CT LVAS
Instructions for Use
AUS & NZ

Contents

1. Preface

These Instructions for Use (IFU) describe the operation of CT LVAS Software, and the CT LVAS Ventilation Report. 4DMedical recommends that the requesting physician 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 detailed ventilation information of pulmonary tissue between inspiratory and expiratory volumes, at regional locations of the lungs. Quantification and statistics are provided in the form of a CT LVAS Ventilation 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.

These regional measures are derived entirely from the lung tissue displacement and the lung volume change between the paired inspiration-expiration chest CT.

4.1 Intended Use and Indications for Use

CT LVAS software is a non-invasive image processing technology that measures volume changes from paired inspiration-expiration CTs to quantify and visualise regional and global ventilation. These regional measures are derived entirely from the lung tissue displacement and lung volume change between the paired inspiration-expiration chest CTs.

CT LVAS is for use in adult patients. Quantification and visualisations are provided in the form of a report.

CT LVAS may be used when physicians need a better understanding of a patient's lung function and/or respiratory condition.

CT LVAS is intended to be used by referral from radiologists, pulmonologists or equivalent. The CT LVAS software can be used to provide these physicians with additional supporting clinical data regarding pulmonary ventilation for use in adult patients.

5. Safety and Regulatory

The CT LVAS Ventilation 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.

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 acquiring the images (i.e., Radiographer) to ensure that the input data is of adequate quality. If the input data is not of adequate quality, the output CT LVAS Ventilation Report results will reflect the quality of the input data.

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 Ventilation 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 Ventilation 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. If the input images do not meet the following criteria, the images will be rejected by the device, and no analysis will be undertaken.

6.1 Image Requirements

4DMedical has conducted performance testing in the form of verification across a wide range of pixel and slice spacings and Signal to Noise Ratios (SNRs). Testing of the quantitative measurements included a combination of synthetically generated phantom image data and clinically acquired data. The clinically acquired data included a range of models, manufacturers and institutions, a range of volume changes between the inspiration and expiration CTs, and a diverse range of patients. The primary sources of variability affecting the quantitative measurements are voxel size and signal-to-noise-ratio (SNR). The Device requires a maximum pixel spacing of 2.5mm x 2.5mm, and a slice spacing/slice thickness of 2.5mm. The verification testing demonstrated that the device was robust within acceptable performance limits across the entire range of these inputs.

6.1.1 CT: Resolution

To produce a CT LVAS Ventilation 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 Lung Volume Difference

The total lung volume difference between the inspiratory and expiratory CT images must be more than 100mL (and more than 5% of the expiration CT volume).

6.1.3 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.

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 Checking Images

The radiographer shall check the two CT series were attained in a single study, the patient was correctly positioned in the supine position, a deep inspiration CT series and a deep expiration CT series is present, the entire lung is within the FOV and that the Pixel Spacing, Slice Spacing and Slice thickness are each ≤2.5mm, before proceeding to order the CT LVAS analysis report.

7.4 Image Transfer and CT LVAS Report Delivery

4DMedical utilises a DICOM routing system to facilitate the transfer of the CT series from healthcare facilities to 4DMedical's SaaS platform for processing. To order a CT LVAS report, starting from the institution's RIS (Radiological Imaging System)/PACS (Picture Archiving and Communication System), enter the relevant CT LVAS exam code, or search for the relevant code, select the code and continue. Once the images have been acquired, the exam code is marked as complete, which will automatically trigger a workflow to send the files to 4DMedical. The automated workflow is initiated in the DICOM routing system hosted at the facility to de-identify (anonymize) the study prior to sending the data to 4DMedical's SaaS platform via a secure channel established between the parties. Upon completion of analysis by the device, the CT LVAS ventilation report is returned via the secure channel, where it is re-identified by the DICOM routing system and saved back into the RIS/PACS.

If your institution requires assistance establishing a connection from its RIS/ PACS to 4DMedical's SaaS platform, please contact your local 4DMedical representative.

8. Performance Testing

CT LVAS was designed, developed, and tested in accordance with the IEC 62304 standard. Known hazards were identified and mitigated in accordance with the ISO 14971 standard. Unit level, performance, and integrated system testing were performed. The results of testing demonstrate that the device is effective and meets the manufacturer's intended performance criteria. Clinical and non-clinical studies were also conducted.

8.1 Verification

4DMedical has conducted performance testing in the form of verification across a wide range of pixel and slice spacings and Signal to Noise Ratios (SNRs). Testing of the quantitative measurements included a combination of synthetically generated phantom image data and clinically acquired data. The clinically acquired data included a range of models, manufacturers and institutions, a range of volume changes between the inspiration and expiration CTs, and a diverse range of patients. The primary sources of variability affecting the quantitative measurements are voxel size and signal-to-noise-ratio (SNR). The Device requires a minimum pixel spacing of 2.5mm x 2.5mm, and a slice spacing/slice thickness of 2.5mm. The verification testing demonstrated that the Device was robust within acceptable performance limits across the entire range of these inputs.

The software verification was completed to assure that the software fully satisfies all expected system requirements and features. Test cases were executed against the system features and requirements.

8.2 Analytical Validation

The software analytical validation was completed to assure the software conforms to user needs and intended use. Workflow testing was conducted to provide evidence that the system requirements and features were implemented, reviewed and met.

8.3 Summary of Non-Clinical Tests

Benchtop Verification and Validation Testing was conducted on CT LVAS. This included generation of synthetic CT images that simulated breath-hold CT pair images of a human. A range of input parameters covering a spectrum of patient anatomies and breathing physiologies was used. These synthetic CT pairs, with known simulated lung physiologies and ventilation volumes (the 'ground truth') were then analysed using the CT LVAS Software. The ventilation measurements derived by CT LVAS were then compared to the 'ground truth' values.

The lung volume measurements and the heterogeneity of lung ventilation output by CT LVAS were shown to be within 5% of the ground truth of the synthetic CT pairs. In addition, the Ventilation Defect Percentage (provided on the Ventilation Histogram) was shown to be within 1% of the ground truth of the synthetic CT pairs.

8.4 Summary of Clinical Studies

The performance of CT LVAS was assessed across a diverse patient population in two clinical studies. These studies were conducted to demonstrate the safety and effectiveness of the Device and included patients presenting with symptoms including shortness of breath, frequent coughing, excessive phlegm (mucus) production and frequent chest tightness. The studies included patients across the spectrum of lung health and included healthy subjects and subjects with Asthma, Chronic Obstructive Pulmonary Disease and Lung Cancer.

The studies compared the regional ventilation measurements output by CT LVAS with gold-standard and best practice measures for respiratory diagnosis. The performance of the Device was assessed both quantitatively and qualitatively to determine consistency of the Device's outputs with the gold-standard measures including Pulmonary function testing (PFT) and Nuclear Medicine Imaging (SPECT and PET).

8.4.1 Clinical Study A

In this clinical study an observational comparison study was conducted using data acquired with the objective of demonstrating agreement between CT LVAS and SPECT ventilation. This study consisted of quantitative, statistical analysis demonstrating the correlation between PFT and CT LVAS metrics, as well as qualitative analysis of five

case studies which compared CT LVAS outputs with SPECT ventilation image data. The target population consisted healthy participants as well as participants with previously diagnosed lung diseases.

A total of 32 participants were included in the study. There were 19 male and 13 female study participants, and their ages ranged from 26 to 78 years of age. The body mass index of the subjects varied between 17.9 and 44.8 kg/m^2. The participants' mean height was 170 cm, and their mean weight was 74 kg. Fifteen (15) patients had received a previous diagnosis of COPD and the remainder were categorized as healthy. The participant cohort included patients presenting with symptoms including shortness of breath, frequent coughing, excessive phlegm production and frequent chest tightness. The study included participants from diverse racial demographic groups with participants self-describing as: Asian or Pacific Islander 3% (n=1); Black or African American 6% (n=2); Hispanic or Latino 22% (n=7); Multiracial or Biracial 3(n=1); and White or Caucasian 63% (n=20).

The study demonstrated the following:

- CT LVAS metrics correlated with PFT metrics. In particular, CT LVAS Inspiratory Volume, Expiratory Volume and Volume Change correlated with Total Lung Capacity (TLC), Functional Residual Capacity (FRC), and Vital Capacity (VC), respectively. Functional metrics ventilation heterogeneity (VH), ventilation heterogeneity small scale (VHSS), ventilation heterogeneity large scale (VHLS) and ventilation defect percentage (VDP) correlated with FEV1 (% predicted) and FEV1/FVC;
- CT LVAS provided information regarding regional ventilation that was complementary to global ventilation metrics provided by PFT; and
- CT LVAS visualisations were consistent overall with SPECT ventilation images, however provided additional clarity for assessment of regional distribution of ventilation.

The Computed Tomography Ventilation (CT LVAS) metrics and ventilation visualisations as tools for lung assessment were further assessed through the evaluation of five individuals, each characterized by different degrees of lung disease, inclusive of a healthy subject. The effectiveness of CT LVAS in providing visualisation and quantifiable data pertaining to regional ventilation variability was demonstrated.

There was demonstrated consistency of CT LVAS outputs with those of gold-standard measures. Specifically, the study supported the conclusion that there is substantial equivalence between CT LVAS and SPECT in the assessment of regional distribution of ventilation, with both modalities also shown to render functional and pathological details of the lungs. The study also demonstrated a statistically significant correlation between the CT LVAS and PFT outputs.

8.4.2 Clinical Study B

A study was performed using a publicly available dataset that was collected from a single institution, in Australia. The study comprised of seventeen (17) lung cancer patients undergoing radiotherapy, each of which had varying lung function. The participants were between 54 and 73 years of age.

This study quantitatively compared the CT LVAS outputs PET (positron emission tomography) using statistical analysis. Like CT LVAS and SPECT, PET outputs three-dimensional ventilation fields. The distribution of lung ventilation for individual lung lobes was reported as a proportion of the ventilation of the entire lung for both CT LVAS and PET.

The study demonstrated consistency between CT LVAS and Nuclear Medicine Imaging in the assessment of spatial ventilation distribution at both lobar and voxel levels. There were no systematic differences in the lobar ventilation between CT LVAS and PET. Furthermore, the absence of mean difference, systematic bias or heteroscedasticity demonstrated that the measurements from CT LVAS and PET detect similarly at the high or low range of lung ventilation. Similarly, voxel-wise analysis via Spearman correlations demonstrated strong association between CT LVAS and Nuclear Medicine Imaging spatial ventilation data.

Given the agreement between PET ventilation scanning and CT LVAS, it was concluded that the methods are substantially equivalent for the purpose of examining the regional distribution of ventilation.

8.4.3 Clinical Studies Conclusion

Overall, the clinical studies conducted for the Device successfully demonstrated the feasibility of generating valid data that is reliable and consistent with Nuclear Medicine Ventilation imaging results.

Clinical Study A demonstrated the equivalence between CT LVAS and SPECT in the assessment of regional distribution of ventilation and that there was a statistically significant correlation between the CT LVAS and PFT outputs.

Based on the clinical performance documented in the clinical studies, CT LVAS Software was found to have a safety and effectiveness profile that is similar to the predicate device. Further, it demonstrated the capability of the Device to provide this information without the use of contrast agents utilized by alternative methods.

8.4.4 Performance Testing Conclusion

The performance testing (verification, analytical validation, non-clinical tests and clinical studies) demonstrated that the CT LVAS Software was found to have a safety and effectiveness profile that is similar to the predicate device but without the need for contrast agents.

9. Information Security Statement

CT LVAS and the resulting CT LVAS Ventilation Report are 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 institution's IT support. Information security is a shared responsibility, please follow your institutions information security protocols. 4DMedical will follow the appropriate jurisdictional requirements in communicating with your institution regarding information security, as required.

10.Support and Notice

10.1 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

10.2 Notice

The information provided in the CT LVAS Ventilation Report is intended to support physicians with their assessment of patients with lung diseases. CT LVAS and the resulting CT LVAS Ventilation Report does not provide a diagnosis of lung health. 4DMedical assumes no responsibility for the improper use of, or self-diagnosis using, CT LVAS and the resulting CT LVAS Ventilation Report.

10.3 Troubleshooting

Issue	Cause	Resolution
Image cannot be analysed, or lung tissue is excluded from analysis.	Confirm the two series CT were: • Completed in single study; • Patient was in supine position; • Patient remained still during acquisition; • Captured at deep inspiration and expiration; • Captured with the entire lung within the FOV, and • Pixel spacing, slice spacing, and slice thickness are each ≤2.5mm.	Complete two series CT using the conditions in Sections 7.1 - 7.3
Report not generated.	Image not transferred correctly.	Complete steps as described in Section 7.4.
	File not standard DICOM.	Ensure file is not compressed, and the CT is in DICOM format.
Image not transferred.	Poor or no connection to 4DMedical SaaS platform.	Complete steps as described in Section 7.4, or contact 4DMedical representative.

For all other issues, please contact 4DMedical (see Section 10.1). Support will be available during 4DMedical's standard business hours.

11. Glossary

See below for more information regarding terms found in the CT LVAS Ventilation Report. For a more detailed explanation of these terms, refer to the how-to-read section of the CT LVAS Ventilation 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. (i.e. normalized by the average of the specific ventilation values).
Ventilation defect percentage	The percentage of ventilation volume below 60% of the mean specific ventilation.
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 greater uniformity ventilation throughout the lung, while high Ventilation Heterogeneity values represent significant variability of the ventilation in the lung.
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 Visualisations)
Change in Volume	The difference in the volume (L) between deep inspiration and deep expiration.