4DMedical™

XV LVAS

XV LUNG VENTILATION ANALYSIS SOFTWARE

Instructions for Use

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Quick Links Guide

For assistance capturing the cinefluorographs, see Section 7 *Imaging Protocol,* page 10.

To contact 4DMedical see Section 10.1 *Support*, page 23.

Document Revision V5

1. Preface

These Instructions for Use (IFU) describe the operation of **XV Lung Ventilation Analysis Software** (XV LVAS™; the Device). Prior to use, read this entire document.

2. Conventions and Acronyms

2.1 Document Conventions

CAUTION
For information related to patient safety.

2.2 Description of Device Markings

Prescription

Consult Electronic Instructions for Use

Manufacturer

Date of Manufacture

MD — Medical Device

UDI — Unique Device Identification

2.3 Acronyms

CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
FOV	Field of View
SID	Source-to-Image Receptor Distance
LAO	Left Anterior Oblique
RAO	Right Anterior Oblique
PA	Posterior Anterior

3. Overview

XV Lung Ventilation Analysis Software (XV LVAS™) reports four-dimensional regional ventilation of pulmonary tissues, throughout the entire lung, and at all phases of the breath. The device is not intended to be a primary clinical data source, it is instead intended to complement and support other clinical data.

This manual describes the steps required to **request** a Report and provides information regarding the **input data** required. The explanation of how to read the Report can be found in the XV LVAS Ventilation Report.

3.1 Intended Use & Indications for Use

The **XV LVAS™** provides reproducible quantification of ventilation for pulmonary tissue, which is essential for providing quantitative support for diagnosis and follow up examinations. For use by referral from a pulmonary specialist or equivalent, the Device can be used to provide the physician with additional clinical data in the diagnosis and documentation of inhomogeneities and defects in pulmonary ventilation. Quantification and statistics are provided in the form of a Report, including:

- The tidal volume (i.e. total lung ventilation), presented as a single value;
- Visualisation of lung ventilation with colour-defined specific ventilation ranges overlaid on the CT slices;
- The heterogeneity of lung ventilation, presented as three values, which quantifies the regional variability of the ventilation; and
- Ventilation graph/ histogram of the classified lung voxel's relative frequencies showing the frequency distribution of regional specific ventilation across the entire lung, including ventilation defect percentage which shows the volume of lung with low ventilation.

The **XV LVAS™** is software-based image processing technology that analyses cinefluorograph images and a CT (can be a previously acquired CT that is representative of the patient's present lung envelope), to quantify ventilation of pulmonary tissue for use in adult patients.

The clinical study used to validate the Device was limited to patients selected to undergo Radiation Therapy (most commonly for breast cancer and oesophageal cancer). In this study these patients were examined using the Device at four time-points over a 13-month period (twice prior and twice following radiation therapy).

3.2 Contraindications for Use

For use by referral from a requesting physician, pulmonary specialist or equivalent

4DMedical recommends that the requesting physician takes note of all advice and precautionary statements included in this manual.

4. Requesting a Ventilation Report (Summary)

To request an XV LVAS™ Report:

1. Review imaging protocol;
2. Acquire the set of five cinefluorograph series;
3. Review imaging data for completeness;
4. Send to 4DMedical:
    a. (Five) Cinefluorograph series;
    b. Computed Tomography (CT) scan.
5. Receive Report (once analysis is complete).

5. Safety and Regulatory

Read all safety information prior to prescribing acquisition of input data.

5.1 Safety Concerns

⚠ **CAUTION** Acquisition of the Device inputs (i.e., cinefluorograph and CT imaging) involves exposure to radiation.

The requesting physician must use their judgement to assess the risk to the patient before proceeding with acquisition of images. For more information on the cinefluorograph acquisition protocol please refer to Section 7. The typical dose for acquiring a set of five cinefluorograph series as described herein is 0.21 mSv - 0.51 mSv, which is equivalent to 2 – 5 chest X-rays or natural background radiation for 3 – 7 weeks.

The qualitative risk level of acquiring the cinefluorograph is considered **minimal to very low risk**, see Table 1.

Table 1 (Radiologyinfo.org[1]) Qualitative risk levels

Risk Level	Description
Negligible risk	Less than 2 days of natural background exposure.
Minimal risk	**More than 2 days and up to 1 month of natural background exposure.**
Very low risk	**More than 1 month and up to 8 months of natural background exposure.**
Low risk	More than 8 months and up to 6 years of natural background exposure.
Moderate risk	More than 6 years of natural background exposure.

A thoracic CT is required for the analysis. The thoracic CT scan can be retrospective, e.g. using an existing CT scan. **The same thoracic CT image can be used for multiple Device analysis Reports**.

If the patient has had surgery on the lungs since the last CT scan, the CT scan may not be suitable. See Section 6.1.1 for guidance on using a previously acquired CT.

5.2 Comparison to PFT

The Device outputs have a weak correlation with PFT measures. A strong correlation is not expected as the Device outputs are derived from regional (4D) values compared to the global (1D) PFT measurements.

5.3 Precautions Relating to Input Data

Metrics presented in the Report are dependent on the correct information being supplied in the input data and associated metadata. The radiographer is responsible for the suitability of the input images (see Section 6 for detailed information about acceptable datasets).

The Report is intended to be interpreted by the requesting physician and they must ultimately use their clinical judgement in making decisions that concern patient management. Areas with

[1] American College of Radiology (ACR). How much dose do I get from different procedures? Radiology (ACR). https://www.radiologyinfo.org/en/info.cfm?pg=safety-hiw_07. Accessed September 17, 2019.

artefacts and anomalies within the imaging may give unpredictable results, and therefore, the XV LVAS results should be interpreted with appropriate clinical judgement.

5.4 Precautions Relating to Cybersecurity

XV LVAS™ is delivered using a Software as a Service (SaaS) model, and it is important to note that cybersecurity is a shared responsibility. Cybersecurity is taken seriously by 4DMedical and the cybersecurity statement can be found in Section 9 of this document.

6. Device Input Requirements

XV LVAS™ requires two types of inputs:

- A Cinefluorograph set (i.e., the five cinefluorograph series) to obtain motion information about the lung; and
- A Computed Tomography (CT) scan to obtain morphological information about the lung.

6.1 Computed Tomography Scan

6.1.1 Using a Previously Acquired CT

The Device allows for the use of a previously acquired (retrospective) thoracic CT. A retrospective CT can only be used if the CT is indicative of the patient's current lung anatomy (and meets the image requirements listed in 6.1.2). Using a retrospective CT will reduce the overall radiation dose that is administered to the patient. The same CT can be submitted with multiple uses of the Device.

If the patient has had lung surgery since the last CT scan (e.g. lung volume reduction surgery), the CT scan may not be suitable. A new thoracic CT of the lungs should ***only*** be acquired if there isn't a retrospective CT that is indicative of the patient's current lung shape, or if the existing CT does not meet the image requirements listed in 6.1.2.

6.1.2 Image Requirements

6.1.2.1 CT: Resolution

The thoracic CT must have:

- An x and y pixel spacing of less than 1.3 mm; and
- A slice spacing of a maximum of 2.5mm

6.1.2.2 CT: Metadata

The CT image must contain the following metadata:

- pixel spacing;
- slice spacing.

6.1.2.3 CT: Age of data

The thoracic CT scan can be:

- A recent thoracic CT from the patient's records

6.1.2.4 CT: Filetype

The CT image must be in DICOM (Digital Imaging and Communications in Medicine) format. DICOM files must remain uncompressed to preserve data integrity. However, compression with a lossless compression algorithm is acceptable.

6.2 X-Ray Cinefluorographs

It is recommended that prior to imaging of patients, 4DMedical personnel, or other qualified professional reviews the cinefluorograph imaging requirements and confirms that the cinefluoroscopic system meets the following requirements.

6.2.1 Hardware Requirements

The cinefluoroscopic hardware must support the following features:

- Pulsed cinefluoroscopic acquisition mode;
- Ability to capture frame rate of 15fps or greater;
- Adjustable Source-to-Image Receptor Distance (SID) to control magnification;
- Suitable for use on stationary fluoroscopes;
- Source-detector axis rotates around a fixed isocentre, with digital read out of angular position;
- Source-detector axis rotates of at least +/- 60degrees from PA (RAO & LAO);
- Automatic Brightness Control capability; and
- A detector panel size of nominally 40 cm x 30 cm (W x H).

6.2.2 Image Requirements

6.2.2.1 Cinefluorograph: Resolution

The fluoroscopy hardware must support the following:

- Acquire images with a resolution of approximately 1024 x 768 px (W x H);
- Have a maximum pixel size of 0.040 cm x 0.040 cm; and
- Acquire images at an image capture rate of at least 15 frames per second.

6.2.2.2 Cinefluorograph: Metadata

The cinefluorographs must contain the following metadata:

- Detector pixel size – DICOM tag (0018,1164);
- Source-to-Image Receptor distance (SID) – DICOM tag (0018,1110);
- Gantry angle attribute position (i.e. source-to-image receptor axis angular (oblique) position around the isocentre) – DICOM tag (0018,1510); and
- Collimator shutter position – DICOM tag (0018,1622).

6.2.2.3 Cinefluorograph: Filetype

The cinefluorographs must be in DICOM (Digital Imaging and Communications in Medicine) format, in **RTIMAGE or XA DICOM type**. DICOM files must remain uncompressed to preserve data integrity. However, compression with a lossless compression algorithm is acceptable.

7. Imaging Protocol

The thoracic CT is acquired using a standard imaging protocol, and therefore no further instructions are provided. The cinefluorographs are acquired on standard equipment using a 4DMedical imaging protocol, the protocol selected is dependent on the equipment which will be utilised to acquire the images. Equipment capable of imaging +/-72˚ refer to Radial (72 ,36, PA) detailed in Section 7.1, the alternative protocol is Radial (60, 36, PA), detailed in Section 7.2.

7.1 Radial (72,36, PA)

XV LVAS™

Lung Imaging Protocol

Radial (72,36,PA) AU

XV Lung Ventilation Analysis Software measures the tissue motion of the lungs, at all locations throughout the lungs, and at all phases of the breath.

It uses these motion measurements to calculate the 4-dimensional ventilation of pulmonary tissues.

The cinefluorograph images are acquired on standard equipment using a 4DMedical imaging protocol. To support the acquisition of these inputs the following imaging protocol is to be utilised.

The thoracic CT is acquired using a standard imaging protocol, and therefore no further instructions are provided.

Important: Pre-Imaging Checklist

- Confirm there is a thoracic CT on file for the patient before acquiring the cineflourograph series.
- Please turn off/ remove screen overlay and burn annotation prior to capturing images (Please consult PACS administrator if you are unsure.)
- In all instances follow your institution's standard practice, such as verifying the patient information or radiation shielding of patients

Confirm the fluoroscope has the capability to:

- Set acquisition frame rate to 15 FPS or greater
- Save image stream to RTIMAGE or XA DICOM, uncompressed format
- Image complete lung (prioritise the area of interest if the entire lung does not fit within the FOV)
- Set desired viewing angle, preferred angles are (72° LAO, 36° LAO, PA, 36° RAO, 72° RAO)
- Use Automatic Brightness Control (either pre-configured to 'ON' or manually set)

Quick Reference

1. Position Patient
2. Select Required Cinefluorograph Settings
3. Set Isocentre
4. Confirm Consistent Patient Breathing
5. Acquire Images at Each Angle
6. Complete Image Analysis
7. Review Data Check List

XV LVAS™ Lung Imaging Protocol - Radial (72,36,PA)

1 Position Patient

- Supine position, remain still
- Position at head of the table
- Ensure patient is not rotated or tilted
- Remove pillow and elevate chin as this provides better visualisation of apices
- Ensure arms are out of the Field of View (FOV) (e.g. comfortably above or behind the head, or otherwise supported)

Figure 1

2 Select Required Cinefluorograph Settings

- Move C-arm into head position
- Select (cine)fluoroscopic mode
- Ensure Automatic Brightness Control (ABC) is active
- Select 15 Frames Per Second (FPS)
- Place detector in Landscape mode
- Do not use digital zoom/magnification
- Maximise the Field of View (FOV)

Figure 2

Figure 3

Tip: If you collimate the image, it may reduce the FOV which is utilized for the analysis

3 Set Isocentre

- Bring detector close to the patient's chest, without impeding breathing. Take a snapshot
- Adjust table or detector position to centre the patient's lungs. Take a snapshot. Confirm lungs are centred to ensure the entire lung fields are in the FOV. This FOV will be a direct correlation to the output of the ventilation report
- Lock table to ensure no movement.
- Rotate C-Arm to Lateral Position. Take a snapshot. Confirm lungs are centred. If necessary, raise or lower table to centre the lungs
- Isocentre is to remain unchanged

Figure 4

XV LVAS™ Lung Imaging Protocol - Radial (72,36,PA)

4 Confirm Consistent Patient Breathing

- Prior to scan, remind patient that unlike other chest studies, this exam does not require breath hold
- Observe patient's breathing pattern for a few breaths. Ensure breathing pattern appears consistent and tidal
- Breathing shall be free from hiccups, sneezes, sniffing, coughing and hyper-ventilation, in each sequence
- Do not coach the patient on breathing techniques

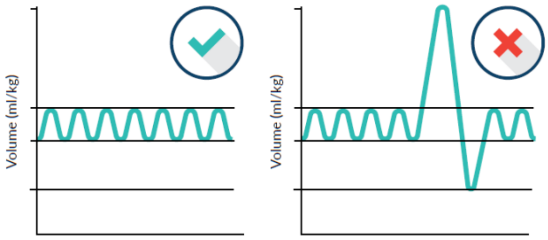

Figure 5

5 Acquire Images at Each Angle

- All five sequences must be taken while maintaining isocentre
- Acquire images at the required angles:
  - 72° LAO
  - 36° LAO
  - PA
  - 36° RAO
  - 72° RAO
- Begin image capture mid-expiration, capture a complete continuous breath during stable tidal breathing
- Stop image capture at the beginning of inspiration
- Ensure that each cinefluorograph series is saved prior to moving to the next position

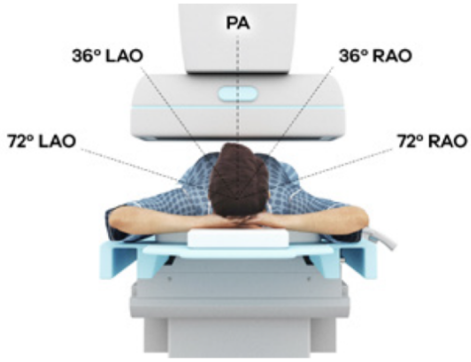

Figure 6

6 Complete Image Analysis

- Verify that all five cinefluorograph series are saved (RTIMAGE or XA DICOM)
- Review capture of a full tidal breath at each angle
- Send the cinefluorograph series from each designated angle to equal a total of 5 series

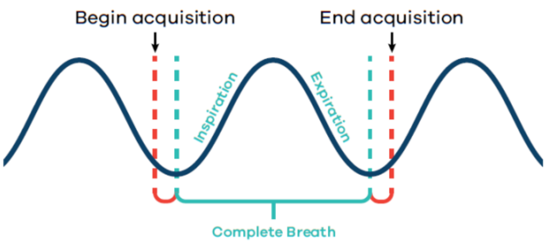

Figure 7

XV LVAS™ Lung Imaging Protocol - Radial (72,36,PA)

7 Review Data Check List

Review each Cinefluorograph sequence using

INHALE-5;

- **I** Isocentre is maintained
- **N** No breathing anomalies occurred
- **H** Habitual tidal breathing imaged
- **A** Arms are out of FOV
- **L** Laying still for imaging duration
- **E** Entire breath captured
- **5** 5 unique angles were acquired

7.2 Radial (60,36, PA)

XV LVAS™

Lung Imaging Protocol

Radial (60,36,PA) AU

XV Lung Ventilation Analysis Software measures the tissue motion of the lungs, at all locations throughout the lungs, and at all phases of the breath.

It uses these motion measurements to calculate the 4-dimensional ventilation of pulmonary tissues.

The cinefluorograph images are acquired on standard equipment using a 4DMedical imaging protocol. To support the acquisition of these inputs the following imaging protocol is to be utilised.

The thoracic CT is acquired using a standard imaging protocol, and therefore no further instructions are provided.

Important: Pre-Imaging Checklist

- Confirm there is a thoracic CT on file for the patient before acquiring the cineflourograph series.
- Please turn off/ remove screen overlay and burn annotation prior to capturing images (Please consult PACS administrator if you are unsure.)
- In all instances follow your institution's standard practice, such as verifying the patient information or radiation shielding of patients

Confirm the fluoroscope has the capability to:

- Set acquisition frame rate to 15 FPS or greater
- Save image stream to RTIMAGE or XA DICOM, uncompressed format
- Image complete lung (prioritise the area of interest if the entire lung does not fit within the FOV)
- Set desired viewing angle, preferred angles are (60° LAO, 36° LAO, PA, 36° RAO, 60° RAO)
- Use Automatic Brightness Control (either pre-configured to 'ON' or manually set)

Quick Reference

1. Position Patient
2. Select Required Cinefluorograph Settings
3. Set Isocentre
4. Confirm Consistent Patient Breathing
5. Acquire Images at Each Angle
6. Complete Image Analysis
7. Review Data Check List

XV LVAS™ Lung Imaging Protocol - Radial (60,36,PA)

1 Position Patient

- Supine position, remain still
- Position at head of the table
- Ensure patient is not rotated or tilted
- Remove pillow and elevate chin as this provides better visualisation of apices
- Ensure arms are out of the Field of View (FOV) (e.g. comfortably above or behind the head, or otherwise supported)

Figure A1

2 Select Required Cinefluorograph Settings

- Move C-arm into head position
- Select (cine)fluoroscopic mode
- Ensure Automatic Brightness Control (ABC) is active
- Select 15 Frames Per Second (FPS)
- Place detector in Landscape mode
- Do not use digital zoom/magnification
- Maximise the Field of View (FOV)

Figure A2

Figure A3

Tip: If you collimate the image, it may reduce the FOV which is utilized for the analysis

3 Set Isocentre

- Bring detector close to the patient's chest, without impeding breathing. Take a snapshot
- Adjust table or detector position to centre the patient's lungs. Take a snapshot. Confirm lungs are centred to ensure the entire lung fields are in the FOV. This FOV will be a direct correlation to the output of the ventilation report
- Lock table to ensure no movement.
- Rotate C-Arm to Lateral Position. Take a snapshot. Confirm lungs are centred. If necessary, raise or lower table to centre the lungs
- Isocentre is to remain unchanged

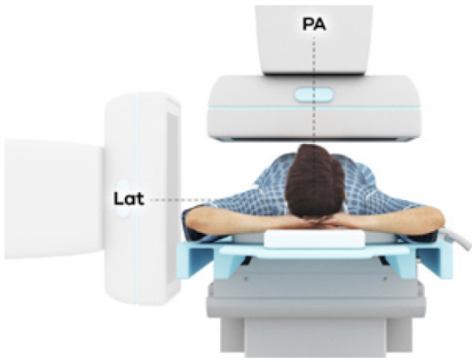

Figure A4

XV LVAS™ Lung Imaging Protocol - Radial (60,36,PA)

4 Confirm Consistent Patient Breathing

- Prior to scan, remind patient that unlike other chest studies, this exam does not require breath hold
- Observe patient's breathing pattern for a few breaths. Ensure breathing pattern appears consistent and tidal
- Breathing shall be free from hiccups, sneezes, sniffing, coughing and hyper-ventilation, in each sequence
- Do not coach the patient on breathing techniques

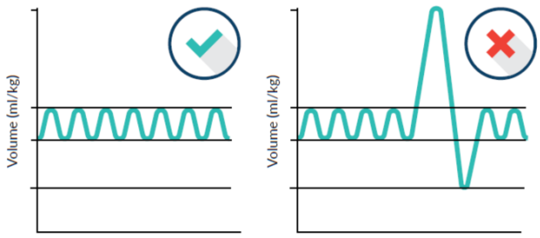

Figure A5

5 Acquire Images at Each Angle

- All five sequences must be taken while maintaining isocentre
- Acquire images at the required angles:
  - 60° LAO
  - 36° LAO
  - PA
  - 36° RAO
  - 60° RAO
- Begin image capture mid-expiration, capture a complete continuous breath during stable tidal breathing
- Stop image capture at the beginning of inspiration
- Ensure that each cinefluorograph series is saved prior to moving to the next position

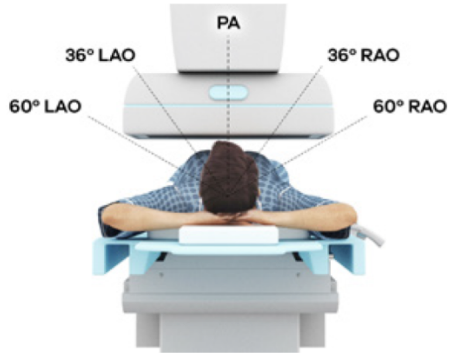

Figure A6

6 Complete Image Analysis

- Verify that all five cinefluorograph series are saved (RTIMAGE or XA DICOM)
- Review capture of a full tidal breath at each angle
- Send the cinefluorograph series from each designated angle to equal a total of 5 series

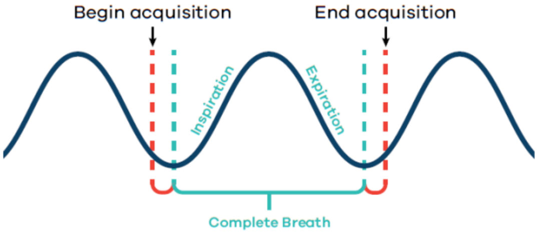

Figure A7

XV LVAS™ Lung Imaging Protocol - Radial (60,36,PA)

7 Review Data Check List

Review each Cinefluorograph sequence using

INHALE-5;

- **I** Isocentre is maintained
- **N** No breathing anomalies occurred
- **H** Habitual tidal breathing imaged
- **A** Arms are out of FOV
- **L** Laying still for imaging duration
- **E** Entire breath captured
- **5** 5 unique angles were acquired

8. Image Transfer and Report Delivery

4DMedical XV LVAS™ utilises DICOM routing systems that are managed by your institution to transfer the set of cinefluorograph series and CT scan to 4DMedical's SaaS platform.

The set of five cinefluorograph series acquired should be sent to your institution's DICOM routing system (e.g. Kailo Hub by Kailo Medical), for example via the modality or PACS system. The precise details will vary for each site's workflow and PACS/modality vendor. By default, on receipt of the DICOMs, the DICOM routing system is configured to automatically send the set of cinefluorograph series and the CT scan to 4DMedical.

If your institution's configuration allows for files to be manually selected and sent to 4DMedical, contact support for the manual instructions specific to your DICOM routing system.

8.1 Report Delivery Timeline

The expected delivery time of a Report will be as per the institution service agreement.

8.2 Viewing the Report

The Ventilation Report can be viewed in a PDF reader, such as Adobe Reader. In the Report select the green box (shown in Figure 8) on the top right to view the HTML version of the Report on the XV Technology™ **Report Viewer.** Information on how to read the report can be found in the XV LVAS Ventilation Report.

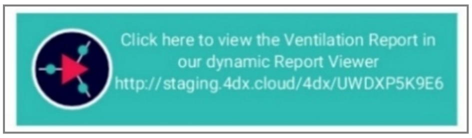

Figure 8 Link to HTML Report Viewer

8.3 Sample Report

The physician will receive a multipage report, with an executive summary showing key metrics followed by the detailed results and how to read instructions.

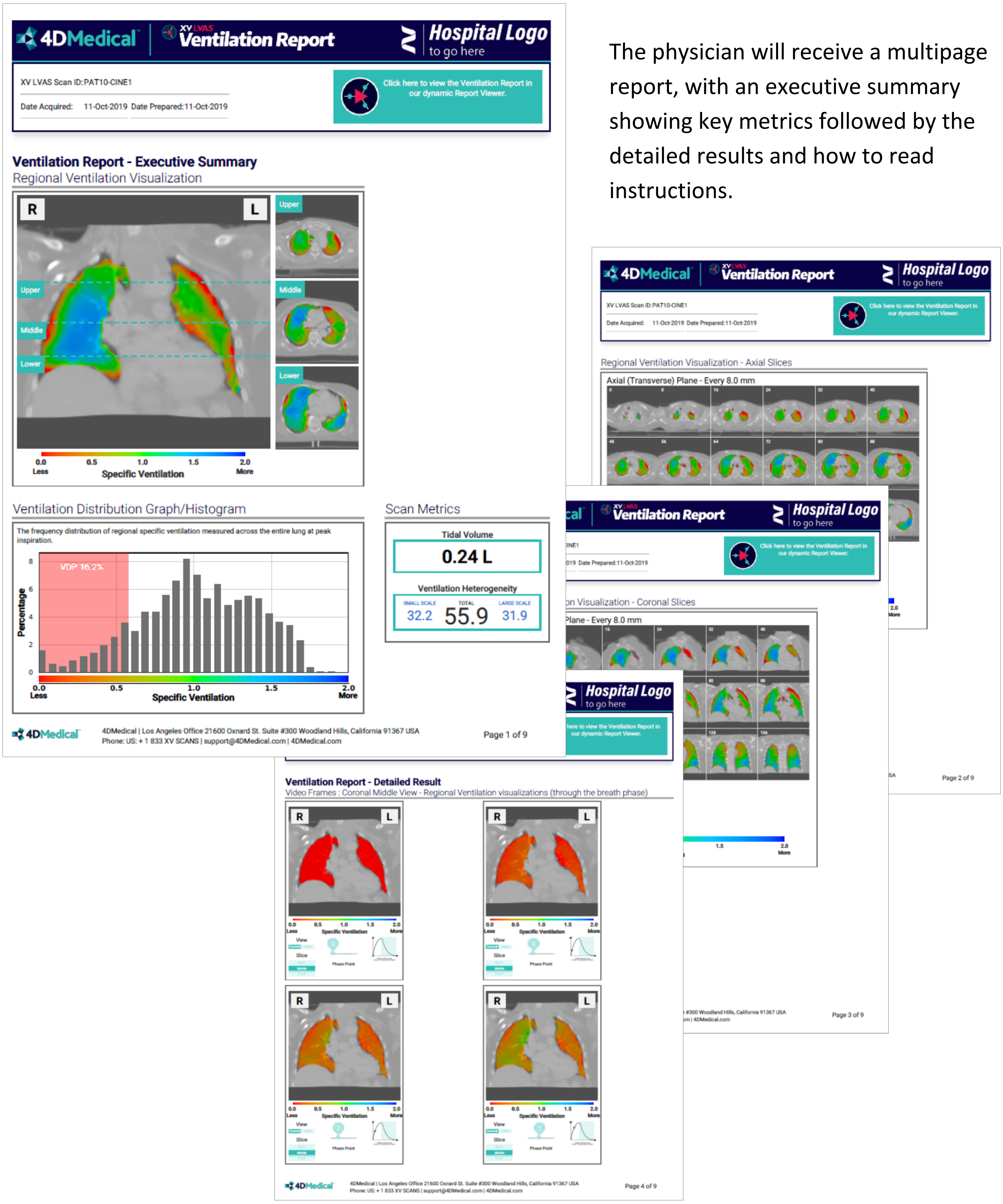

Figure 9 Sample Report

9. Cybersecurity Statement

XV LVAS™ is delivered using a Software as a Service (SaaS) model, with only two in-hospital components that need to be managed by your local IT support. It is important to note that in this deployment model cybersecurity is a shared responsibility.

9.1 Guidance for Secure Configuration and Use

Your integration partner will configure the in-hospital components, the DICOM routing system (e.g. Kailo Medical's (Victoria, 3124) product Kailo Hub) to integrate with the institution's systems. The following security precautions and configuration principles should be applied, in addition to standard best practices for Windows-based Servers:

- Your integration partner will enable Transport Layer Security (TLS) for communication between the DICOM routing system installation and the relevant 4DMedical SaaS environment. This protects the integrity and security of patient data and must not be disabled.
- Your integration partner will configure the DICOM routing system to de-identify all patient data transmitted to the 4DMedical SaaS environment. This should not be disabled. Local institution policies and guidance regarding the scope and extent of de-identification (outside of the attributes listed in DICOM Confidentiality profile) should be reviewed and compared with the DICOM routing system configuration.
- Local IT should ensure a firewall is present between the DICOM routing system installations and the public internet. The firewall should only allow incoming DICOM TLS connections and outgoing DICOM TLS connections to/from the 4DMedical SaaS environment and the local DICOM routing system installation.
- Local IT should configure user authentication to restrict access to the DICOM routing system to only those staff members authorized to request and view scans. Shared accounts should not be used.
- Local IT should restrict administrative access to the DICOM routing system web interface, if available, and Windows login access to the machines hosting your DICOM routing system. 4DMedical recommends that access is logged and regularly reviewed to ensure anomalies can be identified.
- Local IT should establish a regular patching and maintenance schedule for your DICOM routing system.

9.2 Mandatory Breach and Coordinated Disclosure

4DMedical takes the security and privacy of customer and patient information seriously, and continuously monitors and works to improve our surveillance of potential information breaches. In the case of an identified breach, 4DMedical will:

- Notify your nominated Privacy Officer when first becoming aware of the breach.
- Take immediate steps to contain the breach, up to and including disabling services or functionality until 4DMedical is satisfied that service can be resumed without further compromise. Continue to inform you via your Privacy Officer as the situation develops.
- Inform your Privacy Officer, if after subsequent investigation, the scope or extent of the breach is more severe than originally determined.
- Contact law enforcement, as appropriate.

4DMedical operate a Coordinated Disclosure Program, whereby we can be securely notified of potential vulnerabilities or potential unauthorized information disclosure. For more information, please see contact: infosec@4dmedical.com

10. Support, Labelling and Notice

10.1 Support

For all information, troubleshooting, feedback, suggestions, comments, and issues with the Device, please contact 4DMedical, between 8am to 4pm Monday to Friday Australian Eastern Standard Time (AEST) or UTC+11:00:

Australia & New Zealand

Phone: +61 1800-XV-SCAN (+61 1 800 987 226)

Address: Level 7, 700 Swanston Street
Carlton, Victoria
3053
Australia

Email: support@4DMedical.com | 4DMedical.com/ventilation-support

10.2 Labelling

Labelling is applied to the Report (example shown in Figure 10).

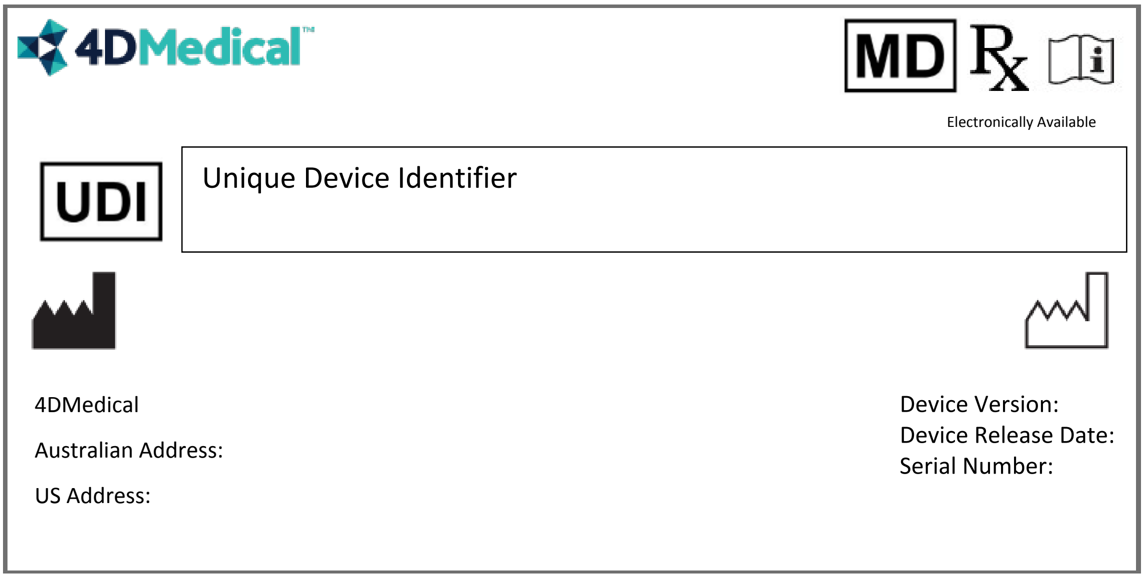

Figure 10: Device Label

10.3 Notice

The Device provides information to support physicians with their assessment of patients with lung diseases. The Device does not, in itself, provide a diagnosis of lung health. 4DMedical assumes no responsibility for the improper use of, or self-diagnosis using, the Device.

11. Glossary

Phase point	Refers to the phase of breath to which a particular frame corresponds.
Specific ventilation	Defined as the ratio of the change in volume of a region of the lung (ΔV) following an inspiration, divided by the end-expiratory volume (V_0) of that same lung region. Presented values are normalized by mean specific ventilation.
Tidal volume	The Tidal Volume provides the volume of air inhaled from start inspiration to peak inspiration (i.e. the change in volume of the lung over the breath), expressed in litres (L) of air. The tidal volume is calculated from the regional ventilation to peak inspiration. Abnormal tidal volume is an important biomarker of lung disease.
Ventilation defect percentage	The percentage of ventilation volume below 60% of the mean specific ventilation. High VDP has been associated with larger defect regions and abnormal lung function[1–10].
Ventilation Heterogeneity	The regional variability of the ventilation. This is the ratio of the interquartile range to the mean of the specific ventilation. Low Ventilation Heterogeneity values are associated with uniform ventilation throughout the lung, while high Ventilation Heterogeneity values represent significant variability in the lung. High ventilation heterogeneity values (large scale, small scale, and total) have been associated with abnormal lung function[11–24].
Ventilation heterogeneity: large scale	The degree of heterogeneity within larger regions of the lung (e.g. lobar and larger), calculated after first filtering out small scale variations (i.e. scales smaller than 64 mm / 2.5”).
Ventilation heterogeneity: small scale	The degree of heterogeneity within local regions of the lung (e.g. alveolar to lobar size), calculated after first filtering out large scale variations (i.e. scales larger than 64 mm / 2.5”).
Ventilation heterogeneity: total	The overall value of heterogeneity, calculated using all regional specific ventilation data (as displayed in the Ventilation Report Regional Ventilation Visualizations)

12. References

1. Young HM, Guo F, Eddy RL, Maksym G, Parraga G. Oscillometry and pulmonary MRI measurements of ventilation heterogeneity in obstructive lung disease: relationship to quality of life and disease control. *Journal of Applied Physiology*. 2018;125(1):73-85. doi:10.1152/japplphysiol.01031.2017

2. Svenningsen S, Eddy RL, Lim HF, Cox PG, Nair P, Parraga G. Sputum Eosinophilia and Magnetic Resonance Imaging Ventilation Heterogeneity in Severe Asthma. *Am J Respir Crit Care Med*. 2018;197(7):876-884. doi:10.1164/rccm.201709-1948OC

3. He M, Driehuys B, Que LG, Huang Y-CT. Using Hyperpolarized 129Xe MRI to Quantify the Pulmonary Ventilation Distribution. *Academic Radiology*. 2016;23(12):1521-1531. doi:10.1016/j.acra.2016.07.014

4. Thomen RP, Walkup LL, Roach DJ, Cleveland ZI, Clancy JP, Woods JC. Hyperpolarized 129Xe for investigation of mild cystic fibrosis lung disease in pediatric patients. *Journal of Cystic Fibrosis*. July 2016. doi:10.1016/j.jcf.2016.07.008

5. Leary D, Svenningsen S, Guo F, Bhatawadekar S, Parraga G, Maksym GN. Hyperpolarized 3He magnetic resonance imaging ventilation defects in asthma: relationship to airway mechanics. *Physiological Reports*. 2016;4(7):e12761. doi:10.14814/phy2.12761

6. Hahn AD, Cadman RV, Sorkness RL, Jarjour NN, Nagle SK, Fain SB. Redistribution of inhaled hyperpolarized 3He gas during breath-hold differs by asthma severity. *Journal of Applied Physiology*. 2016;120(5):526–536. doi:10.1152/japplphysiol.00197.2015

7. Sheikh K, Paulin GA, Svenningsen S, et al. Pulmonary ventilation defects in older never-smokers. *Journal of Applied Physiology*. 2014;117(3):297–306. doi:10.1152/japplphysiol.00046.2014

8. Mummy DG, Kruger SJ, Zha W, et al. Ventilation defect percent in helium-3 magnetic resonance imaging as a biomarker of severe outcomes in asthma. *Journal of Allergy and Clinical Immunology*. 2018;141(3):1140–1141.e4. doi:10.1016/j.jaci.2017.10.016

9. Farrow CE, Salome CM, Harris BE, Bailey DL, Berend N, King GG. Peripheral ventilation heterogeneity determines the extent of bronchoconstriction in asthma. *Journal of Applied Physiology*. 2017;123(5):1188–1194. doi:10.1152/japplphysiol.00640.2016

10. Lee E, Seo JB, Lee HJ, et al. Quantitative Assessment of Global and Regional Air Trappings Using Non-Rigid Registration and Regional Specific Volume Change of Inspiratory/Expiratory CT Scans: Studies on Healthy Volunteers and Asthmatics. *Korean J Radiol*. 2015;16(3):632. doi:10.3348/kjr.2015.16.3.632

11. Downie SR, Salome CM, Verbanck S, Thompson B, Berend N, King GG. Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation. *Thorax*. 2007;62(8):684–689. doi:10.1136/thx.2006.069682

12. Vidal Melo MF, Winkler T, Harris RS, Musch G, Greene RE, Venegas JG. Spatial Heterogeneity of Lung Perfusion Assessed with 13N PET as a Vascular Biomarker in Chronic Obstructive

Pulmonary Disease. *Journal of Nuclear Medicine*. 2010;51(1):57–65. doi:10.2967/jnumed.109.065185

13. Salito C, Barazzetti L, Woods JC, Aliverti A. Heterogeneity of Specific Gas Volume Changes. *Chest*. 2014;146(6):1554–1565. doi:10.1378/chest.13-2855
14. Lui JK, Lutchen KR. The role of heterogeneity in asthma: a structure-to-function perspective. *Clinical and Translational Medicine*. 2017;6(1). doi:10.1186/s40169-017-0159-0
15. Lui JK, Parameswaran H, Albert MS, Lutchen KR. Linking Ventilation Heterogeneity Quantified via Hyperpolarized 3He MRI to Dynamic Lung Mechanics and Airway Hyperresponsiveness. Sznitman J, ed. *PLOS ONE*. 2015;10(11):e0142738. doi:10.1371/journal.pone.0142738
16. Cotes JE, Chinn DJ, Miller MR. Inter-Relations between Lung Ventilation and Perfusion (VA/Q). In: *Lung Function*. Blackwell Publishing Ltd.; 2006:209–223. http://onlinelibrary.wiley.com/doi/10.1002/9781444312829.ch18/summary.
17. Venegas JG, Winkler T, Musch G, et al. Self-organized patchiness in asthma as a prelude to catastrophic shifts. *Nature*. 2005;434(7034):777-782. doi:10.1038/nature03490
18. Jacob RE, Carson JP. Automated measurement of heterogeneity in CT images of healthy and diseased rat lungs using variogram analysis of an octree decomposition. *BMC medical imaging*. 2014;14(1):1.
19. Teague WG, Tustison NJ, Altes TA. Ventilation heterogeneity in asthma. *Journal of Asthma*. 2014;51(7):677–684. doi:10.3109/02770903.2014.914535
20. Brennan D, Schubert L, Diot Q, et al. Clinical Validation of 4-Dimensional Computed Tomography Ventilation With Pulmonary Function Test Data. *International Journal of Radiation Oncology*Biology*Physics*. 2015;92(2):423-429. doi:10.1016/j.ijrobp.2015.01.019
21. Musch G, Layfield JDH, Harris RS, et al. Topographical distribution of pulmonary perfusion and ventilation, assessed by PET in supine and prone humans. *Journal of Applied Physiology*. 2002;93(5):1841–1851. doi:10.1152/japplphysiol.00223.2002
22. Kaireit TF, Sorrentino SA, Renne J, et al. Functional lung MRI for regional monitoring of patients with cystic fibrosis. Latzin P, ed. *PLoS ONE*. 2017;12(12):e0187483. doi:10.1371/journal.pone.0187483
23. Bhatt SP, Bodduluri S, Newell JD, et al. CT-derived Biomechanical Metrics Improve Agreement Between Spirometry and Emphysema. *Academic Radiology*. 2016;23(10):1255-1263. doi:10.1016/j.acra.2016.02.002
24. Wellman TJ, Winkler T, Costa ELV, et al. Effect of regional lung inflation on ventilation heterogeneity at different length scales during mechanical ventilation of normal sheep lungs. *Journal of Applied Physiology*. 2012;113(6):947-957. doi:10.1152/japplphysiol.01631.2011