

Chronic thromboembolic pulmonary hypertension: time for research in pathophysiology to catch up with developments in treatment

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Abstract

The modern treatment era in chronic thromboembolic disease has seen significant advances in both surgical and medical treatment. One such treatment, the pulmonary endarterectomy (where established chronic organized thrombus is removed), has dramatically affected morbidity and mortality. These advances have outstripped basic research into the causes and pathophysiology of disease, which remain largely poorly understood. In this review, we will set out to explain some of the historical reasons for this, including the difficulties inherent in human studies and the lack of good animal models. We will review some of the recent advances in pathophysiology from registries and translational research, and we will summarize the treatment options, with some discussion of very recently published work, including medical and surgical treatments, both traditional and more experimental work in non-invasive techniques.

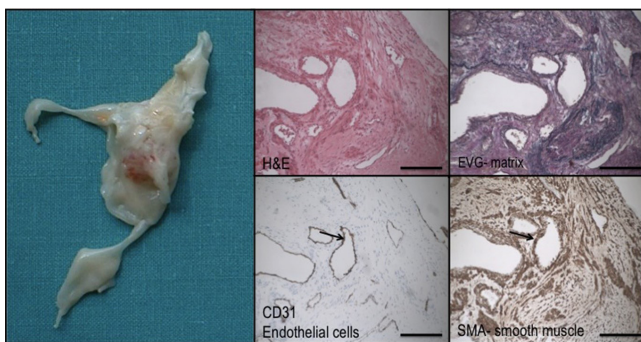
Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) represents the consequences of failure of thrombus resolution after the establishment of thrombosis within the elastic pulmonary arteries. Thrombotic material becomes fibrosed, with occlusive vascular remodeling and the development of a secondary small vessel arteriopathy, termed the two-compartment model [1], and a resultant increase in pressure and vascular resistance in the pulmonary vasculature. This leads eventually to right heart failure. Pathologically, within the organized thrombus, there is deposition of matrix, mixed cellularity and variable small vessel recanalization (Figure 1). There is heterogeneity of all of these processes in specimens from pulmonary endarterectomy [2], partly depending on the freshness of thrombus. The angiogenesis or neovascularization seen within the thrombus is not to be confused with bronchial collateralization (which also occurs in CTEPH), and depends on the vasa vasorum of the systemic bronchial arteries. There are, however, suggestions that the ability to neovascularize the thrombus may influence the

clinical course in animal models, as described more fully in a recent review [3] and discussed later.

CTEPH was first recognized as a potential consequence of pulmonary emboli as far back as the 1920s [4] but has only gained prominence in the last 15 years after the advent of potentially curative surgical techniques. With greater awareness of the disease, it is being more widely recognized, with estimates following an episode of acute pulmonary embolus ranging from 0.8 to 8% in autopsy series, US healthcare insurance databases, and retrospective and prospective studies [5-10]. To put this into perspective, this would mean a prevalence of between 11 and 109 per million cases. These estimates do not take into account the rates of cases presenting with no acute pulmonary embolus, which can range anywhere from 25 to 63% of all cases with CTEPH [11-13]. The advent of the pulmonary endarterectomy, pioneered by Jamieson and his colleagues in San Diego [14], has sharpened attention on this orphan disease, with significant improvements in both mortality and morbidity. Despite the added

Figure 1. Macroscopic image of specimen from pulmonary endarterectomy



Microscopic organised thrombus from established distal tail of specimen with matrix deposition, endothelial channels and smooth muscle cells/myofibroblasts distributed throughout the specimen. Scale bar = 100 μ m. Abbreviations: H&E, haematoxylin and eosin staining; EVG, elastic van Gieson staining (black = elastin, red = collagen; SMA, smooth muscle actin).

focus this has provided, our understanding of the pathobiology has not progressed in parallel. This review will clarify current understanding of disease pathophysiology, introduce the difficulties of relevant animal and human models and discuss exciting new treatment developments, both in medical and surgical management.

Pathophysiology: what are the problems?

The process of coagulation and fibrinolysis is well-studied and summarized elsewhere extensively [15,16]. Despite this, we still do not understand what happens when these pathways fail. There are two critical barriers in human studies. The first is studying the right patients at the right time. As discussed earlier, although estimates vary, between 0.5 and 8 in 100 patients with acute pulmonary embolus will develop CTEPH. Therefore, to capture the relevant phase of their disease (where clot resolution is failing) would require the screening of very large numbers of patients from presentation. The second factor is equally important: the simple inability to study patients off anti-coagulation. Almost all patients will be treated with anti-coagulation drugs and this makes the interpretation of the major pathways of thrombus formation and resolution technically very challenging. By definition, CTEPH will not be diagnosed unless there is chronic evidence of disease on anti-coagulation (usually for a period of 3-6 months) [17]. Therefore, it is difficult to interpret coagulation and fibrinolysis pathways in this context.

Does more thrombus form?

Despite the difficulties in studying patients, some surprising findings are made apparent from demographic analyses.

The many known factors associated with thrombosis are not uniformly associated with CTEPH. For example, the classical risk factors for recurrent thrombosis, such as antithrombin deficiency, protein C and S, prothrombin mutations and factor V Leiden, are not independently associated with CTEPH [13]. In other words, factors that increase the risk of thrombosis will be present in the CTEPH population but not necessarily more than in populations of patients with deep vein thrombosis (DVT) or pulmonary emboli. There are, however, several risk factors emerging robustly from international registries. These include iatrogenic physical causes of thrombus, such as ventriculoarterial shunts, and indwelling venous catheters and leads. Other important risk factors include inflammatory bowel disease, non-O blood group, malignancy, splenectomy and thyroid replacement [13].

Despite the lack of association of some traditional thrombotic risk factors, there is evidence of a prothrombotic milieu. Plasma concentrations of factor VIII and von Willebrand Factor, which circulate bound to each other, are increased in CTEPH [18]. In 122 patients with CTEPH, levels were significantly elevated (233 \pm 83IU/dL) *vs.* healthy controls (123 \pm 40IU/dL) and a disease comparator group of other pulmonary arterial hypertension ([PAH] 158 \pm 61IU/dL). Of note, this study did not compare levels to the obvious disease control of patients with resolved pulmonary emboli, but the levels were potentially biologically significant. The elevated levels of von Willebrand Factor persisted after a successful pulmonary endarterectomy, suggesting more than a bystander role in the context of established thromboembolism. In addition to a prothrombotic milieu, some groups are also contending that there is an, as yet, unclearly delineated role for inflammation. The C-reactive protein has been noted to be elevated in CTEPH *vs.* healthy controls (4.9 *vs.* 2.3 mg) and weakly correlates with New York Heart Association measures of disease severity and 6-minute walk distance [19]. It has been suggested that tumor necrosis factor (TNF) and interleukin-6 are increased, though compared to post-pulmonary endarterectomy sampling and not controls [20], and monocyte chemoattractant protein-1 has also been found to be correlated to hemodynamics in CTEPH (though in this study TNF was not) [21]. This study also did not compare to a control group, describing in-group correlations. Related to inflammation, it has been suggested that chronic infection is associated with CTEPH. However, the best evidence is observational in ventriculoarterial shunts and pacemaker lines associated with CTEPH, where DNA from *Staphylococcus aureus* was found in explanted tissue from pulmonary endarterectomy in patients already suspected of having chronic infection [22]. Given that this

is a small sub-group of patients with CTEPH, and the possible contribution of low-level chronic inflammation rather than the infection primarily, it is difficult to be clear on the relevance of these findings.

Is thrombus resolution significantly impaired?

Impaired fibrinolysis is the next obvious area for study. Plasminogen activator inhibitor-1, an inhibitor of fibrinolysis, is increased in endothelial cells lining fresh thrombus in conjunction with low tissue-type plasminogen activator antigen levels, suggesting that the endothelium interaction with thrombus may be phenotypically altered [23]. Myofibroblasts postulated to be potential multipotent mesenchymal progenitors are a prominent feature of established thrombus and it is not yet clear if they have a positive or negative effect in fibrotic repair/misrepair [24]. Morris *et al.* demonstrated a relative resistance of patient fibrin to plasmin-mediated lysis in patients with CTEPH, though the effect was modest [25]. We have previously demonstrated a potential genetic susceptibility with an increase in the fibrinogen A α Thr312Ala polymorphism in CTEPH (35.5%) *vs.* normal controls (27.5%, $P = 0.03$) [26]. This has subsequently been confirmed in a Chinese population where they additionally demonstrated an increase when compared to a patient cohort of pulmonary embolus [27]. This polymorphism has been demonstrated to modify fibrin structure in clots with increased alpha chain cross-linking [28]. Subsequently, Morris *et al.* have gone on to show that in a small cohort of 33 patients with CTEPH, five fibrinogen variants with corresponding heterozygous gene mutations were observed: B β P235L/ γ R375W, B β P235L/ γ Y114H, B β P235L, A α L69H, and A α R554H [29]. Further extending this work, they have demonstrated that, compared to normal fibrinogen, CTEPH-associated dysfibrinogenemias exhibited fibrinolytic resistance [30]. It does, therefore, appear that mutations in fibrinogen have a potential causative role, though their impact has not yet been fully established.

Are these problems not amenable to animal modeling?

Although acute embolism is not difficult to mimic or induce, thrombus resolution has proven intractable to model accurately. This is perhaps unsurprising given the relative low frequency in human studies. Models have focused on trying to replicate the physiology of disease. The traditional reliance on lower cost murine models has significantly hampered this. For example, pathologically, CTEPH will often involve significant bronchial collateralization, but the mouse does not have a collateral circulation. Fibrinolytic pathways vary in animal models [31], and there is the additional problem of the

two-compartment model. This model is generally accepted and states that, in addition to an obstructed vascular bed, there is a second “compartment” of unobstructed vasculature, subject to increased flow, high pressures, shear stress and the development of small vessel changes typical in other forms of pulmonary hypertension [1]. Some features, such as plexiform lesions, have been difficult to model across all pulmonary hypertension animal models, not just CTEPH. The most recent attempt to resolve some of these issues used a piglet model with a left pulmonary artery ligation and weekly embolization with Histoacryl, a tissue adhesive [31]. This achieved a good medium-term increase in pulmonary vascular resistance (PVR) with significant pulmonary vascular remodeling. This will be useful in assessing therapies and right ventricular remodeling, but not in understanding pathogenesis. An example of how animal models may help pathophysiology was very recently published looking at splenectomies in mice [32]. Well established (as discussed earlier) as a risk factor, this was modeled in mice, where a splenectomy was combined with stagnant flow mimicking DVT. Larger and more persistent thrombus was linked to an increase in circulating microparticles and negatively charged phospholipids [32]. The stagnant flow model has also been used very recently to try to understand the contribution of impaired neovascularization to disease progression, with endothelial cell-specific deletion of *Kdr* and stagnant venous flow, perhaps not unexpectedly influencing thrombus resolution [33]. The contribution of the endothelial cell itself to both the impaired resolution of thrombus and neoangiogenesis is poorly understood and could be addressed using mouse models. We do know from human studies that pulmonary artery endothelial cells from CTEPH patients may be subtly different with, for example, different responses to mitogenic stimuli *in vitro* [34], and the cellular origins of some of the endothelial channels have been called into question with the demonstration of CD133+ve endothelial cells in the neovessels [35].

How do the pulmonary circuit and heart adapt?

The right ventricle undergoes a process of “left ventricularization” in response to increased afterload as assessed by conductance catheter pressure volume loops [36]. Interestingly, this can be seen even without the development of pulmonary hypertension, in patients with significant chronic thromboembolic disease and pulmonary artery pressures <25 mmHg. Increased resistance, decreased compliance and hence increased afterload contribute to diastolic, as well as systolic, dysfunction. This process, in the context of CTEPH, is potentially reversible with some reverse remodeling demonstrated after pulmonary endarterectomy [37]. There is some debate about whether these

relationships are fixed through the spectrum of diseases causing pulmonary hypertension but, in proximal operable CTEPH at least, it appears that decreased compliance can be demonstrated, potentially putting an extra burden on the right ventricle [38]. With increased awareness of CTEPH, the field is recognizing an increasing proportion of patients with chronic thromboembolic disease without PAH, and as yet it is not clear if these patients are being picked up earlier in their disease process (and have, therefore, not developed PAH/right ventricle dysfunction), or if they are adapting better for as yet unknown reasons. This area is fertile for future research and may provide insights into the differences in right ventricle adaptation.

Treatment: a surgical success story

Without question, the major success in CTEPH has been the development of the pulmonary endarterectomy. Mortality rates have come down, with the best centers now routinely describing rates comparable to more commonly undertaken cardiothoracic procedures, and most series will demonstrate reductions in PVR in the region of 400-500 $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$ [39-41]. San Diego, the most experienced world center with the largest historical cohort reports on an in-hospital mortality rate now down to 2.2%. At our center, contemporaneous in-hospital mortality is 2-3% [42]. These compare favorably with improvements made with medical therapy in other pulmonary hypertension disease classes, and long-term survival at 5 years in experienced centers is around 90%. The symptomatic improvements seen are maintained in a long-term follow-up [39-41]. Therefore, despite the initial controversy of the operation, the undoubted institutional learning curve required, and the high mortality rates in the early days, the pulmonary endarterectomy has established itself as the gold standard in CTEPH treatment. It has unequivocally proven that, despite the two-compartment model suggesting that thrombus removal alone would not abolish disease, curative treatment is a possibility if resistance comes down enough. This is an important lesson for the other causes of pulmonary hypertension.

Despite the success of the pulmonary endarterectomy, not all patients are suitable for surgical intervention. This is predominantly related to the distal, surgically inaccessible distribution of thrombus, and additional co-morbidities. Medical therapies have, so far, been less successful in this group. The broad success of the vasodilation therapeutic strategy in group I PAH has not been as convincingly replicated in CTEPH. Despite initially promising open-label studies, the first double-blinded randomized control trials (RCT) in sildenafil and bosentan were equivocal, using the traditional endpoints of the 6-minute walk

distance and hemodynamics [43,44]. There is a debate around the correct endpoints for pulmonary hypertension, but this is outside the scope of this review. For clarity purposes, the trials in class 1 PAH single therapies were generally positive using these endpoints and are directly comparable. Last year, however, the first definitively positive large-scale trial was reported with a novel compound, riociguat, which targets pulmonary vasodilation through soluble guanyl cyclase stimulation. The CHEST-1 double-blinded RCT in 261 patients with inoperable and post-operative residual disease reported a 6-minute walk distance improvement of 39 m, compared with a decrease of 6 m in the placebo group (95% confidence interval, 25 to 67; $P < 0.001$). PVR decreased by 226 $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$ compared with a decrease of 23 $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$ in the placebo group (95% confidence interval, -303 to -190; $P < 0.001$). It is still not clear why the more traditional and established vasodilators were apparently less successful in CTEPH, though caution is needed in overinterpreting a small sample size of only two RCTs.

Surgery, therefore, is well established, and medical therapy is establishing a role in inoperable disease. More controversial is the emergence of less-invasive operative techniques. The first reported case series of balloon angioplasty was in 2001 by Feinstein and his colleagues in Boston [45]. The technique met with initial skepticism, and was not repeated in more than sporadic cases, until 2012 [46]. A series of case studies, predominantly from Japan [47-50], have now confirmed that balloon angioplasty is feasible and potentially results in significant lowering of PVR and improvements in morbidity, though there is variation in both endpoints and results. However, there are some significant caveats to the interpretation of this work. Firstly, although the stated intention of the majority of these studies was to trial inoperable CTEPH, it is clear from some of the reporting that patients were included who would have been deemed operable in other centers. For example, Sugimura *et al.* [48] report 12 cases where the mean segmental procedure was 14, which would definitely be deemed technically operable by most specialist centers. In addition, the lack of well-developed pulmonary endarterectomy services has been a significant driver of this innovation, meaning the assessment for operability is in the hands of less experienced operators. The procedures are long, involve multiple visits (an average of three-four), high doses of radiation, significant rates of reperfusion injury and the additional risk of pulmonary dissection. Despite these caveats, we feel it is likely that angioplasty has a role, and careful multi-center randomized trials with well-phenotyped and -characterized patients are now needed.

Conclusions

The international visibility of CTEPH has never been higher, driven largely by innovations in treatment. Research in pathophysiology is lagging significantly behind, partly for technical reasons. It is likely that a better understanding of the pathophysiology will help identify at-risk patients, changing the treatment paradigm to a preventative strategy. As yet this remains only an aspiration, and will not impact on the significant population who do not present with acute venous thromboembolism. Although traditionally viewed as a rare disease, CTEPH is actually not an uncommon complication of a common disease, and these authors think that the advent of large-scale registries, efforts to improve animal models and affordable genome-wide screening tools will see the uncovering of novel contributors to pathophysiology. Until then, the pulmonary endarterectomy leads the way as a treatment paradigm and demonstrates that pathophysiology can be reverse remodeled, with important lessons for consideration across the pulmonary hypertension disease spectrum.

Abbreviations

CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; TNF, tumor necrosis factor; RCT, randomized control trials.

Disclosures

The authors declare that they have no disclosures.

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