Atypical “ARDS” and ventilation-perfusion mismatch in COVID-19 - A rapid review of the evidence

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17/04/2020

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Suggested Citation: Kirk L., (17/04/20). *Atypical “ARDS” and ventilation-perfusion mismatch in COVID-19 - A rapid review of the evidence*. ANU College of Health and Medicine COVID-19 Evidence Team, Canberra, Australia.

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COVID19 Canberra Health Service and ANU College of Health and Medicine – Atypical "ARDS" and V/Q mismatch

17/4/20, L KIRK

Acronyms:

- WHO: World Health Organization, CDNA: Communicable Diseases Network Australia, PPE: Personal protective equipment, HCW: Healthcare worker, IMV: invasive mechanical ventilation, NIV: non-invasive ventilation, HFNC: high-flow nasal cannula, PP: prone position, WOB: work of breathing, SCM: sternocleidomastoid, CVVHF: continuous venovenous hemofiltration

Summary:

- *This provides some information regarding the Type L and Type H phenotypes proposed primarily by Luigi Camporota and teams in the UK and Italy. It does not provide a comprehensive overview of management of critical care of COVID-19 patients and is not comprehensive.*

- *Initial information regarding management of COVID-19 was 1. Intubate early as patients were presenting w/ severe hypoxaemia, and 2. Treat as per ARDS protocols. New information counters this and suggests that early in the disease course, treating as per ARDS protocols may cause harm.*
- Initial reports from Europe were that there was a <u>dissociation between relatively "well preserved" lung mechanics and severity of hypoxaemia</u>
    - Have relatively high compliance indicating well preserved lung gas volume, in contrast to expectation for ARDS
    - Appeared to have loss of lung perfusion regulation and loss of hypoxic vasoconstriction → perfusion of gasless tissue
- Two proposed phenotypes:
    - **Type L: hypothesis** → modest interstitial oedema subpleural and along fissures but **vasoplegia drives hypoxaemia** → inc. minute ventilation by inc. tidal vol. → inc. intrathoracic insp. pressure
        - **Low elastance, low V**:**Q ratio, low lung weight**, l**ow lung recruitability**
    - Type L patients may remain unchanged for a period → then improve or worsen
        - Inc. intrathoracic inspiratory pressure + increased lung permeability due to inflammation → inc. interstitial oedema
        - Inc. interstitial oedema → inc. lung weight + inc. dependent atelectasis → decreased gas volume → dec. tidal vol.
        - Dec. tidal vol. → dyspnoea → further worsens lung injury
    - **Type H: more classical ARDS**
        - **High elastance, high R to L shunt:** perfusion of non-aerated tissue (increased oedema and atelectasis), **high lung weight, high lung recruitability**
- Proposed Mx of Type L:
    - Reverse hypoxaemia via increased FiO2
    - If dyspnoeic → HFNC, CPAP or NIV for TIME LIMITED TRIAL → ensure monitored WOB
        - In some increased PEEP may decrease cycle of lung injury, but for others high PEEP w/ normal compliance can be detrimental on haemodynamics
    - If intubated → PEEP of 8-10 cmH2O
- For Type H, treat as severe ARDS
    - Type L and Type H best distinguished by CT

EVIDENCE BASE AND SOURCE	SUMMARY – ATYPICAL "ARDS", V/Q MISMATCH AND MICROEMBOLI

30/03/20, Letter: ***COVID-19 does not lead to a "typical" acute respiratory distress syndrome***[1]
 	
https://www.atsjournals.org/doi/abs/10.1164/rccm.202003-0817LE
	- *Letter reporting on experience of disease progression of COVID19 patients in Italy*
	- "… patients with COVID-19 pneumonia, fulfilling the Berlin criteria of ARDS, present an atypical form of the syndrome"
	- Have found that there is a dissociation between relatively "well preserved" lung mechanics and severity of hypoxaemia
	  o Have relatively high compliance indicating well preserved lung gas volume, in contrast to expectation for ARDS
	- Thought to be explained by a loss of lung perfusion regulation and loss of hypoxic vasoconstriction
	  o VQ showed hyperperfusion of gasless lung tissue
	- Based on this, need to consider:
	  o If treated with CPAP or NIV and are presenting with excessive inspiratory effort, intubation should be prioritised to avoid excessive intrathoracic negative pressures
	  o High PEEP in a poorly recruitable lung leads to severe haemodynamic impairment and fluid retention
	  o Prone positioning can lead to modest benefit at the cost of high demand for already stressed and stretched human resources
	- **Buy time with minimal additional damage, the lowest possible PEEP and gentle ventilation… be patient**

14/04/20, Editorial (Germany, Italy, UK): ***COVID-19 pneumonia: different respiratory treatments for different phenotypes?***[2]
 	
https://link.springer.com/article/10.1007/s00134-020-06033-2
	- Although COVID19 is often meeting the Berlin definition of ARDS, it "is a specific disease"
	- Severe hypoxaemia often associated w/ near normal respiratory system compliance → Not normally seen in severe ARDS
	- Same disease is presenting heterogeneously → Severely hypoxemic but not dyspnoeic, or hypoxemic and dyspnoeic
	- Have characterised two predominant phenotypes: **Type L** and **Type H**
	- **Type L: hypothesis →** modest interstitial oedema subpleural and along fissures but **vasoplegia drives hypoxaemia** → inc. minute ventilation by inc. tidal vol. → inc. intrathoracic insp. pressure
	  o **Low elastance:** near normal compliance → normal gas volume
	  o **Low V**:**Q ratio:** if gas volume is normal, hypoxemia is best explained by loss of regulation of perfusion → vasoplegia → loss of hypoxic vasoconstriction
	  o **Low lung weight**: ground-glass opacities primarily subpleural + along fissures → minimal inc. in lung weight
	  o **Low lung recruitability**: amount of *non*-ventilated tissue is low → therefore, low recruitability
	- Type L patients may remain unchanged for a period → then improve or worsen
	  o Inc. intrathoracic inspiratory pressure + increased lung permeability due to inflammation → inc. interstitial oedema
	  o Inc. interstitial oedema → inc. lung weight + inc. dependent atelectasis → decreased gas volume → dec. tidal vol.
	  o Dec. tidal vol. → dyspnoea → further worsens lung injury
	- **Type H: more classical ARDS →** high elastance, high R→ L shunt, high lung weight, high recruitability
	  o **High elastance:** inc. interstitial oedema → dec. gas volumes → inc. elastance (dec. compliance)
	  o **High R to L shunt:** perfusion of non-aerated tissue (as a result of inc. oedema and atelectasis)
	  o **High lung weight:** Quantitative analysis via CT shows increased lung weight
	  o **High lung recruitability:** increase amount of non-aerated tissue is associated w/ increased recruitability
	- Proposed management of Type L:

	○ Reverse hypoxaemia via increased FiO2 ○ If dyspnoeic → HFNC, CPAP or NIV → ensure monitored WOB ▪ In some increased PEEP may decrease cycle of lung injury, but for others high PEEP w/ normal compliance can be detrimental on haemodynamics ○ If intubated → PEEP of 8-10 cmH2O - For Type H, treat as severe ARDS - Type L and Type H best distinguished by CT
13/04/20, Accepted article (US): ***Basing respiratory management of coronavirus on physiological principles[3]*** *https://www.atsjournals.org/doi/pdf/10.1164/rccm.202004-1076ED*	- "The dominant respiratory feature of severe COVID-19 is arterial hypoxaemia, greatly exceeding abnormalities in pulmonary mechanics (decreased compliance)" - Hypoxaemia in COVID-19 is usually accompanied by an increased alveolar-to-arterial oxygen gradient - Many patients with COVID-19 are intubated because of hypoxaemia with little dyspnoea or distress ○ When assessing for dyspnoea, assure open-ended questions are being used - Tachypnoea alone should rarely be the primary reason for intubation ○ Tachypnoea is an expected response to lung inflammation → palpation of the SCM is a better assessment of WOB - Infiltrates alone should not be the sole indication for intubation → accompanied by gas abnormalities or increased WOB - Weanability from mechanical ventilation should occur from 24hrs following intubation
16/03/20, Guideline: ***The ANZICS COVID-19 Guidelines (Version 1)*** *https://www.anzics.com.au/coronavirus-guidelines/*	- *Treatment guidelines now incorporated into Australian Living Guidelines (see below)*
23/03/20, Research article: ***Lung recruitability in SARS-CoV-2 associated acute respiratory distress syndrome: a single-center, observational study[4]*** *https://www.atsjournals.org/doi/abs/10.1164/rccm.202003-0527LE*	- *Study aimed to determine if lungs are recruitable with high PEEP in patients with ARDS due to COVID19* - Recently, group described an index to quantify patient potential for lunch recruitment (recruitment-to-inflation ratio, R:I) ○ Estimates how an increase in end-expiratory lung volume is distributed between newly recruited lung, and hyperinflation of already inflated lung ○ Ranges from 0 to 2.0 → higher value suggests higher likelihood of recruitment ▪ Ie. R:I of 1.0 suggests increased volume from increased PEEP to be distributed between already inflated lung, and newly recruited lung ○ R:I could be used to measure recruitment in patients with COVID19, and assess the effect of body positioning - Was a retrospective observational study of 12 patients with SARS-CoV-2 admitted to ICU, and receiving IMV - Seven patients received at least one session of prone positioning ○ Alternating between prone and supine positioning was associated with increased lung recruitability (stat. sig) ▪ Also had increased PaO2/FiO2 when prone, but not stat. sig (P=0.065) - Majority of patients had poorly recruitable lung with high PEEP, but recruitability changed with prone positioning

05/04/20, Personal communication: ***COVID19 Communication for the UK***[5]	- *Letter from a Professor of Anaesthesia, at the Royal Free Hospital, London* → The letter contained information regarding <u>ventilation, fluid balance, renal function, and workforce</u> planning → only information regarding <u>ventilation and fluid balance</u> is summarised here
	- Ventilation
	  o **"Early high PEEP is probably not the right strategy… this is not ARDS in the early phase of the illness."**
	  ▪ Less aggressive PEEP early in disease course → prone early
	  o Evidence of microemboli formation in pulmonary circulation + wedge infarcts (w/o evidence of DVT)
	  ▪ Prevalent → look for it
	  o Inhaled nitric oxide and prostacyclin appear to have good effect (tachyphylaxis w/ NO after 4-5/7)
	  o High reintubation rate
	- Fluids and renal
	  o High rates of AKI and CVVHF → many initially dehydrated + overzealous use of frusemide
	  o Avoid large positive fluid balance, but be careful of a strict zero balance, particularly in hyperpyrexia
	  o CVVHF requirements higher than predicted → hypovolaemia + microthrombi → AKI
	  o Having difficulty with CVVHF systems clotting frequently → some facilities now fully anticoagulating the patient

31/03/20, Blog post: ***COVID-19 Hypoxemia: A better and still safe way***[6]
 	
https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/
	- *Blog post discusses range of issues, including distance travelled of aerosolised particles using HFNC and NIV*
	- Reports that although disease process has been categorised like ARDS, it it not necessarily ARDS
	  o Often have normal lung compliance and often not in respiratory distress despite low SpO2
	  o SpO2 may not correlate with symptoms
	  o HOWEVER, there are patients presenting more traditionally with Sx matching SpO2
	- Target SpO2 88-92% with FiO2 ≤0.6
	  o If not, consider use of HFNC + PP, or then NIV + PP

10/04/20, Blog post: ***COVID-19 ICU: Treat individual pathophysiology not standard ARDS***[7]
 	
https://www.medscape.com/viewarticle/928507#vp_2
	- *Interview with Dr Nathalie Stevenson (ICU and anaesthetics consultant at the Royal Free London), and Prof Gary Mills (ICU and anaesthetic consultant at Sheffield Teaching Hospital)*
	- Infection control and prevention must be considered → avoiding use of HFNC → generates significant aerosols and uses up significant oxygen supplies
	  o Preferring CPAP
	- COVID-19 doesn't appear to behave exactly like ARDS, particularly in the early stages.
	  o In ARDS should normally aim for tidal volumes <6 mls/kg, however, many patients with COVID-19 initially have very compliant lungs and low tidal volumes lead to atelectasis and collapse
	  o High PEEP >15 cmH2O may not be required early on in COVID-19 → may cause further lung damage and haemodynamic instability
	  o In ARDS would normally fluid restrict, but are seeing a high incidence of AKI and fluid restriction may not be appropriate
	- CPAP use for longer?

	○ Limited by practicalities of supplying enough. oxygen for the hospital ○ However, are using CPAP in patients in negative pressure rooms. ○ Concern about over-inflation in very compliant lungs (but difficult to assess compliance when not intubated) - How do you determine which patient receives which therapeutic strategy? ○ Many patients present late and very ill → Type H (hyper-inflammatory) → treat as per ARDS ○ However, some are hypoxic but appear relatively well → give time limited trial of CPAP → if no improvement or deterioration, intubate - Proning ○ Type L → can self/auto/awake-prone → improves V/Q mismatch ○ Type H → prone → improves ventilation in normally dependent areas
07/04/20, Blog post: ***Coronavirus disease 2019. (COVID-19)***[8] *https://litfl.com/coronavirus-disease-2019-covid-19/*	- *This is a large but clear summary of lots of important information regarding COVID19 – updated weekly* *Only information regarding ventilation presented here* - Pneumonia phenotypes ○ L-phenotype → early viral pneumonitis ▪ Hypoxaemia w/ preserved CO2 clearance (T1 resp. failure) ▪ Low: elastance, V/Q matching (?abnormal hypoxic vasoconstriction), recruitability (poor response to PEEP) ▪ Implications • May be able to avoid mechanical ventilation w/ appropriate O2 therapy • May be responsive to pulmonary vasodilators ○ H-phenotype → later illness and more classic ARDS → prolonged NIV (P-SILI from volutrauma and barotrauma) ▪ Hypoxaemia +/- impaired CO2 clearance (T1 or T2 respiratory failure) ▪ High: elastance, V/Q matching (high shunting), recruitability (good response to PEEP and proning) ▪ Implications • May benefit from protective lung ventilation and usual ARDS therapy - Oxygenation → SpO2 92-96% for most patients (SpO2 of 88-92% for CO2 retainers) ○ Both HFNC and NIV can create dispersal jets of droplets and aerosols → Must be used with airbone precautions ○ HFNC → supported by ANZICS guidelines ○ NIV → NOT recommended by ANZICS guidelines, but recommended by WHO ▪ Should be used cautiously → time limited trial over 1-2hrs ▪ May be used for optimisation of oxygenation prior to planned intubation ▪ Use of either HFNC and NIV should not delay intubation - *Info regarding intubation protocols not included here* - Mechanical vent settings ○ Most information is based on ARDS management → protective lung vent stratergy is recommended ▪ Tidal columes 4-6 mL/kg PBW ▪ Plateau pressures <30cmH2O

	○ Role of PEEP is controversial ▪ ANZICS guidelines recommended high PEEP >15cm H2O and can use ARDSNet ventilation strategy ▪ However, lower PEEP may be appropriate for Type-L phenotypes → high compliance w/ low recruitability - Inhaled nitric oxide and pulmonary vasodilators (eg. Prostacyclin) not currently recommended for routine use
16/04/20, Clinical guideline: ***Australian guidelines for the clinical care of people with COVID-19***[9] *https://app.magicapp.org/app#/guideline/4169/section/48779*	- *Guideline updated 16/04/20 – only information on "Respiratory support" included here* - Use of respiratory support must consider risk of infection of HCWs - **HFNC:** should be considered to maintain SaO2 ≥92%. (use lowest flow possible to maintain ○ **Use in negative pressure room** → if unavailable use in single room or shared space with confirmed COVID19 only ▪ **Do NOT** use in shared wards with non-COVID19 or in ED cubicles ○ Ensure staff are using airborne precautions - **NIV:** do NOT routinely use NIV → consider early intubation in deteriorating patients ○ If NIV is appropriate for alternative clinical presentations (COPD w/ T2 resp failure or APO) and COVID19 positive, ensure airborne precautions - *No mention of inhaled pulmonary vasodilators*
11/03/20, Clinical update: ***Care for critically ill patients with COVID-19***[10] *https://jamanetwork.com/journals/jama/article-abstract/2762996*	- *Summary letter on critical care of COVID19 patients – I have briefly summarised here but it provides a good overview* - Patients requiring critical care tended to be: older, have comorbidities (commonly diabetes and cardiac disease) - Med duration between onset of symptoms and ICU admission has been 9 to 10 days - 2/3 patients meet criteria for ARDS - Evidence-based treatment for ARDS should be followed, including prone positioning - Septic shock and AKI are occurring in a significant proportion of patients and should be treated according to guidelines
02/04/20, Webinar: ***How to ventilate in COVID-19*** *https://www.esicm.org/blog/?p=2744*	- *See notes attached below* - *See figures below*

FIGURES

Fig 1. L and H Phenotypes in COVID-19

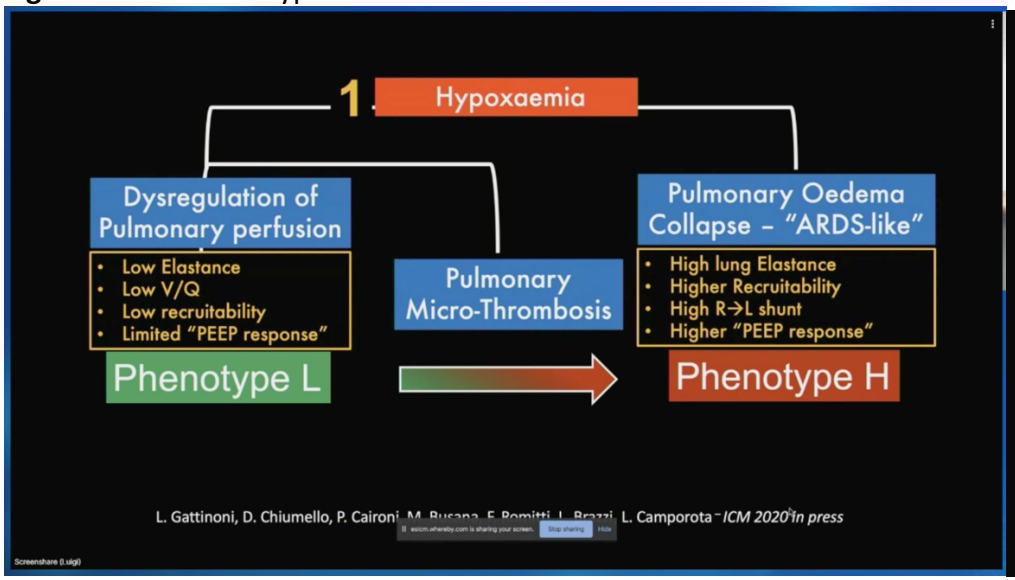


Fig 2. Consideration of respiratory drive and interventions

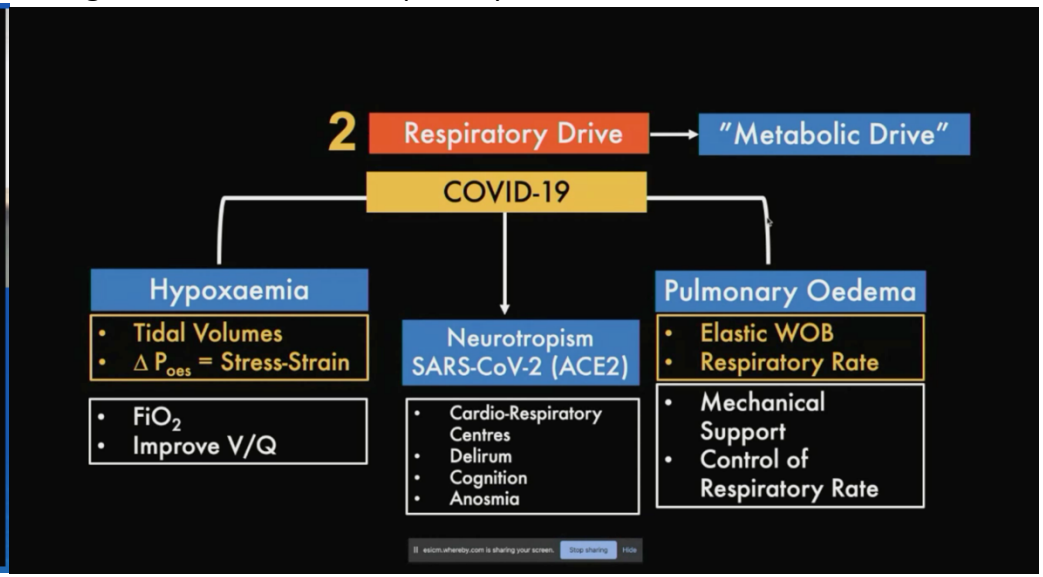


Fig 3. Transition from L to H phenotype

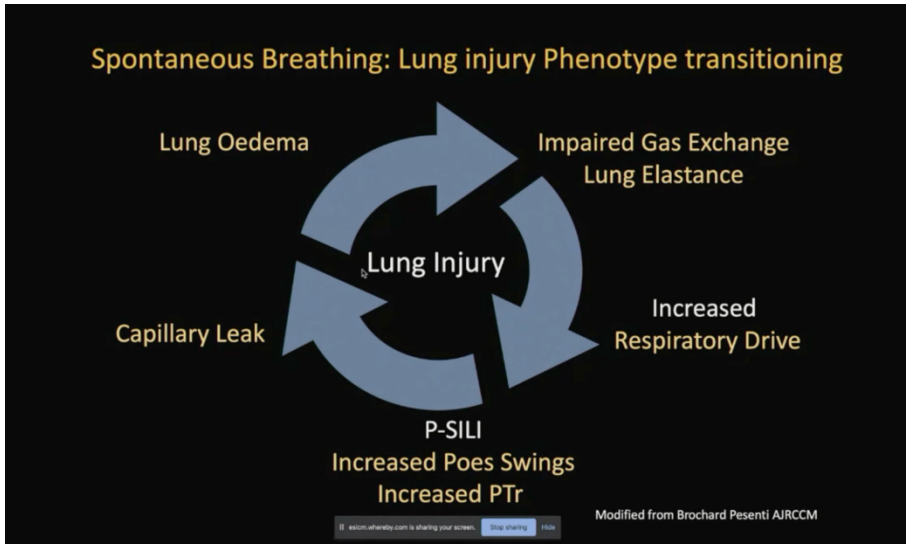
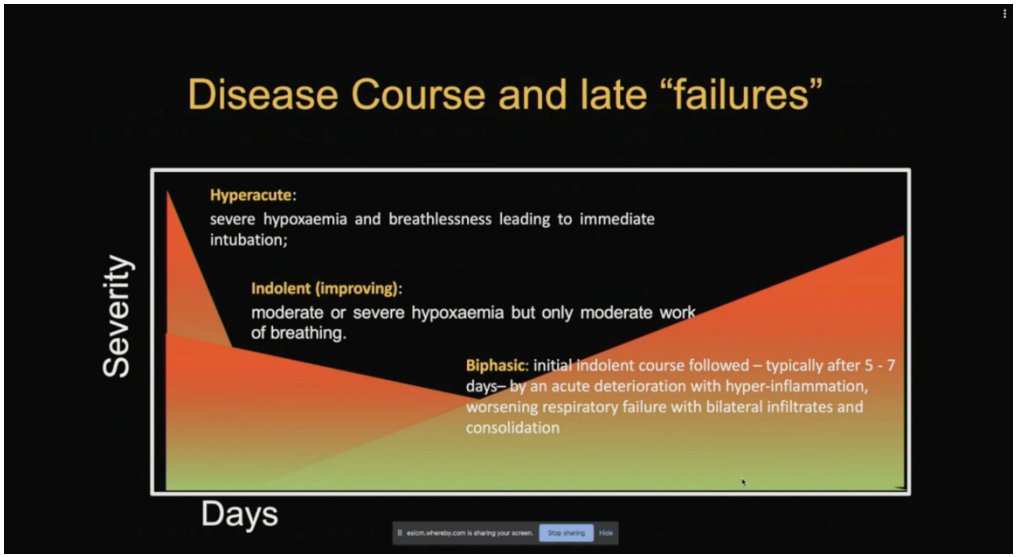


Fig 4. Disease course and progression



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European Society of Intensive Care Medicine
"How to ventilate in COVID-19" – Webinar 02/04/20

L. Camporata, C. Guerin

https://esicm-tv.org/webinar1_live_20-how-to-ventilate-in-covid-19.html

Pathophysiology of hypoxaemia in COVID-19 patients

- Pathophysiology of hypoxaemia in COVID-19 patients
    - **Phenotype L: Dysregulation of pulmonary perfusion → high compliance model**
        - Low elastance, low V/Q, low recruitability (therefore, low response to PEEP)
    - **Pulmonary micro-thrombosis**
        - Increasing dead space → Inc. CO2
    - **Phonotype H: Pulmonary oedema – "ARDS-like" → low compliance**
        - High elastance, high recruitability, increasing R→ L shunt → therefore, PEEP responsive
- **Having patients w/ similar PaO2/FiO2 ratio, but very different chest imaging**
    - Consider the phenotype
    - Spectrum and often progression from Type L to Type H
- Consider the effect of the SARS-CoV2 virus on ACE II- R → ATR I and AT R II
    - Initially profound vasodilatory effect → loss of hypoxic vasoconstriction → then progression to inflammation and vasoconstriction → fibrosis
- Compared to classical definition of ARDS, doesn't strictly fit definition
    - Timing
    - Imaging
- COVID-19 pneumonitis is not necessarily equal to ARDS
    - Treatment should vary dependent on the phenotype presentation

Management of hypoxaemia in COVID-19 patients (8:13)

- Treatment dependent on phenotype
- 1. Assess shunt fraction and severity of hypoxaemia → "Non-invasive assessment"
    - Assess WOB → if increased WOB, treat more aggressively
    - If WOB is low, consider a time limited NIV trial → with strict monitoring
    - Consider the cause of the respiratory drive
        - "Metabolic drive" – inflammatory state?
        - Neurotropism of SARS-CoV-2 → may have significant WOB but LOW subjective dyspnoea
        - Pulmonary oedema
            - Mechanical support
    - What to do next? Consider:
        - 1. Infection control – are you allowed to use NIV?
        - 2. Support required – WOB, failure rate, level of hypoxaemia, control of TPP
        - 3. Duration of disease – long duration, likely less responsive to short duration of high PEEP
        - 4. Resources – ICU beds, staff, ventilators, O2
    - Oxygenation:
        - Use of CPAP can be associated with a decrease in CO → apparent increase in PaO2/FiO2 ratio
        - Ensure use of NIV does not lead to a delay in intubation in patients who needed it
    - WOB:
        - CPAP and NIV may support WOB, but needs to be monitored
        - Excessive WOB should instigate intubation
- 2. Then considered risk of P-SILI → progression from Phenotype L to Phenotype H
    - Impaired gas exchange and low lung elastance → increased respiratory drive → increases transpulmonary pressure (P-SILI) → capillary leak → interstitial pulmonary oedema
    - Three main patterns:
        - **Hyperacute**: severe hypoxaemia + dyspnoea → early intubation
        - **Indolent**: moderate or severe hypoxaemia but only moderate WOB

        - **Biphasic**: initially indolent → followed by acute deterioration and worsening respiratory failure after 5-7 days → hyper-inflammation and bilateraly infiltrates
- 3. Then consider the phenotype screening of strain (end tidal volumes)
    - Do not want to underventilate if normal compliance → consider driving pressure
        - Match tidal volume to driving pressure
- 4. Then differentiate the phenotype and treat accordingly (PEEP and prone)
    - Titrate PEEP → then measure compliance
    - If compliance is near normal → Phenotype L
        - Trial PRONE POSITION → optimise V/Q
        - Trial pulmonary vascular reactivity test +/- vasodilators
    - If decreased compliance → Phenotype H w/ decreased FRC
        - PEEP responsive
        - Prone positioning
- 5. Failure and escalation (24min)
    - Some patients have a rapid, fulminant progression
    - Consider – particularly if resource limited:
        - 1. Is the pathology reversible? PATIENT SELECTION
        - 2. Is the patient able to recover? PATIENT SELECTION
            - Frailty and comorbidities → can they sustain a prolonged course of ECMO and rehabilitation
        - 3. Is gas exchange severe and life threatening? TIMING AND INDICATION
            - Do we need to do something now?
        - 4. Is mechanical ventilation injurious? TIMING AND INDICATION
- SUMMARY – things we've learnt
    - 1. **Early recognition of hyper-acute disease is important**
        - Immediate intubation
        - High risk of cardiovascular events → may be centrally mediated (viral midbrain effect), or cardiomyopic process
    - 2. **Short and judicious use of CPAP/NIV for haemodynamically stable patients w/ moderate hypoxaemia**
        - They may have a low respiratory drive and a low inflammatory phenotype (L type)
        - <u>Beware of biphasic course → may fail quite late</u>
    - 3. **Early differentiation of L phenotype** (preserved compliance and dysregulated pulmonary perfusion)
        - Balance use of PEEP and perfusion
            - Do not use high PEEP or PEEP/FiO2 scales → This is NOT AREDS