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Editorial

A challenging global pandemic of magnitude not seen in the recent past has mankind in an acutely critical health crisis. The COVID-19 is a novel disease with a fairly significant mortality rate of about 3-5% defying the very best of our current scientific knowledge, practice and supportive capacity of critical care facilities. It is caused by the SAR-COV2 virus and shows a predilection for mucosal colonization with the respiratory system being the main site of infection and entry with deleterious pulmonary effects leading to hypoxemia and eventual multi-organ dysfunction in a percentage of some patients.

In line with this, our first article makes a summary of the known pathophysiology of this novel virus collated from various articles and the pharmacological basis of varied interventions available that have been studied so far. The subsequent two articles are broad reviews of the physiology behind three systems that are involved in disease progression in the critically ill and the impact of the physiological data obtained from measurement and the interventions with their clinical effects.

The COVID-19 pandemic has made a hugely negative impact and strain on healthcare systems globally with a high toll on frontline healthcare workers exposed to infection often succumbing to illness. However, there have also been a number of positive outcomes in terms of lessons learned and a global focus on a need to evaluate and strengthen public health systems in addressing diseases (communicable or otherwise) and medical interventions including in anaesthesiology and critical care. Some of the lessons learned locally include the need to make efforts to upscale critical care capacity in terms of infrastructure and human resource of various cadres but especially having programs modified for medical officers capable of intensivist supervised medical officers working in these units.

Infrastructure expansion of these critical care units must be in a structured manner in terms of multi-organ support equipment and the requisite consumables as well as the necessary laboratory testing, imaging services and leveraging on the use of tele-ICU to enable real time consultation. Further, COVID crisis has brought to the fore the mental strain that anaesthesiolgists, intensivists and other frontline healthcare workers often go through in the high pressure resource limited working environment which also poses a danger to their own very wellbeing.

This necessitates active support for various programs aimed at their mental health in both short and occasionally long-term. The mantra of the 3Cs of the philosophy of stoicism does help in enhancing mental strength in these high pressure resource limited environments on a daily basis especially when tinged with empathy for both the patient and their family and a strong understanding of the whole healthcare team dynamics at play: these Cs are

- Control what you can manage.
- Cope with what you can't control.
- Concentrate on what you need to manage and control.

Due to limitation of resources coupled with the human tendency to often reduce the decision making to a binary approach, focus on other health matters maybe temporarily lost as we tackle the COVID pandemic. In a bid to obviate this, this edition has an article reviewing practitioners' experiences in the use of dexmedetomidine in paediatric sedation, an area that still remains a challenge for many in clinical practice.

Clinical Presentation, Pathophysiology and Therapeutic Options in COVID-19 Infection for the Intensivist

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Abstract

There is an ongoing pandemic caused by the SARS CoV-2, which mainly affects the respiratory system. The serious consequence is refractory hypoxemia associated with both ARDS and non-ARDS pictures; often with thick mucus. The pathology is not clearly understood and shares common features with ARDS and cystic fibrobrosis. There is compelling evidence that neutrophils through formation of Neutrophil extracellular Traps (NET) could be part of the mechanism of this disease. Therapies based on targeting NETS seem rational.

Introduction

In November 2019, an outbreak of a new viral strain was reported in Wuhan province of China, the infection of which has evolved to the current pandemic status. This highly contagious disease is transmitted through the respiratory route mainly by droplets. The virion thrives best at low temperatures and easily killed by heat such that 4 ^{o}C confers higher survival than 22 ^{o}C. Viability on various surfaces has been demonstrated to increase in the following order: aerosols < copper < cardboard < stainless steel < plastics.[1]

The symptoms and signs are dry cough, fever, dyspnea and radiological findings of bilateral glassy opacities which may rapidly progresses to respiratory failure requiring ventilatory support. Sneezing, running nose and phlegm are not typical presentations. The presence of pyrexia, cough and fatigue differentiates COVID-19 disease from common cold.[1]

The pre-intubation dry cough evolves into a very thick viscid mucous that may lead to airway obstruction unless relieved by airway suctioning. There is severe hypoxemia in the setting of relatively maintained lung mechanics, lung volumes and respiratory drive. The clinical picture is sometimes akin to Acute Respiratory Distress Syndrome (ARDS) which can progress to septic shock, necessitating critical care therapy. In some phenotypes of this disease, hypoxemia is not correctable with high oxygen concentrations indicating pulmonary shunt like states.[2] Age above 60 years, smoking and comorbidities such as hypertension and diabetes are independent predictors of mortality. The elderly and smokers have a higher ACE receptor expression than the general population. This partly explains the aggressive clinical course of diseases in these groups.[1]

Pathology

COVID-19 disease is caused by RNA virus of the family SARS-CoV-2 genetically similar to SARS Corona Virus 1 (SARS-CoV-1). It has a glycoprotein that binds onto Angiotensin Converting Enzyme 2 (ACE 2) receptors on pulmonary pneumocyte type II.[3] It has a high protein manufacturing stress that eventually leads to host cell apoptosis. The viral RNA acts as a pathogen molecular pattern (PAMP) that induces alveolar macrophages to release chemokines that lead to neutrophil migration and activation.[1]

Blood count in COVID-19 patients shows normal or low leukocytes together with lymphocytopenia. Their plasma contains high levels of pyrogenic cytokines such as IL-6, IL-10, as well as IL-2, IL-7, and TNF-alpha. Other findings include neutrophilia, D-Dimers, macrophage inflammatory protein, monocyte chemoattractant protein-1 and monocyte CSF. The disease is marked by what is called cytokine storm.[4]

Anecdotal clinical observations report findings of pulmonary microthrombi in association with severely hypoxemic shunt like conditions, Neutrophil Extracellular Traps (NETs) in plasma, lungs and phlegm. The presence of NETs shares similarities with severe sepsis, collagen connective diseases such as SLE, and cystic fibrosis. This evidence has formed the basis of clinical trials for therapeutics used in SLE and possibly cystic fibrosis as potential rational management of COVID-19 disease.

Role of Neutrophil Extracellular Traps (NETs)

During infections, neutrophils respond by releasing soluble chemicals such as myeloperoxidase (MPO) and neutrophil elastase (NE) that destroy invading pathogens. In addition, nuclear material commonly referred to as Neutrophil Extracellular Traps (NETs) consisting of DNA and histones are released extracellularly. NETs formation involves autophagy and membrane recycling.[3] The beneficial effect of NETs are entrapment and killing of invading pathogens (bacteria, fungi and viruses) thus preventing their spread.[5] Conversely, they could go overboard and indiscriminately lead to tissue damage as evidenced by epithelial denudation, chronic inflammation, microbial film formation, and pleural fluid exudation.[6]

NETs have been implicated in a number of pulmonary diseases such as COPD, ARDS and cystic fibrosis.[7] Similar to the condition in COVID-19, the common presentation is hypoxemia and thick viscous mucous. Several studies have demonstrated presence of NETs in respiratory airway and bronchoalveolar lavage of cystic fibrosis leading to the conviction that they contribute not only to lung damage but also bronchiolar blockage.[7,8,9,10,11,12] The amount of NETs in mucus correlates to extent of airway obstruction.[13] NETs is now recognized as an integral component of pathophysiology of cystic fibrosis.[10]

NETs has extensively been implicated in thrombosis via platelet activation.[14] There is extensive literature linking cross talk between NETS, sepsis and thrombosis leading to the concept of immunothrombosis.[15, 16] NETosis is involved in sepsis induced coagulopathy and DIC.[17] However, the pathophysiology is wider and goes beyond the traditional cascade or waterfall concept of coagulation in that the NETs not only induces tissue factor expression from monocytes, but also elaboration of ultra large von Willebrand Factors (ULvWF) from damaged endothelium.[18] Thus there is activation of extrinsic pathway of coagulation as well as procoagulant ULvWF that contribute to thrombus formation in the microvasculature. Indeed, recognition of interplay between ULvWF-ADAMTS 13-platelets in endotheliopathy contributes to microthrombi observed at autopsies in over 85% specimens examined from patients who die from ARDS.[19]

Therapeutics options in COVID-19 Disease

1. Chloroquin and hydroxychloroquin

Chloroquine and hydroxychloroquine are established antimalarials that are also used as disease modifiers in connective tissue disorders. The virucidal activity of chloroquine has been demonstrated in in vitro studies. Chloroquine raises the pH of lysosomal vesicles enhancing its killing power. It also interferes with autophagic vesicles thus preventing membrane recycling needed during replication. Its immunomodulating property may be useful in suppressing the cytokine storm in COVID-19 disease. Chloroquine also interferes with virion receptor glycosylation and may impair cellular entry mechanisms.

2. Anti virals

Antiviral agents such as remdesivir, lopinavir & ritonavir, umifenovir were developed against Ebola, HIV and influenza viruses respectively. They are currently undergoing clinical trials for effectiveness and safety in COVID-19.

3. Vitamins C & D

Vitamin C (ascorbic acid), when given intravenously has pleotropic effects of reinforcing epithelial barrier as well as upregulating protein channels (CFTR, aquaporins, ENaC and Na+/K+) which regulates epithelial fluid clearance. It also reduces plasma cell free DNA component of NETs that facilitate inflammatory response and membrane barrier destruction. The efficacy and safety of high dose intravenous vitamin c (12 g) in viral illnesses as including COVID-19 disease is being evaluated.

Vitamin D is known to have permissive role in maintaining integrity of epithelial barriers and immunomodulation. Studies have shown its protective role in viral diseases, an effect enhanced if given in deficiency states such as in the Northern hemisphere. Clinical trials are ongoing of its role in COVID-19 disease.

4. Angiotensisn Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor-1 Blocker

The rationale is to decrease the virion binding onto their pulmonary receptors thus decrease viral shedding. Concurrently, there is general agreement to continue ACE-I and ARBs as hypertension is a comorbidity that increases mortality. Whereas they appear protective to the lungs, there are concerns of increasing SARS-CoV 2 infectivity.[20]

5. Antipyretics

Since fever is a cardinal feature, antipyretics are rational. WHO approved paracetamol as the first line for treating COVID-19 related fever. Ibuprofen has been associated with increased ACE2 receptor expression in the respiratory system. Its use remains controversial, given the risk of acute kidney injury in the setting of absolute or relative hypovolemia.

6. Steroids

There are clinical trials of steroids (methylprednisolone) to ameliorate the inflammatory response. Their unrestricted use could lead to flaring up of viral infections. They may increase the risk of co-infection with bacteria and other viruses, prolonging viral shedding and precipitation of ARDS. Low dose steroids may be used in fluid and catecholamine refractory septic shock.

7. Potential novel therapeutics targeting NETs to consider

a. DNAse: rhDNAse aims at degrading NETs thus liquefaction of thick viscid mucus opening the respiratory airways. It also has additional thrombolytic effects.[7] Clearance of mucus is key to effective ventilation. It has been approved for use in cystic fibrosis. A recent Cochrane review report beneficial effects in cystic fibrosis in clinical trials.[21]

b. N-Acetylcysteine: It has effect against reactive oxygen species (ROS) that are released from inflammatory cells that contributes to membrane peroxidation and damage. Therapeutic applications are in SLE, owing to beneficial effects observed in laboratory animals.[7]

c. Hypertonic saline: Nebulized hypertonic (3 or 4%) saline has an established role in liquefying thick mucus in cystic fibrosis. A Cochrane review reaffirmed the benefit of hypertonic saline in cystic fibrosis.[22] It is worth considering in COVID-19 since there similarities in mucous characteristics.

Conclusion

Knowledge about pathology of COVID-19 disease is still evolving. There are similarities and variances in pulmonary presentation with ARDS which remains largely un-investigated. There is compelling body of evidence linking COVID-19 disease with NETs. With the limited information available about treatment of COVID-19 disease, therapies based on targeting NETs that have been found useful in other clinical conditions such as ARDS and cystic fibrosis warrant clinical trials.

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Understanding Respiratory Mechanics in Mechanically Ventilated Patients

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Abstract

Respiratory Mechanics involve the expression of lung function through the measures of pressure, volume or flow; and time. From these primary parameters, derived indices may be obtained e.g. compliance, resistance, time constant, and work of breathing. Modern day ventilators are capable of measuring and displaying respiratory mechanical indices in real time to assist the bedside clinician in decision making regarding the care of mechanically ventilated patients. Such information is useful in making diagnosis, assessing disease evolution and response to therapy; as well as optimizing ventilator settings.

Introduction

Pressure, volume and flow are primary indices of lung mechanics. (1) They are usually displayed as scalars and loops for analysis during mechanical ventilation.(2) Pressure is defined as force per unit area. During mechanical ventilation, pressure gradients influence the flow of gases into the lungs (inhalation) and out of the lungs (exhalation). Volume is a measure of the space occupied by a given amount of fluid (liquids and gases). Flow on the other hand is the rate of change of volume per unit time. Relationships between pressure and volume, and pressure and flow have been described as derived indices. The goal of measuring primary and derived lung indices is to evaluate lung function and disease evolution. This would help bedside clinicians to personalize and optimize mechanical ventilation and monitor response to therapy.(3)

The lung is not a perfectly elastic organ (lacks homogeneity). (4) This lack of homogeneity tends to be exaggerated during lung disease e.g. Acute Respiratory Distress Syndrome.(5)(6) It therefore means that the relationships that exist among the aforementioned variables may be true only to a certain extent. During their measurements, two major assumptions are made. One is that the lung is a homogenous single compartment and their values reflect global rather than regional lung function. The other is that a linear relationship exists between volume and pressure over certain ranges of volume and pressure; above and below which it becomes non-linear. (1) The true behavior of the lung is that of a multi-compartment model exhibiting nonlinear compliance, resistance and time-constant patterns.(7)

Objectives

1. To review the Pressure-Volume (Compliance) relationship in critically ill mechanically ventilated patients.
2. To review the Pressure-Flow (Resistance) relationship in critically ill mechanically ventilated patients.
3. To review the Compliance-Resistance (Time Constant) relationship in critically ill mechanically ventilated patients.

Compliance

Respiratory Compliance (Crs) is defined as change in lung volume (V) per unit change in pressure (P).(8)

$$Crs=\Delta V/\Delta P$$

Where volume is in cubic centimeters(cc) and pressure is in cmH2O, giving cc/ cmH2O as the unit of compliance. Normal compliance is estimated to be equal to 1 cc/ cmH2O / kilogram predicted body weight. Predicted body weight is influenced by weight and biologic gender.

Predicted Body Weight (Males)=Height(cm)-100

Predicted Body Weight (Females)=Height(cm)-105

In the pediatric population, compliance varies with age. In pre-term newborns, compliance may be as low as 1.5 cc/cmH2O. It increases to 5 cc/cmH2O in a term baby, and 15 cc/cmH2O by the age of one year.(9)

During mechanical ventilation, compliance is measured by using the inspiratory pause maneuver whereby the lung is held in inspiration by closing both inspiratory and expiratory valve. This reduces the inspiratory flow to zero and the measurement obtained is referred to as static compliance.(10)

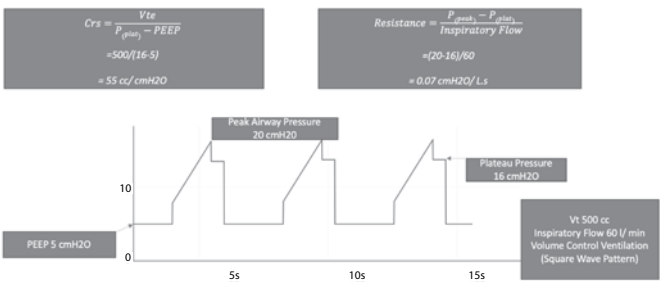

Figure 1: The Inspiratory Pause

Different factors may influence respiratory system compliance. It tends to be low at low lung volumes (below Functional Residual Capacity) and at high lung volumes (distension). At these two extremes, the pressure volume relationship may not be linear. It is also lower during inspiration than expiration (the hysteresis loop).

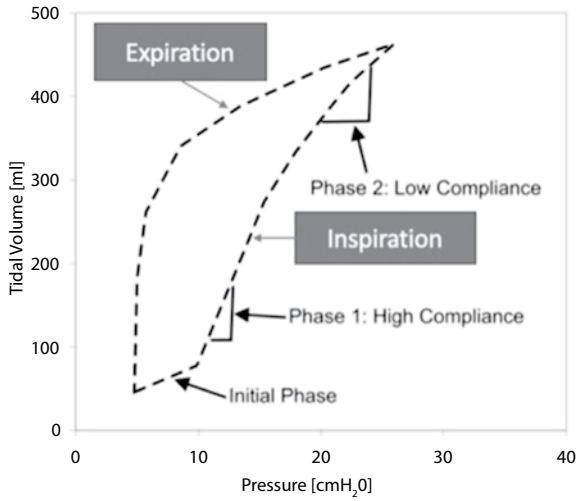

Figure 2: The Hysteresis Loop (Pressure Volume Loop)

Atelectasis is one of the commonest causes of reduced pulmonary system compliance. Various mechanisms, for example loss of surfactant leads to generalized atelectasis that is characteristic of ARDS, Respiratory Distress of the Newborn and chemical pneumonitis (paraffin aspiration).(11) In this groups of patients, atelectasis is amplified by loss of muscle tone from neuromuscular blockade during anesthesia. Adsorption atelectasis happens with exposure to high flow, high concentration oxygen. Oxygen tends to displace nitrogen from the alveolar sacs. Two molecules of oxygen replace three molecules of nitrogen displaced, with a resultant reduction alveolar volume and eventual atelectasis.(12)

Compression atelectasis results when pressure in the adjacent compartments increase above the alveolar pressure e.g. tension pneumothorax, and abdominal compartment syndrome. Restrictive lung syndromes e.g. one lung ventilation, fibrotic lung disease, morbid obesity, and chest wall eschars also reduce compliance. Emphysema on the other hand, increases lung compliance.

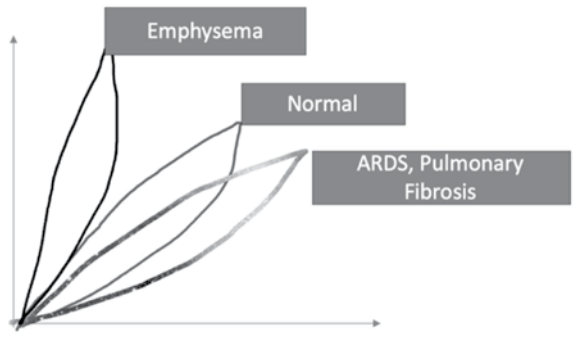

Figure 3: Diseases Specific P-V Loops

ARDS is a heterogenous lung syndrome comprised of many phenotypes.(13) One of the phenotypes is characterized by stiff lungs, whereby the measured compliance is almost 1/3 of the predicted compliance. Part of the management protocol involves lung recruitment maneuvers which aim at improving lung compliance early in the disease (before formation of hyaline membrane).(14) Compliance is also useful in titration of end expiratory pressure (PEEP).

In as much as monitoring of respiratory system compliance is a bedside tool of great utility, it is not without limitations. Given its non-linear behavior at extremes of volume and pressure, and lack of homogeneity in lung disease; optimum compliance may mean a balance between areas of atelectasis and overdistension. Compliance thus therefore may not be useful in assessing regional aeration.(1)

Computer tomogram (CT) of the chest may be better in evaluating regional aeration. CT chest of ARDS patients in the supine position always reveal atelectasis in the dorsal region and aeration in the ventral region and may help in visualizing the amount of functional lung.(15) The only setback with CT scan is that it is not a bedside tool and would therefore need transport which may be associated with PEEP breakage and potential lung de-recruitment.

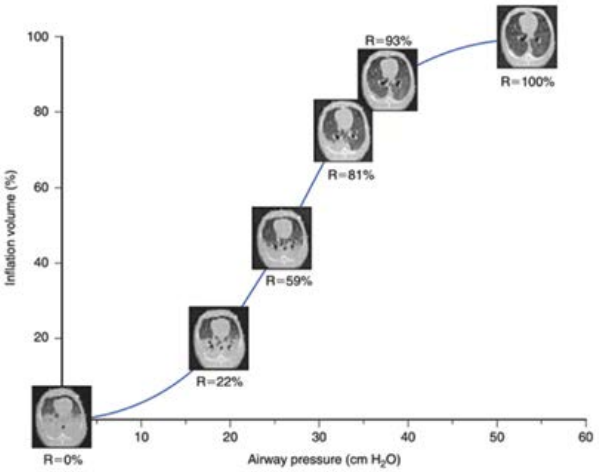

Figure 4: Aeration of the Lungs occurs along the P-V Loop (From Gattinoni L, Pietro C, Pelosi P, et al: Am J Respir Crit Care Med 164:1701, 2001.)

Electrical Impedance Tomography (EIT) is a relatively new technology that combines the convenience of being a bedside tool and the ability to show regional lung aeration. It is a non-invasive form of imaging in which electrical conductivity, permittivity and impedance of the chest is inferred from surface electrodes. High resolution and dynamic images of the lung are generated, which provide great utility in bedside clinical decision making.(16)

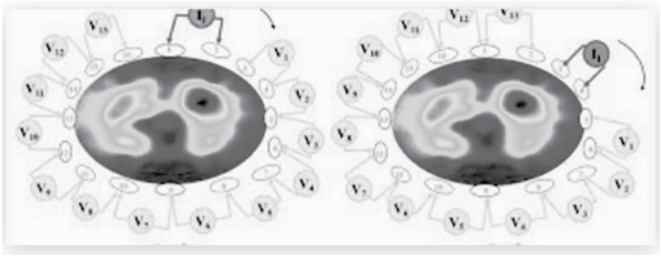

Figure 5: Electrical Impedance Tomography: Electrode Placement and Image Generation

Airway Resistance

This describes the resistance to flow of air through the respiratory tract during inspiration and expiration. It is the ratio of driving pressure to the rate of airflow in the airways. (17) Airway resistance is determined by the radius of the of the bronchial tree, and type of flow (laminar versus turbulent). Certain equations have been used to elucidate airway resistance.

Ohm's Law

This law has been used to describe the relationship between flow, pressure and resistance.

$$Pressure = Flow * Resistance$$

$$Resistance = \frac{Pressure}{Flow} = \frac{cmH20}{L/s} = cmH2O/\ L.s$$

This demonstrates that as airway resistance increases, airway pressure gradient must increase to maintain the same inspiratory flow to the alveoli.(18)

Hagen-Poiseuille Equation

This equation relates resistance to diameter of the airway.

$$Resistance = \frac{8nl}{Pi * r^4}$$

Where n is viscosity of inspiratory and expiratory gases, l is the length of the airway; and r is the radius of the airway.

This shows that resistance is inversely related to the radius. (19) Using computational modelling, based on cross-sectional areas at each airway generation, resistance initially falls from the trachea to generation 4. It the rises from generation 5-8 (mid-sized bronchi) before dramatically reducing in the subsequent generations.(20)

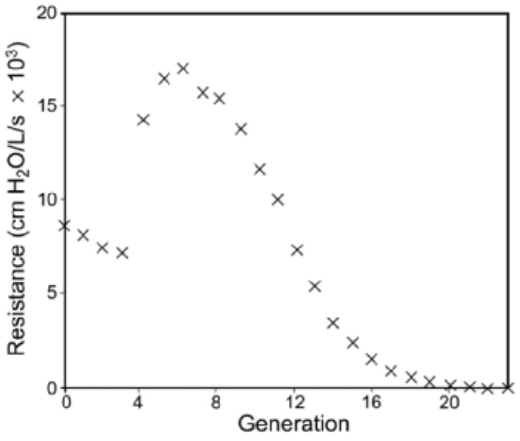

Figure 6: Airway Generations and their Relative Contributions to Total Airway Resistance in Normal Physiology

During disease states, asthma for example the smaller airways (bronchioles) become important in contributing to airway resistance.(21)

Resistance also is inversely related to age. It is highest in premature newborns (80 cmH2O/ L.s) and may increase to > 150 cmH2O/ L.s after endotracheal intubation. It reduces to 40 cmH2O/ L.s in term newborns, and 15 cmH2O/ L.s in infants. In older children and adults resistance is expected to be less than < 15 cmH2O/ L.s.(9)

Respiratory Time Constant

The change in lung volume (V) is dependent on the respiratory system compliance (C) and the change in pressure (P) that the lung is subjected to. Since the lungs are not perfectly elastic, the change in volume with time is not linear during both inspiratory and expiratory phases of the ventilatory cycle. When pressure is applied on the respiratory system, the time needed to achieve 63% of volume change is the time constant (t).(1) Thus, both inspiratory and expiratory time constants can be estimated on modern day ventilators as dynamic indices of lung function.

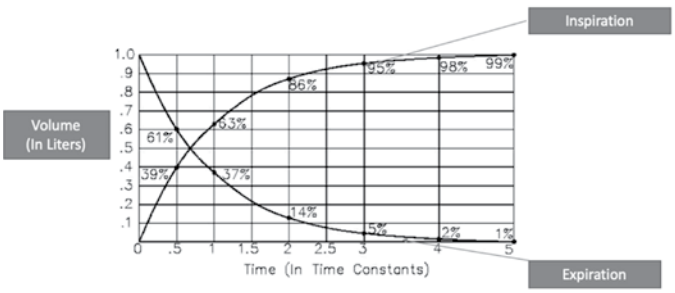

Figure 7: Respiratory Time Constant

Mathematically, the respiratory time constant is a product of compliance (C) and resistance (R).(1)(22)

$$TC = R * C$$

Given that inspiratory and expiratory compliance and resistance can be measured, it is possible to establish both inspiratory and expiratory time constants. Thus:

$$TC_{insp} = R_{ins} * C_{insp}$$

$$TC_{exp} = R_{exp} * C_{exp}$$

For adequate inflation of the lung (>95% of expected tidal volume), 3 to 5-time constants must elapse.

$$T_{insp} = 3 \text{ to } 5 * TC_{insp}$$

However, it is worth knowing that inspiratory time can be manipulated. During inverse ratio ventilation for poorly compliant lungs, inspiratory time may be deliberately prolonged beyond 5-time constants e.g. in Airway Pressure Release Ventilation (APRV). (23)

$$T_{insp} > 5\ TC_{insp}$$

Figure 8: Airway Pressure Release Ventilation

For adequate exhalation to happen (deflation of the lung by >95% or end expiratory flow close to zero), 3 to 5-time constants must similarly elapse. (24)

$$T_{exp} = 3 \text{ to } 5 * TC_{exp}$$

Shortening the expiratory time to less than 3-time constants will lead to gas trapping which may lead to volutrauma and reduced venous return.(25) Increasing the expiratory time to more than 5-time constants confers no added benefits. In fact, it gives an expiratory pause which may actually contribute to atelectasis. Therefore, the expiratory time constant may be the only true pulmonary mechanical index and changes in real time with different pulmonary syndromes.

For the purpose of illustration, an asthmatic is on volume controlled mechanical ventilation at a rate of 30 breaths per minute with an inspiratory time of 0.5 seconds and an expiratory time of 1.5 seconds. The estimated compliance is 30 cc / cmH20, with a resistance of 40 cmH20/ L.s.

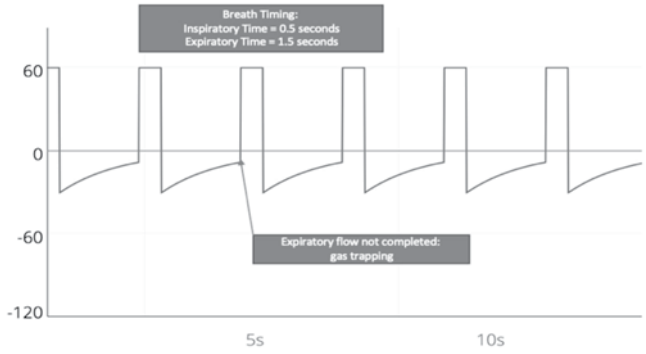

Figure 9: Inadequate Expiratory Time

The above flow-time scalar shows that his expiratory flow is incomplete (end expiratory flow is greater than zero) after 1.5 seconds. The appropriate expiratory time would be > 3-time constants.

$$T_{exp} = 3(40*30) = 3600 \text{ milliseconds}$$

Reducing the respiratory rate from 30 to 14 per minute while maintaining the inspiratory time at 0.5 seconds would increase the expiratory time to 3.7 seconds (3700 milliseconds) which would allow for adequate expiration (End Expiratory Flow of Zero).

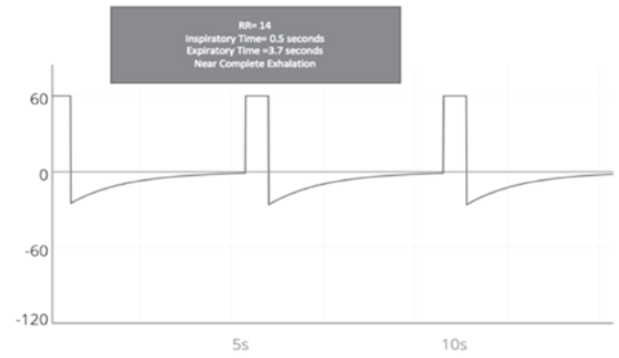

Figure 10: Adequate Expiratory Time

Reducing the rate to 8 breaths per minute while maintaining the inspiratory time at 0.5 seconds would give 7.0 seconds for expiration which exceeds 5 expiratory time constants. The extra 1 second at the expiration is period of no flow (expiratory pause).

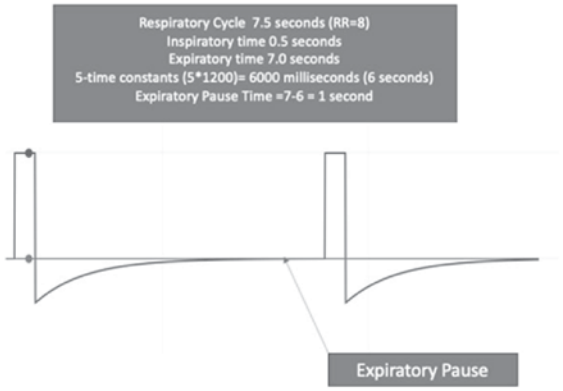

Figure 11: Prolonged Expiratory Time

Respiratory time constant is crucial for understanding the mechanical consequences of respiratory system illnesses. Breath-timing, respiratory rate, auto-PEEP and dynamic hyperinflation are important aspects of managing various chest syndromes e.g. asthma, acute respiratory distress syndrome and chronic obstructive airway disease.

A short expiratory time constant (<0.5 seconds) means there is reduced lung or chest wall compliance resulting ARDS, lung fibrosis, atelectasis, kyphoscoliosis and abdominal compartment syndrome. A long expiratory time constant (> 0.7 seconds) suggests increased resistance due to the patient or endotracheal tube factors e.g. COPD, asthma, bronchospasm or endotracheal tube blockade. A normal time constant (0.5-0.7 seconds) on the other hand may mean either normal lung or mixed disease e.g. COPD and ARDS.(26)

Conclusion

A lot of data is emerging regarding the care of critically ill patients on mechanical ventilation. It may be difficult to come up with guidelines that suit every patient. Real-time analysis of lung mechanics should be utilized at the bedside. This would go a long way in personalizing and optimising mechanical ventilation. Every patient should be treated as their own phenotype. It may be time to practice precision medicine.

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Haemodynamic Monitoring In The Intensive Care Unit

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Abstract

Haemodynamic monitoring is a core duty of the Intensive Care Unit (ICU) clinical practitioner, and involves measuring and recording key indicators of how the cardiovascular system is functioning. The parameters measured include arterial blood pressure, central venous pressure as well as blood flow through different sections of the cardiovascular system. This monitoring is important in the critically ill patient because it informs the clinician about the adequacy of tissue perfusion.

Traditionally, haemodynamic monitoring is done using static markers of the macrocirculation. This include the measurement of blood pressure, heart rate, central venous pressure, pulmonary artery wedge pressure, and to some extent oxygen saturation in arterial blood. As much as these measurements are important, they are not always a true reflection of the actual state of perfusion at the tissue level. Multiple studies have demonstrated that normalizing macrocirculation parameters does not always translate to better outcomes in critically ill patients, and sometimes even leads to patient harm.

As much as macrocirculation parameters are important, recent evidence points to microcirculation a key area that needs to be monitored in critically ill patients. This is the location where actual exchange of substrates between the tissues and the circulatory system occurs. The ultimate goal of haemodynamic monitoring in the critically ill patients should therefore be the ability to monitor the microcirculation. This will enable the clinician to tailor their intervention to individual patients regardless of what the macrocirculation parameter readings are.

Objectives

After reading this article, you should be able to:

- Understand the common methods used for haemodynamic monitoring in ICU
- Explain the rationale behind use of various haemodynamic monitoring systems
- Explain the limitations of traditional haemodynamic monitors in critically ill patients
- Understand the importance of assessing the adequacy of the microcirculation in critically ill patients.
- Static Haemodynamic Parameters

One of the commonest indication for admitting patients to critical care units is to facilitate haemodynamic monitoring and support.(1) The core function of the cardiovascular system is to facilitate adequate blood flow to and from the tissues in various organ systems; this is maintained by a complex system regulated largely by the brain through the autonomic nervous system.(2) Monitoring and support of the cardiovascular system is one of the core duties of a critical care practitioner, and it involves measuring and recording key indicators of how this system is functioning. It is these measured parameters that are then interpreted by the clinician and a decision made on whether the cardiovascular system is meeting the metabolic needs of different organ systems and if not, how to artificially support it in achieving this goal.

This article reviews the traditional parameters for monitoring the cardiovascular system in critically ill patients, highlights the limitations of these parameters and discusses some of the novel methods being applied currently in view of our improved understanding of organ dysfunction in these patients.

Static Haemodynamic Parameters

Arterial Blood Pressure

Arterial Blood Pressure (ABP) is one of the most commonly measured vital sign in the hospital set up. For critically ill patients, the blood pressure (invasive or non-invasive) is used to make critical decisions regarding fluid resuscitation as well as use of vasoactive drugs. As illustrated in fig 1, the mean arterial blood pressure (MAP) is determined by several factors, each being amenable to therapeutic manipulation. The ABP is important because it is used to indirectly assess perfusion, and this is one of its inherent weakness.(3) Blood flow in the cardiovascular system is predominantly laminar, as opposed to turbulent.(4) Based on the Hagen-poiseuille's equation, despite pressure gradient (difference between mean arterial pressure and mean central venous pressure) being one of the determinants of laminar flow; the greatest contributor to laminar flow is the vessel caliber (radius).

$$Q = \frac{\Delta P \pi R4}{8\mu L}$$

Q – Blood flow

ΔP – Pressure difference between MAP and CVP

R – Radius of the blood vessel

L – Length of blood vessels (normally constant)

μ – Viscosity of the fluid (blood)

Several studies in critically ill patients may have indirectly demonstrated this phenomenon, with some "normotensive" patients having signs of poor organ perfusion (reduced blood flow) while "hypotensive" patients have relatively good organ perfusion.(5)(6)(7)(8)(9) In addition, studies have demonstrated benefit from using vasodilators in septic shock patients to improve the microcirculation, a concept that sounds counterintuitive.(10)(11)(12)

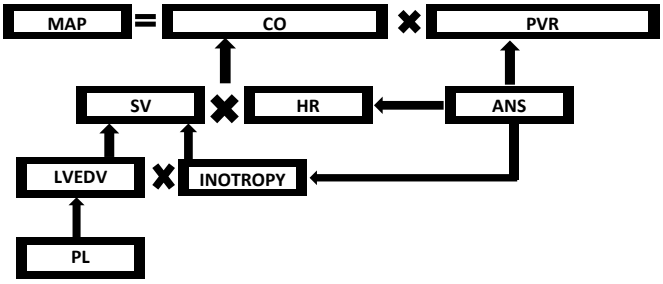

Fig 1. The various physiological parameters determining the blood pressure. MAP – Mean Arterial Pressure, CO – Cardiac Output, PVR – Peripheral Vascular Resistance, SV – Stroke Volume, HR – Heart Rate, ANS – Autonomic Nervous System, LVEDV – Left Ventricular End Diastolic Volume, PL – Preload, INOTROPY – Contractility of the Left Ventricular Myocardial cells.

Central Venous Pressure

This parameter was once synonymous with haemodynamic monitoring in the Intensive Care Unit (ICU).(13)(14) Over time, it was realized that the accuracy of the Central Venous Pressure (CVP) is to a large extent dependent on patients having normal cardiopulmonary anatomy, a fact that may not be applicable to a significant number of critically ill patients.(15) There are still some instances when measurement of the central venous pressure (CVP) is useful for patient management, but these are largely limited to recording of extreme values (high/low) or monitoring the trend over time during therapeutic interventions such as fluid therapy.(16)

Pulmonary artery occlusion pressure

Pulmonary artery catheter (Swan-Ganz) insertion is necessary for the measurement of pulmonary artery occlusion pressure (PAOP) and other intracardiac pressures, cardiac output as well as mixed venous oxygen saturation. The PAOP is used as an indirect measure of the left atrial pressures. This practice has been largely abandoned in the majority of critical care patients due to the invasiveness of the procedure and the numerous complications associated with the insertion of the Swan-Ganz; in addition to limited benefit demonstrated with its use in majority of the critically ill.(17)

Echocardiography

The use of point of care ultrasonography (POCUS) has markedly improved the ability of intensivists to assess the cardiovascular system in real time. Bedside echocardiography is used to assess both right and left ventricular function in critically ill patients and aid in the diagnosis of different causes of haemodynamic instability such as hypovolaemia, pulmonary embolism, myocardial infarction, cardiac tamponade among other acute pathologies.(18) The main limitation to bedside use of echocardiography is availability of equipment and trained practitioners, especially in a resource limited setting.(19)

Dynamic Haemodynamic Parameters

Commonly used dynamic parameters are based on the cyclic variation of the left ventricular stroke volume, and stroke volume related parameters resulting from cyclic changes in intrathoracic pressure in mechanically ventilated patients. Intrathoracic pressures increase during inspiration leading to a decrease in right ventricular preload and left ventricular afterload, while increasing right ventricular afterload and left ventricular preload.(20) Based on these changes, multiple measurements and calculations can be carried out to determine the fluid responsiveness of critically ill patients. Causes of inaccurate interpretation include: cardiac arrhythmias, spontaneous ventilation, small tidal volumes of <8mls/kg and intra-abdominal hypertension.(21)

Stroke Volume Variation

Stroke volume is the amount of blood ejected from the ventricles during each contraction. Mechanical ventilation causes an increase in left ventricular stroke volume during inspiration and a reduction during expiration. These changes can be measured using an indwelling arterial catheter and proprietary algorithms such as LIDCO and PICCO used to calculate stroke volume variation.(22)(23)(24) Patients in whom the stroke volume increases by at least 15% after a fluid challenge are classified as fluid responders.

$$\%SVV = \frac{SV_{max} - SV_{min}}{SV_{mean}}$$

SVV – Stroke Volume Variation

SV_{max} - Maximum Stroke Volume

SV_{min} – Minimum Stroke Volume

SV_{mean} – Mean Stroke Volume $\{(SV_{max} + SV_{min})\}$

Pulse pressure variation

Pulse pressure is the difference between systolic and diastolic blood pressure. Pulse pressure variation, a derivative of pulse pressure is measured based on the same principles used for measuring stroke volume variation. Physiologically, pulse pressure is directly proportional to stroke volume but inversely proportional to arterial compliance. The variation in pulse pressure will therefore occur as a result of changes in stroke volume during mechanical ventilation. This variation is then calculated as a percentage (using a formula similar to the one for calculating stroke volume variation) and a value above 13% interpreted as indicating fluid responsiveness.(25)(26)

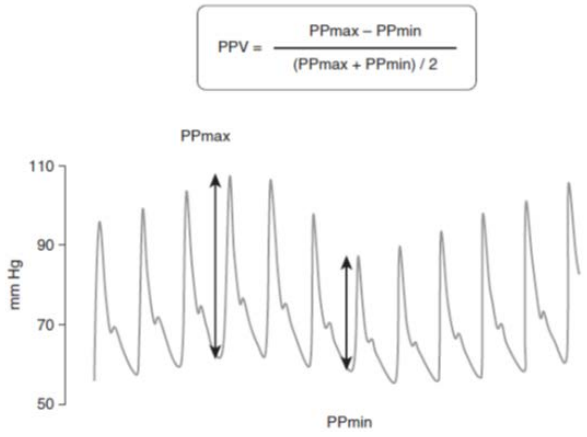

Fig 2. Calculation of pulse pressure variation (PPV) from arterial pressure curve. PP – pulse pressure.

Pleth Variability index

This method of measuring fluid responsiveness is different from most dynamic haemodynamic monitors due to its non-invasiveness. It is based on the variations of the photoplethysmographic waveform obtained using pulse oximetry. The proprietary algorithms calculate the Perfusion Index (PI) using the infrared wavelength used in pulse oximetry and determines the Pleth Variability Index (PVI) using the maximum and minimum PI during one or more complete respiratory cycles.(27)

Microcirculation

The ability to monitor the microcirculation is vital for determining actual tissue perfusion. Multiple studies have demonstrated lack of correlation between macro circulatory parameters and actual tissue perfusion in some critically ill patients; therefore, establishing adequacy of the microcirculation is perhaps the only sure way of ascertaining good end organ perfusion. It is impractical to assess the state of the microcirculation for all organs: therefore, techniques have been developed for monitoring microcirculation in a few easily accessible anatomical areas. These findings are then used as surrogate markers for the general state of the microcirculation. Measurement of sublingual Microvascular Flow Index (MFI) is currently the most common method of assessing the microcirculation. This is accomplished using Orthogonal Polarization Spectral (OPS), Side stream Dark Field (SDF) or more recently Incident Dark Field illumination (IDF). Several studies have showed improved outcomes in critically ill patients resuscitated based on microcirculation rather than macrocirculation parameters. In addition, there is evidence suggesting better outcomes in patients given drugs targeting the microcirculation as opposed to macrocirculation haemodynamic parameters.(28)(29)

Clinical haemodynamic monitoring

Despite having sophisticated equipment for monitoring haemodynamic parameters, there is room for clinical examination and assessment of indirect markers of adequate end organ perfusion. These include assessment of skin temperature gradients, skin mottling scores, capillary refill time, urine output, and serum lactate. The greatest shortcoming of these assessments is their lack of specificity in detecting inadequate tissue or end organ perfusion, thereby denying the clinician the ability to confidently identify inadequate perfusion solely based on these findings.(30)

Conclusion

Monitoring the haemodynamic status of critically ill patients is of paramount importance. This has traditionally been accomplished using macrocirculation indicators: however, there is evidence to suggest presence of discordance between macrocirculatory and microcirculatory parameters. This discordance is largely due to the inherent limitations of macrocirculation haemodynamic parameters. It is therefore prudent if practical to assess the microcirculation in critically ill patients rather than relying solely on the normalization of macrocirculation parameters

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Perioperative Thrombosis and Hemostasis: Pitfalls and Tribulations of Relying on Routine Coagulation Tests

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Abstract

Coagulopathy, either as bleeding or thrombosis is commonly experienced in the perioperative period. Routine coagulation tests are often ordered to identify the cause or to guide interventions. Accumulating evidence is increasingly casting doubt on the performance of these tests to predict bleeding or thrombosis. It is emerging that there is incongruence between the tests and recommended interventions such as administration of fresh frozen plasma. It is clear that indiscriminate preoperative testing is not warranted. These tests are inadequate and have poor predictive value for bleeding and thrombosis in the perioperative period. For the routine laboratory coagulation tests to be of value, they need to be ordered and interpreted in the context of well-structured history and clinical evaluation. The pitfall is ordering test when not indicated, and tribulation lies in interpreting the results when clinically meaningless.

Background

Hemorrhage or thrombosis are serious clinical complications associated with surgery. Perioperative physicians have to constantly make decisions to avoid or manage the problems based on objectively measurable laboratory tests. Routine coagulation laboratory tests such as prothrombin time (PT) or its derivative International Normalized Ratio (INR), activated partial thrombin time (APTT) and Thrombin Time (TT) are the mainstream of laboratory coagulation investigations. On many occasions, the tests may be normal in the presence of clinically significant hemorrhage. The reverse may also be true. The trigger values, roles and applicability of these tests as well as interventions based on them such as fresh frozen plasma have come into question in the perioperative areas. This review will focus on the pitfalls and tribulations of relying on these tests for clinical decision-making and highlight the historical developments of their place in medicine, and how to rationally utilize them.

Historical origin and tests performance

Routine coagulation tests, or sometimes referred to as standard coagulation tests, consist of PT, INR, APTT, TT and sometimes fibrinogen levels. Whereas the PT/INR was designed to monitor dosage of Coumadin vitamin K antagonists, the APTT was designed for heparin dosing.[1] Both tests have found applicability in screening for inherited or acquired coagulation factor deficiencies.[2]

Indications for routine coagulation testing

Coagulation tests are widely used in outpatient medicine, surgery and trauma. They may be used to monitor anticoagulant therapy or screen patients who are likely to benefit from hemostatic interventions. Such patients may have unexplained bleeding, disseminated intravascular coagulopathy, upper gastrointestinal bleeding or severe sepsis. The tests may also be useful in assessing the synthetic function of the liver.[3]

When performed in the perioperative period, they serve the purpose of either assessing the risk of bleeding before invasive procedures, or to identify underlying coagulopathy as well as guiding intra-operative and/or post-operative blood component therapy. [2]

The role of pre-procedural testing may be supported by patient history and clinician data. From this data, Rappaport proposed four levels of recommendations to guide laboratory testing.[4,5]

Level I: No screening necessary. This applies to patients undergoing minor surgical procedures, such as excisional biopsy of a wart with negative bleeding history.

Level II: Screening is done to assess the risk of life-threatening bleeding from major surgery from unsuspected acquired bleeding disorder in conditions such as uremia, myeloproliferative disorders or gammopathy. These patients also have negative history of bleeding.

Level III: Coagulation screening recommended. History is suggestive of possibility of defective hemostasis. The proposed surgical procedure has an inherent risk of altering hemostasis, such as cardiac surgery on pump. Procedures requiring high level of hemostasis, such as central nervous or spine surgery also fall in this group.

Level IV: Coagulation screening is mandatory. Additionally, tests such as platelet function, and factor assays are done for both major and minor surgical procedures. These patients have documented positive history of bleeding disorders such as hemophilia.

Scientific Repudiation

The tests are performed on plasma with exogenous activators, with exclusion of cellular elements interacting with vascular endothelium such as RBC and platelets and in addition gives no information about fibrinolysis. The normal ranges were determined as ± 2SD from samples obtained from normal healthy population such that 2.5% outliers may have abnormal results but not symptomatic (Watson, 2008). Furthermore, tests are performed outside the body physiology, with results obtained after some time thus not reflective of current

status and therefore may lead to delayed or inappropriate intervention.[1]

At the point of visual clot formation, whereas only 5% of thrombin formed and 15% of thrombin acting on fibrinogen, the maximum rate of thrombin generation is reached several minutes after clot time. At the same time, whereas 80% of fibrinogen is depleted from fluid phase, only 35-45% Fibrinopeptide A is released.[6] These demonstrate that the conventional clotting time as an end point in routine coagulation tests is just the beginning of elaborate biochemical processes that ensue thereafter.

In advanced liver cirrhosis, routine coagulation tests are usually prolonged. However, thrombin generation in such cases is either intact or enhanced, suggestive of hypercoagulable state.[7] This therefore demonstrates that the routine tests are poor predictors of thrombin potential.[8,9,10,11] These patients, despite having prolonged routine coagulation tests and high thrombin have low regulatory anticoagulants (Protein C & S, TFPI and anti-thrombin) but high FVIII. So infusion of fresh frozen plasma restores the anticoagulants therefore explaining the variable response.[12]

From a methodological point of view, the normal Tissue factor (initiator of extrinsic cascade) level is 5 picomoles. However, up to 30 picomoles is required for normal blood clot formation beyond which there is no change in clotting time.[13,14] During laboratory testing 200-300 picomoles are exogenously added, indicating that the coagulation testing is not truly physiological.[13]

Performance of tests in relation to surgery

Generalized microvascular bleeding not surgically correctable represents defects in hemostasis. The causes could be disorders of primary (platelets), secondary (coagulation factors) and tertiary (fibrinolysis), or combination of these called disseminated intravascular coagulopathy (DIC).

Preoperative coagulation testing is usually performed to screen patients for risk of bleeding. In a study involving 514 patients, 4.1% of the tests done were abnormal and were not associated with clinically significant coagulopathy. Out of the tests that were performed based on clinical indication, only 7.1% were abnormal. The study concluded that indiscriminate coagulation screening has a low yield and therefore not clinically useful.

In a single-center laboratory-based study, 318 out of 671 (47.1%) samples were taken for anticoagulation monitoring. The remaining samples, 353 out of 671 (52.6%), were taken for coagulation screening. Prothrombin time (PT) and activated partial thrombin time (APTT) were prolonged in only 5.4% of the samples taken for screening. This is beyond cut off 1.1% of samples, based on population studies. However, none of the abnormal results were associated with bleeding.[3] These were consistent with other studies that showed unregulated routine tests do not predict bleeding in many surgical operations in procedures such as tonsillectomy, liver biopsy, and central venous line placement.[5,16]

In a study of coagulation testing during surgery, it was found that 9 out of 12 patients had laboratory evidence of prolonged PT and APTT, none of whom had evidence of clinical bleeding. If the laboratory criteria were used, these patients would receive fresh frozen plasma with clinical futility. Contrastingly, in 4 out of seven patients who had normal laboratory values, clinical bleeding requiring transfusion was observed.[17] It can be concluded that routine tests in this study demonstrated poor predictive value, or were not reflective of the perioperative hemostasis status, similar to findings in other studies.[18,19]

Review of publications from 1996 to 2005 concluded that routine perioperative coagulation testing had poor predictive value for bleeding. These conclusions necessitated the formulation and adoption of a bleeding assessment tool by the British Hematology Association.[20]

In a study involving trauma patients requiring massive transfusion, the incidence of microvascular bleeding not amenable to surgical control was 25%. However, PT and PTT had low sensitivity and low positive predictive values for bleeding. The specificity of PT or PTT was only increased if the test values were prolonged beyond 1.8 times the control values. The data showed that 30-35% of variability in PT, and 15-20% variability in PTT was unrelated to clotting factor levels. Only low platelet count ($\leq 50X\ 10^9$) and fibrinogen (0.5 g/dL) levels were predictive of microvascular bleeding.[21] Similar findings of predictive value of platelet count and fibrinogen levels but not PT or PTT had earlier been documented in bleeding massively transfused patients.[22]

The diagnostic cut off point for routine coagulation tests is 1.5 times that of normal values.[21, 22, 23] However, this cut off value was neither designed nor validated for perioperative decision making.[2] Most of the studies citing the trigger value are found in trauma cases where it has been associated with high mortality.[2]

Thrombocytopenia has been sighted as the commonest cause of microvascular bleeding during surgery. Therefore, administration of platelet concentrates rather than fresh frozen plasma improves hemostasis in this patient population.[22,24]

Indications for fresh frozen plasma in surgery include prevention of bleeding (prophylaxis), treating of established bleeding (therapeutic), and plasma exchange.[25] Most guidelines (Table 1) recommend FFP as an intervention to correct either abnormal routine coagulation tests or microvascular bleeding.[25,26,27,28,29] However, a study comparing cardiopulmonary bypass with and without fresh frozen plasma found no difference in blood loss, transfusion requirements or change in routine coagulation parameters (PT and PTT). Therefore, the routine use of plasma in such operations has unclear benefits and is not recommended.[30,31,23,32]

Holland et al found that mild elevation in INR (< 1.6) resolved without the need for FFP if the underlying condition was treated.[23,32] In fact, FFP transfusion is ineffective in correcting mildly elevated INR.[33,23,32] It often results in insignificant or partial normalization of PT in 0.8% patients.[34,35,36,37,38,39]

The dosage of FFP needed to correct deranged coagulation is still controversial (Table 1). It ranges from 10 - 50 ml/Kg.[25,26] Many studies have found that INR either remains uncorrected or marginally changed if FFP is transfused at 12-15 ml/Kg, or corrected only if FFP is used at doses above 30ml/Kg.[18,33,39] Since in many clinical situations, FFP is administered at 12-15 ml/Kg or below, the studies illustrate the widespread inappropriate and ineffective usage of FFP in either adults or children.[36]

Table.1 Summary of professional society's guidelines on Perioperative routine coagulation testing and FFP as intervention

Professional body	Year of publication	Recommendation on Coagulation monitoring and cut off values	FFP and platelets dose	Remarks
AAGBI and NATA[26]	2016	PT>1.5 INR>1.5 Fibrinogen<1.5 g/dL Platelets<75X10^9/L	Platelets=10– 20 ml/kg • Fresh frozen plasma= 10–15 ml/kg	Routine tests designed for congenital deficiencies, not for bleeding during surgery
ESA[40]	2017	Discourages use of Routine tests. Recommends fibrinogen cut off <1.5-2 g/dL Platelets<50X10^9/L	Against FFP in mild to moderate INR elevation Strongly recommends factor concentrates Fibrinogen concentrate 25-50 mg/Kg Cryoprecipitate 4-6 ml/Kg	Structured questionnaire for bleeding history. VHA if available Preoperative platelet function testing if positive bleeding history
ASA[28]	2015 (updated version of 2006 guidelines)	PT>1.5 times normal APTT>2 times normal INR>2.0 Fibrinogen <80-100 mg/dL Platelet count<50X10^9/L	FFP=10-15 ml/Kg	FFP to achieve 30% normal factor levels. Presence of microvascular bleeding
BSH[25]	2018	Abnormal PT& APTT are poor predictors of bleeding prior to invasive procedures, though could be considered in moderate to high risk of bleeding; insufficient evidence to base recommendation on threshold for fibrinogen though levels <1.0 g/L should be considered	Insufficient evidence to base optimal dose for FFP in patients with abnormal tests. Prophylactic use not recommended; evidence of impact to correct clotting tests or reduce bleeding risks in INR 1.5-1.9 limited	Recommend taking of good bleeding history and clinical evaluation. Role of routine coagulation tests and FFP as intervention questionable. Vitamin K injection in abnormal PT prior to intervention. Against FFP and cryoprecipitate in low risk, non-bleeding patients

It is worth noting that most batches of FFP have variable INR, ranging from 1.2 to 1.3, thus explaining its ineffectiveness in borderline INR <1.5.[41] The INR of FFP increases with time after thawing as a result of reduction in coagulation factor V, VIII and vWF activity.[42,43] Because of wide individual variability in coagulation factor contents in blood products administered, it is not unusual to find minimal response in INR when FFP is administered.[44]

Due to delay in performance of routine coagulation lab tests, which take a minimum of 60 minutes turn-around time, most clinical decisions are made to transfuse FFP empirically. However, evidence indicates that FFP transfusion only correct PT/INR/APTT in few of the cases only, begging the question whether routine coagulation tests could appropriately guide transfusion therapy.[2]

Limitations of Routine coagulation Tests [45, 16]

i. Normal values obtained from tests performed in pooled plasma, therefore do not represent any specific individual phenotype.
ii. Normal biological variation, therefore in absence of relevant clinical information, are not useful.
iii. Low disease prevalence of inherited or acquired disorders therefore lowering their predictive value.
iv. Insensitivity to clinically relevant bleeding disorders such as platelet disorders, vWF, FXIII & alpha 2-antiplasmin deficiencies. Tests usually normal despite ongoing perioperative bleeding. Moreover, some factor deficiencies such as FXII, Kallikrein and HMWK may cause prolongation of APTT but no associated hemorrhage.
v. Low predictive value for bleeding.
vi. High prevalence of false positive or false negative, are transient or of no clinical significance.[5]
vii. Tests were designed in inherited single coagulation factor deficiencies, but in presence of multiple factor deficiencies, they are variable and less predictably prolonged.[2]
viii. Tests may miss mild hemophilia, vWD and platelet disorders.[3]

Alternative or adjuncts to routine tests

It is documented that a well taken bleeding history with structured questionnaire focusing on previous surgeries, dental procedures, childbirth, family history of bleeding diathesis and medications likely to impair hemostasis identifies most cases of coagulopathy.[3] A number of structured, validated and sensitive assessment tools have been developed to assist

with identification of patients likely to bleed from surgical interventions.[46] However, history is subjective and clinical symptoms are found in up to 25% of patients with factor deficiencies.[5]

In surgery or trauma, microvascular bleeding not amenable to mechanical surgical control due to low platelets usually presents with easy or excessive bruising (purpura), superficial bleeding into the skin that appears as a rash of pinpoint-sized reddish-purple spots (petechiae), usually on the lower legs, and prolonged bleeding from cut surfaces. History also reveals that they bleed from mucosal surfaces such as gums or nose (epistaxis), blood in urine or stools, unusually heavy menstrual flows (for females).[47,48,49,24]

The recommended investigations to confirm and support the suspicion are platelet count and bleeding time, functional tests such platelet function analyzer (PFA-100 or 200), Light Transmission Aggregometry (LTA) and Thrombelastography / Thromboelastometry (TEG/TEM).[40] However, these tests are not readily available and are laborious to perform. Moreover, there is no general agreement on the trigger values in surgery as opposed to medical patients, role of prophylactic platelet administration, dosage, optimal storage conditions as well as monitoring transfusion efficacy.[50]

Another cause of microvascular bleeding is hyper fibrinolysis seen during surgery or trauma. The cardinal feature of bleeding due to fibrinolysis is delayed clot lysis - clot formation precedes its dissolution. The usual screening tests for fibrinolysis are fibrinogen levels and thrombin time (TT), immunological demonstration of biomarkers such as D-Dimers (cross linked fibrin degradation products), fibrin split products (FDP), and plasmin-anti plasmin complexes (PAP). More specific but less sensitive tests are euglobulin lysis time (ELT) and Thromboelastography or thromboelatometry percentage (%) lysis time.[40] However, these tests have limitations of sensitivity, specificity and technical performance in real time.

Conclusions

Unregulated pre-operative coagulation screening has low yield of abnormal results, majority of abnormal results have no relation to bleeding risks and may unjustifiably delay procedures.[3,16] In this scenario of unpredictability, patients may be subjected to unwarranted further tests. [51] It is recommended that tests must take into account clinical setting, diseases prevalence, performance characteristics of tests, cost and consequences of false positives and negatives. It is not true that routine coagulation tests have no value. The fact is that they are being increasingly employed to answer a question they were not designed for, or ill equipped to be of value.

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A Prospective Observational Study On The Use Of Bolus Intravenous Dexmedetomidine Sedation For Paediatric MRI

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Introduction

Magnetic resonance imaging (MRI) plays a crucial role in the diagnosis and evaluation of acute and chronic disease in the paediatric population. For optimum image quality there must be minimal patient movement for the duration of the scan. The challenge to lie as still as possible is magnified by the loud noise of the scanner and the intimidating 'dark tunnel' that can induce fear and anxiety. (2, 3, 4)

Techniques to minimise these intra-scan motion artefacts will vary according to the age of the patient. In small infants and neonates, this may be achieved by the "feed and swaddle" technique. If adequately prepared, children older than 4 to 6 years of age may be able to lie still for MRI scans without pharmacological intervention. (5,6,7) However, the failure rate of 10-15% for this technique, necessity for flexibility with time slots, and the requirement for skilled play therapists or specialised rooms with simulation equipment limit the use of this technique, particularly in resource challenged settings.

Children aged between 1 and 7 years, children with learning difficulties, neurobehavioral disorders, children with claustrophobia or uncooperative children will invariably require the use of sedatives or general anaesthesia to achieve the optimal patient immobility. (1,2) Compared with general anaesthesia, sedation may be less invasive, cost and time saving, but there is a variable rate of failure and incidence of complications. (3)

The properties of the ideal sedative include: reliability of sedation, predictability of duration, rapid recovery time, and minimal cardiorespiratory effects. (2,4) Whilst no sedative agent meets all of these criteria, dexmedetomidine appears to have several advantages over other sedatives. Through its action on the 2-adrenergic receptors in the locus coeruleus, it provides relatively fast onset of sedative properties mimicking natural sleep, with minimal respiratory depression. (5,6) The use of infusions for sedation for MRI in the paediatric population has been well described in high-income countries.(2,6–10) In a resource challenged environment the option of an infusion is often limited by the lack of availability of an MRI compatible infusion pump, and there are currently no published studies on the use of intravenous bolus sedation for MRI without maintenance infusions.

At the Red Cross Children's Hospital, a tertiary referral centre in Cape Town, approximately 990 MRI scans are performed annually. Approximately 70% of these children will require administration of sedation or general anaesthesia. Historically the majority of children were sedated for MRI with chloral hydrate, but a change in licensing of the drug in South Africa, has dramatically increased its cost and reduced its availability. An unpublished retrospective audit conducted on sedation practices in MRI between January 2014 and December 2015 found that boluses were now used for more than 90% of cases. 34% used only dexmedetomidine for sedation, and 65% involved an additional sedative agent. Additional sedative agents included; propofol boluses, midazolam, opioids, ketamine, and in 5 cases inhalational agents (sevoflurane, isoflurane) were administered via nasal cannula. The mean total dose of intra-venous dexmedetomidine given was 1.1 mcg. kg-1, which is significantly lower than that reported in other studies. (8,9) This is likely due to the practice of combining the bolus with another sedative agent.

This prospective observational study aimed to further delineate the success of bolus sedation for completion of paediatric MRI scans, and the association with adverse events.

Method

This prospective observational study was conducted at a tertiary paediatric hospital, in Cape Town. Ethical approval for the study was obtained from the University of Cape Town Human Research Ethics Committee (HREC REF: 99617). After obtaining written consent from the primary caregiver, or legal guardian, 54 children sedated using dexmedetomidine for MRI were enrolled over a ten-week period from June to August 2017. The attending anaesthesiologist filled in the data collection form (see Appendix A).

Eligibility criteria were all children < 18 years booked for MRI under sedation. Exclusion criteria were the following: patient deemed unsuitable for sedation by primary anaesthetist, parental/guardian/competent patient refusal to consent for participation, allergy to dexmedetomidine, and patients who were already intubated.

Data collection

Data were collected and entered into a data collection tool. Patient identity was pseudo-anonymized by the provision of a unique identifier for each patient. Patient characteristics recorded included; age, sex, type of MRI, diagnosis, comorbidities, presence or absence of a working intravenous cannula.

The following variables were collected: timing and doses of dexmedetomidine used, timing and doses of adjuvant drugs used, physiological variables were recorded every 5 minutes, including; pulse oximetry, heart rate, and capnography via a nasal cannula (with concomitant oxygen delivery if needed) and any interruptions to scanning, or adverse events during

the scan or in recovery The time taken to sedate the patient, time needed to obtain the imaging study, and discharge time, defined as time from the end of the procedure to actual time when the patient was ready for discharge from recovery were also recorded. Noninvasive blood pressure is not routinely measured at our institution as the inflation and deflation of the cuff causes a disturbance to the moderately sedated patient so this measurement was not collected. Administration of contrast was not considered to be an interruption to the scan.

Adverse events were defined as; spontaneous patient movement resulting in scan interruption, airway obstruction, apnoea, bradycardia requiring intervention, requirement of supplemental oxygen after the start of sedation, desaturation <92%, conversion to general anaesthesia, requirement of cardiopulmonary resuscitation and unplanned ICU admission.

Statistical Analysis

A total of 54 patients undergoing 54 MRI scans were enrolled in the study (Table 1). The success rate of sedation was calculated as the number of patients who had a successful MRI sedation without requiring interruption of the MRI to administer rescue doses or interventions for adverse effects. Based on a previous study stating an 83% of successful MRI sedation using intravenous bolus dexmedetomidine followed by an infusion (20), the calculated sample size required using Fischer's formula with a 10% absolute error, was 54 patients. All descriptive and analytical statistics were performed using Microsoft ® Excel ®2016 (version 1804).

Results

A total of 54 consecutive patients between the age of 20 days to 13 years, with a median age of 3.27 years (IQR 1.32-4.99 years) were enrolled during a ten-week period (Table 1). 10/54 children were age less than 1 year, and this included 1 neonate. The median weight was 14.4 kg (IQR 11.9-19.1kg). The median length of MRI scan was 35 minutes (IQR 27 - 44 minutes). Over half of the scans performed were brain MRI's (Table 1). The most common indications for MRI were the presence of congenital abnormalities and global developmental delay (Table 1). 44/54 (81%) MRI scans were completed without interruption.

All of the patients included in the study received IV dexmedetomidine boluses, as their primary sedation agent, with supplemental adjuvant sedation at the discretion of the anaesthetist. The median bolus dose of dexmedetomidine administered for induction was 1.2 mcg.kg-1 (IQR 1.0 -1.3 mcg.kg-1). 13/54 (26%) children did not require additional medication to achieve a level of sedation necessary for the MRI. The remaining 41 patients (74%) all received an adjuvant propofol bolus with a median dose of 0.83 mg.kg-1 (IQR 0.48-1.03 mg.kg-1), and one patient received 1 mg.kg-1 ketamine.

14/54 patients (26%) received a second dose of dexmedetomidine at a median dose of 0.5 mcg.kg-1 (IQR 0.35-0.82 mcg. kg-1) This was administered at a median time of 31.5 minutes (IQR 23.5-37.5 minutes) after the induction dose. 12/14 patients who received a second dose of dexmedetomidine were also given an additional bolus of propofol, with a median dose of 1 mg.kg-1 (IQR 0.5-1.0 mg.kg-1). The most common reason for additional boluses was patient movement (8/14). Top up doses of dexmedetomidine were given at the anaesthetist's discretion in the other 6 patients (who did not move), but in whom the anaesthetist anticipated the patient may wake before the end of the scan or prior to the administration of contrast (1/12). Only one patient received more than two bolus doses of dexmedetomidine (Table 2).

Adverse Events

14 (25.9%) patients had an adverse event documented during their sedation. Overall there were 18 adverse events (Table 3).

The commonest reason for scan interruption was due to spontaneous patient movement in 9 patients. Patient movement occurred at median time of 31.5 minutes (IQR 23.5-37.5 minutes) after the last bolus of dexmedetomidine. All of these patients received propofol as a rescue medication.

Desaturation <92% was the second most common adverse event, occurring in 5 (9.2%) of patients. All of these patients had received propofol as an adjuvant, 3/5 had a current upper respiratory tract infection (URTI). The desaturation event was usually transient and only one patient required interruption of the scan to administer supplemental oxygen therapy. 5 patients received supplemental oxygen during the MRI. This included 2 patients in whom supplemental oxygen was commenced during sedation, presumably due to low oxygen saturation levels, and 3 patients already on oxygen therapy prior to sedation. 1 patient had both movement and desaturation during their sedation and required oxygen supplementation.

One patient, aged 2 year 9-months, with a facial malformation, compromised airway patency and a current URTI required interruption of the scan and conversion to general anaesthesia with a laryngeal mask airway. This was due to desaturation and airway obstruction with sedation which did not resolve despite the insertion of an oropharyngeal airway.

No patient had bradycardia requiring intervention, or required cardiopulmonary resuscitation, there were no unplanned ICU admissions, and no adverse events occurred in recovery.

Time until ready for discharge

The median time to recovery was 10 minutes from the end of MRI scan (IQR 7-14.25 minutes). There was no relation between the dose of DEX used and recovery time (Figure 1).

The median and average time to recovery to satisfy discharge to ward criteria after administration of last dose of dexmedetomidine was 54 and 57 minutes respectively.

Clinician satisfaction with the sedation

As evaluated using a three-point scale: excellent, acceptable and poor, the lead radiologist and anaesthetist were 100% satisfied the sedation was acceptable in all cases except the

case in which conversion to general anaesthesia was required. The sedation was felt to be excellent in 80% of cases.

Discussion

In this study, 98.1% of children with a variety of co-morbidities aged between 26 days and 13 years were successfully sedated for MRI for a range of indications using IV dexmedetomidine bolus(es), either as the sole agent or in combination with propofol boluses, and in one case in combination with ketamine.

One patient did require conversion to general anaesthesia due to desaturation and airway obstruction. This patient had a facial malformation and an upper respiratory tract infection (URTI) with compromised airway patency that necessitated the MRI scan. Whilst we have found that due to the relative preservation of airway tone (11), dexmedetomidine can be very well tolerated even in patients with airway obstruction, this patient was unable to maintain an unobstructed airway for the entire duration of the scan, even after insertion of an oropharyngeal airway. There were no significant sequelae from the failed sedation event, but it does highlight the importance of back up equipment and vigilance during sedation.

44/54 (81%) patients had an uninterrupted scan to completion, with spontaneous patient movement being the commonest cause of interruption. This is comparable to other studies, including Koroglu et. al. who had an 83% success rate of uninterrupted scans with a loading dose of 1 mcg.kg-1 bolus followed by an infusion of 0.5 mcg.kg-1.hr-1 (9). Mason et. al. also demonstrated a varying success rate with up to 19.2% of patients requiring repeat bolus(es) of dexmedetomidine for awakening in scanner (14.6%-19.2%) despite using significantly larger initial dexmedetomidine doses and infusion rates (8).

Our practice of using only boluses of dexmedetomidine, even when combined with another sedative agent, demonstrates a significantly shorter recovery time compared with using an infusion, despite the similar success rate for uninterrupted scan to completion (9). It is our opinion that the use of a propofol bolus in the patients in whom sedation is not achieved by dexmedetomidine alone allows the patient to achieve a deeper level of sedation, which is then maintained by the longer acting dexmedetomidine. Mason and colleagues (12) have demonstrated an overall 99.7% success rate for sedation for paediatric nuclear medicine imaging using bolus doses of intravenous dexmedetomidine. In their study the patients received an initial dexmedetomidine dose of 2.0 mcg/kg 3 0.2 (median, 2.0 mcg/kg; range, 0.5–3.0 mcg/kg). A total of 111 patients (16.6%) required a second bolus, and 19 (2.8%) patients required a third bolus. They noted the benefit of predictable sedation conditions, a brief recovery period, and a lack of important adverse events, when using dexmedetomidine as a sedative for nuclear medicine imaging in children.

The cost of dexmedetomidine and the need for an MRI compatible syringe driver has limited its use in resource challenged settings, but by using lower doses and/or combining it with low doses of other sedative agents, we have found this to be a cost-effective way of ensuring adequate, safe sedation without the need for a general anaesthetic in our resource constrained setting.

Limitations

The study population was heterogenous with varied co-morbidities, which may have had an impact on the success of the sedation. The dose of dexmedetomidine, choice and dose of adjuvant sedative was subjective based on the preference of the individual anaesthetist. This would have been influenced by factors including prior experience, the child's pre-existing illness, and state of agitation.

There were different indications for MRI within the study population, and differing duration of scans. The practice at our centre is to administer a single bolus dose of dexmedetomidine, and the decision to give adjuvant sedatives and further boluses of dexmedetomidine are at the discretion of the anaesthetist. The median length of scan in our study was 44 minutes and it may reasonably be expected that this technique would become increasingly unreliable with longer scans.

Non-invasive blood pressure (NIBP) monitoring is not routinely used in our institution as the inflation and deflation of the cuff can causes enough stimulation to wake the moderately sedated patient. It is possible that relevant fluctuations in blood pressure may have been missed, although studies have shown that dexmedetomidine sedation provides a stable cardiovascular status even when using larger doses.(7–9,11,13)

Conclusion

The results of this study support the use of IV bolus dexmedetomidine with or without adjuvant sedation for MRI across a wide range of ages, weight and co-morbidities. This technique appears to be as successful as an infusion regime, without any serious adverse events, and a quicker time to discharge from recovery. The use of dexmedetomidine boluses with or without adjuvant sedation, can be a suitable alternative to administration of general anaesthetic for MRI in children. This may be of benefit when considering the potential association between general anaesthesia and neurotoxicity in the developing brain. It also supports the use of dexmedetomidine sedation for MRI even within a resource challenged environment without the option to run sedative infusions.

Disclosures

1. Ethical approval for the study was granted by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC REF: 99617)
2. No funding required.
3. No conflict of interest

Tables

Parameter	Result
Age (y)*	3.27 (1.3-4.99)
Weight (kg)!	14.4 (11.9-19.1)
Sex	
Male	26(48)
Female	28(52)
Type of MRI	
Brain	31 (57.4)
Brain/spine	9 (16.7)
Spine	6 (11.1)
Abdomen	2 (3.7)
Face	1 (1.9)
Limbs	1 (1.9)
Other	4 (7.4)
Diagnosis	
Congenital anomalies	22 (40.7)
Global developmental delay	10 (18.5)
Seizure disorder	6 (11.1)
Trauma	5 (9.3)
Autistic spectrum	2 (3.7)
Acute flaccid paralysis	2 (3.7)
Malignancy	3 (5.6)
Cerebral palsy	1 (1.9)
Cerebro-vascular accident	1 (1.9)
Moya Moya disease	1 (1.9)
Gait abnormality	1 (1.9)

Note – Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages.

*Data are median age, and interquartile ranges. Mean age was x years +/- SD years

!Data are median weight, and interquartile ranges. Mean weight was x kg +/- SD kg

Table 1: Clinical data in 54 patients

Age	Weight (kg)	Indication for MRI	MRI type	Induction DEX dose (mcg.kg-1)	Adjuvant propofol dose (mg. kg-1)	Time since last DEX bolus (mins)	Reason for scan interruption	Rescue sedation	
								Propofol (mg.kg-1)	DEX (mcg.kg-1)
10m	11.8	VP shunt	Brain	1.2	None	23	Movement	1	None
2y 10m	12	Cerebral palsy	Brain	1.0	0	18	Movement	1	1
2yr 9m	14	Facial malformation with upper airway obstruction*	Face	1	0.7	48	Desaturation, Airway obstruction	0	Conversion to GA at 55 mins
4y 2m	14	Cervical injury	Brain & spine	1.1	0.7	36	Movement	0.7	0.3
3y 9m	15	Burkitts lymphoma	Abdomen	1.0	1.3	33	Movement	1.3	1
2y 7m	17	Lower limb weakness	Brain & spine	1.1**	1.1	20	Movement, desaturation	0.5	1mcg.kg at 15min 0.5mcg/kg at 20mins 1mcg/kg at 70min
4y 11m	17	Brain and Spine	Brain & spine	1.1	1.1	40	Movement	1.1	1.1
6y	20	Seizure disorder	Brain	1.0	None	22	Movement	0.5	0.5
5y 10m	20	Urinary incontinence in corrected Hirschsprung's disease	Spine	1.0	1	33	Movement	0.5	0.3
7y 8m	21	Chiari malformation	Brain & spine	1.4	None	58	Movement	0.5	0.5

*This patient had airway obstruction and desaturation at 48minutes after induction. Converted to General anaesthesia and Laryngeal Mask Airway Inserted at 55 minutes.

**This patient had 3 a total of 2.5 mcg.kg-1 in top-up doses of DEX prior to movement interrupting the scan, also had desaturation episode after propofol bolus

Table 2: Patients with interrupted scans

Event during scan	n, (%)
Spontaneous movement interrupting scan	9, (16.6)
Desaturation SpO_2<92%	5, (9.2)
Additional supplemental oxygen received during scan	2, (3.6)
Airway obstruction requiring oropharyngeal airway	1, (1.8)
Repositioning after scan started	1, (1.8)
Conversion to general anaesthesia	1, (1.8)

Table 3: Adverse events during scan

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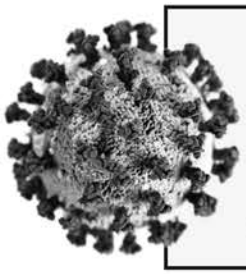

IDENTIFICATION OF MODERATE AND SEVERE COVID-19 DISEASE AFTER CONFIRMATION OF TESTS

Conversion Tables

1. Estimating PaO_2 from a given SO_2

SO_2 (%)	PaO_2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

2. Estimating FiO_2

Method	O_2 flow (l/min)	Estimated FiO_2 (%)
Nasel cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask	5	40
	6-7	50
	7-8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95

ARDS is when PAO_2 /$Fi0_2$ = 300 or less.

The lower the figure the more severe the disease.

MODERATE COVID-19 INFECTION: COURSE AND MANAGEMENT

- **Feeling worse, tachypnoec i.e breathing fast and shallow but no shortness of breath.**
- **Fever unrelenting.**
- **Nausea and diarrhoea (if present), persists.**
- **Unable to get out of bed for natural calls.**

MODERATE COVID-19 INFECTION: MANAGEMENT

- **Requires oxygen supplementation by high flow non rebreather oxygen mask and associated monitoring using pulse oximetry and continuous ECG.**

SEVERE COVID-19 INFECTION: COURSE AND MANAGEMENT

- **Should call for an ambulance to take them to hospital, (discourage relatives / friends from doing this).**
- **Should be picked by a team wearing PPE's.**
- **Typically require 2 - 8 litres of Oxygen per minute via nasal prongs / simple face mask / (hood for children if available).**
- **NIV, Nasal CPAP not recommended because of aerosolization of viral particles.**
- **Have difficulty mobilizing thick secretions.**
- **Often require volume resuscitation, but do not overdo this.**
- **CXR shows typical picture of diffuse infiltrates.**
- **CT Scan shows typical picture.**
- **Can last for hours to days before progressing or waning.**
- **Oxygen requirements start increasing to above 8 litres/ minute to keep saturations above 92%.**
- **Coughing requires increasing effort and secretions worsening.**
- **Patient more anxious and subjective shortness of breath.**
- **Worsening CXR. (CCSK recommends to avoid repeating CXR/CT's at this time, but to make decisions based on the clinical picture).**
- **Period last hours to a few days (non-defined so far).**
- **Arrange transfer to ICU for controlled Rapid Sequence Intubation (RSI) with an appropriate sized endotracheal tube.**

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