August 15, 2017

CTS INSPIRATIONS

CTS NEWS

President's Letter

We are very excited to announce the annual **California Thoracic Society Southern California Fall Conference** that will offer two simultaneous meetings at the beautiful **UCSD MET** center in La Jolla CA:

The **CTS Multidisciplinary COPD Advanced Skills Training Symposium** will be held on **Saturday September 30** and will offer the latest in the science and application of advanced COPD diagnosis and management, and hands on skills training for all pulmonary clinicians. The CME / CEU course will provide both expert lecture and hands on small group skills training on key clinical diagnostic and management skills. CTS is grateful to again be working with the CSRC to promote this event.
Event Registration link: https://calthoracic.org/events/fall-symposium-educational-conference/

The **2-day Ultrasound skills course on Saturday September 30** and **Sunday October 1** targets both novice and veteran ultrasound users seeking a refresher course to improve the practice of ultrasound in managing patients with critical illness in ICU and in pulmonary outpatient setting. The course includes both didactic lectures and hands-on sessions on live models and ultrasound simulators. **Please note** in order to provide a rich and enhanced 1:1 hands-on experience with live models and faculty, course enrollment is **limited to the first 20-25 registered attendees**.

More information on both courses and registration can be found at:
https://calthoracic.org/events/fall-symposium-educational-conference/

Our sincere thanks to Philippe Montgrain, Shazia Jamil, Dan Sweeney, Trina Limberg, Ni-Cheng Liang, Bill Stringer, the members of CTS planning, multidisciplinary and education committees, and our outstanding administrative leads Phil Porte, Vickie Parshall, Dave Eubanks and Karen Lui. **We hope to see you there!**

CTS Inspirations Newsletter offers opportunities and important updates geared toward the spectrum of CTS members. This edition features two outstanding abstracts presented at the CTS Carmel meeting earlier this year that highlight both rising stars and established experts in pulmonary and critical care medicine. Our thanks to Laren Tan and his team for overseeing and coordinating the world class fellows and multidisciplinary scientific poster competition that supports scholarly presentations of important research and case reports in a collegial setting at the CTS Carmel meeting at Quail Lodge. We are also excited to introduce our new team members to the CTS scientific poster planning committee, Walter Klein, MD from Riverside University Medical Center and Nicholas (Nikko) Arger, MD from UCSF. Stay tuned for details about the January 2018 competition.

Our newsletter also offers opportunities for CTS members from every role of the clinical and research team to submit cutting edge 'need to know' updates on important pulmonary, critical care and sleep topics. For questions, please contact Angela Wang a1wang@icloud.com or Chris Garvey chris.garvey@ucsf.edu

Coming soon…. CTS will be offering a new institutional membership that provides greater levels of benefit to smaller medical groups and practices in the next few weeks. Stay tuned.

Thanks to our sister societies for your partnership and collaboration including the California Society for Respiratory Care, the American Lung Association of California, the National Association of Medical Directors of Respiratory Care, and California Society for Pulmonary Rehabilitation, and thanks to Rick Robbins for generously sharing the outstanding Southwest Journal of Pulmonary and Critical Care. We thank all of our colleagues and sister societies for your collaboration and improving pulmonary care in CA and beyond.

CTS Scholars 2017

TITLE: PROTECTIVE EFFECTS OF POSITIVE END-EXPIRATORY PRESSURE IN SHORT-TERM POSITIVE-PRESSURE VENTILATION IN A MOUSE MODEL OF VENTILATOR-INDUCED ACUTE LUNG INJURY

Authors: Cagle LA, Franzi LM, Linderholm AL, Last, JA, Kenyon NJ


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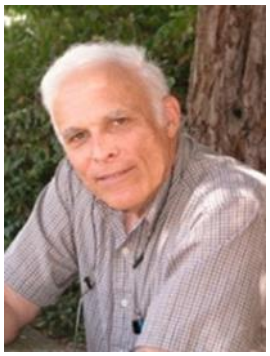

Jerold Last


Nicholas Kenyon

Main Points

- Ventilator-induced lung injury can occur as early as 2 hours after initiation of ventilation
- Disruption of the endothelium and resultant influx of albumin into the alveolar space occurs initially, followed by evidence of an inflammatory response (influx of neutrophils into the airways and increased proinflammatory cytokines) at 4 hours after initiation of ventilation
- Positive end-expiratory pressure (PEEP) and recruitment maneuvers (RM) are protective against worsening VILI in short- and long-term ventilation

Research Presentation

Protective ventilation was established due to the high mortality rate in acute respiratory distress syndrome (ARDS); however, positive-pressure ventilation can worsen lung injury and cause ventilator-induced lung injury (VILI). VILI results from overdistension of the lung parenchyma leading to volutrauma and/or repetitive collapse of alveoli leading to atelectrauma. Reduction in tidal volume ventilation and implementation of positive end-expiratory pressure resulted in dramatic improvements in mortality rates in ARDS. Controversy exists over the use of recruitment maneuvers due to concern for cardiovascular comprise and questionable benefit. Using pulmonary compliance as an output, we hypothesized that recruitment maneuvers would be beneficial in protective ventilation and sought to identify the time point that acute lung injury occurs with short-term ventilation.

Methods

BALB/c mice, 16–24 g, 5–12 week old females were sedated with dexmedetomidine, tiletamine-zolazepam, and buprenorphine for 2 or 4 hours of positive-pressure ventilation. Mice (n=5 per group) were assigned to low tidal volume (LTV, 8 ml/kg) or high tidal volume (HTV, 15 ml/kg) groups with either 0 or 4cmH_20 PEEP and recruitment maneuvers (20 cmH_20 PEEP for 10 seconds every 20 minutes). Dynamic compliance and resistance were measured with a plethysmograph. Mice were humanely euthanized with an overdose of pentobarbital. Whole lung lavage was performed for total and differential cells counts, total protein, albumin, and cytokine measurements. Lungs were fixed for histopathologic assessment using a standardized histology injury score.

Results

Absolute neutrophil counts were significantly increased in the HTV group at 4 hours, but not at 2 hours (15,667 cells, 1938 cells). Bronchoalveolar lavage albumin was significantly increased in the HTV groups at 2 and 4 hours compared to the air control (314 µg/ml, 153 µg/ml, 5.5 µg/ml). Histological evidence of tissue injury was apparent at 4 hours of HTV and zero PEEP (0.4645), but not at 2 hours (0.1843). Compliance was significantly decreased and resistance was significantly increased in both HTV groups compared to the LTV groups. TNF-a, MIP-2, KC, and IL-6 were significantly increased in the HTV group at 4 hours of ventilation, but not at 2 hours. Compliance was significantly increased with the addition of recruitment maneuvers in the LTV group (0.0463, 0.0116 ml/cmH_20).

Discussion

Signs of ventilator-induced lung injury are evident in our model soon after the introduction of high tidal volume ventilation, even as early as 2 hours. Lung injury worsens with longer-term ventilation (4 hours) as demonstrated by tissue histology, alteration of the alveolar-capillary barrier, and an inflammatory response with an influx of neutrophils into the lung accompanied by an increase in proinflammatory cytokines. We evaluated the impact of PEEP and recruitment maneuvers on this lung injury model. Recruitment maneuvers are used to reopen unstable airless alveoli through a transient increase in transpulmonary pressure with the intent to improve gas exchange and prevent atelectrauma.[1] Recruitment maneuvers in the use of lung protective ventilation are controversial due to a lack of standardization as well as contradictory results regarding clinical benefits and the risk of hemodynamic compromise.[1-8] Application of PEEP and RM are protective against worsening VILI across all time points, suggesting that early application of lung protective ventilation strategies may be critical for preventing VILI. We have developed a single-hit ventilator-induced acute lung injury model that recapitulates the histologic and inflammatory marker findings of acute lung injury in humans and offers a novel tool in the study of acute lung injury. Both recruitment maneuvers and PEEP are important interventions that can have protective effects against VILI during periods of short term ventilation.

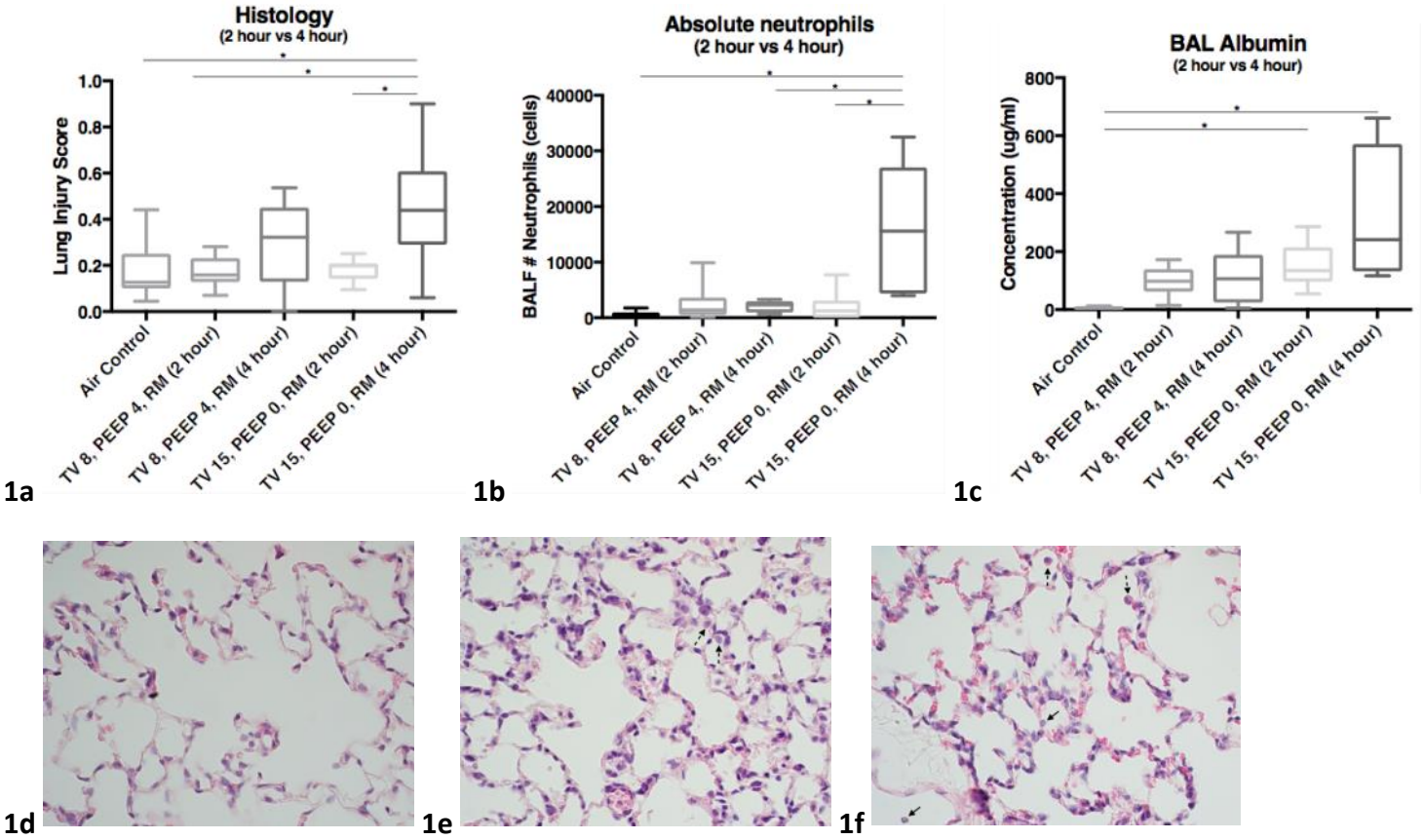


Figure 1: Positive-pressure ventilation (2-hour vs 4-hour) 1a Standardized histology scores were significantly higher in the HTV group at 4 hours compared to the air control, LTV group at 2 hours, and HTV group at 2 hours (p=0.0002) **1b** Absolute neutrophils were significantly elevated in the injurious ventilation group (TV 15, PEEP 0, RM) at 4 hours, but not at 2 hours of positive-pressure ventilation (p = 0.0046) and were significantly elevated in the injurious ventilation group compared to the non-injurious ventilation group (p=0.0079) **1c** Bronchoalveolar lavage albumin was significantly increased in the HTV groups at 2 and 4 hours compared to the air control (p=0.0046) **1d** Lung histology image stained with H&E of air control **1e** Lung histology images stained with H&E of injurious ventilation (TV 15, PEEP 0, RM (2 hour)) **1f** Lung histology image stained with H&E of injurious ventilation (TV 15, PEEP 0, RM (4 hour)). Data in boxplots is presented in median ± minimum and maximum values. *Neutrophils are denoted with an arrow, macrophages with a dotted line arrow, and proteinaceous debris with a curved line arrow*

References

1. Fan E, Wilcox ME, Brower RG, Stewart TE, et al. Recruitment maneuvers for acute lung injury – a systematic review. Am J Respir Crit Care Med. 2008 Dec 1;178(11):1156-63. PMID: 18776154.
2. Badet M, Bayle F, Richard JC, Guerin C. Comparison of optimal end-expiratory pressure and recruitment maneuvers during lung-protective mechanical ventilation in patients with acute lung injury / acute respiratory distress syndrome. Respiratory Care. 2009 Jul;54(7):847-54. PMID: 19558735.
3. Pelosi P, Goldner M, McKibben A, Adams A, et al. Recruitment and derecruitment during acute respiratory failure: an experimental study. Am J Respir Crit Care Med. 2001 Jul 1;164(1):122-30. PMID 11435250.
4. Crotti S, Mascheroni D, Caironi P, Pelosi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. Am J Respir Crit Care Med. 2001 Jul 1;164(1):131-40. PMID 11435251.

5. Lim SC, Adams AB, Simonson DA, Dries DJ, et al. Transient hemodynamic effects of recruitment maneuvers in three experimental models of acute lung injury. Crit Care Med. 2004 Dec;32 (12):2378-84. PMID 15599139.

6. Nielsen J, Nilsson M, Freden F, Hultman J, et al. Central hemodynamics during lung recruitment maneuvers at hypovolemia, normovolemia, and hypervolemia. A study by echocardiography and continuous pulmonary artery flow measurements in lung-injured pigs. Intensive Care Med. 2006 Apr;32(4):585-94. PMID: 16520996.

7. Odenstedt H, Aneman A, Karason S, Stenqvist O, et al. Acute hemodynamic changes during lung recruitment in lavage and endotoxin-induced ALI. Intensive Care Med. 2005 Jan;31(1):112-20. PMID: 15605230.

8. Borges 2006 JB, Okamoto VN, Matos GF, Caramez MP, et al. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. Am J Respir Crit Care Med 2006 Aug 1;174(3):268-278. PMID: 16690982.

Title: Mistaken Identity: Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) and CVID Initially Diagnosed as Sarcoidosis

Authors: Nicholas Arger, MD; Jenna Nguyen, MD; Katherine Gundling, MD; Kirk Jones, MD; and Laura Koth, MD

Nicholas Arger, MD

Laura Koth, MD

High Yield Points:

- Patients with common variable immune deficiency (CVID) are at risk for developing systemic granulomatous disease, which often affects the lungs, irrespective of their treatment status with intravenous immunoglobulin (IVIg) therapy.
- Granulomatous and lymphocytic interstitial lung disease (GLILD) in the setting of CVID has several radiographic patterns, but can present with nodules and lymphadenopathy, making it difficult to distinguish from sarcoidosis. Biopsy of lymph nodes or lung parenchyma typically shows non-caseating granulomas, which are also difficult to distinguish from sarcoidosis.
- Patients diagnosed with sarcoidosis who have prior histories of recurrent or atypial infections should be screened for CVID with serum IgG, IgM, and IgA levels along with workup for other causes of immunodeficiency, e.g. HIV. This is especially important prior to starting chronic immunosuppression.

- Patients with complicated sarcoidosis and GLILD should be referred to centers that can offer a multidisciplinary approach that includes pulmonologists, immunologists, radiologists, and pathologists given the complex nature of these diseases.

Case Presentation:

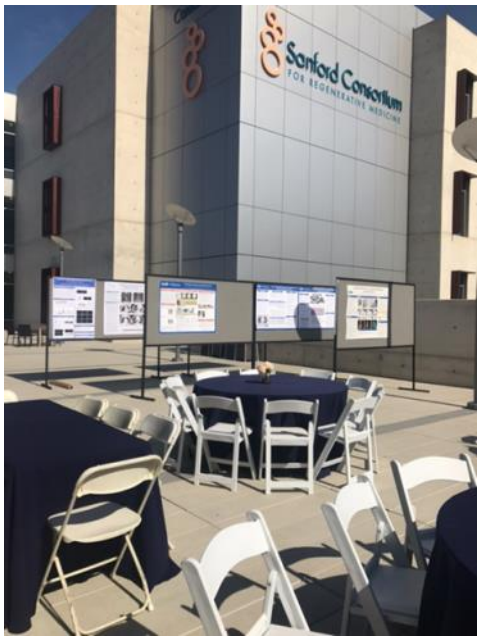
A 27 year-old man was referred to our UCSF Sarcoidosis Clinic for further evaluation for his ILD. He was otherwise healthy until two years prior when he developed subacute onset of productive cough, shortness of breath, and wheezing. His chest CT at the time showed hilar adenopathy for which he underwent mediastinoscopy, which was interpreted as “non-caseating granulomas.” He was thus started on 40 mg oral prednisone for sarcoidosis; mycophenolate mofetil was later added for potential cardiac sarcoidosis. Subsequently, he developed disseminated varicella zoster and respiratory failure characterized by diffuse parenchymal ground glass opacities and consolidations requiring intubation and several months of recovery. After another clinical flare where CT findings again showed diffuse ground glass opacities and consolidations, he was referred to our UCSF Sarcoidosis Clinic. Review of his prior mediastinal lymph node biopsy showed a histiocyte-rich inflammatory process with less-defined granulomas as would be expected in sarcoidosis, and raising concern for immunodeficiency syndromes. These findings along with his atypical radiographic pattern prompted workup for immune deficiency and GLILD. All of his immunoglobulin classes and vaccine-specific antibodies were either significantly low or undetectable, as were his absolute natural killer cells and T lymphocytes (total CD3+, CD4+, and CD8+). He was thus diagnosed with CVID and started on IVIg while weaning prednisone and initiating azathioprine for his GLILD. He eventually showed improvement of his radiographic findings and stability in his symptoms and lung function.

Discussion:

This case demonstrates the complexities with the diagnosis and treatment of patients with CVID and GLILD**.** The characteristic immunoglobulin deficiencies in CVID have been linked with B cell maturation defects; however, T cell abnormalities also occur. The associated granulomatous disease resembles sarcoidosis and affects 10-20% of CVID patients, with approximately 50% of these patients having lung disease (GLILD). While the radiographic and pathologic features of GLILD and sarcoidosis are similar, GLILD is typically NOT associated with upper lobe predominance and more poorly formed granulomas on biopsy. This case is unusual in that our patient’s diagnosis of CVID was made two years after his initial workup and aggressive immunosuppressive treatment. It demonstrates that when making the diagnosis of sarcoidosis, clinicians must consider other forms of granulomatous lung disease, especially in the setting of inconsistent radiographic or histologic patterns. CVID should always be considered in this context, especially prior to starting immunosuppression, given the potential for severe complications, as occurred in this case. Although IVIg therapy is used to prevent infections in CVID, it does not affect the course of GLILD. Complete remissions in GLILD are infrequently achieved with prednisone, methotrexate, or cyclophosphamide and other therapies such as azathioprine, rituximab, and Cellcept have had varying success. Despite treatment, CVID patients with GLILD have a poorer prognosis due to their often-progressive respiratory failure. Given these complicated diagnostic and management aspects of the disease, our case also demonstrates the importance of a multidisciplinary approach to the care of these patients given their pulmonary and immunologic challenges.

Science Comes at you Fast: The Current "Future" of Rare Disease Research

Researchers, clinicians and family advocates came together on July 6-7 to discuss cutting edge clinical knowledge and basic research at the "Rare Pediatric Respiratory Disease (RPRD): Science Shapes Precision Care" conference at the Sanford Consortium for Regenerative Medicine in La Jolla. It was a unique conference that united experts in different fields to share their knowledge for a more integrative approach to investigating rare lung diseases. Sponsors were UCSD Pediatrics, Rady Children's Hospital, Connect the Docs, and the Systemic Juvenile Inflammatory Arthritis, Primary Ciliary Dyskinesia, and Childhood Interstitial Lung Disease Foundations. Topics discussed included genomics, epigenomics, technical advances such as single cell sequencing and lung "organoids," advanced imaging techniques (yes, MRI for the lungs is coming soon), in vivo and in vitro models and regenerative medicine approaches using patient-specific induced pluripotent stem cells.



There were three family speakers, including a very articulate and compelling 10 year old! Check him out at: https://www.lungmap.net/news-and-events/view/21 Audio of the talks, as well as slide sets for most of them, are available at: https://www.lungmap.net/resources/themes/viewstory/17. 77 attendees from as far away as Sweden and Vietnam participated (including 43 from California), and 17 presented abstracts. There was a great deal of time for networking; several groups came away with new or refined research agendas *and potential collaborations*. The tone was optimistic. Attendees were encouraged to advocate for continued support of research. With focus and collaboration, we hope many "RPRD"s can be RePaiReD--soon!

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Title (Click on title to be taken to the manuscript, **CME in Bold**)	**Section**	**First Author**	**Year**	**Vol**	**Issue**	**Pages**	**Date Posted**
Telemedicine Using Stationary Hard-Wire Audiovisual Equipment or Robotic Systems in Critical Care: A Brief Review	Critical Care Journal	Nikhanj N	2017	15	1	50-3	7/27/17
Medical Image of the Week: Coral Reef Aorta	Imaging	Eberson L	2017	15	1	49	7/26/17
Medical Image of the Week: Hematopneumatoceles from Pulmonary Lacerations	Imaging	Chaddha U	2017	15	1	46-8	7/19/17
Senate Health Bill Lacks 50 Votes Needed to Proceed	News	Moore NS	2017	15	1	45	7/18/17
Medi-Cal Blamed for Poor Care in Lawsuit	News	Robbins RA	2017	15	1	42-4	7/14/17
Senate Republican Leadership Releases Revised ACA Repeal and Replace Bill	News	Moore NS	2017	15	1	41	7/13/17
Medical Image of the Week: Idiopathic Subglottic Stenosis	Imaging	Van Hook CJ	2017	15	1	39-40	7/12/17
Carotid Cavernous Fistula: A Case Study and Review	Critical Care	Ganapathiraju I	2017	15	1	32-8	7/11/17
Tip of the Iceberg: 18F-FDG PET/CT Diagnoses Extensively Disseminated Coccidioidomycosis with Cutaneous Lesions	Pulmonary	Nia BB	2017	15	1	28-31	7/10/17
July 2017 Imaging Case of the Month	**Imaging**	**Gotway MB**	**2017**	**15**	**1**	**17-27**	**7/6/17**
Medical Image of the Week: Zenker's Diverticulum	Imaging	Stockdall C	2017	15	1	15-6	7/5/17
July 2017 Critical Care Case of the Month	**Critical Care**	**Raschke RA**	**2017**	**15**	**1**	**7-14**	**7/2/17**
July 2017 Pulmonary Case of the Month	**Pulmonary**	**Viggiano RW**	**2017**	**15**	**1**	**1-6**	**7/1/17**

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