CT LVAS™

Instructions for Use US

This edition is valid for Device release from V1.3.x

CT LVAS™ Instructions for Use

US

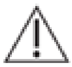
Contents

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 labeling and/or instructions for use are as follows:

	CAUTION for information related to patient safety
	Consult Electronic Instructions for Use
	Manufacturer
	Date of Manufacture (YYYY-MM-DD)
MD	Medical Device
UDI	Unique Device Identifier
LOT	Batch Code (Device Version)
SN	Serial Number
Rx	Caution: Federal law restricts this device to sale by or on the order of a physician.

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 analyzes two non-contrast CT images, reporting detailed ventilation information of pulmonary tissue, at regional locations of the lungs between inspiratory and expiratory volumes. Quantification and statistics are provided in the form of a CT LVAS Ventilation Report, including:

- The volume of ventilation, presented as three values;

• Visualization of lung ventilation with color-defined normalized 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 normalized 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 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 visualize 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 visualizations 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.

4.2 Intended Use

The CT LVAS is intended to be used by referral from thoracic 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 artifacts 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., Radiologic Technologist) 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.

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.

5.1 Information Relating to Input Data

Values presented in the 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.

The Report output is dependent on the quality of input images. Images containing motion artifacts 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

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	≤1.0 mm
Slice Spacing	≤2.5 mm
Slice Thickness	≤2.5 mm

Lung Volume Difference

⚠ **CAUTION:** The total lung volume difference between the inspiratory and expiratory CT images must be more than 0.5 liters (and more than 10% of the expiration CT volume). If the measured volume is less than 0.5 liters or 10% of the expiration CT volume, then no Report will be generated.

NOTICE: If the expiratory to inspiratory volume change is less than 0.8 Liters and 20% of expiratory volume, the low values may be related to the image acquisition process and may not be representative of the patient's actual lung function.

If the notice is present on the Report and is not believed to be due to an error in the image acquisition, please contact 4DMedical using the information inSection 11.

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

The imaging protocol for a CT LVAS is documented in *DOC-4554 CT LVAS Imaging Protocol*.

7.1 Image Transfer and CT LVAS Ventilation Report Delivery

4DMedical utilizes data transfer and sharing systems to facilitate the transfer of CT series from healthcare facilities to the Device for processing. To order a CT LVAS report, follow these steps:

1. **Create an Order:** At your institution, create an Exam with CT LVAS procedure code.
2. **Acquire Images:** Acquire images required for input as per the Imaging Protocol, refer to Section 6 for Device Input Requirements.
3. **Initiate Data Transfer:** Once the images have been acquired, initiate the data transfer at your facility. The images will be transmitted to the Device for processing. For technical details about data sharing, consult your facility's *Guide to Data Transfer*.
4. **Receive the Report:** After the Device completes analysis, the CT LVAS Report will be returned to your facility via the same data transfer system.

Need Assistance?
If your institution requires help setting up the data transfer process to 4DMedical's platform, please contact your local 4DMedical representative.

8 Device Outputs

How to read the CT LVAS Analysis Report is described in the following sections:

8.1 Regional Ventilation Visualization

The Regional Ventilation Visualizations indicates, through color, regional specific ventilation at deep inspiratory breath-hold for a mid-coronal slice and three (3) axial slices (Upper, Middle, Lower). Ventilation values are normalized by the mean specific ventilation. Red depicts regions of relative low ventilation, green depicts regions of average ventilation and blue depicts regions of relative high ventilation.

Measurements are only provided for the regions that have been captured in the CT images (i.e. areas not imaged do not contribute to the measurements).

Specific ventilation is the ratio of the volume of a region of lung divided by the volume at start inspiration. Presented values are normalized by the mean specific ventilation of the patient.

8.2 Normalized Specific Ventilation Histogram

The Ventilation Histogram provides the frequency distribution of regional specific ventilation measured across the entire lung, at deep inspiratory breath-hold. Ventilation values are normalized by the mean specific ventilation. The Ventilation Histogram summarizes the information contained in the Regional Ventilation Visualizations. It includes the Ventilation Defect Percentage (VDP), which is the percentage of ventilation data points below 60% of the mean specific ventilation. The low specific ventilation range has a colored background to highlight the data points that are included in the VDP value. An increased VDP indicates a larger proportion of the lung volume with low ventilation. Figure 1 illustrative histogram (a) shows a histogram having a relatively tight distribution (most of the lung volume on or close to the average ventilation), resulting in a low Total Ventilation Heterogeneity and a low VDP. Illustrative histogram (b) shows a histogram having a significant portion of the lung with low specific ventilation, resulting in an increased VDP (compared to (a)). Illustrative histogram (c) shows a histogram having a very broad distribution, resulting in an increased Total Ventilation Heterogeneity.

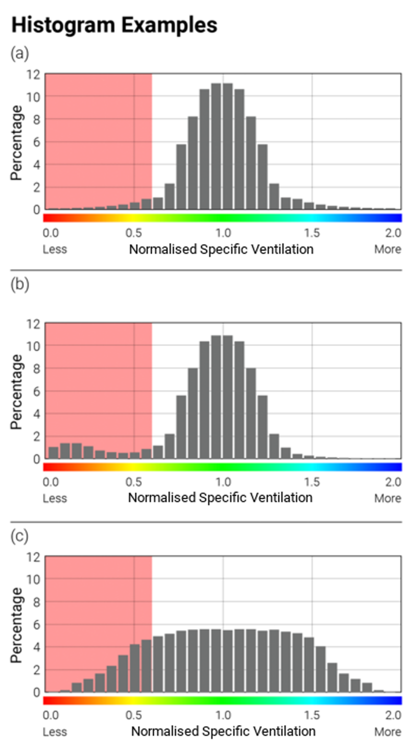


Figure 1: Illustrative histogram examples.

8.3 Ventilation Heterogeneity

Ventilation Heterogeneity quantifies the regional variability of the ventilation. The measure is the ratio of the interquartile range to the mean of the specific ventilation. Low Ventilation Heterogeneity values are associated with uniform ventilation through-out the lung, while high Ventilation Heterogeneity values represent significant variability in the lung. Ventilation Heterogeneity is widely published as a recognized indicator of lung health. The Ventilation Heterogeneity is presented as three indices; Total: the overall value of heterogeneity, calculated using all regional specific ventilation data (as displayed in the Regional Ventilation Visualizations). 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"). 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").

Figure 2 illustrative visualization (a) shows a variation between the right and left lungs, and (b) shows a checkerboard variation. Case (a) results in a high Total Ventilation Heterogeneity, a high Large Scale Ventilation Heterogeneity, and a low Small Scale Ventilation Heterogeneity. Case (b) results in a high Total Ventilation Heterogeneity, a high Small Scale Ventilation Heterogeneity, but a low Large Scale Ventilation Heterogeneity.

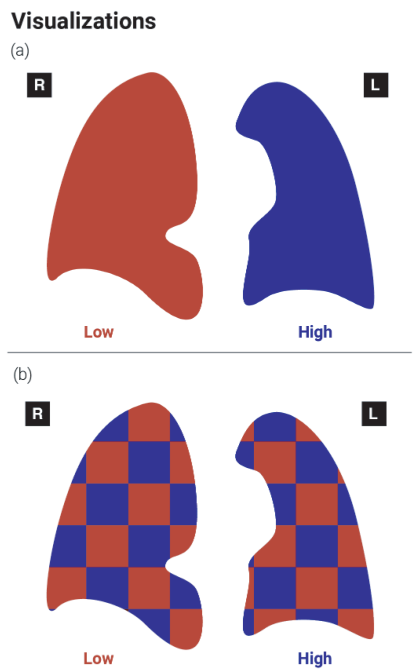


Figure 2: Illustrative visualization of ventilation heterogeneity.

8.4 Lung Volumes

Volume Change - the difference in the volume (L) between deep inspriation and deep expiration. Inspiration Volume - total volume (L) of lung tissue at end inspiration. Expiration Volume - total volume (L) of lung tissue at end expiration.

8.5 Regional Ventilation Visualization Slices

The Regional Ventilation Visualizations (Axial and Coronal Slices) indicates, through color, regional specific ventilation at peak inspiration. Ventilation values are normalied by the mean specific ventilation. Red depicts regions of low ventilation, green depicts regions of average ventilation and blue depicts regions of high ventilation.

9 Performance Testing

The CT LVAS Software was designed, developed, and tested in accordance with the ISO 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.

9.1 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 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.

9.2 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.

9.3 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.

9.4 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).

Clinical Study 1

The first clinical study was an observational comparison study conducted using data acquired in the USA 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 of 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/m2. The participants' mean height was 67 inches, and their mean weight was 163 pounds. 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 representative of the USA's population, 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 visualizations 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 visualizations 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 visualization and quantifiable data pertaining to regional ventilation variability was demonstrated.

Clinical Study 1 showed the 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.

Clinical Study 2

The second 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.

9.5 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.

9.6 Performance Testing Conclusion

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

10 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.

11 Support and Notice

11.1 Support

For support, contact 4DMedical using the details below during standard business hours.

Contact 4DMedical U.S.

Phone: +1-833-XV-SCANS (+1 833 98 72267)
Address: 21255 Burbank Blvd. Suite 120
Woodland Hills, California
91367
U.S.A
Email: support@4DMedical.com | 4DMedical.com/ventilation-support

11.2 Labelling

Labelling is applied to the Report (example shown in Figure 3).

Figure 3: Example device label

11.3 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, in itself, 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.

11.4 Troubleshooting

Issue	Cause	Resolution
Image cannot be analysed, or lung tissue is excluded from analysis.	Confirm the two series CT were: • Completed in a 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 ≤ 1.0 mm, slice spacing and slice thickness are both ≤ 2.5 mm	Complete two series CT using the conditions in *DOC-4554 CT LVAS Imaging Protocol*
Report not generated.	Image not transferred correctly.	Complete steps as described inSection 7.1.
	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 7.1, or contact 4DMedical representative.

For all other issues, please contact 4DMedical (see Section 11.1). Support will be available during 4DMedical's standard business hours.