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ORIGINAL ARTICLE

Diagnostic performance comparison of the Chartis System and high-resolution computerized tomography fissure analysis for planning endoscopic lung volume reduction

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ABSTRACT

Background and objective: **Endobronchial valve (EBV) therapy is optimized in patients who demonstrate little or no collateral ventilation (CV). The accuracy of the Chartis System and visual assessment of high-resolution computerized tomography (HRCT) fissure completeness by a core radiology laboratory for classifying CV status was compared by evaluating the relationship of each method with target lobe volume reduction (TLVR) after EBV placement.**
Methods: **Retrospective HRCT fissure analysis of a study population who underwent catheter-based measurement of CV followed by complete occlusion of the targeted lobe by EBV. Accuracy, sensitivity, specificity, positive predictive value and negative predictive value of the HRCT fissure analysis and the catheter-based measurement of CV for predicting TLVR was determined.**
Results: **Accuracy for correctly classifying TLVR with EBV was similar for Chartis System and HRCT fissure analysis (74 vs 77%). The sensitivity and specificity of the Chartis measurement were 86% and 61% and those of HRCT fissure analysis 75% and 79%. Patients with TLVR ≥350 mL had statistically significant improvement in respiratory function, exercise performance and quality of life measures.**
Conclusions: **When evaluating patients for likelihood of successful EBV therapy, the Chartis System CV assessment and HRCT fissure analysis appear to have comparable accuracy. Both techniques were found to be beneficial for EBV procedure planning.**

SUMMARY AT A GLANCE

Valve therapy presents an effective treatment in emphysema patients. The presence of CV could undermine the effectiveness of the valve treatment. The Chartis System and CT fissure analysis provide quantification of CV prior to valve therapy. We compare the two methods with respect to CV quantification.

Key words: bronchoscopy and interventional technique, collateral ventilation, emphysema, Endoscopic Lung Volume Reduction, valve therapy.

Abbreviations: CV, collateral ventilation; EBV, endobronchial valve; HRCT, high resolution computerized tomography; TLVR, target lobe volume reduction; VENT, Endobronchial Valve for Emphysema Palliation Trial.

INTRODUCTION

In the past 10 years, endoscopic lung volume reduction (ELVR) is used as a less invasive method to perform lung volume reduction to palliate symptoms associated with emphysema.[1,2] Nowadays, several techniques of ELVR are available, whereby the implantation of valves is the best studied method. Endobronchial valves (EBV, Zephyr) are designed to block inspired air while allowing trapped air to escape from the occluded region. This can lead to a lung volume reduction resulting in improvement of lung function, exercise capacity and quality of life. The first prospective clinical controlled, randomized trial was

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the 'Endobronchial Valve for Emphysema Palliation Trial' (VENT).[3] In the VENT, unilateral EBV placement in patients with emphysema was found to be associated with significantly improved lung function and exercise tolerance compared to medical management. Similar results could be obtained in the European cohort of VENT.[4]

Key findings of the VENT and Euro-VENT data indicated that EBV therapy was optimized in patients who had high-resolution computed tomography (HRCT) findings suggestive of a complete fissure between the EBV-treated lobe and the adjacent lobe.[3,4] A complete fissure is thought to correspond to lack of interlobar collateral ventilation (CV).[5] Researchers have theorized that presence of interlobar CV is likely to mitigate clinical response to EBV treatment.[6–8]

Another method to quantify CV prior to valve placement is an invasive, catheter-based measurement by using the Chartis Pulmonary Assessment System (Pulmonx Inc., Redwood City, CA, USA). This Chartis System allows sealing of a lung compartment and measurement of air pressure and flow from the sealed compartment.[9] Based on these measurements, the Chartis System classifies CV status in a target lobe. Safety and feasibility of CV measurements using the Chartis System has been confirmed in a prospective pilot study.[10]

A subsequent larger-scale study—the multicentre Chartis study—evaluated the ability of the Chartis System to predict EBV treatment response by determining the presence of CV.[11] In this trial, the Chartis System had an accuracy of 75% in predicting whether the predetermined target lobe volume reduction (TLVR) cut-off would be reached. Those predicted to respond showed significantly greater TLVR and forced expiratory volume in 1 s (FEV_1) improvement than those predicted not to respond.

To date, there are no data comparing the CT fissure analysis and the Chartis measurement of CV. The aim of this retrospective analysis was to compare the accuracy of the Chartis System and visual assessment of HRCT fissure completeness by re-examining the previously published multicentre Chartis trial.[11]

METHODS

Study design

This is a retrospective analysis based on data collected in the prospective multicentre Chartis study—a post-marketing study conducted at five clinical study sites located in Germany, the Netherlands and Sweden (NCT01101958).[11] The multicentre study was approved by the Ethics Committee overseeing each participating clinical site. As previously described, patients with heterogeneous emphysema who were considered appropriate candidates to undergo unilateral EBV treatment were enrolled.[11] After written informed consent, the patients underwent CV measurement by using the Chartis Pulmonary Assessment System followed by a complete occlusion of the target lobe by EBV (Zephyr, Pulmonx Inc.) (Fig. 1).

Figure 1 Endobronchial valve (Zephyr, Pulmonx Inc.).

CV measurement by using the Chartis System

The Chartis measurement has been described previously.[11] In brief: Prior to the bronchoscopy procedure, target lobe was identified by visually assessing emphysema destruction on the CT scan. The most emphysematous destroyed lobe was considered as target. The Chartis catheter was inserted into the lobar bronchi leading into the targeted lobe, and the balloon was inflated to occlude the lumen (Fig. 2) to assess the presence (CV+) or absence (CV–) of CV.

HRCT fissure analysis

In the prospective trial, HRCT was performed on one of five different CT platforms, and sites were provided the same image acquisition guidelines as those used in the VENT.[3] Adherence to the suggested protocol varied both from site to site and within patients at the same site, resulting in a range of image acquisition (including non-volumetric and volumetric) and reconstruction protocols between 0.635 and 10 mm thick.

The retrospective assessment of fissure integrity was performed by a single reader at the core radiology laboratory who visually assessed the baseline HRCT scan in a slice-by-slice multiplanar fashion. The fissure of interest for this study was the fissure between the EBV-treated lobe and the adjacent lobe(s). A 'complete' fissure was arbitrarily defined as having more than 90% of the fissure present and no evidence of segmental vessels crossing over lobe boundaries on thin-slice HRCT on all axes (sagittal, axial or coronal views). In contrast, an 'incomplete' fissure was defined as having less than 90% of the fissure present (Fig. 3a,b).

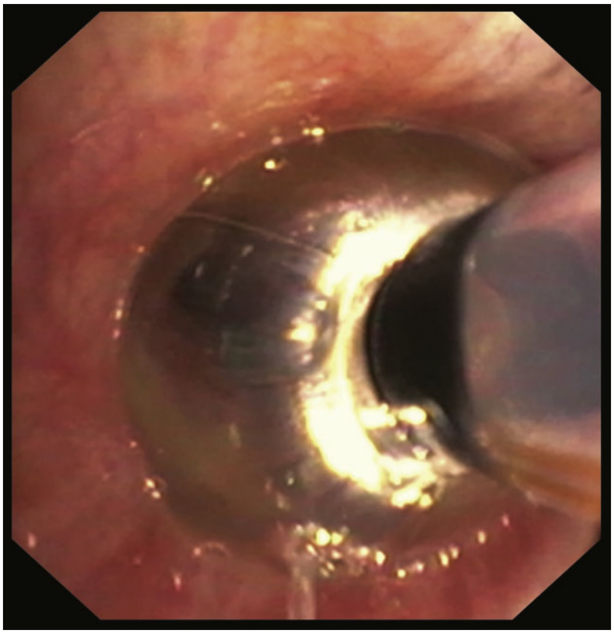

Figure 2 Measurement of collateral ventilation using the Chartis Pulmonary Assessment System (Pulmonx Inc.).

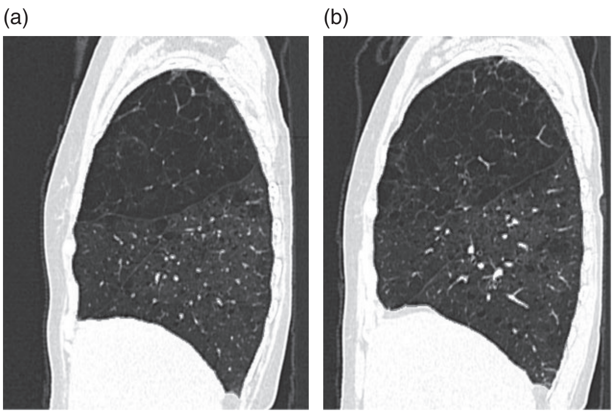

Figure 3 High-resolution computed tomography. Sagittal view. Right lung of one patient. (a) Intact interlobar fissures at the periphery. (b) Same patient closer to the hilum. The fissures are harder to visualize and were deemed to be incomplete.

TLVR assessment

As previously described, TLVR was determined by calculating the volumetric change between the baseline and 30-day scans in the target treatment lobe using a semi-automated Computer Aided Diagnosis (CAD) algorithm[3,12] by a core radiology laboratory that was blinded to all clinical details and the results of the Chartis measurements.

Clinical outcome measures

Clinical outcomes were assessed using spirometry and body plethysmography measures, the 6-minute walk distance (6MWD) and the St. George's Respiratory Questionnaire (SGRQ).

Statistical analysis

Chartis measurement versus CT fissure analysis

The presence or absence of CV as assessed by the Chartis System was evaluated for agreement with the results of HRCT fissure integrity. Accuracy, sensitivity, specificity, positive predictive value and negative predictive value of each method for predicting TLVR was determined. The estimates of agreement between the two assessment methods were evaluated by determining overall per cent agreement, positive per cent agreement and negative per cent agreement. Diagnostic accuracy of the Chartis System and of HRCT fissure analysis was assessed by calculating estimates of sensitivity and specificity pairs. For this analysis, a 'true positive' would correspond to a patient classified by the Chartis System as CV– or by HRCT fissure analysis as having complete fissure who had TLVR ≥350 mL. A 'true negative' would be a patient classified by the Chartis System as CV+ or HRCT fissure analysis as having incomplete fissure who had TLVR <350 mL.

Relationship between TLVR and clinical response

TLVR ≥350 mL in the EBV-treated lobe was defined *a priori* as representing a clinically meaningful threshold for treatment effect. The clinical significance of achieving TLVR ≥350 mL with EBV treatment was evaluated by determining the mean change between pre-and post-EBV procedure clinical outcomes measures and then calculating confidence bounds (95%) for the mean change for patients dichotomized by TLVR response (<350 mL and ≥350 mL).

RESULTS

One hundred five patients were enrolled in the prospective study and underwent CV measurement by using the Chartis System.[11] In seven patients, the Chartis assessment was unsuccessful. In two patients, EBV were not placed, leaving 96 patients who underwent the Chartis assessment and EBV placement. In six patients, HRCT data were missing and 10 patients either did not complete the study or were lost to follow-up so that the results of the multicentre Chartis study covers 80 patients. Furthermore, in 11 patients their HRCT could not be assessed for fissure completeness either due to slice thickness or other acquisition parameters so that the final analysis of the current study ran on 69 patients (Fig. 4). Patients' demographics are described in Table 1 demonstrating that the study cohort ($n = 69$) had similar baseline characteristics to the complete EBV-treated cohort ($n = 96$) (Table 1).

CV measurement by using the Chartis System

As previously described, 51 out of the 80 patients who underwent Chartis measurement were prospectively classified as CV–, and 29 were classified as CV+.

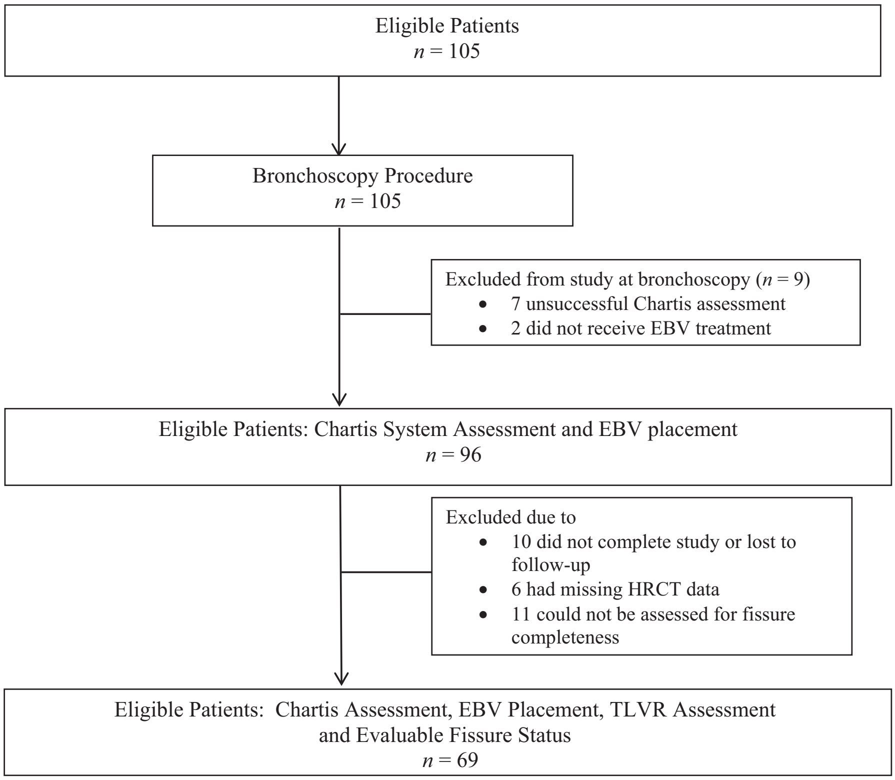

Figure 4 Accountability for the Chartis System and high-resolution computed tomography assessments.

Regarding the study population of 69 patients, 44 were classified as CV−, and 25 were classified as CV+ (Table 2). The TLVR results showed that 31 of the 44 CV− patients had TLVR that exceeded the 350 mL study threshold. For the CV+ patients, 20 of 25 patients had TLVR <350 mL (Table 3).

HRCT fissure analysis

In 34 out of the 69 patients (49%), a complete interlobar fissure could be evaluated; in 35 patients (51%) an incomplete fissure could be assessed (Table 2). Twenty-seven out of the 34 patients with a complete fissure had TLVR ≥350 mL; 26 out of 35 patients with an incomplete fissure had TLVR <350 mL (Table 3).

Chartis measurement versus CT fissure analysis

The accuracy of the Chartis System and HRCT fissure analysis assessments for selecting patients who would achieve TLVR ≥350 mL was similar. Accuracy of both assessments for correctly classifying patients who did or did not respond to EBV treatment, as measured using the HRCT-based TLVR response, was approximately three of four patients.

The diagnostic performance of the Chartis System and HRCT fissure analysis were compared (Table 4). The sensitivity and specificity of the Chartis measurement were 86% and 61%, and those of HRCT fissure analysis 75% and 79%.

The Chartis System and HRCT fissure analysis assessments were concordant in 47 patients (68.1%) and discordant in 22 (31.9%). In the discordant cases, the Chartis System correctly predicted TLVR response in 45% (10/22) and HRCT correctly predicted TLVR response in 55% (12/22) (Table 5).

Relationship between TLVR and clinical response

The clinical relevance of achieving TLVR ≥350 mL with EBV treatment was assessed by calculating the pre- to post-procedure changes in clinical outcomes in patients dichotomized by TLVR response (<350 mL vs. ≥350 mL). Study participants having TLVR ≥350 mL met or exceeded the minimal clinically important difference (MCID) for FEV_1, 6MWD, SGRQ and residual volume (RV) at 30 days (Table 6).

DISCUSSION

In the past 10 years, EBV placement has emerged as a potentially effective therapy for properly selected patients with advanced heterogeneous emphysema. Valve implantation may lead to TLVR that is associated with clinical response and subsequent improved quality of life. In previous trials, low interlobar collateral ventilation has been demonstrated to be a predictive factor for an excellent outcome of valve

Table 1 Baseline characteristics

Variable	All (n = 96)	Final analysis (n = 69)
Demographics		
Age (yrs)	63 ± 9	63 ± 9
Males (n, %)	49 (51)	33 (48)
Body mass index (kg/m^2)	24.3 ± 3.4	24.3 ± 3.4
Former smokers (n, %)	93 (97)	67 (97)
Alpha-1 antitrypsin deficiency (n, %)	3 (3)	3 (4)
Prior LVR procedure (n, %)	7 (7)	7 (10)
Lung function		
FEV_1 (litres)	0.85 ± 0.34	0.84 ± 0.34
Per cent of predicted value	31 ± 10	32 ± 10
FVC (litres)	2.28 ± 0.86	2.33 ± 0.90
Per cent of predicted value	67 ± 18	70 ± 18
DL_{CO} (mL CO/min/mmHg)	2.75 ± 1.45	2.89 ± 1.46
Per cent of predicted value	36 ± 15	37 ± 15
RV (litres)	5.2 ± 1.5	5.1 ± 1.3
Per cent of predicted value	241 ± 68	241 ± 62
TLC (litres)	7.8 ± 1.7	7.7 ± 1.6
Per cent of predicted value	133 ± 23	135 ± 20
RV/TLC (ratio)	0.67 ± 0.10	0.66 ± 0.10
Exercise performance, quality of life		
6MWD (metres)	303 ± 115	312 ± 108
SGRQ (points)	64 ± 12	63 ± 12

6MWD, 6-minute walk distance; DL_{CO}, diffusing capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVR, lobe volume reduction; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

Table 2 Results of the collateral ventilation measurement using the Chartis Pulmonary Assessment System and of the computed tomography fissure analysis (n = 69)

		Chartis measurement		
		CV negative	CV positive	
CT fissure analysis	Complete fissure	28	6	**34**
	Incomplete fissure	16	19	**35**
		44	**25**	

CT, computed tomography; CV, collateral ventilation.

Table 3 Accuracy of both assessments for predicting TLVR with EBV treatment

		HRCT TLVR ≥350 mL		
		Yes	No	Total
Chartis System Assessment				
Collateral ventilation	No CV	**31**	13	44
	CV	5	**20**	25
	Total	36	33	69
HRCT analysis				
Fissure integrity	Complete	**27**	7	34
	Incomplete	9	**26**	35
	Total	36	33	69

EBV, endobronchial valve; HRCT, high-resolution computerized tomography; TLVR, target lobe volume reduction.

Table 4 Diagnostic performance of the Chartis System assessment and the HRCT fissure analysis to predict target lobe volume reduction with endobronchial valve treatment (95% confidence interval)

	Chartis System	HRCT fissure
Accuracy (%)	74	77
Sensitivity [true positive rate] (%)	86.1 (70.5, 95.3)	75.0 (57.8, 87.9)
Specificity [true negative rate] (%)	60.6 (42.1, 77.1)	78.8 (61.1, 91.0)
Positive predictive value (%)	70.5	79.4
Negative predictive value (%)	80.0	74.3

HRCT, high-resolution computerized tomography.

Table 5 Comparison of discordant cases

Chartis System	HRCT fissure integrity	n	HRCT TLVR ≥350 mL Yes	No
No CV	Incomplete	16	8	8
CV	Complete	6	4	2

CV, collateral ventilation; HRCT, high-resolution computerized tomography; TLVR, target lobe volume reduction.

treatment.[3,4] Estimation of CV prior to EBV treatment can be obtained by either the HRCT fissure analysis or the catheter-based measurement using the Chartis System.

When evaluating patients for likelihood of successful EBV treatment in this study, both techniques, the Chartis System and HRCT fissure analysis, appear to have comparable accuracy: fissure analysis correctly predicted the TLVR in 74% of patients with the Chartis System and in 77% with HRCT. One month following treatment, patients who had a TLVR ≥350 mL demonstrated clinically meaningful improvement in respiratory function, exercise performance and quality of life measures. This result demonstrates the importance of the pre-interventional quantification of CV.

In both techniques, there are advantages and disadvantages. The Chartis System provides a direct measure of CV and can be performed by a pulmonologist during a bronchoscopic procedure. Radiologic expertise is not required. This examination presents a real-time measurement of physiological

Table 6 Change in lung volume (body plethysmography) and clinical outcomes in patients dichotomized by TLVR response after EBV treatment

	HRCT TLVR response	
	≥350 mL (*n* = 36)	<350 mL (*n* = 33)
TLC		
Absolute Δ (litres)	−0.59 ± 0.66	−0.09 ± 0.56
95% confidence bounds (litres)	[−0.82, −0.37]	[−0.29, 0.11]
Per cent Δ	−8 ± 9	−1 ± 7
95% confidence bounds (%)	[−10, −5]	[−3, 2]
RV		
Absolute Δ (litres)	−0.82 ± 0.84	−0.19 ± 0.71
95% confidence bounds (litres)	[−1.10, −0.54]	[−0.44, 0.06]
Per cent Δ	−16 ± 16	−2 ± 13
95% confidence bounds (%)	[−21, −11]	[−6, 3]
RV/TLC		
Absolute Δ	−0.06 ± 0.08	−0.01 ± 0.05
95% confidence bounds	[−0.09, −0.04]	[−0.03, 0.00]
Per cent Δ	−10 ± 12	−2 ± 7
95% confidence bounds (%)	[−14, −6]	[−4, 1]
FEV_1		
Absolute Δ (litres)	0.20 ± 0.21	0.00 ± 0.08
95% confidence bounds	[0.13, 0.27]	[−0.03, 0.03]
Per cent Δ	22 ± 24	0 ± 10
95% confidence bounds (%)	[14, 30]	[−4, 4]
6MWD		
Absolute Δ (meters)	34 ± 59	9 ± 39
95% confidence bounds	[13, 55]	[−5, 23]
Per cent Δ	18 ± 47	8 ± 32
95% confidence bounds (%)	[2, 35]	[−4, 20]
SGRQ		
Absolute Δ (points)	−13 ± 14	−4 ± 13
95% confidence bounds	[−19, −7]	[−9, 2]
Serious adverse events		
Pneumothorax	4	0
COPD exacerbation	2	2
Dyspnoea	0	1

Plus-minus values are means ± SD.

6MWD, 6-minute walk distance; COPD, chronic obstructive pulmonary disease; EBV, endobronchial valve; FEV_1, forced expiratory volume in 1 s; HRCT, high-resolution computerized tomography; TLC, total lung capacity; TLVR, target lobe volume reduction; RV, residual volume.

circumstances. However, the Chartis measurement is complicated in patients with difficult anatomy, coughing or mucous clogging at the tip of the Chartis catheter. Furthermore, the measurement is invasive and prolongs the bronchoscopic procedure.

In the first trial with the Chartis System, successful CV measurement was observed in 20 out of 25 patients.[10] The accuracy of correctly predicting the advent of atelectasis in the post-procedural chest X-ray was found to be 90%. These encouraging results were confirmed by the subsequent multicentre Chartis trial, the results of which were presented in this manuscript: the diagnostic accuracy of the Chartis System for prospectively classifying the presence or absence of CV in a lobe targeted for EBV treatment was 75%.[11]

HRCT fissure analysis has been performed for several years, however, only a few trials focus on patients with emphysema.[13–15] These publications demonstrate the difficulty of the fissure analysis that presupposes a high degree of experience. Pu *et al*. discovered that the inter-reader variability related to fissure analysis was statistically significant.[13] Similarly, Koenigkam-Santos and colleagues studied the agreement of pulmonologists and radiologists visually evaluating the fissure integrity.[14] They concluded that pulmonologists and radiologists agreed at fair to moderate rates in fissures analysis. Experienced readers might be required as were the readers in the core radiology laboratory of our study. Another trial evaluating fissure completeness using automatic quantification was published by van Rikxoort *et al*.[15] In this trial, the fissure completeness score of the automatic method was compared to a visual consensus read by three radiologists. The results demonstrated the usability of the automatic method in quantifying the fissure completeness comparable to the visual read. The greatest disagreement among the readers was observed in the area of fissures visually thought to be either complete or incomplete to a small degree. The radiologists mostly agreed that there could be a gap in the fissure; however, they were often not able to exactly quantify the fissural gap. Hence, the authors proposed the use of automated methods to support radiologists making visual readings and provide them with exact quantifications.

A limitation of the present trial is its retrospective character. In this post-market study, the Chartis assessments were performed across a number of centres, by a range of operators, who utilized various patient management protocols and who had differing levels of training with the Chartis System. All of the Chartis assessments and their interpretation were independently performed by the treating centre. A post hoc review of the Chartis waveforms revealed that a number of assessments would have been considered unacceptable by more experienced users. Although they were included in the statistical analysis, it is likely that these poorer assessments negatively affected the accuracy of the Chartis System. Further evaluation indicated that the poorer quality waveforms were associated with patient sedation techniques, cough management, pre-procedure mucus clearing and catheter tip positioning. With clinical experience, poor assessments from the Chartis System may be avoided.

With respect to the HRCT analysis, the study had several limitations of which the most important appeared to be variation in reconstruction interval and breath hold. For reliable visual assessment of fissure integrity, volumetric thin section acquisition and reconstruction (≤1.5 mm) are required. In order to accomplish this, the patient must sustain a breath hold for the entire acquisition to avoid motion artefacts. In this study, <50% of the baseline studies met these requirements. Thus, the accuracy for assessing fissure integrity was likely to have been negatively impacted. Furthermore, the fissure was considered complete for the right upper lobe if both the right major and minor fissures were entirely visually complete that may sometimes result in a 'false incomplete statement'. For example, a gap in the lower third of the right major fissure does not affect the right upper lobe. Again, appropriate training and adherence to clear protocols that define data collection is likely to preclude these issues.

In summary, both techniques appear to be able to assess CV and were found to be beneficial as a means for optimizing procedure planning prior to EBV treatment. The choice of using the Chartis System or CT to assess patients requires consideration of several factors, including logistics, cost, patient tolerance of invasive techniques, radiation risk, site equipment and expertise.

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