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REVIEW

Pulmonary Hypertension due to Radiofrequency Catheter Ablation (RFCA) for Atrial Fibrillation: The Lungs, the Atrium or the Ventricle?

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Atrial fibrillation is the most common heart rhythm disorder in United States, characterised by rapid and irregular beating of both the atria resulting in the similar ventricular response. While rate and rhythm control using pharmacological regimens remain the primary management strategies in these patients, radiofrequency catheter ablation (RFCA) is rapidly rising as an alternative modality of treatment. Increase in the incidence of RFCA has shed light on complications associated with this procedure. Pulmonary hypertension (PH) is one of the long-term complications that has been observed postcatheter ablation. There have been multiple mechanisms which have been proposed to explain these elevated pulmonary pressures. These include the involvement of the lungs due to pulmonary vein stenosis, pulmonary vein occlusion and, rarely, pulmonary embolism. Radiofrequency catheter ablation can also lead to scarring of the atrium which can cause left atrial diastolic dysfunction leading to elevated pulmonary pressures. Recently, it was also proposed that elevated pulmonary pressure was related to the unmasking of left ventricular diastolic dysfunction occurring after this procedure. In this article, we review all the mechanisms that are associated with the development of pulmonary hypertension in patients undergoing RCFA for atrial fibrillation and the approach to diagnosis and management of such patients.

Keywords RFCA • Pulmonary hypertension • Atrial fibrillation • Stiff Atrial Syndrome • PVS

Introduction

Atrial fibrillation is the most common heart rhythm disorder affecting around 2.5 million people in United States. It is characterised by rapid and irregular beating of both the atria resulting in the similar ventricular response. It is associated with the risk of stroke and heart failure resulting in increased morbidity and mortality [1]. The treatment of atrial fibrillation involves rate control with anti-arrhythmic drugs like beta blockers, digoxin and amiodarone. Cardioversion is recommended in case of haemodynamic instability or after failure of pharmacological therapies. Anti-arrhythmic drugs have reasonable efficacy in controlling atrial fibrillation but are also associated with the potential of adverse effects with

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long-term use. Therefore, radiofrequency catheter ablation (RFCA) is rapidly rising as an alternative to anti-arrhythmic drug therapy. It has shown superior efficacy over anti-arrhythmic drugs in maintaining sinus rhythm in various randomised control trials conducted over the past few years. [2–4]. As per American College of Cardiology (ACC)/ Heart Rhythm Society (HRS)/American Heart Association (AHA) guidelines of 2014, catheter ablation is recommended as a first line therapy for patients with symptomatic paroxysmal atrial fibrillation when rhythm control is required. It can also be used in patients with persistent atrial fibrillation who are intolerant to anti-arrhythmic drugs.

Technique and Complications

Ablation works on the principle of Cox maze procedure, which was first introduced by Dr. James Cox at Barnes Jewish hospital in 1987. It involves creating surgical incisions in both right and left atria to form a scar [5]. The scar prevents the propagation of electrical activity and blocks macro-reentrant circuits thereby terminating atrial fibrillation. Catheter ablation involves creation of linear lines by using the same principle but different sources of energy like radiofrequency, cryoablation, laser, microwave and high-frequency ultrasound [5]. Pulmonary vein antral isolation (PVAI) is one of the strategies, where circular lines are created within the atrium around the pulmonary veins. Apart from PVAI, other strategies include linear lesions, ganglionated plexi ablation, and rotor ablation. [6]. Despite its ability to treat atrial fibrillation, many adverse effects have been found to be associated with catheter ablation. Complications of RFCA include aorto-oesophageal fistula, systemic emboli, pericardial effusion and pulmonary dysfunction. Pulmonary hypertension (PH) is one of the long-term complications that have been observed postcatheter ablation. As per ACC/AHA, PH is defined as the pulmonary arterial pressure (PAP) of >25 mmHg in resting state and >30 mmHg on exercise. There have been multiple mechanisms which have been proposed to explain these elevated pulmonary pressures. In this article, we review the mechanisms leading to pulmonary hypertension in patients undergoing RFCA for atrial fibrillation

The Lung

Pulmonary vein stenosis (PVS) post-RFCA is the first proposed mechanism resulting in PH in the literature. Pulmonary vein stenosis is defined as the reduction in the total diameter of pulmonary veins more than 50% from the diameter present before the ablation [7]. It results from the radiofrequency energy delivered at the ostia or within the lumen of pulmonary veins [8–10]. Ernest et al. reported thickening of venous walls from myoblast proliferation and luminal sclerosis of veins characteristic of venous occlusive syndrome secondary to radiofrequency [11]. Previous literature reviews report 1.3 to 15.6% incidence of PVS. In a retrospective study done by Lu et al., two out of five cases had PVS after RFCA [12]. Similarly, prospective studies have also described PVS in patients undergoing RFCA [13,14]. Symptomatic PVS can present within a few hours to years after the ablation procedure. Chronic and untreated PVS can lead to total pulmonary vein occlusion (PVO) and eventually PH [15,16]. Single PVO is usually asymptomatic but in the presence of ipsilateral PVS/PVO, the patient can present with severe symptoms [15]. Part of the evolution in the treatment of AF has been wide area circumferential ablation (WACA), in which the encircling point-by-point PV lesions are performed 1-2 cm away from the ostia of the PV's. While this approach reduces the incidence of PVS, it increases the risk of leaving gaps in ablation lesions of the PV leading to recurrent arrhythmias [17]. A decreased incidence of PVS is seen in patients in whom local extensive encircling pulmonary vein antral isolation (EEPVI) is used as the technique for RFCA [18]. While there have been reports of PVS with other techniques of ablation like cryoablation and pulmonary vein catheter ablation, the occurrence is rare [19–21]. No cases of PV stenosis have been reported so far with the use of laser balloon for PVI [22,23].

Pulmonary embolism is another life-threating condition seen post-RFCA which can lead to elevated pulmonary pressures and acute right heart failure. Patients with acute pulmonary embolism usually present within 24 hours of the procedure with acute dyspnoea [24]. Given that AF ablation is usually offered in patients who are therapeutically anticoagulated, this complication in less likely. It is more commonly seen in patients undergoing RFCA for other supraventricular or ventricular arrhythmias [24].

The Atrium

Stiff atrial syndrome after RFCA has been described as new onset of dyspnoea and congestive heart failure with PH and left atrial diastolic dysfunction (Table 1). These patients typically do not have mitral valve inadequacy, pulmonary stenosis or other factors contributing to the patient's symptoms. It has been described as occurring within days to months after surgery [25]. A meta-analysis of 17 trials done in the past showed that RFCA resulted in a decrease in the size and volume of atria (Table 2) [26]. It has been suggested that the reduction in the left atrial volume after RFCA may be due to remodelling of the left atrium after AF is controlled. However, both Reant et al. [27] and Muller et al. [28] found that patients undergoing RFCA had reduced left atrial volume and dimensions in spite of recurrence of AF. In a comparison of patients undergoing different interventions for AF, it was noted that the reduction in the volume of the LA was greater in patients undergoing RFCA as compared to patients undergoing cardioversion [29]. This suggests that while the reduction of left atrial volume might be due to the control of AF itself, RFCA can worsen it further thus contributing to PH.

Wylie et al. have suggested that RFCA can lead to impaired left atrial systolic function and the degree of impairment may be affected by the extent of the scar tissue after the intervention [30]. Subsequently, abnormal left atrial systolic function

Table 1 Cases describing pulmonary hypertension due to stiff left atrial syndrome from RFCA.

Case Report/ Series	Age and Sex	Presenting complaint	Number of ablations	ECHO/ Catherisation	Diagnostic Criteria	LA diameter in parasternal axis	Outcomes
Witt et al. [42]	53-year-old male	Dyspnoea	3	Right Heart Catheterisation	Elevated LA pressure – 27 mmHg Large v-waves of 55 mHg RA mean pressure 18 mmHg Mild elevation in LVEDP	-	Previous normal ECHO before ablation Diagnosis of stiff atrial syndrome made due to scar formation
Clare et al. [43]	56-year-old male	Dyspnoea	2 and atrial appendage resection	Transseptal	Preablation: LA pressure of 15 mmHg and peak v wave of 30 mmHg Postablation: LA pressure of 18 mmHg and peak v-wave of 50 mmHg	45 mm	Right to left shunt on TEE with peak end systolic gradient of 28 mmHg followed by diagnosis of stiff left atrial syndrome
Wong et al. [39]	72-year-old female	Dyspnoea on exertion	2 ablations 4 years apart	ECHO followed by RHC	Mpap: 38mmHg PASP on ECHO: 65 mmHg RHC: PASP of 85 mmHg, mPaP of 58 mmHg, Mpawp of 26 mmHg, Peak v wave Mean RAP of 27 mmHg Normal LVEF and LVEDP	45mm	Left atrial dysfunction confirmed with catheterisation. Treatment with diuresis, spironolactone followed by 12 months of sildenafil showed improvement in exercise capacity on 6 min walk test.

LA: left atrium; RA: right atrium, LVEDP: left ventricular end diastolic pressure; mpap: mean pulmonary artery pressure; RAP: right atrial pressure; PASP: pulmonary artery systolic pressure; Mpawp: mean pulmonary artery wedge pressure.

Table 2 Meta-analysis analysing the effect of RFCA on volume of atrium and ventricle

Study	Population	Change in volume of atrium & ventricle	Conclusion
Jeevanantham et al. [26] Meta-analysis of 17 studies	N=869	Decrease in LAD (WMD −1.67 mm, 95% CI −2.80 to −0.54;), LAVmax (WMD −6.57 ml, 95% CI −10.09 to −3.05;), and LAVmin (WMD −2.61 ml, 95% CI −5.13 to −0.09;) during follow-up after ablation therapy.	Successful RFCA in patients with atrial fibrillation significantly decreased left atrial size and volumes and did not seem to adverse affect left atrial function

LAD: left atrial diameter; LAV: left atrial volume.

can lead to left atrial diastolic dysfunction due to incomplete emptying [25]. Thus extensive ablation by electrophysiologists to reduce the extent of recurrence of atrial fibrillation can lead to PH due to scar formation and fibrosis.

Gibson et al. [25] performed the first prospective study to assess this complication in patients undergoing ablation. Presence of PH was assessed by the presence of large V-waves (>7 mm) on pulmonary capillary wedge pressure (PCWP) tracings or left atrium (LA) tracings after excluding mitral valve regurgitation. The study showed 1.4% incidence of PH secondary to atrial diastolic dysfunction in these patients. This atrial diastolic dysfunction was also associated with increased atrial scar formation. The atrial and left ventricular systolic function was found to be preserved in this study.

Yang et al. have also suggested a role of reduced response of the left atrial baroreceptors and elevated plasma arginine vasopressin levels in the development of increased left atrial and pulmonary pressures in patients after RFCA [31,32]. Apart from the above mechanisms, other factors, which were found to independently predict the risk of stiff atrial syndrome post RFCA, included LA size of <45 mm, diabetes, OSA and high LA pressures.

The Ventricle

Will et al. conducted a retrospective study of 449 patients in 2013 to assess the cause of increased pulmonary artery pressures post-RFCA [33]. Right ventricular systolic pressure (RVSP) was used to measure PH. Mitral valve E/A and E/E′ ratio were used as the indicators to assess left ventricular diastolic dysfunction. The study demonstrated that the increase in mitral valve E/A and E/E′ ratio post-RFCA was associated with increased RVSP on echocardiogram. This study demonstrated that there was no association of the decrease in LA size and LV ejection fraction to the increased RVSP in these patients. Thus the PH in these patients was attributed to the left ventricular diastolic dysfunction. Possible theories for LV diastolic dysfunction included constrictive pericarditis from pericardial inflammation, or coronary artery injury by radiofrequency used in the procedure or from natural progression of the disease.

Another theory suggested by the Witt et al. proposed that the unmasking of the existing LV diastolic dysfunction might have caused the PH. They hypothesised that the increased LA size preablation was acting as a reservoir for reduced compliance of left ventricle. The reduction in LA size postablation thereby led to increased volume thus unmasking an underlying LV diastolic dysfunction [33,34]. These studies involving the atrium and the ventricle causing PH in patients undergoing RFCA are described in Table 3.

Clinical Presentation and Diagnosis

Presenting signs and symptoms of PH are similar regardless of the aetiology. Patients usually present with respiratory symptoms such as chronic dyspnoea. The onset of symptoms can be acute to chronic based on the aetiology. An accurate history and physical examination is essential in narrowing down the list of differential diagnosis leading to PH. Patients with pulmonary embolism may present with dyspnoea of acute onset [24]. Pulmonary hypertension from PVS can present within hours to months after the procedure. Unilateral PVS is usually asymptomatic and is found only on screening the patients postablation whereas the presence of ipsilateral PVS/PVO can lead to severe symptoms [15]. Pulmonary hypertension from stiff atrial syndrome can present with unexplained dyspnoea for months up to six years after the RFCA [25,34]. Signs of right ventricular dysfunction/ right heart failure can also be the presenting symptom in cases of chronic pulmonary hypertension. Initial diagnostic evaluation involves the exclusion of primary cardiac causes of dyspnoea including ischaemia. Echocardiogram is the non-invasive technique used to assess ventricular function and screen patients for pulmonary hypertension. It helps us to assess atrial and ventricular pressures, size and index. Elevated left atrial pressures and elevated RVSP are associated with pulmonary hypertension. Increased E/A and E/E′ gradient on ECHO is associated with left ventricular diastolic dysfunction. Lung ventilation-perfusion scan is used to diagnose acute PE and PVS [15]. Computed tomography (CT) of pulmonary veins has more sensitivity and specificity in diagnosing PE and also PVO/PVS. Combination of CT and ventilation can also be used to diagnose PVS [13]. Angiography of pulmonary veins is the gold standard but an invasive procedure that is used not only to confirm but also correct PVS [14]. In the absence of findings of PVS on CT and perfusion scans, cardiac catheterisation is recommended to look for cardiac causes of PH. Left heart catheterisation (LHC) is undertaken to assess ventricular function, coronary anatomy and mitral valve regurgitation. Right heart catheterisation (RHC) is used to look for PCWP and mean pulmonary artery pressure (mPAP) to aid with diagnosis and classification of pulmonary hypertension. Patients are also assessed for elevated V-waves on PWP tracings. In the absence of mitral regurgitation (on LHC or Echo), large V waves on PWP tracings are secondary to decreased atrial compliance [34]. Other tests include a chest X-ray, pulmonary function tests and high resolution CT of the chest to rule out pulmonary causes of PH.

Treatment

The treatment modalities differ in terms of the aetiology of PH post-RFCA. In the case of PVS/PVO, pulmonary vein balloon angioplasty and stent deployment can be performed. Early interventions of the affected veins have shown significant improvement in restoring the perfusion of the lung [15]. It is also important to assess the ipsilateral veins in case of total PVO because the lung perfusion is dependent on the ipsilateral veins. So, the intervention is needed if ipsilateral vein is stenosed or occluded. In a study done by Prieto et al., dilation and bare metal stent deployment of vein with size

Table 3 **Studies assessing the incidence and cause of pulmonary hypertension in patients undergoing RFCA**

Study	Population	Criteria for PH	Technique	Incidence	Mean PAP (RVSP/mPAP) in PH population	Calculated Parameters	Conclusion
ATRIUM							
Gibson et al. 2011 [25] Prospective	N=1380 Mean age: 62+/-11(75%male)	PAP>25 mmHg at rest and >35 mmHg at exercise	Transthoracic ECHO and Right Heart Catheterisation	New onset or worsening PH with diastolic abnormalities in 19 (1.4%) patients post RFCA	Average PASP 45+/-17 mmHg Average LA systolic pressure 29+/-6 mmHg	LAP (S) 29+/-6 mmHg LAP(D) 11+/-4 mmHg LA scar 84% LA size 4.6 cm+/-0.7 cm LVEF 61+/-9	Stiff LA syndrome after catheter ablation for AF is a potential complication of the procedure but has a low prevalence.
VENTRICLE							
Witt et al. 2014 [33] Retrospective	N=499 Mean age: 60.7+/-10.8(71.9%male)	Total RVSP>35 mmHg or Increase in RVSP>10mmHg	Transthoracic ECHO	New or worsening PH in 41 (8.2%) patients	Avg RVSP – (pre: 27.7+/-5.1 & post: 43.8+/-8.3 mmHg	E/A ratio (rre 1.3+/-0.3 & post 2.1+/-1.2) E/E'ratio (pre 9.9+/-2.9 & post 14.7+/-8.4) Postablation, in the increased PA pressure group had higher E/A (2.12 vs. 1.49, p<0.01) and E/e' (14.7 vs. 11.2, p<0.01 ratios. LA expansion index values were lower in the increased PA pressure group preablation (51 vs. 92%, p<0.01), but not significantly different postablation (82 vs. 88%, p = 0.44).	Increased PAP was associated with new onset or unmasking of the previously present LV diastolic dysfunction.

LA: left atrium; RA: right atrium, LVEDP: left ventricular end diastolic pressure; mpap: mean pulmonary artery pressure; RAP: right atrial pressure; PASP: pulmonary artery systolic pressure; Mpawp: mean pulmonary artery wedge pressure; RVSP: right ventricular systolic pressure.

greater than 6-7 mm has shown significant improvement but the veins with a diameter of <6 mm showed complete occlusion despite initial dilation and stent [13]. The rate of restenosis was found to be 47 to 61% in the case of balloon dilation alone whereas in the case of stent deployment, it has shown a significant decrease ranging from 0 to 47% [8,35]. Drug eluting stents are an option but more studies are needed to determine the efficacy and safety of the stents for treating PVS/PVO [9,36]. There is no role for stents in the treatment of PH when PVS is absent.

Amongst the oral drugs used for PH, sildenafil has been studied for PH secondary to left heart failure (Group II). It is a novel drug that inhibits Phosphodiesterase 5 enzyme that metabolises cyclic guanosine monophosphate (cGMP). Increased cGMP mediates arterial vasodilation by relaxation of smooth muscle cells. It has shown significant improvement in the exercise capacity of patients with PH [37]. In a trial conducted by Guzzie et al., it has shown significant improvement in PAP and RV pressures in patients with HFpEF (heart failure with preserved ejection fractions), but exercise capacity was not assessed in that study [38]. Recently, it has also been used in the treatment of PH from stiff atrial syndrome postablation, where it significantly improved exercise capacity and pulmonary arterial pressure of the patient [39]. Multiple trials are in progress to assess the efficacy and safety of the drug in PH secondary to HFpEF.

Apart from sildenafil, other oral drugs which have been studied for Group II PH include the guanyl cyclase activator, riociguat. It increases the formation of cGMP resulting in vasodilation and also inhibits smooth muscle proliferation and vascular remodelling. In the DILATE-1 trial, riociguat did not show any improvement in pulmonary arterial pressures and exercise capacity in patients with HFpEF [40]. Another class of oral drugs used for PH is selective endothelin-A receptor antagonist (EDRA) – sitaxsentan [41]. EDRAs act on enodothelin receptor-A present on vascular smooth muscle cells thereby promoting vasodilation. This drug has also shown improvement in PH secondary to HFpEF in the clinical trials but has yet not been studied in patients with PH secondary to RFCA for atrial fibrillation.

Gibson et al. noted an improved NYHA functional capacity from grade III to grade I in most of their patients treated with diuretics. This was maintained during follow-up [25]. Thus, diuretics might be considered for treatment for symptomatic patients with PH due to RFCA.

Conclusion

The trend of use of RFCA to treat AF has recently been on the rise. These patients can develop PH postoperatively. It is thus necessary to look for the presence of PH in the patients presenting with dyspnoea or signs of right heart failure after RFCA. It is essential to identify the aetiology of PH in these patients so that prompt treatment measures and interventions can be instituted. Interventional procedures like stent deployment have shown improvement in the case of PH due to PVS. While multiple oral medications are approved for PH, these medications have not been studied in patients presenting with PH post-RFCA. Sildenafil has been used on a case-by-case basis, but the efficacy and safety of these drugs in this subgroup is relatively unknown. Thus, with the potentially increasing incidence of this complication, further prospective studies need to be done to assess the possible mechanisms and treatment modalities to treat PH in patients undergoing RFCA.

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Conflict of Interest

The authors report no conflict of interest.

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Ethical Statement

This article is not under consideration in any other journal and this manuscript has not been published elsewhere.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hlc.2016.05.125.

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