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When can computed tomography-fissure analysis replace Chartis collateral ventilation assessment in the prediction of patients with emphysema who might benefit from endobronchial valve therapy?

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Summary

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was when can computed tomography-fissure analysis replace Chartis collateral ventilation assessment in the prediction of patients with emphysema who might benefit from endobronchial valve therapy? Twelve papers were chosen to answer the question. The authors, date, journal, country of publication and study type; patient group studied; relevant outcomes and results of these papers were tabulated. Five studies retrospectively compared the prognostic value of 2 methods. They found that when computed tomography-fissure analysis showed an intact fissure more than 95%, both methods were equivalent in correctly predicting a positive response to valve therapy. Concordant results were found in two-thirds of patients, and the additional evaluation with Chartis did not confer a significant advantage. Yet the increasing cost and time to procedure, the different ranges of Chartis findings patterns not correlated with lung volume reduction and the unfeasibility of the measurements (reported in 6–17% of the most series) due to difficult anatomy are additional limitations for its use. Conversely, in patients with fissure integrity between 75% and 90%, Chartis assessment could improve the patient selection, because the computed tomography-fissure analysis alone is unable to predict a successful treatment. In this situation, Chartis had a 31% ability to predict those patients who can be successfully treated. In BeLieVer-HIfi Study, *post hoc* analysis revealed that the additional use of Chartis for patient selection significantly improved outcomes. Similarly, STELVIO, LIVE and IMPACT studies, where only patients with complete fissure and negative Chartis measurement were treated, showed significant benefits after valve treatment. Finally, in patients with fissure integrity below 75%, the negative predictive value for lobar atelectasis is 100%. Thus, in these patients, it could be futile even considering a Chartis assessment.

Keywords: Chartis collateral ventilation • Computed tomography-fissure analysis • Bronchoscopic lung volume reduction • Endobronchial valves • Emphysema

INTRODUCTION

A best evidence topic was constructed according to a structured protocol fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [patients with severe emphysema therapy] is [computed tomography (CT)-fissure analysis] or [Chartis collateral ventilation (CV) assessment] the best for [predicting a successful placement of an endobronchial valve]?

CLINICAL SCENARIO

A patient with severe emphysema and unfit for surgery is referred to your attention for endoscopic lung volume reduction (LVR). The heterogeneity of the disease is mainly localized at left upper lobe, and the patient fulfils the criteria for an endobronchial valve for emphysema according to the Endobronchial Valve for Emphysema Palliation Trial (VENT) criteria [2]. You ask for a quantitative CT-fissure integrity score, and the oblique fissure has a score of 88% integrity. The patient asks you what the chance is with your treatment and also your theatre staff are asking whether you want to also perform an intraoperative Chartis assessment before the placement of the valve.

SEARCH STRATEGY

Medline 1990 to January 2017 using OVID interface: [endobronchial valve] AND [lung volume reduction] AND [emphysema] AND [Chartis Collateral ventilation] OR [CT fissure analysis]. Finally, a hand search was performed to search references from the retrieved study.

SEARCH OUTCOME

One hundred and fifty-five papers were found using the reported search strategy. Twelve papers (Table 1) were identified that provided the most applicable evidence to answer the question.

RESULTS

Herth *et al.* [3] prospectively evaluated Chartis CV in 80 patients undergoing endobronchial valve (EBV) therapy. CV- ($n = 51$) vs CV+ patients ($n = 29$) had higher incidence of target lobe volume reduction (TLVR) ≥350 ml (71% vs 17%) and an improvement in forced expiratory volume in 1 s (FEV1%) (16 ± 22 vs 1 ± 15; $P = 0.0013$), in 6-min walking test (6MWT) (24 vs 10; $P > 0.05$) and in St. George's Respiratory Questionnaire (-10 vs -5; $P > 0.05$). Chartis assessment was impracticable in 7% of cases.

Reymond *et al.* [4] retrospectively evaluated the role of CT-fissure assessment to predict CV in 30 patients. In 5 (17%) patients, Chartis assessment was unfeasible. Twenty-five patients were included, and a total of 37 target lobes were assessed. Both tests were concordant in 73% of cases. CT-fissure assessment was highly sensitive (95%) but not specific (44%) for predicting CV. CV was present in 20 of 29 (69%) target lobes with a different grade of fissural defect and in only 1 of 8 (12%) target lobes with complete fissures.

Gompelmann *et al.* [5] retrospectively compared the predictive value of Chartis CV and CT-fissure analysis to predict TLVR ≥350 ml in 69 patients treated with EBV. Chartis and CT-fissure analysis presented similar diagnostic accuracy (74% vs 77%, respectively). Discordant results were found in 22 (31.9%) cases.

Davey *et al.* [6] conducted a single-centre randomized controlled trial (RCT), where 50 patients with heterogeneous emphysema and a target lobe with intact interlobar fissure (BeLieVeR-HIFi Study) were randomized to receive EBV ($n = 25$) or sham valve placement ($n = 25$). All patients also underwent Chartis assessment that was unfeasible in 12% of cases. Treated group versus control group showed significant improvement in FEV1% (20.9; $P = 0.0326$) and in 6MWT (33; $P = 0.012$). Four (17%) patients were CV+, despite the presence of intact fissures. *Post hoc* analysis revealed that the additional use of Chartis for patient selection could improve outcomes.

Schumann *et al.* [7] retrospectively compared the predictive value of Chartis CV and CT-fissure analysis to predict TLVR ≥350 ml in 33 of 146 emphysematous patients treated with EBV. Chartis and CT-fissure analysis presented similar sensitivity (88.9% vs 77.8%) and specificity (66.7% vs 73.3%). Discordant results were found in 11 (33.4%) of 33 cases.

Gesierich *et al.* [8] retrospectively evaluated 92 patients undergoing Chartis evaluation. Four different Chartis findings (CV-/CV+/collapse phenomenon/unclear) were found and correlated with CT-fissure analysis. In CV- patients ($n = 46$), 34 patients had lobar atelectasis; of these, 31 patients had fissure integrity showing a comparable predictive value of both methods. In collapse phenomenon patients ($n = 20$), 11 patients with fissure integrity were responders. Chartis assessment was unfeasible in 6.5% of cases.

Klooster *et al.* [9] conducted a single-centre RCT (Stelvio Study), where 68 patients with severe emphysema, Chartis CV- and CT-fissure integrity were randomized to receive EBV ($n = 34$) or medical therapy ($n = 34$). Treated group versus control group showed significant LVR (-0.83; $P < 0.001$) and improvement in FEV1% (17.8; $P = 0.001$), in 6MWT (74; $P < 0.001$) and in St. George's Respiratory Questionnaire (-14.7; $P < 0.001$).

Koster *et al.* [10] retrospectively evaluated the prognostic value of CT-fissure analysis and Chartis CV to predict TLVR ≥350 ml. High-resolution CT analysis and Chartis had similar accuracy (80.6% vs 83.3%, respectively); combining both methods in patients with incomplete fissure, the accuracy increased to 89.5%.

Herzog *et al.* [11] retrospectively evaluated 406 Chartis measurements in 166 patients and described 4 different findings (CV-/CV+/low flow/low plateau). Patients with CV- target lobe or low flow target lobe and ipsilateral adjacent CV- lobe had a significant improvement in FEV1% ($P < 0.05$), vital capacity (VC) ($P < 0.05$) and significant TLVR ($P < 0.05$) after valve insertion. Chartis assessment was unfeasible in 10% of cases.

de Oliveira *et al.* [12] retrospectively evaluated the prognostic value of CT-fissure integrity in 38 of 108 emphysematous patients undergoing EBV therapy. The positive predictive values for TLVR ≥350 ml were 83.9%, 70% and 90.5% for fissure integrity ≥75%, fissure integrity between 75% and 90% and fissure integrity >90%, respectively. The negative predictive value in case of fissure integrity <75% was 100%.

Skowasch *et al.* [13] conducted a multicentre RCT (LIVE Study), where 498 patients with severe emphysema were selected for EBV therapy with Chartis. Compared with the baseline value, a significant LVR (-0.42; $P < 0.0001$) and improvement in FEV1% (11.9; $P < 0.0001$), forced vital capacity (12.15%; $P < 0.0001$) and modified medical research council dyspnea scale (mMRC scale) (-0.49; $P < 0.0001$) were observed. Chartis assessment was unfeasible in 12.7% of cases.

Valipour *et al.* [14] conducted a multicentre RCT (IMPACT Study), where 93 patients with severe homogeneous emphysema were randomized (1:1) to receive EBV ($n = 43$) or medical therapy ($n = 50$). CV+ patients ($n = 17$) were excluded. Treated group versus control group showed significant improvement in LVR (-0.48; $P = 0.001$), FEV1% (17.0; $P < 0.001$), 6MWT (40; $P = 0.002$) and St. George's Respiratory Questionnaire (-9.64; $P < 0.001$).

CLINICAL BOTTOM LINE

This analysis shows that in patients with a grade of CT-fissure integrity ≥95% [5, 7, 8], valves can be directly implanted, whereas in patients with fissure integrity between 75% and 90% [4, 10] to confirm the absence of CV, Chartis assessment could be required before proceeding with valve implant. Finally, in patients with fissure integrity below 75%, the negative predictive value for lobar atelectasis is 100% [12]. Thus, in these cases, it could be futile even considering a Chartis assessment.

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Herth *et al.* (2013), Eur Respir J, Europe [3] Multicentre prospective non-RCT (level 2a)	80 patients with HE undergoing EBV were evaluated with Chartis (51 CV-/29 CV+)	TVLR ≥350 ml (responder)	CV-: 36/51 (71%, PPV) CV+: 5/29 (17%, PPV) Accuracy: 75%	Chartis predicts TVLR with an accuracy of 75%
		ΔFEV1% (before and after treatment)	CV-: 16 ± 22, $P = 0.0013$ CV+: 1 ± 15	
		Δ6MWT m (before and after treatment)	CV-: 24, $P > 0.05$ CV+: 10	
		ΔSGRQ score (before and after treatment)	CV-: -10, $P > 0.05$ CV+: -5	
		Chartis failure	7%	
Reymond *et al.* (2013), Am J Roentgenol, France [4] Retrospective unicentre study (level 3b)	37 emphysematous lobes were evaluated with CT-fissure analysis (29 CF/8 IF) and Chartis (16 CV+/21 CV-)	Size fissure defect (cm^2)	CV+: 21.2, $P = 0.04$ CV-: 3.4	CT-fissure assessment is sensitive but not specific for predicting CV
		Accuracy of CT-fissure evaluation to predict CV	Sensibility: 95% Specificity: 44% PPV: 69% NPV: 88% Concordant results in 73% of cases. CV was present in 20/29 (69%) lobes with fissural defect and in 1/8 (12%) with complete fissures	
		Chartis failure	17% (5/30)	
Gompelmann *et al.* (2014), Respirology, Europe [5] Retrospective multicentre study (level 3a)	69 patients with HE undergoing EBV were evaluated with Chartis (25 CV+/44 CV-) and QCT-fissure analysis (34 CF/35 IF)	TVLR ≥350 ml (responder)	Chartis Sensibility: 86.1% Specificity: 60.6% PPV: 70.5% NPV: 80% Accuracy: 74% QCT fissure Sensibility: 75% Specificity: 78.8% PPV: 79.4% NPV: 74.3% Accuracy: 77%	Both techniques have comparable accuracy
		Comparison of QCT and Chartis	Concordant: 47 (69.1%) Discordant: 22 (31.9%) 10/22 (45%) correctly predicted by Chartis 12/22 (55%) correctly predicted by QCT	
Davey *et al.* (2015), Lancet, UK [6] Unicentre RCT (level 1b)	50 patients with HE and a target lobe with intact interlobar fissure received EBV ($n = 25$) or sham valve placement ($n = 25$) All treated patients underwent Chartis assessment Randomization 1:1 BeLieVeR-HIFi Study	ΔFEV1% (treatment vs control)	20.9 (4.3, 37.5), $P = 0.0326$	HE and CF were associated with marked clinical response
		Δ6MWT m (treatment vs control)	33 (-3.69), $P = 0.012$	
		ΔSGRQ score (treatment vs control)	-5.1 (-14.4, 4.3), $P = 0.345$	
		ΔRV l (treatment vs control)	-0.37 (-0.72, -0.03), $P = 0.079$	
		CV+	4/23 (17%)	
		Chartis failure	6 (12%)	

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Schuhmann *et al.* (2015), Am J Respir Crit Care Med, Europe [7] Multicentre retrospective study (level 3a)	34/146 patients with HE treated with EBV were evaluated with QCT-fissure analysis and Chartis ($n = 33$)	TVLR $\geq$350 ml (responder)	Sensibility QCT: 88.9% (16/18) Chartis: 77.8% (14/18) Specificity QCT: 66.7% (10/15) Chartis: 73.3% (11/15)	QCT-fissure analysis and Chartis had comparable results
		Comparison of QCT and Chartis	Concordant: 22/32 (66.6%) Discordant: 11/33 (33.4%) 5 misclassification by QCT (4 upper lobes) 6 misclassification by Chartis (5 lower lobes)	
Gesierich *et al.* (2015), Eur Respir J, Germany [8] Multicentre retrospective study (level 3b)	92 patients with HE were selected for EBV with Chartis (15 CV+/50 CV-/21 CP/6 unclear) and HRCT-fissure analysis 72 patients underwent EBV therapy	Lobar atelectasis (responder)	2 CV+ treated: no responder 46 CV- treated: 34 responders; 31 with CF 20 CP treated: 11 responders with CF 4 unclear treated: 3 responders; 2 with IF	In the absence of CP, both methods are comparable; in patients with CP, treatment decision should be based on HRCT-FI
		Chartis failure	6/92 (6.5%)	
Klooster *et al.* (2015), N Engl J Med, Netherlands [9] Unicentre RCT (level 1b)	68 patients with HE received EBV ($n = 34$) or medical treatment ($n = 34$) after Chartis evaluation Randomization 1:1 STELVIO Study	ΔFEV1% (treatment vs control)	17.8 (7.6, 28), $P = 0.001$	The absence of CV improved clinical outcomes
		Δ6MWT m (treatment vs control)	74 (47, 100), $P < 0.001$	
		ΔSGRQ score (treatment vs control)	-14.7 (-21.8, -7.6), $P < 0.001$	
		ΔRV l (treatment vs control)	-0.83 (-1.10, -0.56), $P < 0.001$	
Koster *et al.* (2016), Respiration, Europe [10] Multicentre retrospective study (level 3b)	217 patients with HE undergoing EBV therapy Patients with QCT-fissure integrity were evaluated with Chartis	TVLR $\geq$350 ml (responder)	QCT alone PPV: 88.1% NPV: 68.3% Accuracy: 80.6% Chartis alone Accuracy: 83.3% QCT + Chartis PPV: 88.1% NPV: 92.9% Combined accuracy: 89.5%	Chartis can be used selectively only in patients with incomplete fissure
Herzog *et al.* (2016), Respiration, Germany [11] Multicentre retrospective study (level 3b)	166 patients with HE were evaluated with Chartis (154 CV+: 154/167 CV-/76 LF/9 LP)	TVLR $\geq$350 ml (responder)	CV- UL: 86% $P = 0.5$ CV- LL: 69% LF LL: 75%	Patients with CV- target lobe or LF target lobe and ispilateral adjacent CV- lobe may be successfully treated with valves; it is unclear whether patients with LP target lobe improve after EBV therapy
		ΔFEV1% (before vs after treatment)	CV- UL: 26.9 ± 6 $P = 0.7$ CV- LL: 21.7 ± 7 LF LL: 20.3 ± 6	
		ΔVC% (before vs after treatment)	CV- UL: 16.5 ± 5 $P = 0.5$ CV- LL: 19.5 ± 5 LF LL: 29.5	
		Chartis failure	10%	

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
de Oliveira *et al.* (2016), Respiration, Brazil [12] Unicentre retrospective study (level 3b)	38/108 patients with HE undergoing EBV therapy were evaluated with QCT-fissure analysis	Correlation between fissure integrity and TVLR ≥350 ml TVLR ≥350 ml	r = -0.6, P < 0.01 for fissure integrity ≥75% PPV Integrity ≥75%: 83.9% Integrity between 75% and 90%: 70% Integrity >90%: 90.5% NPV Integrity <75%: 100%	Additional measurement with Chartis is needed in patients with fissure integrity between 75% and 90%
Skowasch *et al.* (2016), Respiration, Germany [13] Multicentre RCT (level 1b)	In 487/498 patients with HE undergoing EBV therapy, Chartis evaluation was performed (414 CV-/7 CV+/62 inconclusive/4 missing data) LIVE Study	ΔFEV1% (before vs after treatment) ΔFVC% (before vs after treatment) ΔRV l (before vs after treatment) ΔmMRC score (before vs after treatment) Chartis failure	11.9% (8.74, 15.11), P < 0.0001 12.15% (8.70, 15.60), P < 0.0001 -0.42 (-0.56, -0.29), P < 0.0001 -0.49 (-0.62, -0.37), P < 0.0001 12.7%	Chartis predicts lobar occlusion and clinical benefits
Valipour *et al.* (2016), Am J Respir Crit Care, Europe [14] Multicentre RCT (level 1b)	93 patients with homogeneous emphysema received EBV (n = 43) or medical treatment (n = 50) after Chartis Randomization 1:1 17 CV+ were excluded IMPACT Study	ΔFEV1% (treatment vs control) Δ6MWT m (treatment vs control) ΔSGRQ score (treatment vs control) ΔRV l (treatment vs control)	17.0 (8.1, 25.8), P < 0.001 40 (15, 65), P = 0.002 -9.64 (-14.1, -5.2), P < 0.001 -0.48 (-0.84, -0.11), P = 0.001	EBV in patients with homogeneous emphysema without CV results in clinically meaningful benefits

6MWT: 6-min walking test; CF: complete fissure; CP: collapse phenomenon; CV: collateral ventilation; EBV: endobronchial valve; FEV1%: forced expiratory volume in 1 s; FVC: forced vital capacity; HE: heterogeneous emphysema; HRCT: high-resolution computed tomography; IF: incomplete fissure; LF: low flow; LH: low heterogeneous; LL: lower lobe; LO: lobar occlusion; LP: low plateau; NPV: negative predictive value; PPV: positive predictive value; QCT: quantitative computed tomography; RCT: randomized controlled trial; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; TVLR: total volume lung reduction; UL: upper lobe; mMRC: modified medical research council dyspnea scale.

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REFERENCES

[1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. Interact CardioVasc Thorac Surg 2003;2:405–9.

[2] Sciurba FC, Ernst A, Herth FJF, Strange C, Criner GJ, Marquette CH *et al.* A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233–44.

[3] Herth FJ, Eberhardt R, Gompelmann D, Ficker JH, Wagner M, Ek L *et al.* Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302–8.

[4] Reymond E, Jankowski A, Pison C, Bosson JL, Prieur M, Aniwidyaningsih W *et al.* Prediction of lobar collateral ventilation in 25 patients with severe emphysema by fissure analysis with CT. AJR Am J Roentgenol 2013;201:W571–5.

[5] Gompelmann D, Eberhardt R, Slebos DJ, Brown MS, Abtin F, Kim HJ *et al.* Diagnostic performance comparison of the Chartis System and high-resolution computerized tomography fissure analysis for planning endoscopic lung volume reduction. Respirology 2014;19:524–30.

[6] Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD *et al.* Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeRHIFi study): a randomised controlled trial. Lancet 2015; 386:1066–73.

[7] Schuhmann M, Raffy P, Yin Y, Gompelmann D, Oguz I, Eberhardt R *et al.* Computed tomography predictors of response to endobronchial valve

lung reduction treatment. Comparison with Chartis. Am J Respir Crit Care Med 2015;191:767–74.
[8] Gesierich W, Samitas K, Reichenberger F, Behr J. Collapse phenomenon during Chartis collateral ventilation assessment. Eur Respir J 2016;47: 1657–67.
[9] Klooster K, ten Hacken NHT, Hartman JE, Kerstjens HAM, van Rikxoort EM, Slebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med 2015;373:2325–35.
[10] Koster TD, van Rikxoort EM, Huebner RH, Doellinger F, Klooster K, Charbonnier JP *et al*. Predicting lung volume reduction after endobronchial valve therapy is maximized using a combination of diagnostic tools. Respiration 2016;92:150–7.
[11] Herzog D, Thomsen C, Poellinger A, Doellinger F, Schreiter N, Froeling V *et al*. Outcomes of endobronchial valve treatment based on the precise criteria of an endobronchial catheter for detection of collateral ventilation under spontaneous breathing. Respiration 2015;91:69–78.
[12] de Oliveira OH, Freitas FG, Ladeira RT, Fischer CH, Bafi AT, Azevedo LC *et al*. Comparison between respiratory changes in the inferior vena cava diameter and pulse pressure variation to predict fluid responsiveness in postoperative patients. J Crit Care 2016;34:46–9.
[13] Skowasch D, Fertl A, Schwick B, Schäfer H, Hellmann A, Herth FJ; LIVE Study Investigators. A Long-Term Follow-Up Investigation of Endobronchial Valves in Emphysema (the LIVE Study): study protocol and six-month interim analysis results of a prospective five-year observational study. Respiration 2016;92:118–26.
[14] Valipour A, Slebos DJ, Herth F, Darwiche K, Wagner M, Ficker JH *et al*; IMPACT Study Team. Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT Study. Am J Respir Crit Care Med 2016;194:1073–82.