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XV Report - User Guide

XV Lung Ventilation Analysis and Metrics

XV lung ventilation analysis measures lung tissue expansion during breathing, which is used to calculate regional ventilation at over 6,000 loci within the small animal lung.

Regional ventilation is quantified into a dimensionless unit called *specific ventilation.* Specific ventilation is defined as the ratio of the change in volume of a region of the lung (ΔV) following inspiration, divided by the end-expiratory volume (V0) of that same lung region. It is a key variable in lung mechanics and important in the pathogenesis of lung conditions [1].

Specific ventilation measurements are presented:

- visually using Regional Ventilation Visualisation Maps; and,
- as whole-lung metrics, including *tidal volume*, *ventilation heterogeneity* (VH) and *ventilation defect percentage* (VDP).

Unless otherwise stated, all outputs for XV lung ventilation analysis are inspiration only.

[1] Wellman TJ, Winkler T, Costa EL, et al. Measurement of regional specific lung volume change using respiratory-gated PET of inhaled 13N-nitrogen. *J Nucl Med*. 2010;51(4):646-653. doi:10.2967/jnumed.109.067926

Regional Ventilation Visualisation Maps

Technical Description:

Regional ventilation is visually represented using coloured contour maps, termed *ventilation visualisation maps*. The ventilation visualisation maps are superimposed (co-registered) with corresponding CT chest images to facilitate correlation between lung ventilation and structure.

The visualisation maps denote specific ventilation values, normalised by the mean specific ventilation, at peak inspiration. For the coloured contour maps, red depicts regions of relative low ventilation, green depicts regions of average ventilation, and blue depicts regions of relative high ventilation.

The visualisation maps are shown as:

- Executive Summary [Report Page 1] showing mid-coronal slice and axial slices from the upper, middle and lower zones (see Figure 1);
- Multi-slice axial and coronal images [Report Pages 2 and 3]; and,
- Mid-coronial slices showing seven [7] phase points between end-expiration and peak inspiration, inclusive of the latter [Report Page 4].

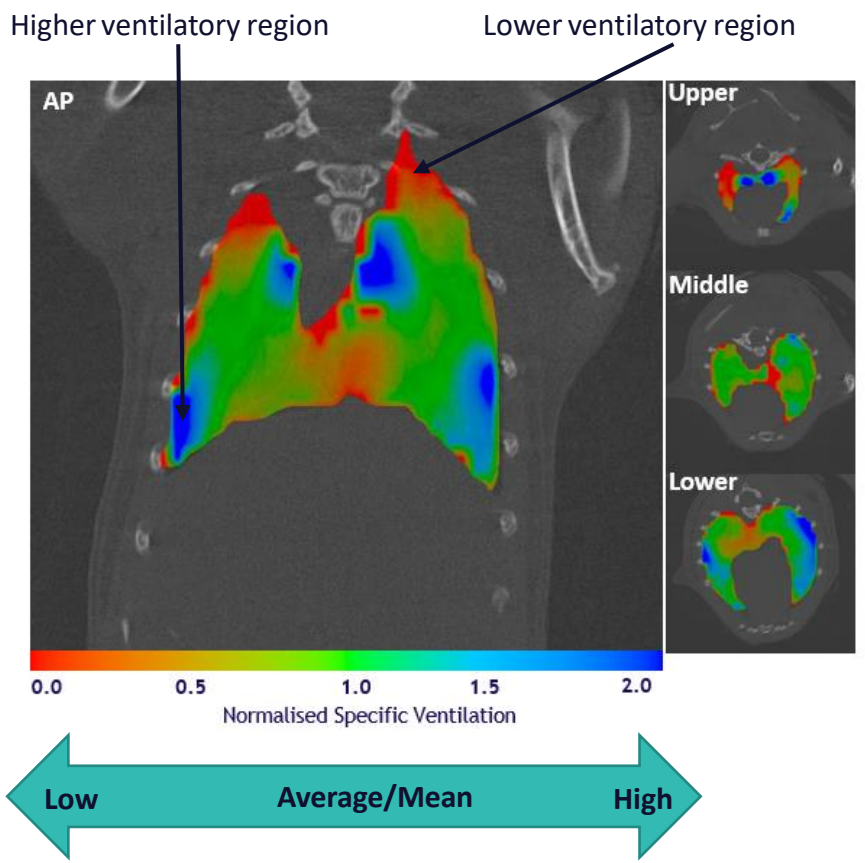
Visualisation maps are only provided for the lung regions that have been captured in the images (i.e. lung regions that are not imaged do no contribute to the measurements).

Usefulness:

The ventilation visualisation maps allow for spatial detection of regional ventilation changes and correlation to underlying lung structure.

The ventilation visualisation maps showing the seven phase points allow for detection of temporal changes in regional ventilation in the mid-coronal plane.

Figure 1: Executive Summary showing mid-coronal [AP] and axial slices [Upper, Middle and Lower]



Ventilation Distribution Histogram

Technical Description:

The *Ventilation Distribution Histogram* provides the frequency distribution of specific ventilation values across the whole lung, at peak inspiration.

The x-axis shows specific ventilation values. The values are normalised by the mean specific ventilation. Therefore, a value of 1.0 corresponds to the mean ratio.

The y-axis is the percentage of lung region with the corresponding specific ventilation value.

Usefulness:

The histogram shows the overall distribution of specific ventilation values and a measure of heterogeneity.

While spatial information cannot be inferred from the histogram, it provides a summary of regional ventilation across the whole lung in one image (see Figure 2).

The profile of the histogram, including its skewness and kurtosis, may be helpful in characterising/phenotyping lung conditions and quantifying their treatment effects. Skewness is a measure of the lack of symmetry of the histogram, whereas kurtosis is a measure to which the distribution is peaked relative to a normal distribution.

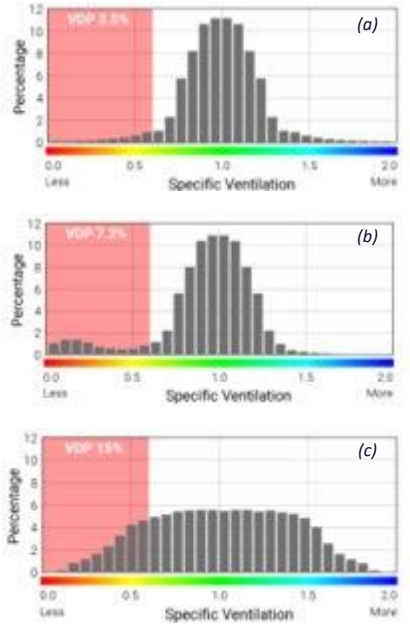
In a homogeneously ventilated lung, a relatively tight, normal distribution (see Figure 2a) is observed.[2] In respiratory conditions with 'patchy' disease, the distribution is more variable and tends to be skewed, multimodal (see Figure 2b) and/or flattened (i.e. platykurtic) (see Figure 2c).[2]

Figure 2: Ventilation Distribution Histograms

Relatively tight distribution: (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 Ventilation Heterogeneity and a low VDP.

Substantial portion of lung with low specific ventilation (b) shows a histogram having a significant portion of the lung with low specific ventilation, resulting in an increased VDP (compared to (a)).

Very broad distribution (c) shows a histogram having a very broad distribution, resulting in an increased Ventilation Heterogeneity.



[2] Werdiger, F., Donnelley, M., Dubsky, S. et al. Quantification of muco-obstructive lung disease variability in mice via laboratory X-ray velocimetry. *Sci Rep* 2020;10:10859. doi:10.1038/s41598-020-67633-y

Ventilation Defect Percentage (VDP)

Technical Description:

VDP is defined as the percentage of lung regions with a specific ventilation below 60% of the mean specific ventilation.

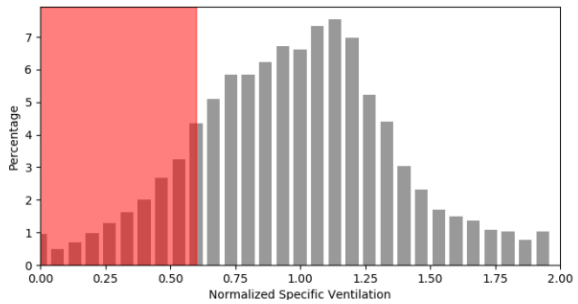
VDP is denoted on the histogram as the area shaded in red and presented as a percentage value (see Figure 3a).

Usefulness:

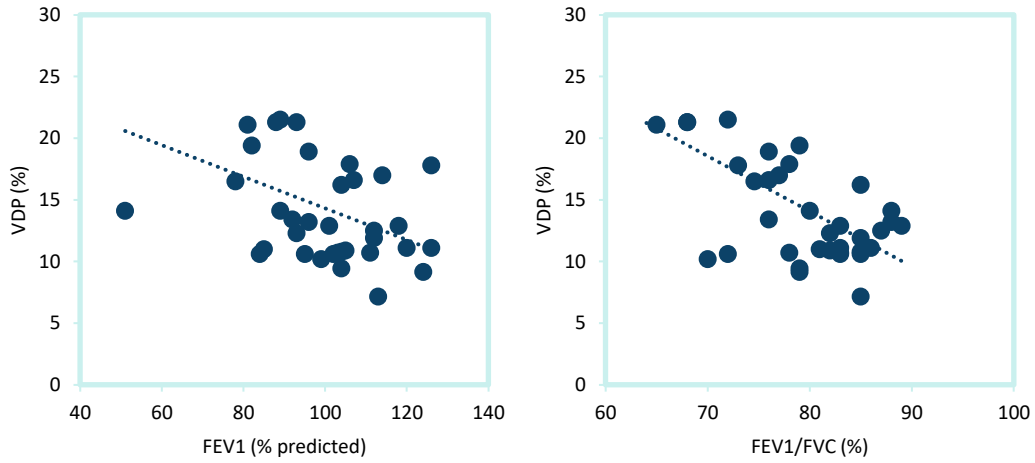
VDP as measured by XV demonstrates a moderate, negative correlation with spirometric measures of FEV1 and FEV1/FVC (see Figure 3b) [3]. A strong correlation was not expected since XV metrics are derived from more detailed regional data than is available from spirometry.

VDP is a recognised measure of regional ventilation and utilised in functional MRI (fMRI) techniques, although values are not directly comparable between fMRI and XV techniques. For reference, in fMRI studies, VDP has been shown to correlate with severity of exacerbations in asthma and COPD cohorts [4].

Figure 3: Ventilation Defect Percentage



(a) VDP = lung regions with specific ventilation values less than 60% of mean specific ventilation (shown in red)



(b) Correlation between VDP and spirometric measures in human studies. Pearson correlation coefficients and p-values are shown.

[3] Unpublished data
[4] 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

Ventilation Heterogeneity (VH)

Technical Description:

VH quantifies the variability of regional ventilation.

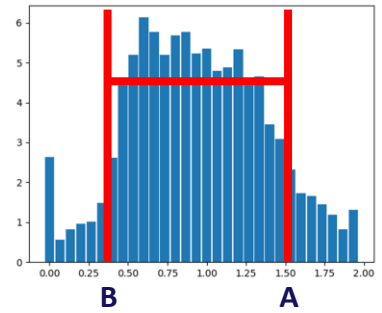
VH is calculated using the interquartile range of the distribution of specific ventilation values, divided by the mean specific ventilation (see Figure 4a). The interquartile range is utilised to account for non-normally distributed data and helps to reflect the increased spread of values seen in respiratory conditions. The interquartile range is presented as a percentage of the mean ratio, which indicates how closely the ratio is clustered around the mean, similar to coefficient of variation.

VH is presented as:

- VH (Total) – inclusive of all specific ventilation values, and therefore represents heterogeneity across the whole-lung;
- VH (Large Scale) – excludes small scale variations*, and therefore represents heterogeneity across larger regions of the lungs (see Figure 5a);
- VH (Small Scale) – excludes large scale variations*, and therefore represents heterogeneity within local regions of the lung (see Figure 5b).

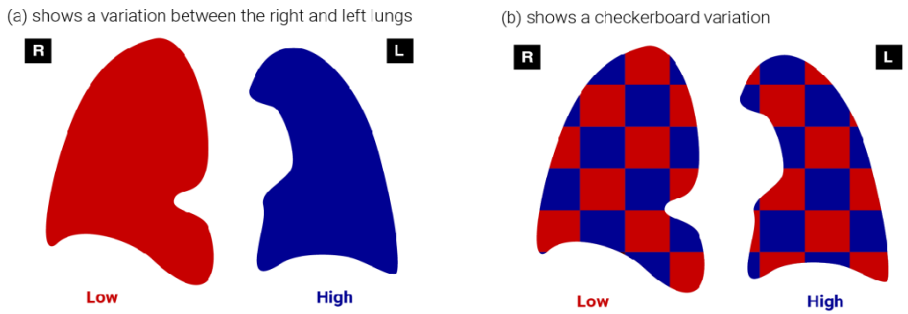
** A 3D Gaussian filter is applied where the width of variation is calculated as the full width at half maximum [FWHM] = (CT voxel size) x 2.355. The filter is applied to the post-processed images, prior to calculation of VH values.*

Figure 4: Ventilation Heterogeneity [VH] methodology



VH= [(A-B) / mean specific ventilation] x 100%

Figure 5: Illustrative depiction of large scale (a) and small scale (b) variations



Ventilation Heterogeneity (VH)

Usefulness:

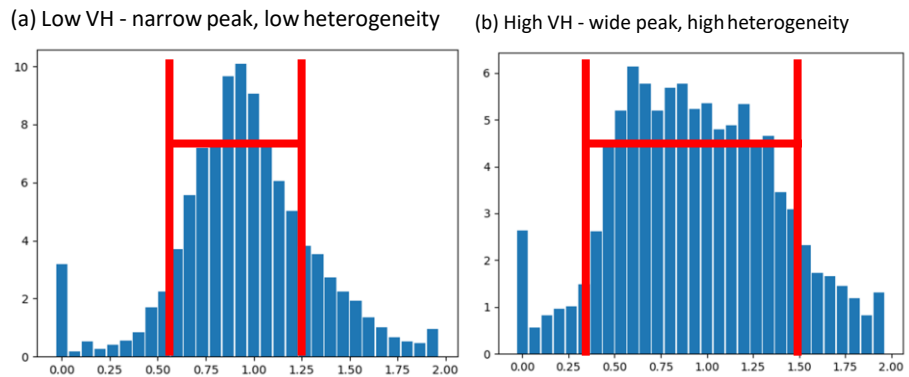
VH is an imaging biomarker for respiratory conditions.

Ventilation Heterogeneity is used to see how uniform ventilation is across the lung. Generally, the lower the VH, the more uniform the regional ventilation (see Figure 6a). A higher VH suggests a lack of uniformity (see Figure 6b).

VH (Total) for a hypothetical, perfectly ventilated lung would be zero; however, in real world conditions, there is a degree of VH in healthy lungs, and it dramatically increases with respiratory conditions.

VH (Large Scale) and VH (Small Scale) values provide information about large-scale and small-scale topographical ventilation heterogeneity, i.e. differences in regional ventilation between lung units ranging approximately from acini to lung segments (i.e. small scale) and lung segments to lobes, and between right and left lungs (i.e. large scale), respectively.

Figure 6: Low vs high ventilation heterogeneity



Contact Information:

4DMedical Limited

Melbourne Office
Level 7 Melbourne Connect
700 Swanston Street
Melbourne, Victoria
3053
Australia

AU: + 61 3 9545 5940

Los Angeles Office
21600 Oxnard Street
Suite #300
Woodland Hills, California
91367
USA

US: +1 818 794 6467

info@4dmedical.com | www.4dmedical.com

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