

AC with in hospital survival

- 3/14/20-4/11/20: 2773 pts with COVID at Mt Sinai
- 786 received systemic AC, median time from admission – 2 days
- Serious bleeding in 3% AC vs 1.9% non AC (P=0.2) and ~40% of the AC group bleeds occurred prior to the start of AC.
- AC group more likely to require mech vent (30% vs 8%, p<0.001)
- In hospital Mortality similar: 22.5% AC vs 22.8% non AC
- Median survival increased in AC group 21 vs 14 for non AC
- Multivariate proportional hazard model longer duration of AC was associated with reduced risk of mortality (HR 0.86/day, p<0.001)


No in-hospital anticoagulation
Received treatment-dose anticoagulation during hospitalization
A
All Patients (N= 2773)
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Days Since Admission
In-hospital Anticoagulation
Number at Risk
Yes 786 538 266 90 19 3
No 1987 977 296 71 13 1
B
Patients Requiring Mechanical Ventilation (N= 395)
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Days Since Admission
In-hospital Anticoagulation
Number at Risk
Yes 234 197 137 65 14 3
No 161 100 54 25 7 1

Covid-19 and hypercoagulable state

- ~ 90% of inpatients with PNA had increased coagulation marked by increased d-dimer concentration
  - Specifically, d-dimer > 1ug/mL associated with fatal outcome by Zhou et al.

- **Proposed mechanisms**
  - Systemic proinflammatory cytokine responses
    - Drive plaque rupture through local inflammation, procoagulant factors, and hemodynamic changes predisposing to ischemia and thrombosis

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

Summary

Background Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.

Methods In this retrospective, multicentre cohort study, we included all adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death.

Findings 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03–1·17, per year increase; p=0·0043), higher Sequential Organ Failure Assessment (SOFA) score (5·65, 2·61–12·23; p<0·0001), and d-dimer greater than 1 μg/mL (18·42, 2·64–128·55; p=0·0033) on admission. Median duration of viral shedding was 20·0 days (IQR 17·0–24·0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.

Interpretation The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 μg/mL could help clinicians to identify patients with poor prognosis at an early stage. Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future.

Funding Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences; National Science Grant for Distinguished Young Scholars; National Key Research and Development Program of China; The Beijing Science and Technology Project; and Major Projects of National Science and Technology on New Drug Creation and Development.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., . . . Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet, 395*(10229), 1054-1062. doi:10.1016/S0140-6736(20)30566-3

Laboratory features associated with severe COVID-19 [1-6]

Abnormality	Possible threshold
Elevations in:	
▪ D-dimer	>1000 ng/mL (normal range: <500 ng/mL)
▪ CRP	>100 mg/L (normal range: <8.0 mg/L)
▪ LDH	>245 units/L (normal range: 110 to 210 units/L)
▪ Troponin	>2× the upper limit of normal (normal range for troponin T high sensitivity: females 0 to 9 ng/L; males 0 to 14 ng/L)
▪ Ferritin	>500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L)
▪ CPK	>2× the upper limit of normal (normal range: 40 to 150 units/L)
Decrease in:	
▪ Absolute lymphocyte count	<800/microL (normal range for age ≥21 years: 1800 to 7700/microL)

Although these laboratory features are associated with severe disease in patients with COVID-19, they have not been clearly demonstrated to have prognostic value. We use the thresholds listed above to identify patients who may be at risk for severe disease; they are extrapolated from published cohort data and individualized to the reference values used at our laboratory. However, the specific thresholds are not well established and may not be applicable if laboratories use other reference values.

COVID-19: coronavirus disease 2019; CRP: C-reactive protein; LDH: lactate dehydrogenase; CPK: creatine phosphokinase.

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5. *Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020.*
6. *Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020.*

Proposed Mechanism

- D-dimer elevation – concerns for pro-coagulable state
- Cytokine storming
- Cardioembolism from virus-related cardiac-injury
- Cardiac injury 20-30% of patients
  - Direct invasion
- Sepsis-induced coagulopathy (SIC)
  - High d-dimer, elevated fibrinogen
  - Precursor to DIC
    - Elevated PT and D-Dimer, Thrombocytopenia, without hypofibrinogenemia

Markus, H. S., & Brainin, M. (2020). COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke, 15*(4), 361-364. doi:10.1177/1747493020923472

Hess, D. C., Eldahshan, W., & Rutkowski, E. (2020). COVID-19-Related Stroke. *Transl Stroke Res, 11*(3), 322-325. doi:10.1007/s12975-020-00818-9

Mechanism

- Endothelial dysfunction and micro-thrombosis with organ failure and usually no bleeding
- In a multivariate analysis of a retrospective series of 440 severe COVID-19 patients, the predictors of 28-day mortality were age, prothrombin time, D-dimer levels, and thrombocytopenia.
  - Patients with elevated d-dimer or SIC score, lower mortality when treated with LMWH

Hess, D. C., Eldahshan, W., & Rutkowski, E. (2020). COVID-19-Related Stroke. *Transl Stroke Res, 11*(3), 322-325. doi:10.1007/s12975-020-00818-9

Lung, Cardiac, Brain – Is it all related?

- A case series of 3 patients with respiratory failure and high D-dimer levels reported transient improvement in respiratory parameters with the use of tissue plasminogen activator
  - Microvascular thrombosis – tPA seems to help

- Antiphospholipid Ab
  - Reported in 3 patients
    - Associated with arterial and venous thrombotic events
  - All 3 patients had cerebral infarcts, one with multi-limb ischemia
  - All had elevated IgA anticardiolipin antibodies and elevated IgA and IgG beta 2
  - Glycoprotein I antibodies with prolonged activated partial thromboplastin times and prothrombin times but no lupus anticoagulant
- Unsure if SIC vs. AP ab were the cause of the strokes

Hess, D. C., Eldahshan, W., & Rutkowski, E. (2020). COVID-19-Related Stroke. *Transl Stroke Res, 11*(3), 322-325. doi:10.1007/s12975-020-00818-9

Wang, J., Hajizadeh, N., Moore, E. E., McIntyre, R. C., Moore, P. K., Veress, L. A., . . . Barrett, C. D. (2020). Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. *J Thromb Haemost*. doi:10.1111/jth.14828

Stroke Etiology

- Hypercoagulability from COVID illness
- Cardioembolic from virus related cardiac injury
- Direct vessel injury from viral infection

12 patients had shock requiring vasopressors, and 11 patients had renal failure requiring continuous renal replacement therapy (CRRT). All patients received anticoagulation according to an institutional protocol based on data suggesting increased venous thromboembolism rates when D-dimer concentrations exceed 3 µg/mL.[2] Five patients with D-dimer concentrations of 3 µg/mL or higher and known (or highly suspected) thrombosis received therapeutic anticoagulation. Two of the patients received intravenous heparin, and three patients received a direct thrombin inhibitor (argatroban or bivalirudin) because of heparin resistance or concern for heparin-induced thrombocytopenia. Four patients with D-dimer concentrations below 3 µg/mL received low-dose thromboprophylaxis with low-molecular-weight heparin (LMWH) or subcutaneous heparin. Six patients with D-dimer concentrations of 3 µg/mL

fibrinogenaemia in patients with COVID-19, our patients had substantially increased fibrinogen concentrations (median 708 mg/dL, range 459–1188; normal reference range 200–393).[4] Further study is needed to evaluate which plasma components, including acute phase proteins such as fibrinogen, contribute to COVID-19-associated hyperviscosity.

Our novel observation might provide an important link between inflammation and coagulopathy in critically ill patients with COVID-19. We are actively exploring any beneficial role of therapeutic plasma exchange, a highly effective treatment for symptomatic hyperviscosity in other conditions such as hypergammaglobulinaemia, in the clinical management of these patients.[5] Finally, any causal relationship between hyperviscosity and thrombotic complications in COVID-19 warrants immediate investigation given the potential to impact clinical care.

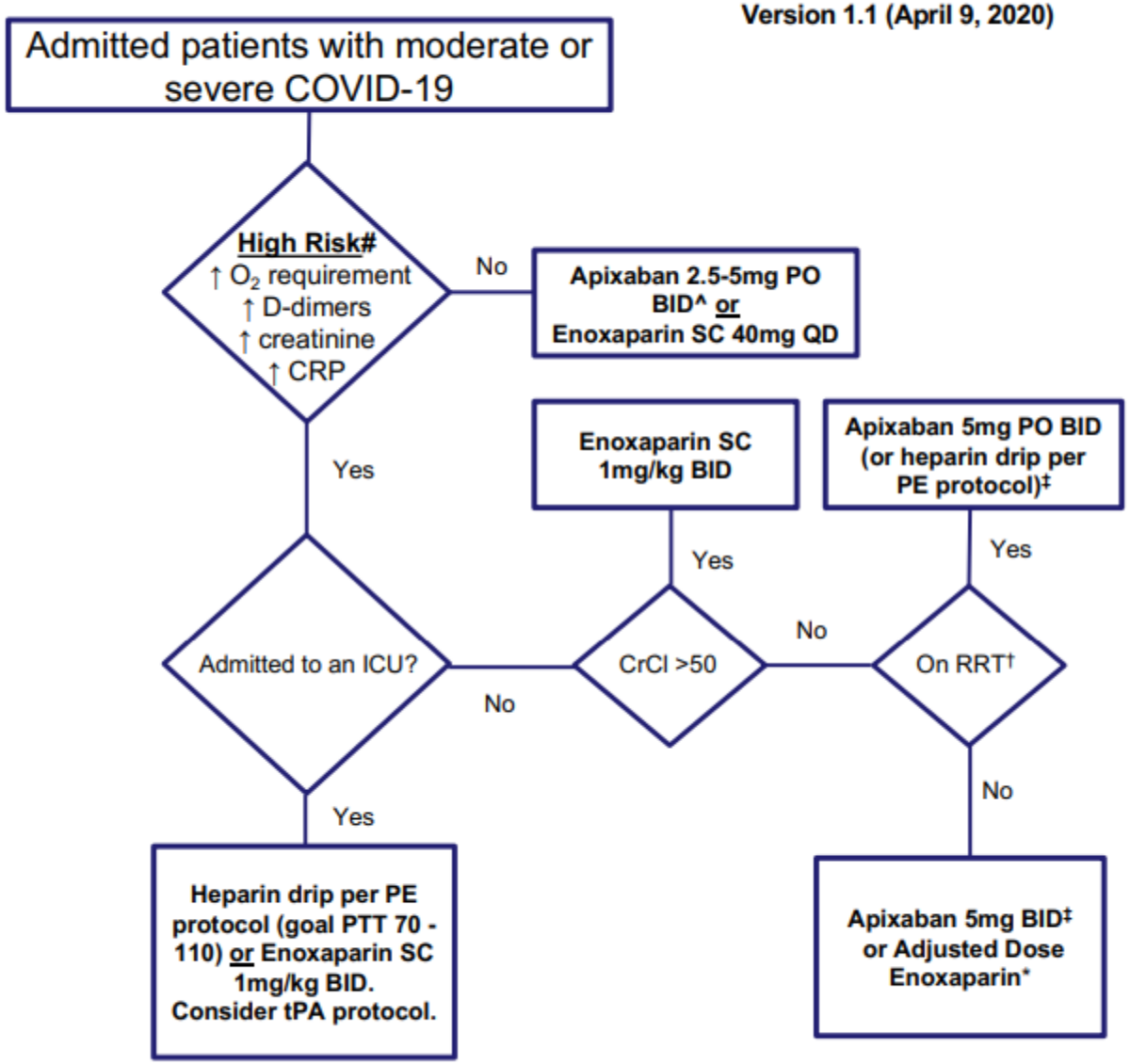
eighth special issue. *J Clin Apher* 2019; **34:** 171.

Anticoagulation protocols

- Add Buffalo Protocol

Mount Sinai COVID-19 Anticoagulation Algorithm

Version 1.1 (April 9, 2020)



Inclusion: All admitted patients with moderate or severe COVID-19
Exclusion: High risk of bleeding as judged by treating physician

Obtain at baseline and daily:
- CBC, PT/PTT, D-dimer

Hold anticoagulation if:
- Platelet count <50,000; INR>1.5
- Evidence of current or recent bleeding

If patients take AC at home:
- May switch to therapeutic enoxaparin or heparin (as per algorithm) for the duration of hospitalization, unless contraindicated

Rivaroxaban may be used in place of Apixaban at any indication

Discharged COVID-19 patient on therapeutic anticoagulation while hospitalized

Consider Prophylactic AC for 2 weeks post discharge (Apixaban 5mg PO BID for 2 wks)

#High Risk: No precise metrics exist. Consider exam (eg O_2 sat<90%, RR >24), ↑O_2 requirement (eg, ≥4L NC), labs (eg, ↑d-dimers, C-reactive protein)
^Efficacy and dose not established; prophylactic or treatment doses acceptable

†RRT – Renal Replacement Therapy
‡ If ≥80 years of age or weight ≤60 kg, reduce apixaban to 2.5 mg BID
* If CrCl <30: enoxaparin 0.5mg/kg BID with anti-Xa level after 3rd dose

Mount Sinai COVID-19 Anticoagulation Algorithm

Definition of high risk for progression to ICU

- There is insufficient evidence to precisely define “high-risk” or provide specific cut-off values for individual factors
- Clinicians should consider a combination of exam findings (e.g, labored breathing, RR >24, decreased O_2 sat<90%), increased O_2 requirement (eg, ≥4L NC), and lab biomarkers (eg, elevated CRP, elevated creatinine, rising d-dimer >1.0).

Rationale for early anticoagulation

- Pathophysiology of COVID-19 associated respiratory disease is consistent with pulmonary vascular thromboemboli with increased dead space ventilation
- Autopsy studies have demonstrated venous thromboembolism in deceased coronavirus patients[1]
- Early anticoagulation is necessary to prevent propagation of microthrombi at disease presentation
- Anticoagulation may be associated with decreased mortality[2]

Rationale for choice of anticoagulant

- Heparins bind tightly to COVID-19 spike proteins[3,4]
- Heparins also downregulate IL-6 and directly dampen immune activation[5]
- DOACs do not appear to have these anti-inflammatory properties
- Rivaroxaban can be used in place of Apixaban in this algorithm

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Version 1.1 (April 9, 2020)

REVIEW ARTICLE

OPEN ACCESS

N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why

Giancarlo Aldini[a], Alessandra Altomare[a], Giovanna Baron[a], Giulio Vistoli[a], Marina Carini[a], Luisa Borsani[b] and Francesco Sergio[c]

[a]Department of Pharmaceutical Sciences, Università degli Studi di Milano, Milan, Italy; [b]Global Medical Information, Zambon S.p.A., Bresso, Italy; [c]Global Respiratory Medical Affairs, Zambon S.p.A., Bresso, Italy

ABSTRACT

The main molecular mechanisms explaining the well-established antioxidant and reducing activity of N-acetylcysteine (NAC), the *N*-acetyl derivative of the natural amino acid L-cysteine, are summarised and critically reviewed. The antioxidant effect is due to the ability of NAC to act as a reduced glutathione (GSH) precursor; GSH is a well-known direct antioxidant and a substrate of several antioxidant enzymes. Moreover, in some conditions where a significant depletion of endogenous Cys and GSH occurs, NAC can act as a direct antioxidant for some oxidant species such as NO_2 and HOX. The antioxidant activity of NAC could also be due to its effect in breaking thiolated proteins, thus releasing free thiols as well as reduced proteins, which in some cases, such as for mercaptoalbumin, have important direct antioxidant activity. As well as being involved in the antioxidant mechanism, the disulphide breaking activity of NAC also explains its mucolytic activity which is due to its effect in reducing heavily cross-linked mucus glycoproteins. Chemical features explaining the efficient disulphide breaking activity of NAC are also explained.

- How can we help GSHPX to be in reduced form of 2 GSH to take care of this? Helping alleviate oxidative stress.
- NAC – antioxidant and disulphide breaking agent
  - Highly linked cross linked mucus gels treated with NAC breaks disulfide bonds and **reduces viscosity.** Used by inhaling to break up thick mucus!
  - NAC through Acylase I to Cys which recharges GSH (Tylenol overdose toxicity Tx mechanism)

- Article goes on to talk about all the ways GSH can become depleted in the body (colds, etc)
- GSH role in ENT conditions (rhinitis, allergic rhinitis, chronic rhinosinusitis, otitis media with effusion, chronic otitis media, COM with cholesteatoma, tonsillitis, meniere disease, laryngeal conditions, chronic cough are all associated with oxidative stress and decreased GSH both locally and systemically.
- Decreased GSH levels are also associated with aging as well as a wide range of neurodegenerative disorders (Parkinsons Disease, Alzheimer's disease)
- Significant depletion of GSH has been reported in lung fluids in different lung diseases.

Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment.

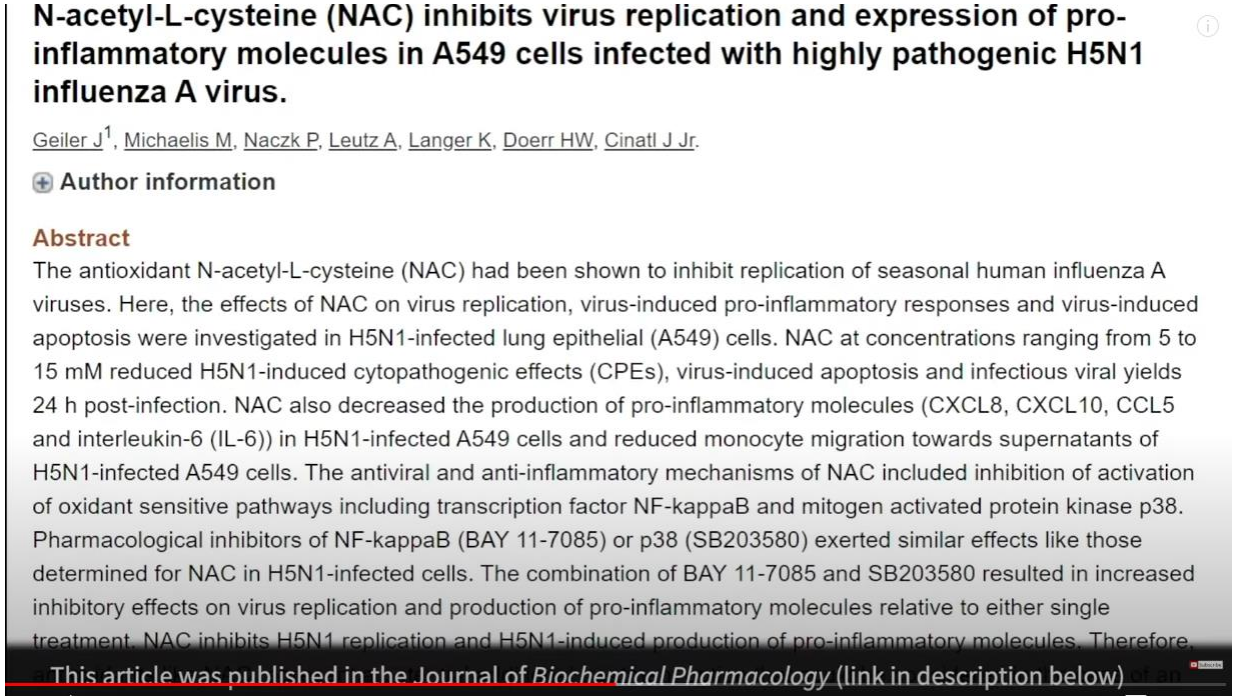
De Flora S[1], Grassi C, Carati L.

Author information

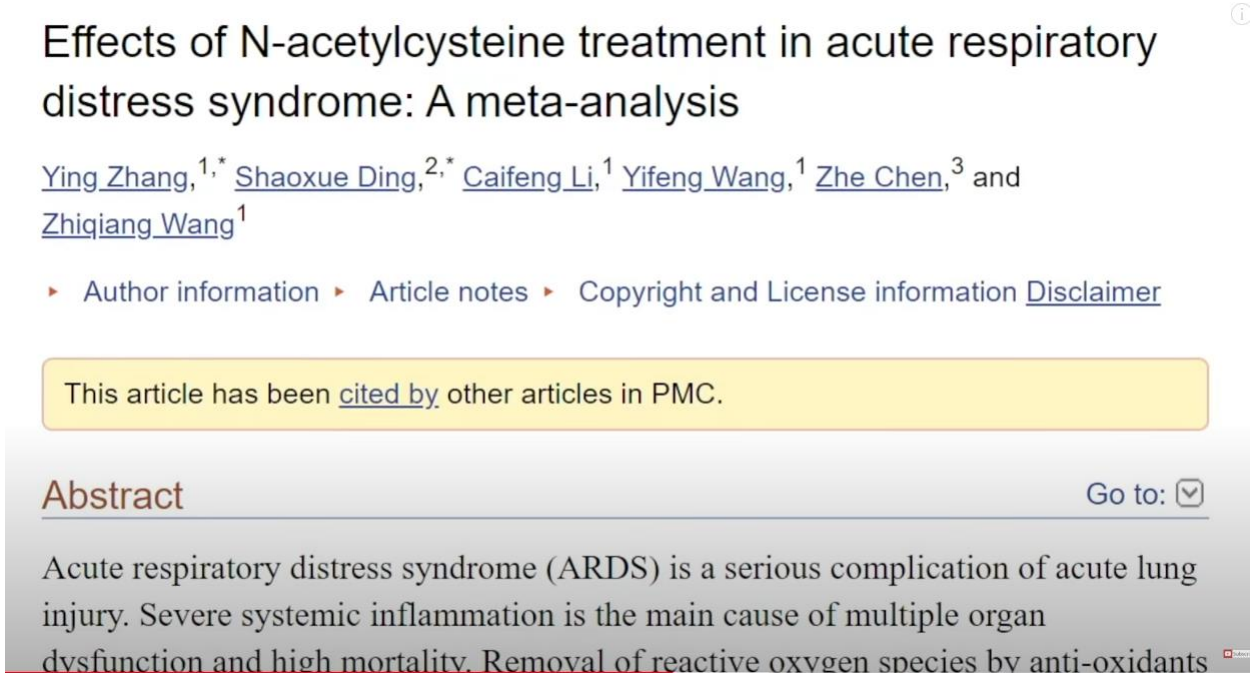
Abstract

N-acetylcysteine (NAC), an analogue and precursor of reduced glutathione, has been in clinical use for more than 30 yrs as a mucolytic drug. It has also been proposed for and/or used in the therapy and/or prevention of several respiratory diseases and of diseases involving an oxidative stress, in general. The objective of the present study was to evaluate the effect of long-term treatment with NAC on influenza and influenza-like episodes. A total of 262 subjects of both sexes (78% > or = 65 yrs, and 62% suffering from nonrespiratory chronic degenerative diseases) were enrolled in a randomized, double-blind trial involving 20 Italian Centres. They were randomized to receive either placebo or NAC tablets (600 mg) twice daily for 6 months. Patients suffering from chronic respiratory diseases were not eligible, to avoid possible confounding by an effect of NAC on respiratory symptoms. NAC treatment was well tolerated and resulted in a significant decrease in the frequency of influenza-like episodes, severity, and length of time confined to bed. Both local and systemic symptoms were sharply and significantly reduced in the NAC group. Frequency of seroconversion towards A/H1N1 Singapore 6/86 influenza virus was similar in the two groups, but only 25% of virus-infected subjects under NAC treatment developed a symptomatic form, versus 79% in the placebo group. Evaluation of cell-mediated immunity showed a progressive, significant shift from anergy to normoergy following NAC treatment. Administration of N-acetylcysteine during the winter, thus, appears to provide a significant attenuation of influenza and influenza-like episodes, especially in elderly high-risk

- Randomized double blind trial, 262 subjects (78% >65), 20 centers in Italy for 6 months
- H1N1 flu…both had same amount of flu (placebo and NAC Tx (600 mg BID) had similar seroconversion rates)
  - **79% had Sx (clinically apparent disease) in placebo vs 25% in NAC Tx (NNT = 2)**
  - **NAC during winter significant decreased influenza like episodes, especially in elderly.**



- NAC may directly inhibit virus replication
- And decrease production of proinflammatory molecules and IL-6



Effects of N-acetylcysteine treatment in acute respiratory distress syndrome: A meta-analysis

Ying Zhang,[1,*] Shaoxue Ding,[2,*] Caifeng Li,[1] Yifeng Wang,[1] Zhe Chen,[3] and Zhiqiang Wang[1]

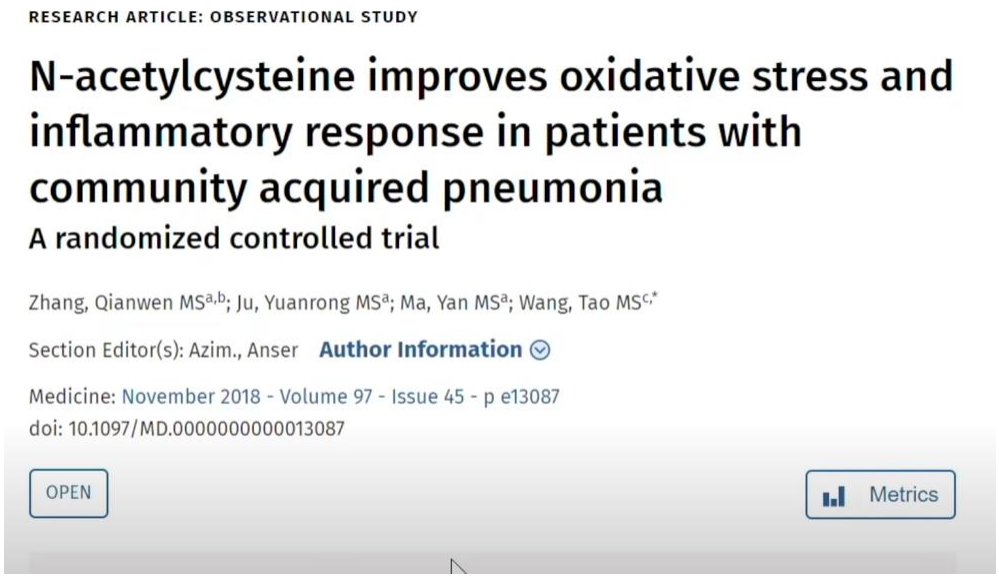
Abstract

Go to:

Acute respiratory distress syndrome (ARDS) is a serious complication of acute lung injury. Severe systemic inflammation is the main cause of multiple organ dysfunction and high mortality. Removal of reactive oxygen species by anti-oxidants

NAC for all types of ARDS, metanalysis
Statistically significant difference in length of ICU stay
No difference in mortality
No severe adverse reactions.

Comment that removal of reactive oxygen species by anti-oxidants is important and that NAC is the most commonly used anti-oxidant.



RESEARCH ARTICLE: OBSERVATIONAL STUDY

N-acetylcysteine improves oxidative stress and inflammatory response in patients with community acquired pneumonia

A randomized controlled trial

Zhang, Qianwen MS[a,b]; Ju, Yuanrong MS[a]; Ma, Yan MS[a]; Wang, Tao MS[c,*]

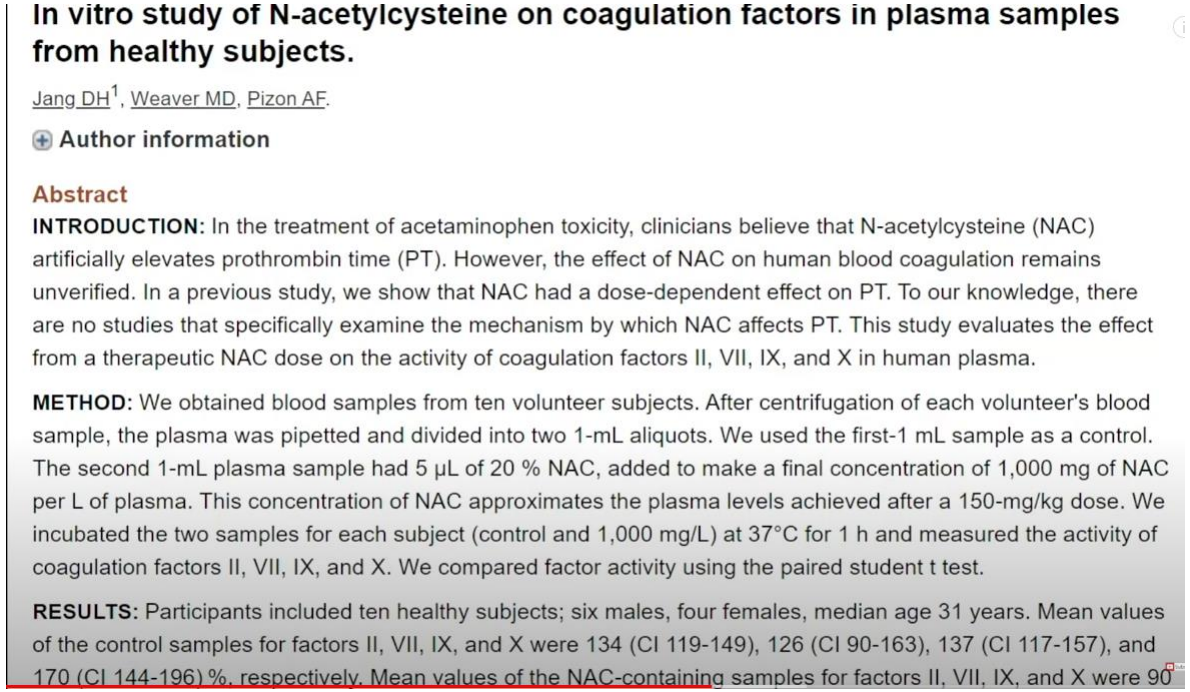
Section Editor(s): Azim., Anser **Author Information**

Medicine: November 2018 - Volume 97 - Issue 45 - p e13087
doi: 10.1097/MD.0000000000013087

OPEN

Metrics

- NAC for CAP.
- Looked for different levels of oxidative stress (MDA, TAOC, SOD, TNF-alpha) – similar in both groups at the start
  - Plasma levels of MDA and TNFa decreased statistically significantly in NAC group than Non NAC, and a statiscally significant improvement in TAOC (total anti oxidant capacity).
  - No NAC related adverse effects



In vitro study of N-acetylcysteine on coagulation factors in plasma samples from healthy subjects.

Jang DH[1], Weaver MD, Pizon AF.

Author information

Abstract

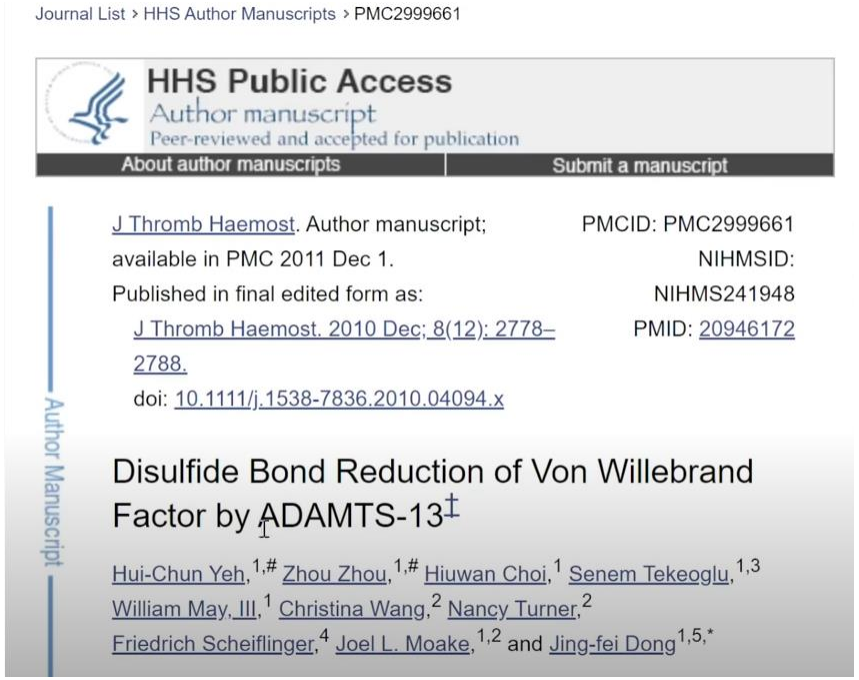
INTRODUCTION: In the treatment of acetaminophen toxicity, clinicians believe that N-acetylcysteine (NAC) artificially elevates prothrombin time (PT). However, the effect of NAC on human blood coagulation remains unverified. In a previous study, we show that NAC had a dose-dependent effect on PT. To our knowledge, there are no studies that specifically examine the mechanism by which NAC affects PT. This study evaluates the effect from a therapeutic NAC dose on the activity of coagulation factors II, VII, IX, and X in human plasma.

METHOD: We obtained blood samples from ten volunteer subjects. After centrifugation of each volunteer's blood sample, the plasma was pipetted and divided into two 1-mL aliquots. We used the first-1 mL sample as a control. The second 1-mL plasma sample had 5 µL of 20 % NAC, added to make a final concentration of 1,000 mg of NAC per L of plasma. This concentration of NAC approximates the plasma levels achieved after a 150-mg/kg dose. We incubated the two samples for each subject (control and 1,000 mg/L) at 37°C for 1 h and measured the activity of coagulation factors II, VII, IX, and X. We compared factor activity using the paired student t test.

RESULTS: Participants included ten healthy subjects; six males, four females, median age 31 years. Mean values of the control samples for factors II, VII, IX, and X were 134 (CI 119-149), 126 (CI 90-163), 137 (CI 117-157), and 170 (CI 144-196) %, respectively. Mean values of the NAC-containing samples for factors II, VII, IX, and X were 90

- THIS MIGHT BE VERY IMPORTANT FOR COVID
- Oxidative stress may lead to thrombosis from hypercoagulable state from vWF
- So…NAC might not just help oxidative stress state…but might also address vWF

- NAC – demonstrates a significant decrease in activity of coagulation factors II, VII, IX, and X
  - so pts blood would be thinner.



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J Thromb Haemost. Author manuscript; available in PMC 2011 Dec 1.
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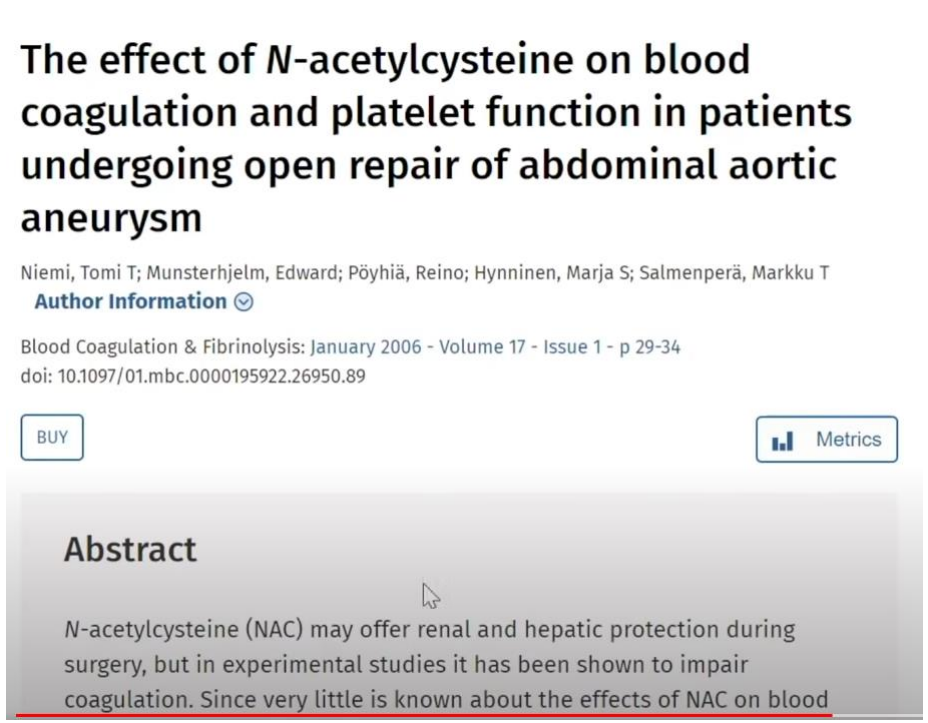
doi: 10.1111/j.1538-7836.2010.04094.x

PMCID: PMC2999661
NIHMSID: NIHMS241948
PMID: 20946172

Disulfide Bond Reduction of Von Willebrand Factor by ADAMTS-13‡

Hui-Chun Yeh,[1,#] Zhou Zhou,[1,#] Hiuwan Choi,[1] Senem Tekeoglu,[1,3] William May, III,[1] Christina Wang,[2] Nancy Turner,[2] Friedrich Scheiflinger,[4] Joel L. Moake,[1,2] and Jing-fei Dong[1,5,*]

vWF polymerized by Disulfide bonds



The effect of *N*-acetylcysteine on blood coagulation and platelet function in patients undergoing open repair of abdominal aortic aneurysm

Niemi, Tomi T; Munsterhjelm, Edward; Pöyhiä, Reino; Hynninen, Marja S; Salmenperä, Markku T
Author Information

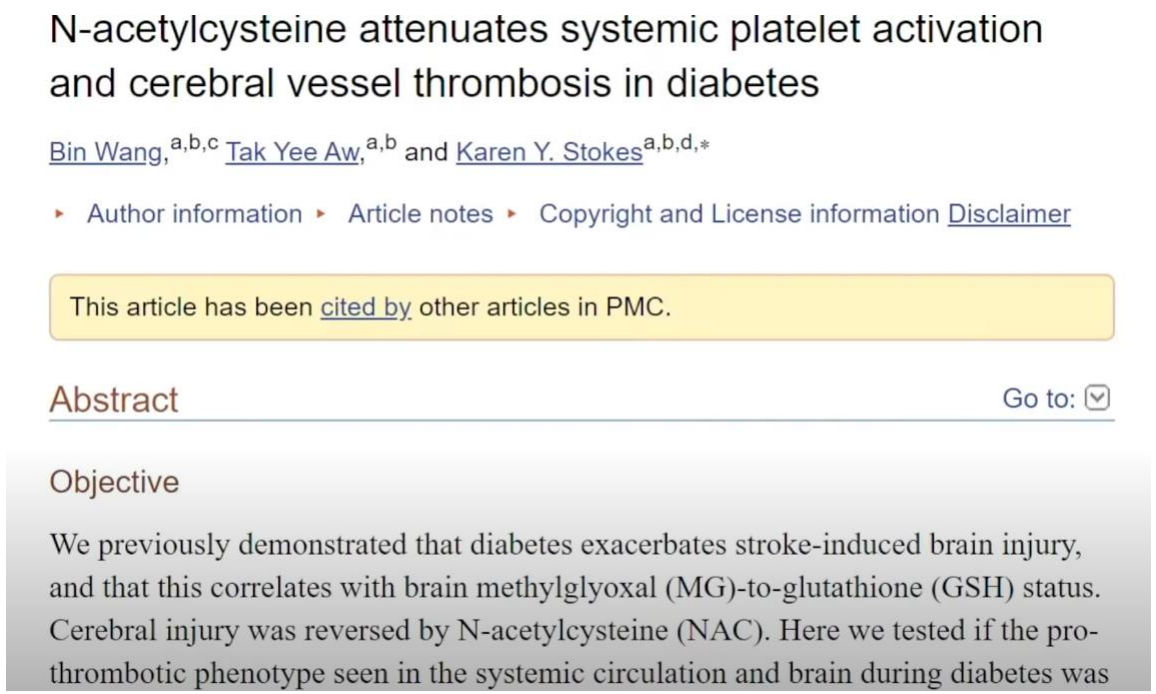
Blood Coagulation & Fibrinolysis: January 2006 - Volume 17 - Issue 1 - p 29-34
doi: 10.1097/01.mbc.0000195922.26950.89

BUY Metrics

Abstract

N-acetylcysteine (NAC) may offer renal and hepatic protection during surgery, but in experimental studies it has been shown to impair coagulation. Since very little is known about the effects of NAC on blood

NAC has a anticoagulant and platelet inhibiting property in patients undergoing major vascular surgery



N-acetylcysteine attenuates systemic platelet activation and cerebral vessel thrombosis in diabetes

Bin Wang,[a,b,c] Tak Yee Aw,[a,b] and Karen Y. Stokes[a,b,d,*]

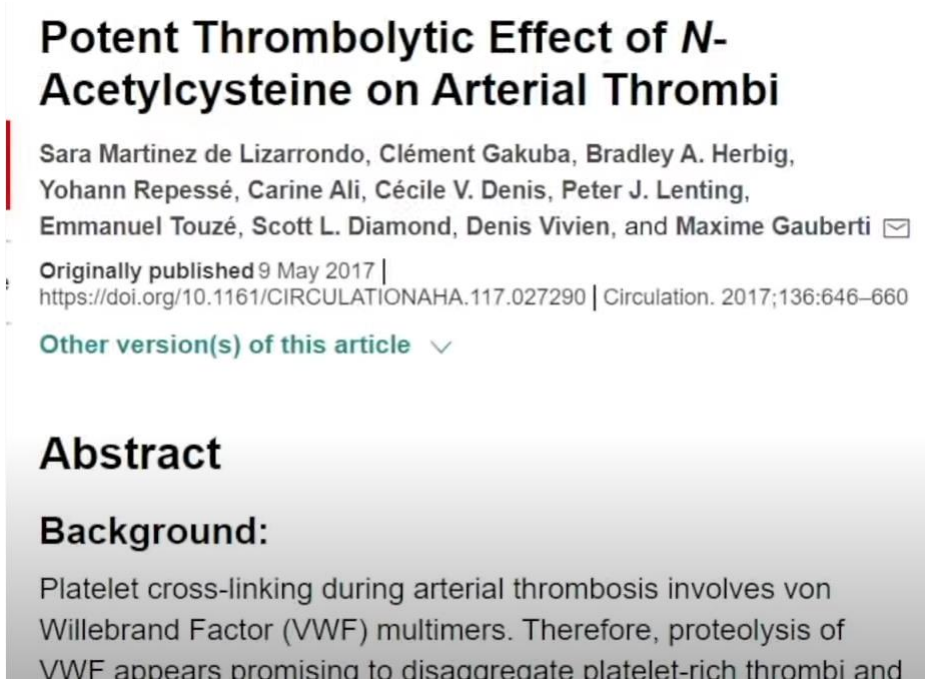
Abstract

Objective

We previously demonstrated that diabetes exacerbates stroke-induced brain injury, and that this correlates with brain methylglyoxal (MG)-to-glutathione (GSH) status. Cerebral injury was reversed by N-acetylcysteine (NAC). Here we tested if the pro-thrombotic phenotype seen in the systemic circulation and brain during diabetes was

- DM exacerbates stroke induced brain injury
- Correlated with brain methylglyoxal to GSH status
- Cerebral injury was reversed by NAC

- Diabetic blood and brain became progressively more susceptible to platelet activation and thrombosis. NAC given after establishment of DM may offer protection against risk of stroke by altering both systemic and vascular prothrombic reponses via enhancing platelet GSH, and GSH dependent MG elimination as well as correcting levels of antioxidants such as SOD and GPx



Potent Thrombolytic Effect of *N*-Acetylcysteine on Arterial Thrombi

Sara Martinez de Lizarrondo, Clément Gakuba, Bradley A. Herbig, Yohann Repessé, Carine Ali, Cécile V. Denis, Peter J. Lenting, Emmanuel Touzé, Scott L. Diamond, Denis Vivien, and Maxime Gauberti

Originally published 9 May 2017 | https://doi.org/10.1161/CIRCULATIONAHA.117.027290 | Circulation. 2017;136:646–660

Other version(s) of this article

Abstract

Background:

Platelet cross-linking during arterial thrombosis involves von Willebrand Factor (VWF) multimers. Therefore, proteolysis of VWF appears promising to disaggregate platelet-rich thrombi and

- Proteolysis of VWF appears promising to disaggregate platelet rich thrombi and restore vessel patency in acute thrombotic disorders such as acute ischemic stroke, acute coronary syndrome, or acute limb ischemia.
- NAC can reduce intrachain disulfide bonds in large polymeric proteins.
- This study postulated that NAC might cleave VWF multimers inside occlusive thrombi leading to dissolution and arterial recanalization.

- RESULTS: demonstrated lysis of arterial thrombi that are resistant to conventional approaches such as tPA, direct thrombin inhibitors, and antiplatelet treatment.
- The effect is augmented by combination with GpIIb/IIIa inhibitor.
- Large vessel thromboembolic stroke model in mice, improved ischemic lesions size and neurologic outcome without worsening hemorrhagic stroke transformation.

MYELOID NEOPLASIA | JANUARY 24, 2020

N-acetylcysteine inhibits thrombosis in a murine model of myeloproliferative neoplasm

Brianna M. Craver, Gajalakshmi Ramanathan, Summer Hoang, Xinyue Chang, Laura F. Mendez Luque, Stefan Brooks, Hew Yeng Lai, Angela G. Fleischman

Check for updates

Blood Adv (2020) 4 (2): 312–321.

https://doi.org/10.1182/bloodadvances.2019000967

Article history

Split-Screen Share Tools PDF

Key Points

- The antioxidant NAC extends survival of the *Vav*-Cre:JAK2^{V617F} knockin murine model of polycythemia vera.
- NAC has the potential to inhibit thrombosis caused by the JAK2^{V617F} mutation.

N-acetylcysteine reduces the size and activity of von Willebrand factor in human plasma and mice.

Chen J[1], Reheman A, Gushiken FC, Nolasco L, Fu X, Moake JL, Ni H, López JA.

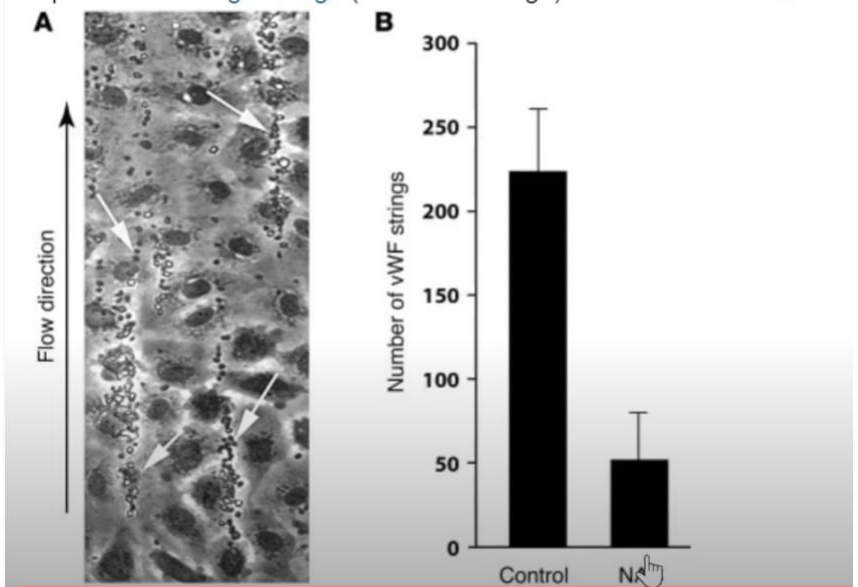
Author information

Abstract

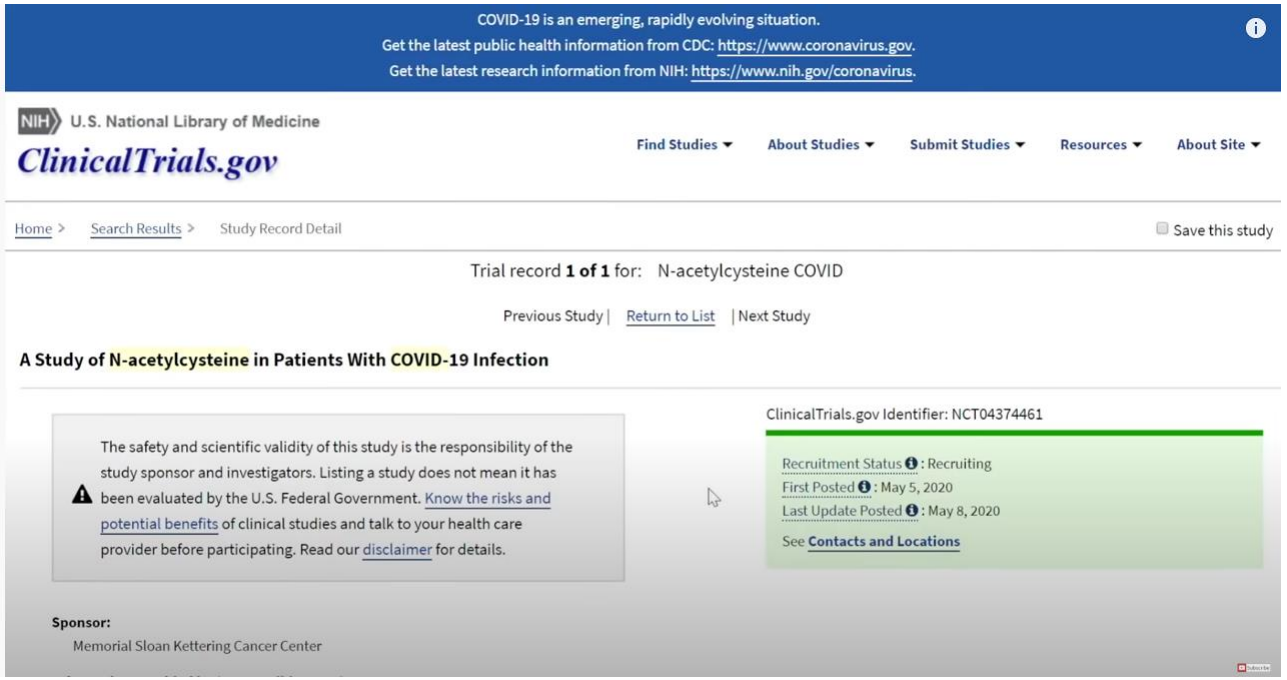
Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease characterized by systemic microvascular thrombosis caused by adhesion of platelets to ultra-large vWF (ULVWF) multimers. These multimers accumulate because of a deficiency of the processing enzyme ADAMTS13. vWF protein forms long multimers from homodimers that first form through C-terminal disulfide bonds and then join through their N termini by further disulfide bonding. N-acetylcysteine (NAC) is an FDA-approved drug that has long been used to treat chronic obstructive lung disease and acetaminophen toxicity and is known to function in the former disorder by reducing mucin multimers. Here, we examined whether NAC could reduce vWF multimers, which polymerize in a manner similar to mucins. In vitro, NAC reduced soluble

Effect of NAC on platelet–vWF strings under flow.

Options: View larger image (or click on image) Download as PowerPoin



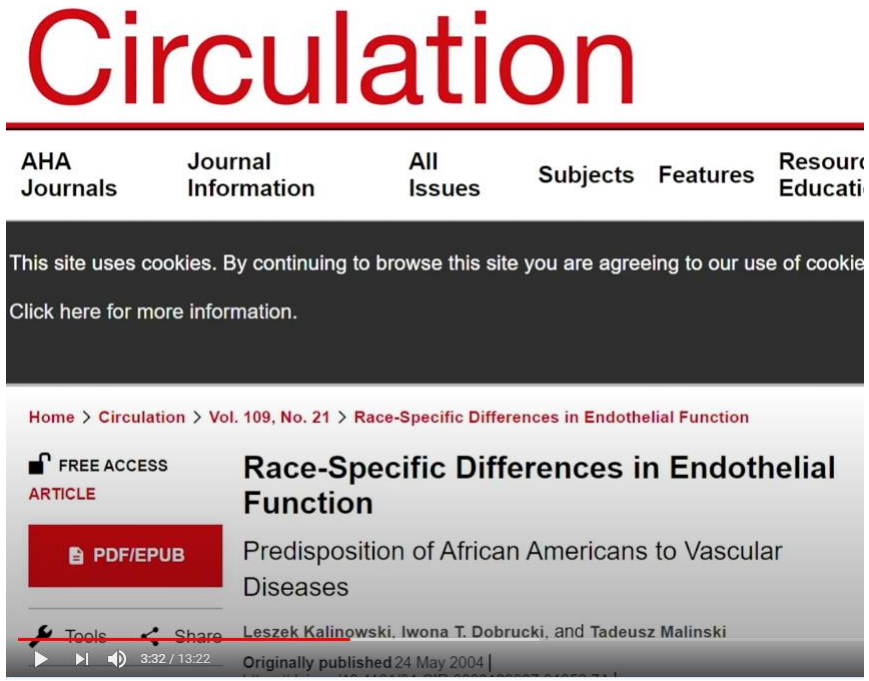
This review only focuses on acute respiratory disorders
(not vascular disorder with endothelial damage and thrombosis)

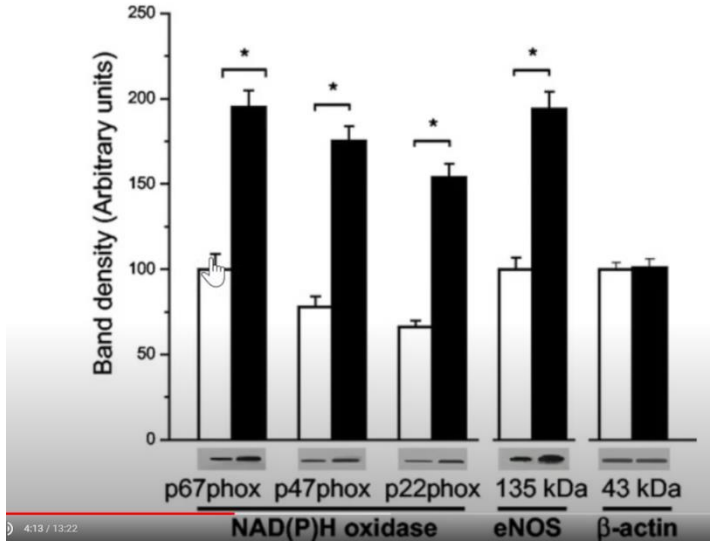


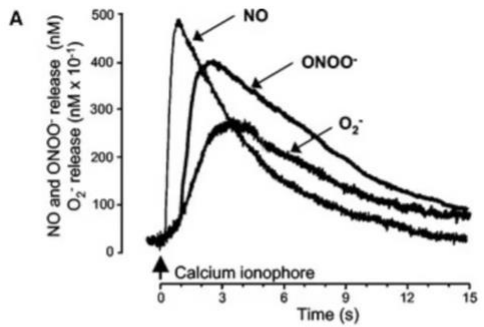
Severe disease
Looking for 86 participants, Phase 2 study
NAC IV 6 gm/day up to 3 weeks

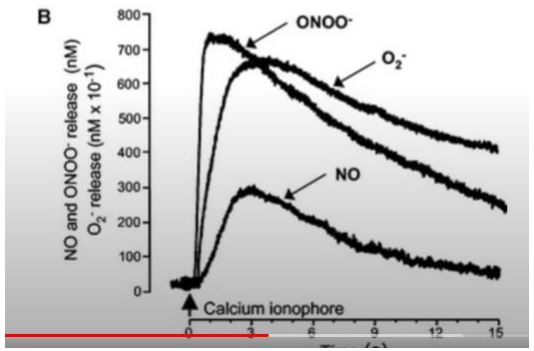
IRB

- Labs: D Dimer, PTT, aPTT, fibrinogen, viscosity, fibrin, CRP, LDH
  - VWF Ag and activity, Factor VIII activity
- Tx:
  - NAC - oral
  - LMWH anticoagulation
  - AT 1,7

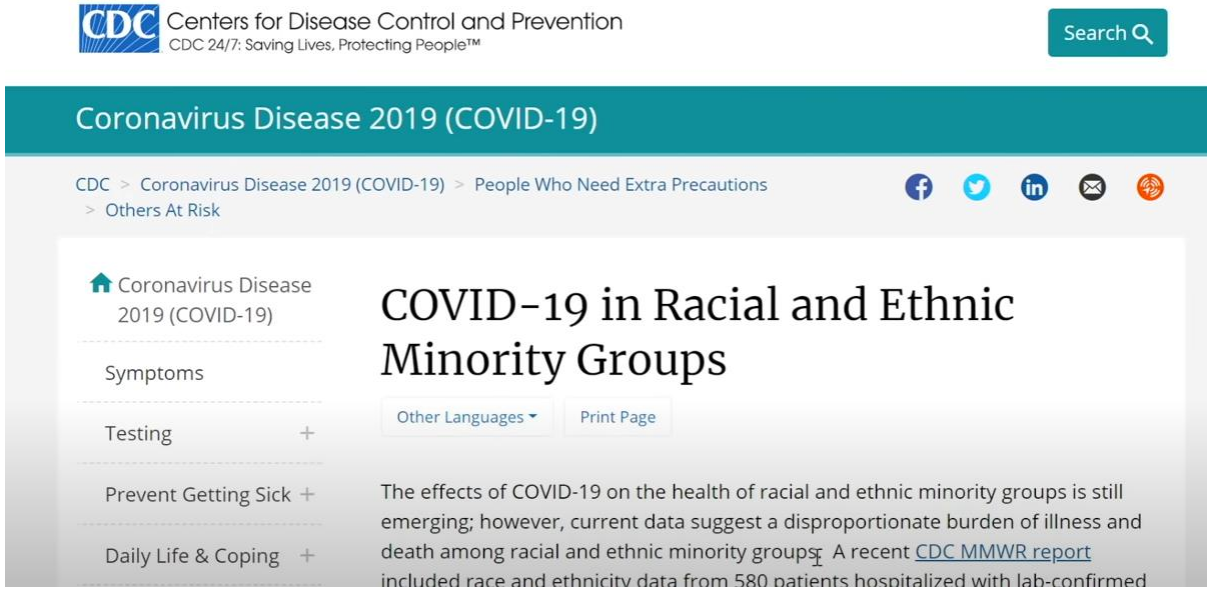








Oxidative stress in endothelium
Nanosensors (HUVECs) isolated from blacks and whites
NADPH oxidase expressed more in blacks
May be gender and age difference in redox state.



Miller and colleagues [18] studied the effect of ABO blood type and race on plasma VWF levels and found that Caucasians had significantly lower levels than African-Americans. Interestingly, ABO and race showed independently effects accounting for 19 and 7 percent of the total variance in VWF:Ag levels, respectively.

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Kawasaki Disease as a Systemic Vasculitis in Childhood

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Nobuyuki Hiruta, MD, Ph.D,[2] and Shiro Naoe, MD, Ph.D[3]

- Blood vessels become inflamed
- Systemic vasculitis syndrome in childhood (<5 yo)
- Medium sized muscular arteries (including coronary arteries).
- Focus has been because coronary often cause of death…so looked at lesions in other whole organs
- IgA plasma cells infiltrated vascular and non vascular tissues. Hypothesize primarily vascular issue.
- Hypothesized virus trigger via respiratory or digestive organ is processed by the lymph.
- Cytoplasmic inclusion bodies identified in bronchial epithelium.
- Also show diffuse alveolar damage.
- **So we have a vascular disease that also causes a lung disease…interesting if we have a lung disease now that can also cause a vascular disease.**