

# Experience with Argon Plasma Coagulation in Treatment of Recurrent Epistaxis in Patients with Hereditary Hemorrhagic Telangiectasia

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**Cite this article as:** Alžběta F, Dostálová L, Plzák J. Experience with argon plasma coagulation in treatment of recurrent epistaxis in patients with hereditary hemorrhagic telangiectasia. 2022;18(2):85-90.

## ABSTRACT

**Objective:** Hereditary hemorrhagic telangiectasia, or Rendu-Osler-Weber disease, is an autosomal dominant genetic disorder characterized by abnormal vessel formation. Otorhinolaryngologists often struggle with recurrent epistaxis caused by telangiectasias of the nasal mucosa. Many types of local treatments have been reported, including argon plasma coagulation, which is a non-contact electrocoagulation method used widely in surgery. The goal of this retrospective study was to enlist all patients with hereditary hemorrhagic telangiectasia treated with argon plasma coagulation for recurrent epistaxis at our department and to assess our experiences with the method.

**Methods:** This study includes all hereditary hemorrhagic telangiectasia patients treated by argon plasma coagulation at our department starting from 2010, the year when we began using the method, until 2019. Most patients also applied topical estriol ointment in conjunction with the treatment. All patients complained of frequent heavy epistaxis before the surgery and some even required repeated blood transfusions.

**Results:** Thirty-six patients underwent argon plasma coagulation in the monitored period (2010-2019) with mean age 54.75 and median age 59.5 years. All patients had telangiectasias in the nasal cavity. The oral mucosa and skin were also frequently affected, and 2 patients had telangiectasias in other organs. Twenty-two patients had more than 1 procedure, with a maximum of 16. All patients were satisfied with the effect of argon plasma coagulation on the severity and frequency of their epistaxis, and no major complications during or after the surgery were reported.

**Conclusion:** Argon plasma coagulation seems to be a safe, minimally invasive, and effective method in managing recurrent epistaxis in hereditary hemorrhagic telangiectasia patients.

**Keywords:** Argon plasma coagulation, epistaxis, estriol nasal ointment, hereditary hemorrhagic telangiectasia, Rendu-Osler-Weber disease

## Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is an autosomal dominant genetic disorder of the fibrovascular tissue.<sup>1</sup> The disease was named after Rendu (1896), Osler (1901), and Weber (1907), who first described the congenital vascular disorder independently in their publications.<sup>2</sup> It is characterized by abnormal vessel formation, including arteriovenous malformations and telangiectasias. Telangiectasias represent so-called minor lesions that occur on mucocutaneous surfaces of the nose, oral cavity, skin, or gastrointestinal tract. Major lesions are arteriovenous malformations that can be found anywhere in the body, such as in the central nervous system, lungs, or liver.<sup>3</sup> Hereditary hemorrhagic telangiectasia is genetically heterogenous disease,

mutations in multiple genes in the transforming growth factor-beta (TGF- $\beta$ ) signaling pathway have been described. The most commonly affected genes are *ENG* (encoding for the protein endoglin), *AVRL1* (which encodes for the receptor-like kinase 1, *ALK1*), and *MADH4* (encoding for the protein *SMAD4*).<sup>4</sup> However, considerable variability in the disease onset and clinical severity has been described, even in patients with identical mutation.<sup>5</sup> The diagnosis of HHT is clinically based on the Curacao diagnostic criteria, which were proposed by the Scientific Advisory Board of the HHT Foundation International in 2002. The criteria are recurrent epistaxis, positive family history, multiple telangiectasias, and visceral lesions. Hereditary hemorrhagic telangiectasia is confirmed if 3 or 4 criteria are met, probable with the presence of 2, and unlikely when less than 2 criteria are present.<sup>6</sup> More than 90%

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**Received:** March 5, 2021 **Accepted:** February 24, 2022

Available online at [www.b-ent.be](http://www.b-ent.be)



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of HHT patients suffer from recurrent epistaxis, therefore ENT physicians play an important role in the diagnosis of the disease.<sup>7</sup> Gastrointestinal bleeding is the second most common symptom and together with epistaxis often causes chronic iron-deficiency anemia.<sup>8</sup> Skin lesions are common but usually asymptomatic.<sup>9</sup>

The severity of epistaxis varies greatly, in some patients even blood transfusions are required repeatedly.<sup>10</sup> Epistaxis often reaches its maximum frequency and severity during the middle age.<sup>11</sup> First-line treatment for acute epistaxis in emergency ought to be nasal tamponade with resorbable material, non-resorbable packing should be avoided.<sup>12</sup> Many therapeutic approaches have been described for the treatment of recurrent epistaxis. They are based on the destruction of telangiectasias, reduction of blood perfusion, and trauma prevention. In case of severe epistaxis, unresponsive to local measures, arterial embolization of the maxillary artery can be performed.<sup>13</sup> For the local destruction of telangiectasias, endonasal argon plasma coagulation (APC), laser coagulation (Nd:YAG and KTP lasers), electrocoagulation, radiofrequency, cryosurgery, or chemical cautery can be used.<sup>14,15</sup>

Argon plasma coagulation represents a non-contact form of monopolar electrocoagulation. Argon gas is conducted through a tubelike applicator and ionized at its tip, where it becomes electrically conductive.<sup>16</sup> Its advantage is a limited penetration depth, as well as being better at resolving slight intraoperative bleeding than laser coagulation.<sup>17,18</sup> It is well known that estrogens induce metaplasia of the nasal mucosa to keratinizing squamous epithelium, so the nasal lesions become more covered and less vulnerable to local trauma.<sup>19</sup> Systemic hormonal treatment is associated with many side effects, so nowadays in the case of recurrent epistaxis in patients with HHT, the local application of estrogen ointment is preferred as its therapeutic effect has been proved.<sup>20,21</sup>

The aim of this study was to enlist all patients with HHT treated with APC for recurrent epistaxis in our department and to assess our experiences with the method.

## Methods

This retrospective analysis included patients with HHT treated for recurrent epistaxis with APC between the years 2010 and 2019 at Department of Otorhinolaryngology and Head and Neck Surgery 1st Faculty of Medicine, Charles University,

Faculty Hospital Motol, Postgraduate Medical School, Prague, Czech Republic. Before 2010, no patients were treated with this method.

All patients complained of frequent heavy nosebleeds, which adversely affected their quality of life and required repeated medical treatment. Twenty patients had even obtained blood transfusions because of severe anemia due to major nasal bleeding sometime during their life. The lowest recorded hemoglobin level was 47 g/L. All patients were subjected to clinical ENT examination including careful nasal rigid or flexible endoscopy on the first visit to the outpatient office. The APC procedure was performed under general anesthesia. For visualization and documentation, a rigid nasal 30°, 4-mm endoscope connected to a video device (Karl Storz, Tuttlingen, Germany) was used (Figure 1). Before the surgery, the nasal mucosa was anesthetized with a gauze impregnated with solution Hirsch 2% (2% cocaine hydrochloride). The generator for high-frequency current was set at 60 W and the argon flow at 1.8 L/min (ERBE, Tübingen, Germany) and a rigid resterilizable applicator with ceramic tip were used for nasal application (Figure 2). The telangiectasias were treated with APC in noncontact mode under endoscopic control until the paling and shrinkage of the telangiectasias were seen (Figure 3). To avoid septal perforation, the APC treatment was not performed on both septal sides simultaneously. At the end of the procedure, the nose was packed with Framykoin ointment (bacitracin zincum, neomycini sulfas) and absorbable gelatin sponge. The majority of patients



Figure 1. Arrangement in the operating theater.

### Main Points

- ENT specialists play a key role in diagnosing of the Rendu-Osler-Weber disease.
- Argon plasma coagulation is a contact-free technique where a high-frequency current is applied to the tissue through electrically conductive ionized argon gas. The penetration is limited to 1-2 mm, so the risk of damage to the adjacent tissue is very low.
- Our 9 years experience shows that argon plasma coagulation is a safe and very efficient method in the treatment of epistaxis in Rendu-Osler-Weber patients.





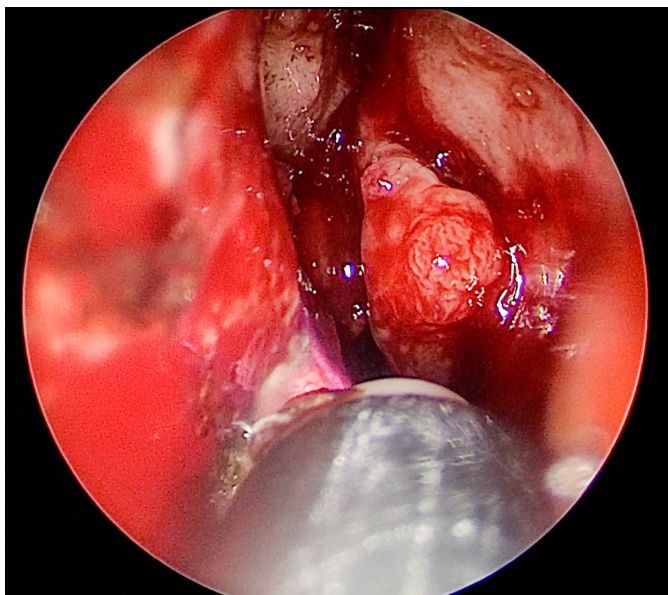
**Figure 2.** Nasal applicator of the argon plasma flow.

used estriol ointment before and after the procedure, in accordance with previous clinical findings reported in the literature.<sup>16</sup>

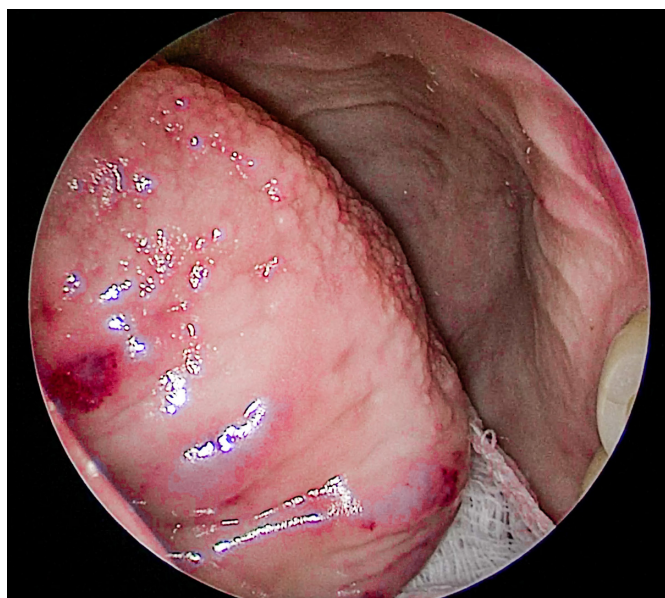
Due to the nature of the data, software statistical analysis wasn't necessary. In Charles University, Faculty Hospital Motol, the approval of the ethics committee or informed consent is not required for retrospective studies only based on the patient data analysis.

**Results**

In the monitored 9-year period (2010-2019) a total of 36 patients with HHT were treated with APC for recurrent epistaxis, 20 males (55.6%) and 16 females (44.4%). The ages at the time of the first surgery ranged from 21 to 74 years, with a mean age of 54.8 and a median age of 59.5 years. Two treated patients were father and son, proving genetic inheritance. During ENT examination telangiectasias were found in the nasal cavity in every case, frequently the oral mucosa and skin were also affected. Two patients had telangiectasias in other



**Figure 3.** Application of the argon plasma flow.



**Figure 4.** Telangiectasias of the oral cavity.

organs (Figure 4). Two patients had a septal perforation before the application of APC, which was treated with a silicone button in 1 patient. Two other patients had previously undergone Young procedure (surgical closure of the nasal cavity). One patient had Young procedure only on 1 side and the other side was then treated with APC. The second patient had bilateral dehiscence after the Young procedure and after APC he underwent resuture. Another patient had a dermoplasty, and 2 patients had a septoplasty, which were done at another clinical ENT department. Fourteen patients (38.9%) had only 1 APC treatment. Twenty-two patients (61.1%) had more than 1 procedure, 1 patient had 16 consecutive APC in 8 years (Table 1). The intervals between interventions varied from 1 month to 8 years. Together, 94 APC were performed in the monitored period. One patient had an inflammatory complication treated with systemic antibiotics which resulted in minor septal perforation. In the second patient, septal perforation appeared after the first APC treatment and enlarged slightly after the 3 consecutive procedures. No other preoperative or postoperative complications were seen. Minor nasal bleeding was controlled during the surgery and no nasal packing was needed. All patients were satisfied with the postoperative result and reported a reduction in the frequency and intensity of the bleeding. Three patients died from a cause not related to APC or epistaxis.

**Discussion**

Recurrent epistaxis affects more than 90% of patients with HHT and in most patients it is the first clinical symptom, therefore ENT specialists play a key role in diagnosing this disease.<sup>22,23</sup> No curative method for the treatment of HHT is available. Nowadays, the therapeutic options are intended

**Table 1. Number of Procedures and Patients**

Number of procedures	1	2	3	4	5	6	16
Number of patients	14	12	3	2	1	3	1

to reduce symptoms, in particular the bleeding. In terms of the systemic therapy, the use of hormonal agents has been proposed. Estrogens induce a squamous metaplasia of the fragile respiratory epithelium, so the vessels are better protected.<sup>24</sup> An antiestrogenic drug tamoxifen was also tested with promising results, but it did not receive wider use.<sup>25</sup> However, this hormonal therapy remains controversial due to its side effects.<sup>5,26</sup> Thalidomide suppresses angiogenesis and stimulates vascular maturation and current evidence suggests that its low-dose administration reduces epistaxis frequency and duration.<sup>27</sup> Moreover, there is an effort to introduce targeted therapy emerging from the field of molecular biology. The anti-angiogenic drug bevacizumab (anti-VEGF antibody, Avastin) has been used in clinical trials with auspicious results.<sup>28,29</sup> Furthermore, other preclinical studies have identified new molecular targets directly related to the affected signaling pathways.<sup>30</sup>

There are many available therapeutic treatments for epistaxis, including both conservative and surgical methods. The basis of conservative treatments is the application of different nasal ointments, mostly on a lipid base to decrease dryness and crust formation.<sup>31</sup> Bergler et al demonstrated the superior effect of APC with a topical estrogen cream compared to APC with dexpanthenol ointment.<sup>16</sup> Al Kahad and company has proposed an individually made nasal olive used for a few hours a day to reduce trauma and create a humid nasal environment.<sup>2</sup> A similar effect is achieved with the Young procedure, which involves closure of the nares.<sup>32</sup> Although the nasal bleeding is significantly reduced, due to the disadvantages of continuous mouth breathing and loss of olfaction, the procedure should be used only as a final option.<sup>33</sup> Furthermore, in 1 patient from our cohort appeared a dehiscence after the Young procedure accompanied by recurrent epistaxis, which was treated with APC and resuture. Another surgical method named septodermoplasty was described by Saunders in 1960. He replaced the fragile respiratory epithelium with a free split skin transplant.<sup>34</sup> The limit of this method is that the graft cannot cover the whole nasal cavity, and the recurrence of telangiectasias is inevitable.<sup>35</sup> However, less invasive methods have been developed in recent decades, such as a local destruction of telangiectasias by electrocoagulation, different types of laser, and APC.

The benefit of APC is that it is a contact-free technique where a high-frequency current is applied to the tissue through electrically conductive ionized argon gas.<sup>36</sup> The penetration is limited to 1–2 mm due to surface coagulation and drying, which means that the risk of damage to the adjacent tissue is very low and serious cartilage damage such as perforation can be prevented.<sup>20,37</sup> The other advantages are that the coagulation effect is best in tissues with high electrical conductivity such as vessels and bleeding lesions and the absence of the carbonization effect.<sup>38,39</sup> Our department started using APC for treating epistaxis in patients with HHT in 2010. Thirty-six patients underwent this procedure until 2019. Based on the study of Sadick and co-workers, the application of an estriol ointment was also recommended to the patients.<sup>20,40</sup> All patients reported that the procedure was effective and the frequency and severity of the nosebleeds were reduced (observation time 12 months to 9 years). The majority of patients had more than 1 surgery, which agrees with what is reported by several

authors who describe short disease-free intervals after the APC procedure.<sup>20,37</sup> Papispyrou et al could not demonstrate any advantage of Nd:YAG laser and APC over Nd:YAG laser monotherapy and suggests that Nd:YAG laser therapy creates a greater zone of inflammation and fibrosis that damage bleeding blood vessels, so the epistaxis-free intervals are longer.<sup>39</sup> However, Pagella et al proved in their study that APC is effective as a first-line procedure in patients with severe epistaxis and guarantees free of blood transfusions for a long period.<sup>41,42</sup> Moreover, APC has a much wider application, even in otorhinolaryngology. It can be used for the reduction of nonallergic hypertrophic inferior nasal turbinates, for tonsillectomy, or in the treatment of recurrent papillomatosis.<sup>43-45</sup> Argon plasma coagulation is also an important method in gastroenterology for the management of gastrointestinal bleeding.<sup>46</sup> Bin Shi et al reported successful resolution of bleeding in the small intestine caused by multiple telangiectasias in a patient with HHT with APC under double-balloon enteroscopy.<sup>47</sup> This study describes our experiences with APC combined with estriol ointment in the treatment of recurrent epistaxis in HHT patients, which is in concordance with recent findings. Except for 2 recorded septal perforations, it did not cause any further complications. Pagella and coworkers recorded 75 septal perforations among 323 patients. However, 31 patients had septal perforation already before the surgery and only 44 patients (13,6%) developed a septal perforation during APC treatment. Unfortunately, he did not mention the power of the generator in his paper.<sup>48</sup> On the other hand, Bergler et al set the generator at 40 to 60 W, but they did not indicate the rate of septal perforations.<sup>16</sup> Sadick and coworkers used the same power of 60 W like us and did not record any septal perforation among 69 patients treated with APC.<sup>20</sup> The low frequency of septal perforations in our cohort (5.5%) could be also explained by its smaller size. Argon plasma coagulation represents an effective and minimally invasive method, which is well tolerated by patients. However, sometimes it can be very challenging because of the reduced clarity of the operative field due to the preoperative bleeding. The repetition of the procedure is common.

**Ethics Committee Approval:** In Charles University, Faculty Hospital Motol, the approval of the ethics committee is not required for retrospective studies only based on the patient data analysis.

**Informed Consent:** Informed consent is not necessary due to the retrospective nature of this study.

**Peer Review:** Externally peer-reviewed.

**Author Contributions:** Concept – J.P.; Design – A.F.; Supervision – J.P.; Resources – A.F.; Materials – A.F., L.D.; Data Collection and/or Processing – F.A., L.D.; Analysis and/or Interpretation – A.F.; Literature Search – A.F., J.P.; Writing Manuscript – A.F.; Critical Review – J.P.

**Acknowledgments:** The authors would like to thank the nurses and technical staff who were present during the interventions, for their professional assistance and also the authors would like to thank Erick Harr for proofreading.

**Declaration of Interests:** The authors have no conflict of interest to declare.

**Funding:** The authors declared that this study has received no financial support.



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