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Contribution of cardiac implantable electronic devices (CIEDs) to thrombus formation in patients with chronic thromboembolic pulmonary hypertension (CTEPH)

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Abstract
Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating disease, now potentially curable with the advent of pulmonary thromboendarterectomy (PTE).
Objective: This study aimed to identify the prevalence of cardiac implantable electronic devices (CIEDs) in the PTE population and describe associated disease burden. The contribution of CIEDs to thrombosis in this patient population has not been previously studied.
Methods: The charts of 982 CTEPH patients, who underwent PTE between January 1, 2009 and December 31, 2015 at UC San Diego (UCSD) Medical Center, were reviewed for pacemaker or ICD leads implanted prior to surgery. All statistical analyses were completed using SPSS software. Continuous variables were analyzed with t-tests for normally distributed data; categorical variables were compared with chi-squares.
Results: Among 982 total CTEPH patients who underwent PTE, 14 had pacemakers and 3 had ICD leads, for a total of 17 CIEDs and a prevalence of 1.7%. Of these 17 CIEDs, 6 devices were extracted intraoperatively, and 5 of 6 devices were replaced with epicardial leads. Furthermore, of the 950 patients classified by intraoperative UCSD Level, 12 of 17 (70.6%) patients with CIEDs had distal disease versus 241 of 933 (25.8%) patients without CIEDs (p =.0002). The prevalence of known venous thromboembolism (VTE) was 50% in CIED patients compared to 78.6% in patients without CIEDs (p=.018). There were no significant differences in demographics, preoperative hemodynamics, and postoperative hemodynamics between CTEPH patients with CIEDs and those without CIEDs.
Conclusion: At 1.7%, the prevalence of CIEDs in the PTE population is higher than previously reported values, which estimated CIED prevalence between 0.16% and 0.47% in the general population. Moreover, CTEPH patients with CIEDs are more strongly associated with distal disease burden and less likely to have had prior VTE, suggesting that CIEDs may be a nidus for small clots which embolize distally in the pulmonary vasculature.

Introduction
Pulmonary hypertension, characterized by mean arterial pressure ≥25mm Hg at rest in the pulmonary vasculature, is a progressive and debilitating disease with a number of underlying etiologies.[1,2] One such cause of pulmonary hypertension is chronic pulmonary thromboembolic disease, characterized by recurrent, obstructive clots within the pulmonary vasculature.[3] Thrombi within the pulmonary vasculature can occur in the aftermath of an incompletely resorbed pulmonary embolism (PE), and over time, constant obstruction and vascular remodeling within the pulmonary artery can lead to chronic thromboembolic pulmonary hypertension (CTEPH).[4]

Unlike other causes of severe pulmonary hypertension, CTEPH is potentially curable without lung transplantation through a surgical procedure known as pulmonary thromboendarterectomy (PTE). The surgery effectively removes obstructing thrombi from the pulmonary vasculature and significantly reduces disease burden by improving V/Q mismatch, right heart dysfunction, and tricuspid regurgitation.[1,2,5] PTE has achieved remarkable results in decreasing CTEPH disease burden and can deliver a complete cure in greater than 90% of patients.[5,6]

One of the central questions when thinking about CTEPH is why some patients are more susceptible than others in developing recurrent thromboembolic disease. CTEPH patients are likely more coagulopathic than the general population but it is important to consider other contributing factors as well. We have observed incidental lead thrombi in CTEPH patients with cardiac implantable electronic devices (CIEDs), suggesting that leads may be a nidus for clot formation in these patients. Leads as a potential contributor to thrombus formation in CTEPH patients is a topic that has not been formally studied in the literature. This study aimed to identify the prevalence of CIEDs in patients who underwent PTE at UCSD Medical Center and describe associated disease burden.

Methods

Chart Review

The study included 982 patients who underwent PTE between January 1, 2009 and December 31, 2015 at UCSD Medical Center. Each patient's electronic medical record was reviewed for presence of CIED implanted prior to surgery. Device type and model, lead indication and intraoperative changes in lead management including extraction and replacement were obtained. Demographic information, including age, sex, BMI, functional capacity (WHO), and comorbidities, was collected. Preoperative and postoperative hemodynamic data were also recorded.

Level of Disease

During surgery, the endarterectomy specimens of CTEPH patients are classified by intraoperative UCSD level depending on what level of the pulmonary vasculature has been affected. The classification system is as follows: Type 1 refers to proximal, large vessel clot in the main pulmonary artery. Type 2 refers to chronic, fibrotic disease in the main pulmonary artery and clot in lobar vessels. Type 3 represents distal clot in segmental and subsegmental branches. Finally, Type 4 disease affects intrinsic small vessels and is often inoperable.[5,6] Patients with Type III or IV lesions bilaterally are designated as having distal disease; all other patients are classified as having proximal disease. During chart review, each patient's disease level was documented from the PTE operative notes.

Statistical Analysis

All statistical analyses were completed using SPSS software. Continuous variables were expressed as mean ± standard deviation; categorical variables were expressed as counts and percentages. Continuous variables were analyzed with Student's t-tests for normally distributed data. Categorical variables were compared with chi-squares and Fisher's exact test for small sample sizes. A two-sided p-value of <0.05 was used for all analyses.

Results

Demographics

The study included 17 CTEPH patients with CIEDs (70.6% male; mean age, 58.0 ± 14.4 years) and 965 CTEPH patients without CIEDs (51.2% male; mean age, 52.1 ± 14.7 years).

Compared to CTEPH patients without CIEDs , patients with CIEDs had a distribution of World Health Organization (WHO) functional class that was more severe (p=0.03). The CIED group had higher prevalence of coronary artery disease (35.3% vs. 14.4%, p= 0.02) and chronic kidney disease (29.4% vs. 13.3%, p=0.05), but other comorbidities such as diabetes, hypertension, hyperlipidemia, COPD, and asthma were similar between the two groups. The prevalence of known prior VTE was 50% in CIED patients compared to 78.6% in patients without CIEDs (p=.018). Additional demographic information is shown in Table 1.

Preoperative and Postoperative Hemodynamics

As shown in Table 2, CTEPH patients with CIEDs had a preoperative mean pulmonary artery (PA) pressure of 41.8 ± 6.1 mmHg, cardiac index of 2.2 ± 0.5 L/min/m^2, and pulmonary vascular resistance (PVR) of 600.9 ± 243.0 dyn-s/cm^5. CTEPH patients without CIEDs had comparable preoperative hemodynamics (Table 2). CTEPH patients with CIEDs had a left ventricular ejection fraction (LVEF) of 62.9 ± 11.9% compared with an LVEF of 67.4 ± 7.0% in CTEPH patients without CIEDs (p = 0.01)

Postoperatively, CTEPH patients with CIEDs did not significantly differ from those without CIEDs in mean PA pressure (25.8 ± 7.4 mmHg vs. 24.3 ± 7.2 mmHg; p = 0.42). Final mean PVR in the CIED group was 256.9 ± 106.0 dyn-s/cm^5 compared with 242.0 ± 122.2 dyn-s/cm^5 in patients without CIEDs (p = 0.63). The change in PVR between groups following surgery was also not significant (343.9 ± 242.3 dyn-s/cm^5 vs. 429.5 ± 328.7 dyn-s/cm^5, p = 0.09; Table 3).

Prevalence of CIEDs in PTE population

Among 982 total CTEPH patients who underwent PTE, 14 had pacemakers and 3 had ICD leads giving a total of 17 CIEDs, for a prevalence of 1.7%. The 14 pacemakers were further categorized as dual chamber (n=7), single chamber unipolar (n=1), single chamber bipolar (n=1), and unknown (n=5), and all 3 of the ICD devices were dual chamber. Indications for CIED placement included sick sinus syndrome (n=9), symptomatic bradycardia (n=2), idiopathic cardiomyopathy (n=2) third degree AV block (n=1), tachycardia-bradycardia syndrome (n=1), prolonged QT syndrome (n=1), and junctional rhythm (n=1).

Intraoperative Lead Management and Level of Disease

Among the 17 CTEPH patients with CIEDs, 6 patients (35.3%) had their devices extracted intraoperatively, and 5 of these 6 patients (83.3%) had their devices replaced with epicardial leads (Table 4). One patient had a new dual chamber permanent pacemaker placed during surgery. Furthermore, patients with CIED had more distal chronic thromboembolic disease than those without devices defined as UCSD level III or IV. Of the 950 patients classified by intraoperative UCSD level, 12 of 17 (70.6%) patients with CIEDs had distal disease versus 241 of 933 (25.8%) patients without CIEDs (p =.0002; Table 5).

Discussion

In this retrospective analysis of patients referred for pulmonary thromboendarterectomy, we found a CIED prevalence of 1.7% among patients with CTEPH; furthermore, CIED was associated with an increased prevalence of distal chronic thromboembolic disease. The prevalence of CIEDs in worldwide or national populations has not been well described in the cardiac electrophysiology literature. A number of national registries have focused on recent trends in pacemaker incidence and evolving lead technology, but do not specifically study prevalence.[7-10] Previous studies conducted in the United States and Denmark in the 1990s estimated CIED prevalence in the general population as 0.26% and 0.16%, respectively.[11,12] A more recent study from Australia has described prevalence of 0.47%.[13]

At 1.7%, the CIED prevalence in the UCSD PTE population is much higher than all previously reported national estimates of CIEDs in the general population. Futhermore, the incidence of known VTE in the CIED population who were diagnosed with CTEPH was significantly lower than the CTEPH population at-large. This suggests that CIEDs may give rise to small thrombi on the wires that may cause silent pulmonary emboli. Ultimately, these silent pulmonary emboli may contribute to the development of CTEPH in susceptible individuals. The role of blood-contacting medical devices such as stents, vascular grafts, and heart valves in thrombus formation has been well documented in the biomaterials literature. It is likely that CIEDs, like other artificial surfaces in the blood stream, promote clotting through a complex cascade of protein adsorption, cell adhesion, thrombin generation, and complement activation.[14]

Previous studies have mentioned that CIEDs may be a potential risk factor for distal disease burden in CTEPH patients, but none have formally studied or quantified this hypothesis.[5] Our analysis demonstrated that CTEPH patients with CIEDs are more strongly associated with distal disease, suggesting that leads may be a nidus for the development of small clots which embolize to the segmental and subsegmental vessels of the pulmonary vasculature. Thrombi within these more distal vessels are more difficult to remove during surgery and may even make the disease inoperable at some institutions.[15] However, at UCSD, despite higher risk of distal disease, CTEPH patients with CIEDs had very comparable post-operative hemodynamics and outcomes as CTEPH patients without devices. This implies that CTEPH patients with CIEDs are good candidates for PTE, and that surgeons should continue to operate on these patients while considering the removal of CIEDs from the blood stream to decrease the risk of recurrent disease.

In conclusion, CIEDs are more prevalent in the CTEPH population than the general population and associated with more distal disease. Electrophysiologists should consider CTEPH as a potential cause of dyspnea in patients with long-standing devices and those with known clots on wires. These patients can be screened for CTEPH with a VQ scan; those with abnormal perfusion should be referred for thorough evaluation of CTEPH and determination of surgical candidacy by centers offering PTE surgery.

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Tables & Figures

Table 1: Demographics of CTEPH patients with and without CIEDs

Characteristic	CTEPH patients with CIED (n=17)	CTEPH patients without CIED (n= 965)	p-value
Age, years	58.0 ± 14.4	52.1 ± 14.7	0.11
Sex no. (%)			
Male	12 (70.6)	494 (51.2)	0.11
Female	5 (29.4)	471 (48.8)	
BMI	27.5 ± 5.2	30.5 ± 7.3	0.10
WHO functional class no. (%)			
1	0 (0)	6 (.9)	0.03
2	2 (12.5)	156 (17.3)	
3	10 (62.5)	695 (76.9)	
4	4 (25.0)	47 (5.2)	
Comorbidities no. (%)			
Diabetes	3 (17.6)	111 (11.5)	0.34
Hypertension	5 (29.4)	299 (30.9)	0.89
Hyperlipidemia	3 (17.6)	172 (17.8)	0.88
Coronary artery disease	6 (35.3)	139 (14.4)	0.02
Chronic kidney disease	5 (29.4)	128 (13.3)	0.05
COPD	3 (17.6)	112 (11.6)	0.34
Asthma	0 (0)	111 (11.5)	0.18
Smoking history no (%)			
Never	7 (41.2)	460 (47.7)	0.85
Former	8 (47.1)	354 (36.7)	
Current	0 (0)	34 (3.5)	
Unknown	2 (11.8)	115 (11.9)	
Known VTE History (%)	50	78.6	0.018

Note: Data are mean ± standard deviation or number (%) and were analyzed with Student's t test or χ^2, respectively. BMI: body mass index; WHO: World Health Organization; COPD: chronic obstructive pulmonary disease. VTE: Venous Thromboembolism.

Table 2: Preoperative hemodynamic characteristics of CTEPH patients with and without CIEDs

Characteristic	CTEPH patients with CIED (n=17)	CTEPH patients without CIED (n=965)	p-value
RA pressure, mean mmHg	9.4 ± 3.8	10.4 ± 5.9	0.54
PA pressure, mmHg			
Systolic	71.1 ± 12.2	74.1 ± 20.1	0.56
Diastolic	25.2 ± 5.9	26.5 ± 8.8	0.56
PA pressure, mean mmHg	41.8 ± 6.1	44.1 ± 11.7	0.43
Cardiac output, L/min	4.4 ± 1.3	4.5 ± 1.4	0.64
Cardiac index, L/min/m^2	2.2 ± 0.5	2.2 ± 0.6	0.62
PVR, dyn-s/cm^5	600.9 ± 243.0	669.7 ± 369.0	0.46
TPR mmHg-min/mL	824.9 ± 262.0	879.0 ± 419.4	0.61
Ejection Fraction, %	62.9 ± 11.9	67.4 ± 7.0	0.01

Note: Data are mean ± standard deviation and were analyzed with Student's t test. RA: right atrium; PA: pulmonary artery; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance

Table 3: Postoperative hemodynamic characteristics of CTEPH patients with and without CIEDs

Characteristic	CTEPH patients with CIEDs (n=17)	CTEPH patients without CIEDS (n=965)	p-value
PA pressure, mmHg			
Systolic	42.7 ± 13.1	39.3 ± 12.7	0.29
Diastolic	16.1 ± 4.4	15.6 ± 5.2	0.72
PA pressure, mean mmHg	25.8 ± 7.4	24.3 ± 7.2	0.42
Cardiac output, L/min	5.4 ± 1.0	5.7 ± 1.3	0.39
Cardiac index, L/min/m^2	2.6 ± 0.3	2.8 ± 0.5	0.23
PVR, dyn-s/cm^5	256.9 ± 106.0	242.0 ± 122.2	0.63
ΔPVR, dyn-s/cm^5	343.9 ± 242.3	429.5 ± 328.7	0.09
TPR mmHg-min/mL	397.8 ± 134.7	363.8 ± 151.8	0.38

Note: Data are mean ± standard deviation and were analyzed with Student's t test. RA: right atrium; PA: pulmonary artery; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance

Table 4. Prevalence of CIEDs in CTEPH population and lead management during PTE

Characteristic	Number of patients
Total CTEPH patients s/p PTE	982
Patients with CIEDs	17
Pacemakers	14
ICD leads	3
Device extracted intraoperatively	6
Change to epicardial leads	5
Prevalence of CIEDs in PTE population (%)	1.7

Table 5: Disease burden in CTEPH patients with and without CIEDs

Characteristic	CTEPH patients with CIEDs (n=17)	CTEPH patients without CIEDs (n=933)	p-value
Proximal disease	5	692	
Distal Disease	12	241	
Percentage with distal disease, %	70.6	25.8	0.0002

Note: Data are counts and were analyzed with Fisher's exact test.

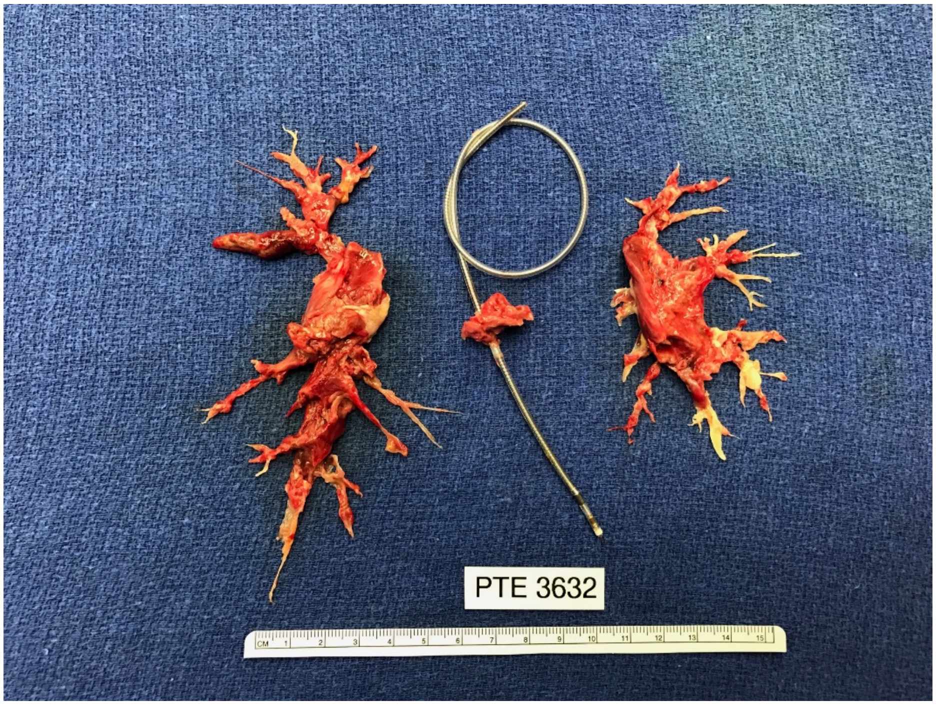

Figure 1. Thromboembolic specimen removed from CTEPH patient during PTE. Thrombus is present on extracted pacemaker lead.

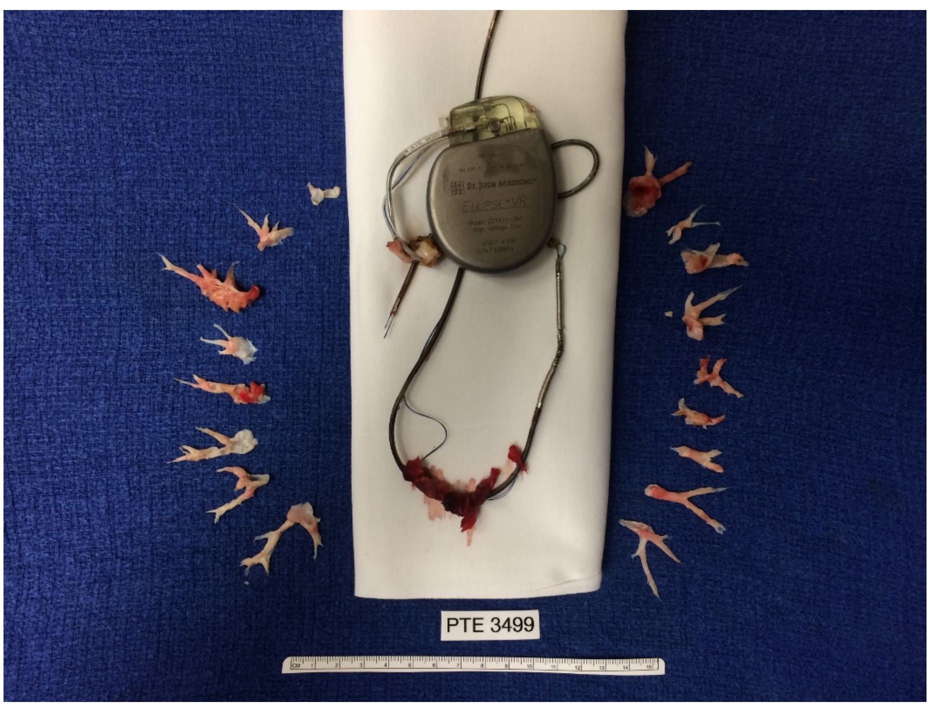

Figure 2. Thromboembolic specimen isolated from CTEPH patient during PTE. Thrombus is present on extracted ICD device.