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Occlusion pressure analysis role in partitioning of pulmonary vascular resistance in CTEPH

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Abstract

Flow-directed pulmonary artery occlusion is posited to enable partitioning of vascular resistance into small and large vessels. As such it may have a role in assessment for pulmonary endarterectomy.

To test if the occlusion technique distinguished small from large vessel disease we studied 59 subjects with CTEPH, idiopathic PAH, and connective tissue disease (CTD) PAH. At right heart catheterisation, occlusion pressures were recorded. With fitting of the pressure decay curve, PVR was partitioned into downstream (small vessels) and upstream (large vessels, R*up*).

47 patients completed the study; 14 operable CTEPH, 15 non-operable CTEPH, 13 idiopathic or CTD-PAH, 5 post-operative CTEPH. There was a significant difference in mean R*up* in the proximal operable CTEPH group 87.3(95%CI 84.1;90.5); non-operable CTEPH mean 75.8(95%CI 66.76;84.73) p=0.048; and IPAH/CTD, mean 77.1(95%CI 71.86;82.33) p=0.003. ROC curves to distinguish operable from non-operable CTEPH demonstrated an AUC of 0.75, p=0.0001. A cut off of 79.3 gave sensitivity 100%(CI 73.5-100%) but specificity 57.1%(CI 28.9-82.3%). In a subgroup analysis of multiple lobar sampling there was demonstrable heterogeneity.

R*up* is significantly increased in operable proximal CTEPH compared with non-operable distal CTEPH and IPAH/CTD. R*up* variability in patients with CTEPH and PAH is suggestive of pathophysiological heterogeneity.

Introduction

The pulmonary artery occlusion technique has emerged as a possible way of partitioning vascular resistance across the pulmonary vascular bed. This is of particular relevance in chronic thromboembolic disease (CTEPH). In CTEPH the ability to discriminate the contribution of small vessel vasculopathy from organised thrombus in large vessels is critical to treatment decisions. The gold standard treatment of choice is pulmonary endarterectomy (PEA) surgery. Distal disease, whether vasculopathic or small vessel thrombotic, is a major risk factor for poorer outcome [1-3]. It has however been demonstrated that patients with high PVR can still potentially benefit from operative intervention. *Thistlethwaite et al* have reported a greater reduction in systolic pulmonary artery pressure and PVR in a cohort of patients with a very high mean pulmonary vascular resistance of 1299 dynes sec cm^{-5} when compared to a cohort of more modest PVR (832.5 dynes sec cm^{-5}) [4] although the high PVR group had a lower survival (89.2% vs 96.5%). Additional discriminators to identify those at risk of poor outcome are therefore desirable. In this context *Kim et al* have previously reported results in a cohort of patients undergoing PEA that suggest the occlusion technique is able to effectively partition resistance into small and large vessel compartments. The occlusion derived partition of resistance correlated strongly with immediate post-operative results and additionally demonstrated promise in identifying those at high operative risk regardless of PVR [5].

There are issues related to the validity of the technique in this context. There are questions about the size of vessel that partitioning segregates, and it is possible that it

does not properly assess the contribution of clinically relevant small vessel vasculopathy. There is additionally concern that a single measurement may not produce an accurate reflection of what is a heterogeneous disease.

To test the hypothesis that the occlusion technique is able to discriminate large vessel organised thrombus from distal vasculopathy we performed occlusion pressures on patients with operable CTEPH, distal inoperable CTEPH and post-PEA residual CTEPH. In addition we also undertook measurements in patients with idiopathic or connective tissue associated PAH (CTD PAH) as additional controls, where distal vasculopathy is traditionally accepted as predominant. In a select group of CTEPH patients we performed multiple measurements in different pulmonary segments to determine if there were differences within segments in the same patients.

Methods

Subjects

59 subjects gave full written informed consent to these studies. The study was approved by the Local Research Ethics Committee (Huntington, Cambridgeshire, UK) and conformed with the principles outlined in the Declaration of Helsinki. Subjects were diagnosed with CTEPH, idiopathic and connective tissue associated PAH (IPAH/ CTD PAH) according to standard classification [6, 7]. The diagnosis and decision on operability was made by a multi disciplinary team of PEA surgeons, physicians and radiologists blinded to the results of the study using additionally a minimum two out of 4 imaging modalities; ventilation/perfusion scanning, conventional pulmonary angiography, CT pulmonary angiography and MRI

pulmonary angiography. Patients were deemed successfully operable if there was a technically good clearance of proximal disease and an intra-operative drop in mPAP. Subjects were routinely catheterised according to local protocol at 3 months post-PEA and therefore medium term follow up haemodynamics were available for analysis.

Right heart catheterisation

Right heart catheterisation was undertaken with the patient lying supine and breathing room air. Pulmonary hemodynamic measurements of mPAP and pulmonary artery occlusion pressure (PAOP) were recorded using a 7 Fr Swan–Ganz catheter (Edwards Lifesciences) inserted via the right internal jugular vein. Cardiac output (Q) was determined using the thermodilution method. Systemic arterial pressure and oxygen saturation (SaO2) measurements were obtained non-invasively at five minute intervals throughout the procedure. Pulmonary Vascular Resistance (PVR) was calculated using standard hemodynamic formulae.

Occlusion pressure technique and analysis

The catheter was positioned using fluoroscopic monitoring distally in a pulmonary artery. The wire directed approach involved a wire being passed into an alternative segmental artery and subsequently being floated into a distal artery in the same manner as the standard flow-directed measurement. Therefore although wire-directed these are still also flow-directed measurements in patent vessels of the same calibre. The vascular pressure signals were sampled at 200 Hz with the use of an analogue-to-digital converter (DAQCard-AI-16XE-50, National Instruments) and displayed and stored data encrypted on a personal computer. After single inflation of the pulmonary artery catheter, occlusion waveforms were recorded during breath-holding for 8

seconds at end-expiration. Measurements were performed in triplicate. In a sub-group of 7 subjects with CTEPH multiple sites were sampled by flow direction and additional catheter wire directed methods. A separate, blinded investigator performed a biexponential fitting of the pressure decay curve between the moment of occlusion and the PAOP, with normalization to the mPAP. This has been previously described and is used here to derive occlusion pressure (Poccl) [5,8]. R*up* (upstream pressure) was calculated as follows: R*up* % = 100 x (mPAP - Poccl) / (mPAP - PAOP).

Statistics

Relationships between variables and R*up* values were analyzed using linear regression and calculation of the Pearsons correlation coefficient. Adherence to a Gaussian distribution was determined using a Kolmogorov-Smirnov method and between group differences were determined using a one way ANOVA test. Results are presented as mean/SD unless otherwise stated. A receiver operating characteristic (ROC) curve was generated to establish a cut-off value for differentiating between operable and non-operable CTEPH. For all statistical tests a p-value < 0.05 was considered significant.

Results

Subjects

59 patients were sampled with 47 patients completing the full protocol. In 3 subjects it was not possible to obtain an occlusion pressure, 3 were unable to breath-hold for the required time and 6 subjects had respiratory artefact in their baseline occlusion pressure and therefore it was not possible to calculate their pressure decay accurately.

Of these 12 subjects, 8 were in the first 30 tested with the remaining 4 in the last 29 and therefore there was a clear operator learning curve. Despite this the blinded observer ensured that only tracings of sufficient quality were analysed.

Of the 47 patients with analysable tracings 14 had operable CTEPH, 15 had non-operable CTEPH, 13 had idiopathic or connective tissue disease associated PAH and 5 subjects had residual distal post-operative CTEPH *(table 1)*. Of the operable patients 2 died and therefore were not included in the successfully operable disease group. Both had significant distal disease on pre-operative assessment. The remainder of the operable group were surgically classified at the time of operation (using the *Thistlethwaite et al* classification [9]) as predominantly type II/ III disease and adjudged to have good technical clearance *(table 1).*

In CTEPH Rup is not uniformly distributed across the pulmonary circulation

R*up* repeatability within single locations was good with a mean standard deviation of 3.4% and within subject's coefficient of variation of 4.4%. In the 7 patients with multiple lobe sampling there was wide variation *(table 2)*.

Flow directed Rup is significantly increased in proximal CTEPH

There was a significant difference in *Rup* between the operable subjects and the 2 predominantly distal vasculopathic groups: operable CTEPH mean 87.3 (95% CI 84.1; 90.5); non-operable CTEPH mean 75.8 (95% CI 66.76; 84.73) p=0.048; IPAH/ CTD PAH mean 77.1 (95% CI 71.86; 82.33) p=0.003 *(figure 1).* Looking at the sensitivity and specificity of the Rup in distinguishing between operable and inoperable disease, ROC curves demonstrate that Rup is capable of distinguishing between operable and non-operable disease with a significant area under the curve

(AUC) p=0.001 *(figure 1C)*. If we therefore assume the purpose of the test is to identify non-operable disease the cut off point of 79.3 gives a 100% sensitivity (CI 73.5-100%) and specificity of 57.1% (CI 28.9-82.3%). The optimum point for improving specificity on the ROC curve would be 83.8 which gives a sensitivity of 83.3% (CI 51.6-97.9%) and specificity of 71.4% (CI41.9-91.6%). If we adopt the more stringent definition of successful operative intervention of reduction to a PVR of less than 300 dynes/s/cm^5 there is no change to the results *(figure 1)*. In the operable group both of the patients who died were not included in the analysis as they could clearly not be classified as successfully operable disease but these 2 subjects had the lowest R*ups* in the operative cohort (68% and 73%). One patient had significant post operative PH at 3 months despite a drop post-operatively, with a PVR of 1040 dynes/s/cm^5. Interestingly this patient had a flow directed R*up* of 96%, but was also in the subgroup with multiple measurements and the wire directed additional measurement was 49% (the lowest in the whole operative cohort). Post-operative mPAP did not correlate with *Rups (figure 2)*. Haemodynamic variables at 3 months also demonstrated no correlation to R*ups* either using the flow directed measurements, or including the multiple sampling group (data not included) but our data was not statistically powered for this. Of interest R*up* did correlate moderately with PVR in the IPAH/ CTD PAH group r=0.59 p=0.03 *(figure 2)*.

Discussion

There are a number of observations to be made from this work. From a technical view-point we have demonstrated that R*up* measurements are reliably repeatable, although there are a significant proportion of subjects in whom they are not

obtainable. It is likely that there is an operator learning curve as demonstrated by the higher success rates towards the end of the study. There was significant heterogeneity when contralateral lung multiple wire-directed sites were sampled and compared to the flow directed measurements. It is possible that this represents the technical differences between a flow-directed measurement and a wire-directed measurement, which one might expect to end in a less well-perfused segment. This does fit well with our understanding of the differences between CTEPH and IPAH, and in particular the heterogeneity of disease distribution. Perhaps more surprising is the demonstration that although there are statistically significant differences in partitioned small vessel resistance between disease categories, there does appear to be a spectrum of resistance across all of the disease groups. This may have importance in understanding pathophysiology and response to treatment.

Flow-directed R*ups* are higher in operable predominantly proximal CTEPH than in inoperable CTEPH and IPAH/CTD. For the single measurement technique ROC curves demonstrate good sensitivity but lower specificity for distinguishing between operable and non-operable disease. One explanation for this is the heterogeneous nature of disease means that distal vasculopathy can be missed by a single measurement. Another explanation is that the technique partitions at a vessel size that misses significant downstream resistance. The occlusion technique is suggested to estimate pressure in vessels above 100-150μm (with the rest being made up of vessels below 150μm, capillaries and veins) [10]. Anatomical studies show that in humans the muscularized small arteries are to be found in vessels larger than 100μm [11]. These small muscularized arteries have long been held to be the major contributors to resistance in PAH [12]. It is therefore possible that the occlusion technique does not

interrogate the correct range of vessel calibre, or in other words is mislabelling a significant portion of resistance in these small vessels as upstream. If this is the case, it is possible that by changing the analysis of the decay curve we can capture more clinically relevant resistance in vessels larger than 100-150μm. The mislabelled resistance hypothesis is supported by the fact that the IPAH/CTD and distal CTEPH cohorts had a much higher Rup than would be expected if the resistance had been accurately partitioned into clinically relevant small and large vessels. Despite this there was a moderate correlation between R*up* and mPAP in IPAH/CTD. In other words, as would be expected in distal predominant pathology, as the distal component of resistance increases so does the pulmonary artery pressure. Therefore although Rup partitioning may miss a component of downstream resistance, it still increases relative to traditional haemodynamic parameters. The occlusion pressure technique is currently the only technique able to compartmentalise resistance in vivo.

In our studies a low single flow-directed R*up* was a risk factor for operative mortality. Previously a flow-directed R*up* of <60% was demonstrated to be a significant risk factor for mortality [5]. Both of the subjects who died in our cohort had a higher threshold than this (at 68% and 73%). The flow-directed R*ups* did not pick up the patients with significant post operative pulmonary hypertension. Although multiple sampling was not undertaken in all of the CTEPH subjects, if the multiple wire-directed values are included, the subject with the highest post-operative PVR also had the lowest R*up* in the operable cohort (49%). This subject had been identified as high risk pre-operatively with possible mixed proximal/distal disease and a PVR before targeted therapy of 1040 dynes/s/cm^5. There was a post operative fall in PA pressure and PVR and CTPA at 3 months confirmed clearance, but with some residual distal

disease. Despite this, post-operatively at 3 months targeted therapy had to be restarted after demonstration of significant residual pulmonary hypertension that had increased after withdrawal of bosentan. In addition the other subject in the multiple sampling group with a PVR of above 300 at 3 months (424 dynes/s/cm^5) had a wire directed Rup of 71.5%. Because multiple sampling was only obtained in a sub-group we cannot comment on its comparative benefit in the study. When multiple sites were sampled there was heterogeneity within different lobes. The heterogeneity of disease may mean it is possible to miss significant distal disease with one measurement, but the presence of a low R*up* is again confirmed to be an indicator of distal vasculopathy.

A potential criticism of this work is the definition of operable CTEPH. This is a difficult area as there is no gold standard definition of success. Additionally thresholds for surgical operability differ worldwide, mainly dependent on surgical experience. In our study the subjects were carefully diagnosed in a multidisciplinary meeting with 3-4 imaging modalities. We present in our analysis all the patients who survived the operation despite 6 subjects having PVRs above 300 dynes/s/cm^5. All of these patients were adjudged to have a good technical clearance by the attending surgeon and on subsequent imaging, with an immediate post-operative reduction in PVR and improvement in 6-minute walk. Regardless, if more stringent criteria are adopted (a post-operative PVR of below 300 dynes/s/cm^5) the same results are generated. Additionally it is possible that distal inoperable disease has been misclassified. To address this we performed a post hoc analysis case review to exclude anyone with any doubt about the clarity of the diagnosis of operable CTEPH vs non-operable (supplemental figure 1) but again this did not significantly alter our results. There remains the possibility that in the subjects diagnosed as inoperable,

there are proximal lesions contributing to vascular resistance. It is reassuring in this regard that our current screening criteria is confirmed by Rup analysis to select out patients with significant distal resistance. To mitigate this criticism we have included subjects with IPAH, CTD associated PAH and residual post-operative CTEPH. In these subjects, who have distal pathology, we see the same statistically significant difference in mean R*ups* but with a higher than expected proportion of upstream resistance.

In conclusion we have found that R*up* as measured by the occlusion technique is increased in operable predominantly proximal CTEPH when compared with inoperable CTEPH and IPAH/CTD. This technique is confirmed as reliable and repeatable and can be performed during standard right heart catheterisation. Given that all patients undergoing assessment for pulmonary endarterectomy have a right heart catheter as part of their work up, it would not be technically difficult or expensive to perform the analysis, although there is a demonstrable operator learning curve. As yet our data does not support the clinical use of this technique in routine assessment. If further work is to be done, thought needs to be given to the analysis of the decay curve, and wire-directed measurement may provide additional information on disease heterogeneity in CTEPH.

Table 1

	Age (SD)	Sex M/F	mPAP mmHg (SD)	sPAP mmHg (SD)	dPAP mmHg (SD)	Pulse Pressure mmHg (SD)	CO L/min (SD)	PVR dynes/ s/cm^5 (SD)	R*up* % (SD)	Intra-operative surgical classification	
										Left (%)	Right (%)
Operable proximal CTEPH (14)	52.9 (16)	6/8	50.7 (13)	80.8 (14.3)	30.9 (8.1)	46.1 (18.1)	3.8 (1.1)	927 (557)	86.7 (7.1)	Type I 14.3 Type II 28.5 Type III 57.2	Type I 7.1 Type II 50 Type III 36.8 Type IV 7.1
Inoperable CTEPH (15)	63.8 (8.5)	4/11	52.9 (10.1)	94.1 (17.1)	33.2 (7.3)	60.9 (14.6)	3.4 (1.0)	1056 (400)	75.8 (16.2)		
Post-op residual CTEPH (5)	63.3 (6.1)	1/4	42 (5.6)	72.8 (10.9)	24.6 (6.0)	48.2 (9.7)	4.7 (0.9)	564 (280)	77.1 (7.7)		
IPAH (9)/ CTD (4)	52.9 (16.3)	1/12	51.5 (12.8)	87.9 (22.1)	33.2 (9.6)	49.2 (23.6)	4.3 (1.1)	792 (317)	85.16 (3.8)		

Table 1: Haemodynamics of subjects

(SD) standard deviation; mPAP mean pulmonary artery pressure; CO cardiac output;

PVR pulmonary vascular resistance; R*up* upstream resistance

Table 2

	Diagnosis	pre- op PVR dynes/s/ cm^5	Flow Guided Rup (%)	Wire directed Rup (%)	Post-op 3 month PVR dynes/s/cm^5
Subject 1	Operable CTEPH	968	89.3	93	256
Subject 2	Operable CTEPH	416	96	49	1040
Subject 3	Operable CTEPH	800	94.5	71.5	424
Subject 4	Operable CTEPH	2216	73	90.8	Died
Subject 5	Inoperable CTEPH	1664	37	73	Not applicable
Subject 6	Inoperable CTEPH	1152	83.7	78	Not applicable
Subject 7	Inoperable CTEPH	1440	78	67	Not applicable

Table 2: Subjects with multiple sampling

PVR pulmonary vascular resistance; R*up* upstream resistance

Figure 1: R*up* in pulmonary hypertension

A R*up* in all groups. **B** R*up* if cut-off for successfully operable disease is set as a 3 month PVR of < 300 dynes/s/cm^5 **C** ROC curves for sensitivity/ specificity of the Rup in distinguishing operable from non-operable CTEPH

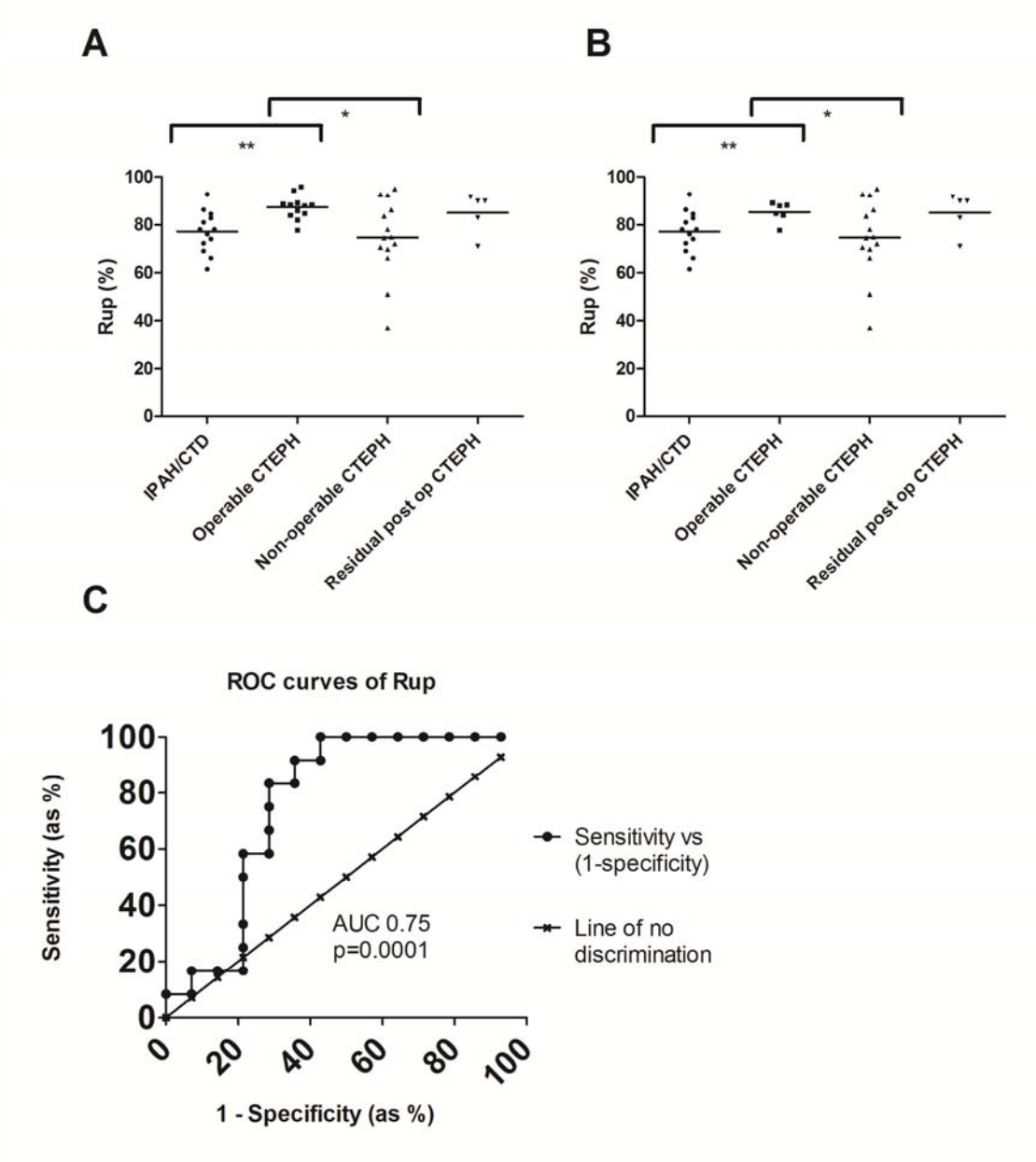
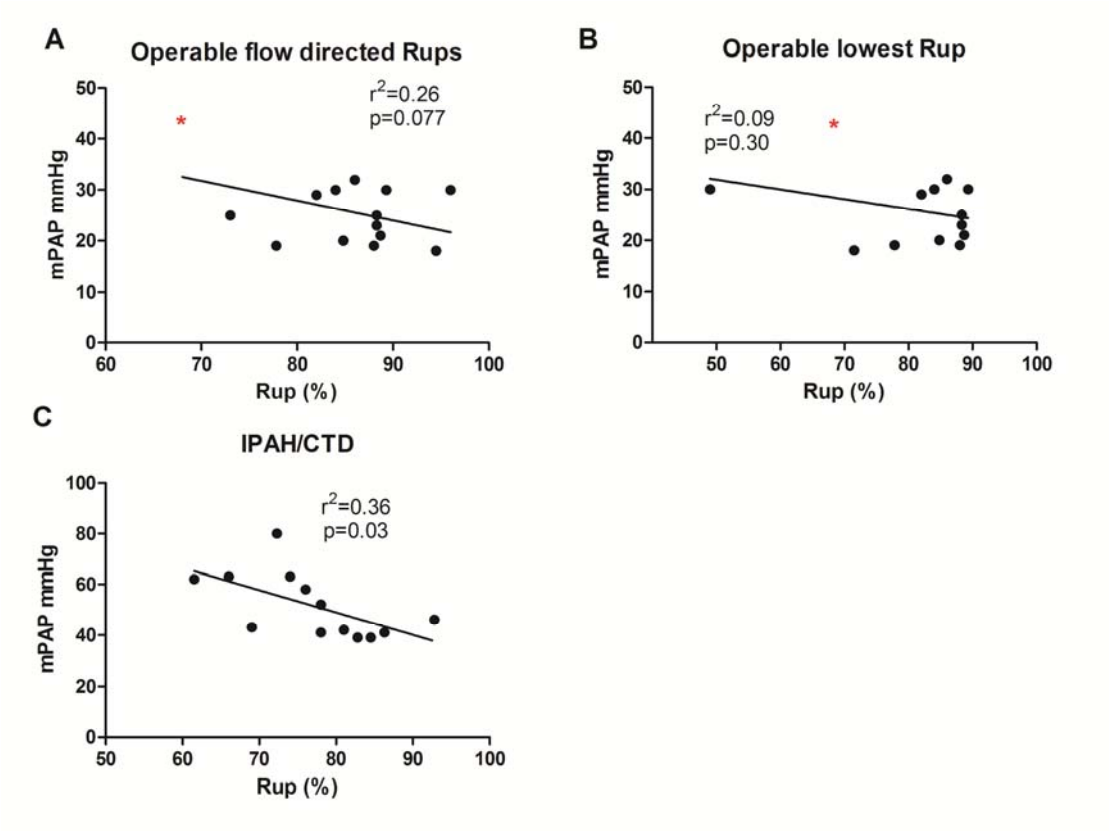


Figure 2: Correlations between Rup and immediate post operative mPAP in operable CTEPH and IPAH/CTD

A Correlation in operable cohort with flow-directed occlusion based measurements. * Subject died in post-operative period. **B** Correlation in operable cohort using the lowest measurement including flow-directed and wire-directed occlusion based measurements. **C** Correlation in idiopathic PAH and connective tissue disease associated PAH



References

([1)] D'Armini AM, Cattadori B, Monterosso C, Emmi V, Piovella F, Vigano M. Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension: hemodynamic characteristics and changes. *Eur J Cardiothorac Surg* 2000 December;18(6):696-701.

[2] Masuda M, Nakajima N. Our experience of surgical treatment for chronic pulmonary thromboembolism. *Ann Thorac Cardiovasc Surg* 2001 October;7(5):261-5.

[3] Tscholl D, Langer F, Wendler O, Wilkens H, Georg T, Schafers HJ. Pulmonary thromboendarterectomy--risk factors for early survival and hemodynamic improvement. *Eur J Cardiothorac Surg* 2001 June;19(6):771-6.

[4] Thistlethwaite PA, Kemp A, Du L, Madani MM, Jamieson SW. Outcomes of pulmonary endarterectomy for treatment of extreme thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg* 2006 February;131(2):307-13.

[5] Kim NH, Fesler P, Channick RN, Knowlton KU, Ben-Yehuda O, Lee SH, Naeije R, Rubin LJ. Preoperative partitioning of pulmonary vascular resistance correlates with early outcome after thromboendarterectomy for chronic thromboembolic pulmonary hypertension. *Circulation* 2004 January 6;109(1):18-22.

[6] Klepetko W, Mayer E, Sandoval J, Trulock EP, Vachiery JL, Dartevelle P, Pepke-Zaba J, Jamieson SW, Lang I, Corris P. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004 June 16;43(12 Suppl S):73S-80S.

[7] Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009 June 30;54(1 Suppl):S43-S54.

[8] Fesler P, Pagnamenta A, Vachiéry JL, Brimioulle S, Abdel Kafi S, Boonstra A, Delcroix M, Channick RN, Rubin LJ, Naeije R. Single arterial occlusion to locate resistance in patients with pulmonary hypertension. *Eur Respir J* 2003 January;21(1):31-6.

[9] Thistlethwaite PA, Mo M, Madani MM, Deutsch R, Blanchard D, Kapelanski DP, Jamieson SW. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg* 2002 December;124(6):1203-11.

[10] Kafi SA, Melot C, Vachiery JL, Brimioulle S, Naeije R. Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. *J Am Coll Cardiol* 1998 May;31(6):1372-6.

[11] Harris P & Heath D. The human pulmonary circulation.Edinburgh: Livingstone; 1962. p. 62-3.

[12] Wagenvoort CA, Wagenvoort N. Primary Pulmonary Hypertension: A Pathologic Study of the Lung Vessels in 156 Clinically Diagnosed Cases. *Circulation* 1970;42:1163-84.