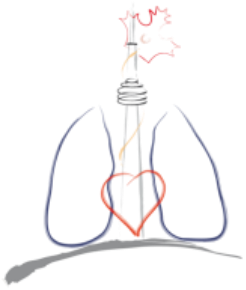
UNIVERSITY OF TORONTO | Interdepartmental Division of Critical Care Medicine



ART SLUTSKY RESEARCH DAY

Interdepartmental Division of Critical Care Medicine
University of Toronto

Tuesday June 20, 2023
Campbell Conference Facility
Munk School of Global Affairs and Public Policy
Trinity Site, 1 Devonshire Place, Toronto ON M5S 3K7
University of Toronto

8:00 –8:55 am Registration and Light Breakfast

8:00 – 8:45 am Poster Set-Up

Posters should be on display until **3:00 pm** so they are available for viewing both at the designated time with the authors (see below), and informally (without authors) at coffee breaks and lunch.

Please set up posters before the start of the oral presentations to avoid interruptions.

We will supply push pins

8:55 – 9:00 am **Welcome and Introductory Remarks / Land Acknowledgement**

IDCCM Research Director: Dr. Margaret Herridge

9:00 – 9:45 am **Oral Presentations I: Mix of abstract types**

Chairs: Drs. Christie Lee, Matteo Parotto

Each presentation is 10 min followed by 5 min discussion.

All speakers will be requested to strictly adhere to the time limit.

9:00 – 9:15 am **Presentation 1**: **Igor Novitsky-Basso**
Decidual Stromal Cells for the Treatment of Severe COVID-19 ARDS: a safe and effective option

9:15 – 9:30 am **Presentation 2: Francois Mathieu**
Optimization and multicentre external validation of a deep learning model for segmentation and quantification of traumatic brain injury lesions on head CT

9:30 – 9:45 am **Presentation 3: Eleonora Balzani**
The Association between Daily Driving Pressures and Mortality in Patients supported with Veno-venous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome.

IDCCM Faculty Presentation

Session Chair: Dr. Gordon Rubenfeld

9:45 – 10:10 am **Featured Speaker**

Dr. Hannah Wunsch
A Journey into Publishing

10:10- 10:20 am **Discussion**

10:20 - 11:00 am Morning Break

11:00 – 11:45 am **Oral Presentations II : Mix of abstract types**

Chairs: Dr. Jeff Man, Dr. Mike Sklar

11:00 – 11:15 am **Presentation 4: Jose Dianti**
Sedation-Ventilation Interaction in Acute Hypoxemic Respiratory Failure

11:15 – 11:30 am **Presentation 5: Alicia Gibbs**
Molecular interaction between ICAM-1 and LPS in mediating inside-out inflammatory signaling

11:30 – 11:45 am **Presentation 6: Cecilia Bianchi**
A non-invasive and continuous method to calculate respiratory muscle pressure from airway pressure and flow: a validation study

11:45 am – 1:30 pm **Poster Judging/Viewing and Lunch**

11:45 am – 12:45 pm Poster discussion
Presenting authors must be with their posters

11:45 pm – 1:30 pm Lunch and unaccompanied poster viewing

1:30 – 2:00 pm **Oral presentations III: Mix of abstract types**

Chairs: Dr. Andre Amaral, Dr. Mika Hamilton

1:30 – 1:45 pm **Presentation 7: Irene Telias**
Influence of the magnitude and synchrony of breathing efforts on lung stress-strain and alveolar pressure is modified by the mode of ventilation during early acute hypoxemic respiratory failure

1:45 – 2:00 pm **Presentation 8: Constanza Velasco**
Characteristics and Timing of Detection of Brain Abnormalities on Cranial Ultrasound in Pediatric Extracorporeal Cardiopulmonary Resuscitation

IDCCM Special Presentations

2:00 – 2:20 pm **State of the IDCCM**, University of Toronto
Dr. Laurent Brochard

Session Chairs: Dr. Elaine Gilfoyle, Dr. John Marshall

2:20 – 2:45 pm **Featured Speaker**

Dr. Adrienne Randolph
Sepsis Research: Progress Made and Challenges Ahead

2:45 – 2:55 pm **Discussion**

2:55 – 3:30 pm	Afternoon Break
3:30 –3:45	**Transitions**
3: 45 – 4:45 pm	**Presentation of Certificates of Training Completion** **Presentation of Site Teaching/ Fellow Awards** Drs. Dave Hall/Jenna Spring/Alex Floh **Presentation of Research/ Education / Interprofessional Awards** Dr Laurent Brochard/Dr. Stephen Schwartz
4:45-5:00 pm	**Presentation of Research Day Prizes and Closing Remarks** Drs. Margaret Herridge and Hannah Wunsch

Please stay for end of Year Group Photo in Courtyard- Weather Permitting

Thank you!

Have another great year of research and education and see you next year!

Art Slutsky Research Day 2023
IDCCM Chair: Dr. Laurent Brochard
IDCCM Director of Research: Dr. Margaret Herridge
IDCCM Associate Director of Research: Dr. Hannah Wunsch

GUEST SPEAKERS

Featured Speakers

Hannah Wunsch

Dr. Hannah Wunsch is an intensivist in the Department of Critical Care Medicine at Sunnybrook Hospital and Professor in the Department of Anesthesiology and Pain Medicine and the Interdepartmental Division of Critical Care Medicine at the University of Toronto. She is the Associate Director of Critical Care Research at the University of Toronto and holds a Tier 2 Canada Research Chair in Critical Care Organization and Outcomes. She is the author of the book, The Autumn Ghost: How the Battle Against a Polio Epidemic Revolutionized Modern Medical Care.

She is a bibliophile, theater lover, tennis player, and an avid (but terrible) ice hockey player. She lives in the Annex in Toronto, Ontario and the village of Woods Hole on Cape Cod, Massachusetts

Adrienne Randolph

Dr. Adrienne Randolph is a pediatric critical care specialist at Boston Children's Hospital and Professor of Anaesthesia and Pediatrics at Harvard Medical School. She founded the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network in 2002 that now has over 80 pediatric sites internationally. In 2008, she developed the Pediatric Intensive Care Influenza (PICFLU) Network, which she continues to direct across 32 U.S. pediatric hospitals with ongoing funding from NIAID. In response to the SARS-CoV-2 pandemic in 2020, PICFLU expanded into the Overcoming COVID-19 Network across 65 U.S. sites with funding from the U.S. Centers for Disease Control and Prevention. Dr. Randolph has over 250 publications. Her areas of expertise are pediatric sepsis, acute lung injury, and severe respiratory infections in children. In 2023, she became Chair of the International Sepsis Forum.

ABSTRACT JUDGES

Basic Science Category	Dr. Haibo Zhang Dr. Warren Lee
Clinical Research/Health Services Research Category	Dr. Chris Yarnell Dr. Matteo Parotto Dr. Bruno Ferreyro Dr. Anne-Marie Guerguerian
Physiology Category	Dr. Irene Telias Dr. Mike Sklar Dr. Alice Grassi Dr. Lorenzo Delsorbo
Quality Category	Dr. Alberto Goffi Dr. Jenna Spring Dr. Elaine Gilfoyle Dr. Nava Maham
Systematic Review/Case Report/Education Category	Dr. Briseida Mema Dr. Dominique Piquette Dr. John Granton

POSTER MODERATORS FOR ART SLUTSKY DAY

Basic/Translational Science Category I:	Dr. Haibo Zhang Dr. Jane Batt
Basic/Translational Science Category II:	Dr. John Marshall Dr. Alex Floh
Clinical Research/Health Services Research Category I:	Dr. Matteo Parotto Dr. Haley Christian
Clinical Research/Health Services Research Category II:	TBD Dr. Lorenzo Delsorbo
Clinical Research/Health Services Research Category III:	Dr. John Granton Dr. Elaine Gilfoyle

Clinical Research/Health Services Research Category IV:	Dr. Stephen Lapinsky Dr. Anne Marie Guerguerian
Physiology Category I:	Dr. Alice Grassi Dr. Gail Annich
Physiology Category II:	Dr. Antenor Rodrigues Dr. Jeff Man
Quality Category I:	Dr. Jenna Spring Dr. Alberto Goffi
Systematic Review/Case Report/Education Category I:	Dr. Andrew Helmers Dr. Mika Hamilton
Systematic Review/Case Report/Education Category II:	Dr. Christie Lee

ORAL PRESENTATION JUDGES

Dr. Laurent Brochard
Dr. Margaret Herridge
Dr. Adrienne Randolph
Dr. Hannah Wunsch

Decidual Stromal Cells for the Treatment of Severe COVID-19 ARDS: A Safe and Effective Option

Submission ID

23

AUTHORS

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* These authors contributed equally.

INTRODUCTION

Despite recent improvements in treatment, acute respiratory distress syndrome (ARDS) remains a significant cause of COVID-related mortality. Severe COVID is characterized by high levels of circulating pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which orchestrate an intricate cytokine storm, while dysregulated immune cell populations, such as T cells and monocytes, contribute to immune dysfunction. Recent systematic reviews have suggested that stromal cells (SC), including MSC, have potential immunomodulatory benefits in COVID-ARDS with few reported adverse effects [1, 2]. Stromal cells from the decidual membranes of the placenta (decidual stromal cells, DSC) are more immunosuppressive and more anti-proliferative than bone marrow-derived MSC (BM-MSC).[3] However, no previous studies have evaluated DSC in severe COVID-ARDS.

OBJECTIVES

In this pilot study we evaluated the safety and efficacy of DSC of placental origin on outcomes of patients with severe COVID-ARDS. Clinical outcomes were compared to a contemporaneous group of patients at the same centres that were not treated with DSC.

HYPOTHESIS

DSC will be safe and lead to a more rapid resolution of ARDS compared to a matched cohort of patients with COVID-ARDS.

METHODS

The DSC-COVID study (NCT04451291), a pilot open-label prospective study, investigated the safety and efficacy of DSC in 19 adult patients with severe COVID-ARDS requiring invasive mechanical ventilation in Ontario, Canada between January and June 2021. Patients were given a dose of $1x10^6$/kg DSC within 72 hours of randomization, with the option of a second dose if there was no clinical improvement within 5-8 days. Patients were eligible for the study if they were invasively ventilated <72 hours, met the 2013 Berlin diagnosis for ARDS, and had a positive COVID PCR test from a respiratory source. Patients were excluded if they had a severe comorbidity with life expectancy <3 months, were pregnant or breastfeeding, had proven or suspected active bacterial or fungal infection, were immunosuppressed, had known hypersensitivity to dimethyl sulfoxide or porcine or bovine proteins, had participated in another trial of immune modulating therapies, refused blood products, or had significant comorbid conditions prior to ICU admission Standard-of-care therapies, including steroids, tocilizumab and remdesivir, were permitted. Informed consent from the patient's substitute decision-maker was required before enrolment.
Clinical outcomes were compared to a contemporaneous propensity-matched control group (n=38) selected using pre-morbid risk factors. Primary endpoints were safety and ventilator-free days at D28 post-infusion. For multivariate analysis, backwards stepwise selection procedure was applied including variables of clinical interest (age, sex, receipt of DSC, PaO_2/FiO_2 (P/F) ratio at D0 and number of comorbidities).

RESULTS

Nineteen patients received at least one dose of DSC. Seven of 19 patients met criteria for a second DSC infusion. Reasons for not receiving a second dose included: interval use of ECLS (3 patients), transfer to a non-participating hospital (4 patients), rapid improvement leading to extubation (3 patients), clinical instability (4 patients).
Median age was 54 years (25-70) and 11/19 (57%) were male (**Table 1**). Comorbidities included obesity (n=8), asthma (n=7), diabetes mellitus (n=5), and hypertension (n=4). Propensity score matching generated a group of 38 mechanically ventilated patients admitted to the same ICUs with COVID-ARDS during the period of the DSC trial who were similar with respect to hospital site, age, sex, number of comorbidities, treatment with tocilizumab and steroids, and baseline P/F ratio (**Table 1**). In the matched cohort, 11/38 (30%) patients went on to receive ECLS.
Mean P/F ratio on D0 was 151 mmHg (range:80-220 mmHg, n=19) for the DSC group, and 147 mmHg for the PSM group (range: 69-243 mmHg, n=36, p=0.57). The mean minimum P/F ratio was 94 mmHg (95% CI: 78-110 mmHg) in the DSC group and 77 mmHg (95% CI: 63 – 90 mmHg) for the PSM group (p=0.08). Mean SOFA score on D0 was 7.6 (±0.65, n=19) for the DSC group, and 7.8 for the PSM group (±0.41, n=38, p=0.91).
The safety profile of the DSC in our study appears similar to other reports. One brief event of desaturation and 2 events of worsening hypoxemia, deemed potentially attributable to DSC were reported.
DSC treatment led to significant improvements in clinical outcomes, with a probability of extubation at D28 of 63.2% (DSC, n=19, 95% CI [confidence interval]: 36.5-81.1) vs 39.50% (PSM, n=38, 39.5% [23.9-54.7], p=0.09) p=0.09, and survival to hospital discharge of 84.2% (58.7-94.6) vs 50% % (33.0-64.5), p=0.015 (**Figure 1**). Multivariable analysis found DSC were protective from death up to Day-90, hazard ratio (HR) 0.24 (0.07 – 0.84, p=0.025), while age was hazardous HR 1.08 (1.03 – 1.12, p≤0.01).
Analysis of inflammatory cytokines levels the DSC-treated patients showed that IL-6 and IL-8 levels were associated with mortality. IL-6 levels were significantly higher consistently in those patients that died (p<0.01); similarly, IL-8 levels were significantly elevated (p=0.04), particularly in the first 4 days in those patients that demised (**Table 2**). However, in the present study, TNFα did not significantly correlate with

outcomes. Given the absence of a comparator group, it is unclear whether this was a function of DSC treatment.

CONCLUSION

This study suggests that placenta-derived DSC therapy is a safe and promising treatment for COVID-ARDS. Further research is needed to confirm these findings.

Baseline Characteristic	**DSC (n=19)**	**PSM (n=38)**	**p-value**
Toronto General	11	21	0.99
Osler Health Sciences	8	17	
Age, mean (range)	54 (25-70)	53 (22-74)	0.77
Sex (M/F)	11/8	23/15	0.99
Tocilizumab, N(%)	15 (79)	29 (76)	0.88
Steroids, N(%)	19 (100)	35 (92)	0.88
No. Comorb (range)	1 (0-3)	1 (0-5)	0.50
0	3 (16)	8 (21)	0.80
1-2	13 (68)	24 (63)	
≥3	3 (16)	6 (16)	
Baseline P/F mean (range)	150.8 (80-220)	146 (69-243)	0.57
SOFA score on Day 0	7.58 (3-12)	7.82 (3-15)	0.91

Table 1: Comparison of selected COVID risk factors between DSC and extracted PSM case-matched controls. DSC, decidual stromal cells; PSM, propensity score matched group.

Cyto-/chemokine	Day 0		Day 2		Day 4		Day 9		P value
	Alive n=15	Dead n=3	Alive n=15	Dead n=3	Alive n=15	Dead n=2	Alive n=10	Dead n=3	
CTAC/CCL27 median (range)	181.86 (77.37-368.25)	244.29 (152.56-402.88)	166.93 (109.18-285.13)	238.48 (147.49-337.86)	198.68 (105.54-440.06)	302.92 (186.31-419.53)	185.06 (112.29-329.80)	425.45** (406.45-455.28)	0.12
IL-2 median (range)	16.19	13.2 (9.25-	21.46 (9.25-	14.32	26.76	10.77	24.80	9.30§ (8.25-	0.80

	(3.89-75.95)	17.38)	40.01)	(7.74-46.24)	(9.59-69.27)	(9.59-11.95)	(7.91-34.83)	14.32)	
IL-1β median (range)	0.78 (0.48-1.53)	0.81 (0.73-0.99)	0.93 (0.60-1.31)	0.79 (0.62-1.21)	0.91 (0.50-1.53)	0.83 (0.72-0.93)	0.93 (0.77-1.23)	1.53 (0.64-2.02)	0.17
IL-6 median (range)	188.33 (10.49-686.59)	626.59* (439.47-764.67)	99.41 (12.63-2597.33)	506.31 (255.04-689.92)	183.30 (14.68-621.59)	258 (110.87-405.83)	95.17 (17.66-401.36)	1615.90 (9.75-3086.50)	0.009
IL-8 median (range)	16.93 (7.55-27.33)	30.14* (26.87-44.39)	12.75 (5.91-138.2)	29.79§ (26.0-31.27)	13.80 (7.95-29.16)	27.74* (26.28-29.19)	16.59 (5.56-47.28)	89.92 (17.17-118.3)	0.04
IL-10 median (range)	4.91 (1.72-9.15)	9.76 (2.96-18.34)	4.98 (2.88-23.94)	3.90 (3.22-7.21)	5.42 (2.44-10.97)	4.63 (3.39-5.87)	4.81 (3.52-11.04)	5.10 (3.94-10.21)	0.16
TNFα median (range)	34.07 (16.04-119.34)	32.07 (22.79-37.30)	36.26 (19.40-58.99)	32.07 (26.55-65.50)	40.64 (19.74-86.75)	34.69 (34.51-34.86)	39.33 (21.09-52.89)	69.86 (24.49-72.78)	0.37
CRP median (range)	67 (4-389)	14 (14-14)	68 (6.7-285)	18 (18-18)	32.7 (4-155)	94.5 (69-120)	77.6 (4-278)	30 (30-30)	0.25

Table 2: Selected proteins measured in blood by multiplex luminex segregated by survival or death. CRP, C reactive protein; TNFα, tumour necrosis factor alpha. §p<0.10, *p<0.05, **p≤0.01 vs Alive. [&] Factorial ANOVA, (dead/alive and days after DSC).

Figure 1: Survival to hospital discharge at day 90 post start of mechanical ventilation. DSC, decidual stromal cells.

REFERENCES

1. Wang W, Lei W, Jiang L, Gao S, Hu S, Zhao ZG, Niu CY, Zhao ZA, (2021) Therapeutic mechanisms of mesenchymal stem cells in acute respiratory distress syndrome reveal potentials for Covid-19 treatment. Journal of translational medicine 19: 198
2. Zanirati G, Provenzi L, Libermann LL, Bizotto SC, Ghilardi IM, Marinowic DR, Shetty AK, Da Costa JC, (2021) Stem cell-based therapy for COVID-19 and ARDS: a systematic review. NPJ Regen Med 6: 73
3. Karlsson H, Erkers T, Nava S, Ruhm S, Westgren M, Ringden O, (2012) Stromal cells from term fetal membrane are highly suppressive in allogeneic settings in vitro. Clinical and experimental immunology 167: 543-555

Optimization and Multicentre External Validation of a Deep Learning Model for Segmentation and Quantification of Traumatic Brain Injury Lesions on Head CT

Submission ID

34

AUTHORS

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INTRODUCTION

Current methods for radiological classification in traumatic brain injury (TBI) such as the Marshall and Rotterdam score provide an incomplete description of intracranial lesion burden, rely on time-consuming manual assessments by experts and are prone to intra- and inter-rater disagreement. To circumvent these limitations, we previously proposed the Brain Lesion Analysis and Segmentation Tool for Computed Tomography (BLAST-CT), a deep learning-based method using convolutional neural networks (CNNs) to perform multiclass, voxel-wise segmentation and quantification of TBI lesions on CT in an automated fashion.[1]

OBJECTIVES

In this study, we expand on our previous work by 1) optimizing the performance of our model using additional training data from CENTER-TBI 2) externally validating the findings reported in our internal development study by applying our algorithm to an independent imaging dataset from the Prophylaxis for Venous Thromboembolism in Severe Traumatic Brain Injury (PROTEST) multicentre randomized controlled trial.

HYPOTHESIS

We hypothesized that retraining our algorithm using additional labeled data from CENTER-TBI would improve lesion segmentation accuracy and minimize the need for manual expert input in future applications. Given that BLAST-CT was developed using a large multicentre imaging dataset derived from multiple

scanner models and which included a wide range of traumatic intracranial injuries, we also hypothesized that it would generalize well when applied to an external TBI imaging dataset.

METHODS

680 scans from CENTER-TBI were annotated by neuroradiological experts and used to retrain the CNN, creating BLAST version 2.0. Traumatic lesions were subdivided into 4 distinct classes: intraparenchymal hemorrhage (IPH), extra-axial hemorrhage (EAH), intraventricular hemorrhage (IVH) and perilesional edema. 51 scans from PROTEST were randomly selected and manually annotated to obtain ground-truth lesion labels on an independent imaging dataset. The same PROTEST scans were then contemporaneously run through version 1.0 and 2.0 of BLAST-CT to evaluate the performance change resulting from the optimization training procedure while calculating segmentation accuracy metrics on an external validation dataset.

RESULTS

The additional training phase implemented for version 2.0 yielded an overall mean Dice similarity coefficient (DSC) improvement of 4% when looking at lesions of any size and class (range 0 to 13% for individual lesion classes). Mean absolute volume errors between automated and ground-truth segmentations also improved for most lesion types (2.94 vs 1.55mL for IPH, 18.44 vs 16.33mL for EAH, 0.74 vs 0.80 for IVH and 1.56 vs 0.27 for perilesional edema using version 1.0 vs 2.0 respectively). Overall, the performance of BLAST-CT on the PROTEST external validation dataset was comparable or better to the results obtained on our internal development sample (median DSC for all lesion classes was 0.60 [IQR 0.0-0.94] on the PROTEST images vs 0.36 [IQR 0.0-63.4] on the CENTER-TBI development dataset). Mean volume differences between the ground-truth and predicted lesion maps were also comparable to the internal sample for most lesion subtypes with the exception of extra-axial hemorrhage, which may be in part explained by the substantially larger mean EAH volume and inclusion of hypo- and isodense hematomas in the PROTEST dataset.

CONCLUSION

We propose one of the first models capable of automated multiclass volumetric lesion segmentation in TBI to be trained and externally validated in a multicentre fashion. After optimizing our model using a large additional training sample from CENTER-TBI, we were able to achieve a level of performance comparable to other state-of-the-art methods. We hope that this step will facilitate its application to large-scale datasets and clinical trials by providing a robust and validated platform for efficient quantitative analysis of neuroimaging in TBI. Ultimately, we hope that integrating such imaging biomarkers with other relevant patient data will improve prognostic models and contribute to phenotyping TBI patients into more therapeutically meaningful categories.

REFERENCES

1. Monteiro M, Newcombe VFJ, Mathieu F, et al. Multiclass semantic segmentation and quantification of traumatic brain injury lesions on head CT using deep learning: an algorithm development and multicentre validation study. Lancet Digit Health 2020;2:e314-e22.

ORAL PRESENTATION 3

The Association Between Daily Driving Pressures and Mortality in Patients Supported with Veno-venous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome.

Submission ID

62

AUTHORS

Eleonora Balzani [1], Abdulrahman Al-Fares [1], Eddy Fan [1], Niall Ferguson [1], Lorenzo Del Sorbo [1], Martin Urner[1].

[1] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto (ON), Canada.

INTRODUCTION

Limiting tidal volumes and plateau pressures are the cornerstone of traditional lung-protective mechanical ventilation strategies for patients with hypoxemic respiratory failure. Treatment with veno-venous extracorporeal membrane oxygenation (VV-ECMO) can further facilitate ultraprotective ventilation strategies in patients with particularly severe forms of respiratory failure, thereby mitigating the risk of ventilator-induced lung injury (VILI) while maintaining the patient's gas exchange (1). In recent work, sustained intervention on driving pressure in addition to limiting tidal volumes and plateau pressures has been demonstrated to lower mortality of mechanically ventilated patients (2) . If changes in driving pressure are associated with differences in mortality of patients that supported with VV-ECMO is currently unclear. A small randomized controlled trial comparing transpulmonary pressure-guided ventilation during the initial 120 hours of VV-ECMO showed that the receipt of transpulmonary pressure-guided ventilation resulted in lower 60-day mortality rates, reduced levels of pro-inflammatory cytokines, and increased levels of anti-inflammatory cytokines, compared to standard ultraprotective ventilation (3). In contrast, the LIFEGARDS study found no association between driving pressure during the first 48 hours and long-term mortality (4).

OBJECTIVES

In the present work, we investigated the association between daily driving pressure levels and mortality in patients with severe ARDS and supported by VV-ECMO.

HYPOTHESIS

We hypothesized that a reduction in either daily driving pressure or esophageal pressure swings was associated with a change in mortality up to 21 days of patients with Acute Respiratory Distress Syndrome (ARDS) that were supported with VV-ECMO in the Medical/Surgical Intensive Care Unit (ICU) at Toronto General Hospital.

METHODS

A descriptive analysis was conducted on a historical cohort of 115 patients diagnosed with severe ARDS and supported by VV-ECMO at the medical-surgical ICU of Toronto General Hospital. Ventilatory settings and demographic variables, including age and sequential organ failure assessment (SOFA) score at admission, and comorbidities were recorded from 24 hours after initiating ECMO support until day 21. The primary outcome was all-cause mortality, and the patients were followed until either death, discharge due to clinical improvement, or treatment for 21 days, whichever occurred first. Clinical variables, like tidal volume, respiratory rate, positive end-expiratory pressure (PEEP), driving pressure (ΔP), plateau pressure, and mechanical power were collected daily. In a pre-specified subgroup of 40 patients, respiratory effort (ΔP_{es}), transpulmonary pressure (ΔP_L), direct measurement of P_L at end-inspiration, direct measurement of P_L at end-expiration (5), and elastance-derived end inspiratory P_L (5) using an esophageal balloon catheter (EBC) were measured. Bayesian Joint Models for longitudinal and time-to-event outcomes were used to measure the association between changes in either daily ΔP or daily esophageal swing and mortality.

RESULTS

A total of 80 (70%) of 115 patients supported with VV-ECMO survived during the follow-up, including 26 (65%) of 40 patients with esophageal balloon catheter (EBC) measurements. In the overall population, the median age (interquartile range, IQR) in survivors was 45 (34 to 52) years and 47 (32 to 57) years in non-survivors. In the subgroup of patients with EBC measurements, the median age (IQR) was 46 (35 to 53) years in survivors and 48 (30 to 57) years in non-survivors. The median baseline SOFA score (IQR) in survivors in the overall population was 11 (9 to 13) and 13 (10 to 15) in non-survivors. In the subgroup of patients with EBC measurements, the median baseline SOFA score was 11 (9 to 13) for survivors and 12 (10 to 15) for non-survivors. Respiratory system compliance at baseline showed a significant difference between survivors and non-survivors in the overall population (p=0.016), but not in the EBC group (p=0.180). In the joint model analyses, estimated mean ΔP (95% credible intervals, 95% CrI) during mechanical ventilation was 12 (11 to 13) cmH_2O. An increase in daily ΔP was not associated with a change in mortality (hazard ratio [HR] 1.07, 95%CrI: 0.93 to 1.20, p=0.397). In the subgroup of patients with EBC measurements (n=40), estimated mean esophageal pressure swing (95% CrI) during mechanical ventilation was -3 (-5 to -2) cmH_2O. Changes in daily esophageal pressure swings were not associated with a change in mortality (HR 1.07, 95%CrI: 0.96 to 1.21, p=0.229).

CONCLUSION

In this single-center, retrospective cohort study including 115 patients with severe ARDS and supported with VV-ECMO, changes in daily driving pressure or esophageal pressure swings were not associated with a difference in mortality up to 21 days. However, daily driving pressures varied within a very narrow range between 11 and 13 cmH_2O, which might have influenced the ability to measure an effect of changes in driving pressure on mortality. Further research is needed to understand better how ventilation strategies during support with VV-ECMO can influence the mortality of patients with severe hypoxemic respiratory failure.

REFERENCES

1 Rozencwajg S, Guihot A, Franchineau G, Lescroat M, Bréchot N, Hékimian G, et al. Ultra-Protective Ventilation Reduces Biotrauma in Patients on Venovenous Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. Crit Care Med. 2019;47(11):1505-12.
2 Urner M, Jüni P, Rojas-Saunero LP, Hansen B, Brochard LJ, Ferguson ND, et al. Limiting Dynamic Driving Pressure in Patients Requiring Mechanical Ventilation. Crit Care Med. 2023.
3 Wang R, Sun B, Li X, Tang X, He H, Li Y, et al. Mechanical Ventilation Strategy Guided by Transpulmonary Pressure in Severe Acute Respiratory Distress Syndrome Treated With Venovenous Extracorporeal Membrane Oxygenation. Crit Care Med. 2020;48(9):1280-8.

4 Schmidt M, Pham T, Arcadipane A, Agerstrand C, Ohshimo S, Pellegrino V, et al. Mechanical Ventilation Management during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. An International Multicenter Prospective Cohort. Am J Respir Crit Care Med. 2019;200(8):1002-12.
5 Grieco DL, Chen L, Brochard L. Transpulmonary pressure: importance and limits. Ann Transl Med. 2017;5(14):285.

ORAL PRESENTATION 4

Sedation-Ventilation Interaction in Acute Hypoxemic Respiratory Failure

Submission ID

20

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INTRODUCTION

Patients with acute hypoxemic respiratory failure (AHRF) often present exagerated respiratory effort and are at risk of ventilator induced lung and diaphragm injury[1]. Ventilation and sedation are used to manage patients with AHRF, but their effects on the determinants of risk for ventilation-associated lung injury and ventilator-induced diaphragm dysfunction have not been systematically described.

OBJECTIVES

To evaluate the individual and interactive effects of ventilator settings, sedation, and extracorporeal life support on respiratory effort and lung-distending pressure in AHRF.

HYPOTHESIS

The primary hypothesis of this analysis is that the influence of mechanical ventilation settings on respiratory effort depends on the level of sedation with propofol and on the concomitant application of extracorporeal CO_2 removal. Secondary hypotheses are: a) increasing PEEP will reduce respiratory effort and lung distending pressure only in patients in which higer PEEP levels result in an improvement in compliance, and b) respiratory effort and lung-distending pressure vary according to patient physiological characteristics, specifically dead space (as reflected by ventilatory ratio) and respiratory system elastance.

METHODS

Secondary analysis of a trial of lung and diaphragm protection in AHRF. Inspiratory pressure, sedation, PEEP, and venovenous extracorporeal membrane oxygenation (VV-ECMO) were systematically manipulated to optimize respiratory effort (absolute value of esophageal pressure swing, |ΔPes|) and lung-distending pressure (dynamic transpulmonary driving pressure, $\Delta P_{L,dyn}$). Associations were evaluated using linear mixed effect regression models including pre-specified terms for potential interactions.

RESULTS

The study included 235 individual measurements of |ΔPes| and $\Delta P_{L,dyn}$ from 30 patients. Propofol attenuated |ΔPes| (–2.5 cm H_2O, 95% CI –3.5, –1.5) and $\Delta P_{L,dyn}$ (–1.5 cm H_2O, 95% CI –2.5, –1). The effect of inspiratory pressure on |ΔPes| varied depending on propofol dose; increasing inspiratory pressure resulted in higher $\Delta P_{L,dyn}$ in patients receiving higher propofol dose. In comparison to patients not on VV-ECMO (n=14), patients on VV-ECMO (n=16) had significantly lower |ΔPes| (–10 cm H_2O, 95% CI –17.5, –2.5) and required less sedation to reduce |ΔPes|. Increasing PEEP reduced respiratory effort and lung distending pressure only in patients in whom higher PEEP resulted in improved lung compliance. Patients with higher respiratory system elastance and ventilatory ratio presented higher respiratory effort and lung distending pressure.

CONCLUSION

Mechanical ventilation settings, sedation, and VV-ECMO exert interdependent effects on respiratory effort and lung-distending pressure in AHRF. The effect of increasing inspiratory support on respiratory effort depends on the propofol dose. Patients receiving VV-ECMO require less sedation to control respiratory effort. Patients with higher respiratory system elastance and ventilatory ratio are more likely to develope higher lung distending pressure.

REFERENCES

1 Dianti, J., Fard, S., Wong, J., Chan, T. C. Y., Sorbo, L. D., Fan, E., Amato, M. B. P., Granton, J., Burry, L., Reid, W. D., Zhang, B., Ratano, D., Keshavjee, S., Slutsky, A. S., Brochard, L. J., Ferguson, N. D., & Goligher, E. C. (2022). Strategies for lung- and diaphragm-protective ventilation in acute hypoxemic respiratory failure: a physiological trial. *Critical Care*, *26*(1), 259. https://doi.org/10.1186/s13054-022-04123-9

Molecular Interaction Between ICAM-1 and LPS in Mediating Inside-out Inflammatory Signaling

Submission ID

57

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INTRODUCTION

Gram-negative bacterial infections are reported to be responsible for about two-thirds of sepsis cases[1]. Lipopolysaccharide (LPS) is a major component of gram-negative bacteria's outer membrane. It is composed of 3 covalently linked regions: outer O-antigen, core oligosaccharide, and inner lipid A anchor and is classically recognized by TLR4[2]. Pulmonary epithelial cells don't express cell surface TLR4; however, they still produce cytokines in response to LPS challenge. Intracellular Adhesion Molecule-1 (ICAM-1), a receptor found on the surface of lung epithelial cells, consists of 5 extracellular immunoglobulin domains (D1-D5), a hydrophobic transmembrane domain, and a short cytoplasmic domain[3]. Past studies using LPS-treated ICAM-1 knockout (KO) mice showed a reduced inflammatory response compared to wild-type (WT) mice, suggesting its potential role in mediating LPS signalling[4].

OBJECTIVES

Objective #1: To determine if the extracellular portion of ICAM- is a direct binding partner with LPS in solution using Isothermal Titration Calorimetry (ITC).
Objective #2: To establish an ICAM-1 Domain 3 knockout cell line in BEAS-2B cells and demonstrate that LPS binds exclusively to Domain 3 of ICAM-1.
Objective #3: To investigate ICAM-1 Internalization In Vivo.

HYPOTHESIS

We hypothesize that ICAM-1 acts as a direct binding partner with LPS, leading to its internalization which triggers an inflammatory response.

METHODS

We used isothermal titration calorimetry (ITC) to measure the binding affinity and thermodynamics between ICAM-1 and full-length or detoxified LPS lacking Lipid A moiety. Next, we used CRISPR/Cas9 to KO IgD3 of ICAM-1 in human lung BEAS-2B cells. The KO was verified using DNA gel electrophoresis and Sanger sequencing. Finally, we performed intratracheal LPS installation in WT, ICAM-1, TLR4, and ICAM-1/TLR4 double KO mice to study their inflammatory response by analyzing lung neutrophil infiltration.

RESULTS

ITC results showed a direct interaction between full-length LPS + ICAM-1 [binding affinity (Kd) of 0.41±0.14 μM]. Detoxified LPS + ICAM-1 showed a similar Kd of 0.43±0.24 μM. The ICAM-1 IgD3 KO cells showed no bands of similar size to BEAS-2B control cells after gel electrophoresis and a 419 base pair deletion encompassing IgD3 following Sanger sequencing. In vivo results will soon be analyzed and ready for presentation.

CONCLUSION

Our results demonstrated that LPS binds ICAM-1 at a location other than its Lipid A moiety. We will thus focus future investigation on other moieties of LPS and 2) our ICAM-1 IgD3 KO cell model to study LPS internalization and resulting cytokine levels between control and KO cells treated with LPS.

REFERENCES

1 Sakr Y, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA, et al. Sepsis in intensive care unit patients: Worldwide data from the intensive care over nations audit. Open Forum Infect Dis 2018;5(12).

2 Simpson BW, Trent MS. Pushing the envelope: LPS modifications and their consequences. Nat Rev Microbiol2019;17(7):403–16.

3 Jun CD, Carman C V., Rediek SD, Shimaoka M, Eriekson HP, Springer TA. Ultrastructure and Function of Dimeric, Soluble Intercellular Adhesion Molecule-1 (ICAM-1). Journal of Biological Chemistry 2001;276(31):29019–27.

4 King PD, Sandberg ET, Selvakumar A, Fang P, Beaudet AL, Dupont B. Novel isoforms of murine intercellular adhesion molecule-1 generated by alternative RNA splicing [Internet]. 1995. Available from: http://www.jimmunol.org/content/154/11/6080

A Non-Invasive and Continuous Method to Calculate Respiratory Muscle Pressure from Airway Pressure and Flow: A Validation Study

Submission ID

45

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INTRODUCTION

In a mechanically ventilated patient with spontaneous breathing effort, the pressure provided by the ventilator is augmented by the respiratory muscle pressure (Pmus). Monitoring both pressures is crucial for providing lung and diaphragm-protective ventilation and limiting the risk of patient self-inflicted injury [1]. The gold standard for monitoring Pmus is the esophageal balloon catheter. However, it is invasive, requiring specific equipment and careful titration for balloon position and volume. Pmus can also be difficult to calculate because of cardiac artifact and spasms and the lack of knowledge of chest wall compliance [2]. Until now, there has been no continuous and non-invasive technique to obtain a quantitative value of Pmus at the bedside.

OBJECTIVES

Our main objective was to validate the calculated respiratory muscle pressure (cPmus) provided by the CVENT software against the Pmus obtained through a reference method. The first step reported here involves a preclinical validation of the cPmus by comparing it to the Pmus set in a breathing simulator. The next step will be validation in patients using esophageal manometry.

HYPOTHESIS

The CVENT (which denotes Computational VENTilation) is a software designed and developed by Dr. Lu Chen, which learns a patient's breathing pattern from several consecutive breaths (e.g., 20 breaths) and then predicts Pmus continuously based on the changes in airway pressure and flow. In this study, we hypothesized that CVENT can accurately estimate Pmus from airway pressure and flow waveforms without applying any intervention or interruption to the patient.

METHODS

We used the ASL 5000 breathing simulator (IngMar Medical) to simulate Pmus, simulating different breathing patterns and lung mechanics, and connected to a Drager EVITA XL ventilator. We simulated three scenarios: a subject with "normal" lungs (Crs 60 ml/cmH_2O; Raw 6 cmH_2O/L/s), an Acute Respiratory Distress syndrome (ARDS) patient (Crs 30 ml/cmH_2O; Raw 8 cmH_2O/L/s) and a Chronic Obstructive Pulmonary Disease (COPD) patient (Crs 60 ml/cmH_2O, Raw 20 cmH_2O/L/s) ventilated in pressure support mode. To ensure a high variability of the waveform, each parameter set in the ASL simulator was repeated 1000 times during each simulation, following a randomized Gaussian distribution mathematical model. We defined the ranges as follows: Respiratory Rate (RR) 11-25 bpm for normal patients, 15-25 bpm for ARDS and COPD patients; Inspiratory effort (Pmus) 1-20 cmH2O for normal patients, 1-30 cmH2O for ARDS and COPD patients. The Paw and Flow waveforms of roughly 1000 breaths were recorded using the ASL 5000 software and analyzed with CVENT software to obtain cPmus.
To assess the accuracy of cPmus waveform we calculated the root mean square error (RMSE) and the normalized root mean square error (NRMSE) point by point, taking both magnitude and timing synchrony of waveforms into account. As a rule of thumb, an NRMSE < 10% indicates excellent prediction, 10% < NRMSE < 20% suggests good prediction, and 20% < NRMSE < 30% means fair prediction. Additionally, we evaluated correlation, bias, and agreement for the swings (i.e., delta) of Pmus and cPmus using linear regression and Bland-Altman analysis.

RESULTS

In all simulations we compared Pmus and cPmus as illustrated by figure 1.
RMSE showed for Normal patient 0.34 cmH_2O; for ARDS 0.33 cmH_2O and for COPD 0.41 cmH_2O.
NRMSE showed for Normal patient 1.7%; for ARDS 1.3% and for COPD 1.6%.
The linear regression analysis had an adjusted R-square for Normal 0.995 – ARDS 0.999 – COPD 0.999.
The Bland-Altman plots give values for bias: Normal 0.075, ARDS 0.279 and COPD 0.246; and for precision (2SD), expressed as Level of agreement (LoA_{lower} — LoA_{upper}), of Normal -0.070 — -0.57; ARDS -0.127 — 0.686 and COPD -0.161 — 0.653 (Figure 2).

Figure 1. Waveforms of flow, pressure, Pmus and cPmus in five breaths of a normal simulated patient

Figure 2. Bland-Altman plot between Pmus and cPmus swing in simulated normal patient (A), ARDS simulated patient (B) and COPD simulated patient (C).

CONCLUSION

Our bench simulation preclinical analysis demonstrates excellent agreement between the Pmus set by ASL (the reference) and the cPmus calculated by the CVENT software using the pressure and flow. The next step will involve a clinical validation of cPmus against directly measured Pmus using an esophageal manometry in a cohort of patients.

REFERENCES

1. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit Care Med. 2017 Feb 15;195(4):438–42.
2. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, et al. The PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine), Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. Intensive Care Med. 2016 Sep;42(9):1360–73.

ORAL PRESENTATION 7

Influence of the Magnitude and Synchrony of Breathing Efforts on Lung Stress-Strain and Alveolar Pressure is Modified by the Mode of Ventilation During Early Acute Hypoxemic Respiratory Failure

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59

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INTRODUCTION

Consequences of breathing effort depend on stress, strain, and absolute alveolar pressure (PAlv). How the magnitude and synchrony of effort during mechanical ventilation (MV) influences these factors during acute hypoxemic respiratory failure (AHRF) while on different modes of MV remains unknown.

OBJECTIVES

Describe the influence of the magnitude and synchrony of breathing effort on lung stress-strain and PAlv in AHRF according to the mode of MV.

HYPOTHESIS

The stronger the magnitude of breathing effort the higher the influence on lung stress-strain and PAlv in patients with AHRF with the effect being modified based on timing of effort (*i.e.,* synchrony). These relationships differ significantly according to the mode of MV the patients are on.

METHODS

The BEARDS study (NCT03447288) aimed at describing prevalence, determinants, and consequences of breathing effort in AHRF. Patients with moderate to severe AHRF were included and had respiratory recordings including esophageal pressure for up to 7 days. For this analysis, patients were selected if they contained recordings with passive and active breaths.

Effort was quantified with muscular pressure (Pmus)[1]; subtraction of resistive pressure from airway and transpulmonary pressures (based on the equation of motion) allowed calculation of alveolar and trans-alveolar pressures (Palv and PTAlv) and a stress surrogate (driving PTAlv [DPTAlv]). Tidal volume increase [VT] was a strain surrogate. To assess synchrony breathing efforts were classified into, patient-triggering (PatT), reverse-triggering (RevT), with and without breath-stacking (BS). RevT events without BS were further classified into early, mid, and late based on timing of the start and peak of effort relative to insufflation-exhalation.

Impact of Pmus according to synchrony (i.e., type of breath) was estimated based on the difference between all variables during breaths with effort vs passive breaths within each recording.

Linear mixed-effects models were used for the association between Pmus and changes in DPTAlv, VT, and Palv. Interaction terms were introduced for the differential effects of Pmus according to synchrony and mode of ventilation.

RESULTS

60 patients (451 recordings; 300,443 breaths; 158,599 efforts) were included, 20 (33%) female, mean(SD) age 62(14) years, and hospital mortality of 40%.

Figure1A displays Pmus according to synchrony; Figure1B, the influence of Pmus on the occurrence of PAlv below PEEP; Figure1C, impact on a lung stress surrogate; and Figure1D, impact on a lung strain surrogate, all according to synchrony.

Figure 2A displays Pmus according to the mode of ventilation; Figure2B relationship between PAlv and Pmus according to type of breath and mode of ventilation; Figure2C influence of Pmus on stress; Figure2D impact on strain according to the mode of ventilation and presence of breath-stacking.

Figure 1

Figure legend

1A Median[IQR] Pmus measured for each type of breath ($p<0.001$ for all comparisons). **1B** Relationship between the difference PAlv-PEEP and Pmus according to the type of breath. Only breaths without BS were included. A horizontal red dashed line intercepts the y-axis at zero cmH_2O. Significant overall inverse linear relationship between Pmus and the difference PAlv-PEEP ($p<0.001$). This relationship was significantly modified by synchrony ($p<0.001$ for the interaction between Pmus and type of breath). During late RevT, PAlv remained above PEEP; **1C** Difference in DPTAlv between active and median value for passive breaths with the same recording [surrogate of "excess stress" generated by effort] as a function of Pmus according to the type of breath. Only breaths without BS were included. Significant overall linear increase in "excess stress" with higher Pmus ($p<0.001$). This relationship was significantly modified by synchrony ($p<0.001$ for the interaction between Pmus and type of breath). **1D** Difference in VTI/IBW between active and median value for passive breaths with the same recording [surrogate of "excess strain" generated by effort] as a function of Pmus according to the type of breath. Significant overall linear increase in "excess strain" with higher Pmus ($p<0.001$). This relationship was significantly modified by synchrony ($p<0.001$ for the interaction between Pmus and type of breath).

List of abbrevations: IQR interquartile range; Pmus maximum deflection in muscular pressure for each breath; VCV volume-control, PCV pressure-control, PSV pressure-support, PAV+ proportional-assist ventilation with adjustable gain factors; CPAP continuous positive airway pressure; PAlv alveolar pressure; PEEP positive

end-expiratory pressure; PatT patient-trigger; RevT reverse-trigger; early RevT effort's start and peak occur during insufflation; mid RevT effort starts during insufflation and peaks during exhalation; late effort's start and peak occur during exhalation; BS breath-stacking; DPTAlv driving trans-alveolar pressure; VTI/IBW ratio of tidal volume over ideal body weight.

Figure 2

2A Median[IQR] Pmus measured at each mode of ventilation (comparisons: $p<0.001$ for all vs VCV; $p<0.001$ for PCV vs PAV+; $p=0.03$ for PSV vs PAV+; $p=0.27$ for PSV vs PCV; $p=0.39$ for CPAP vs VCV; $p>0.80$ for CPAP vs other modes probably due to low number of events and only one recording included on CPAP) **2B** Relationship between the difference PAlv-PEEP and Pmus according to the type of breath and mode. Only breaths without BS were included. Significant inverse linear relationship between Pmus and the difference PAlv-PEEP for all types of breaths ($p<0.001$); interaction term for Pmus and mode was significant for PatT, and mid RevT ($p<0.001$ for both). The difference PAlv-PEEP was more negative during VCV vs other modes at any given level of Pmus except during late RevT. **2C** Change in stress (DPTAlv) with increasing Pmus according to the mode of ventilation. Only breaths without BS were included. Each line represents a linear regression for each recording. Blue lines are those where DPTAlv significantly increased with Pmus ($p <0.05$ for the regression and a slope of the regression > $0.1 cmH_2O/cmH_2O$ change in Pmus). Horizontal red dotted line is placed at a DPTAlv > 12 cmH_2O (putative threshold for excessive stress) **2D** VT/IBW as a function of Pmus according to the mode and the presence of BS. Each line represents a linear regression for each recording. In red are recordings with more > 10 BS events (median[IQR]56[20-119]). Grey rectangles represent a usual target range for safe tidal volume in AHRF (6-8ml/kg). VT/IBW linearly increased with higher Pmus ($p<0.001$) and this relationship was significantly modified by the mode ($p<0.001$ for the interaction) and presence of BS ($p<0.001$ for the interaction).
List of abbrevations: IQR interquartile range; Pmus maximum deflection in muscular pressure for each breath; VCV volume-control, PCV pressure-control, PSV pressure-support, PAV+ proportional-assist ventilation with adjustable gain factors; CPAP continuous positive airway pressure; PAlv alveolar pressure; PEEP positive end-expiratory pressure; PatT patient-trigger; RevT reverse-trigger; early RevT effort's start and peak occur during insufflation; mid RevT effort starts during insufflation and peaks during exhalation; late effort's start and peak occur during exhalation; BS breath-stacking; DPTAlv driving trans-alveolar pressure.

CONCLUSION

Stronger breathing efforts are associated with potentially excessive stress, strain, and reduced (potentially negative) PAlv. There is a differential effect of the magnitude of effort on these variables based on the synchrony and mode of ventilation.
Stress and strain increase with Pmus in all pressure-regulated modes and often exceeds potentially safe thresholds. In volume-control, stress and strain often remain within set limits independently of Pmus. With excessive Pmus and breath-stacking, volume-control behaves similarly to pressure-control but results in a lower PAlv

REFERENCES

1 Telias I, Madorno M, Pham T, Piraino T, Coudroy R, Sklar MC, Kondili E, Spadaro S, Becher T, Chen CW, Mauri T, Piquilloud L, Brochard LJ. Magnitude of Synchronous and Dyssynchronous Inspiratory Effort During Mechanical Ventilation: A Novel Method.(2023). *Am J Respir Crit Care Med.* 2023 May 1;207(9):1239-1243

Characteristics and Timing of Detection of Brain Abnormalities on Cranial Ultrasound in Pediatric Extracorporeal Cardiopulmonary Resuscitation

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56

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INTRODUCTION

Extracorporeal cardiopulmonary resuscitation (ECPR) had been used in the last two decades as an alternative to support conventional cardiopulmonary resuscitation (CPR) in pediatric patients with refractory cardiac arrest. Severe neurological injury is a frequent cause of death or withdrawal of life-sustaining therapy among children who undergo ECPR. Infants are the most common age group to receive ECPR in pediatrics population. Different imagining techniques had been used to diagnoses and follow up the neurological lesions of patients during the ECMO support and immediately after the decannulation, most common is the use of cranial ultrasound in newborn and infants. The timing and features of brain injury have not been well characterized in this population. Understanding the type of injury and their evolution may help tailor the: management, needs of neuromonitoring, the timing of interventions that may alter the risk of secondary injury (e.g., clamp and weaning trials, rewarming) and the timing of neuro-prognostication.

OBJECTIVES

To characterize the type and timing of neurological abnormalities visible on Cranial Ultrasound (US) in a cohort of infant undergoing to ECPR.

HYPOTHESIS

We hypothesized that the frequency of hemorrhagic abnormalities would be higher than ischemic ones.

METHODS

Retrospective observational study that includes the in-hospital events of ECPR in the Hospital of the Sick Children of Toronto (January 2015 and December 2020). The inclusion criteria were age under 2 years old, In-hospital events of ECPR, 1 participant could present more than 1 event of ECPR, daily US starting on day-1 after ECMO cannulation. All the US reports were anonymized and classified independently by two blinded coders, using a standardized system.

RESULTS

92 ECPR events were reviewed, and 23 participants met inclusion criteria. Participants had between 1 up to a maximum of 24 US. A total of 126 cranial US were reviewed: a total of 164 abnormalities were found and only 2 participants were found without any abnormalities. In this study the most prevalent findings were hypoxic ischemic-type abnormalities (47 %) where the more common were abnormal gray-white matter differentiation (51%). A total of 35 hemorrhages were described, intraparenchymal hemorrhages type (66%) were the most frequent. A total of 7 participants (30 %) presented simultaneously hemorrhages and hypoxic ischemic lesions. Most of the abnormal findings were observed for the first time in the period between the first and sixth US. Most of the hemorrhagic lessons were diagnosed in the first US and the ischemic lesson in the second US. Increase of the extra-axial CSF space was described in 34 studies and abnormal ventricles in 31 studies.The In-hospital survival was 22%. All the survivors had a favourable neurological outcome (Pediatric Cerebral Performance Category 1-3).

CONCLUSION

Among infants who undergo ECPR, there was high rate of brain abnormalities detected on cranial ultrasound. Most of the findings were related to hypoxic ischemic lesions. This is different than previous neonatal ECMO studies where the high prevalence of hemorrhagic lesions. We speculate that these findings may be associated with the ischemia re-perfusion from cardiac arrest and E-CPR and early factors on initiation of ECMO that may contribute to cerebral ischemia. The increase in extra-axial cerebral spinal fluid space deserves more study given the brain volume loss reported by some following ECMO in MRI studies. Further study of the characteristics and time-course post-ECPR brain injury may inform clinical strategies to improve neurological outcomes.

REFERENCES

1. Wien MA, Whitehead MT, Bulas D, Ridore M, Melbourne L, Oldenburg G, Short BL, Massaro AN. Patterns of Brain Injury in Newborns Treated with Extracorporeal Membrane Oxygenation. American Journal of Neuroradiology 2017;38:820-6. 10.3174/ajnr.a5092 https://dx.doi.org/10.3174/ajnr.a5092.
2. Van Heijst AF, de Mol AC, Ijsselstijn H. ECMO in neonates: neuroimaging findings and outcome. Semin Perinatol 2014;38:104-13. 10.1053/j.semperi.2013.11.008.
3. Taylor G, Fitz C, Kapur S, Short B. Cerebrovascular accidents in neonates treated with extracorporeal membrane oxygenation: sonographic-pathologic correlation. American Journal of Roentgenology 1989;153:355-61. 10.2214/ajr.153.2.355 https://dx.doi.org/10.2214/ajr.153.2.355
4. Garcia G., Zorzelaa, L., Robertsona, C., Altona, G., Joff, R., Khodayari, E., Dinub, I., Rossa, D., Rebeykaa, I., Lequiera, L., for the Western Canadian Complex Pediatric Therapies Follow-up Group. Survival and neurocognitive outcomes in pediatric extracorporeal-cardiopulmonary resuscitation. Resuscitation 96 (2015) 208–213 http://dx.doi.org/10.1016/j.resuscitation.2015.07.034
5. Tian, F. PhD1; Farhat, A.; Morriss, C.; Tweed, J.; Li, X.; Huet, B.; Thiagarajan, R. Raman, L. Cerebral Hemodynamic Profile in Ischemic and Hemorrhagic Brain Injury Acquired During Pediatric Extracorporeal Membrane Oxygenation. Pediatr Crit Care Med. 2020 Oct;21(10):879-885. doi: 10.1097/PCC.0000000000002438

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