



# A novel treatment for emphysema in a porcine model: extracorporeal radiofrequency

Copyright ©The authors 2025

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact [permissions@ersnet.org](mailto:permissions@ersnet.org)

Received: 19 Feb 2025

Accepted: 29 April 2025

## To the Editor:

Lung volume reduction surgery remains the only intervention shown to significantly reduce both morbidity and mortality in selected patients with severe emphysema [1, 2]. The excision of emphysematous tissue enhances lung mechanics, subsequently improving outcomes in COPD patients. Nevertheless, the substantial perioperative risks and costs associated with lung volume reduction surgery have limited its clinical utilisation [1–3]. Radiofrequency (RF) treatment is a novel non-invasive treatment for emphysema tested in pre-clinical studies. Previous studies indicate that extracorporeal application of RF selectively heats emphysematous tissue – characterised by diminished perfusion compared to healthy tissue – thereby initiating a localised inflammatory response and subsequent healing. We have demonstrated that RF treatment improves lung compliance and morphologic scores for emphysema in rats and improves exercise capacity in a murine model of emphysema [4, 5]. However, small rodents have very different lung and chest wall morphology compared with humans. For ultimate clinical translation, the next step is to validate these results in larger animals. To this end, we have successfully developed a unilateral emphysema model in pigs by instilling intratracheally 725–750 U·kg<sup>-1</sup> of porcine pancreatic elastase (PPE) [6]. Here, we determined the effects of RF therapy in pigs with unilateral emphysema. Pulmonary artery occlusion was used in a subset of animals to further reduce perfusion in the PPE-treated tissue to better reflect what might be observed in human emphysema patients.

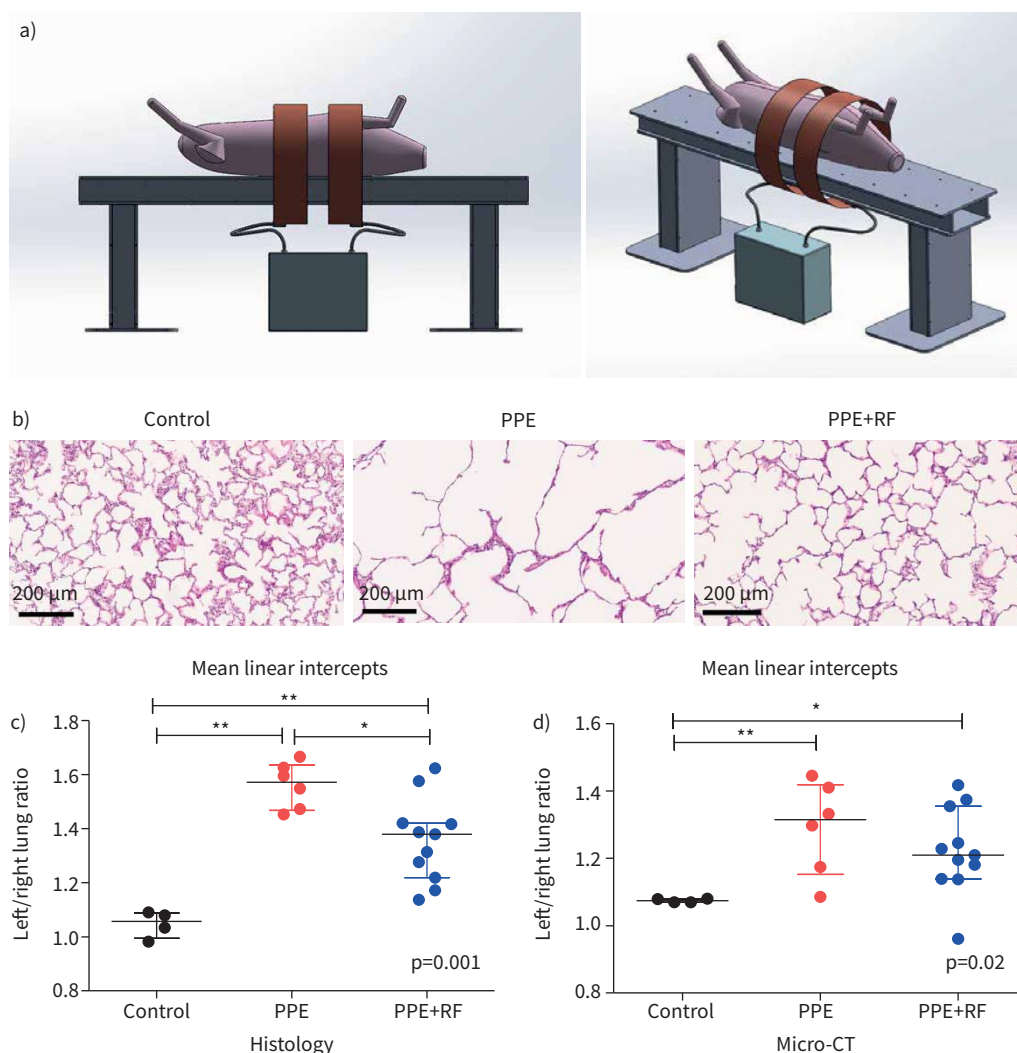
23 female Yucatan pigs, aged eight to 16 months, were selected for this study. Animals were housed at the University of British Columbia (UBC) Centre for Comparative Medicine. All experimental protocols were approved by the UBC Animal Care Committee (Approval No. A20-0200). The PPE instillation adhered to the methodology outlined in a prior publication [6], with PPE instilled solely into the left lung, leaving the untreated right lung as an internal control. Six weeks after PPE instillation, the pigs underwent approximately 30 min of RF treatment under general anaesthesia and ventilator support in a supine position. The RF treatment was delivered via a cuff applicator at 6.78 MHz, using a mean RF duration of 28 min (24–32 min) and a maximum RF power of 619 Watts (521–650 W) (figure 1a). Left pulmonary artery occlusion (L-PAO) was temporarily induced during RF treatment in some of the treatment animals. A Swan–Ganz catheter was inserted into the left pulmonary artery via the jugular vein, and balloon occlusion was confirmed using a fluoroscopic contrast medium. Throughout the RF procedure, temperatures were closely monitored with fiberoptic probes inserted in the airways and positioned across the body. To measure the thermal dose administered, temperature readings were converted to the cumulative number of equivalent minutes at 43°C (CEM43), a metric used in thermal medicine to monitor treatment effects [7]. RF application was determined based on the relationship between complications and CEM43 from prior studies [8, 9]. To prevent burns to the muscles and skin, we applied cooling with water-filled bags after the RF treatment until the completion of general anaesthesia. Six weeks post-RF treatment, the pigs were euthanised, and lung tissue was collected as previously described [6]. Histological analysis followed procedures previously outlined [6]. The severity of emphysema was estimated by measuring the mean linear intercept length (Lm). Lm was calculated from the length of the lines projected onto histology slides multiplied by the number of the lines divided by the sum of all counted intercepts [10, 11]. After data normalisation, we evaluated left–right lung differences within each animal, expressed as the Lm ratio (Lm of left lung/right lung) and compared them across groups using a Wilcoxon signed rank test. For inter-group comparisons, a Mann–Whitney test was employed, and a Kruskal–Wallis test was used for comparisons involving three or more groups.



Shareable abstract (@ERSpublications)

**Radiofrequency treatment significantly reduces emphysema in large animals, offering a promising nonsurgical approach to lung volume reduction. This safe and minimally invasive method shows potential to improve outcomes for patients with severe emphysema.** <https://bit.ly/3YA6Lg8>

**Cite this article as:** Sasaki T, Cheung CY, Tajima Y, et al. A novel treatment for emphysema in a porcine model: extracorporeal radiofrequency. *ERJ Open Res* 2025; 11: 00231-2025 [DOI: 10.1183/23120541.00231-2025].



**FIGURE** a) Radiofrequency (RF) device used in the experiment. b) Haematoxylin and eosin staining of lung tissue. Emphysematous changes were seen in the PPE (porcine pancreatic elastase) group. c) Mean linear intercept (Lm) comparison on histological sections normalised with left lung/right lung. The Kruskal–Wallis test showed a significant difference ( $p=0.001$ ). Significant differences were found between Control and PPE, PPE and PPE+RF, and Control and PPE+RF. d) Lm comparison on micro-computed tomography (CT) normalised with left lung/right lung. The Kruskal–Wallis test showed a significant difference ( $p=0.02$ ). Significant differences were found between Control and PPE, and Control and PPE+RF. Data are presented as median (line) with interquartile range (error bars) (\*:  $p<0.05$ ; \*\*:  $p<0.01$ ).

There were three arms to the study: a control group (no intervention)  $N=4$ ; a PPE group (PPE instillation in the left lung)  $N=6$ ; and a PPE+RF group (RF treatment with or without L-PAO after PPE instillation)  $N=11$  (PPE+RF alone  $N=7$ , PPE+RF+L-PAO  $N=4$ ). Weight gain was noted across the study period in the PPE+RF group. Median weight at the time of RF treatment was 49 kg and 54 kg after 6 weeks, at sacrifice. The median of the maximum left lung temperature during RF was 42.7°C (41.4–44.5°C) with a median CEM43 in the left lung of 5.12 min (2.00–47.3 min). Regarding adverse effects, only mild superficial skin burns were observed, and no other significant side effects occurred. This suggests that RF treatment can be applied safely within the tested parameters.

Based on histology, PPE instillation significantly increased the Lm ratio by 0.51 from 1.06 in the control group to 1.57 in the PPE group ( $p=0.009$ ), representing a 48.1% ( $0.51/1.06 \times 100$ ) increase. In the PPE+RF group, the Lm ratio was significantly reduced by 0.19 from 1.57 to 1.38 ( $p=0.01$ ), representing a 37.2% ( $0.19/0.51 \times 100$ ) reduction relative to the effect caused by PPE but without RF treatment (figure 1b and c). There was no significant difference in the Lm ratio between the PPE+RF alone and PPE+RF+L-PAO (PPE+RF alone 1.38 (1.17–1.58) versus PPE+RF+L-PAO 1.35 (1.23–1.42),  $p=1.00$ ). However, the median CEM43 in the left lung was 2.94 min (0.259–5.12) in the PPE+RF alone and 48.2 min (23.7–63.8) in the

PPE+RF+L-PAO ( $p=0.006$  comparison between the groups); there was no significant correlation between Lm and CEM43. Similarly, micro-computed tomography (CT) analysis showed that PPE increased the Lm ratio from 1.07 to 1.32 ( $p=0.02$ ), a 23.4% rise. This increase was attenuated to 1.21 in the PPE+RF group, indicating a 44.0% relative reduction, although not statistically significant (figure 1d), which likely reflects reduced sensitivity of micro-CT compared with standard histology in assessing Lm in these animals.

COPD patients with emphysema are more symptomatic and experience an accelerated disease progression compared with patients who have a predominance of airway disease [12]. However, there is currently a scarcity of disease-modifying therapy for emphysema. Human emphysema develops over many decades. In animals, emphysema is artificially induced over several weeks. Thus, in most cases, the animals develop only mild (patchy) emphysema. To better mimic the human condition where we observe both airway and vascular remodelling [13, 14], we performed L-PAO using an intravascular catheter in a select number of animals. However, we did not observe any impact on the overall emphysema burden or modifying effects of RF treatment. In addition to CT, micro-CT, and water displacement were performed, but no significant differences were observed [4, 5].

One limitation of the study was that the porcine model we developed demonstrates mild emphysema, and there are inherent differences between human and porcine models as reported in previous studies [6]. Another limitation was the shape of the chest wall of pigs. Because of the thick subcutaneous layer of the chest wall, there was a relatively low ceiling in the amount of RF energy that could be administered before these pigs experienced significant side effects. This may have also limited the RF's effectiveness in treating the emphysema. While the effect of RF therapy on emphysema burden as measured by Lm was encouraging, we could not determine the exact mechanisms by which RF ameliorated the emphysema; there are ongoing experiments to determine potential mechanistic pathways. Due to the limited sample size in the PPE+RF+L-PAO group ( $N=4$ ), we have combined it with the PPE+RF alone group for the primary analysis, with subgroup analyses conducted separately. However, in future studies, we will increase the number of samples in the PPE+RF+L-PAO group to better evaluate the effects and further elucidate the mechanisms involved. It should be noted that the measurement of Lm was not blinded and was conducted by a single evaluator with extensive training in applied stereology of the lung. In a significant proportion of the cases, double reading was done independently by two trained investigators, which showed good concordance ( $r=0.92$ ;  $p<0.001$ ). One important advantage of our model was the unilateral nature of the emphysema, which enabled us to use the right lung as the animal's own internal control. This reduced biological variability and thus enhanced the signal to noise ratio.

Our study results demonstrate the potential therapeutic effect of extracorporeal RF given as one dose in a large animal model of unilateral emphysema, which may be a novel way of non-surgically achieving "lung volume reduction". In sum, we have shown that external RF therapy can significantly reduce emphysema in large animals.

Taketo Sasaki<sup>1</sup>, Chung Yan Cheung<sup>1</sup>, Yuki Tajima<sup>1</sup>, Mai Tsutsui<sup>1</sup>, Edward Z. Li<sup>1</sup>, Sean He<sup>1</sup>, Laura Mowbray<sup>2</sup>, Evan Goodacre<sup>3</sup>, Corey Myrdal<sup>3</sup>, Kim Wolff<sup>3</sup>, Eran Elizur<sup>3</sup>, Dragoş M. Vasilescu<sup>1</sup> and Don D. Sin<sup>1,4</sup>

<sup>1</sup>Centre for Heart Lung Innovation, St Paul's Hospital, University of British Columbia, Vancouver, BC, Canada. <sup>2</sup>Centre for Comparative Medicine, University of British Columbia, Vancouver, BC, Canada. <sup>3</sup>Ikomed Technologies Inc., Vancouver, BC, Canada. <sup>4</sup>Division of Respiratory Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.

Corresponding author: Don D. Sin ([Don.Sin@hli.ubc.ca](mailto:Don.Sin@hli.ubc.ca))

Acknowledgments: The authors acknowledge Dr Aaron Barlow, Darren Sutherland, Amrit Samra and Annie Li from the UBC Centre for Heart Lung Innovation for technical support.

Provenance: Submitted article, peer reviewed.

Ethics statement: All experimental protocols were approved by the UBC Animal Care Committee (approval number A20-0200).

Conflict of interest: IKOMED holds a patent on extracorporeal radiofrequency therapy. The academics on this paper hold no financial interest in the technology.

Support statement: D.D. Sin is supported by a Tier 1 Canada Research Chair in COPD and holds the de Lazzari Family Chair at the Centre for Heart Lung Innovation; the study was sponsored by IKOMED Technologies Inc., Vancouver, BC; MITACS; and the Canadian Institutes of Health Research. Funding information for this article has been deposited with the Open Funder Registry.

## References

- 1 Fishman A, Martinez F, Naunheim K, *et al.* A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
- 2 Naunheim KS, Wood DE, Mohsenifar Z, *et al.* Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. *Ann Thorac Surg* 2006; 82: 431–443.
- 3 Washko GR, Martinez FJ, Hoffman EA, *et al.* Physiological and computed tomographic predictors of outcome from lung volume reduction surgery. *Am J Respir Crit Care Med* 2010; 181: 494–500.
- 4 Wada T, Jaw JE, Tsuruta M, *et al.* External radiofrequency as a novel extracorporeal therapy for emphysema. *Eur Respir J* 2020; 56: 2001422.
- 5 Tsutsui M, Cheung CY, Wada T, *et al.* Radiofrequency therapy improves exercise capacity of mice with emphysema. *Sci Rep* 2021; 11: 20056.
- 6 Tajima Y, Seow CY, Dong SJ, *et al.* Development of a unilateral porcine emphysema model induced by porcine pancreatic elastase. *J Appl Physiol (1985)* 2023; 135: 1001–1011.
- 7 Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol Biol Phys* 1984; 10: 787–800.
- 8 van Rhoon GC, Samaras T, Yarmolenko PS, *et al.* CEM43°C thermal dose thresholds: a potential guide for magnetic resonance radiofrequency exposure levels? *Eur Radiol* 2013; 23: 2215–2227.
- 9 van Rhoon GC. Is CEM43 still a relevant thermal dose parameter for hyperthermia treatment monitoring? *Int J Hyperthermia* 2016; 32: 50–62.
- 10 Hsia CC, Hyde DM, Ochs M, *et al.* An official research policy statement of the American Thoracic Society/ European Respiratory Society: standards for quantitative assessment of lung structure. *Am J Respir Crit Care Med* 2010; 181: 394–418.
- 11 Vasilescu DM, Phillion AB, Kinose D, *et al.* Comprehensive stereological assessment of the human lung using multiresolution computed tomography. *J Appl Physiol (1985)* 2020; 128: 1604–1616.
- 12 Yuan R, Hogg JC, Paré PD, *et al.* Prediction of the rate of decline in FEV1 in smokers using quantitative computed tomography. *Thorax* 2009; 64: 944–949.
- 13 Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32: 1371–1385.
- 14 Gotoh M, Okamoto T, Yamamoto Y, *et al.* Development of a canine model of pulmonary emphysema and imaging of the emphysematous lung with infrared thoracoscopy. *J Thorac Cardiovasc Surg* 2003; 126: 1916–1921.