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Contributors Toward Pulmonary Vein Restenosis Following Successful Intervention

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ABSTRACT

OBJECTIVES This study sought to identify clinical and procedural risk factors associated with pulmonary vein (PV) restenosis.

BACKGROUND Pulmonary vein stenosis (PVS) is a rare but morbid complication of PV isolation for atrial fibrillation (AF) ablation. Interventions such as PV balloon angioplasty (BA) or stenting achieve excellent acute success; however, subsequent restenosis is common.

METHODS A total of 113 patients underwent invasive treatment for severe PVS between 2000 and 2014 and were followed prospectively. Baseline patient and lesion characteristics were abstracted from chart review and analyzed. Univariate and multivariate analyses were performed using patient and procedural characteristics to determine which factors were associated with an increased risk for subsequent PV restenosis.

RESULTS Over a median follow-up of 4.6 years there was PVS recurrence in 75 veins; 52 veins (57%) were treated with index BA and 23 veins were treated with stenting. After multivariate analysis, the only patient factor that was significantly associated with restenosis was a history of more than 1 AF ablation (hazard ratio [HR]: 1.91; 95% confidence interval [CI]: 1.07 to 3.41; $p = 0.03$). Multivariate analysis on a per-vein level demonstrated a significantly lower risk of restenosis in veins treated with a stent (HR: 2.84; 95% CI: 1.75 to 4.61; $p < 0.0001$). In veins treated with BA alone, inflation of the balloon to higher atmospheres significantly reduced the risk of recurrence (HR: 0.87; 95% CI: 0.78 to 0.98; $p = 0.02$).

CONCLUSIONS Restenosis is common after a successful PV intervention and the risk of restenosis is highest in those with a history of multiple AF ablations and in those treated with BA. Proceduralists should take into account the number of AF ablations a patient has undergone and should strongly consider stent deployment when intervening on PVS to reduce risk of restenosis. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Pulmonary vein stenosis (PVS) is a rare, and potentially serious, complication of atrial fibrillation ablation and is believed to complicate between 0.3% and 3.4% of pulmonary vein (PV) isolation procedures (1-3). Symptoms are nonspecific and include cough, chest pain, dyspnea, hemoptysis, and pulmonary infarction (4-6). Despite advances in interventional treatments for PVS, restenosis occurs in approximately one-third of treated PV (6). Identification of patient and procedural factors that are

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BA = balloon angioplasty
CI = confidence interval
CT = computed tomography
HR = hazard ratio
PV = pulmonary vein
PVS = pulmonary vein stenosis

associated with restenosis is essential to guiding the type of intervention performed and to optimize strategies for surveillance post-intervention. Therefore, we evaluated our center's experience with a large cohort of PVS patients who underwent intervention and sought to identify characteristics associated with an increased risk of restenosis.

METHODS

PATIENT SELECTION. From February 1, 2000 to November 1, 2014, 113 patients underwent invasive treatment as index cases for severe PVS referred to the Mayo Clinic and were followed prospectively afterward. Our study protocol has previously been described in detail (4-6). In brief, patients were followed from the time of PVS diagnosis until the date of last follow-up, or if receiving on-going care until April 2015. Severe PVS was defined as >75% luminal narrowing on the pre-intervention computed tomography (CT) scan. In addition to the 113 patients requiring invasive management, 4 patients had complete occlusions of their PV on CT and did not receive intervention, and 7 patients were asymptomatic and not taken to the cardiac catheterization laboratory. These patients were carefully monitored for symptom progression with no particular treatment undertaken (4-6). No patients in this cohort underwent further PVI after index treatment for PVS. Interventional data were collected including vein location, baseline, and post-intervention PV to left atrium pressure gradient, balloon and stent size, and deployment atmospheres. After intervention, patients were followed at set intervals with repeat CT imagining at 3 to 4 months, 9 to 12 months, and 18 to 24 months. Subsequent imaging evaluation was then guided by clinical symptoms. If patients followed up with local providers, all records and imaging studies were requested and reviewed. Data were recorded on the occurrence of restenosis and need for repeat interventions on the original stenotic PV or development of a new lesion in a different vein. All patients provided consent to participate and have their data reviewed in this institutional review board-approved study.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD. The cumulative probability of restenosis was estimated using the Kaplan-Meier method. Potential risk factors for this endpoint were evaluated using Cox proportional hazards models. In the models estimating restenosis on a per-vessel basis, the Cox model was used, but sandwich-estimated robust SE were used to estimate the significance. This was completed to adjust for multiple vessels from some individuals in the study (7). Univariate models were developed to identify patient and procedural characteristics that may be associated with restenosis. Variables with a p value of 0.10 or lower on univariate analysis, or those felt to be clinically relevant, were included in multivariate models to assess which factors were most associated with subsequent restenosis. All analysis was performed using SAS (version 9.4, SAS Institute, Cary, North Carolina). A significant difference was defined as a 2-sided p value of <0.05.

RESULTS

A total of 113 patients were initially diagnosed as having severe PVS by cardiac CT and underwent attempted index intervention on a total of 219 veins. Baseline patient characteristics are listed in **Table 1**. In 42 veins, intervention could not be performed secondary to complete occlusion or was deferred because of hemodynamically insignificant stenosis, and these patients were not included in the analysis (8). Intervention was successfully carried out in 113 patients, encompassing 177 veins, including 91 veins treated with balloon angioplasty (BA), 82 veins treated with peripheral or biliary bare-metal stents,

TABLE 1 Baseline Characteristics of Patients Who Underwent Intervention for PVS

	Overall (N = 113)	Restenosis (n = 45)	No Restenosis (n = 63)
Age, yrs	49.7 ± 11.0	49.0 ± 10.6	50.4 ± 11.6
Male	84 (78)	35 (78)	49 (78)
BMI, kg/m^2	28.2 ± 4.9	27.5 ± 4.9	28.6 ± 4.6
LVEF, %	60.6 ± 7.0	60 ± 6.2	62 ± 5.9
Hypertension	40 (36)	12 (27)	23 (37)
CAD	9 (8)	3 (7)	4 (6)
HLD	36 (32)	12 (27)	24 (39)
Diabetes	3 (3)	0	3 (5)
TIA/stroke	9 (8)	5 (11)	4 (6)
CHA_2DS_2-VASc	0.9 ± 1.1	0.7 ± 1.0	0.9 ± 1.1
Sleep apnea	10 (9)	1 (3)	9 (22)
PVI, n	1.5 ± 0.9	1.8 ± 1.0	1.2 ± 0.7
Time from ablation, months	12.9 ± 25.2	5.1 ± 5.4	13.5 ± 20.8
Time of diagnostic delay, months	5.2 ± 4.2	3.3 ± 3.5	4.4 ± 6.0

Values are mean ± SD or n (%). Five patients went to procedure but did not undergo intervention secondary to occluded vein or lack of significant stenosis. $p < 0.05$.

BMI = body mass index; CAD = coronary artery disease; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category; HLD = hyperlipidemia; PVI = pulmonary vein isolation; TIA = transient ischemic attack.