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Radiofrequency Ablation in Primary Aldosteronism

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ABSTRACT

The radiofrequency ablation (RFA) technique has been extensively used in the treatment of primary malignancies and metastases and has been recently deployed for the treatment of unilateral primary aldosteronism (PA) as an alternative to whole unilateral adrenalectomy.

Current evidence comparing RFA with unilateral adrenalectomy in the treatment of PA so far has been variable, with studies being retrospective and small-scale, but it remains a very attractive option as a potentially less invasive treatment option compared to adrenalectomy.

This review article describes the procedure, and provides evidence and the possible future direction of RFA in the treatment of unilateral PA.

Introduction

The diagnosis of primary aldosteronism (PA) in people with hypertension provides the potential for treatment with curative unilateral adrenalectomy. Several techniques have emerged as potential candidates for non-surgical 'cytoreductive' treatment of aldosterone-producing adrenal adenomas (APAs), including radiofrequency ablation (RFA), cryoablation, and microwave therapy. The latter two are, numerically, less extensively published than RFA in the treatment of adrenal disease [1]. There are preliminary reports also of adrenal artery ablation using ethanol; the technique has been used to treat both APAs and those without apparent APAs [2, 3]. This short review will focus on RFA in APAs.

Why consider radiofrequency ablation as a treatment for primary aldosteronism?

There are a number of potential attractions of RFA compared to adrenalectomy as a treatment for PA. First, although randomized studies are awaited, there is a general consensus that it is less invasive than laparoscopic surgery and, as a result, associated with lower post-procedure analgesia, reduced length of hospital stay, and earlier return to work. Related to this, difficulties with predicting surgical outcomes lead some patients to a reluctance to undergo abdominal surgery for a 'benign' condition with no promise of a complete (tablet-free) cure. Third, recent data point to significant improvements in cardiac parameters (left ventricular end-diastolic volume and N-terminal pro-brain natriuretic peptide levels) with

surgery and that these improvements correlate most strongly with a reduction in plasma aldosterone concentrations [4]. It could therefore be the case that for selected patients at high cardio-metabolic risk who are unlikely to be cured by surgery, lowering aldosterone levels by selective nodule ablation is clinically beneficial. RFA is, theoretically, a potentially attractive option for patients with marked visceral obesity, for whom the risk of conversion from laparoscopic to open adrenalectomy is higher, but the same anatomical issues may make the ablation procedure more challenging. Last, nodule ablation opens up the theoretical possibility of treating bilateral disease without rendering patients adrenocortically insufficient.

From a healthcare economics perspective, RFA is less expensive than surgical adrenalectomy. A prospective study on RFA in PA showed that RFA is 2 to 3 times less costly than surgery [5]. If the diagnosis were to be made in all 5–10 % of hypertensive people who are estimated to have PA, there would be a large number of surgical referrals for adrenalectomies [6, 7]. This would put a significant demand on surgical capacities, which was present before, but has been augmented after the Coronavirus disease 2019 pandemic.

The published literature on the use of RFA for PA is limited to single-center experiential reports, with important questions awaiting randomized studies regarding cure rates, safety, and long-term follow-up.

In this article, we will describe the procedure, the evidence, our experience, and the future directions of RFA.

Radiofrequency ablation – general principles

RFA, a form of thermal ablation, is not a new procedure and has been extensively used in the treatment of non-operable primary malignancies and metastases. During RFA, high-frequency alternating current leads to frictional agitation at an ionic level, generating heat. Temperatures > 50 °C induce cell death by coagulative necrosis. The RFA needle is insulated except for its tip, with the result that its effect is limited to the location of the non-insulated needle tip. However, high temperatures at the needle tip can dehydrate tissue and impede energy penetration into the circumjacent tissue. To overcome this, the radiofrequency energy is pulsed and given at varying lengths to achieve the desired area of thermally induced cell death. Another challenge to RFA occurs when the proposed ablation is near a large blood vessel (such as the inferior vena cava). High-volume blood flow can carry away heat, thereby making the hyperthermic effects less pronounced. This effect is termed 'heat sink' and is thought not to be an issue with microwave ablation [1].

Most studies of RFA in adrenal disease have utilized a single needle electrode, but other devices exist, such as an umbrella-shaped needle electrode. An open, prospective study of RFA in PA suggested that umbrella-shaped needle electrodes may increase the rate of clinical success, but at the possible expense of a higher incidence of adverse events [8].

Radiofrequency ablation – access and anatomy

Percutaneous RFA is a procedure performed by interventional radiologists, guided by real-time computed tomography (CT) imaging. The patient lies either prone or in the lateral decubitus position depending on the optimal access route for RFA needle ablation. To limit patient movement, the procedure is usually done under general anesthesia.

Not all patients who qualify for adrenalectomy are candidates for radiofrequency ablation. In some cases, the location of the nearby organs, like the inferior vena cava, may deem the procedure too unsafe for a percutaneous approach. In addition, not all patients will have nodules that are visible on imaging, and therefore, there will be no specific target for the RFA needle. Adrenal artery ablation has been studied in people without an apparent APA. This procedure is performed via a catheter similar to adrenal vein sampling, and the adrenal artery is ablated with ethanol. As this procedure is done via a venous puncture, in theory, this could be done in people whom percutaneous procedures may be deemed too unsafe due to nearby vital structures. An initial study showed that it is an effective and safe treatment with a reported complete clinical success in 9/36 (25 %) participants and partial clinical success in 13/36 (36.1 %) participants, as judged by the Primary Aldosteronism Surgical Outcome (PASO) criteria [2, 9]. A further randomized study compared artery ablation with medical treatment showed a decrease in office and average 24-hour blood pressure with no significant difference between the two groups, but the adrenal artery ablation group had a significant decrease in defined daily doses of their medications [3]. In this randomized control trial, the patients were not limited to only those without apparent APAs. There have been no studies comparing this procedure with adrenalectomy.

Although RFA is an attractive option due to its less invasive nature and the avoidance of surgical complications, it is still not without risks. One of the potential risks is a catecholamine surge from stimulation of the adrenal medulla, leading to a hypertensive crisis. This has been described in early case reports of RFA treatment of adrenal metastasis and also observed in RFA studies in the treatment of PA [10]. In adrenalectomy, the adrenal vein is ligated early on in the procedure, and the adrenal medulla is not disturbed, so hypertensive crises tend not to occur. Although not formally studied, it seems prudent and pragmatic to involve anesthetists experienced in the management of pheochromocytoma in the preparation of patients for the treatment of PA by RFA.

Other reported complications are mostly a result of the placement of the ablation needle in preparation for the ablation of adrenal nodule and they include pneumothorax, hemothorax, vascular thrombosis, and visceral perforation. This is further described in ▶ **Table 1**.

For left-sided adrenal nodules, endoscopic ultrasound (EUS) guidance is an attractive option to percutaneous RFA due to the proximity of the left adrenal gland in relation to the stomach, thereby reducing any potential damage to adjacent vessels or organs as the RFA needle is deployed. This procedure is novel in adrenal disease but has been employed in other epigastric lesions, more notably pancreatic lesions [11]. In our center, a safety and feasibility study of EUS-RFA has been performed on 28 patients and is due to be reported.

Judgment of complete ablation

With conventional whole adrenalectomy, the persistence of PA indicates that the pre-operative PA investigations indicating unilateral aldosterone excess were incorrect. With RFA, it is not possible to distinguish this scenario from a lack of cure due to incomplete

▶ **Table 1** A comparison of the published literature of radiofrequency ablation (RFA) in primary aldosteronism (PA).

Reference	Study type	Number of patients	Size of nodule in RFA arm (mm), Mean; SD	Clinical success in RFA	Clinical success in adrenalectomy	Complications	Length of follow up	Other comments
Bouhanick et al. (2021) [8]	Prospective, all received RFA.	30 RFA	14.9; 5.4	47 % (14/30) daytime BP < 135/85 at 6 months measured by ABPM, without antihypertensive treatment or a decrease in daytime SBP 20 mmHg or DBP 10 mmHg.	Not applicable	No hypertensive crises. 14 RFA-related adverse events (3 pneumothorax, 3 transient post-RFA pain, 1 retroperitoneal hematoma, 1 infection).	6 months	
Cano-Valderrama et al. (2021) [18]	Retrospective, comparing adrenalectomy with RFA. Decided by the physician.	34 (24 adrenalectomy, 10 RFA)	Not given	0 % complete clinical success (blood pressure controlled with no antihypertensive drug), 70 % improved. (fewer antihypertensive drugs and/or blood pressure improved when compared with pre-intervention).	29.2 % (7/24) complete clinical success, 50 % improved.	Hypertensive crises (1/34 in adrenalectomy group, 7/10 in the RFA group).	46.2 months (median)	
Liu et al. (2016) [15]	Retrospective, comparing adrenalectomy with RFA. Decided by the patient.	63 (27 adrenalectomy, 36 RFA)	16; 5	36 % (13/36) patients with BP < 140/90 mmHg without antihypertensive medications for 1 year.	70 % (19/27) patients with BP < 140/90 mmHg without antihypertensive medications for 1 year.	Hypertensive crises (2/27 in adrenalectomy group, 3/36 in the RFA group). In the RFA group, 1 infected retroperitoneal hematoma, 3 pneumothorax, 3 retroperitoneal hematoma.	5.7 years (median)	Used posture test and CT for lateralization. AVS not used.
Sarwar et al. (2016) [12]	Retrospective, comparing adrenalectomy with RFA. Decided by the patient and referring endocrinologist.	44 (32 adrenalectomy, 12 RFA)	15.5; 5	17 % (2/12) normotensive without antihypertensive medications, 58 % (7/12) requiring fewer antihypertensive medications.	38 % (12/32) normotensive without antihypertensive medications, 40 % (13/32) requiring fewer antihypertensive medications.	Hypertensive urgency (3/32 in adrenalectomy group, 8/12 in the RFA group. Procedural complications in 5/32 adrenalectomy patients and in none of the RFA patients.	346 days	Not pre-treated with alpha/beta blockers.
Yang et al. (2016) [13]	Retrospective, comparing adrenalectomy with RFA. Decided by the patient.	25 (18 adrenalectomies and 7 RFA)	18 (range 8–25)	29 % (2/7) without antihypertensive medications, 71 % (5/7) with reduced number of medications	44 % (8/18) without antihypertensive medications, 50 % (9/18) reduced number of medications.	1 hypertensive crisis in the RFA group.	6 months	Lateralization by CT. AVS not routine.
Szejnfeld et al. (2015)[19]	Prospective, all received RFA.	9 RFA	18.4 (range 15–22)	0 % without antihypertensive medication. Significant decrease in blood pressure in the first week after the procedure and maintained at follow-up.	Not applicable	No major complications.	12 weeks	AVS not used in all cases to determine lateralization. No pre-treatment with alpha blockers.

AVS: adrenal venous sampling; BP: blood pressure; CT: computed tomography; RFA: radiofrequency ablation; SD: standard deviation.

nodule ablation. In the studies evaluating RFA in PA, repeat CT imaging was used to reassess the ablated nodule post-RFA [8, 12–16]. The absence of intravenous contrast enhancement at the location of the nodule was used to judge complete ablation.

However, it is known from CYP11B2 immunohistochemistry that the pre-operatively identified adrenal nodule may not be the only source of aldosterone production [17]. In our center, we have access to functional (molecular) imaging (positron emission tomography–computed tomography [PET-CT] using ^{11}C Metomidate or ^{18}F CETO as a tracer) to make this judgment, and this aspect of our pilot safety study of endoscopic RFA is currently undergoing analysis [4]. Together with biochemical and clinical assessment, consideration may be given for repeat RFA if there is no cure.

Evidence

Several studies have investigated RFA as a therapy for PA, and are summarized in ▶ **Table 1**; some were reported before the widespread adoption by the international PA community of the PASO criteria, making comparisons difficult [8, 9, 12, 13, 15, 18, 19]. They are all of modest size (the largest is 36 participants in the RFA arm), and the comparison studies with adrenalectomy are all non-randomized and retrospective. In these studies, the complete clinical cure rates range from 0–47 %. In three out of four of the comparison studies listed, adrenalectomy performed better than RFA in hypertension cure rates (partial and complete). In all the studies, the decision for RFA was made by the participant and the physicians, with some participants choosing RFA because of comorbidities, with the inevitable result that the RFA groups were likely to have inherently lower rates of clinical success by PASO criteria. Further, three of the studies did not use AVS to lateralize the participants but instead used the posture test and/or CT imaging to determine lateralization and identify the nodule for ablation [13, 15, 19].

The frequency of intra-procedural hypertensive urgencies or hypertensive crises was highly variable between 0–70 %, likely due to the small number of participants, differing ablation protocols, and pre-ablation alpha and beta blockade preparations (in two studies, no pre-procedural alpha and beta blockade were used) [12, 19]. In one of these studies, the rate of hypertensive urgency was 67 % (8/12 participants; duration 7–12 minutes), although none of these participants had any reported clinical sequelae [12].

In summary, the evidence shows that RFA has potential as a less invasive alternative to adrenalectomy, but the studies have all been retrospective, small, and their results only short term. A prospective, randomized study comparing RFA to adrenalectomy is underway (NCT05405101) and should provide valuable data. This is further described below.

Our experience

Our experience with RFA was initially with the FABULAS study (**F**easibility study of radiofrequency endoscopic **AB**lation, with **UL**trasound guidance, as a non-surgical, **A**drenal **S**paring treatment for aldosterone-producing adenomas) (NCT03405025). This is the first study evaluating EUS-RFA for left-sided adrenal lesions. The primary outcome is safety, and the secondary outcome is the efficacy of EUS-RFA as judged by PASO criteria. Adverse event reporting was reviewed by an independent safety committee. The efficacy of EUS-RFA will be measured using clinical, biochemical, and radiological parameters involving a PET-CT (^{11}C Metomidate or ^{18}F CETO as a tracer) before and 3 months post-ablation. The study is now closed, and the results are due to be reported [20].

Following this study, recruitment has commenced into WAVE (A prospective randomized trial comparing radiofrequency ablation **W**ith laparoscopic **A**drenalectomy as an alternati**VE** treatment for unilateral asymmetric primary aldosteronism) (NCT05405101). This prospective, randomized, open-label with blind endpoint (PROBE) study, will be run in five centers in England, aiming to recruit 110 participants. The primary objective is to test the hypothesis that RFA is non-inferior to surgery in the biochemical and clinical cure of unilateral PA, according to the international consensus PASO criteria [9]. The participants will be randomized in a 1:1 fashion to either intervention. 24-hour ambulatory blood pressure monitoring will be used to assess blood pressure before and after the intervention. For participants randomized to RFA, RFA will be delivered either under CT- or EUS-guidance. Molecular imaging with PET CT (^{11}C Metomidate or ^{18}F CETO as a tracer) before and after the ablation will be used to identify the treatment target and judge the completeness of its ablation. To our knowledge, this is the first study of this kind.

Future directions

RFA is a promising new treatment in the field of PA. Prospective randomized studies such as WAVE should provide important information that will guide clinicians on the potential deployment of non-surgical cytoreductive treatment of PA. Questions around recurrence, patient selection, and the potential treatment of bilateral disease all lend themselves to future studies, along with protocols testing the efficacy of other 'cytoreductive' therapies such as microwave ablation, cryoablation, and adrenal artery ablation with ethanol. It seems likely that there will still be a role for adrenalectomy in cases where there is no visible nodule or where the nodule is inaccessible due to the anatomy or its proximity to vital organs and vessels.

Conflict of Interest

The authors declare that they have no conflict of interest.

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