CT LVAS
Instructions for Use
AUS & NZ

Contents

1. Preface

This Instructions for Use (IFU) describes the operation of CT LVAS, and resulting CT LVAS Report. 4DMedical recommends that the requesting clinician takes note of all advice and precautionary statements included in this manual. Prior to use, please read this entire document.

2. Symbols

The meaning of the symbols shown on the labelling and/or the instructions for use are as follows:

CAUTION
For information related to patient safety.

Prescription

Consult Electronic Instructions for Use

Manufacturer

Date of Manufacture (YYYY-MM-DD)

Medical Device

Unique Device Identifier

3. Acronyms

CT	Computed Tomography
CT LVAS	Computed Tomography Lung Ventilation Analysis Software
DICOM	Digital Imaging and Communications in Medicine
FOV	Field of View
SaaS	Software as a Service

4. Product Overview

CT LVAS is a software-based image processing technology that analyses two non-contrast CT images, reporting three-dimensional ventilation information of pulmonary tissue, at regional locations of the lungs between two points of the breath. Quantification and statistics are provided in the form of a CT LVAS Report, including:

- The volume of ventilation, presented as three values;
- 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 histogram of lung voxels' relative frequencies showing the frequency distribution of regional specific ventilation measured across the entire lung, including ventilation defect percentage which shows the volume of lung with low ventilation.

4.1 Intended Use

CT LVAS provides reproducible quantification of ventilation for pulmonary tissue, which is essential for providing quantitative support for diagnosis and follow up examinations. CT LVAS can be used to support the clinician in the diagnosis and documentation of inhomogeneities and defects in pulmonary ventilation. Quantification and statistics are provided in the form of a CT LVAS Report.

4.2 Indications for Use

The intended users for CT LVAS are radiologists, pulmonary specialists or equivalent. CT LVAS can be used to provide the clinician with supporting additional clinical data regarding pulmonary ventilation for use in adult patients.

4.3 Contraindications for Use

This software is designed to run on any input data that satisfies the criteria in Section 6. It is the responsibility of the medical professional who is using the software (i.e., the Radiologist, Pulmonary specialist or Radiology Technologist) to ensure that the input data is of adequate quality. If the input data is not of adequate quality, the output CT LVAS Report results will reflect the input data quality.

5. Safety and Regulatory

The CT LVAS 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 (See Section 6 for detailed information about acceptable datasets). Areas with artefacts and anomalies within the imaging may give unpredictable results, and therefore, the CT LVAS results should be interpreted with appropriate clinical judgement.

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

5.1 Precautions

⚠ **CAUTION** Acquisition of CT LVAS inputs involves exposure to radiation. A paired inspiration-expiration chest CT is required for the analysis. 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 image acquisition protocol please refer to Section 7.

⚠ **CAUTION** Values presented in the CT LVAS Report are dependent on the correct information being supplied in the input data and associated metadata. The requesting physician is responsible for the suitability of the input images.

⚠ **CAUTION** The CT LVAS Report output is dependent on the quality of input images. Images containing movement artefacts or the presence of foreign objects (e.g., metallic components) may impact the quality of the Report outputs.

6. Device Input Requirements

CT LVAS requires a pair of inspiratory and expiratory chest CT images, captured in a single study.

6.1 Image Requirements

6.1.1 CT: Resolution

To produce a CT LVAS Report, the inspiration and expiration CT images must meet the following requirements:

Name	Required Value
Pixel Spacing	≤2.5mm
Slice Spacing (Interval/Increment)	≤2.5mm
Slice Thickness	≤2.5mm

6.1.2 CT: Filetype

The CT images must be in DICOM (Digital Imaging and Communications in Medicine) format. An uncompressed DICOM format is preferred, however, a lossless compression algorithm is acceptable.

If the input images do not meet the above criteria, the images will be rejected and no analysis will be undertaken.

7. Imaging Protocol

For the chest CT scans, the radiological technologist shall acquire a paired inspiration-expiration chest CT of the patient. A standard non-contrast CT Chest protocol is recommended, with CT scans acquired at deep inspiration and at deep expiration.

Section 7.1 and 7.2 detail instructions to generate suitable chest CT scans.

7.1 Patient Setup and Configuration

- The paired inspiration-expiration CT shall be captured in a single study.
- Scan patient in a supine position aligning longitudinal axis of the body with longitudinal axis of the CT scanning bed.
- Use imaging and reconstruction parameters consistent with a standard non-contrast CT Chest protocol.
- Ensure patient's arms are out of the Field of View (FOV), for example, by placing them above the head.

7.2 Imaging Requirements

7.2.1 Inspiration CT

- Ensure image resolution settings meet the requirements outlined in Section 6.1.1
- Position patient in **supine position**
- Capture a breath hold CT image at **deep inspiration**
- Ensure coverage is cranial-caudal lung apices through to lung bases
- FOV shall include the entire lungs (e.g., 1cm beyond the edge of the patient)

7.2.2 Expiration CT

- Use the **same resolution settings** as the inspiration CT
- Keep the patient in **supine position**
- Capture a breath hold CT image at **deep expiration**
- Ensure coverage is cranial-caudal from lung apices through to lung bases
- FOV shall include the entire lungs (e.g., 1cm beyond the edge of the patient)

7.3 Image Transfer and CT LVAS Report Delivery

4DMedical utilises a DICOM routing system to transfer the CT scan to 4DMedical's SaaS platform for processing, that is managed by your institution. If your institution requires assistance establishing a connection to 4DMedical's SaaS platform, please contact your local 4DMedical representative.

8. Cybersecurity Statement

CT LVAS is delivered using a Software as a Service (SaaS) model, with one main component, commonly referred to as a DICOM Router, which needs to be managed by your local IT support. It is important to note that in this deployment model cybersecurity is a shared responsibility.

8.1 Guidance for Secure Configuration and Use

Your integration partner will configure the DICOM Router within the site network to integrate with your 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 Router 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 Router to de-identify all patient data transmitted to the 4DMedical SaaS environment. This should not be disabled. Local hospital and clinic 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 Router configuration.
- Local IT should ensure a firewall is present between the DICOM Router installation 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 local DICOM Router installation.
- Local IT should configure user authentication to restrict access to the DICOM Router user interface 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 Router and login access to the machines hosting it. 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 Router.

8.2 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 take action including (but not limited to):

- Notifying your nominated Privacy Officer (or other appropriate contact) 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.

9. Support and Notice

9.1 Support

To contact 4DMedical please use the details below. Support will be available during 4DMedical's standard business hours.

Contact 4DMedical

4DMedical
Level 7/700 Swanston Street
Carlton, VIC, 3053 Australia

Phone: +61 1800-XV-SCAN (+61 1 800 987 226)
Email: support@4DMedical.com | 4DMedical.com/ventilation-support

9.2 Notice

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

10. Glossary

See below for more information regarding terms found in the CT LVAS Report. For a more detailed explanation of these terms, refer to the how-to-read section of the CT LVAS Report.

Expiration Volume	The total volume (L) of lung tissue at deep expiration.
Inspiration Volume	The total volume (L) of lung tissue at deep inspiration.
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 normalised by mean specific ventilation.
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)
Change in Volume	The difference in the volume (L) between deep inspiration and deep expiration.

11. 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. *J Appl Physiol*. 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 YCT. Using Hyperpolarized 129Xe MRI to Quantify the Pulmonary Ventilation Distribution. *Acad Radiol*. 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. *J Cyst Fibros*. Published online 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. *Physiol Rep*. 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. *J Appl Physiol*. 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. *J Appl Physiol*. 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. *J Allergy Clin Immunol*. 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. *J Appl Physiol*. 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. *J Nucl Med*. 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. *Clin Transl Med*. 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 Med Imaging*. 2014;14(1):1.

19. Teague WG, Tustison NJ, Altes TA. Ventilation heterogeneity in asthma. *J 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. *Int J Radiat Oncol*. 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. *J Appl Physiol*. 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. *Acad Radiol*. 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. *J Appl Physiol*. 2012;113(6):947-957. doi:10.1152/japplphysiol.01631.2011