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Early View

Research letter

Limitations of resting haemodynamics in chronic thromboembolic disease without pulmonary hypertension

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Limitations of resting haemodynamics in chronic thromboembolic disease without pulmonary hypertension

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There is renewed interest in the haemodynamic definitions of pulmonary hypertension reigniting an old debate about diagnostic thresholds (1). Recent prospective data supports work dating back over 40 years demonstrating patients with “borderline” pulmonary hypertension (PH), mean pulmonary artery pressure (mPAP) <25 mmHg, can still have significant morbidity and mortality (2). Therefore lowering the mPAP threshold for the diagnosis of precapillary PAH has been discussed at World Symposium on Pulmonary Hypertension in Nice in 2018. A potentially different approach has arisen in group 4 (chronic thromboembolic pulmonary hypertension (CTEPH)), where the concept of chronic thromboembolic disease without PH (CTED) has gained traction. This describes a population of patients with mPAP <25 mmHg, with no lower limit, who have persistent vascular obstructions, impaired response to exercise and a high impact of disease on symptoms and quality of life. The 25 mmHg threshold is important partly because it excludes patients who might benefit from treatment, and then precludes their participation in clinical trials, forming a cycle that prevents regulatory approved treatment in the future. In the CTED to CTEPH spectrum it is unclear if reducing the threshold is the best way to address this inequity, as minimal data exists detailing outcomes below 25mmHg. In the UK we have undertaken pulmonary endarterectomy (PEA) on a selected, symptomatic cohort of operable CTED patients with good results (3), which were recapitulated by others (4, 5). A valid criticism of our previous work (3) is the retrospective, selective nature of the subjects and a lack of understanding about the natural history of the disease without treatment. Here, we present the first prospective cohort of patients with operable CTED (IRB project reference S02297) and hypothesised that clinically meaningful symptoms, limitation and physiology would relate to haemodynamics. Royal Papworth Hospital is the

national PEA referral centre and to minimise tertiary speciality referral bias we have included only regional non-specialist referrals. Regional incident cases referred 2015-2017 with suspected CTED/CTEPH were prospectively assessed. All patients were reviewed at the national CTEPH MDT. Patients with operable CTED underwent standard CTEPH investigations (6) with additional exercise right heart catheterization (RHC) and incremental cardiopulmonary exercise testing (CPET)(7). Zero reference was set at the midthoracic level . During exercise RHC patients were asked to pedal for 5 min at 40% of workload achieved during incremental CPET (load range 9-104W, maximal supine exercise test could not been performed due to technical limitation of ergometer). The mPAP, pulmonary wedge pressure (measured over 3 breath cycles, when feasible), mixed venous saturation, heart rate (HR) and systemic blood pressure (BP) were measured followed by cardiac output (CO) measurement using the thermodilution technique. Pulmonary vascular resistance, total pulmonary resistance, cardiac index, pulmonary artery compliance and mPAP-CO slope were calculated. All patients diagnosed with operable CTED were followed up for a minimum of one year.

Baseline characteristics were expressed as numbers and percentages for categorical variables and mean ± standard deviation or median [interquartile range] for continuous variables according to data distribution. Between-group and within groups comparisons were made using the parametric and non-parametric test as appropriate. A p-value of <0.05 was considered significant. Correction for multiple testing where necessary was performed and both adjusted and unadjusted p-values were reported. Statistical analysis was performed with R (https://www.r-project.org).

Out of 176 patients referred for suspected CTED/CTEPH, 34 were diagnosed with CTED and 125 with CTEPH. An alternative diagnosis was made in the remaining 17 (multifactorial pulmonary hypertension – 7, asymptomatic with proximal persistent perfusion defects – 6, asymptomatic with distal persistent perfusion defects - 2, heart failure with preserved ejection fraction – 1, severe aortic stenosis – 1). CTED patients had technicaly operable disease. All patients were treated for at least three months with anticoagulation and were PAH-targeted therapy naïve. CTED patients were younger than CTEPH (54[39;66] vs 66[55;73] p=0.001), had a better functional status (WHO class I/II 50% vs 19% p<0.001) and higher 6MWT (396(123) vs 278(119) p<0.001). In CTED total pulmonary vascular obstruction index (TPVOI)(8) was lower (33%(14) vs 43%(14), p <0.001) and modestly correlated with mPAP (r=0.25, p<0.001).

Fifteen patients had a resting mPAP between 21 and 24 mmHg and 19 had mPAP ≤20 mmHg. There were no between-group differences in age, BMI, comorbidities, WHO class, 6MWT, symptom scoring or functional assessment. Exercise RHC at 40% of maximal load (n=25) demonstrated an increase from baseline in mPAP, CO and drop of TPR (Table 1). There was a strong correlation between resting and exercise mPAP (r=0.66 [0.36;0.84], p=0.004). Six of the 34 patients were offered and accepted surgical treatment. The decision regarding surgery was made in CTEPH MDT meeting and was independent of the study and based on the results of clinical tests, quality of life, comorbidities, risk-benefit ratio and patient preferences. Operated patients were characterised by lower peak O_2 consumption (peakVO_2) and peak O_2 pulse, higher ventilatory equivalents for CO_2 at anaerobic threshold (VE/CO_2 at AT) and TPVOI, and worse self-reported QoL (Table1).

There was no operative mortality in this cohort. Non-operated patients were followed-up for a minimum of 1 year. None of the patients were treated with PAH targeted therapy but all were anticoagulated. In non-operated patients, CAMPHOR symptoms (11[5;16] vs 1 year 9[6;15]) and QoL (5[1;12] vs 6[4;11]) did not change. There were no significant differences in peakVO_2 (94%[83;100] vs 1 year 104%[83;110]), 6MWT (388m[362;460] vs 419m[330.5;511]) or NT-proBNP (55pg/dl[32;82] vs 65pg/dl[36;112]). Two patients died within one-year, both malignancy-related. One patient delayed follow-up for treatment of a new cancer and 6 patients were clinically stable, electing to have follow-up at their local centre. At 3 to 6 months follow-up, operated patients showed haemodynamic (mPAP 21(2) vs 16(3) mmHg, p=0.007), symptomatic (CAMPHOR symptoms 14(5) vs 7(6), p=0.029) and functional (6MWD 404m(118) vs 454m(109), p=0.006) improvement. Furthermore, CPET ventilatory measures also improved (VE/VCO_2 at AT 42(5) vs 33(5), p = 0.003, $PETCO_2$ at AT 27(3) vs 34(3) mmHg, p=0.009).

This is the first prospective cohort of patients systematically assessed for operable CTED with medium-term follow-up. Most patients are not offered surgery, and remain symptomatic, but are clinically and objectively stable, therefore treatment options can be carefully considered. Despite the small cohort of patients undergoing PEA, there were significant differences, consistent with our previous reports, in baseline physiology on exertion, and CAMPHOR scores in QoL (3, 9-11).

We are therefore operating on a sub-group of patients where resting haemodynamics are of limited use, but who have worse pathological and physiological impairment on exercise,

and who self-report a lower quality of life. Although resting haemodynamics are critical to establishing the diagnosis of pulmonary hypertension, a more lenient definition of PH to 20 mmHg will be of debatable additional benefit as symptoms and abnormal physiology do not relate to resting pressures or pulmonary resistance. Consistent with our retrospective study where 48% of the operated population had an mPAP of ≤20 mmHg, in our prospective study of predominantly non-operated patients this was 56%. With the advent of balloon pulmonary angioplasty, medical therapeutic options and physical rehabilitation programmes there is now a need for consensus on disease classification. International prospective registry data will be critical in guiding this effort. Our data reinforces the concept that for technically operable CTED/CTEPH patients, lowering the haemodynamic thresholds may still miss symptomatic patients with abnormal physiology. Notably, all but one of our patients were under the 3 WU threshold. We demonstrate that patients can have a clinically meaningful burden of disease with impaired physiology and report significant symptoms in the context of “normal” resting haemodynamics. Studies in this group of patients will need a different trial design from traditional PAH and CTEPH studies. Resting haemodynamics and 6-minute walk test are unlikely to be feasible endpoints, time to clinical worsening will not be useful and more extensive exercise physiology measurements will be required to fully interrogate symptomatic limitation.

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Table 1. Cohort characteristics

	All (n=34)	21-24 mmHg (n=15)	≤ 20 mmHg (n=19)	p-value	Non-operated (n=28)	Operated (n=6)	p-value
Age [years] §	53 (17)	58 (16)	48 (17)	0.087	55 (17)	43 (14)	0.103
WHO FC†				0.187			0.842
1	4 (12%)	0 (0%)	4 (21%)		4 (14%)	0 (0%)	
2	13 (38%)	7 (47%)	6 (32%)		10 (36%)	3 (50%)	
3	17 (50%)	8 (53%)	9 (47%)		14 (50%)	3 (50%)	
CAMPHOR							
Symptom§	11 (7)	12 (5)	10 (8)	0.308	10 (7)	14 (5)	0.141
Activity‡	6 [3;12]	7 [5;13]	3 [2;11]	0.139	6 [2;11]	6 [4;11]	0.833
QoL‡	5 [1;13]	6 [3;13]	5 [0;14]	0.556	4 [0;12]	14 [9;16]	0.030
BMI [kg/m^2] §	29 (5)	30 (4)	28 (6)	0.307	29 (6)	28 (3)	0.643
6MWT [m] §	402 (114)	389 (115)	412 (116)	0.598	401 (116)	404 (118)	0.955
Peak VO_2 % predicted§	88 (17)	83 (11)	91 (20)	0.142	92 (16)	70 (10)	0.001*
Peak O_2 pulse % predicted §	88 (22)	85 (19)	91 (24)	0.459	93.9 (20.1)	65.2 (9.70)	<0.001*
VE/VCO_2 at AT [mmHg] §	36 (8)	38 (8)	35 (7)	0.310	34 (7)	43 (6)	0.009*
mPAP [mmHg]	20 [18;22]	23 [22;23]]	18 [15;19]	<0.001*	20 [16;22]	22 [20;23]	0.159
CO [L/min] §	5.3 (1.0)	5.3 (1.1)	5.2 (1.0)	0.959	5.3 (1.0)	4.9 (1.2)	0.409
PVR [WU] ‡	1.9 [1.4;2.4]	2.3 [2.0;2.8]	1.4 [1.2;1.8]	0.003*	1.7 [1.3;2.2]	2.5 [2.2;2.6]	0.061
TPR [WU] ‡	3.7 [3.1;4.2]	4.1 [3.7;4.8]	3.2 [2.8;3.7]	0.001*	3.6 [3.0;4.0]	4.2 [4.0;4.4]	0.071
PAC [ml/mmHg]	4.1 [2.8;5.6]	3 [2.6;4.4]	4.7 [3.9;5.7]	0.058	4.4 [2.8;5.6]	3.8 [2.9;4.0]	0.633
Exercise mPAP [mmHg] §	29 (7)	34 (7)	26 (5)	0.006*	30 (8)	28 (3)	0.582
Exercise TPR [WU] ‡	2.7 [2.2;3.6]	3.5 [2.6;3.7]	2.3 [2.1;2.9]	0.022	2.9 [2.2;3.7]	2.6 [2.3;2.9]	0.505

Exercise CO [L/min] §	10.4 (3.1)	10.0 (2.1)	10.9 (3.9)	0.497	10.4 (3.4)	10.9 (1.4)	0.591
mPAP-CO slope	1.6 [1.1;3.4]	2.8 [1.4;3.7]	1.5 [1.1;2.5]	0.301	2.5 [1.4;4.0]	1.1 [1.0;1.2]	0.088
TPVOI [%]†	34 (14)	37 (13)	31 (15)	0.287	31 (13)	51 (6)	0.001*

Data shown as † n (%) § mean (SD) or ‡ median [interquartile range] dependent on normality distribution; WHO FC - World Health Organisation functional class, 6MWT – 6-minute walk test, mPAP - mean pulmonary artery pressure, CO - cardiac output, TPR – total pulmonary resistance, BMI – body mass index, peak VO_2 – peak oxygen consumption, peak O_2 pulse – peak oxygen pulse, VE/VCO_2 at AT – ventilatory equivalents for carbon dioxide at anaerobic threshold, TPVOI – total pulmonary vascular obstruction index(8), * Significant after False Discovery Rate (FDR) correction