This paper presents a novel multiclass system designed to detect pleural effusion and pulmonary edema on chest X-ray images, addressing the critical need for early detection in healthcare. A new comprehensive dataset was formed by combining 28,309 samples from the ChestX-ray14, PadChest, and CheXpert databases, with 10,287, 6022, and 12,000 samples representing Pleural Effusion, Pulmonary Edema, and Normal cases, respectively. Consequently, the preprocessing step involves applying the Contrast Limited Adaptive Histogram Equalization (CLAHE) method to boost the local contrast of the X-ray samples, then resizing the images to 380 × 380 dimensions, followed by using the data augmentation technique. The classification task employs a deep learning model based on the EfficientNet-V1-B4 architecture and is trained using the AdamW optimizer. The proposed multiclass system achieved an accuracy (ACC) of 98.3%, recall of 98.3%, precision of 98.7%, and F1-score of 98.7%. Moreover, the robustness of the model was revealed by the Receiver Operating Characteristic (ROC) analysis, which demonstrated an Area Under the Curve (AUC) of 1.00 for edema and normal cases and 0.99 for effusion. The experimental results demonstrate the superiority of the proposed multi-class system, which has the potential to assist clinicians in timely and accurate diagnosis, leading to improved patient outcomes. Notably, ablation-CAM visualization at the last convolutional layer portrayed further enhanced diagnostic capabilities with heat maps on X-ray images, which will aid clinicians in interpreting and localizing abnormalities more effectively.

Image classification

decision support system

EfficientNet-V1-B4

AdamW optimizer

pulmonary edema

pleural effusion

chest X-rays

1. Introduction

Detecting pulmonary edema and pleural effusion using chest X-rays is crucial for the diagnosis of diseases [[1](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-1),[2](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-2)]. Pulmonary edema occurs due to fluid buildup in the lungs’ alveoli [[3](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-3)]. Conversely, pleural effusion is a disorder indicated by the abnormal fluid buildup in the membranes surrounding the lungs [[4](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-4)]. [Fig. 1a](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-1) depicts pulmonary edema [[5](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-5)] and [Fig. 1b](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-1) shows pleural effusion [[6](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-6)].

1. [Download: Download high-res image (634KB)](https://ars.els-cdn.com/content/image/1-s2.0-S1546221824005265-CMC_51420-fig-1_lrg.gif)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S1546221824005265-CMC_51420-fig-1.gif)

Figure 1. (a) Pulmonary edema (Reprinted from reference [[5](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-5)]); (b) Pleural effusion (Reprinted from reference [[6](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-6)])

In this context, it is crucial to classify whether the fluid is located inside the lung tissue and air sacs (pulmonary edema) or within the pleural space (pleural effusion) [[7](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-7),[8](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-8)]. Therefore, diagnostic imaging techniques, such as X-rays, are paramount in identifying the presence and extent of these medical conditions, enabling healthcare practitioners to make timely and precise diagnoses [[9](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-9)]. Overall, the complexity in detecting pulmonary edema and pleural effusion underscores the need for a multidisciplinary approach involving clinicians, radiologists, and other specialists to ensure accurate diagnosis and appropriate management.

Additionally, the distinction between pulmonary edema and pleural effusion using chest X-rays will lead to identification the underlying causes of fluid accumulation in the chest. It will also help medical professionals suggest the appropriate management of these disorders and an appropriate treatment approach. For instance, detection of pulmonary edema might indicate congestive heart failure or pneumonia, necessitating specific therapeutic interventions [[10](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-10)]. Conversely, the detection of pleural effusion would require different treatment strategies involving drainage through thoracentesis and chest tube [[11](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-11)].

Likewise, accurately classifying the location of the fluid helps in determining the precise underlying causes, ensuring that patients receive the most effective and tailored care to improve their overall health outcomes [[8](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-8),[12](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-12)].

Deep learning techniques have demonstrated remarkable advancements in the domain of medical image analysis, particularly in disease detection and diagnosis [[13](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-13)–[15](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-15)]. Deep Convolutional Neural Networks (CNNs) have proven exceptional capabilities in extracting intricate features from complex images, making them an ideal candidate for the detection of pulmonary edema and pleural effusion [[16](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-16)–[18](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-18)].

EfficientNet is a family of CNNs that excel at achieving high accuracy and is computationally efficient [[19](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-19)]. EfficientNet was developed to scale the depth, width, and resolution of the model using a compound coefficient to optimize performance [[20](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-20)]. This approach has led to state-of-the-art results on the task of image classification for various applications while minimizing computational demands [[21](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-21)]. In particular, the EfficientNet-V1-B4 architecture is known for its exceptional efficiency in terms of the model size and computational resources. It achieves superior performance with fewer parameters compared to traditional architectures, making it well-suited for resource-constrained environments commonly encountered in medical settings. This efficiency translates to faster inference times and reduced computational costs, facilitating the real-time or near-real-time analysis of medical images for timely diagnosis and intervention. Coupled with the AdamW optimizer, which integrates the advantages of the Adam optimizer with weight decay techniques, detection algorithms can achieve superior convergence rates and model generalization. AdamW is an extension of the Adam optimizer commonly used for training neural networks [[22](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-22)]. It directly incorporates weight decay into its formulation improving generalization by preventing excessive weight growth. This modification helps control model complexity and enhances training stability.

Accordingly, by introducing EfficientNet-V1-B4 Architecture and AdamW in medical imaging analysis, healthcare professionals can expect improved diagnostic accuracy, faster processing times, and enhanced decision-making capabilities, ultimately leading to better patient outcomes and more effective treatment plans.

The contributions of this study are as follows:

* A multi-class medical diagnosis system was developed to describe the accumulation of fluid in the lungs from perspective of image processing. Thus, the system categorizes three patterns using chest X-ray images including pleural effusion, pulmonary edema, and normal cases.
* The utilization of the EfficientNet-V1-B4 architecture associated with the AdamW optimizer in the context of pulmonary edema and pleural effusion detection from chest X-ray images represents a novel application and exploration of deep learning models for medical image analysis.
* The localization of pleural effusion and pulmonary edema diseases is accomplished by utilizing the ablation-CAM technique and is graphically presented using heatmap data visualization.

By automating this classification process, medical professionals can save valuable time by achieving early diagnosis while ensuring more accurate diagnoses. The remainder of this paper is organized as follows. The related work is presented in [Section 2](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "s2). [Section 3](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "s3) describes the research methodology. The empirical results are analyzed and discussed in [Section 4](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "s4). The conclusions of this research and future work are presented in [Section 5](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "s5).

2. Related Work

Fluid accumulation in the lungs is a life-threatening medical emergency that requires timely diagnosis and intervention and is known as pulmonary edema. Traditional methods for detecting pulmonary edema in medical imaging have limitations, leading to the demand for more accurate and efficient approaches. The promising results of artificial intelligence in various medical fields, including the detection of pulmonary edema, have encouraged the development of advanced methodologies. One major challenge hindering the advancement of CNNs in medical image analysis is the necessity of constructing ground-truth data based on specialists’ opinions.

Deep CNNs have been applied in research [[23](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-23)–[27](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-27)] to classify different types of radiographs, such as X-rays, CT scans, and ultrasounds. CNNs are used to diagnose various diseases, such as pulmonary edema, pulmonary effusion, pneumonia, COVID-19, and pneumothorax. Despite demonstrating promise for radiographic interpretation, these early studies generally lacked the level of specificity and granularity required for practical diagnostic utility.

Based on the expansion of using Artificial Intelligence (AI) in detecting diseases, Wang et al. [[28](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-28)] compared several deep learning techniques for diagnosing pulmonary edema and estimating the severity of the case, and the dataset used was MIMIC-CXR for images and reports [[29](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-29)]. According to previous studies [[30](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-30),[31](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-31)], there are approximately 77% accuracy among radiologists and 59% accuracy among ED physicians. Edema severity was classified in 3058 cases as mild, 1414 moderate cases, and severe in 296 cases.

2.1. Related Studies on CNN-Based Detection of Pulmonary Edema

Serte et al. [[18](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-18)] studied pulmonary edema disease as a result of heart failure depending on chest radiographs. Researchers constructed a dataset of 27,748 front-chest radiographs over nearly six years. The collected images were in the range of 1.4–4.7 k in height and width with 80% training set, 10% validation, and a test group of 10%. Training was carried out in two stages (pipelines) to train a branched CNN based on ResNet152v2 architecture. The goal is to cooperatively predict B-type Natriuretic Peptide (BNP) or BNPP (BNP precursor) cases. With a preset learning rate of 1e-5 and a patch size of 16, Adam’s optimizer was used to train all CNNs. The region of attention was determined using a heatmap. Another factor that is considered is the blur sensitivity. Consequently, the trained models attained an AUC of 0.801 for the detection of pulmonary edema.

In [[32](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-32)], a 2.5D CNN model was developed to detect multiple diseases, such as: atelectasis, pneumonia, edema, and nodules. The study investigated 5000 CT images that contained 156 edema cases, 225 pneumonia cases, and other cases. The research split the image set for each disease into training, validation, and test sets. The model achieved accuracies of 0.963, 0.818, 0.878, and 0.784, for edema, atelectasis, pneumonia, and nodule, respectively. Moreover, AUC of 0.940, 0.891, 0.869, and 0.784 were obtained for categorizing edema, atelectasis, pneumonia, and nodule diseases, respectively.

In [[33](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-33)], a 2.5D CNN model was developed to detect multiple diseases, that are: atelectasis, pneumonia, edema, and nodules. The study investigated 5000 CT images that contained 156 edema cases, 225 pneumonia cases, and other cases. The research split the image set for each disease into training, validation, and test sets. As a result, the model achieved an accuracy of 0.963, 0.818, 0.878, and 0.784, for edema, atelectasis, pneumonia, and nodule, respectively. Moreover, The AUC of 0.940, 0.891, 0.869, and 0.784 were attained for categorizing edema, atelectasis, pneumonia, and nodule diseases, respectively. As shown in [Table 1](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#table-1), a summary of previous studies on the detection of pulmonary edema using CNN models from chest X-ray images is provided.

Table 1. Summary of previous studies on the detection of pulmonary edema using CNN models from chest X-ray images

| **Study** | **Architecture** | **Performance** |
| --- | --- | --- |
| Serte et al. [[18](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-18)] | ResNet152v2-CNN | AUC = 0.801 |
| Hayat [[32](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-32)] | DesneNet-CNN | AUC = 0.714 |
| Geng et al. [[33](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-33)] | 2.5D-CNN | ACC = 0.963 |
| AUC = 0.940 |

2.2. Related Studies on CNN-Based Detection of Pleural Effusion

Previous studies in the domain of pleural effusion detection have explored various approaches and architectures to improve the accuracy and efficiency of diagnostic systems. With the aim of automating Lung Ultrasound (LUS) image evaluation for pleural effusion detection, Hammon et al. [[30](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-30)] employed a deep-learning model that was constructed based on the Regularized Spatial Transformer Network (Reg-STN) architecture to perform binary classification of pleural effusion in clinical LUS imaging. The dataset, obtained from the Royal Melbourne Hospital, consisted of 623 videos containing 99,209 2D LUS images obtained from examinations of 70 patients using a phased array transducer. This model was trained using weakly supervised and supervised methodologies utilizing a video-based labeling approach, resulting in an accuracy of 91.1%, and a frame-based labeling approach, resulting in an accuracy of 92.4%. Notably, the reference was proficient clinicians who assessed the interpretation of images.

Researchers in [[34](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-34)] applied a deep learning model based on the ResNet18 architecture to the chest radiography images. The model was applied to identify pleural effusion arising from three types of respiratory disorders, namely tuberculosis, COVID-19, and pneumonia. Hence, the developed system can detect these three diseases once they occur at an early stage before evolving into pleural effusion. Three experiments were conducted for binary classification. Consequently, the performance in terms of accuracy for early detection of pleural effusion disease from tuberculosis, COVID-19, and pneumonia was 99%, 100%, and 75%, respectively. In contrast, a multiclass experiment was applied, which included the following categories: tuberculosis, COVID-19, pleural effusion, bacterial pneumonia, and viral pneumonia. Thus, the best result was obtained for bacterial pneumonia detection, with an accuracy of 83% and an AUC of 81%. Furthermore, the multiclass system detected pleural effusion with an accuracy of 82% and AUC of 77%.

In a study by Bar et al. [[35](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-35)], the identification of various pathologies, such as right pleural effusion, from chest radiographs was investigated. Their analysis utilized a CNN trained on non-medical data, achieving an AUC of 0.95. Lakhani et al. [[36](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-36)] explored deep-learning approaches for tuberculosis detection on chest radiographs containing pleural effusion, miliary patterns, and cavitation, and achieved an impressive AUC of 0.99. As shown in [Table 2](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#table-2), a summary of previous studies on the detection of pleural effusion using CNN models from chest X-ray images is provided.

Table 2. Summary of previous studies on the detection of pleural effusion using CNN models from chest X-ray images

| **Study** | **Architecture** | **Performance** |
| --- | --- | --- |
| Serte et al. [[34](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-34)] | ResNet18-CNN | ACC = 0.82 |
| AUC = 0.77 |
| Bar et al. [[35](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-35)] | CNN + classical features | AUC = 0.95 |
| Lakhani et al. [[36](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-36)] | DCNNs (AlexNet and GoogLeNet) | AUC = 0.99 |

3. Material and Methodology

As essential as it is in practice, this study developed an AI system to detect fluid buildup in the lungs by categorizing three patterns using chest X-ray images including pleural effusion disease, pulmonary edema disease, and normal cases as illustrated in [Fig. 2](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-2). The proposed computer vision-based medical classification system encompassed various stages including Data Preprocessing, Build and Training Model (learning), and Model Output (testing). [Fig. 2](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-2) illustrates the research methodology. From this perspective, chest X-ray images will pass through a preprocessing stage before being fed into the training model. Furthermore, the output of the system includes class activation mapping and the category to which each test image belongs.

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Figure 2. The research methodology

3.1. Datasets

With the aim of conducting a classification task to reveal the presence or absence of pleural effusion and pulmonary edema disorders in the lungs using X-ray images, a new dataset of 28,309 samples was formed by combining several public datasets, including ChestX-ray14 [[37](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-37)], PadChest [[38](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-38)], and CheXpert [[39](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-39)]. The new dataset under consideration was distributed among three classes as follows: approximately 10,287 samples depicting pleural effusion, about 6022 samples representing pulmonary edema, and 12,000 samples exhibiting normal cases.

3.2. Data Preprocessing

During this stage, a stratified split of the medical image dataset was conducted, with 85% allocated to the training set and 15% to the test set. Thus, the training and test sets are independent. This stratification was aimed at maintaining a consistent distribution of classes across both the training and test sets. Particularly, pixel normalization was excluded from the preprocessing steps, as empirical evidence suggests its unnecessary approach in certain medical image classification tasks [[40](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-40)].

To achieve the computer vision classification goal, the image data should be handled properly before reaching the input layer of the model. For the application at hand, a dedicated pipeline was employed on the image data by conducting three sequential steps, as illustrated in [Fig. 3](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-3). First, enhancing the contrast of the chest X-ray images was enhanced using the CLAHE approach. Second, all images were resized to 380 × 380 pixels. Lastly, multiple data augmentation techniques were employed.

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Figure 3. Preprocessing steps

3.2.1. CLAHE Technique

The CLAHE technique has been used in various image processing applications because of its capability to enhance image contrast by partitioning the image into small blocks and equalizing the histogram of each block. This method also mitigates contrast amplification within each block, thus minimizing noise amplification [[41](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-41)]. It serves to improve image contrast, facilitates better visibility and interpretation, and is adept at enhancing image details [[42](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-42)]. [Fig. 4a](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-4) shows the original X-ray image selected from the data under consideration. Conversely, [Fig. 4b](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-4) illustrates the enhanced X-ray image after employing the CLAHE technique, which demonstrates the contrast improvement compared to the original X-ray image proving the effectiveness of applying CLAHE in rendering certain lung details more discriminant.

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2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S1546221824005265-CMC_51420-fig-4.gif)

Figure 4. (a) The original X-ray image; (b) The enhanced X-ray image after employing CLAHE

3.2.2. Resize

Determining the image size for training CNN is important when considering the trade-offs between accuracy, speed, and memory requirements [[43](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-43)]. Larger image sizes typically exhibt better accuracy, but they also require more computation and memory [[44](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-44)]. Additionally, the benefits of using larger images tend to diminish as the size increases [[45](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-45)].

CNNs frequently downsample the dimensions of an input image, resulting in an irregular final size [[46](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-46)]. To avoid this, it is advisable to employ a square image size during the training phase [[47](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-47)]. In our approach, we resized all images to 380 × 380 pixels, maintaining the original aspect ratio and implementing zero-padding as needed.

3.2.3. Data Augmentation

To improve the performance of the deep learning model and promote its capacity for generalization, a data-augmentation approach was employed. Data augmentation involves integrating subtly modified versions of current data or generating synthetic data based on existing samples, thereby expanding the effective dataset size. For this purpose, a total of six augmentation methods were adopted, including: CutMix [[48](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-48)], MixUp [[49](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-49)], CenterCrop, RandomChannelShift [[50](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-50)], RandomGaussianBlur [[51](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-51)], and Random Brightness [[50](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-50)] transformations during the training process, aiming to improve the robustness of the model.

3.3. Build and Training Model

Attaining superior performance for image categorization necessitates not only creating a superb architecture but also selecting an appropriate optimizer that can significantly minimize the loss function. Thus, this study presents a deep learning model that was constructed based on the EfficientNet-V1-B4 architecture along with the AdamW optimizer that was utilized for training this model.

3.3.1. EfficientNet-V1-B4 Architecture

The EfficientNet-V1 architecture was introduced by Tan and Le in 2019 [[20](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#ref-20)] in which a novel compound scaling approach was proposed. In this view, the EfficientNet-V1 model uses R to uniformly scale all the dimensions of the network including the width, depth, and resolution. Thus, the scaling method of the model is mathematically described as follows [[20](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-20)]:depth=αR,(1)width=βR, andresolution=γRs.t.α.β2.γ2≈2α≥1,β≥1, andγ≥1where the coefficients α,β, andγ are constant, and they are specified by a small grid search, whereas the value of (R) is determined by the user depending on the available resources to scale the model. As illustrated in [Eq. (1)](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "eqn-1), the Floating-Point Operations (FLOPs) of the ordinary convolution operation are typically proportional to α.β2.γ2. Considering the restriction of α.β2.γ2≈2, such that for each change in the value of R, the overall FLOPs roughly increase by 2R.

Therefore, it can be straightforward to increase the dimensions of the network by (R) if there is a need to use 2R times more computational resources. Hence, utilizing the abovementioned compound scaling strategy has an intuitive implication if there is a larger input image that requires additional layers in the network to expand its receptive area and additional channels to obtain more fine-grained patterns. Hence, scaling the network dimensions leads to a systematic increase in the performance of the model.

Furthermore, there are eight variations of EfficientNet-V1, referred to as EfficientNet-V1-B0 through EfficientNet-V1-B7. This study employs EfficientNet-V1-B4. [Fig. 5](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-5) depicts the details of the EfficientNet-V1-B4 architecture considered in this study. The architecture of EfficientNet-V1-B4 is segmented into seven blocks, called Mobile Inverted Bottleneck Convolution (MBConv), which are the elementary building blocks of EfficientNet-V1-B4, followed by a fully connected layer. For a particular stage(s) within this architecture, the block appears as MBConvX×L, where the notation X = 1 and X = 6 indicate the block type signify the standard Swish activation function, and (L^s) denotes the number of layers. The kernel size associated with the MBConvX block also appears under the block type.

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Figure 5. The EfficientNet-V1-B4 architecture

Lastly, the input resolution (H^s×W^s), and the number of output channels (C^s), is depicted as (H^s×W^s×C^s), respectively. For example, in the second stage of the architecture where (S = 2), the MBConv1 × 2 notation indicates that the MBConv1 block is repeated twice (L=2), the kernel size is (k3×3), and the notation (190×190×24) implies the input resolution which is (190×190), and the number of channels is (24).

In this study, the optimal performance was pursued by fine-tuning the pre-trained weights of EfficientNet-V1-B4 using Noisy Student data. Subsequently, a fully connected layer with three neurons was used to represent the class scores (i.e., the output layer).

Furthermore, the MBConvX blocks utilize the Swish activation function and squeeze-and-excitation (SE) optimization which enables the efficient extraction of high-quality features, and minimize computational complexity while maximizing accuracy. Additionally, MBConv’s lightweight design extracts informative features from early stages, while SE dynamically refines them, resulting in sharper detections and improved accuracy compared to traditional Convolutional Neural Networks. [Fig. 6a](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-6) illustrates MBConv1, while [Fig. 6b](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-6) presents MBConv6, both representing distinct design points in the EfficientNet-V1-B4 architecture. MBConv1 emphasizes early feature extraction with minimal computational cost, making it particularly well-suited for the initial stages of the network. By contrast, MBConv6 concentrates on advanced feature refinement, achieving heightened accuracy although with a modest increase in complexity. The deliberate utilization of MBConvX variants in this manner enables EfficientNet-V1-B4 to achieve a balance between efficiency and accuracy.

1. [Download: Download high-res image (262KB)](https://ars.els-cdn.com/content/image/1-s2.0-S1546221824005265-CMC_51420-fig-6_lrg.gif)
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Figure 6. The MBConv blocks in the EfficientNet-V1-B4 architecture. (a) MBConv1; (b) MBConv6

3.3.2. AdamW Optimizer

An AdamW optimizer was used to train the model. The AdamW optimizer is an extension of the Adam optimizer with the addition of a weight decay regularization approach [[22](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-22)]. Furthermore, weight decay serves as a method to mitigate overfitting by imposing penalties on substantial weights.

Accordingly, the Adam optimizer exhibited comparatively reduced efficiency in weight regularization when compared to alternative optimizers, such as SGD with momentum. However, AdamW disentangles the weight decay from the adaptive estimation of the first and second moments of the gradients. This decoupling empowers AdamW to enhance the weight regularization more efficiently without compromising the speed of convergence.

4. Model Outputs

In this section, the experimental settings, and results for the dataset under consideration are illustrated. The performance of the classification model was evaluated based on complexity and different metrics including accuracy (A), precision (P), recall (R), and F1-score. Finally, Ablation-based Class Activation Mapping (Ablation CAM) was employed to provide meaningful and interpretable explanations of the results.

4.1. Experiments Setting

In this study, TPU 3-8 was utilized to train the network. Subsequently, the training and testing phases occurred within the same environment, employing the Keras deep learning framework and Python 3.8 as the programming language. Network training involved the utilization of the hyperparameters outlined in [Table 3](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "table-3).

Table 3. Hyperparameters

| **Parameter** | **Value** |
| --- | --- |
| Input size | 380 × 380 × 3 |
| Batch size | 256 |
| Learning rate | 1e-4 |
| Optimizer | AdamW |
| Epochs | 70 |
| Loss function | Categorical crossentropy |

4.2. Computational Complexity

The computational complexity of a CNN is an important consideration for its practical deployment and can be analyzed along two dimensions which are spatial and temporal [[52](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-52)]. The spatial complexity (SC) indicates the storage requirements (i.e., disk space) of a trained CNN model, including both its parameters and intermediate feature maps. The temporal complexity (TC) reflects the computational cost, commonly measured in floating-point operations per second (FLOPS), required for the CNN to make predictions. For the proposed CNN model evaluated in this study, we obtained SC of 243 MB and TC of 4.51 GigaFLOPS. These values can be used to assess the resource requirements and inference speed of a model in real-world applications.

4.3. Classification Performance Evaluation

The performance evaluation of the proposed model on the test set relies on the utilization of a confusion matrix. The accurate determination of this matrix requires knowledge of the true values associated with the validation data. As illustrated in [Fig. 7](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-7), the confusion matrix was implemented to evaluate the performance of the model. In this view, multiple measures were computed including P, R, A, and F-1, utilizing the predetermined methods described in previous research [[53](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-53)]. The formulations for these evaluation measures are detailed in [Eqs. (2)](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "eqn-2) through [(5)](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "eqn-5).

1. [Download: Download high-res image (149KB)](https://ars.els-cdn.com/content/image/1-s2.0-S1546221824005265-CMC_51420-fig-7_lrg.gif)
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Figure 7. The confusion matrix for chest X-ray images

(2)P=TPTP+FP(3)R=TPTP+Fn(4)A=TP+TNTP+TN+FP+FN(5)F1=2⋅PRP+R

Specifically, the TP represents True Positives, denoting correctly identified positive instances. TN represents True Negatives, signifying correctly identified negative instances. FP represents False Positives, indicating instances incorrectly identified as positives. FN represents False Negatives, representing instances incorrectly identified as negatives.

The results of the calculation of the aforementioned matrices are presented in [Table 4](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "table-4), which shows that the developed system classifies pleural effusion, pulmonary edema, and normal patterns with a high classification rate compared with previous studies as shown in [Tables 1](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "table-1) and [2](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "table-2). According to this viewpoint, the average achieved accuracy was approximately 0.983, the average accomplished precision was approximately 0.987, the attained average recall value was roughly 0.983, and the average F-1 was score approximately 0.987. These findings confirm that the classification system is precise and robust in identifying pleural effusion and pulmonary edema disorders using X-ray images.

Table 4. The classification report of our proposed approach to X-ray images

| **Classes** | **Precision** | **Recall** | **F1-score** | **Accuracy** |
| --- | --- | --- | --- | --- |
| Edema | 0.99 | 0.98 | 0.98 | 0.98 |
| Effusion | 0.98 | 0.98 | 0.99 | 0.98 |
| Normal | 0.99 | 0.99 | 0.99 | 0.99 |
| **Average** | **0.987** | **0.983** | **0.987** | **0.983** |

Finally, we confirmed a comprehensive evaluation of the model’s performance across various sensitivity and specificity thresholds. The ROC curve tool was used specifically to analyze three medical classes: pulmonary edema, pleural effusion, and normal cases using the dataset of X-ray images under consideration in this study, as represented in [Fig. 8](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-8). The results revealed that the AUC was 1.00 for pulmonary edema and normal cases. Additionally, the AUC was 0.99 for pleural effusion disease. These ROC evaluations confirmed the robustness of the developed categorization system that differentiated between pulmonary edema, pleural effusion, and normal cases, thus providing valuable insights into its diagnostic capabilities.

1. [Download: Download high-res image (84KB)](https://ars.els-cdn.com/content/image/1-s2.0-S1546221824005265-CMC_51420-fig-8_lrg.gif)
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Figure 8. ROC curves for pulmonary edema, pleural effusion, and normal cases using chest X-rays

This work proves the effectiveness of the proposed neural network architecture combined with the AdamW optimizer for the detection of Pulmonary Edema and Pleural Effusion diseases. The results were compared with well-known classification architectures such as VGG19, DenseNet121, InceptionV3, EfficientNet, and ResNet101. Hence, the average accuracy of these architecture models was assessed using various training-based optimizers including SGD, Adagrad, RMSprop, Adam, Radam, and AdamW. [Table 5](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "table-5) compares the aforementioned optimizers and architectures. As a result, the proposed model achieved the highest average accuracy of 0.983 when employing the AdamW optimizer across EfficientNet-V1-B4 compared to the others utilizing the same datasets applied in this study.

Table 5. Comparison of various optimizers applied to renowned architectures in terms of average accuracy on the datasets used in this study

| **Model** | **SGD** | **Adagrad** | **RMSprop** | **Adam** | **Radam** | **AdamW** |
| --- | --- | --- | --- | --- | --- | --- |
| VGG19 | 0.820 | 0.814 | 0.81 | 0.822 | 0.825 | 0.83 |
| DenseNet121 | 0.850 | 0.832 | 0.844 | 0.858 | 0.861 | 0.864 |
| InceptionV3 | 0.832 | 0.834 | 0.830 | 0.845 | 0.847 | 0.85 |
| ResNet101 | 0.871 | 0.870 | 0.871 | 0.879 | 0.883 | 0.881 |
| EfficientNetV1-B0 | 0.932 | 0.924 | 0.92 | 0.948 | 0.95 | 0.951 |
| EfficientNetV1-B1 | 0.935 | 0.927 | 0.921 | 0.95 | 0.951 | 0.957 |
| EfficientNetV1-B2 | 0.945 | 0.935 | 0.933 | 0.955 | 0.966 | 0.968 |
| EfficientNetV1-B3 | 0.951 | 0.947 | 0.949 | 0.967 | 0.968 | 0.97 |
| **EfficientNetV1-B4** | 0.961 | 0.953 | 0.959 | 0.975 | 0.979 | **0.983** |
| EfficientNetV1-B5 | 0.961 | 0.951 | 0.96 | 0.97 | 0.973 | 0.981 |
| EfficientNetV1-B6 | 0.961 | 0.952 | 0.962 | 0.972 | 0.975 | 0.978 |
| EfficientNetV1-B7 | 0.962 | 0.955 | 0.964 | 0.971 | 0.976 | 0.979 |
| EfficientNetV1-L2 | 0.962 | 0.957 | 0.964 | 0.974 | 0.976 | 0.980 |
| EfficientNetV2-B0 | 0.928 | 0.923 | 0.92 | 0.941 | 0.947 | 0.948 |
| EfficientNetV2-B1 | 0.93 | 0.925 | 0.922 | 0.943 | 0.950 | 0.950 |
| EfficientNetV2-B2 | 0.935 | 0.928 | 0.925 | 0.948 | 0.953 | 0.955 |
| EfficientNetV2-B3 | 0.943 | 0.938 | 0.935 | 0.952 | 0.956 | 0.956 |
| EfficientNetV2T | 0.953 | 0.95 | 0.946 | 0.957 | 0.958 | 0.961 |
| EfficientNetV2\_GC | 0.957 | 0.963 | 0.958 | 0.976 | 0.978 | 0.972 |
| EfficientNetV2S | 0.96 | 0.957 | 0.951 | 0.976 | 0.978 | 0.979 |
| EfficientNetV2M | 0.963 | 0.96 | 0.956 | 0.979 | 0.979 | 0.981 |
| EfficientNetV2L | 0.969 | 0.966 | 0.96 | 0.976 | 0.974 | 0.979 |
| EfficientNetV2XL | 0.968 | 0.964 | 0.96 | 0.978 | 0.980 | 0.978 |

4.4. Localization Using Ablation-CAM

In the context of medical image classification using deep learning, it is imperative to enhance the interpretability and significance of the results. Ablation-CAM emerged as a gradient-free methodology designed to provide visual explanations for models based on deep CNNs [[54](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-54)]. This technique operates by selectively ablating (removing) individual units within feature maps and measuring the subsequent drop in the activation score for the target class. The significance of each feature map unit was then quantified as the proportion of decrease in the activation score.

To generate the ablation-CAM map, feature map units are weighted based on their calculated importance and superimposed onto the original image. The outcome is a coarse localization map that accentuates the pivotal regions in the image, thereby influencing the model’s concept predictions.

Notably, ablation-CAM exhibits superiority over the state-of-the-art Grad-CAM technique across diverse image classification tasks [[55](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "ref-55)]. Because ablation-CAM is more resilient to local irregularities and saturations within the neural network, it is considered an effective and robust approach to visual interpretation. To utilize this functionality, ablation-CAM was applied after the prediction of the class label by the developed classification system. Further, we visualized the effect of employing the ablation-CAM technique on X-ray test images. [Fig. 9a](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-9) shows the heatmap for a test image from the pulmonary edema class; [Fig. 9b](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-9) depicts the heatmap for a test image from the pleural effusion class; and [Fig. 9c](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-9) exhibits the heatmap for a test image from the normal cases class.

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Figure 9. Visualization of the effect of employing the ablation-CAM technique on X-ray test images. (a) The heatmap for a test image from the pulmonary edema class; (b) The heatmap for a test image from the pleural effusion class; (c) The heatmap for a test image from the normal cases class

Based on radiographic differences, a normal chest X-ray ([Fig. 9c](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-9)) shows clear lungs at which there is no buildup in the person’s lungs and a physician can define the borders of the vessels very well because they appear sharp and demarcated. Moreover, the vessels in the upper lung were relatively smaller than the vessels in the lower lungs of a person with a healthy lung. Besides, the pleural cavity typically contains approximately 15 ml of pleural fluid.

In contrast, increased hydrostatic pressure leads to pulmonary vascular congestion and cephalization of the pulmonary vasculature. This case is not yet edema because the fluid is still in the pulmonary vessels. Consequently, once the fluid leaves the pulmonary vessels and enters the interstitial space, the patient will develop interstitial pulmonary edema (actual edema). Subsequently, the fluid spills into the alveolar space in which the patient will get alveolar pulmonary edema (airspace edema). The appearance of edema was heterogeneous with interstitial and airspace edema. Hence, if a patient develops pulmonary edema, there may be two signs. First, the upper lungs are much more indistinct which means that the edema fluid has moved from the vessels to the interstitial space, and the vessels seem to be more enlarged and not well-defined. The other sign is, that the patient has interlobular septal thickening, which is manifested by Kerley B lines, which are typically less than 1 cm in length at the lung periphery and represent fluid in the interstitial space ([Fig. 9a](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-9)).

On the contrary, pleural effusion is excess fluid that accumulates between two layers of the plural including the parietal pleura and visceral pleura. Because the lungs are always in motion, there must be some fluid between the two layers of the pleura to protect them from injury by friction. Furthermore, pleural effusion is the result of any process that causes more fluid to develop than it can be absorbed (>15 ml in the pleural cavity). Typically, the area that is the first to present plural effusion is the right and left costophrenic angle. This is because the fluid is heavier than the lung and it must fall towards gravity. In the normal case ([Fig. 9c](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265#fig-9)), the appearance of both costophrenic angles was clear and sharp. In contrast, left-sided pleural effusion is present in [Fig. 9b](https://www.sciencedirect.com/org/science/article/pii/S1546221824005265" \l "fig-9), because the left costophrenic angle is blunt and is not visible due to the high fluid level.

Lastly, based on the abovementioned analysis of X-rays for normal cases, pulmonary edema disease, and pleural effusion disease, it is obvious that employing the ablation-CAM technique on X-ray test images provides meaningful insight into the chest X-rays of the target medical application.

5. Conclusion

There is a growing need to promote the advancement of medical image classification systems that demonstrate superior performance in diagnosing diseases within the field of pathology. Therefore, this study incorporated a deep learning model based on the EfficientNet-V1-B4 architecture with the training-based AdamW optimization method. Consequently, the developed system operated on chest X-ray, which required passing through a preprocessing stage before being fed into the training model. The preprocessing stage involves enhancing the contrast of the chest X-ray images using the CLAHE approach, resizing images to 380 × 380 resolution, and applying the data augmentation process.

To carry out the classification task, a new dataset of 28,309 samples was formed by combining several publicly available datasets. This dataset comprised three patterns: pleural effusion, pulmonary edema, and normal cases. Further, the dataset was divided into 85% samples for training the model and 15% samples for testing the model. The results show that the developed system achieved a classification rate of approximately 0.983. In addition, the achieved AUC was 1.00 for pulmonary edema and normal cases, and the obtained AUC for pleural effusion disease was approximately 0.99. Additionally, the categorization system utilizes ablation-CAM which provides meaningful insight into the chest X-rays of the target medical application.

In summary, early and accurate detection of pulmonary conditions such as edema and effusion can significantly influence patient outcomes. This study has the potential to revolutionize the detection of pulmonary edema and pleural effusion, leading to improvements in patient care, healthcare efficiency, and accessibility of advanced diagnostic tools. In line with this, the study may contribute to reducing the workload of radiologists and healthcare providers. Automating the initial screening and diagnosis process can allow specialists to focus on more complex cases and patient care, thereby enhancing the overall healthcare efficiency.

Future work should focus on further validating the suitability of the model under consideration in this research to identify other diagnoses using larger and more diverse datasets. Further research can be conducted using the EffiecientNet-V2 model and examining its performance on smaller X-ray image sizes to reduce memory usage for the image classification problem under investigation.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: Anas AbuKaraki, Khalid Alemerien; data collection: Malek Zakarya Alksasbeh; analysis and interpretation of results: Anas AbuKaraki, Malek Zakarya Alksasbeh, Sumaya Abusaleh, Hamzah Alshamaseen; draft manuscript preparation: Bilal Alqudah, Tawfi Alrawashdeh. All authors reviewed the results and approved the final version of the manuscript.

**INTRODUCTION:** Re-expansion pulmonary edema (REPE) is a complication of pneumothorax or pleural effusion drainage, leading to rapid respiratory distress and hemodynamic instability. The pathophysiology has not been established, but it has been hypothesized that the involvement of hydrostatic pressure and vascular permeability plays a significant role.

**CASE PRESENTATION:** A 66-year-old man was referred to the emergency department (ED) by his oncologist after an incidental right-sided pneumothorax was detected during a routine chest CT scan. Further investigation revealed a recent onset of dyspnea, chest pain, and cough lasting approximately 24 hours. His medical history included stage IV colon cancer, lung adenocarcinoma, and COPD.Upon presentation, the patient was hemodynamically stable and showed no respiratory distress. A chest X-ray confirmed the right-sided pneumothorax with significant collapse of the right lower and middle lobes. A right-sided chest tube thoracostomy was placed, and a post-procedure chest X-ray showed significant improvement in the pneumothorax with lung reexpansion.About an hour after chest tube placement, the patient experienced new onset of frothy sputum, dyspnea, and hypoxia, requiring non-invasive bi-level ventilation to achieve 93% oxygen saturation. The patient also became hemodynamically unstable, with a blood pressure of 75/55 mmHg and a heart rate of 136 beats/min. He received crystalloid fluids and required vasopressors to maintain blood pressure. Subsequent chest X-rays confirmed a significant pulmonary infiltrate in the right lung, confirming the diagnosis of re-expansion pulmonary edema.The patient was admitted to the critical care unit. Pressure support was gradually weaned off, and diuretic use was minimized due to hypotension. Follow-up chest X-rays showed resolution of the pulmonary edema. The chest tube was eventually removed, and the patient was discharged home without needing supplemental oxygen after a five-day hospital stay.

**DISCUSSION:** Chest tube thoracostomy is widely used for managing pneumothorax or pleural fluid drainage, but it can lead to complications like tube malposition, infection, or bleeding. REPE has been described in up to 1% of cases in most available literature. Primary risk factors include young age (<40 years), lung collapse for more than 24 hours, a large pneumothorax, and the use of suction after the chest tube is placed. In our patient, a history of chest discomfort for more than 24 hours and a large pneumothorax increased his risk. Various methods have been described to reduce the risk of REPE, including connecting the tube to water seal without negative pressure and closely monitoring patients in the first 2 hours after chest tube placement due to an increased risk of this complication. The image findings on a chest X-ray show a unilateral alveolar filling pattern, and on a CT chest, there will be mainly ground-glass opacities on the affected side, primarily involving the peripheral areas. The treatment is mainly supportive, including diuretics, oxygen therapy with possible mechanical ventilation, and hemodynamic support if required.

**CONCLUSIONS:** Physicians should closely monitor patients following thoracentesis and chest tube placement, especially those with pneumothorax or pleural effusions of unknown duration.

Background

[Blunt chest trauma](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-blunt-trauma) can present with variable intrathoracic organ involvement, including valvular dysfunction. [Mitral valve](https://www.sciencedirect.com/topics/medicine-and-dentistry/mitral-valve) chordal rupture is a more common cause of heart failure post [chest trauma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thorax-injury), while [aortic valve](https://www.sciencedirect.com/topics/medicine-and-dentistry/aortic-valve) abnormalities are rare.

Case

59-year-old male presented with a traumatic fall from a ladder. He sustained left clavicular and [spinal fractures](https://www.sciencedirect.com/topics/medicine-and-dentistry/spine-fracture). He was hemodynamically stable and had no prior known [cardiac disease](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/heart-disease). He underwent clavicle fracture repair and [spinal fusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/spinal-fusion), with post-op [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema). Transthoracic echo revealed severe [aortic regurgitation](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/aortic-regurgitation) (AR). Transesophageal echo (TEE) revealed an avulsed right coronary cusp (Fig. 1), with resultant severe aortic insufficiency by [color Doppler](https://www.sciencedirect.com/topics/medicine-and-dentistry/color-doppler-flowmetry) (Fig. 2) and by pressure half-time (Fig. 3).

Decision-making

Despite the [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema), which responded to IV [diuretics](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/diuretic-agent), the patient remained hemodynamically stable. Given the acuity of the [AR](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/aortic-regurgitation), which was anticipated to be poorly tolerated, the decision was to perform [aortic valve replacement](https://www.sciencedirect.com/topics/medicine-and-dentistry/aortic-valve-replacement). The patient wanted to be physically active and elected to have a [bioprosthetic valve](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-valve-bioprosthesis) to avoid long term [anticoagulation](https://www.sciencedirect.com/topics/medicine-and-dentistry/anticoagulation). He underwent successful aortic valve replacement with a tissue prosthesis (Fig. 4).

Conclusion

[Blunt chest trauma](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-blunt-trauma), including falling from heights, can result in valvular rupture. In the setting of new pulmonary edema, this should be suspected, and proper studies performed so that prompt medical and/or surgical therapy can be undertaken.

Abstract

Purpose

To determine the accuracy of quantitative CT to diagnose pulmonary edema compared to qualitative CT and [CXR](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) and to determine a threshold Hounsfield unit (HU) measurement for pulmonary edema on CT examinations.

Method

Electronic medical records were searched for patients with a billing diagnosis of heart failure and a Chest CT and CXR performed within three hours between 1/1/2016 to 10/1/2016, yielding 100 patients. CXR and CT examinations were scored for the presence and severity of edema, using a 0–5 scale, and CT HU measurements were obtained in each lobe. Polyserial correlation coefficients evaluated the association between CT HUs and CXR scores, and receiver operating characteristic (ROC) curve analysis determined a cutoff CT HU value for identification of pulmonary edema.

Results

Correlation between CT HU and CXR score was moderately strong (r = 0.585−0.685) with CT HU measurements demonstrating good to excellent accuracy in differentiating between no edema (grade 0) and mild to severe edema (grades 1–5) in every lobe, with AUCs ranging between 0.869 and 0.995. The left upper lobe demonstrated the highest accuracy, using a cutoff value of -825 HU (AUC of 0.995, sensitivity = 100 % and specificity = 95.1 %). Additionally, qualitative CT evaluation was less sensitive (84 %) than portable CXR in identifying pulmonary edema. However, quantitative CT evaluation was as sensitive as portable CXR (100 %) and highly specific (95 %).

Conclusions

Quantitative CT enables the identification of pulmonary edema with high accuracy and demonstrates a greater sensitivity than qualitative CT in assessment of pulmonary edema.

1. Introduction

[Pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) is one of the most common entities that is encountered on routine [chest imaging](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest-imaging) in both the inpatient and outpatient settings. Cardiogenic pulmonary edema is commonly caused by [acute decompensated heart failure](https://www.sciencedirect.com/topics/medicine-and-dentistry/acute-decompensated-heart-failure). The chest x-ray (CXR) is one of the most frequently utilized noninvasive [diagnostic tests](https://www.sciencedirect.com/topics/nursing-and-health-professions/diagnostic-test) ordered to confirm or rule out pulmonary edema. CXR assessment of pulmonary edema has been shown to correlate with volume status, total [blood volume](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/blood-volume) [[[1]](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0005), [[2]](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0010), [[3]](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0015)], and other indicators of heart failure [[4](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0020)]. Snashall, et al. demonstrated that changes in water lung volume in animal models as low [as 35](https://www.sciencedirect.com/topics/nursing-and-health-professions/9-4-acetyl-3-hydroxy-2-propylphenoxy-methyl-3-1h-tetrazol-5-yl-4h-pyrido1-2-apyrimidin-4-one) % can be detected on CXR [[5](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0025)].

Chest [computed tomography](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) (CT) has also been used in the noninvasive evaluation of pulmonary edema and offers the added value of allowing for the quantitative assessment of lung density as a proxy for alterations in lung [water content](https://www.sciencedirect.com/topics/nursing-and-health-professions/water-content). Several different methods of quantifying lung density have been described, including the sector method [[6](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0030)], in which the density of a peripheral area of [lung parenchyma](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-parenchyma) is measured, and the whole lung method [[7](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0035)] in which the mean HU (Hounsfield unit) measurement of the [lung parenchyma](https://www.sciencedirect.com/topics/immunology-and-microbiology/lung-parenchyma) and central [vascular structures](https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-vessel) is quantified. CT lung density measurements have been shown to increase with worsening pulmonary edema, as defined by severity of pulmonary edema on CXR, and also to correlate with increasing [pulmonary artery wedge pressures](https://www.sciencedirect.com/topics/nursing-and-health-professions/lung-wedge-pressure) [[8](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0040)].

CT is believed to have a greater sensitivity for the detection of many [pulmonary disease](https://www.sciencedirect.com/topics/medicine-and-dentistry/silo-fillers-disease) conditions when compared to conventional chest radiography. However, the authors have noted that mild pulmonary edema is often identified on CXR but not on concurrent CT examinations. To our knowledge, no studies have evaluated the sensitivity of CT versus CXR in the detection of pulmonary edema. We hypothesize that CXR evaluation for pulmonary edema is more sensitive than qualitative (visual) CT evaluation in the [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of lung density measurements on CT. Our results imply the necessity to establish the Hounsfield unit (HU) threshold to distinguish between patients with and without pulmonary edema for the routine chest CT examinations.

2. Materials and methods

2.1. Patient selection

IRB approval was obtained, and [informed consent](https://www.sciencedirect.com/topics/medicine-and-dentistry/informed-consent) was waived for our HIPAA-compliant retrospective study. The [electronic medical records](https://www.sciencedirect.com/topics/immunology-and-microbiology/electronic-medical-record) were searched for patients with a billing diagnosis of heart failure who had a [CXR](https://www.sciencedirect.com/topics/nursing-and-health-professions/thorax-radiography) and Chest [CT](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/computed-tomography) performed on the same day between 1/1/2016 to 10/1/2016. Patients with contrast enhanced CTs and those with [CXR](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) and [CT](https://www.sciencedirect.com/topics/immunology-and-microbiology/computer-assisted-tomography) performed greater than three hours apart were excluded from analysis. The electronic medical record was also reviewed for demographic information including age and sex.

2.2. Imaging acquisition and interpretation

Portable supine AP and upright PA and lateral [CXRs](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest-radiograph) (2-view) were included for analysis. Two thoracic subspecialty trained radiologists (HH, 20+ years of experience and MH, 2 years of experience) analyzed the CXRs *in consensus*. The severity of [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) was graded on CXRs using a scale of 0–5 (0: no edema, 1: mild, 2: mild to moderate, 3: moderate, 4: moderate to severe, 5: severe). Additionally, the presence of [emphysema](https://www.sciencedirect.com/topics/nursing-and-health-professions/emphysema), [pleural effusions](https://www.sciencedirect.com/topics/nursing-and-health-professions/pleura-effusion), parenchymal consolidations, and [intubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/intubation) status were recorded.

[CT](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) examinations were performed using a tube voltage of 100–120 kVp. The data was then reconstructed using a lung kernel and 3.0 mm thick slices. One radiologist (MB, a thoracic radiologist with 3-year experience) manually drew ROIs (Region of Interest) on axial images in the right and left upper lobes, right and left lower lobes, lingula, and right middle lobe using the sector method. The central [vasculature](https://www.sciencedirect.com/topics/immunology-and-microbiology/vascularization), including the main and lobar [pulmonary arteries](https://www.sciencedirect.com/topics/immunology-and-microbiology/pulmonary-artery), [pulmonary veins](https://www.sciencedirect.com/topics/immunology-and-microbiology/pulmonary-vein) and airways were excluded from the ROI. The average [CT](https://www.sciencedirect.com/topics/nursing-and-health-professions/computer-assisted-tomography) density within the ROI in HU was recorded. ROIs were not calculated in lobes which contained [emphysema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/emphysema), lobar [atelectasis](https://www.sciencedirect.com/topics/medicine-and-dentistry/atelectasis), or pneumonia.

CT examinations corresponding to patients with portable CXR were visually evaluated by HH and MH *in consensus* for the presence and severity of [pulmonary edema](https://www.sciencedirect.com/topics/nursing-and-health-professions/lung-edema), using a 0–5 scale (0: no edema, 1: mild, 2: mild to moderate, 3: moderate, 4: moderate to severe, 5: severe) ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "fig0005), [Fig. 2](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "fig0010), [Fig. 3](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "fig0015)). As the same two readers analyzed both CXR and CT images, the analysis of CT examinations was performed after greater than a 3 month wash out period. All CTs were viewed on a [PACS system](https://www.sciencedirect.com/topics/nursing-and-health-professions/picture-archiving-and-communication-system) with a window width and level of 1500 HU and -700 HU, respectively. Additionally, the presence or [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of the following was recorded: ground-glass opacity, [pleural effusions](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleura-effusion), and interlobular septal thickening. The radiologists were blinded to the CXR pulmonary edema scores and the Hounsfield unit measurements of each lobe.

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Fig. 1. 87 y.o. female status post a fall with mild to moderate pulmonary edema on portable CXR (CXR score 2) and no pulmonary edema on CT (CT score 0), RUL -705 HU and LUL -763 HU.

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Fig. 2. 64 y.o. neutropenic male with [tachypnea](https://www.sciencedirect.com/topics/medicine-and-dentistry/tachypnea) and moderate to severe pulmonary edema on portable CXR (CXR score 4) and mild pulmonary edema (CT score 1), RUL -747 HU, LUL -800 HU.

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Fig. 3. 38 y.o. female with [congenital heart disease](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/congenital-heart-disease) and hypotension with moderate pulmonary edema on portable CXR (CXR score 3) and with mild pulmonary edema on CT (CT score of 1), RUL -815 HU, and LUL -774 HU.

2.3. Statistical analysis

Polyserial [correlation coefficients](https://www.sciencedirect.com/topics/nursing-and-health-professions/correlation-coefficient) were used for evaluating the association between continuous values of CT HU measurements in each lobe and categorical values of the CXR scores for pulmonary edema. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff value of CT HU measurements for differentiation between CXR score 0 (no evidence of pulmonary edema) and CXR scores 1–5 (mild to severe edema). All statistical analyses were performed using R version 3.5.2 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient demographics and CXR scores

Patient demographics and CXR pulmonary edema scores are summarized in [Table 1](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "tbl0005). Of the 100 chest radiographs, 64 [CXRs](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest-radiograph) were obtained in the [supine position](https://www.sciencedirect.com/topics/medicine-and-dentistry/supine-position) using AP portable technique and the remaining 36 cases were obtained in the upright position using a 2-view technique. Of the 100 cases, 15, 33, 22, 19, 10 and 1 cases were classified as CXR scores 0–5, respectively. Twenty-five cases had an [endotracheal tube](https://www.sciencedirect.com/topics/nursing-and-health-professions/endotracheal-tube) or [tracheostomy tube](https://www.sciencedirect.com/topics/nursing-and-health-professions/tracheostomy-tube) in place. [Pleural effusions](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pleura-effusion) and [emphysema](https://www.sciencedirect.com/topics/nursing-and-health-professions/emphysema) were seen in 29 and 8 CXRs, respectively.

Table 1. Demographics, CXR scores, and CT HU measurements of the study population.

| Empty Cell | **All** | **Portable CXR** | **Two views CXR** |
| --- | --- | --- | --- |
| **n** | 100 | 64 | 36 |
| **Age** | 21−101 | 22−101 | 21−89 |
| **Sex, male/female** | 65/35 | 77/23 | 88/12 |
| **CXR** |  |  |  |
| **Score0** | 15 | 9 | 6 |
| **1** | 33 | 13 | 20 |
| **2** | 22 | 16 | 6 |
| **3** | 19 | 15 | 4 |
| **4** | 10 | 10 | 0 |
| **5** | 1 | 1 | 0 |
| **Intubation** | 25 | 21 | 4 |
| **Effusion** | 29 | 20 | 9 |
| **Emphysema** | 8 | 2 | 6 |
| **Consolidation** | 22 | 13 | 9 |
| **CT HU measurements median HU, (n)** |  |  |  |
| **RUL** | −753.0 (79) | −725.5 (50) | −793.0 (29) |
| **RML** | −795.0 (77) | −786.0 (48) | −811.0 (29) |
| **RLL** | −746.0 (69) | −732.0 (42) | −776.0 (27) |
| **LUL** | −768.0 (79) | −755.0 (49) | −790.0 (30) |
| **Lingula** | −766.0 (71) | −760.5 (44) | −798.0 (27) |
| **LLL** | −745.5 (64) | −737.0 (37) | −770.0 (27) |

CT, computed tomography; CXR, chest X-ray radiograph; HU, Hounsfield unit; LLL, left lower lobe, LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe.

3.2. Qualitative (visual) CT assessment for pulmonary edema

CT images for patients with portable CXRs were qualitatively scored for the presence of pulmonary edema (0 = no edema, 1 = mild edema through 5 = severe edema), blinded to the CT attenuation HU measurements, corresponding CXR images and scores. [Fig. 4](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "fig0020)a shows how these scores compared to the portable CXR scores for each patient. The sensitivity of qualitative (visual) CT assessment for pulmonary edema (score > 1) compared to portable CXR (score > 1) was 84 %, with a specificity of 78 %. Of note, this sensitivity and specificity is less than that of [quantitative CT](https://www.sciencedirect.com/topics/medicine-and-dentistry/quantitative-computed-tomography), which yielded a sensitivity of 100 % and specificity of 95 % using a HU threshold of -825 in the LUL.

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Fig. 4. a. Bubble plot showing qualitative CT score for pulmonary edema based on visual assessment (score 0-5) versus portable CXR score (score 0-5) of pulmonary edema. The number inside each circle corresponds to the number of patients with that combination of CXR and CT scores. b. Beeswarm boxplots demonstrating the relationship between CT HU versus CXR scores for pulmonary edema (portable and 2-view combined).

3.3. Quantitative CT assessment of pulmonary edema using CT Hounsfield unit measurements

CT HU measurements of the right upper lobe (RUL), the right middle lobe (RML), the right lower lobe (RLL), the left upper lobe (LUL), the lingula (Lingula), and the left lower lobe (LLL) were measurable in 79, 77, 69, 79, 71, and 64 cases, respectively. Beeswarm boxplots of CT HU versus CXR scores (portable and 2-view combined) are shown in [Fig. 4](https://www.sciencedirect.com/science/article/pii/S2352047720300629#fig0020)b. The polyserial correlation analysis demonstrated moderate to strong correlations between CT HU measurements in each lobe and CXR score with portable and 2-view data combined (correlation coefficients: RUL 0.642, RML 0.616, RLL 0.585, LUL 0.685, Lingula 0.671, and LLL 0.599).

To evaluate for differences in detection of pulmonary edema between portable and 2-view techniques, Beeswarm boxplots of CT HU versus CXR scores for both techniques were created and are shown in [Fig. 5](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "fig0025)a and b. There were moderate to strong correlations between CT HU measurements in each lobe and portable CXR score (correlation coefficients: RUL 0.626, RML 0.625, RLL 0.548, LUL 0.734, Lingula 0.668, and LLL 0.638). CT HU measurements and 2-view CXR scores in each lobe also showed moderate to strong correlation, but the coefficients were smaller than those of portable chest radiographs (correlation coefficients: RUL 0.506, RML 0.404, RLL 0.556, LUL 0.590, Lingula 0.612, and LLL 0.393).

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Fig. 5. a. Beeswarm boxplots demonstrating the relationship between CT HU versus CXR scores for pulmonary edema based on portable CXR. b. Beeswarm boxplots demonstrating the relationship between CT HU versus CXR scores for pulmonary edema based on 2-view CXR.

ROC analysis results of CT HU measurements for diagnosis of pulmonary edema (CXR score 0 versus CXR scores 1–5) are shown in [Fig. 6](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "fig0030)a and b. The largest [area under the curve](https://www.sciencedirect.com/topics/nursing-and-health-professions/area-under-the-curve) (AUC) for portable CXR was 0.995 in LUL with the cutoff value of -825 HU (sensitivity = 100 % and specificity = 95.1 %). The second highest AUC of 0.978 was observed in the RUL with the cutoff value of -822 HU (sensitivity = 87.5 % and specificity = 100 %). The AUCs were 0.869, 0.861, 0.882, and 0.890 for RML, RLL, Lingula, and LLL, respectively. For two-view CXR, the highest AUC was observed in RLL as 0.736 (sensitivity = 60 %, specificity = 90.9 %). The AUCs in the RUL, RML, LUL, Lingula and LLL were 0.504, 0.663, 0.632, 0.582, and 0.717, respectively.

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Fig. 6. a. Receiver operator characteristic (ROC) analysis results of CT HU measurements for diagnosis of pulmonary edema based on portable CXR. b. Receiver operator characteristic (ROC) analysis results of CT HU measurements for diagnosis of pulmonary edema based on 2-view CXR.

4. Discussion

Our study demonstrates a moderately strong correlation between CT HUs and CXR pulmonary edema grade in every lobe by analyzing a series of near-concurrent chest CTs and CXRs. Additionally, we showed that CT HU measurements demonstrate excellent accuracy in differentiating between no edema (grade 0) and mild to severe edema (grades 1–5) in the upper lobes with [AUCs](https://www.sciencedirect.com/topics/nursing-and-health-professions/area-under-the-curve) as high as 0.995 in the LUL. Moreover, our work showed that by using a HU cutoff of -825 in the LUL, [quantitative CT](https://www.sciencedirect.com/topics/medicine-and-dentistry/quantitative-computed-tomography) analysis yielded a higher sensitivity (100 %) and specificity (95 %) to qualitative (visual) CT analysis (sensitivity 84 % and specificity 78 %) for pulmonary edema. To our knowledge, our study is the first to demonstrate the superiority of quantitative CT for this purpose.

Prior work supports our finding of a strong correlation between CT Hounsfield unit measurements with CXR assessment of pulmonary edema. Kato et al. used CXR and [pulmonary capillary wedge pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-artery-occlusion-pressure) to divide patients into two groups: edema and no edema and then measured CT HUs in each patient. They found that worsening CT measurements of pulmonary edema correlated linearly with mean [pulmonary capillary wedge pressure](https://www.sciencedirect.com/topics/nursing-and-health-professions/pulmonary-artery-occlusion-pressure) [[9](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0045)]. Morooka et al. also correlated CT Hounsfield unit measurements not only with [pulmonary artery](https://www.sciencedirect.com/topics/immunology-and-microbiology/pulmonary-artery) wedge pressure measurements but also with [NYHA](https://www.sciencedirect.com/topics/medicine-and-dentistry/new-york-heart-association-class) functional classification of heart failure [[8](https://www.sciencedirect.com/science/article/pii/S2352047720300629#bib0040)]. They concluded that CT HU measurements were significantly higher in the patients with CHF [NYHA](https://www.sciencedirect.com/topics/nursing-and-health-professions/new-york-heart-association-class) classification of II or greater. Moreover, they showed that CT HU measurements increased with severity of edema and PCWP measurements in their [canine model](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/canine-model).

Our study also demonstrates a correlation between CT HU and worsening pulmonary edema on CXR. While there was no significant difference in AUCs amongst all lobes, the right and left upper lobes demonstrated the highest accuracy. The decreased accuracy in the lower lobes is likely related to [atelectasis](https://www.sciencedirect.com/topics/medicine-and-dentistry/atelectasis) either due to gravity or adjacent pleural effusions. Previous studies have documented that while there is no cranio-caudal gradient of lung density measurements, the dependent portions of the lungs demonstrated higher attenuation values in [normal subjects](https://www.sciencedirect.com/topics/immunology-and-microbiology/normal-human) without pulmonary edema [[8](https://www.sciencedirect.com/science/article/pii/S2352047720300629#bib0040),[10](https://www.sciencedirect.com/science/article/pii/S2352047720300629" \l "bib0050)]. This has been postulated to be attributed to the gravitational effects on the lower lobes causing compression of the [lung parenchyma](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-parenchyma) in addition to increase in lung [blood volume](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/blood-volume) with subsequent increases in lung density. Thus, the upper lobes may more reliably reflect changes in total lung water given the absence of additional factors which may confound density measurements.

We observed that while both portable and 2-view CXR techniques demonstrated moderate to strong correlation between CT HU and CXR score in each lobe, there was a stronger correlation with the portable CXRs than the 2 view CXR. Additionally, we noted that the CT HU for mild pulmonary edema (CXR score of 1) seen on portable CXRs was greater than the CT HU for mild pulmonary edema seen on 2-view CXR. While the cause of this phenomenon is uncertain, the results suggest that 2-view CXRs are more sensitive for early pulmonary edema than portable CXR. Indeed, the very earliest findings of pulmonary edema on CXR, namely pulmonary vascular redistribution and vascular [engorgement](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/engorgement), occur before water extends into the alveoli. With purely vascular engorgement, we would not expect the CT lung density to increase significantly. Portable CXR is less able to demonstrate these subtle, early findings, particularly because of supine positioning and smaller lung volumes. Thus, early edema on portable CXR likely corresponds to early alveolar edema which is associated with an increase in CT lung density. These findings also suggest that CT is less sensitive for the earliest findings in pulmonary edema. It may be that quantitative measurement of the branch pulmonary [artery size](https://www.sciencedirect.com/topics/nursing-and-health-professions/artery-diameter) in these patients would be better able to distinguish patients with early pulmonary edema.

We found that qualitative (visually assessed) CT evaluation was less sensitive and specific (sensitivity 84 %) than portable CXR for the presence of pulmonary edema. However, quantitative CT evaluation was as sensitive as portable CXR (sensitivity 100 %). Additionally, quantitative CT demonstrated a very high specificity (95 %), better than qualitative CT (specificity 78 %). To our knowledge, no prior studies have evaluated the sensitivities of these two imaging modalities. The results suggest that CT readers using only visual assessment tend to underestimate the presence of pulmonary edema, and radiologists may benefit from quantitative methods such as CT HU measurements of the lung attenuation, an easy and simple ROI measurement in LUL taking a few seconds. A cutoff value of -825 HU in the LUL has a sensitivity of 100 % and a specificity of 95 % in diagnosing pulmonary edema. Thus, CT HU measurements may be used to improve assessment of the earliest signs of edema.

The current study has several limitations, the first being that our study did not include correlation with an invasive measurement of cardiogenic pulmonary edema such as [pulmonary capillary wedge pressure](https://www.sciencedirect.com/topics/immunology-and-microbiology/pulmonary-artery-occlusion-pressure). However, prior studies have established a strong correlation between CT HU measurements and wedge pressure measurements as well as NYHA functional classification of cardiogenic pulmonary edema [[8](https://www.sciencedirect.com/science/article/pii/S2352047720300629#bib0040)]. Second, the near concurrent images (CXR and CT) were obtained up to three hours apart. Although unlikely, the possibility for changes in medication or treatment during the time period between studies could not be eliminated. Third, CT measurement may be affected if the patient has underling [lung disease](https://www.sciencedirect.com/topics/medicine-and-dentistry/silo-fillers-disease) such as subtle emphysema (underestimation) and [pulmonary fibrosis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-fibrosis) (overestimation). Similarly, the presence of effusions and [atelectasis](https://www.sciencedirect.com/topics/nursing-and-health-professions/atelectasis) could confound the interpretation of edema on CXR, particularly one-view portable CXR. Lastly, lung volumes could not be controlled for and the potential effects of [mechanical ventilation](https://www.sciencedirect.com/topics/nursing-and-health-professions/artificial-respiration) on lung density measurements are unclear. Presumably, ventilator settings such as [tidal volume](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/tidal-volume) and pressure settings could alter lung density measurements independent of the severity of pulmonary edema.

In conclusion, we have shown that quantitative CT analysis strongly correlates with pulmonary edema identified by CXR. Moreover, quantitative CT analysis was more sensitive and specific than qualitative CT analysis for pulmonary edema. In particular, a cutoff of -825 HU in the left upper lobe showed a 100 % sensitivity and 95 % specificity for the presence of pulmonary edema. These findings suggest that radiologists should employ quantitative CT analysis more routinely in assessment of pulmonary edema, as a qualitative analysis will miss a number of cases. Further work is needed to validate these findings in an independent cohort.

Background

[Pneumonectomy](https://www.sciencedirect.com/topics/medicine-and-dentistry/pneumonectomy) in the adult patient is associated with a mortality of 1–9%. Death is often due to post pneumonectomy pulmonary oedema (PPPO). The use of balanced [chest drainage](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-drainage) system (BCD) in the setting of post pneumonectomy has been reported to be of benefit in the prevention of PPPO. This study seeks to compare the incidence of PPPO in patients who underwent pneumonectomy and whose empty [pleural space](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleural-cavity) was managed either with CRD or BCD.

Methods

This retrospective observational cohort study involved 98 patients who were operated on by one surgeon at Liverpool Hospital, Sydney, Australia from 1997 to 2019. The patients were divided into two groups according to the era in which they had their pneumonectomy. Group 1 consisted of 18 patients managed with clamp-release drainage between 1997 and 2002. Group 2 consisted of 80 patients managed with balanced [chest drainage](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-drainage) between 2003 and 2019. The primary outcomes of interest were the development of PPPO and death. Demographic and clinico-pathological variables between the groups were compared including whether the [phrenic nerve](https://www.sciencedirect.com/topics/medicine-and-dentistry/phrenic-nerve) was sacrificed, volume of infused intraoperative fluid, duration of single [lung ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-ventilation), intraoperative [tidal volumes](https://www.sciencedirect.com/topics/medicine-and-dentistry/tidal-volume), agents of [anaesthetic induction](https://www.sciencedirect.com/topics/medicine-and-dentistry/anesthesia-induction) and maintenance, mean urine output in the first 4 postoperative hours, institution of a postoperative 1.5 L fluid restriction, total chest drainage, day of chest drain removal, presence of radiological postoperative mediastinal shift, post-pneumonectomy pulmonary oedema and death. Group characteristics were compared using t-test and chi-squared for continuous and categorical variables respectively. Univariate and [multivariate analysis](https://www.sciencedirect.com/topics/medicine-and-dentistry/multivariate-analysis) was also undertaken using the Firth method of [logistic regression](https://www.sciencedirect.com/topics/medicine-and-dentistry/logistic-regression-analysis) for rare occurrences in a stepwise fashion.

Results

Through univariate analysis, balanced chest drainage, postoperative fluid restriction and intraoperative [fluid infusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/infusion-fluid) showed significant effect on PPPO. Through [multivariate analysis](https://www.sciencedirect.com/topics/medicine-and-dentistry/multivariate-analysis), balanced chest drainage was found to have independent protective value for PPPO and mortality.

Conclusion

Compared with clamp-release drainage, balanced chest drainage results in a lower incidence of post-pneumonectomy pulmonary oedema and death.

Methods

In this single-centre, retrospective, observational cohort study, all patients who underwent pneumonectomy at Liverpool Hospital, NSW Australia between 1997 and 2019 were included. Patients fell into two groups depending on the type of postoperative chest drainage used. These two groups were then compared. These groups corresponded to the era in which they had their pneumonectomy. Group 1 consisted of patients managed with CRD between 1997 and 2002 and Group 2 consisted of patients managed with

Results

There were 98 patients who underwent pneumonectomy in the study period. Eighteen (18) patients were managed with CRD between 1997 and 2002. Eighty (80) patients were managed with BCD between 2003 and 2019. Comparing the two groups, there were no statistically significant differences found in the age, gender or weight of the patients studied (Table 1).

Comparing intraoperative management variables, there were no significant differences in the side of the pneumonectomy, the numbers of phrenic

Discussion

The mortality from pneumonectomy has been quoted at 1–9% with PPPO implicated as a leading contributor [[1], [2], [3], [4]]. A number of factors have been associated with the development of PPPO including right pneumonectomy [3,4,9], repeat thoracotomy [3], excess perioperative fluids [1,3,6,7,[9], [10], [11], [12]], previous radiotherapy [13] alveolar barotrauma due to mechanical high pressure one-lung ventilation [12,14,15], endothelial damage due to oxidative stress [16,17], relatively

Conclusion

In this study comparing CRD and BCD and its effect on PPPO, BCD was found to be associated with reduced rates of PPPO on multivariate analysis. We therefore recommend BCD as the method of choice for management of the empty pleural space following pneumonectomy.

Abstract

Background

Reexpansion [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (RPE) is a rare complication that may occur after treatment of [lung collapse](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/atelectasis) caused by [pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/pneumothorax), atelectasis or [pleural effusion](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pleura-effusion) and can be fatal in 20% of cases. The pathogenesis of RPE is probably related to histological changes of the [lung parenchyma](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-parenchyma) and reperfusion-damage by [free radicals](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/free-radical) leading to an increased [vascular permeability](https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-vessel-permeability). RPE is often self-limiting and treatment is supportive.

Case report

A 76-year-old patient was treated by intercostal drainage for a traumatic [pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pneumothorax). Shortly afterwards he developed reexpansion pulmonary edema and was transferred to the [intensive care unit](https://www.sciencedirect.com/topics/medicine-and-dentistry/intensive-care-unit) for ventilatory support. Gradually, the edema and dyspnea diminished and the patient could be discharged in good clinical condition.

Conclusion

RPE is characterized by rapidly progressive respiratory failure and [tachycardia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tachycardia) after intercostal [chest drainage](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-drainage). Early recognition of [signs and symptoms](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/physical-disease-by-body-function) of RPE is important to initiate early management and allow for a favorable outcome.

Introduction

We describe the case of a patient suffering from reexpansion [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (RPE) after [chest drainage](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-drainage) for [pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/pneumothorax). This condition is a relatively unknown complication of intercostal chest drainage and is potentially lethal in 20% of cases [[1]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib1). Therefore, early recognition of [signs and symptoms](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/physical-disease-by-body-function) is important since inadequate or delayed treatment may lead to a fatal outcome.

Case report

A 76-year-old male patient suffering from Alzheimer's and [Parkinson's disease](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/parkinsons-disease) had difficulties walking and was admitted to the [neurology](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurology) ward because of frequent falls. Two days after admission, the patient was delirious and fell out of bed again. The neurological resident who examined the patient found absent [breathing sounds](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/abnormal-respiratory-sound) on the left hemi [thorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest). A chest X-ray showed a complete left-sided [pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pneumothorax) and a single, non-dislocated fracture of the seventh rib ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "fig1)). An intercostal drainage tube (ICD) was inserted and 350 mL of serosanguineous fluid was instantly drained whilst suction of 15 cm H2O was applied. A second chest X-ray showed a fully re-expanded left lung ([Fig. 2](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "fig2)) and [oxygen saturation](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxygen-saturation) was 100% with 2 L of oxygen. However, 2 h after the insertion of the ICD, the patient became severely dyspneic and his oxygen saturation level dropped to 66%. Neither severe [blood loss](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/bleeding), air leakages from the ICD or serum abnormalities (Hb, Leucocytes) were observed.

1. [Download: Download high-res image (118KB)](https://ars.els-cdn.com/content/image/1-s2.0-S221300711400046X-gr1_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S221300711400046X-gr1.jpg)

Fig. 1. Complete left-sided pneumothorax, costa 7 fracture.

1. [Download: Download high-res image (116KB)](https://ars.els-cdn.com/content/image/1-s2.0-S221300711400046X-gr2_lrg.jpg)
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Fig. 2. Fully expanded lung after intercostal drain (ICD) insertion.

A repeated chest X-ray showed signs of severe pulmonary edema on the left side ([Fig. 3](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "fig3)). The patient was transferred to the [intensive care unit](https://www.sciencedirect.com/topics/medicine-and-dentistry/intensive-care-unit) (ICU) and received [continuous positive airway pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/continuous-positive-airway-pressure) (CPAP) therapy. The pulmonary edema diminished gradually within a week ([Fig. 4](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "fig4)) and the patient could be transferred back to the neurology ward for further treatment of his [Parkinson's disease](https://www.sciencedirect.com/topics/medicine-and-dentistry/parkinsons-disease). He was discharged to a nursing home three weeks later in good condition.

1. [Download: Download high-res image (112KB)](https://ars.els-cdn.com/content/image/1-s2.0-S221300711400046X-gr3_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S221300711400046X-gr3.jpg)

Fig. 3. Reexpansion pulmonary edema 2 h after drainage.

1. [Download: Download high-res image (112KB)](https://ars.els-cdn.com/content/image/1-s2.0-S221300711400046X-gr4_lrg.jpg)
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Fig. 4. Diminished pulmonary edema after 7 days, ICD removed.

Discussion

History and epidemiology

In 1853, Pinault was the first to describe the formation of [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) after [thoracocentesis](https://www.sciencedirect.com/topics/medicine-and-dentistry/thoracentesis) [[2]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib2). More than a century later, Carlson described the first case of pulmonary edema after [pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/pneumothorax) [[3]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib3).

Mahfood et al. published a review of 47 case reports of RPE in 1959 [[1]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib1). In this study population, the male to female ratio was 38:9 and the mean age was 42 years. In 83% of the cases, the [pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pneumothorax) was present for at least three days; in seven patients however, it had been present for just a couple of hours. Edema developed within 1 h after ICD placement in 64% of the cases. All other patients developed edema within 24 h. Almost all patients (94%) had ipsilateral edema whereas three patients suffered from bilateral edema.

The incidence of RPE described in the literature varies remarkably. This maybe due to the large variety of [symptomatology](https://www.sciencedirect.com/topics/medicine-and-dentistry/symptomatology) and unfamiliarity with the diagnosis. In two studies that investigated [spontaneous pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/spontaneous-pneumothorax) (400 and 375 cases respectively) no cases of RPE were reported [[4]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib4), [[5]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib5). Matsuura et al. on the other hand reported RPE in 14% of 146 patients with [spontaneous pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/spontaneous-pneumothorax) and in 17% of the patients with a total pneumothorax [[6]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib6).

The [mortality rate](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mortality-rate) of patients suffering from RPE is reported to be up to 20% [[1]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib1).

Clinical presentation and treatment

Patients typically present with rapidly progressive dyspnea and [tachypnea](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tachypnea), usually within 1 h after intercostal drainage. Other symptoms include productive [cough](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/coughing), [tachycardia](https://www.sciencedirect.com/topics/medicine-and-dentistry/tachyarrhythmia), hypotension, [cyanosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/cyanosis), fever, [chest pain](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thorax-pain), nausea and vomiting [[1]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib1), [[7]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib7). Symptoms may vary from mild radiographic changes to respiratory failure and signs of [adult respiratory distress syndrome](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/acute-respiratory-distress-syndrome) (ARDS).

A chest X-ray may show a unilateral alveolar filling pattern within 2–4 h after reexpansion, which may progress over 48 h and persist for 4–5 days. The edema resolves in 5–7 days without remaining radiographic abnormalities [[7]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib7). The most common findings on a [computed tomography](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/computed-tomography) (CT)-scan include ipsilateral ground-glass opacities, septal thickening, foci of consolidation, and areas of [atelectasis](https://www.sciencedirect.com/topics/medicine-and-dentistry/atelectasis) [[8]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib8). RPE is usually a self-limiting disease and most often does not need any intervention [[13]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib13). Almost all patients who recover do so within a week.

The treatment of RPE is supportive and consists of oxygen or [CPAP](https://www.sciencedirect.com/topics/medicine-and-dentistry/continuous-positive-airway-pressure) support. In some cases [intubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/intubation) and [mechanical ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/artificial-respiration) with positive end expiratory pressure (PEEP) will be necessary. Intrapulmonary shunting of lung tissue can create [hypoxia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hypoxia) and/or [hypovolemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/hypovolemia). In this case, administration of fluids, [plasma expanders](https://www.sciencedirect.com/topics/medicine-and-dentistry/plasma-substitute) and/or [inotropics](https://www.sciencedirect.com/topics/medicine-and-dentistry/inotropism) are required whereas [diuretics](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/diuretic) are contra-indicated because they can exacerbate [hypovolemia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hypovolemia) [[13]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib13). Lateral [decubitus](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/decubitus) positioning on the affected side can reduce shunting and improve oxygenation. Unilateral ventilation is seldom necessary [[18]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib18).

Pathophysiology

In the 1980s, RPE was thought to originate from an increased permeability of damaged [pulmonary blood vessels](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/pulmonary-blood-vessel), caused by a swift reexpansion of the lung tissue [[9]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib9). According to Sohara, blood vessels are vulnerable to this traction because of histological changes that occur during the chronic lung collapse [[9]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib9), whereas Gumus et al. suggested that after reexpansion, reperfusion of the ischemic lung will increase free oxygen radicals and anoxic stress, leading to damage of the [vascular endothelium](https://www.sciencedirect.com/topics/medicine-and-dentistry/vascular-endothelium) [[10]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib10). As an alternative explanation, Sue et al. postulated that the lung tissue consists of heterogenous areas of hypoxic [vasoconstriction](https://www.sciencedirect.com/topics/medicine-and-dentistry/vasoconstriction) and that pulmonary edema will originate because of hydrostatic pressure in these areas where high perfusion pressure is combined with more negative pressure, decreased [lymph flow](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/lymph-flow) or [venous constriction](https://www.sciencedirect.com/topics/medicine-and-dentistry/venoconstriction) [[11]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib11). Although all factors might contribute to formation of RPE, maybe none of them is essential. This might be why predicting the occurrence of RPE is so difficult.

Risk factors

Multiple authors have investigated possible risk factors for RPE. Matsuura et al. reviewed 146 cases of spontaneous pneumothorax and found that RPE incidence was significantly higher in patients aged 20–39 years than in patients aged >40 years. No statistically significant differences in incidence of RPE were noted for gender, side of collapsed lung, pulmonary co-morbidities, history or [signs and symptoms](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/physical-disease-by-body-function) of pneumothorax [[6]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib6). Not one patient suffering from a pneumothorax sized less than 30% of lung fields developed RPE. In contrast, 17% of the patients with pneumothorax sized >30% of lung fields and 44% of the patients with [tension pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/tension-pneumothorax) developed RPE [[6]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib6).

In animal studies performed by Miller et al., RPE did not develop when a pneumothorax was drained within 3 days [[12]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib12). In humans however, duration maybe of less importance than the size of the pneumothorax. Probably, patients with a larger pneumothorax may seek medical help more quickly because of more severe symptoms. Still, Matsuura et al. suggest that in patients with a moderate extent of lung collapse, longer duration of symptoms is possibly associated with higher rates of RPE when compared to the duration of symptoms for less than one day [[6]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib6).

Prevention

No [randomized clinical trial](https://www.sciencedirect.com/topics/medicine-and-dentistry/randomized-clinical-trial) has yet been performed to compare the effects of different methods of drainage but many articles suggest that the method of [chest drainage](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-drainage) and thus the rapidity of reexpansion might play a role in the development of RPE [[1]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib1), [[3]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib3), [[6]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib6), [[7]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib7), [[9]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib9), [[13]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib13).

In concordance with a consensus statement of an American College of Chest Physicians, most authors advise to drain not more than 1 L of fluid or air at once and to use water valves instead of suction, even though Abunasser and Brown concluded that a large-volume thoracentesis is a safe procedure to perform [[14]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib14), [[15]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib15), [[16]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib16).

The maximal volume of air or fluid to be drained at once is estimated to be 1200–1800 mL. It is advised to stop drainage when the patient starts coughing, as it might be a first sign of edema formation [[7]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib7).

Several studies have been performed to investigate the usefulness of interventions such as oxygen supplementation or the administration of anti-oxidants during reexpansion. The authors concluded that these interventions could prevent RPE, but these studies concern only small study populations [[10]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib10), [[16]](https://www.sciencedirect.com/science/article/pii/S221300711400046X#bib16), [[17]](https://www.sciencedirect.com/science/article/pii/S221300711400046X" \l "bib17).

Conclusion

RPE is a possibly life-threatening but relatively unknown condition. Therefore its occurrence is often not recognized as a complication of chest drainage after pneumothorax. Signs and symptoms include dyspnea, [tachypnea](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tachypnea) and low saturation levels usually within an hour after intercostal drainage.

[Risk factors](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/risk-factor) include younger age, more severe or longer existing pneumothorax and maybe a swift drainage of large amounts of fluids or air. Especially in the presence of risk factors, close [patient monitoring](https://www.sciencedirect.com/topics/medicine-and-dentistry/patient-monitoring) is indicated during the first hours after drainage.

To prevent RPE it is advised to use water valves instead of vigorous suction and to drain small volumes of air or fluids. The disease is often self-limiting and therapy is supportive.

Abstract

[Valvular heart disease](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/valvular-heart-disease) in a parturient presenting for [Cesarean section](https://www.sciencedirect.com/topics/medicine-and-dentistry/cesarean-section) is challenging. A 25 year old [primigravida](https://www.sciencedirect.com/topics/medicine-and-dentistry/primigravida) parturient with severe [mitral stenosis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mitral-valve-stenosis), mild [mitral regurgitation](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mitral-valve-regurgitation), mild [aortic regurgitation](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/aortic-regurgitation), and mild [pulmonary arterial hypertension](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pulmonary-hypertension) required Cesarean delivery after developing [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema). Low-dose spinal with hyperbaric bupivacine 0.5% 1.8 mL plus 25 μg of [fentanyl](https://www.sciencedirect.com/topics/medicine-and-dentistry/fentanyl) was used for anesthesia. Chest [ultrasonography](https://www.sciencedirect.com/topics/medicine-and-dentistry/echography) (US) and [transthoracic echocardiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/transthoracic-echocardiography) (TTE) were used for monitoring purposes. Spinal-induced [preload](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-preload) reduction improved the [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema), as evidenced by chest US. Chest US and TTE helped in fluid management.

Introduction

Rheumatic heart diseases (RHD) are common in developing countries. It commonly affects multiple heart valves. Symptomatic RHD, especially mitral stenosis in pregnancy, increases the risk of adverse maternal and neonatal outcomes [1]. An emergency Cesarean delivery was performed successfully in a 25 year old parturient with severe mitral stenosis, mild mitral regurgitation (MR), and mild aortic regurgitation (AR) complicated by pulmonary edema with low-dose spinal anesthesia. Ultrasonography (US) was used as a monitoring tool. Chest US was performed for detection and monitoring of pulmonary edema in the perioperative period. Written, informed consent was obtained from the patient.

Case report

A 25 year old, 51 kg primigravida at full term presented with active labor pain. She complained of dyspnea at rest and coughing that produced pink frothy sputum. She was referred to our hospital while receiving oxygen supplementation delivered by facemask. She had a diagnosed case of mitral stenosis associated with mild mitral regurgitation, aortic regurgitation, and mild pulmonary arterial hypertension. Her electrocardiogram (ECG) showed left atrial (LA) enlargement with right ventricular (RV)

Discussion

The parturient with heart disease is always challenging. Pregnancy and labor adds additional stress to an already compromised cardiovascular system. Patients with mitral stenosis have reduced blood flow from the LA to the left ventricle (LV) and increased LA pressure. Increased heart rate in pregnancy aggravates this condition by reducing diastolic filling time, leading to deceased LV filling and increased pulmonary blood volume, which causes more chances for pulmonary edema. After delivery of

Abstract

Background

Primary [Spontaneous Pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/spontaneous-pneumothorax) (PSP) is usually considered as a benign pathology occurring in young people. In about half of cases, observation only is purposed. In case of intervention, chest tube drainage remains the preponderant strategy even if no studies conclude about superiority of drainage or aspiration. Re-expansion [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (REPE) is a rare but potentially severe complication of chest tube drainage. Risk factors are not well identified, but REPE is more frequent for patients with diabetes, younger than 40 years, with large [pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/pneumothorax), [lung collapse](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/atelectasis) more than one week and fast re-expansion.

Case report

We report a case of a 19-year old male presenting to the [Emergency Department](https://www.sciencedirect.com/topics/medicine-and-dentistry/emergency-department) with a first episode of PSP. He was treated by chest tube drainage with immediate suction. He developed a REPE 3 hours after chest tube drainage with suction. Conservative management and oxygen therapy led to withdrawing the chest tube 9 days later.

Conclusion

For the initial management of PSP, prevention of this complication is essential. In case of risk factors, prevention consist of [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of immediate suction after chest tube drainage and suction should be reserved in case of failure of initial treatment after 24 hours. Even if chest tube drainage is a common gesture, clinical presentation of REPE must alert physicians taking care of these patients.

1. Introduction

Primary [spontaneous pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/spontaneous-pneumothorax) (PSP) is usually considered a benign pathology occurring in young people. In about half of the cases, observation only is proposed. In case of intervention, chest tube drainage remains the preponderant strategy even though no studies have concluded on the superiority of drainage or aspiration. Re-expansion [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (REPE) is a rare but potentially severe complication of chest tube drainage. The risk factors are not clearly identified, but REPE is more frequent in patients with diabetes, those younger than 40 years, with large [pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pneumothorax), [lung collapse](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/atelectasis) lasting more than 1 week, and fast re-expansion. For the management of PSP in an [emergency department](https://www.sciencedirect.com/topics/medicine-and-dentistry/emergency-department) (ED), prevention of this complication by emergency physicians is essential. Even if chest tube drainage is a common act in EDs, clinical presentations must alert physicians.

2. Case report

A 19-year-old male presented to the [ED](https://www.sciencedirect.com/topics/medicine-and-dentistry/emergency-department) with dyspnea and left [chest pain](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-pain) evolving over 2 weeks. He had no [medical history](https://www.sciencedirect.com/topics/medicine-and-dentistry/medical-history) and declared no smoking habits. Initial vital parameters were stable with blood pressure at 125/86 mmHg and air ambient [oxygen saturation](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxygen-saturation) at 96% without any signs of respiratory failure. [Tachycardia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tachycardia) at 110 beats per minute was noted. The [chest radiograph](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S2213007119300966#fig1)) showed a large left primary [spontaneous pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/spontaneous-pneumothorax) (PSP). First-line treatment consisted of a single aspiration, but incomplete re-expansion of the lung was observed. Secondarily, a chest tube drainage was performed with an immediate suction at −20 cm H2O. The success of this strategy was highlighted by a second chest radiograph completed after the procedure. However, 3 h later, [acute respiratory failure](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/acute-respiratory-failure) with dyspnea, [cough](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/coughing), and [hypoxemia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hypoxemia) with an oxygen saturation level that had dropped to 85% required oxygen therapy at 3 L/min. Interstitial opacities of the left lung on the chest radiograph ([Fig. 2](https://www.sciencedirect.com/science/article/pii/S2213007119300966#fig2)) was interpreted as re-expansion [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (REPE). The chest [computed tomography](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) confirmed the diagnosis ([Fig. 3](https://www.sciencedirect.com/science/article/pii/S2213007119300966#fig3)). The patient was admitted to an [intensive care unit](https://www.sciencedirect.com/topics/medicine-and-dentistry/intensive-care-unit). Conservative management and oxygen therapy led to withdrawing the chest tube 9 days later. Antalgics and physiotherapy were prescribed after discharge.

1. [Download: Download high-res image (446KB)](https://ars.els-cdn.com/content/image/1-s2.0-S2213007119300966-gr1_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S2213007119300966-gr1.jpg)

Fig. 1. Anteroposterior chest radiograph showing a large left spontaneous pneumothorax (black arrow).

1. [Download: Download high-res image (465KB)](https://ars.els-cdn.com/content/image/1-s2.0-S2213007119300966-gr2_lrg.jpg)
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Fig. 2. Anteroposterior chest radiograph showing left-sided pulmonary edema (black arrow 1) 3 h after tube [thoracostomy](https://www.sciencedirect.com/topics/medicine-and-dentistry/thoracostomy) (black arrow 2).

1. [Download: Download high-res image (257KB)](https://ars.els-cdn.com/content/image/1-s2.0-S2213007119300966-gr3_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S2213007119300966-gr3.jpg)

Fig. 3. Axial CT of the chest showing re-expansion pulmonary edema with ipsilateral ground-glass opacities (black arrow 1) and septal thickening (black arrow 2).

3. Discussion

3.1. Management of PSP: less invasive strategy to prevent complication

Management of PSP consists of an immediate resolution of pleural air or observation. The optimal initial approach in the management of SP remains the subject of debate, with no superiority of [thoracic drainage](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-drainage) versus aspiration as first-line treatment [[1](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib1)]. In the [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of international consensus, the choice of first-line treatment is left to the discretion of the practitioners caring for these patients. In real-life conditions, even if drainage is a more invasive strategy, it remains the preponderant first-line strategy in the management of SP [[2](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib2)]. Furthermore, the indication of invasive treatment depends on the size of SP, which is not consensual according to the British Thoracic Society and the American College of Chest Physicians guidelines [[3](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib3)]. For about half of the patients, observation can be retained.

In case of intervention, REPE is a rare but major complication of [thoracentesis](https://www.sciencedirect.com/topics/medicine-and-dentistry/thoracentesis), occurring in less than 1% of cases. The [mortality rate](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mortality-rate) is about 20%.

3.2. Physiopathology of REPE

[Physiopathology](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pathophysiology) of REPE is not well known and several theories were evoked. REPE has the characteristic of hydrostatic edema [[4](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib4)]. Some authors have suggested that REPE could be explain by histological changes due to [lung collapse](https://www.sciencedirect.com/topics/medicine-and-dentistry/atelectasis), occurring [bloods vessels damage](https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-vessel-injury) and an increase of [capillary permeability](https://www.sciencedirect.com/topics/medicine-and-dentistry/capillary-permeability) [[5](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib5)]. Anoxic stress linked with reperfusion of lung after reexpansion could also can initiate REPE by [endothelium damage](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/endothelium-lesion) [[6](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib6)]. Then, hydrostatic forces in the lung [microcirculation](https://www.sciencedirect.com/topics/medicine-and-dentistry/microcirculation) generated by rapid reexpansion of the collapsed lung may contribute to the development of REPE [[7](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib7)].

3.3. Clinical presentation of REPE and risk factors

REPE usually develops between 1 h and 24 h after treatment [[8](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib8)], mostly ipsilateral. Some cases of [contralateral](https://www.sciencedirect.com/topics/medicine-and-dentistry/contralateral) or bilateral REPE have been described. Risk factors have not been clearly identified, but REPE is more frequent in patients with diabetes, those younger than 40 years, and in case of large [pneumothorax](https://www.sciencedirect.com/topics/medicine-and-dentistry/pneumothorax) and [lung collapse](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/atelectasis) lasting more than 1 week [[[9]](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib9), [[10]](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib10), [[11]](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib11)]. Another risk factor is fast re-expansion, as in our case. Dyspnea and [cough](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/coughing) are the first signs. The onset of these symptoms after chest tube drainage must alert emergency physicians. A [chest radiograph](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) confirms the diagnosis, and chest [computed tomography](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) demonstrates ground-glass opacities, septal thickening, consolidation, and persistent areas of atelectasis.

3.4. Treatment and prevention of REPE

The treatment of REPE consists of supportive care with oxygen and [CPAP](https://www.sciencedirect.com/topics/medicine-and-dentistry/continuous-positive-airway-pressure) if necessary. Mechanical [intubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/intubation) and [inotropics](https://www.sciencedirect.com/topics/medicine-and-dentistry/inotropism) could be used in the most serious cases. Lateral [decubitus](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/decubitus) on the affected side could be purposed for unilateral case to reducing the [pulmonary shunt](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-shunt) and improving oxygenation.

Attention should be paid to the rapidity of reexpansion, which could favorise development of REPE. Oxygen supplementation or anti-oxidants have been purposed by some authors to prevent REPE, but it appears difficult to concluded about the impact of these interventions [[6](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib6),[12](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib12),[13](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib13)].

3.5. Impact of initial suction in the development of REPE

According to previous guidelines [[14](https://www.sciencedirect.com/science/article/pii/S2213007119300966#bib14)], suction should not be routinely employed in most cases of SP managed in the ED and should be reserved in case of failure of initial treatment after 24 h. Suction remains necessary for the management of secondary spontaneous [pneumothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pneumothorax) with signs of poor tolerance and in case of pneumothorax under [mechanical ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/artificial-respiration).

4. Conclusion

Although chest tube drainage is a common act in [emergency medicine](https://www.sciencedirect.com/topics/medicine-and-dentistry/emergency-medicine) practice in cases of pneumothorax, major complications such as REPE can occur. The risk factors of REPE include young age as well as large and prolonged pneumothorax. In these cases, prevention of REPE consists of the [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of immediate suction after chest tube drainage.

Abstract

Objective

[Chest trauma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thorax-injury) remains a leading cause of trauma-death. Since [lung contusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-contusion) is one of the most important lesions implicated, the aim of this experimental study was to evaluate the [cardiorespiratory](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiorespiratory) consequences of an isolated [lung contusion](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-contusion) model.

Methods

Twenty-eight anesthetized pigs were studied during four hours. We induced a right [lung contusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-contusion) with five bolt shots (70 joules each) using a 22-caliber charge in twenty of them. Eight others pigs constituted the control group. The [trauma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/injury) consequences were assessed by histology, measurements of arterial oxygenation, plasma cytokines, pressure-volume mechanics, [hemodynamic monitoring](https://www.sciencedirect.com/topics/medicine-and-dentistry/hemodynamic-monitoring) using the PiCCO system and a [pulmonary artery catheter](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-artery-catheter). The extra-vascular lung water was measured using the gravimetric method.

Results

Histology confirmed an isolated right [lung contusion](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-contusion) without cardiac injury. Compared to baseline values, the [trauma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/injury) group was characterized by a decrease in cardiac index (3.3 ± 0.8 vs 3.9 ± 1.2 l/min/m2; *P* < .05) and [mean arterial pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/mean-arterial-pressure) (80 ± 21 vs 95 ± 16 mmHg; *P* < .05) without [preload](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-preload) or afterload modification. Oxygenation (PaO2/FiO2: 349 ± 87 vs 440 ± 75; *P* < .05) and static compliance (26.3 ± 7.4 vs 30.3 ± 7.8 ml/cmH2O; *P* < .05) were also impaired during two hours compared to baseline. No edema was noticed in either group whatever the lung considered. All measured cytokines were below the detection threshold.

Conclusions

An isolated right lung contusion is associated with rapid but transient [cardiorespiratory](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiorespiratory) impairments. Despite the large extent of the lung contusion, no [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) appeared during the period studied.

Introduction

Severe chest trauma remains a leading cause of trauma-death after head injury [1]. In this specific population, the impairment of pulmonary function is frequent and multifactorial involving lung contusion, pleural effusion, ventilation to perfusion abnormalities [2] and inflammatory injury [3]. Specifically, lung contusion appears to be an independent risk for the development of pneumonia, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [4]. Indeed, after determination of the contusion volume using tomography, Miller et al have reported an association between the extension of lung contusion and the development of ARDS, without relation to the initial hypoxemia [5]. Conversely, Leone et al demonstrated that pulmonary contusion alters gas exchange but does not increase the morbidity and mortality of multiple-trauma patients with head trauma [6].

Considering actual controversies of lung contusion participation in blunt chest trauma pathophysiology, reliable and reproducible animal models for isolated lung contusion are mandatory. In this way, Raghavendran et al. have recently developed an isolated bilateral lung contusion rat model demonstrating that severe isolated lung contusion could lead to transient lung injury with relatively rapid recovery [7]. Larger animal models provide more similarity with humans especially with regards to cardio-pulmonary interactions and allow medical management easily transposable to clinical protocols [8]. Nevertheless, animal models have several limitations including potential association with mediastinal trauma or pleural effusion [9].

We report the evaluation of a pig model of blunt chest trauma characterized by an extensive right contusion associated with rib fractures but without pleural effusion nor mediastinal injury. This model allows us to explore cardiopulmonary consequences, biological reaction and histopathological assessments of pulmonary contusion, using a modern and comprehensive monitoring.

Section snippets

Methods

This protocol was performed in agreement with the guidelines for care and use of experimental animals and was approved by the local veterinary ethics committee. Twenty-eight 4 months old female pigs with a mean weight of 34 ± 3 kg were studied. Twenty pigs were included in the blunt chest trauma group and eight in the control group.

Results

Our model mimicked a typically blunt chest trauma. It caused a pulmonary contusion that included middle and lower right pulmonary lobes in all cases. Most of the pigs had two or three rib fractures, without pneumothorax or significant hemothorax. Two of the pigs died immediately after the chest trauma and one during the instrumentation. These three pigs were excluded from the data, leaving the eighteen surviving pigs of the trauma group and the seven control group pigs.

Discussion

Blunt chest trauma is a common and life threatening injury encountered in trauma patients [12]. Thoracic trauma accounts for 20-25% of adults deaths caused by trauma [1]. Lung contusion is the most frequently diagnosed intrathoracic injury resulting from blunt trauma, and is an important risk factor for the development of pneumonia and ALI/ARDS [4]. Studies examining the pathophysiology and cellular molecular mechanisms of pulmonary contusion require meaningful and reproducible animal models

Conclusions

The reproducibility and the isolated nature of the lung contusion model presented in this study demonstrate that lung contusions are associated with a significant but transient hemodynamic impairment. The respiratory impairments observed in the early phase of lung contusion seemed rather linked with ventilation to perfusion abnormalities than with edema. Although our experimental conditions did not fully reflect the reality of the clinical situation, our model could be use to evaluate the

Abstract

Objective

We sought to investigate the relationship between thoracic impedance (Zo) and [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) on [chest radiography](https://www.sciencedirect.com/topics/nursing-and-health-professions/thorax-radiography) in patients presenting to the [emergency department](https://www.sciencedirect.com/topics/medicine-and-dentistry/emergency-department) (ED) with [signs and symptoms](https://www.sciencedirect.com/topics/nursing-and-health-professions/physical-disease-by-body-function) of [acute decompensated heart failure](https://www.sciencedirect.com/topics/medicine-and-dentistry/acute-decompensated-heart-failure) (ADHF).

Design

This was a prospective, blinded convenience sample of patients with [signs and symptoms](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/physical-disease-by-body-function) of ADHF who underwent measurement of Zo with concomitant [chest radiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography). Attending physicians blinded to the Zo values interpreted the radiographs, categorizing the severity of [pulmonary edema](https://www.sciencedirect.com/topics/nursing-and-health-professions/lung-edema) as normal (NL), cephalization (CZ), interstitial edema (IE), or alveolar edema (AE). Intergroup comparisons were analyzed with a 2-way analysis of variance (ANOVA), with *P* < .05 considered statistically significant and reported using 95% confidence intervals (CIs).

Setting

We enrolled patients (≥18 years) presenting to a [tertiary care medical](https://www.sciencedirect.com/topics/nursing-and-health-professions/tertiary-health-care) center ED with signs and symptoms consistent with ADHF.

Results

A total of 203 patients were enrolled, with 27 (14%) excluded because of coexisting [pulmonary diseases](https://www.sciencedirect.com/topics/medicine-and-dentistry/silo-fillers-disease). The mean Zo values were inversely related to the 4 varying degrees of radiographic pulmonary [vascular congestion](https://www.sciencedirect.com/topics/medicine-and-dentistry/vascular-congestion) as follows: NL, 25.6 (95% CI, 22.9-28.3); CZ, 20.8 (95% CI, 18.1-23.5); IE, 18.0 (95% CI, 16.3-19.7); and with AE, 14.5 (95% CI, 12.8-16.2) (ANOVA, *P* < .04). A Zo less than 19.0 ohms had 90% sensitivity and 94% specificity (likelihood ratio [LR], − 0.1; LR + 15) for identifying radiographic findings consistent with pulmonary edema. Females had an increased mean Zo value compared to males (*P* < .03).

Conclusion

The Zo value obtained via thoracic bioimpedance monitoring accurately predicts the presence and severity of pulmonary edema found on initial chest radiograph in patients suspected of ADHF.

Introduction

Acute decompensated heart failure (ADHF) is a common and costly emergency department (ED) presentation, with ED admissions for ADHF increasing for the past 20 years [1], [2], [3], [4]. The survival of patients after an episode of ADHF remains poor, with annual mortality rates of 10% and exceeding 50% for those with New York Heart Association class IV disease [3], [4].

Successful management of ADHF in the ED requires an accurate assessment of the patient's cardiac function and pulmonary fluid status. Traditionally, physicians have relied on vital signs, oxygen saturation, and physical findings, but these fail to accurately differentiate treatment classes of ADHF or guide treatment [5], [6]. B-type natriuretic peptide (BNP) measurement is now available in the ED, but there is some controversy regarding its contribution to clinical diagnosis and management [7], [8], [9], [10], [11], [12]. None of these auxiliary tests continuously assess the degree of pulmonary vascular congestion, much less cardiac output and cardiac function during treatment. In addition, adjunct laboratory analysis, such as BNP, is often only helpful as a diagnostic marker 30 to 60 minutes after treatment decisions have been made and is therefore not useful in real time. B-type natriuretic peptide also does not correlate well with pulmonary capillary wedge pressure (PCWP) [13].

Thoracic impedance (Zo), a measure of the biologic resistance of current flow across the chest cavity, has been evaluated in heart failure in both chronic [14] and acute heart failure and demonstrates significant prognostic ability [15]. It improves clinical decision making in the ED by helping identify subtle ADHF [16]. Thoracic impedance also has the potential, unlike the chest radiograph and BNP, to be a real-time reflection of the volume status of the patient during short-term management. The largest prior study to date [17] found significant differences between normal and abnormal chest radiographs but did not demonstrate a relationship between impedance and radiographic findings. To show that Zo can be used as a real-time measure of volume, one must first show there is a correlation between the two, which can be done indirectly in the ED by correlation with chest radiograph. Our goal was to compare the Zo measured from thoracic electrical bioimpedance (TEB) with the degree of radiographic pulmonary congestion and edema on initial chest radiograph during immediate presentation to the ED. We hypothesized that in patients with signs and symptoms of ADHF, thoracic electrical bioimpedance, as measured by Zo, would accurately predict the degree of pulmonary venous congestion as measured by previously validated findings on chest radiograph.

Study design

This was an institutional review board–approved, prospective, observational study enrolling a convenience sample of patients with signs and symptoms of ADHF.

Study setting and population

This study was performed in the ED of a tertiary care medical center in patients with signs and symptoms consistent with ADHF.

Study protocol

A bioimpedance cardiac output monitor (IQ Monitor, Model 2001; Renaissance Technologies, Newtown, PA) was placed on study subjects upon arrival after informed consent was obtained. Monitor and supporting data were

Results

Of 203 enrolled patients, 27 (14%) met exclusion criteria. The mean patient age was 67.7 ± 18.3 years; 57.1% of the subjects were male. Of the subjects, 82% required hospital admission; 14% of these were admitted to the medical intensive care unit, 56% to the coronary care unit (CCU), 30% to general medical floors, and 18% were discharged home.

The mean Zo values on the initial chest radiographs demonstrated intergroup differences, with mean Zo values inversely related to 4 varying degrees of

Discussion

The need for a quantitative assessment of ADHF to diagnose and guide treatment has never been greater as the acuity and frequency of ADHF continues to increase [19], [20]. The literature demonstrating the poor accuracy of physical examination findings [6], [21], [22], [23], [24], [25], [26] is well known and has prompted the search for other parameters with which to evaluate ADHF. As the population becomes more ill, intravenous vasoactive agents such as nitroglycerin are playing a larger part

Conclusions

The bioimpedance-derived Zo accurately predicts the presence of pulmonary edema found on initial chest radiograph and may serve as an important adjunct in the management of patients with signs and symptoms of ADHF.

Background

The comet-tail technique [of chest ultrasonography](https://www.sciencedirect.com/topics/medicine-and-dentistry/ultrasonography-of-chest) has been described for the diagnosis of cardiogenic [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema). This is the first report describing its use for the diagnosis and monitoring of high-altitude [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (HAPE), the leading cause of death from [altitude illness](https://www.sciencedirect.com/topics/medicine-and-dentistry/altitude-sickness).

Methods

Eleven consecutive patients presenting to the Himalayan Rescue Association clinic in Pheriche, Nepal (4,240 m) with a clinical diagnosis of HAPE underwent one to three chest ultrasound examinations using the comet-tail technique to determine the presence of extravascular lung water (EVLW). Seven patients with no evidence of HAPE or other [altitude illness](https://www.sciencedirect.com/topics/medicine-and-dentistry/altitude-sickness) served as control subjects. All examinations were read by a blinded observer.

Results

HAPE patients had higher comet-tail score (CTS) [mean ± SD, 31 ± 11 vs 0.86 ± 0.83] and lower [oxygen saturation](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxygen-saturation) (O2Sat) [61 ± 9.2% vs 87 ± 2.8%] than control subjects (p < 0.001 for both). Mean CTS was higher (35 ± 11 vs 12 ± 6.8, p < 0.001) and O2Sat was lower (60 ± 11% vs 84 ± 1.6%, p = 0.002) at hospital admission than at discharge for the HAPE patients with follow-up ultrasound examinations. Regression analysis showed CTS was predictive of O2Sat (p < 0.001), and for every 1-point increase in CTS O2Sat fell by 0.67% (95% confidence interval, 0.41 to 0.93%, p < 0.001).

Conclusions

The comet-tail technique effectively recognizes and monitors the degree of pulmonary edema in HAPE. Reduction in CTS parallels improved oxygenation and clinical status in HAPE. The feasibility of this technique in remote locations and rapid correlation with changes in EVLW make it a valuable research tool.

Patients and Clinical Treatment

From March 3, 2006, to May 20, 2006, 11 consecutive patients with a clinical diagnosis of HAPE were treated at the Himalayan Rescue Association clinic in Pheriche, Nepal (4,240 m). No patients seen at the clinic with a diagnosis of HAPE during that period were excluded from this report. The clinical diagnosis, which was based on the Lake Louise consensus definition of HAPE, was made prior to performing ultrasonography.7 All other patients who underwent chest ultrasonography using the comet-tail

Results

Patients presenting with HAPE had higher CTS (31 ± 11 vs 0.86 ± 0.83) and lower O2Sat (61 ± 9.2% vs 87 ± 2.8%) than control subjects (p < 0.001 for both). CTS correlated with O2Sat (adjusted *R*2 = 0.62, p < 0.001). The distribution of CTS and O2Sat in all patients (HAPE and control) is described in Figure 2.

CTS was significantly higher (35 ± 11 vs 12 ± 6.8, p = 0.002) and O2Sat was significantly lower (60 ± 11% vs 84 ± 1.6%, p < 0.001) at admission than at discharge for the seven HAPE patients

Discussion

Our data demonstrate that ultrasound is an effective diagnostic and monitoring tool for HAPE. CTS correlated closely with clinical course, and with O2Sat. Others4 have alluded to the possible utility of the comet-tail technique for ongoing monitoring of pulmonary edema, but we are the first to report its routine clinical employment in this capacity for any disease process. This study marks the first time a nonradiologic measure of EVLW has been correlated with O2Sat in HAPE. The use of this

Abstract

Unilateral pulmonary edema (UPE) is a rare manifestation of cardiogenic pulmonary edema that is often confused with other causes of unilateral pulmonary infiltrates. A 47-year-old female with a HeartWare left ventricular assist device (LVAD) presented with dyspnea and UPE. Right heart catheterization revealed inadequate left ventricular unloading in the setting of aortic insufficiency and facilitated LVAD speed adjustment leading to resolution of symptoms. Timely diagnosis of UPE is critical because it is related to an independent increased risk of mortality, likely due to initial misdiagnosis and delayed proper treatment. The increasing use of LVADs in patients with advanced heart failure necessitates a thorough understanding of potential device complications and their management.

History of presentation

A 47-year-old female supported by a HeartWare left ventricular assist device (LVAD) (Medtronic) was admitted to the cardiac care unit after presenting to the emergency department with severe shortness of breath. She reported being in her usual state of health until the previous day when she began experiencing progressively worsening dyspnea while shopping. Overnight, she also developed nonbloody, nonbilious emesis and a productive cough. On admission, the patient was afebrile with a heart rate of 58 beats/min, Doppler opening pressure of 110 mm Hg, respiratory rate of 24 breaths/min, and oxygen saturation of 92% on a 15L non-rebreather mask. Her physical examination was notable for tachypnea, diffuse crackles on auscultation, absence of a palpable pulse, and abdominal tenderness at the driveline insertion site without guarding.

Take-Home Messages

* •

Thorough hemodynamics evaluation is essential in clarifying the final diagnosis of cardiogenic UPE in LVAD patients, ensuring appropriate and effective management.

* •

Timely adjustment of LVAD parameters based on hemodynamic studies can significantly improve outcomes, emphasizing the need for clinicians to be vigilant for atypical manifestations such as UPE and promptly adjust treatment protocols.

Past medical history

The patient has a history of end-stage heart failure and was on HeartWare LVAD support for 6 years. Transplant candidacy had been declined due to multiple medical high-risk findings with several adverse events, very significant human leukocyte antigen sensitization, and an elevated Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) score of 57 (indicating a poor candidate). During LVAD support, she experienced numerous clinical complications including multiple cerebrovascular accidents without residual deficits, gastrointestinal bleeding, chronic driveline infection treated with incision and drainage as well as chronic antibiotics, and episodes of ventricular arrhythmia.

Differential diagnosis

The differential diagnosis for acute dyspnea in this patient includes several potential etiologies, including LVAD failure from pump thrombosis, cannula obstruction, motor failure, or inappropriately low pump speed leading to acute pulmonary edema from inadequate left ventricular (LV) unloading. Non–LVAD-related causes include new or worsening valvular insufficiency, ventricular arrhythmia, severe anemia caused by gastrointestinal bleeding, pulmonary embolism, and pneumonia.

Investigations

Electrocardiogram results showed sinus tachycardia. Chest x-ray constituted unilateral, right-sided infiltrates with a moderate size pleural effusion concerning for underlying pneumonia ([Figure 1A](https://www.sciencedirect.com/science/article/pii/S2666084924004911#fig1)). Laboratory testing showed decreased levels of hemoglobin (10.4 g/dL, reference, 12.2-15.3 g/dL), a sub-therapeutic international normalized ratio of 1.6 (goal: 1.8-2.2), an elevated brain natriuretic peptide (3,007 pg/mL, reference <100 pg/mL) and mildly increased transaminase levels (aspartate aminotransferase 108 U/L, alanine aminotransferase 83 U/L, and alkaline phosphatase 173 U/L). White blood cell and platelet count were normal. Plasma free hemoglobin of 24 mg/dL (<40 mg/dL), lactate dehydrogenase of 493 IU/L (<600 IU/L), and absence of hemoglobinuria or bilirubinemia, along with LVAD interrogation showing no acute deviations in pump flow (3.2 L/min), power (3.1 W), and speed (2,460 rpm) from the patient’s baseline made the diagnosis of pump thrombosis unlikely.[1](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib1) Interrogation of the implanted cardioverter-defibrillator (ICD) revealed a normal functioning single-chamber ICD and climbing intrathoracic impedance (OptiVol fluid index) but no recent arrhythmic events to correlate with the presentation. Transthoracic echocardiography depicted severe LV systolic dysfunction with closed aortic valve on all observed beats, moderate-severe aortic insufficiency (AI), moderate-severe tricuspid regurgitation, and severe mitral regurgitation (MR). A point-of-care chest ultrasound to assess pleural effusion revealed unilateral, right-sided small pleural effusion and lung consolidation representing atelectasis or pneumonia. A further infectious work-up with blood cultures, viral and methicillin-resistant *Staphylococcus aureus* swabs, and *Streptococcus pneumonia* urine antigens was ordered.

1. [Download: Download high-res image (673KB)](https://ars.els-cdn.com/content/image/1-s2.0-S2666084924004911-gr1_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S2666084924004911-gr1.jpg)

Figure 1. Chest Radiography

(A) Unilateral, right-sided infiltrates with a moderate size pleural effusion on admission day. (B) Significant improvement of the unilateral pulmonary edema with no pleural effusion 1 day after hemodynamic ramp study.

Management

Bi-level positive airway pressure treatment for hypoxemic respiratory failure was attempted, but it was transitioned back to high-flow nasal cannula 50 L/40% due to intolerance. In addition to continuing levofloxacin (Levaquin) 750 mg/d for chronic driveline infection, the patient was started on empiric broad-spectrum intravenous antibiotics piperacillin/tazobactam (Zosyn) 4.5 g/d, intravenous vancomycin 1 g/d, and intravenous hydrocortisone 200 mg/d for severe pneumonia. To differentiate between pneumonia and unilateral pulmonary edema from inadequate LV unloading, a hemodynamic ramp study with right-heart catheterization was performed. An increase in speed from 2,460 to 2,860 rpm led to a notable reduction of opening pulmonary capillary wedge pressure (PCWP) from 24 to 15 mm Hg and mean pulmonary arterial pressure from 38 mm Hg to 28 mm Hg ([Table 1](https://www.sciencedirect.com/science/article/pii/S2666084924004911" \l "tbl1)). Oxygen saturation remained 100% after weaning the patient from high-flow nasal cannula 50 L/40% to 5 L nasal cannula on the day after the procedure. Given the drastic improvement in oxygenation following LVAD speed adjustment and negative infectious work-up, the patient was diagnosed with unilateral pulmonary edema due to aortic insufficiency in the setting of inadequate LV unloading.

Table 1. Hemodynamic Data During Ramp Test Phases I, II, and III

| Empty Cell | **I: Baseline** | **II: Maximal Speed** | **III: Maintenance Speed** |
| --- | --- | --- | --- |
| **Pump speed, rpm** | 2,460 | 3,000 | 2,860 |
| **MAP, mm Hg** | 104 | 90 | 100 |
| **Heart rate, beats/min** | 75 | 70 | 70 |
| **RAP, mm Hg** | 13 | N/A‡ | N/A |
| **s/d/mPAP, mm Hg** | 45/25/38 | 40/20/33 | 42/19/28 |
| **PCWP, mm Hg** | 24 | 13 | 15 |
| **Fick cardiac index, L/min/m2** | 1.92 | 2.44 | 2.50 |
| **SVR, dynes/s/cm5** | 2,074 | N/A | N/A |

MAP = mean arterial pressure; N/A = not available; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; s/d/mPAP = systolic/diastolic/mean pulmonary arterial pressure; SVR = systemic vascular resistance.

Discussion

We report on an atypical presentation of acute unilateral pulmonary edema (UPE) in a patient with moderate-severe AI during LVAD support and provide guidance for further management.

Typically, acute cardiogenic pulmonary edema presents as bilateral symmetrical perihilar opacities on chest radiography. However, in approximately 2% of cases, it can manifest unilaterally, predominantly affecting the right upper lobe.[2](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib2) Although cardiogenic UPE is strongly related to severe MR, its unilateral appearance on chest x-rays can lead to misdiagnoses, such as pneumonia, neoplasm, lung infarction, atelectasis, and aspiration.[3](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib3) For instance, a large retrospective analysis by Attias et al[2](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib2) involving 869 patients with acute cardiogenic pulmonary edema reported delay in diagnosis and treatment in 33% of cases with UPE.

In our case, the patient had been on LVAD support for 6 years, adding to the diagnostic complexity by necessitating consideration of both LVAD-related and non–LVAD-related causes. The patient's history of chronic driveline infection, unilateral pulmonary opacities, and respiratory distress initially led to the initiation of empiric antibiotics for suspected pneumonia. However, clinical signs of left heart failure, along with echocardiographic findings of moderate-severe AI and severe MR, and markedly elevated brain natriuretic peptide levels without fever or leukocytosis helped differentiate cardiogenic etiology from other diagnoses.[4](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib4) A subsequent hemodynamic ramp study served both diagnostic and therapeutic purposes showing an elevated PCWP, which was significantly improved with increased LVAD speed. These speed adjustments have previously been shown to alleviate the increase in LV pressure due to significant AI during LVAD support.[5](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib5),[6](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib6) The development of moderate to severe AI following LVAD implantation exacerbates heart failure, increases rehospitalization rates, and reduces survival, particularly when the device is used as a destination therapy.[7](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib7) Transcatheter aortic valve replacement (TAVR) has emerged as an effective off-label treatment for selected high-risk patients with de novo AI while on LVAD support, leading to lasting improvements in AI severity, functional status, and quality of life.[8](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib8),[9](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib9) Because AI was the main cause of our patient’s decompensation and recognizing its significant impact on clinical outcomes during LVAD support, especially given the anticipated extended duration of device support, we consulted our multidisciplinary structural heart team for TAVR evaluation. Timely diagnosis is critical, because UPE carries a nearly 7-fold increased mortality risk compared to bilateral pulmonary edema, likely due to delays in proper treatment.[2](https://www.sciencedirect.com/science/article/pii/S2666084924004911#bib2) This case underscores the importance of thorough hemodynamics evaluation to distinguish cardiogenic causes from other potential diagnoses, ensuring appropriate and effective management.

Follow-up

A follow-up chest x-ray 1 day after the pump speed was increased showed significant improvement of the right-sided pulmonary edema with no pleural effusion ([Figure 1B](https://www.sciencedirect.com/science/article/pii/S2666084924004911#fig1)). After 2 days, the patient was breathing comfortably on room air and was discharged on day 4 after admission. Because of the complexity and the need for careful consideration after multimodality imaging, our structural heart team recommended outpatient evaluation for TAVR to address the identified valvulopathy.

Conclusions

The increasing use of LVADs in patients with advanced heart failure necessitates a thorough understanding of potential device complications and their management. This knowledge is essential for ensuring safe long-term care and improving patient outcomes.

Purpose

Cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) may be used as extracorporeal circulation (ECC) during lung transplantation. We aimed to compare CPB and ECMO in terms of short-term outcomes in lung transplantation (LTx).

Methods

Among 185 patients undergoing LTx including 81 living-donor-related LTx from 2008 to June, 2018 in our institution, CPB was used in 41 patients and ECMO in 89 patients. Since 2013, we have routinely used ECMO, while CPB has been selectively used in pediatric and complicated cases requiring PA replacement or ASD closure. We retrospectively evaluated perioperative factors and short-term outcomes including delayed chest closure (DCC), in comparison of CPB group and ECMO group. DCC is required due to primary graft dysfunction manifesting as hypoxia, pulmonary hypertension, and lung edema. Assuming that CPB causes systemic inflammation leading to systemic edema, we also investigated perioperative increase ratio of body weight.

Results

Gender, surgical procedure (single or bilateral), and donor (cadaveric or living) and indications were not significantly different between the two groups, while patients in ECMO group were significantly older (40 vs 32 years, p=0.038), and weighed more (47 vs 38 kg, p=0.001). Thirty-day mortality was similar (1.1% in ECMO group; 2.4% in CPB group). The operation time, ECC time, and the amount of blood loss were not significantly different, while ECMO group was associated with significantly less transfusion intraoperatively (4339 ml in ECMO group; 6753 ml in CPB group, p=0.002). Reoperations for bleeding were less frequently required in ECMO group than in CPB group (7% vs 29%, p=0.003). DCC was less frequently required in ECMO group than in CPB group (9% vs 29%, p=0.013). The increase of body weight measured at the time of ICU admission was significantly remarkable in CPB group than in ECMO group (increased by 9.7% vs by 4.7%, p=0.006).

Conclusion

LTx using ECMO was associated with less intraoperative transfusion, and less postoperative re-exploration to CPB. ECMO was associated with less frequent delayed chest closure, possibly related to less systemic edema.

Ex vivo lung perfusion (EVLP) is used to evaluate donor lungs prior to lung transplantation. Development of pulmonary edema during EVLP is generally thought to represent inflammatory breakdown of the air-fluid barrier and these lungs are declined for transplant. We present the case of a donor lung that underwent stapled wedge resection during cold storage for air leak and the subsequent development of profound (∼650 mL) pulmonary edema around the staple line during EVLP. Nevertheless, the edema cleared shortly after implantation. This report illustrates the potential for significant alveolar fluid clearance and sealing of vascular injury after implantation when edema is not caused by inflammatory injury.

Acellular ex vivo lung perfusion (EVLP) offers the ability to assess donor lungs before transplantation; however, acellular lung physiology affects the interpretation of Po2.[1](https://www.sciencedirect.com/science/article/pii/S2772993124002560#bib1) Instead, the current EVLP evaluation strategy examines surrogates of pulmonary edema development over time. These include perfusate loss, lung weight, chest radiography, metabolites, and physiologic parameters such as compliance and airway pressure.[2](https://www.sciencedirect.com/science/article/pii/S2772993124002560#bib2),[3](https://www.sciencedirect.com/science/article/pii/S2772993124002560#bib3) Pulmonary edema formation during EVLP is thought to represent the inflammatory (ie, acute respiratory distress syndrome-like) microvasculature injury caused by pneumonia, aspiration, or reperfusion injury which would have resulted in primary graft dysfunction following implantation into the recipient. Therefore, edematous lungs during EVLP are declined for transplant.

One additional consideration is that the acellular perfusate used in EVLP lacks clotting factors to plug physical damage to the vasculature. Thus, not all EVLP edema may be due to inflammatory injury. Anecdotally, some lungs become slightly edematous during EVLP, but dry out rapidly after implantation into the recipient. We hypothesized that noninflammatory breakdown of the microvasculature such as from volume overload or mechanical injury may cause edema during EVLP, but these lungs may still be usable, as implantation into the recipient will allow for platelet plugging of the injury and physiologic alveolar fluid clearance mechanisms are preserved.

Herein, we present a case of a pure mechanical injury to the donor lung during EVLP, the resultant profound edema formation during EVLP, and demonstration that this edema can rapidly resolve after implantation into the recipient.

The lung transplant recipient provided consent for publication.

A 62-year-old male patient offered donation after cardiac death and had a P/F ratio of 596 mmHg. The donor arrested at 181 minutes after withdrawal of life-sustaining therapies. Procurement was uncomplicated but an apical bulla at the apex of the right lung with air leak was stapled to prevent deflation after procurement and during cold storage.

Due to the long agonal phase, we elected to assess the lungs on EVLP.

After 1 hour of EVLP, there was significant perfusate loss (650 mL) into the lung. The right upper lobe became profoundly heavy and edematous. Right superior venous gas Po2 was 30 mm Hg and outflow venous Po2 was 369 mm Hg. Bronchoscopy showed edema fluid from the right upper airway. The EVLP lung radiograph showed dense infiltrates limited to the right upper lobe ([Figure 1](https://www.sciencedirect.com/science/article/pii/S2772993124002560#fig1)). We felt that the edema was due to perfusate leak from the staple line into the lung and terminated EVLP prematurely at 1:50 hours.

1. [Download: Download high-res image (738KB)](https://ars.els-cdn.com/content/image/1-s2.0-S2772993124002560-gr1_lrg.jpg)
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Figure 1. (A) Radiograph of ex vivo lung showing opacity in the right upper lobe. (B) Photo of donor lungs after ex vivo lung perfusion.

The recipient was a 68-year-old male individual with end-stage chronic obstructive pulmonary disease. Intraoperative central venoarterial extracorporeal membrane oxygenation (VA ECMO) was used to reduce perfusion to the transplanted lung and the edematous right lung was transplanted first to allow for alveolar fluid clearance. Suctioning of the right upper lobe bronchus was performed prior to implantation to remove edema fluid. The transplant was otherwise uncomplicated and the first postoperative P/F ratio was 480 mm Hg. The chest radiograph upon arrival to the intensive care unit showed a clear right upper lobe ([Figure 2](https://www.sciencedirect.com/science/article/pii/S2772993124002560#fig2)). He remains well 1 year after transplant.

1. [Download: Download high-res image (192KB)](https://ars.els-cdn.com/content/image/1-s2.0-S2772993124002560-gr2_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S2772993124002560-gr2.jpg)

Figure 2. Chest radiograph of recipient upon arrival to the intensive care unit.

Comment

In this case report, we highlight an alternative cause of EVLP pulmonary edema caused by noninflammatory injury during EVLP and the alveolar fluid clearance that can occur in this circumstance.

Stapling of the lung is a common occurrence in lung surgery; however, for this case, the stapling was performed during cold storage without opportunity for platelet plugging and initiation of inflammation. The lung was then perfused with an acellular perfusate, again without opportunity for platelet plugging and inflammation, leading to the development of profound pulmonary edema in the right upper lobe. Despite this, we show that these lungs could be utilized safely for transplantation and that there is rapid clearance of pulmonary edema (almost 650 mL) after implantation.

This case report advances the hypothesis that pulmonary edema during EVLP caused by noninflammatory causes may be safely transplanted due to preserved alveolar fluid clearance mechanisms. For inflammatory lung injury, studies in acute respiratory distress syndrome have demonstrated that the breakdown in the microvascular barrier is accompanied by a reduced ability for lungs to clear alveolar edema fluid.[4](https://www.sciencedirect.com/science/article/pii/S2772993124002560#bib4) However, in lungs without inflammatory microvascular injury, alveolar fluid clearance can be rapid; in a pig model, there was 50% clearance of alveolar fluid by 4 hours.[5](https://www.sciencedirect.com/science/article/pii/S2772993124002560#bib5) Along those lines, we chose to implant the edematous lung first on VA ECMO to reduce hydrostatic pressure in the pulmonary vasculature and to provide time for alveolar fluid clearance mechanisms to work during implantation of the second lung. Indeed, by the time of separation from VA ECMO, the upper lobe was much less edematous and the chest radiograph taken on arrival to the intensive care unit showed a clear right upper lung field and overall excellent lung function and long-term outcome.

EVLP lung evaluation requires clinical judgment and expertise in the physiology of lung injury. Identifying causes of noninflammatory lung injury such as donor volume overload and physical injuries may yet allow for more lungs to be safely transplanted off EVLP.

1. Introduction

Supraclavicular edema is a relatively common condition in medical practice. [Superior vena cava syndrome](https://www.sciencedirect.com/topics/medicine-and-dentistry/superior-vena-cava-syndrome), left [supraclavicular lymph node](https://www.sciencedirect.com/topics/medicine-and-dentistry/supraclavicular-lymph-node), hypothyroidism, and [angioedema](https://www.sciencedirect.com/topics/medicine-and-dentistry/angioedema) are common causes. In some rare cases, lymphatic disorders such as cervical [thoracic duct](https://www.sciencedirect.com/topics/medicine-and-dentistry/thoracic-duct) anomalies are involved. The two main causes of cervical chylous effusion are thoracic duct occlusion and post-traumatic (postoperative or not) leakage [[1]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0005). Once these diagnoses have been ruled out, the occurrence of recurrent, fluctuating, asymmetric, left-sided supraclavicular edema suggests paroxysmal thoracic duct occlusion syndrome, primarily described by Preyer, and named recurrent cervical swelling syndrome (RCSS) by Franceschi or spontaneous cervical swelling syndrome by Betrains [[2]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0010), [[3]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0015), [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0020).

The purpose of this paper is to review the characteristics of RCSS and analyze the presenting signs and symptoms, therapeutic options, and outcome. Herein, we report seven new cases of RCSS and then present a literature review.

2. Case series and literature review

Seven adult patients with recurrent left cervical edema and diagnosis of RCSS, admitted to the [Internal Medicine](https://www.sciencedirect.com/topics/medicine-and-dentistry/internal-medicine) Unit of Saint Antoine Hospital (the French reference center for angioedema) between January 1, 2015 and August 1, 2021 were included ([Table 1](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "t0005)). Differential diagnoses were excluded. Two investigators (EC, TM) then searched MEDLINE, PubMed Central, and Google Scholar for articles in English or French published until December 2021 and containing the keywords “recurrent cervical swelling syndrome, recurrent [lymphangiectasia](https://www.sciencedirect.com/topics/medicine-and-dentistry/lymphangiectasis) of the left supraclavicular fossa, benign supraclavicular tumor, paroxysmal cervical swelling, spontaneous cervical swelling syndrome”. All articles with sufficient data were included in the literature review. Among 676 references screened, we found eight articles describing 19 cases of recurrent, transient, and non-inflammatory left supraclavicular edema with exclusion of differential diagnosis (malignant tumors, cysts) ([Table 2](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "t0010), [Table 3](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "t0015)) [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020), [[5]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0025), [[6]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0030), [[7]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0035), [[8]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0040). Data from seven patients followed at our center ([Table 1](https://www.sciencedirect.com/science/article/pii/S0151963824000425#t0005)) were pooled with six well-documented cases from the literature review ([Table 3](https://www.sciencedirect.com/science/article/pii/S0151963824000425#t0015)).

Table 1. Clinical and therapeutic characteristics of our seven patients presenting with recurrent cervical swelling syndrome.

| **Case No./sex/age BMI (kg/m2)** | **Trigger** | **Duration Frequency of crises** | **Evolution (months) Median number of crises before diagnosis** | **Left cervical swelling associated symptoms** | **Imagery** | **Treatment** | **Efficacy** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1/F/55 BMI: 26 | NS | 3–5 days 1/month | 18 24 | Pleural effusion Ascites Abdominal pain Vomiting | * –   CT scan: pleural effusion and ascites   * –   MRI: focal dilatation supra clavicular lymphatic duct   * –   lymphoscintigraphy: left side asymmetry during the dynamic phase | Low-fat diet and Lanreotide (30 mg SR) | PR (decreased frequency) After 39 months of follow up |
| 2/F/35 sickle cell disease BMI: 27 | Fast food | 3–4 days 1/year | 12 3 | Abdominal pain Diarrhea Ascites Pleural effusion | * –   MRI: left clavicular edema ectasia of the butt of the thoracic duct without visible obstacle | Low fat diet and Lanreotide (30 mg SR) | CR no recurrence after 3 months of follow-up |
| 3/F/28 BMI: NS | NS | 3–5 days 1/6 months | 6 3 | Abdominal pain Diarrhea Ascites | * –   MRI: left clavicular edema   * –   US doppler: normal | Low fat diet | CR no recurrence after 14 months of follow-up |
| 4/F/34 BMI: 21 | Alcohol | 3–4 days 1/3 months | 48 15 | Lumbar pain Abdominal pain | * –   MRI: left clavicular edema | 0 | NS |
| 5/F/63 BMI:19 | Meal containing wild boar | 2–3 days First event | 1 1 | Pleural effusion Ascites Pericardial effusion Abdominal pain Thoracic pain | * –   MRI: left clavicular edema, thoracic duct dilatation without obstruction | Low fat diet preventive enoxaparin | CR no recurrence after 15 months of follow-up |
| 6/F/41 BMI: NS | NS | 2–3 days 1/3 years | 120 7 | Pleural effusion Ascites Abdominal pain | * –   CT scan: left clavicular edema, pleural effusion, ascites   * –   MRI after crises: no compression | Low fat diet | NS |
| 7/F/45 BMI: 18 | NS | 4 1/2 months | 11 5 | Abdominal pain | * –   MRI: left clavicular edema | Low-fat diet and Lanreotide (30 mg SR) | PR 5 months of follow up |

NS: not specified; [Hb](https://www.sciencedirect.com/topics/medicine-and-dentistry/hemoglobins): hemoglobin; Ht: hematocrit; CT scan: computerized tomography scanner; MRI: magnetic resonance imaging; SR [sustained release](https://www.sciencedirect.com/topics/medicine-and-dentistry/sustained-drug-release); CR complete remission; PR partial remission

Table 2. Summary of case reports from the literature review.

| **Case No./sex/age** | **Trigger** | **Duration and frequency** | **Symptoms associated with left cervical swelling** | **Imaging** | **Treatment** | **Efficacy** |
| --- | --- | --- | --- | --- | --- | --- |
| F/56 [[5]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0025) | Hypertension of the spine | NS | Recurrent pleural effusion | * –   Chest X-ray: pleural effusion   * –   Chest CT scan: normal | NS | NS |
| F/67 [[6]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0030) | NS | 2 days | Dyspnea Pleural effusion | * –   Chest X-ray: bilateral pleural effusion   * –   CT scan: normal | NS | NS |
| F/33 [[7]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0035) | NS | 5 days 4 events/3 years | Abdominal pain Weight gain of 1–2 kg | * –   Duplex US: cystic tubular lesion of 30 × 14 × 17 mm in the subcutaneous tissue of the left supraclavicular groove   * –   MRI: cervical soft tissue surrounding the cyst appeared to be infiltrated with edematous fluid | Puncture of cyst | No recurrence |
| F/64 [[9]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0045) | Large fat-rich meal | 3 days 3 events /25 years | Abdominal pain | * –   TDM: diffuse infiltration of the subcutaneous tissue of the left supraclavicular fossa and diffuse edema in the retroperitoneal area   * –   Lymphoscintigraphy: abnormal lymphatic drainage with trace extravasation into the left infraclavicular fossa | Low-fat diet supplemented with medium-chain triglycerides | No recurrence at one year of follow up |
| F/55 [[3]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0015) | NS | NS | NS | * –   ECD: microcystic supraclavicular dilation   * –   ECD demonstrated a dilated non-compressible cervical TD (7 mm diameter) | No treatment | NS |
| F/44 [[3]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0015) | NS | NS | NS | * –   ECD: dilated and obstructed thoracic duct (8 mm)   * –   CT scan: retroperitoneal effusion. | Low-fat diet | NS |
| F/58 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) | NS | 2 days 2 attacks prior to diagnosis | Dyspnea Pleural effusion | * –   ECD: edema of the supraclavicular fossa and left cervical region extending toward the paratracheal region − no distension of the thoracic duct   * –   Chest CT: pleural fluid | NS |  |
| F/46 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) | Physical exercise | 4 days 1 attack prior to diagnosis |  | * –   ECD: edema of the supraclavicular fossa − thoracic duct distension present | NS |  |
| F/65 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) | Physical labor | 3 days 3 attacks before diagnosis | Dyspnea Pleural effusion | * –   ECD: edema of the supraclavicular fossa and left cervical region extending to the paratracheal region – no distension thoracic duct   * –   Chest CT: bilateral pleural fluid   * –   Lymphoscintigraphy: extravasation left cervical region | NS |  |
| F/58 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) | Physical exercise | 3.5 days Recurrent attacks | Dyspnea Pleural effusion | * –   ECD: edema of the supraclavicular fossa and left cervical region—thoracic duct distension absent   * –   Chest CT: bilateral pleural fluid | NS |  |
| F/53 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) | Warm weather | 3.5 days | Pleural effusion | * –   ECD: edema of the supraclavicular fossa and left cervical region extending toward the paratracheal region—thoracic duct distension present   * –   Chest CT: bilateral pleural fluid | NS |  |
| F/38 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) | NS | NS | Pleural effusion | * –   ECD: edema of the supraclavicular fossa and left cervical region—thoracic duct distension absent   * –   Chest CT: bilateral pleural fluid | NS |  |
| F/47 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) | NS | 7 days 2 attacks before diagnosis | Pleural effusion | * –   ECD: edema of the supraclavicular fossa and left cervical region—thoracic duct distension absent   * –   Chest CT: bilateral pleural fluid   * –   Lymphoscintigraphy: Extravasation left cervical region | NS |  |
| F/82 [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020) |  | 2 days | Dyspnea Pleural effusion | * –   ECD: edema of the supraclavicular fossa and left cervical region-thoracic duct distension present | NS |  |
| F/74 [[8]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0040) | high-fat meal and alcohol | Few days | Pleural effusion | * –   CT scan: minor bilateral pleural effusion (predominantly on the left side), infiltration of the left side of the neck extending to the left axilla and the mediastinum | anticoagulant therapy |  |
| F/45 [[8]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0040) | NS | 2 days | Abdominal pain | * –   CT scan: infiltration of subcutaneous tissue in the supraclavicular fossa and in the omohyoid muscle, and extensive inflammatory infiltrate in the retroperitoneum.   * –   MRI: small cyst in the cervical area. |  |  |
| F/65 [[8]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0040) | NS | NS | Dyspnea | * –   Lymphoscintigraphy: impregnation time of 2  h and 45 min on the axillary lymphatic vessel (normal values within 10–30 min) |  |  |
| F/64 [[8]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0040) |  |  |  | * –   CT scan: liquid infiltration in the left supraclavicular hollow in the retroperitoneum and in the mediastinum.   * –   Lymphoscintigraphy: significant delay of the lymphatic flow in the thoracic duct |  |  |
| F/62 [[8]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0040) |  |  |  | * –   CT scan: left supraclavicular mass associated with abdominal infiltration distributed around the colon and minor bilateral pleural effusions.   * –   Pleural puncture: chylous effusion | low-fat diet | No recurrence at 3 months of follow up |

CT scan: Computed Tomography scan, ECD: Echo [Color Doppler](https://www.sciencedirect.com/topics/medicine-and-dentistry/color-doppler-flowmetry); NS: not specified.

Table 3. Characteristics of all patients with recurrent swelling syndrome.

| **Characteristics** | ***N* = 26** |
| --- | --- |
| Age (years;median [IQR]), female (n,%) | 55.5 [30–82], 26 (100%) |
| Duration in days (n, median [IQR]) | 4 [1–7] |
| Pleural effusion (n) | 14 |
| Abdominal pain / Ascites (n) | 10/5 |
| Trigger fat-rich meal / physical exercise (n) | 4/3 |
| Thoracic duct dilatation (MRI) | 7 |
| Treatment | 11 |
| Low fat diet | 6 (4 CR,2 NS) |
| Low fat diet + lanreotide | 4 (2CR, 2 PR) |

IQR: interquartile range, CR: complete response, PR: partial response, NS: not specified; MRI magnetic resonance imaging.

We identified 26 cases of RCSS. All patients were women with left cervical edema lasting between 1 and 7 days ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "f0005)). The median age was 55.5 years old [interquartile range (IQR) 30–82]. The median number of episodes before diagnosis was 3 [IQR 1–24]. The median time from first symptoms to diagnosis was 12 months [range: 1–120]. Clinical and therapeutic characteristics are summarized in [Table 3](https://www.sciencedirect.com/science/article/pii/S0151963824000425#t0015). Fourteen patients had [pleural effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleura-effusion) and one patient had [pericardial effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pericardial-fluid) without cardiac dysfunction. Eleven patients had [gastrointestinal symptoms](https://www.sciencedirect.com/topics/medicine-and-dentistry/gastrointestinal-distress), including: abdominal pain (10/11), [ascites](https://www.sciencedirect.com/topics/medicine-and-dentistry/ascites) (5/11), diarrhea and/or vomiting (3/11). None of the patients had a history of chest wall trauma or [thoracic surgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-surgery). Four of the patients had eaten a high-fat meal in the previous days.

1. [Download: Download high-res image (344KB)](https://ars.els-cdn.com/content/image/1-s2.0-S0151963824000425-gr1_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S0151963824000425-gr1.jpg)

Fig. 1. (a–c) Patients with recurrent swelling syndrome during an attack. (d) Thoracic lymph-node magnetic resonance imaging (T2): left supraclavicular edema (star) and dilated aspect of the [thoracic duct](https://www.sciencedirect.com/topics/medicine-and-dentistry/thoracic-duct) endings (arrow).

Standard laboratory tests, including blood cell count, liver and kidney function, [thyroid stimulating hormone](https://www.sciencedirect.com/topics/medicine-and-dentistry/thyrotropin), lipids, and C-reactive protein were normal in all our patients. One patient had [sickle cell disease](https://www.sciencedirect.com/topics/medicine-and-dentistry/sickle-cell-disease) with a history of [hemodilution](https://www.sciencedirect.com/topics/medicine-and-dentistry/hemodilution). [Protein electrophoresis](https://www.sciencedirect.com/topics/medicine-and-dentistry/protein-electrophoresis) showed no monoclonal peak, and plasma C1 [inhibitor protein](https://www.sciencedirect.com/topics/medicine-and-dentistry/inhibitor-protein) activity was normal in 7/7 patients. Chest [computed tomography](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) (CT) showed no deep [lymphadenopathy](https://www.sciencedirect.com/topics/medicine-and-dentistry/lymphadenopathy) and no [superior vena cava](https://www.sciencedirect.com/topics/medicine-and-dentistry/superior-vena-cava) in all cases. Thoracic magnetic resonance imaging (MRI) of lymph nodes was performed during attacks in 7 patients and showed left supraclavicular edema in all cases and a dilated aspect of the thoracic duct terminal without occlusion or cervical thoracic duct cyst in 5 cases. Two of our patients received [icatibant](https://www.sciencedirect.com/topics/medicine-and-dentistry/icatibant), [antihistamines](https://www.sciencedirect.com/topics/medicine-and-dentistry/histamine-antagonist) and intravenous [corticoids](https://www.sciencedirect.com/topics/medicine-and-dentistry/corticosteroid) for suspected [bradykinin](https://www.sciencedirect.com/topics/medicine-and-dentistry/bradykinin) or histamine angioedema, and one patient received intravenous immunoglobulins for suspected Clarkson’s disease without benefit. Finally, 10 patients were treated with a low-fat diet, and four patients were also treated with [lanreotide](https://www.sciencedirect.com/topics/medicine-and-dentistry/angiopeptin) (30 mg extended-release [intramuscular injection](https://www.sciencedirect.com/topics/medicine-and-dentistry/intramuscular-injection) once a month), which resulted in partial remission in two patients (reduced frequency or duration of attacks) and complete remission in the other two patients.

3. Discussion

Recurrent cervical swelling syndrome (RCSS), also known as paroxysmal thoracic duct occlusion syndrome or recurrent left supraclavicular [lymphangiectasia](https://www.sciencedirect.com/topics/medicine-and-dentistry/lymphangiectasis), is poorly described in the literature [[9]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0045). As indicated above, other causes of supraclavicular edema must be excluded before RCSS can be diagnosed. Preyer et al. were the first to report this rare entity [[2]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0010). Franceschi proposed the term of recurrent cervical swelling syndrome [[3]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0015). Since then, very few cases have been reported. To date, there is no consensus on diagnostic criteria. The diagnosis of RCSS is based on clinical and radiographic signs. Clinically, RCSS is a recurrent left supraclavicular noninflammatory edema, sometimes associated with other signs such as [pleural effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleura-effusion), [pericardial effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pericardial-fluid) and [ascites](https://www.sciencedirect.com/topics/medicine-and-dentistry/ascites). [Thoracic imaging](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest-imaging) such as [CT scan](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) is important to rule out [superior vena cava syndrome](https://www.sciencedirect.com/topics/medicine-and-dentistry/superior-vena-cava-syndrome) and left [supraclavicular lymph node](https://www.sciencedirect.com/topics/medicine-and-dentistry/supraclavicular-lymph-node). Thoracic duct imaging is necessary to rule out endo- or extra-luminal occlusion of the thoracic duct and lymph-node MRI seems to be the best option for this [[10]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0050).

In our series of 7 personal cases and 19 cases from the literature, the duration of left cervical swelling was 1–7 days, with associated signs in all cases. Pleural effusion and dyspnea were more common than abdominal pain and ascites. The [pathophysiology](https://www.sciencedirect.com/topics/medicine-and-dentistry/pathophysiology) of this syndrome is poorly understood. Many variants of terminal thoracic duct (TD) exist but the main termination seems to be on the left side, either in the [internal jugular vein](https://www.sciencedirect.com/topics/medicine-and-dentistry/internal-jugular-vein) or in its confluence with the [subclavian vein](https://www.sciencedirect.com/topics/medicine-and-dentistry/subclavian-vein) [[11]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0055). This preferential localization is the cause of this left supraclavicular edema. With regard to our cases, in which we indicate that a high-fat diet was consumed a few days before the edema, and with regard to the literature review, a possible hypothesis for this rare phenomenon could be that a high-fat diet may cause an influx of [chylomicrons](https://www.sciencedirect.com/topics/medicine-and-dentistry/chylomicron) into the thoracic duct that exceeds the transport capacities, thus causing a temporary and paroxysmal lymphatic stasis in the thoracic duct [[9]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0045). However, diet was not always mentioned in the patients’ [medical history](https://www.sciencedirect.com/topics/medicine-and-dentistry/medical-history) and no rechallenge with a high-fat diet was suggested in our patients. Lipid levels were normal throughout. The other hypothesis could be that of a constitutional abnormality of the thoracic duct such as [ectasia](https://www.sciencedirect.com/topics/medicine-and-dentistry/ectasia), which may favor the extravasation of lymphatic fluid into the [subcutaneous tissue](https://www.sciencedirect.com/topics/medicine-and-dentistry/subcutaneous-tissue) [[12]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0060). No [anatomical abnormalities](https://www.sciencedirect.com/topics/medicine-and-dentistry/clinical-deformity) were described in our series. Finally, in our experience and in the literature, all cases were described in women. No correlation with menstruation was observed; however, estrogenic influence could be implicated in the mechanism of edema. In their series, Betrains et al. suggest a possible role of physical activity and outdoor temperature, which we did not find either in our series or in the other reported cases [[4]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0020). Taken together, a high-fat diet, the influence of female hormones, and thoracic duct ectasia could lead to edema.

In conclusion, we propose three diagnostic criteria for the diagnosis of RCSS:

* (1)

Clinical: Recurrent non-inflammatory left supraclavicular edema,

* (2)

Radiological: CT or lymph node MRI of the neck with evidence of left supraclavicular edema at the end of the thoracic duct, which is normal or dilated,

* (3)

Exclusion of the following diseases: vena cava syndrome, [bradykinin](https://www.sciencedirect.com/topics/medicine-and-dentistry/bradykinin) angioedema, tumor or lymph node, [lymphatic malformation](https://www.sciencedirect.com/topics/medicine-and-dentistry/lymphatic-malformation), and hypothyroidism.

In the absence of large series, the therapeutic options in RCSS are limited. In some cases, a low-fat diet seems to be effective [[9]](https://www.sciencedirect.com/science/article/pii/S0151963824000425#b0045). Second, [lanreotide](https://www.sciencedirect.com/topics/medicine-and-dentistry/angiopeptin), a [somatostatin analog](https://www.sciencedirect.com/topics/medicine-and-dentistry/somatostatin-derivative) also used in Waldmann’s disease, could decrease the [chyle](https://www.sciencedirect.com/topics/medicine-and-dentistry/chyle) flow in the thoracic duct [[13]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0065). With this treatment, two of our patients experienced a reduction in the number and duration of attacks [[14]](https://www.sciencedirect.com/science/article/pii/S0151963824000425" \l "b0070).

Abstract

Background

[Newborns](https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-infant) with critical [congenital heart disease](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/congenital-heart-disease) (CCHD) with increased [pulmonary blood flow](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-blood-flow) (PBF) are at high risk for [congestive heart failure](https://www.sciencedirect.com/topics/medicine-and-dentistry/congestive-heart-failure). In this study, we aimed to evaluate the presence and degree of [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) in newborns with CCHD using lung ultrasound (LUS) during the [perioperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/perioperative-period).

Methods

Prospective [clinical trial](https://www.sciencedirect.com/topics/medicine-and-dentistry/clinical-trial), 44 newborn patients with CCHD were evaluated in this prospective [clinical trial](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/clinical-trial). LUS was repeatedly performed to determine the course of pulmonary edema during the perioperative period. LUS was performed simultaneously with [chest radiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) (CXR), which was the main part of patient management. The primary outcome of this study was to identify whether a correlation existed between LUS and [CXR](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest-radiograph) findings. The secondary outcomes were to determine the relationship between LUS and the need for [respiratory support](https://www.sciencedirect.com/topics/medicine-and-dentistry/assisted-ventilation), [diuretic](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/diuretic-agent) use, vasoactive [inotropic](https://www.sciencedirect.com/topics/medicine-and-dentistry/inotropism) score (VIS), and pro-B-type natriuretic peptide (pro-BNP) levels during the perioperative period.

Results

The mean gestational age of the patients was 38.3 ± 1.7 weeks, with a mean birth weight of 3026 ± 432 g. In the [preoperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/preoperative-period), both LUS and CXR images were consistent with clinical signs of pulmonary edema. On the first postoperative day, pulmonary edema increased compared to the preoperative period but gradually decreased by the 6th [day of surgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/day-of-surgery) (p < 0.05). Positive correlations were observed between the LUS and CXR findings at all study points (p < 0.05). The LUS findings exhibited trends parallel to those of VIS, serum pro-BNP levels, need for respiratory support, and [diuretic](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent) requirements. As expected, these trends were more pronounced in CCHDs where PBF increased.

Conclusion

In CCHD, serial lung ultrasound (LUS) assessments, particularly in cases with increased PBF, can provide valuable guidance for managing patients during the perioperative period.

Keywords

Pulmonary edema

Critical congenital heart disease

Newborn

Lung ultrasound

1. Introduction

[Congenital heart disease](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/congenital-heart-disease) (CHD) is one of the most common [congenital anomalies](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/congenital-malformation), occurring in 8 of 1000 live births. CHDs require angiographic or surgery in the first months of life are defined as critical congenital heart diseases (CCHD) and constitute approximately one-fourth of all CHD cases [[1](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib1)]. Immediately after birth, delayed absorption of fetal lung fluid can lead to respiratory problems in [newborns](https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-infant). Additionally, in some CCHDs, a mismatch between the [systemic blood flow](https://www.sciencedirect.com/topics/medicine-and-dentistry/systemic-circulation) (SBF) (Qs) and [pulmonary blood flow](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-blood-flow) (PBF) (Qp) can disrupt this transitional process, causing complications. The mechanisms of [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) associated with CCHD include [left ventricular failure](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/heart-left-ventricle-failure), congestion due to [pulmonary venous obstruction](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-vein-obstruction), and [interstitial fluid](https://www.sciencedirect.com/topics/medicine-and-dentistry/interstitial-fluid) accumulation due to pulmonary overflow (Qp/Qs > 2). Pulmonary edema observed in the early days of life is associated with respiratory distress symptoms, including [tachypnea](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tachypnea), shortness of breath, subcostal and intercostal retractions, and audible crackles on [auscultation](https://www.sciencedirect.com/topics/medicine-and-dentistry/auscultation). If left untreated, it may result in [vascular remodeling](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/vascular-remodeling) and [pulmonary hypertension](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pulmonary-hypertension) during childhood [[2](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib2)].

During CCHD management, the balance between SBF and PBF is affected by various factors. These include [intravenous fluid](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/infusion-fluid) therapy, [mechanical ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/artificial-respiration) strategies, and the administration of specific medical agents such as [prostaglandins](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/prostaglandin), [inotropes](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/inotropic-agent), and vasopressors. Furthermore, numerous surgical and angiographic interventions, such as the [Blalock Taussig shunt](https://www.sciencedirect.com/topics/medicine-and-dentistry/blalock-taussig-shunt) (BT-shunt), pulmonary banding, ductal stenting and balloon procedures may also affect the Qp/Qs balance in these patients.

Traditional diagnostic tools for assessing pulmonary edema in [neonatal intensive care units](https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-intensive-care-unit) (NICUs) rely on physical examinations, [chest radiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) (CXR) and [echocardiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/echocardiography) (ECHO). However, cumulative radiation exposure from repeated [CXR](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest-radiograph) imaging in neonates with extended hospital stays raises concerns. Furthermore, ECHO has its own drawbacks, including the need for [pediatric](https://www.sciencedirect.com/topics/medicine-and-dentistry/pediatrics) cardiologists to perform the procedure and limited accessibility. With recent technological developments, the use of point-of-care ultrasound (POCUS) has gradually increased because of its noninvasiveness, lack of [ionizing radiation](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/ionizing-radiation), rapidity, relatively low cost, bedside availability, repeatability, and high predictive value [[3](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib3),[4](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib4)]. Furthermore, the thinner chest walls and smaller lung volumes of newborns compared to older children and adults allow LUS to be used as an ideal diagnostic tool [[5](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib5)]. In CCHDs with pulmonary overflow, increased perihilar vascular shadowing on CXR and the appearance of B-lines on LUS reflect [pulmonary congestion](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-congestion) [[6](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib6),[7](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib7)].

To the best of our knowledge, minimal data exists regarding the use of LUS in patients with CCHD [[8](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib8)]. Therefore, in this study, we aimed to elucidate the role of LUS in assessing pulmonary edema during the [perioperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/perioperative-period) in neonates with CCHDs and investigate its concordance with other diagnostic parameters.

2. Material and methods

2.1. Study design

This prospective [clinical trial](https://www.sciencedirect.com/topics/medicine-and-dentistry/clinical-trial) was conducted on [newborns](https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-infant) with [CCHD](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/congenital-heart-disease) hospitalized in the tertiary [NICU](https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-intensive-care-unit) of the Children Heart Center of Dr. Sami Ulus [Maternity](https://www.sciencedirect.com/topics/medicine-and-dentistry/obstetrics) and Children Hospital, Turkey, between January 2020 and September 2021. The Local Ethics Committee of our hospital approved this study (2012-KAEK-15/2045). Written [informed consent](https://www.sciencedirect.com/topics/medicine-and-dentistry/informed-consent) was obtained from all the parents.

2.2. Inclusion and exclusion criteria

Newborns (0–28 days) who were born in our hospital or another health center in Turkey, diagnosed with CHD, and underwent [pediatric](https://www.sciencedirect.com/topics/medicine-and-dentistry/pediatrics) [cardiovascular surgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiovascular-surgery) were included in the study. Newborns with any congenital [thoracic deformity](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-deformity) or [lung anomaly](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-malformation), gestational age <35 weeks, receiving [antenatal steroids](https://www.sciencedirect.com/topics/medicine-and-dentistry/antenatal-steroid), who died in the early [postoperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/postoperative-period) (within one week), and those without family consent were excluded from the study ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S1875957224000391#fig1)).

1. [Download: Download high-res image (465KB)](https://ars.els-cdn.com/content/image/1-s2.0-S1875957224000391-gr1_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S1875957224000391-gr1.jpg)

Fig. 1. Flow diagram of the study.

2.3. Medical data

Medical data included gestational age, birth weight, sex, [prenatal diagnosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/prenatal-diagnosis), postnatal age at admission and diagnosis of [CCHD](https://www.sciencedirect.com/topics/medicine-and-dentistry/persistent-truncus-arteriosus), type of CCHD, clinical findings of [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema), need for [respiratory support](https://www.sciencedirect.com/topics/medicine-and-dentistry/assisted-ventilation), use of [inotropic](https://www.sciencedirect.com/topics/medicine-and-dentistry/inotropism) and/or [diuretic](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent) medication, length of hospital stay and mortality. The presence of pulmonary edema on physical examination, need for [inotropes](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/inotropic-agent) or diuretics, and medication doses were determined by the same neonatologists (D.D., H.A.).

2.4. Physical examination

Pulmonary edema was defined as the abnormal accumulation of [extravascular fluid](https://www.sciencedirect.com/topics/medicine-and-dentistry/extravascular-fluid) in the [lung parenchyma](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-parenchyma). Increased respiratory distress, [tachypnea](https://www.sciencedirect.com/topics/medicine-and-dentistry/tachypnea) and fine or core crepitant rales during examination were evaluated as indicators of pulmonary edema. Similarly, bilateral crepitant rales, changes in [cardiac murmurs](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/heart-murmur), S3 [gallop rhythm](https://www.sciencedirect.com/topics/medicine-and-dentistry/gallop-rhythm), elevated [jugular venous pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/central-venous-pressure) and [peripheral edema](https://www.sciencedirect.com/topics/medicine-and-dentistry/peripheral-edema) supported the diagnosis of cardiogenic edema [[[9]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib9), [[10]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib10), [[11]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib11)].

2.5. Laboratory

Serum pro-B-type natriuretic peptide (pro-BNP) and increased serum pro-BNP levels were used to distinguish between dyspnea due to respiratory problems and cardiac-related dyspnea. Serum pro-BNP levels were measured at two time points: at admission (preoperative) and after surgery (postoperative Day 6). Approximately 2 ml of whole blood was collected from each patient and stored in an EDTA-containing tube. Subsequently, 0.75 ml of blood was aliquoted into a tube containing a pro-BNP quantitative buffer and thoroughly mixed. The pro-BNP level was assayed within 5 min using the Canadian RAMP heart failure diagnostic instrument method with testing materials provided by Response Biomedical Corp. (Vancouver, BC, Canada). Pulmonary edema due to increased BPF was possible if the plasma pro-BNP level was set at ≥598 ng/l [[11](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib11),[12](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib12)].

2.6. Chest X ray and lung ultrasound imaging

Bedside LUS was repeated four times during the study period, simultaneously with CXR, on the first day of NICU admission (preoperatively) and on the second, fourth and sixth postoperative days. The time gap between CXR and LUS was <4 h. Posteroanterior CXRs were evaluated by the same radiologist (Y·S.), who was blinded to the patients' clinical and LUS findings. The presence of [cardiomegaly](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/cardiomegaly), central edema (perihilar bat wing appearance), vascular redistribution, thickened interlobar fissures, and [pleural effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleura-effusion) on CXR were interpreted as cardiogenic pulmonary edema. However, peripheral and irregular edema pattern was considered a sign of non-cardiogenic edema [[13](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib13),[14](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib14)]. All LUS evaluations were performed by the same neonatologist (B·K.), who was experienced in neonatal [POCUS](https://www.sciencedirect.com/topics/medicine-and-dentistry/point-of-care-ultrasound) and was unaware of the patient's clinical findings and CXR evaluations.

A 13 mHz linear probe with pre-warmed gel was used for imaging (Siemens Acuson X 300). While the babies were in the [supine position](https://www.sciencedirect.com/topics/medicine-and-dentistry/supine-position), both hemithoraces were examined in four regions (eight regions in total) within the borders of the parasternal, anterior axillary, and posterior [axillary line](https://www.sciencedirect.com/topics/medicine-and-dentistry/axillary-lines). The probe was inserted vertically (in the longitudinal plane) into the [intercostal space](https://www.sciencedirect.com/topics/medicine-and-dentistry/intercostal-space). The LUS studies did not exceed 8 min. The images were archived as video recordings for later evaluation.

The LUS score was calculated to determine the presence and severity of pulmonary edema. B-lines in all regions were scored separately, and figures from the eight quadrants were mathematically summed; 0: normal, 1: mild pulmonary edema, 2: moderate pulmonary edema 3: severe pulmonary edema (range; 0–24 points) ([Fig. 2](https://www.sciencedirect.com/science/article/pii/S1875957224000391#fig2)). The severity of pulmonary edema was graded according to the calculated score; <5: normal, 5–10: mild pulmonary edema, 10–18: moderate pulmonary edema, and >18: severe pulmonary edema [[15](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib15)].

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2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S1875957224000391-gr2.jpg)

Fig. 2. Pulmonary edema scoring according to LUS imaging; 0: Normal, 1: Mild pulmonary edema, 2: Moderate pulmonary edema, 3: Severe pulmonary edema.

2.7. Differential diagnosis

In this study, the evaluation of B-line distribution and pleural line characteristics on LUS was used to distinguish [pathological processes](https://www.sciencedirect.com/topics/medicine-and-dentistry/pathological-process) involving the [interstitium](https://www.sciencedirect.com/topics/medicine-and-dentistry/interstitium) (pulmonary edema, ALI/ARDS, pneumonia and fibrosis-induced interstitial lung disease).

B-lines due to [pulmonary fibrosis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-fibrosis), inflammation, [ARDS](https://www.sciencedirect.com/topics/medicine-and-dentistry/acute-respiratory-distress-syndrome) usually begin at the posterior [base](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/base) of the lung, often with pleural line irregularities and small subpleural consolidations, followed by decreased lung sliding and air bronchograms [[13](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib13),[16](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib16)]. In critically ill patients, ultrasound demonstration of a dishomogeneous alveolainterstitial syndrome (AIS) with separate areas (preserved areas with normal sonographic lung appearance are often surrounded by areas containing multiple B lines and pleural line irregularities, and pleural line modifications and lung consolidations are strong predictors of early stage non-cardiogenic pulmonary edema) [[17](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib17)]. In contrast, in cardiogenic pulmonary edema, B-lines generally show a more homogeneous distribution influenced by gravity [[[18]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib18), [[19]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib19), [[20]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib20)].

Additionally, the rapid response of edema to [diuretic](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/diuretic-agent) treatment and its early reflection on LUS were interpreted as important findings of cardiogenic pulmonary edema**.**

2.8. Management

During follow-up, patients were monitored by neonatologists and pediatric cardiologists who were blinded to the LUS findings, focusing on signs of pulmonary and/or systemic edema, fluid balance, and urine output. Fluid replacement, diuretic treatment, and inotropic doses were adjusted based on the patients' clinical and [hemodynamic](https://www.sciencedirect.com/topics/medicine-and-dentistry/hemodynamic) parameters.

To evaluate the severity of the patient's condition, vasoactive inotropic scores (VIS) were calculated using the following formula: dopamine dose (mcg/kg/min) min) + [dobutamine](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dobutamine) dose (mcg/kg/min) + 100 × epinephrine dose (mcg/kg/min) + 10 × [milrinone](https://www.sciencedirect.com/topics/medicine-and-dentistry/milrinone) dose (mcg/kg/min) + 10,000 × [vasopressin](https://www.sciencedirect.com/topics/medicine-and-dentistry/vasopressin) dose (U/kg/min) + 100 × [norepinephrine](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/noradrenalin) dose (mcg/kg/min) [[21](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib21),[22](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib22)].

The pro-BNP levels and VIS values were noted before (the last value before surgery) and after cardiac surgery (the highest value within the first three days after surgery). The Society of Thoracic Surgeons-European Association for [Cardiothoracic Surgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-surgery) (STAT) scores were determined according to the type of cardiac surgery [[23](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib23),[24](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib24)].

2.9. Outcomes

The primary outcome of this study was to identify whether there was a correlation between LUS and CXR findings. Secondary outcomes were to demonstrate the relationship between LUS and the need for respiratory support, diuretic use, VIS and serum pro-BNP levels in the [perioperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/perioperative-period).

3. Statistics

All data were analyzed using SPSS Statistics for Windows (IBM SPSS Statistics for Windows, version 24.0). Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to check the normality of the distribution. Accordingly, quantitative variables were expressed as mean ± SD or median with interquartile range (IQR). Qualitative variables are expressed as frequency and percentage values (n, %) and analyzed using the chi-square test. Two independent quantitative variables were compared using the *t*-test if normally distributed; otherwise, the Mann-Whitney *U* test was used. The [Friedman test](https://www.sciencedirect.com/topics/medicine-and-dentistry/friedman-test) was used for multiple comparisons to analyze repeated measures of quantitative variables, whereas the Wilcoxon test was used for pairwise comparisons. The Cochrane Q-test was preferred for the comparison of repeated categorical variables. Pearson's correlation test was used to investigate the relationship between CXR and LUS. A p value of <0.05 was considered statistically significant.

4. Results

Initially, 59 newborns with CCHD were eligible for inclusion. Fifteen patients dropped out due to the exclusion criteria; finally, analyses were performed on 44 patients. Neonatal CCHD subtypes were classified based on the [PBF](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-blood-flow) patterns. Thirty-two (73%) patients with CCHD showed increased PBF ([Fig. 2](https://www.sciencedirect.com/science/article/pii/S1875957224000391#fig2)). The demographic and clinical data of all the patients are provided in [Table 1](https://www.sciencedirect.com/science/article/pii/S1875957224000391#tbl1). The surgical procedures performed included [aortic arch repair](https://www.sciencedirect.com/topics/medicine-and-dentistry/aortic-arch-surgery) (n = 16), [arterial switch surgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/jatene-procedure) (n = 4), hybrid procedure (n = 2), PDA ligation (n = 3), pulmonary banding (n = 5), [aortopulmonary window](https://www.sciencedirect.com/topics/medicine-and-dentistry/aortopulmonary-window) repair (n = 1), total [pulmonary venous return anomaly](https://www.sciencedirect.com/topics/medicine-and-dentistry/anomalous-pulmonary-venous-connection) (TAPVR) repair (n = 1), and BT shunt (n = 12).

Table 1. Demographic and clinical data of all study patients.

| **Characteristics** | **n = 44** |
| --- | --- |
| Gestational age (week), mean ± SD | 38.3 ± 1,7 |
| Birth weight (gram), mean ± SD | 3026 ± 432 |
| Gender (male) n (%) | 28 (64) |
| Cesarean rate, n (%) | 25 (57) |
| APGAR (5th Minute), mean ± SD | 8.7 ± 0.7 |
| Prenatal diagnosis, n (%) | 9 [[21](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib21)] |
| Out-center birth, n (%) | 38 (86) |
| Time of CCHD diagnosis (day), mean ± SD | 8 ± 18 |
| Time of cardiac NICU admission (day), mean ± SD | 9.6 ± 10.1 |
| Time of cardiac surgery (day), mean ± SD | 18 ± 11,3 |
| Duration of mechanical ventilation, (day), median (range) | |
| *Preoperative* | 4 [[[2]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib2), [[3]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib3), [[4]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib4), [[5]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib5), [[6]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib6), [[7]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib7), [[8]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib8), [[9]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib9), [[10]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib10)] |
| *Postoperative* | 9 [[[2]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib2), [[3]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib3), [[4]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib4), [[5]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib5), [[6]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib6), [[7]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib7), [[8]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib8), [[9]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib9), [[10]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib10), [[11]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib11), [[12]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib12), [[13]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib13), [[14]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib14), [[15]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib15), [[16]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib16), [[17]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib17), [[18]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib18), [[19]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib19), [[20]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib20), [[21]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib21), [[22]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib22), [[23]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib23)] |
| *STAT score* | 1.35 ± 0.62 |
| *STAT category* | 3.41 ± 0.99 |
| Time of discharge time (day), mean ± SD | 49 ± 38 |
| Mortality, n (%) | 8 (18.1) |

CCHD: Critical congenital heart disease, NICU: Neonatal intensive care unit.

STAT: The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery.

In parallel with the clinical findings, it was noted that both LUS and CXR results were compatible with pulmonary edema in the [preoperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/preoperative-period).

In the [postoperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/postoperative-period), pulmonary edema increased slightly on postnatal Day 1 compared to the preoperative period, while it decreased steadily towards the 6th postoperative day in most of the study patients (p < 0.05).

The [VIS](https://www.sciencedirect.com/topics/medicine-and-dentistry/inotropism) scores, pro-BNP levels, need for [mechanical ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/artificial-respiration), and [diuretic](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent) requirements also decreased significantly from postoperative days 2–6 (p < 0.05, for all comparisons) ([Table 2](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "tbl2)). [Table 3](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "tbl3) shows the perioperative data regarding clinical findings, laboratory results, and radiological imaging using PBF grouping. It was noted that the changes in the study points were more pronounced in patients with increased PBF.

Table 2. Perioperative data regarding clinical findings, laboratory results, and radiological imaging.

| Empty Cell | **Preop** | **Postop 2** | **Postop 4** | **Postop 6** | ***p value*** |
| --- | --- | --- | --- | --- | --- |
| **Clinical PE, yes, n (%)** | 21 (47.7) | 44 (100) | 40 (90.9) | 29 (65.9) | Preop-Postop 2: <0.001 Postop 2-Postop 4: 0.12 Postop 2-Postop 6: <0.001 <0.001∗ |
| **Respiratory support, n (%)** **NIPPV** **MV** | 11 (25.0) 23 (52.3) | – 44 (100) | 14 (31.8) 30 (68.2) | 26 (59.1) 18 (40.9) | Preop-Postop 2: <0.001 Postop 2-Postop 4: <0.001 Postop 2-Postop 6: <0.001 <0.001∗ |
| **Diuretic+, (+), n (%) Intermittent Infusion** | 6 (13.6) 24 (54.5) | – 37 (84.1) | 7 (15.9) 30 (68.2) | 10 (22.7) 18 (40.9) | Preop-Postop 2: 0.11 Postop 2-Postop 4: 1.0 Postop 2-Postop 6: 0.01 0.009∗ |
| **VIS score** | 3 (0–5) | 10 [[[5]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib5), [[6]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib6), [[7]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib7), [[8]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib8), [[9]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib9), [[10]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib10), [[11]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib11), [[12]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib12), [[13]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib13), [[14]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib14), [[15]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib15), [[16]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib16), [[17]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib17), [[18]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib18), [[19]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib19)] | 5 [[[5]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib5), [[6]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib6), [[7]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib7), [[8]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib8), [[9]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib9), [[10]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib10), [[11]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib11)] | 0 (0–5) | Preop-Postop 2: <0.001 Postop 2-Postop 4: <0.001 Postop 2-Postop 6: <0.001 <0.001∗∗ |
| **Pro-BNP** | 18336 (2846–35000) |  | | 13073 (7560–13886) | 0.02∗∗∗ |
| **Chest X Ray PE yes, n(%)** | 22 (50.0) | 42 (95.5) | 40 (90.9) | 31 (70.5) | Preop-Postop 2: <0.001 Postop 2-Postop 4: 0.68 Postop 2-Postop 6: 0.003 <0.001∗ |
| **LUS score** |  |  |  |  | Preop-Postop 2: <0.001 |
| **<5** | 20 (45.5) | 2 (4.5) | 1 (2.3) | 11 (25.0) | Postop 2-Postop 4: 1.0 |
| **5–10** | 6 (13.6) | 4 (9.1) | 8 (18.2) | 8 (18.2) | Postop 2-Postop 6: 0.01 |
| **>10** | 18 (40.9) | 38 (86.4) | 35 (79.5) | 25 (56.8) | <0.001∗ |

NIPPV: Non-invazive [intermittent positive pressure ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/intermittent-positive-pressure-breathing), MV: Mechanical ventilation, PE: Pulmonary edema, Pro-BNP: Pro-B-type natriuretic peptide, LUS: Lung ultrasound, VIS: vasoactive inotropic score.

+The need of diuretic treatment; Intermittent: 1 mg/kg/dose, twice in a day; infusion; 0.1–0.2 mf/kg/h, 24 h.

∗P value for Cochrane Q test, ∗∗p value for [Friedman test](https://www.sciencedirect.com/topics/medicine-and-dentistry/friedman-test), ∗∗∗p value for [Wilcoxon test](https://www.sciencedirect.com/topics/medicine-and-dentistry/rank-sum-test).

Table 3. Perioperative data regarding clinical findings, laboratory results, and radiological imaging by pulmonary blood flow grouping.

| Empty Cell | **CCHD with increased PBF (n = 32)** | | | | | **CCHD with decreased PBF (n = 12)** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Preop** | **Postop 2** | **Postop 4** | **Postop 6** | ***p value*** | **Preop** | **Postop 2** | **Postop 4** | **Postop 6** | ***p value*** |
| **Clinical PE, yes, n (%)** | 19 (59.4) | 32 (100) | 29 (90.6) | 22 (68.8) | Preop-Postop 2:<0.001 Postop 2-Postop 4:0.08 Postop 2-Postop 6:<0.02 <0.001∗ | 2 (16.7) | 12 (100) | 11 (91.7) | 7 (58.3) | Preop-Postop 2:<0.001 Postop 2-Postop 4:0.08 Postop 2-Postop 6:0.002 <0.001∗ |
| **Respiratory support, n (%)** **NIPPV MV** | 16 (60.0) 8 (25.0) | – 32 (100) | 12 (37.5) 20 (62.5) | 19 (59.4) 13 (40.6) | Preop-Postop 2: <0.001 Postop 2-Postop 4:<0.001 Postop 2-Postop 6:<0.001 <0.001∗ | 3 (25.0) 7 (58.3) | – 12 (100) | 2 (16.7) 10 (83.3) | 7 (58.3) 5 (41.7) | Preop-Postop 2: 0.03 Postop 2-Postop 4: 0.001 Postop 2-Postop 6: 0.008 <0.001∗ |
| **Diuretic+, (+) n (%)** **Intermittent Infusion** | 5 (15.6) 22 (68.8) | – 28 (87.5) | 5 (15.6) 23 (71.9) | 8 (25.0) 14 (43.8) | Preop-Postop 2: 0.22 Postop 2-Postop 4: 0.02 Postop 2-Postop 6: 0.001 0.009∗ | 1 (8.3) 2 (16.7) | – 9 (75.0) | 2 (16.7) 7 (58.3) | 2 (16.7) 4 (33.3) | Preop-Postop 2: 0.01 Postop 2-Postop 4: 0.15 Postop 2-Postop 6: 0.05 0.009∗ |
| **VIS score** | 3 (0–5) | 5 (5–14.3) | 5 (5–11.5) | 0 (0–5) | Preop-Postop 2: <0.001 Postop 2-Postop 4: 0.003 Postop 2-Postop 6:<0.001 <0.001∗∗ | 2.7 (0–7.5) | 17.5 [[[10]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib10), [[11]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib11), [[12]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib12), [[13]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib13), [[14]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib14), [[15]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib15), [[16]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib16), [[17]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib17), [[18]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib18), [[19]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib19), [[20]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib20), [[21]](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib21)] | 10 (5.6–11.8) | 5 (0–12.5) | Preop-Postop 2: 0.01 Postop 2-Postop 4: 0.003 Postop 2-Postop 6:<0.001 <0.001∗∗ |
| **Pro-BNP** | 21320 (6308–35000) | | 13073 (6577–23396) | | 0.02∗∗∗ | 2730 (1625–4633) | | 13222 (7560–22447) | |  |
| **Chest X Ray** **PE yes, n(%)** | 20 (62.5) | 30 (93.8) | 31 (96.9) | 24 (75) | Preop-Postop 2: 0.004 Postop 2-Postop 4: 0.56 Postop 2-Postop 6: 0.03 <0.001∗ | 2 (16.7) | 12 (100) | 9 (75) | 7 (58.3) | Preop-Postop 2: 0.002 Postop 2-Postop 4: 0.08 Postop 2-Postop 6: 0.02 <0.001∗ |
| **LUS score** **<5** **5–10** **>10** | 11 (34.4) 4 (12.5) 17 (53.1) | 2 (6.3) 2 (6.3) 28 (87.5) | – 6 (18.8) 26 (81.3) | 8 [[25](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib25)] 5 (15.6) 19 (59.4) | Preop-Postop 2: 0.003 Postop 2-Postop 4: 0.41 Postop 2-Postop 6: 0.06 <0.001∗ | 9 (75) 2(16.7) 1 (8.3) | 2 (16.7) 10 (83.3) 12 (100) | 1 (8.3) 2 (16.7) 9 (75) | 3 [[25](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib25)] 3 [[25](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib25)] 6 (50) | Preop-Postop 2: 0.003 Postop 2-Postop 4: 0.41 Postop 2-Postop 6: 0.06 <0.001∗ |

CCHD: Critical congenital heart disease, LUS: Lung ultrasound, NIPPV: Non-invasive positive pressure, PE: Pulmonary edema, PBF: Pulmonary blood flow, Pro-BNP: Pro B type natriuretic peptide, VIS: Vasoactive inotrpic score.

+The need of diuretic treatment; Intermittent: 1 mg/kg/dose, twice in a day; infusion; 0.1–0.2 mf/kg/h, 24 h.

∗P value for Cochrane Q test, ∗∗p value for Friedman test, ∗∗∗p value for Wilcoxon test.

[Fig. 3](https://www.sciencedirect.com/science/article/pii/S1875957224000391#fig3) depicts decreased pulmonary edema in the LUS and CXR images from the preoperative period to the 6th postoperative day in a patient who underwent aortic arch repair with [cardiopulmonary bypass](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiopulmonary-bypass).

1. [Download: Download high-res image (467KB)](https://ars.els-cdn.com/content/image/1-s2.0-S1875957224000391-gr3_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S1875957224000391-gr3.jpg)

Fig. 3. Perioperative Chest X-ray and LUS images of the newborn underwent [aortic arch repair](https://www.sciencedirect.com/topics/medicine-and-dentistry/aortic-arch-surgery) with cardiopulmonary by-pass.

1a Preoperative interstitial pulmonary edema on chest X-ray, 2a Preoperative; significant decrease in [lung aeration](https://www.sciencedirect.com/topics/medicine-and-dentistry/respiratory-airflow) in LUS, see vertical B lines, 1b Postoperative 2nd day; central diffuse edema on chest X-ray, 2b Postoperative 2nd day; intense decrease in lung aeration in LUS-compact vertical B lines, 1c Postoperative 6th day; normal aeration on X-ray, 2c Postoperative 6th day: normal horizontal A lines in LUS -

The LUS and CXR findings were positively correlated at all study points; preoperative: r = 0.91, p = 0.01, postoperative Day 2: r = 1.0, p < 0.001, postoperative Day 4: r = 0.48 p = 0.001, and postoperative Day 6: r = 0.89, p < 0.001.

[Fig. 4](https://www.sciencedirect.com/science/article/pii/S1875957224000391#fig4) shows the trend of the data of all patients in the perioperative period for all study points in terms of pulmonary edema on physical examination, CXR, and LUS as well as the need for diuretics and mechanical ventilation.

1. [Download: Download high-res image (284KB)](https://ars.els-cdn.com/content/image/1-s2.0-S1875957224000391-gr4_lrg.jpg)
2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S1875957224000391-gr4.jpg)

Fig. 4. A graph showing the number of patients with pulmonary edema on physical examination, [chest radiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) and lung ultrasound, as well as the need of diuretic and mechanical ventilation in the perioperative period by study points.

CXR: Chest X-Ray, LUS: Lung Ultrasound, MV: Mechanical ventilation, PE: Pulmonary edema, -

The total duration of mechanical ventilation support and hospital stay were longer in newborns with higher LUS scores on postoperative Day 6 (p < 0.05). When evaluated in terms of [diuretic](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/diuretic-agent) requirement, it was found that this rate was 34% (n = 15) in patients with a LUS score >10, 6.8% (n = 3) in those with a score between 5 and 10, and no diuretic requirement in those with an LUS score <5. As for [postoperative complications](https://www.sciencedirect.com/topics/medicine-and-dentistry/postoperative-complication), pleural (n = 2) and pericardial (n = 1) effusions requiring intervention developed in three patients; the effusions were detected only by LUS, while CXR reports were normal in the early period. Drainage fluid analysis results performed under lung ultrasound guidance showed characteristics of [chylothorax](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/chylothorax) and [hemopericardium](https://www.sciencedirect.com/topics/medicine-and-dentistry/hemopericardium).

5. Discussion

In this prospective study, we found that [LUS imaging](https://www.sciencedirect.com/topics/medicine-and-dentistry/ultrasonography) results correlated well with CXR findings and were consistent with clinical pulmonary edema in newborns with CCHD, especially those with increased PBF, in the perioperative period. During the postoperative period, in general, while pulmonary edema increased on the first [day of surgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/day-of-surgery) compared to the [preoperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/preoperative-period), it steadily decreased towards the 6th postoperative day. Moreover, the VIS scores, pro-BNP levels, need for [respiratory support](https://www.sciencedirect.com/topics/medicine-and-dentistry/assisted-ventilation), and necessity for diuretic treatment showed similar trends.

Among POCUS procedures, the use of LUS to guide treatment and support invasive procedures has gradually increased in NICUs. LUS is a fast, easily accessible, non‐invasive, radiation-free, repeatable, and inexpensive tool that has been preferred as an important part of different diagnostic algorithms and [clinical pathways](https://www.sciencedirect.com/topics/medicine-and-dentistry/clinical-pathway) [[25](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib25)].

It has been reported that LUS visualizes pulmonary edema better than CXR. Girona-Alacron et al. showed that LUS is more sensitive than radiography for diagnosing pulmonary edema and has a higher negative predictive value [[26](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib26)]. B-lines (formed by ultrasonographic reflection of the fluid-air interface) are related to the amount of [extravascular fluid](https://www.sciencedirect.com/topics/medicine-and-dentistry/extravascular-fluid), and the presence of B-lines shows high sensitivity and specificity in detecting alveolar-interstitial edema [[14](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib14),[[27]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib27), [[28]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib28), [[29]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib29)]. LUS scoring is a semi-quantitative system that allows serial measurements and has been created to evaluate the degree of [lung ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-ventilation) and oxygenation in newborns to guide management. LUS can detect increases and decreases in [extravascular lung fluid](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-extravascular-fluid) in real time. In one study, pulmonary edema due to CHD was detected using LUS at the 72 nd h after birth [[8](https://www.sciencedirect.com/science/article/pii/S1875957224000391#bib8)]. In our study, we evaluated pulmonary edema using the LUS score in the perioperative period, which is the most critical turning points in newborns with CHD. We speculated that the higher frequency of pulmonary edema on LUS than on CXR might indicate that mild pulmonary edema can be detected earlier with LUS than with CXR. Additionally, LUS can be a valuable tool for managing fluid therapy and optimizing volume status [[[30]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib30), [[31]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib31), [[32]](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib32)]. We observed that patients with high LUS scores had greater need for diuretics. This finding supports the use of LUS to tailor the diuretic treatment in this population. Han et al. studied newborns who underwent cardiac surgery and showed that monitoring the LUS scores reduced the duration of mechanical ventilation and hospital stay [[33](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib33)] In another study, Song et al. reported that perioperative LUS evaluation in pediatric patients who underwent cardiac surgery shortened the duration of mechanical ventilation the postoperative period and reduced the deoxygenation status in the postoperative period [[34](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib34)]. In our study, we found that the total duration of respiratory support was longer in patients with higher LUS scores on the 6th postoperative day.

Vitale et al. emphasized the importance of LUS in detecting complications after [cardiopulmonary bypass](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiopulmonary-bypass) [[35](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib35)]. In our study, we detected pleural and [pericardial effusions](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pericardial-effusion) in three patients using LUS, which could not be detected using CXR. Serum pro-BNP levels increase in patients with heart failure [[36](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib36)]. Pro-BNP levels are related to the volume and pressure load of CCHD patients with left-right shunts and are often used in the follow-up of patients to evaluate their response to treatment. High serum pro-BNP levels are associated with longer hospitalizations and higher [mortality rates](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mortality-rate) [[37](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib37)]. Similarly, in our study, we found that pro-BNP levels were higher in patients with high LUS scores.

Diuretics are used for a variety of [fluid overload](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hypervolemia) conditions in neonates, including renal dysfunction, [postoperative management](https://www.sciencedirect.com/topics/medicine-and-dentistry/postoperative-management), and [extracorporeal membrane oxygenation](https://www.sciencedirect.com/topics/medicine-and-dentistry/extracorporeal-membrane-oxygenation) (ECMO) therapy. Rusu et al. suggested that LUS may provide a safety threshold (LUS score of <15) for fluid management [[38](https://www.sciencedirect.com/science/article/pii/S1875957224000391" \l "bib38)]. In our study, the LUS score was >10 for moderate pulmonary edema, and the diuretic requirement was higher in these patients.

Our study had some limitations. First, the number of patients was insufficient to generalize our results. Additionally, the heterogeneity of the cardiac patients may have affected the results. However, this finding is valuable for guiding studies on the use of LUS in neonatal CCHD.

We would like to state that serial LUS evaluations in CCHD, especially with increased PBF, may provide guidance for the management of these patients in the cardiac NICUs in the perioperative period. Further studies with larger case series are needed to clarify the correlation between LUS and CXR in this population.

Abstract

A 47-year-old man had localized [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (LPE) and a massive [pulmonary embolism](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-embolism). The cause of LPE was believed to be a high [blood supply](https://www.sciencedirect.com/topics/medicine-and-dentistry/vascularity) to the spared pulmonary artery territories without a [thrombus](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thrombus). The patient was successfully treated with unfractionated heparin and [thrombolytic agents](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/fibrinolytic-agent).

Abbreviations and Acronyms

CECT

contrast-enhanced computed tomography

ECG

electrocardiogram

LPE

localized pulmonary edema

LVEDD

left ventricular end-diastolic diameter

RVEDD

right ventricular end-diastolic diameter

t-PA

tissue-type plasminogen activator

Spo2

oxygen saturation

TRPG

tricuspid regurgitation pressure gradient

TTE

transthoracic echocardiography

History of Presentation

A 47-year-old man presented to the [emergency department](https://www.sciencedirect.com/topics/medicine-and-dentistry/emergency-department) with worsening dyspnea on exertion for 3 weeks, [chest pain](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-pain), and pinkish [sputum](https://www.sciencedirect.com/topics/medicine-and-dentistry/sputum). On the day of the visit, the degree of his dyspnea worsened suddenly, and it became noticeable at rest. On arrival at the emergency department, his [chest pain](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thorax-pain) had resolved. However, he presented with severe respiratory failure. His blood pressure was 159/119 mm Hg, his pulse was 126 beats/min, his body temperature was 37.7 °C, his respiratory rate was 36 breaths/min, his [oxygen saturation](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxygen-saturation) (Spo2) was 81% using a reservoir mask at 15 L/min, and [arterial blood gas](https://www.sciencedirect.com/topics/medicine-and-dentistry/arterial-blood-gas) values suggested [respiratory alkalosis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/respiratory-alkalosis) and a widened alveolar-arterial oxygen gradient ([Supplemental Table 1](https://www.sciencedirect.com/science/article/pii/S2666084924001244" \l "mmc7)). Crackles were auscultated in the left upper lung field.

Learning Objectives

* •

To be able to make a differential diagnosis of [LPE](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema), considering the patient’s [medical history](https://www.sciencedirect.com/topics/medicine-and-dentistry/medical-history).

* •

To understand the mechanism and management of LPE secondary to [pulmonary embolism](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-embolism).

Past Medical History

The patient had a history of hypertension and bronchial asthma. He was receiving [amlodipine](https://www.sciencedirect.com/topics/medicine-and-dentistry/amlodipine), montelukast, and [fluticasone furoate](https://www.sciencedirect.com/topics/medicine-and-dentistry/fluticasone-furoate). In addition, he had left [rib fractures](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/rib-fracture) resulting from a fall 1 month before his presentation and that had been managed conservatively. The patient reported a recent decrease in his activity because of the fractures, and he was seated indoors for the whole day, except when sleeping.

Differential Diagnosis

On the basis of the patient’s dyspnea, pinkish [sputum](https://www.sciencedirect.com/topics/medicine-and-dentistry/sputum), respiratory failure, prolonged inactivity, mild fever, and history of [trauma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/injury), the differential diagnoses included [pulmonary embolism](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-embolism), pneumonia, pulmonary [alveolar hemorrhage](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-hemorrhage), and [lung contusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-contusion). [Mitral regurgitation](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mitral-valve-regurgitation) should also be considered in patients with localized [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (LPE) if regurgitated blood flow is blown into the [pulmonary vein](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-vein), thus causing localized [pulmonary consolidation](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-consolidation) associated with the pulmonary vein territory.

Investigations

Blood test results revealed [lactic acidosis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lactic-acidosis) with elevated levels of [troponin I](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/troponin-i), N-terminal pro–B-type natriuretic peptide, and C-reactive protein (0.039 ng/mL, 5,200 pg/mL, and 3.95 mg/dL, respectively). We did not measure [procalcitonin](https://www.sciencedirect.com/topics/medicine-and-dentistry/procalcitonin). [Chest radiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) revealed increased right-sided translucency and consolidation in the left upper lung field ([Figures 1A](https://www.sciencedirect.com/science/article/pii/S2666084924001244#fig1) and [1B](https://www.sciencedirect.com/science/article/pii/S2666084924001244#fig1)). The electrocardiogram (ECG) showed [sinus tachycardia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/sinus-tachycardia), T-wave inversions in the right precordial leads (V1-V4) and inferior leads (II, III, and aVF), a deep S-wave in lead I, a Q-wave in lead III, and clockwise rotation. The QRS interval transition zone was V5 ([Supplemental Figure 1A](https://www.sciencedirect.com/science/article/pii/S2666084924001244#mmc7)). [Transthoracic echocardiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/transthoracic-echocardiography) (TTE) revealed normal [left ventricular function](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-left-ventricle-function) and no [mitral regurgitation](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mitral-valve-regurgitation), although a dilated [right ventricle](https://www.sciencedirect.com/topics/medicine-and-dentistry/right-ventricle), an elevated [tricuspid regurgitation](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tricuspid-valve-regurgitation) pressure gradient (TRPG) (84 mm Hg), an elevated right ventricular end-diastolic diameter–to–left ventricular end-diastolic diameter ratio (RVEDD/LVEDD ratio, 1.42; RVEDD, 47 mm), and a McConnell sign were observed, suggesting significant right-sided [heart overload](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-ventricle-overload) ([Video 1](https://www.sciencedirect.com/science/article/pii/S2666084924001244" \l "mmc1)). Contrast-enhanced [computed tomography](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) (CECT) detected regional infiltrative shadows in the left upper lobe. Although the left upper pulmonary artery remained patent, thrombotic occlusions were noted in the other pulmonary artery branches ([Figures 2A to 2F](https://www.sciencedirect.com/science/article/pii/S2666084924001244#fig2), [Videos 2A](https://www.sciencedirect.com/science/article/pii/S2666084924001244" \l "mmc2) and [2B](https://www.sciencedirect.com/science/article/pii/S2666084924001244" \l "mmc3)). CECT revealed [deep vein thrombosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/deep-vein-thrombosis) in the left [popliteal vein](https://www.sciencedirect.com/topics/medicine-and-dentistry/popliteal-vein). LPE as a consequence of massive pulmonary embolism was diagnosed.

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Figure 1. Chest Radiography

(A) Chest radiography on admission. (B) One day after admission.

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Figure 2. Contrast-Enhanced Computed Tomography on Admission

(A) The mediastinal window, upper lung. (B) Mediastinal window, pulmonary artery trunk level. (C) Mediastinal window, middle pulmonary artery trunk level. (D) Lung window, upper lung. (E) Lung window, pulmonary artery trunk level. (F) Lung window, middle pulmonary artery trunk level.

Management

The patient received oxygen through a high-flow [nasal cannula](https://www.sciencedirect.com/topics/medicine-and-dentistry/nasal-cannula) and a continuous unfractionated heparin infusion to maintain an activated [partial thromboplastin time](https://www.sciencedirect.com/topics/medicine-and-dentistry/partial-thromboplastin-time) within 2 to 3 times the upper normal limit. Antibiotics were also administered because the possibility of aspiration or [bacterial pneumonia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/bacterial-pneumonia) could not be excluded. The following day, the patient continued to experience respiratory distress, and the oxygenation levels or A-a DO2 remained insufficient ([Supplemental Table 1](https://www.sciencedirect.com/science/article/pii/S2666084924001244#mmc7)). On [chest radiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography), the left upper lung consolidation had not changed ([Figure 1B](https://www.sciencedirect.com/science/article/pii/S2666084924001244#fig1)). No signs of [bleeding complications](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/bleeding), such as [alveolar hemorrhage](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-hemorrhage), were observed, and the patient became afebrile. Tissue-type plasminogen activator (t-PA) was administered (13,750 mg/kg; 1,375,000 IU). The day after t-PA administration, the patient’s oxygenation had significantly improved, and the respiratory distress resolved (respiratory rate, 18 breaths/min; [arterial blood gas](https://www.sciencedirect.com/topics/medicine-and-dentistry/arterial-blood-gas) on 6 L/min oxygen through a facial mask: pH, 7.44; Pao2, 95 mm Hg; Paco2, 31 mm Hg; [bicarbonate](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dicarbonate), 21 mmol/L; [base](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/base) excess, −1.3 mmol/L; Spo2, 97%).

On the fourth day after admission, oxygen supplementation was no longer necessary, and the [antithrombotic](https://www.sciencedirect.com/topics/medicine-and-dentistry/antithrombotic) regimen was switched from continuous heparin infusion to oral [rivaroxaban](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/rivaroxaban) (30 mg/day). Chest radiography showed gradual normalization of the increased right-sided translucency and consolidations in the upper left lung field ([Figure 3](https://www.sciencedirect.com/science/article/pii/S2666084924001244#fig3)). The ECG showed slight resolution of the T-wave inversion in the inferior leads ([Supplemental Figure 2](https://www.sciencedirect.com/science/article/pii/S2666084924001244#mmc7)). On follow-up [CECT](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) before discharge, improved blood flow was observed in the embolized pulmonary arteries, and the pulmonary edema in the left upper lung had disappeared ([Figures 4A to 4F](https://www.sciencedirect.com/science/article/pii/S2666084924001244#fig4), [Videos 3A](https://www.sciencedirect.com/science/article/pii/S2666084924001244" \l "mmc4) and [3B](https://www.sciencedirect.com/science/article/pii/S2666084924001244" \l "mmc5)). [TTE](https://www.sciencedirect.com/topics/medicine-and-dentistry/transthoracic-echocardiography) before discharge showed improvement in the right ventricular enlargement, resolution of the McConnell sign, and alleviation of right-sided [heart overload](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-ventricle-overload) (RVEDD/LVEDD ratio, 0.84; RVEDD, 37 mm), although the [TRPG](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tricuspid-valve-regurgitation) could not be measured ([Video 4](https://www.sciencedirect.com/science/article/pii/S2666084924001244" \l "mmc6)). The patient was discharged on the ninth day of hospitalization.

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Figure 3. Chest Radiography Before Discharge

Chest radiography obtained 8 days after admission.

1. [Download: Download high-res image (770KB)](https://ars.els-cdn.com/content/image/1-s2.0-S2666084924001244-gr4_lrg.jpg)
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Figure 4. Contrast-Enhanced Computed Tomography Before Discharge (Day 8)

(A) The mediastinal window, upper lung. (B) Mediastinal window, pulmonary artery trunk level. (C) Mediastinal window, middle pulmonary artery trunk level. (D) Lung window, upper lung. (E) Lung window, pulmonary artery trunk level. (F) Lung window, middle pulmonary artery trunk level.

Discussion

This patient had LPE secondary to massive pulmonary embolism that was successfully treated using intravenous [anticoagulant agents](https://www.sciencedirect.com/topics/medicine-and-dentistry/antithrombotic) and [thrombolytic therapy](https://www.sciencedirect.com/topics/medicine-and-dentistry/fibrinolytic-therapy).

LPE accounts for 2.1% of cases of cardiogenic pulmonary edema.[1](https://www.sciencedirect.com/science/article/pii/S2666084924001244#bib1) Although several factors can trigger LPE, particularly in the right upper lobe, severe mitral regurgitation is the most prevalent cause.[2](https://www.sciencedirect.com/science/article/pii/S2666084924001244#bib2) However, LPE can result from pulmonary embolism (termed overflow pulmonary edema).[3](https://www.sciencedirect.com/science/article/pii/S2666084924001244#bib3) This mechanism is thought to involve the concentration of blood flow into nonthrombosed arteries, thus leading to an increase in the hydrostatic pressure in that segment of the capillary bed.[2](https://www.sciencedirect.com/science/article/pii/S2666084924001244#bib2) The radiologic changes and therapeutic reactions support the diagnosis of LPE in the current patient. The clinical implication of LPE secondary to pulmonary embolism may be as follows: 1) the area affected by the embolism occupies most of the lung and decreases the efficiency of gas exchange in the embolized lung territories; 2) the concentration of blood flow to the remaining healthy lung fields results in pulmonary edema, further reducing the efficiency of gas exchange and increasing pulmonary hydrostatic pressure; and 3) decreased gas exchange and [obstructive shock](https://www.sciencedirect.com/topics/medicine-and-dentistry/obstructive-shock) cause [acidemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/organic-acidemia) and lead to progressive [circulatory failure](https://www.sciencedirect.com/topics/medicine-and-dentistry/ischemia).

This patient experienced rapid symptom improvement after [thrombolysis](https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-clot-lysis). The unclear date of onset, a lack of objective data before the visit, unilateral consolidation of the lung, a history of [trauma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/injury), and pinkish sputum suggestive of alveolar hemorrhage made the decision to administer [thrombolytic](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/fibrinolytic-agent) agents difficult despite the patient’s pulmonary embolism with severe respiratory failure. We thought that the dyspnea that occurred 3 weeks earlier was caused by a small pulmonary embolism and that a more extensive embolism may have happened on the day of the visit. After 1 day of aggressive intravenous [anticoagulant therapy](https://www.sciencedirect.com/topics/medicine-and-dentistry/anticoagulant-therapy), the patient had not improved, and there was no evidence of worsening hemorrhagic complications. Therefore, [thrombolytic agents](https://www.sciencedirect.com/topics/medicine-and-dentistry/thrombolytic-drug) were administered. It is crucial to differentiate complicated diseases adequately so the appropriate therapeutic decisions can be made.

Follow-Up

At a 3-week follow-up appointment, the patient had no symptoms on exertion, and CECT showed a trend of resolution of the pulmonary emboli. Therefore, his [rivaroxaban](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/rivaroxaban) dose was reduced to 15 mg/day, as approved by the [Pharmaceuticals](https://www.sciencedirect.com/topics/medicine-and-dentistry/drug) and [Medical Devices](https://www.sciencedirect.com/topics/medicine-and-dentistry/medical-device) Agency of Japan.[4](https://www.sciencedirect.com/science/article/pii/S2666084924001244#bib4) We plan to continue [rivaroxaban](https://www.sciencedirect.com/topics/medicine-and-dentistry/rivaroxaban) until the pulmonary [thrombus](https://www.sciencedirect.com/topics/medicine-and-dentistry/thrombus) and lower extremity venous [thrombus](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thrombus) disappear on computed tomography.

Conclusions

A patient with LPE secondary to massive pulmonary embolism underwent [antithrombotic therapy](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/antithrombotic-therapy). Before initiating [antithrombotic therapy](https://www.sciencedirect.com/topics/medicine-and-dentistry/antithrombotic-therapy), other differential diagnoses must be excluded on the basis of the patient’s medical history.

Abstract

Negative pressure pulmonary edema (NPPE), also known as post-obstructive pulmonary edema, is a rare and life-threatening condition. It occurs when a person breathes against an obstructed [glottis](https://www.sciencedirect.com/topics/medicine-and-dentistry/glottis), causing negative thoracic pressure in the lungs. This negative pressure can lead to fluid accumulation in the lungs, resulting in pulmonary edema. The obstructed glottis might be caused by [laryngospasm](https://www.sciencedirect.com/topics/medicine-and-dentistry/larynx-spasm), which occurs when the muscles around the [larynx](https://www.sciencedirect.com/topics/medicine-and-dentistry/larynx) involuntarily spasm and can lead to complete upper airway occlusion. This report shares the case of a 33-year-old woman hospitalized for periapical [dental abscess](https://www.sciencedirect.com/topics/medicine-and-dentistry/dental-abscess), facial swelling, and shortness of breath. The patient exhibited signs of poor [oral hygiene](https://www.sciencedirect.com/topics/medicine-and-dentistry/oral-hygiene). After the exacerbation of her symptoms, she showed signs of asphyxia and decreased [oxygen saturation](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxygen-saturation), which led to her [intubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/intubation). Imaging revealed bilateral [pleural effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleura-effusion) and patchy [ground glass opacities](https://www.sciencedirect.com/topics/medicine-and-dentistry/ground-glass-opacity) favoring NPPE. After three days of treatment with [diuretics](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent) and other conservative measures, her condition was alleviated, and she was extubated. Laryngospasm in the presence of a dental abscess is uncommon. Identification of imaging favoring NPPE in this setting is even more rare. In cases of laryngospasm, prompt intubation is crucial. Therapy with diuretics and other conservative measures can effectively treat NPPE following laryngospasm.

1. Introduction

A [periapical abscess](https://www.sciencedirect.com/topics/medicine-and-dentistry/periapical-periodontitis) is a common type of [dental abscess](https://www.sciencedirect.com/topics/medicine-and-dentistry/dental-abscess) and significantly impacts the [alveolar bones](https://www.sciencedirect.com/topics/medicine-and-dentistry/alveolar-bone). Typically, these abscesses occur at the apex of the dental root, the tooth's periodontal membrane, or the adjacent alveolar bone. The spread of infection through the [apical foramen](https://www.sciencedirect.com/topics/medicine-and-dentistry/apical-foramen) triggers an inflammatory reaction that attracts a host of chemical mediators, initiating the periapical pathology. This cascade of events can ultimately lead to the formation of a periapical abscess, [radicular cyst](https://www.sciencedirect.com/topics/medicine-and-dentistry/odontogenic-cyst), or periapical granuloma [[1](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib1),[2](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib2)]. Negative pressure pulmonary edema (NPPE), also known as post-obstructive pulmonary edema, is a rare and life-threatening condition that follows the vigorous relief of [upper airway obstruction](https://www.sciencedirect.com/topics/medicine-and-dentistry/upper-respiratory-tract-obstruction) during [extubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/extubation) in a spontaneously breathing patient after [general anesthesia](https://www.sciencedirect.com/topics/medicine-and-dentistry/general-anesthesia) or negative thoracic pressure induced by inspiratory effort against an obstructed [glottis](https://www.sciencedirect.com/topics/medicine-and-dentistry/glottis) [[3](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib3),[4](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib4)]. However, it can be caused by [laryngospasm](https://www.sciencedirect.com/topics/medicine-and-dentistry/larynx-spasm), [epiglottitis](https://www.sciencedirect.com/topics/medicine-and-dentistry/epiglottitis), tumors, obesity, hiccups, or obstructive sleep. [Tachypnea](https://www.sciencedirect.com/topics/medicine-and-dentistry/tachypnea), coughing, pink frothy [sputum](https://www.sciencedirect.com/topics/medicine-and-dentistry/sputum), bilateral fluffy infiltrates on the [chest radiograph](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography), and the inability to maintain [oxygen saturation](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxygen-saturation) above 95% are common presenting signs that may be mistaken for [pulmonary aspiration](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-aspiration) or [pulmonary embolism](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-embolism) and can cause different diagnostic difficulties, especially for the anesthesiologist [[5](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib5),[6](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib6)]. A limited number of cases have been documented wherein NPPE has been observed following [maxillofacial surgeries](https://www.sciencedirect.com/topics/medicine-and-dentistry/maxillofacial-surgery) during [intubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/intubation) or the surgical procedure [[7](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib7),[8](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib8)]. The occurrence of laryngospasm in the presence of a dental abscess followed by NPPE imaging findings is uncommon. Treatment is generally supportive by maintaining a patent upper airway and oxygen supplementation, as most cases of NPPE resolve without medical intervention within 12–48 hours. [Mechanical ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/artificial-respiration) may sometimes be necessary for a short period [[3](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib3)]. We present a case of NPPE after laryngospasm due to periapical dental abscess.

2. Case presentation

We present a 32-year-old woman referred to the hospital due to facial swelling and shortness of breath. Her lower left [incisor](https://www.sciencedirect.com/topics/medicine-and-dentistry/incisor), molar, and [premolar teeth](https://www.sciencedirect.com/topics/medicine-and-dentistry/premolar) were extracted at a private dentist's office at 8 p.m. On the next day, at 10 a.m., she woke up with pain in the left jaw and swelling that gradually expanded to the left side of her cheek and neck until, at noon (2 p.m.), she reported experiencing shortness of breath after walking approximately 100 m, which caused her to stop and catch her breath before continuing, [hoarseness](https://www.sciencedirect.com/topics/medicine-and-dentistry/hoarseness), and fever, and she reached out to the hospital. She had a history of [polycystic ovaries](https://www.sciencedirect.com/topics/medicine-and-dentistry/polycystic-ovary-syndrome) but mentioned no [medical history](https://www.sciencedirect.com/topics/medicine-and-dentistry/medical-history) in her family. Upon admission, she denied using any drugs, either daily or after the [dental surgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/smear-layer). Her blood pressure was 160/80 mmHg, respiratory rate was 28 per minute, pulse rate was 125 beats per minute, and body temperature was 38 °C. She had an [oxygen saturation](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxygen-saturation) (SpO2) of 58% in the room air, which increased to 85% after receiving 100% oxygen via a reservoir bag and being placed in a sitting position. In the physical examination, her appearance showed swelling and local heat in the left [temporomandibular joint](https://www.sciencedirect.com/topics/medicine-and-dentistry/temporomandibular-joint) (TMJ) and masseter, and her face was asymmetrical. Upon examining the patient's [oral cavity](https://www.sciencedirect.com/topics/medicine-and-dentistry/oral-cavity), she had poor [oral hygiene](https://www.sciencedirect.com/topics/medicine-and-dentistry/oral-hygiene), and other teeth on the right side required [dental treatment](https://www.sciencedirect.com/topics/medicine-and-dentistry/dental-procedure). A tooth located in the upper right molar area had been extracted, and the space was empty. Her left [mandibular region](https://www.sciencedirect.com/topics/medicine-and-dentistry/lower-jaw) was tender, and two mobile, tender lymph nodes were palpable in the left submandibular and anterior cervical regions with an approximate size of 1.5 × 1.5 cm. In [lung auscultation](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-auscultation), crackles and decreased breathing sounds were detectable in the base of the lungs. Due to her condition, she was immediately transferred to the [intensive care unit](https://www.sciencedirect.com/topics/medicine-and-dentistry/intensive-care-unit) (ICU). The [arterial blood gas analysis](https://www.sciencedirect.com/topics/medicine-and-dentistry/arterial-blood-gas-analysis) (ABG) at the ICU showed PH 7.25, PaO2 81%, PaCO2 43.2, and HCO3 18.1. She suddenly experienced [tachycardia](https://www.sciencedirect.com/topics/medicine-and-dentistry/tachyarrhythmia), increased respiratory rate, [cyanosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/cyanosis), gasping respiration, use of accessory muscles, [hypoxemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/hypoxemia), and her SpO2 decreased to 75% with 100% o2 with the reservoir bag mask; her [auscultation](https://www.sciencedirect.com/topics/medicine-and-dentistry/auscultation) showed diffuse [wheeze](https://www.sciencedirect.com/topics/medicine-and-dentistry/wheeze) and crackle along with reduced breath sounds in lower lungs. This sudden worsening of her condition led to [intubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/intubation). The patient was intubated after receiving 100 mcg of [fentanyl](https://www.sciencedirect.com/topics/medicine-and-dentistry/fentanyl) and 2 mg of midazolam. During intubation, the operator claims proximity of the [vocal cords](https://www.sciencedirect.com/topics/medicine-and-dentistry/vocal-folds) and bucking during the endotracheal tube (ETT) passage, along with pink and frothy secretions coming out of the ETT. Her Spo2 after intubation, despite receiving Fio2 100%, increased to 85%. A lung CT scan showed bilateral [pleural effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleura-effusion) and patchy [ground glass opacities](https://www.sciencedirect.com/topics/medicine-and-dentistry/ground-glass-opacity) ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S2405844024045018#fig1)a and b). These findings suggested a viral or bacterial infection, cardiogenic pulmonary edema, or non-cardiogenic pulmonary edema as differential diagnoses. The treatment began with 40 mg of [furosemide](https://www.sciencedirect.com/topics/medicine-and-dentistry/furosemide) amp as a bolus dose and then an infusion of 8 mg/hr., 1 g of [vancomycin](https://www.sciencedirect.com/topics/medicine-and-dentistry/vancomycin) amp two times a day, and 600 mg of [clindamycin](https://www.sciencedirect.com/topics/medicine-and-dentistry/clindamycin) three times a day. During her cardiac consultation and [echocardiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/echocardiography), the cardiologist reported an [ejection fraction](https://www.sciencedirect.com/topics/medicine-and-dentistry/ejection-fraction) of 55%, a [pulmonary artery pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-artery-pressure) (PAP) of 42 mm Hg, and up to moderate posterior [mitral valve regurgitation](https://www.sciencedirect.com/topics/medicine-and-dentistry/mitral-insufficiency). The cardiologist expressed that [cardiac pathologies](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiac-pathology) were less likely based on these findings. All workups for [connective tissue diseases](https://www.sciencedirect.com/topics/medicine-and-dentistry/connective-tissue-disease), vasculitis, COVID-19, and influenza were negative ([Table 1](https://www.sciencedirect.com/science/article/pii/S2405844024045018#tbl1)).

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2. [Download: Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S2405844024045018-gr1.jpg)

Fig. 1. Patient's [chest Imaging](https://www.sciencedirect.com/topics/medicine-and-dentistry/chest-imaging). a, b, chest CT scan at the first day of admission after laryngospasm displaying bilateral pleural effusion (Blue arrow) and bilateral ground glass opacities (Red arrow). c, d, chest radiography at the second and third day of admission. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1. The laboratory results of the patient during her admission.

| **Lab tests** | | **Normal range** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| WBC count, count/mm | | 4000–10000 | 10.100 |  | 9900 |  |  |  | 5800 |
| Hemoglobin, mg/dl | | 12–15 | 13.6 |  | 11.6 |  |  |  | 12.4 |
| MCV, fl | | 80–96 | 87 |  | 85 |  |  |  | 85 |
| ESR, mm/hr | | >21 |  | 26 |  |  |  |  |  |
| CRP | | Neg | Neg. |  |  |  |  |  |  |
| Platelet, count/mm | | 150000–450000 | 303.000 |  | 216.000 |  |  |  |  |
| BUN, mg/dl | | 15–45 | 56 | 55 | 62 | 61 |  | 62 | 59 |
| Cr, mg/dl | | 0.5–1.4 | 1.1 | 1.3 | 1.2 | 1.5 |  | 1.2 | 1.2 |
| INR | | 1–1.4 | 1.1 |  | 1.3 |  |  |  |  |
| Troponin, ng/mL | | 0–0.04 | 0.039 | 0.03 |  |  |  |  |  |
| TSH, micIU/ml | | 0.35–4.94 |  | 1.2 |  |  |  | 2.3 |  |
| LDH, U/L | | 0–500 |  | 539 |  |  |  |  |  |
| AST, IU/l | | <41 |  | 20 |  |  |  |  |  |
| ALT, IU/l | | <41 |  | 24 |  |  |  |  |  |
| CPK, mcg/L | | 0–120 |  | 185 |  |  |  |  |  |
| ALP, IU/l | |  |  | 120 |  |  |  |  |  |
| ds-DNA | | Neg. | Neg. |  |  |  |  |  |  |
| Blood culture | | Neg. | Neg. |  |  |  |  |  |  |
| Urine culture | | Neg. | Neg. |  |  |  |  |  |  |
| C3, mg/dl | | 75 to 175 | 113.8 |  |  |  |  |  |  |
| C4, mg/dl | | 16 to 48 | 22 |  |  |  |  |  |  |
| CH50, U/mL | | 42 to 95 | 110 |  |  |  |  |  |  |
| ANA | | <0.5 | 0.1 |  |  |  |  |  |  |
| P-ANCA | | Neg. | Neg. |  |  |  |  |  |  |
| C-ANCA | | Neg. | Neg. |  |  |  |  |  |  |
| D-dimer | | Neg. | Neg. |  |  |  |  |  |  |
| 24 hr. urine | Cr. Pr. Vol. |  | 13.2 |  |  |  |  |  |  |
|  | 592 |  |  |  |  |  |  |
|  | 1600 |  |  |  |  |  |  |

**WBC**: White blood cells; [Hb](https://www.sciencedirect.com/topics/medicine-and-dentistry/hemoglobins): Hemoglobin **MCV**: Mean corpuscular volume; [LDH](https://www.sciencedirect.com/topics/medicine-and-dentistry/lactate-dehydrogenase): Lactate dehydrogenase; **Cr**: Creatinine; **CRP**: C-reactive protein; **ESR**: [Erythrocyte sedimentation rate](https://www.sciencedirect.com/topics/medicine-and-dentistry/erythrocyte-sedimentation-rate); **INR**: International normalized ratio; **PTT**: [Partial thromboplastin time](https://www.sciencedirect.com/topics/medicine-and-dentistry/partial-thromboplastin-time); [BUN](https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-urea-nitrogen): Blood urea nitrogen; **TSH**: Thyroid-stimulating hormone; **AST**: Aspartate aminotransferase; **ALT**: [Alanine aminotransferase](https://www.sciencedirect.com/topics/medicine-and-dentistry/alanine-aminotransferase); **ALP**: [Alkaline phosphatase](https://www.sciencedirect.com/topics/medicine-and-dentistry/alkaline-phosphatase); **CPK**: Creatinine phosphokinase**; ANA**: Anti-nuclear antibody; **ANCA**: [Antineutrophil cytoplasmic antibodies](https://www.sciencedirect.com/topics/medicine-and-dentistry/neutrophil-cytoplasmic-antibody); **ds-DNA**: Double stranded deoxyribonucleic acid.

Over the next few days, the patient's condition gradually improved. Her fever, as well as the swelling in her face and neck, began to subside. Her Spo2 levels reached 94% with 60% fio2. [Chest radiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) revealed decreased lung involvement on the second and third days ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S2405844024045018#fig1)c and d). By the third day, she was weaned off the mechanical ventilator and transferred to the general ward on the fourth day of admission. On the sixth day, a spiral chest CT scan showed a minimal right pleural effusion ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S2405844024045018#fig1)e and f). Since her dyspnea improved and her SpO2 without oxygen was 96%, she was discharged on the seventh day. Two weeks later, the patient revisited the pulmonologist and was found to be fully recovered. Please refer to [Table 1](https://www.sciencedirect.com/science/article/pii/S2405844024045018#tbl1) for the results of the laboratory test.

3. Discussion

Dental trauma, caries, and poor [oral hygiene](https://www.sciencedirect.com/topics/medicine-and-dentistry/oral-hygiene) often cause [dental abscesses](https://www.sciencedirect.com/topics/medicine-and-dentistry/dental-abscess). When the protective enamel of the teeth breaks down, bacteria from the mouth can enter the tooth cavity (known as the pulp cavity), causing an infection. As this infection grows within the pulp cavity, it can cause severe pain by compressing the inner dentine walls. The infection can then spread downwards through the root canal into the [mandible](https://www.sciencedirect.com/topics/medicine-and-dentistry/lower-jaw) or upwards into the [maxilla](https://www.sciencedirect.com/topics/medicine-and-dentistry/maxilla), depending on the location of the affected tooth. Another cause is a partially erupted tooth, usually a wisdom tooth, where bacteria get trapped between the crown and soft tissues, causing inflammation. Other causes include [genetic factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/heredity) like [amelogenesis imperfecta](https://www.sciencedirect.com/topics/medicine-and-dentistry/amelogenesis-imperfecta), mechanical factors, medical conditions like [Sjogren's syndrome](https://www.sciencedirect.com/topics/medicine-and-dentistry/sjoegren-syndrome), Chemical [irritants](https://www.sciencedirect.com/topics/medicine-and-dentistry/irritant-agent) like smoke from methamphetamine, and [immunosuppression](https://www.sciencedirect.com/topics/medicine-and-dentistry/immunosuppressive-treatment) due to chemotherapy or chronic diseases like HIV/AIDS [[9](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib9),[10](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib10)].

The accumulation of [extravascular fluid](https://www.sciencedirect.com/topics/medicine-and-dentistry/extravascular-fluid) in the [lung parenchyma](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-parenchyma) is known as pulmonary edema. This abnormal buildup can hinder the exchange of gases at the alveolar level and, in severe cases, lead to respiratory failure. This condition can be brought on by cardiogenic causes with the inability to remove enough blood from the [pulmonary circulation](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-circulation), or it may stem from lung tissue damage known as non-cardiogenic etiologies ([Fig. 2](https://www.sciencedirect.com/science/article/pii/S2405844024045018#fig2)) [[11](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib11),[12](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib12)].

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Fig. 2. Differential diagnosis of acute pulmonary edema [[12](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib12)].

In our case, the severity of the respiratory failure, the time course of clinical and radiologic findings, the normal cardiologic evaluation, and the fast resolution of the [pleural effusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/pleura-effusion) and pulmonary edema were not ultimately consistent with these etiologies and favored the NPPE diagnosis. The etiologies for NPPE are presented in [Fig. 2](https://www.sciencedirect.com/science/article/pii/S2405844024045018#fig2). Based on the information presented, it is highly likely that NPPE resulted from a [laryngospasm](https://www.sciencedirect.com/topics/medicine-and-dentistry/larynx-spasm) caused by an infection in the [upper respiratory tract](https://www.sciencedirect.com/topics/medicine-and-dentistry/upper-respiratory-tract) due to a periapical dental abscess.

NPPE was first demonstrated by Moore in 1927 in spontaneously breathing dogs subjected to resistive loading and is a rare noncardiogenic acute pulmonary edema that can be fatal if not diagnosed and treated promptly. For this reason, before diagnosing NPPE, other possible causes of acute pulmonary edema must be considered [[13](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib13),[14](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib14)]. The [pathophysiology](https://www.sciencedirect.com/topics/medicine-and-dentistry/pathophysiology) of NPPE includes the creation of high negative intrapleural pressure through forceful inhalation against an obstructed upper airway in spontaneously breathing patients. This high negative intrapleural pressure augments blood flow to the right side of the heart, which in turn dilates and increases the hydrostatic pressure gradient across the pulmonary vascular bed, promoting the movement of fluid into the interstitial and alveolar spaces from the pulmonary capillaries. This negative pressure also increases the [left ventricle](https://www.sciencedirect.com/topics/medicine-and-dentistry/left-ventricle) afterload, thus decreasing the [ejection fraction](https://www.sciencedirect.com/topics/medicine-and-dentistry/ejection-fraction), which heightens left ventricular end-diastolic pressure, [left atrial pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-left-atrium-pressure), and pulmonary [venous pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/venous-pressure), escalating the development of pulmonary edema via an increase of pulmonary hydrostatic pressure. Additionally, this negative pressure triggers activation of the [sympathetic nervous system](https://www.sciencedirect.com/topics/medicine-and-dentistry/sympathetic-nervous-system), hypertension, and central displacement of blood volume. Together, these factors lead to pulmonary edema by increasing the transcapillary pressure [[15](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib15),[16](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib16)]. This disorder, which frequently manifests in hospital settings, is known to occur after [extubation](https://www.sciencedirect.com/topics/medicine-and-dentistry/extubation) during the [postoperative period](https://www.sciencedirect.com/topics/medicine-and-dentistry/postoperative-period). Anesthesiologists are typically the first to identify and treat this disorder, which occurs while patients are emerging from anesthesia in a state of light sedation. The disorder is categorized into two subtypes: Type I and Type II [[[17]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib17), [[18]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib18), [[19]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib19)]. Type I NPPE, also referred to as laryngospasm-induced pulmonary edema, typically develops soon after acute airway obstruction, as in our patient. In comparison, type II NPPE develops after the resolution of chronic [upper airway obstruction](https://www.sciencedirect.com/topics/medicine-and-dentistry/upper-respiratory-tract-obstruction) [[20](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib20)]. It is worth noting that the incidence of type I NPPE associated with postoperative acute upper airway obstruction is 9.6–12% compared to 44% of type II NPPE. Approximately 50% of adult NPPE events are due to postoperative laryngeal spasms [[21](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib21)]. Young, healthy, athletic patients seem at risk for this disorder because they can generate highly negative intrathoracic pressures during an obstructing event [[22](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib22)].

Characteristic chest radiographic findings consistent with the diagnosis include bilateral focal [pulmonary infiltrates](https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-infiltrate), extensive [vascular pedicles](https://www.sciencedirect.com/topics/medicine-and-dentistry/vascular-pedicle), and a normal [cardiothoracic](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiothoracics) ratio [[4](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib4)]. Another accurate and commonly used imaging modality is CT, which is gaining popularity for diagnosing this disorder, and its typical findings include accentuated consolidation with surrounding ground-glass opacity suggestive of pulmonary edema [[23](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib23)]. However, other abnormal and nonspecific patterns, such as “crazy paving,” which is common in pulmonary edema, may also be evident [[24](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib24)].

NPPE is generally a benign condition that can be quickly controlled if treated on time, and its symptoms may improve between 12 and 48 hours. As a general rule, the treatment of NPPE requires early recognition and is mainly supportive. The currently available treatment modalities emphasize the resolution of upper airway obstruction, which is the primary step, focusing on improving [respiratory function](https://www.sciencedirect.com/topics/medicine-and-dentistry/respiratory-physiology) and, reversing the pathophysiologic cascade, obviating pulmonary edema, and correcting [hypoxemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/hypoxemia) [[5](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib5),[[24]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib24), [[25]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib25), [[26]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib26), [[27]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib27), [[28]](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib28)]. The role of medications such as steroids, [bronchodilators](https://www.sciencedirect.com/topics/medicine-and-dentistry/bronchodilating-agent), and [diuretics](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent) is still controversial, and they have shown contradictory results [[6](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib6),[24](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib24),[29](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib29)]. In our case, conservative treatment with supplemental oxygen was administered as 100% oxygen through [mechanical ventilation](https://www.sciencedirect.com/topics/medicine-and-dentistry/artificial-respiration) and then via the nonrebreather face mask (flow 12 L/min) and initiation of intravenous diuretic (furosemide). The patient's symptoms of pulmonary edema improved rapidly, and this abrupt improvement of the patient's disease represents a typical case of NPPE.

We conducted a literature review on laryngospasm following dental abscess but found no article discussing this subject. In addition, the occurrence of NPPE in this case made it more uncommon. While there have been limited cases of NPPE in [otolaryngology](https://www.sciencedirect.com/topics/medicine-and-dentistry/otorhinolaryngology) settings or [maxillofacial surgeries](https://www.sciencedirect.com/topics/medicine-and-dentistry/maxillofacial-surgery), they usually occur during patient extubation or manipulation of the oropharyngeal area. However, our patient experienced laryngospasm without manipulating the oropharyngeal regions [[7](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib7),[8](https://www.sciencedirect.com/science/article/pii/S2405844024045018#bib8)].

It should be noted that there were a couple of limitations in this case. Firstly, no [head and neck imaging](https://www.sciencedirect.com/topics/medicine-and-dentistry/head-and-neck-imaging) was performed to examine the dental abscess and pharyngeal condition. Secondly, the levels of inflammatory factors (such as ESR and CRP) were not monitored on a daily basis, which would have been ideal. These limitations could be attributed to the rare condition of the patient and the initial suspicion of a cardiogenic source of edema.

4. Conclusion

It is imperative to prioritize hygiene in oral surgeries. Any dental abscess or oral infection should not be neglected, as it may lead to dire consequences such as laryngospasm in rare cases. Although type I NPPE in cases of laryngospasm is rare, its burden is remarkable if left untreated. The main steps in its management are having a high index of clinical suspicion and early supportive treatment by maintaining a patent upper airway and administering supplemental oxygen. Mechanical ventilation may occasionally be needed for a brief period in severe cases. The role of [diuretics](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent) and steroids is still a debate and requires further study.

5. Ethics statement

Written [informed consent](https://www.sciencedirect.com/topics/medicine-and-dentistry/informed-consent) was obtained from the patient to publish this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Data availability statement

The data used in the study is available from the corresponding author upon reasonable request.

To the Editor:

The Radiographic Assessment of Lung Edema (RALE) score is a validated semiquantitative score of the extent of pulmonary edema on chest radiograph (CXR), which may have potential value for the diagnosis of ARDS as per the Berlin definition.[1](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib1),[2](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib2) Higher RALE scores are associated with higher severity and worse outcomes in patients with ARDS, including those with COVID-19.[1](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib1),[3](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib3) Changes in RALE over time have been associated with 90-day survival in an observational study[4](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib4) and in a secondary analysis of a multicenter [randomized controlled trial](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/randomized-controlled-trial).[5](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib5) However, the value of the RALE score as a surrogate outcome measure in clinical trials has not been well investigated.

Study Design and Methods

We therefore tested [RALE](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) as an outcome in a phase 2b/3 [clinical trial](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/clinical-trial) of a 3-day course of IV synthetic [vasoactive intestinal peptide](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/vasoactive-intestinal-polypeptide) (aviptadil) in patients with COVID-19 respiratory failure (oxygen by high-flow nasal cannula > 20 L/min or noninvasive or invasive ventilation).[6](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib6) In this trial, aviptadil significantly improved 60-day survival and arterial oxygenation, as assessed by the Pao2/Fio2 ratio over 7 days. We hypothesized that RALE would improve from study enrollment to day 3 and to day 10 in patients treated with aviptadil vs placebo.

A total of 81 patients were included from the trial cohort (n = 196) if they had CXR collected at enrollment, day 3, and day 10. For each CXR, the RALE score was determined independently by two readers anonymized to treatment assignment, and mean scores were used for analysis. If reader scores differed by > 5 points (out of a maximum of 48 points),[1](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib1) a third reader adjudicated the RALE score for analysis, which occurred for 52 out of 243 radiographs (21%). Changes in RALE from enrollment to day 3 and day 10 were compared between patients treated with aviptadil and placebo using the Mann-Whitney *U* test.

Results

Among participants, 51 received [aviptadil](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/vasoactive-intestinal-polypeptide) and 30 received placebo, with median Pao2/Fio2 at enrollment of 95 (interquartile range [IQR], 66-110) and 81 (IQR, 69-133) mm Hg, respectively ([Table 1](https://www.sciencedirect.com/science/article/pii/S2949788424000352#tbl1)). Median [RALE](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) at enrollment was higher in the aviptadil group than in the placebo group (24.0 [IQR, 18.0-28.0] vs 19.0 [IQR, 17.1-22.9]; *P* = .034). In the 81 included patients, RALE at enrollment was not associated with clinical outcomes including 60-day survival or ventilator-free days. RALE improved significantly in the aviptadil group vs the placebo group at day 3, with a decrease in RALE with aviptadil (median change in RALE, −2.0; IQR, −6.0 to 2.8) compared with an increase in RALE with placebo (median change in RALE, 2.8; IQR, −1.2 to 6.6) (*P* = .006) ([Fig 1](https://www.sciencedirect.com/science/article/pii/S2949788424000352#fig1)). Similar but nonsignificant results were observed for changes in RALE from study enrollment to day 10 (median changes in the placebo and aviptadil groups, 0.5 [IQR, −4.0 to 4.9] and −2.0 [IQR, 6.4-1.5], respectively; *P* = .11).

Table 1. Baseline Characteristics of Patients Treated With Aviptadil or Placebo Who Were Included in the Radiographic Assessment of Lung Edema Secondary Analysis

| **Parameter** | **Aviptadil Group (n = 51)** | **Placebo Group (n = 30)** |
| --- | --- | --- |
| Age, y | 58 ± 12 | 63 ± 12 |
| Male sex | 39 (77) | 25 (83) |
| BMI, kg/m2 | 34 ± 7 | 32 ± 6 |
| BMI ≥ 30 kg/m2 | 28 (55) | 18 (60) |
| Invasive mechanical ventilation | 21 (41) | 6 (20) |
| Noninvasive mechanical ventilation | 30 (59) | 24 (80) |
| Previous antiviral therapy for COVID-19 | 33 (65) | 21 (70) |
| On remdesivir | 32 (63) | 21 (70) |
| On steroids | 19 (37) | 20 (67) |
| On tocilizumab | 7 (14) | 4 (13) |
| On anticoagulants (antiplatelet, heparins, warfarin, and factor Xa inhibitors) | 28 (55) | 19 (63) |
| Pao2/Fio2, mm Hg | 95 (66-110) | 81 (69-133) |
| Pronated | 6 (12) | 1 (3) |

Values are No. (%), median (interquartile range), or mean ± SD.

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Figure 1. Changes in RALE score from study enrollment to day 3 and from study enrollment to day 10 in patients treated with aviptadil or placebo. RALE = Radiographic Assessment of Lung Edema.

Discussion

In this sample of patients with COVID-19 respiratory failure, aviptadil led to a significant improvement in RALE score from study enrollment to day 3, compared with placebo. However, 21% of scores required adjudication by a third reader in this analysis, which could be a potential limitation of the RALE scoring system. This finding builds on a previous study which showed that patients with ARDS with stable or improving RALE scores (rather than those with worsening scores) had a better chance of survival at 90 days.[5](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib5) In the context of the observed improvement in 60-day survival and Pao2/Fio2 over 7 days in the parent trial,[6](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib6) the current findings, although potentially biased by the inclusion of only patients who survived at least 10 days, may further support the evaluation of RALE as a surrogate outcome measure to assess resolution of pulmonary edema and potentially reflect patient-centered outcomes in future [clinical trials](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/clinical-trial) of new therapeutic interventions in ARDS.[5](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib5),[7](https://www.sciencedirect.com/science/article/pii/S2949788424000352#bib7)

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Abstract

[Aneurysmal Subarachnoid Hemorrhage](https://www.sciencedirect.com/topics/medicine-and-dentistry/subarachnoid-hemorrhage) is a life-threatening condition. It can cause [catecholamine](https://www.sciencedirect.com/topics/medicine-and-dentistry/catecholamine) surge leading to [myocardial injury](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/heart-muscle-injury), cardiac dysfunction, and [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) which indicate severity and overall prognosis. Neurocardiogenic pulmonary edema should be suspected in patients with acute pulmonary edema and [neurological symptoms](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurologic-disease). Timely diagnosis and management can prevent life-threatening consequences.

1. Introduction

The syndrome of Neurogenic [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) (NPE) has been recognized for a century, but it is still underdiagnosed in the clinical arena. It is characterized by acute pulmonary edema following a significant [central nervous system](https://www.sciencedirect.com/topics/medicine-and-dentistry/central-nervous-system) (CNS) insult. The etiology is thought to be a surge of [catecholamines](https://www.sciencedirect.com/topics/medicine-and-dentistry/catecholamine) that results in cardiopulmonary dysfunction. A myriad of CNS events, including [spinal cord injury](https://www.sciencedirect.com/topics/medicine-and-dentistry/spinal-cord-injury), Subarachnoid hemorrhage (SAH), [traumatic brain injury](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/traumatic-brain-injury), [intracranial hemorrhage](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/brain-hemorrhage), [status epilepticus](https://www.sciencedirect.com/topics/medicine-and-dentistry/status-epilepticus), meningitis, and [subdural hemorrhage](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/subdural-hematoma) have been associated with this syndrome.[1](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib1) Aneurysmal SAH is a life-threatening condition that can be complicated by cardiac dysfunction and pulmonary edema both of which indicate its severity and overall prognosis.[2](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib2) Patients can develop Takotsubo-like [cardiomyopathy](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/cardiomyopathy) and NPE because of neurogenic overstimulation of the [sympathetic nervous system](https://www.sciencedirect.com/topics/medicine-and-dentistry/sympathetic-nervous-system).[3](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib3)

2. Case report

A 47-year-old lady presented with syncope, breathlessness, dry [cough](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/coughing) and one episode of vomiting. She was hypotensive, dyspneic, and hypoxic. Patient was stabilized with non-invasive ventilation and [inotropic](https://www.sciencedirect.com/topics/medicine-and-dentistry/inotropism) support. ECG showed [sinus tachycardia](https://www.sciencedirect.com/topics/medicine-and-dentistry/sinus-tachycardia), incomplete [right bundle branch block](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/heart-right-bundle-branch-block), deep [T wave inversion](https://www.sciencedirect.com/topics/medicine-and-dentistry/t-wave-inversion) in anterolateral leads, ST depression in inferior leads and QTc prolongation (See [Fig. 1](https://www.sciencedirect.com/science/article/pii/S295046782400006X#fig1)). Cardiac biomarkers were raised. Serum electrolytes were normal. HRCT chest revealed areas of [ground glass opacities](https://www.sciencedirect.com/topics/medicine-and-dentistry/ground-glass-opacity) with a possibility of [pulmonary edema](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lung-edema) more likely than COVID-19 [ARDS](https://www.sciencedirect.com/topics/medicine-and-dentistry/acute-respiratory-distress-syndrome) (See [Fig. 2](https://www.sciencedirect.com/science/article/pii/S295046782400006X#fig2)). COVID RT-PCR test was negative. Patient was started on antibiotics, [low molecular weight heparin](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/low-molecular-weight-heparin), [ecosprin](https://www.sciencedirect.com/topics/medicine-and-dentistry/acetylsalicylic-acid) and [statin](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/statin-protein). After two days of hospitalization, she was referred to our hospital when she complained of [chest pain](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thorax-pain), breathlessness, and [headache](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/headache). She had past history of migraine. Her blood pressure was 100/60 on inotropic support and she maintained saturation with oxygen support. Bilateral fine basal crepitations were present and [cardiovascular examination](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiovascular-examination) was normal. She was conscious and oriented with no evidence of focal neurological deficit. A provisional diagnosis of [Acute coronary syndrome](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/acute-coronary-syndrome) with [cardiogenic shock](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/cardiogenic-shock) and acute pulmonary edema was kept and she was managed with [low molecular weight heparin](https://www.sciencedirect.com/topics/medicine-and-dentistry/low-molecular-weight-heparin), [antiplatelets](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/antiplatelet), statin, [diuretic](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent), inotropic and oxygen support. 2D-echocardiography revealed normal [left ventricular function](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-left-ventricle-function), mild [pulmonary hypertension](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pulmonary-hypertension) with plethoric and non-collapsing [inferior vena cava](https://www.sciencedirect.com/topics/medicine-and-dentistry/inferior-vena-cava). [Coronary angiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/coronary-angiography) revealed minor [coronary artery disease](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/coronary-artery-disease). Hence, [anticoagulant](https://www.sciencedirect.com/topics/medicine-and-dentistry/antithrombotic), and [antiplatelets](https://www.sciencedirect.com/topics/medicine-and-dentistry/antiplatelet) were stopped. She improved clinically and was gradually weaned off oxygen support and vasopressors.

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Fig. 1. 12 lead Electrocardiogram suggestive of [sinus tachycardia](https://www.sciencedirect.com/topics/medicine-and-dentistry/sinus-tachycardia), incomplete [right bundle branch block](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/heart-right-bundle-branch-block), T inversion V1–V5, I, aVL, poor [R wave](https://www.sciencedirect.com/topics/medicine-and-dentistry/r-wave) progression up to V4, P pulmonale, S up to V6, ST depression in II, III, aVF and QTc prolongation (500 milliseconds by Bazett formula).

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Fig. 2. HRCT Chest: Axial plane suggestive of patchy and confluent areas of ground glass density and consolidation in both the lungs predominantly in central and perihilar region with a possibility of pulmonary edema more likely than COVID-19 (CORAD 3) with CT severity score 23/25.

During further hospitalization, her headache and vomiting were persistent. She became drowsy with Glasgow Coma Score of 12 and bilateral [plantar reflex](https://www.sciencedirect.com/topics/medicine-and-dentistry/plantar-reflex) was extensor. CT Head revealed acute [hematoma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hematoma) in parafalcine basifrontal regions with intraventricular and subarachnoid extension and mild [hydrocephalus](https://www.sciencedirect.com/topics/medicine-and-dentistry/hydrocephalus) (See [Fig. 3](https://www.sciencedirect.com/science/article/pii/S295046782400006X#fig3)). She had a Hunt and Hess score of 3+ and a Fisher score of 4 on imaging. Her [National Institute of Health stroke score](https://www.sciencedirect.com/topics/medicine-and-dentistry/national-institutes-of-health-stroke-scale) was +1. After [Neurology](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurology) and [Neurosurgery](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurosurgery) opinion, she was started on [Mannitol](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mannitol), antiepileptics, [analgesics](https://www.sciencedirect.com/topics/medicine-and-dentistry/anodyne), [Nimodipine](https://www.sciencedirect.com/topics/medicine-and-dentistry/nimodipine), [intravenous fluids](https://www.sciencedirect.com/topics/medicine-and-dentistry/infusion-fluid), and supportive treatment. Coagulation profile and platelet counts were normal suggesting that intracranial [bleed](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/ciclonicate) was less likely due to antithrombotic drugs. Considering these new findings, a diagnosis of Neurogenic pulmonary edema seemed more likely. Contrast [CT Angiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/computed-tomography-angiography) of Brain revealed [SAH](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/subarachnoid-hemorrhage) with anterior communicating artery (ACOM) aneurysm. [Digital subtraction angiography](https://www.sciencedirect.com/topics/medicine-and-dentistry/digital-subtraction-angiography) revealed ruptured ACOM aneurysm. Coiling of the ACOM aneurysm was done with good results (See [Fig. 4](https://www.sciencedirect.com/science/article/pii/S295046782400006X#fig4)). Optimal medical management including [Nimodipine](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/nimodipine), hydration and aggressive physiotherapy were continued. Patient recovered gradually and was discharged after 3 weeks of hospitalization. She is doing well and is on regular follow up since last two years.

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Fig. 3. CT Brain: Axial view shows acute [hematoma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hematoma) in parafalcine basifrontal regions with intraventricular and subarachnoid extension and mild dilatation of the supratentorial ventricular system.

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Fig. 4. **A.** CT Brain Angiogram showing Subarachnoid hemorrhage with right [anterior communicating artery](https://www.sciencedirect.com/topics/medicine-and-dentistry/anterior-communicating-artery) (A1) laterally directed aneurysm (arrow). **B.** Post-coiling Digital subtraction Angiogram of left [internal carotid artery](https://www.sciencedirect.com/topics/medicine-and-dentistry/internal-carotid-artery): Anteroposterior cranial 300 view showing post-coiling status for [anterior communicating artery aneurysm](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/anterior-communicating-artery-aneurysm) with coil in situ (arrow).

3. Discussion

Despite decades of case descriptions, the diagnosis and management of NPE remains challenging. The wide variety of clinical situations in which it occurs can obscure diagnosis. The common causes include SAH, enterovirus-71-associated brain-stem encephalitis, [traumatic brain injury](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/traumatic-brain-injury), epilepsy, intracranial [injury](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/injury), [multiple sclerosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/multiple-sclerosis), [electroconvulsive therapy](https://www.sciencedirect.com/topics/medicine-and-dentistry/electroconvulsive-therapy), intracranial/spinal surgery, intoxication, and [hypoxia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hypoxia).[4](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib4) The sudden development of hypoxemic respiratory failure following a [CNS](https://www.sciencedirect.com/topics/medicine-and-dentistry/central-nervous-system) event, which cannot be attributed to other causes of [ARDS](https://www.sciencedirect.com/topics/medicine-and-dentistry/acute-respiratory-distress-syndrome), is the only universally agreed upon characteristic of NPE. A common denominator is a surge of endogenous serum [catecholamines](https://www.sciencedirect.com/topics/medicine-and-dentistry/catecholamine) that results in changes in [cardiopulmonary hemodynamics](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiopulmonary-hemodynamics) and Starling forces.[1](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib1) The ‘NPE trigger zones’ include the [hypothalamus](https://www.sciencedirect.com/topics/medicine-and-dentistry/hypothalamus) and the medulla, specifically area A1, A5, nuclei of solitary tract and [area postrema](https://www.sciencedirect.com/topics/medicine-and-dentistry/area-postrema).[5](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib5) The most frequent underlying factor for NPE is SAH (42.9%).[6](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib6) SAH involves massive [catecholamine release](https://www.sciencedirect.com/topics/medicine-and-dentistry/catecholamine-release) and is responsible for increased [vascular permeability](https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-vessel-permeability), endothelial damage, and [vasoconstriction](https://www.sciencedirect.com/topics/medicine-and-dentistry/vasoconstriction).[7](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib7) Aneurysmal SAH causes permanent disability and high fatality. The prognosis depends on the degree of delayed [cerebral ischemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/brain-ischemia), volume of the [bleed](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/ciclonicate), and re-bleeding.[2](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib2) Other complications include electrocardiographic changes, [troponin](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/troponin) elevation, [anemia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/anemia), [hyponatremia](https://www.sciencedirect.com/topics/medicine-and-dentistry/hyponatremia), and neurogenic stunned [myocardium](https://www.sciencedirect.com/topics/medicine-and-dentistry/myocardium).[8](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib8)

Amongst the two clinical forms of NPE, the early form is the most common and is characterized by symptoms within minutes to hours following neurologic injury, while the delayed form develops 12–24 hours after the CNS insult.[5](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib5) The patient becomes acutely dyspneic and hypoxic within minutes with pink-frothy [sputum](https://www.sciencedirect.com/topics/medicine-and-dentistry/sputum), and bilateral crackles. Sympathetic hyperactivity is common, and the patient may be febrile, tachycardic, and hypertensive. [Chest radiograph](https://www.sciencedirect.com/topics/medicine-and-dentistry/thorax-radiography) will reveal bilateral infiltrates consistent with ARDS.[5](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib5) Symptoms resolve within 24–48 hours; however, in patients with ongoing brain injury and elevated [intracranial pressure](https://www.sciencedirect.com/topics/medicine-and-dentistry/intracranial-pressure), the NPE often persists.[1](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib1)

NPE is diagnosed by the presence of pink-frothy sputum, bilateral opacities on chest radiograph, PaO2/FiO2<200 mmHg, no evidence of left atrial hypertension, [absence](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/epileptic-absence) of alternative causes of ARDS, presence of severe [CNS injury](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/nervous-system-injury) and rapid resolution within 48–72 hours. [1, 4] Measurement of serum [catecholamines](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/catecholamine) may be helpful.[1](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib1) The management is focused on treating the underlying neurological condition including efforts to reduce intracranial pressure, including decompression and clot [evacuation](https://www.sciencedirect.com/topics/medicine-and-dentistry/evacuation), [osmotic diuretics](https://www.sciencedirect.com/topics/medicine-and-dentistry/osmotic-diuretic), anti-epileptics, tumor resection, and steroids.[6](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib6),[9](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib9) The goal of care should focus on maintaining euvolemic status, treatment with [nimodipine](https://www.sciencedirect.com/topics/medicine-and-dentistry/nimodipine), and continuous hemodynamic and neurological monitoring.[10](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib10) The management also includes cardiac evaluation, fluid management, and alpha-adrenergic blocker like [phentolamine](https://www.sciencedirect.com/topics/medicine-and-dentistry/phentolamine).[1](https://www.sciencedirect.com/science/article/pii/S295046782400006X#bib1)

Aneurysmal SAH can cause massive catecholamine surge leading to [myocardial injury](https://www.sciencedirect.com/topics/medicine-and-dentistry/heart-muscle-injury), cardiac dysfunction, and pulmonary edema. Such complications can occur in absence of predominant neurologic [signs and symptoms](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/physical-disease-by-body-function). NPE should be suspected in all patients presenting with acute pulmonary edema and neurological symptoms as timely diagnosis and management can avoid life-threatening consequences.