Review

Advantages and Disadvantages of One-Shot Technologies for Atrial Fibrillation Ablation: Is It Possible to Select the Best Option?

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Review

Advantages and Disadvantages of One-Shot Technologies for Atrial Fibrillation Ablation: Is It Possible to Select the Best Option?

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Abstract

Atrial fibrillation (AF) is one of the most important causes of disability and mortality and is associated with several complications. Rhythm control through AF ablation is strongly suggested with pulmonary vein isolation (PVI) through single-shot ablation devices, like cryoballoon ablation (CBA) and circumferential pulsed-field ablation (PFA). In this review we will analyse the differences between these two techniques, in terms of their efficacy and safety profile. Then we will underline that the debate on the differences in costs between CBA and PFA is still controversial. For the lack of continuous rhythm monitoring during follow-up in most of the studies conducted, it is difficult to establish which one of these two technologies is more suitable for a given patient. Nowadays, the comparison between CBA and PFA is constantly evolving.

Keywords: atrial fibrillation; ablation; one-shot technologies

1. Introduction

Atrial fibrillation (AF) is one of the most globally important causes of disability and mortality and is associated with several complications such as thromboembolic stroke [1], heart failure and cognitive impairment [3]. It is also the most common sustained cardiac arrhythmia affecting millions of patients worldwide. Rhythm control can be performed with PVI [4–7] through catheter ablation techniques, such as focal radiofrequency ablation (RFA) or one-shot ablation devices, like CBA (Figure 1) and PFA (Figure 2) [8]. PVI is recommended in patients with symptomatic paroxysmal AF (PAF) or persistent AF (PeAF) resistant or intolerant to antiarrhythmic drug therapy and also as a first-line therapeutic option in patients with symptomatic PAF [9]. One-shot devices are strongly exploited for PVI in AF. The CBA technologies used are Arctic Front Advance PRO, Medtronic Inc. and POLARx Balloon Catheter, Boston Scientific while the circumferential PFA technologies approved are the Farapulse system (Boston Scientific), adopting a catheter with variable distal shapes (basket and flower), the FARAWAVE (Boston Scientific FARAPULSE) and other systems using circular multielectrode catheters, such as PulseSelect (Medtronic Inc.) and Varipulse (Johnson & Johnson). After analyzing the differences between these two techniques, we will evaluate whether and how it is possible to establish which one of these two technologies is more suitable to a given patient.

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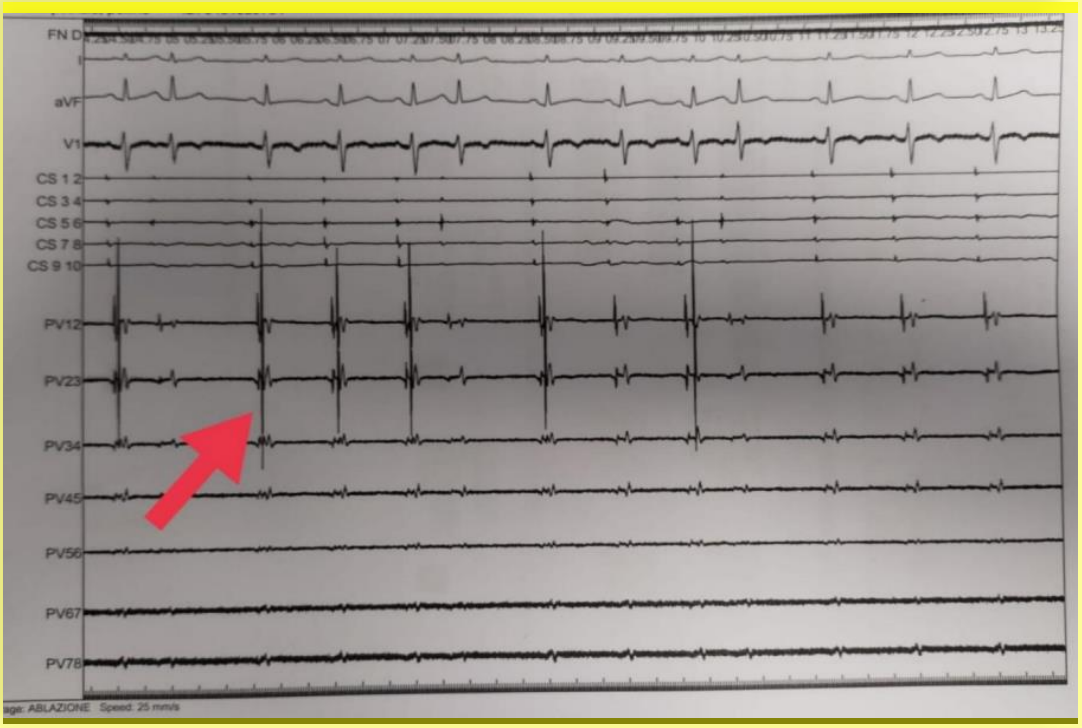

Figure 1. Disappearance of PV potentials after CBA.

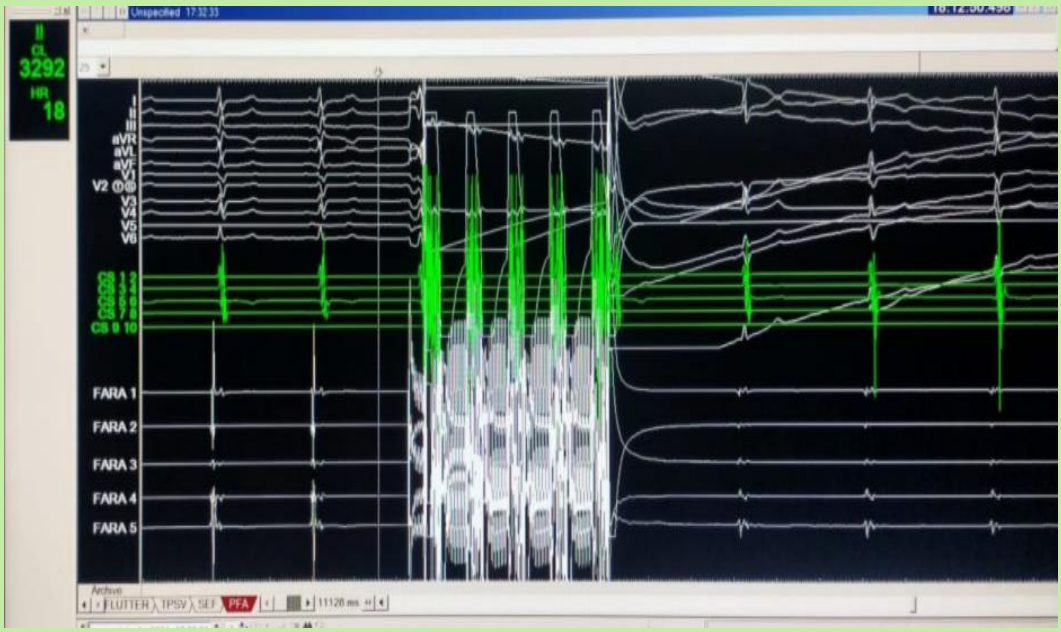

Figure 2. Disappearance of PV potentials after PFA.

2. Biophysical Mechanism of Action

2.1. CBA

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Lesion formation is due to the production of hypothermia at the catheter-tissue interface and is performed through the following phases: the freeze/thaw stage, the hemorrhagic-inflammatory phase and the necrosis and fibrosis stage. In the first phase the hypothermia leads to the slowing down of cell metabolism, decreasing intracellular pH. Moreover, continuous cooling causes the formation of various ice crystals. While the cells are progressively cooled to at least -40°C, ice crystals develop in the extracellular matrix and subsequently in the intracellular space. The production of these ice crystals has two consequences: compression of nuclei and cytoplasmic components and creation of a new established osmotic gradient, resulting in a strong movement of H+ ions out of the cell and of solute ions into the cell. This new intracellular electrolyte organization contributes to protein denaturation and irreversible damage to the plasma and mitochondrial membranes. Meanwhile, the progressive hypothermia causes a microvascular injury because it leads to vessel wall damage and subsequently vascular congestion and obliteration, causing important ischemia. At the end of the freezing stage, the tissue passively returns to the previous physiological temperature, creating a "thawing effect". In this time the rewarming-up causes enlargement and fusion of intracellular and extracellular ice crystals, expanding cellular destruction. The following phase is characterized by hemorrhage and inflammation in the region treated. After that the microcirculation is reestablished in the previously frozen area, the blood flow crosses damaged endothelium, resulting in edema and ischemic necrosis. Then the final phase occurs because activated fibroblasts give rise to replacement fibrosis. At the same time, apoptosis of cells close to the previously frozen area is triggered. This technique leads to the formation of a mature and definite lesion in some weeks [10,11].

2.2. PFA

Lesion formation is carried out thanks to application of pulsed electric field (PEF) at the catheter-tissue interface for few nanoseconds. When the cell membrane is exposed to a PEF, opposite charges are positioned on opposite sides of the membrane, resulting in an additional transmembrane voltage (TMV), termed as induced TMV. If the new combined TMV, that is the sum of resting TMV and induced TMV, reaches a specific threshold for at least few nanoseconds, an irreversible cell permeabilization, called electroporation, happens. This threshold varies according to the cell. Myocardial cells have a 4 times lower threshold than other cells. Moreover, if PEF application is powerful and long enough it determines cellular membrane instability ensuing in cellular death. The exact process of this phenomenon is still debated. Regardless of this mechanism, irreversible electroporation leads to more selective cardiomyocytes death than thermal damage. Causing plasmatic membrane instability, PEF determines influx of Ca2+ from extracellular matrix to intracellular space. Consequently, energy resources, as adenosine triphosphate (ATP), are used for activation of Ca-ATPases, resulting in reduced availability of ATP in mitochondria. Subsequently, there is an overproduction of reactive oxygen species, contributing to severe membrane instability and cellular death. Therefore, an irreversible electroporation (IRE) depends on various electric field parameters [12].

2.2.1. Electric Field Parameters

Electric field strength is the most important determinant of PFA; in particular, the more intense the electric field applied, the more extensive the effect on the target area. Another important electric parameter of PFA is pulse duration. When pulse duration is longer, lower voltages are applied to determine the same quantity of electroporated cells. The relationship between strength and pulse duration is not always inversely related because inverse proportionality constant varies when exposure duration is less than 1 ms. It is intriguing to analyze how the effects of ablation are modified by changing the pulse duration. Indeed, short high-voltage pulses followed by long low-voltage pulses have enhanced the ablation area [13]. Other important determinants of PFA are the number of pulses and pulse repetition rate. The raising of these is associated with a greater ablative effect, although this relationship is not always linear. A lot of pulse shapes are used for PEF and are square, exponential and biphasic and sine waves. Specifically, short (less than 1 **μs**) high-frequency (up to 1

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MHz) pulses with this last pulse shape determine effective lesions without causing muscle contractions. Nowadays, the most used designs of catheter for PFA are basket, flower and circular, all with different electrode size and spacing, which are fundamental for electric field distribution and for lesion formation. Moreover, there is irregularity in electric field distribution for smaller electrodes; therefore, smaller electrodes will have to dispose of a higher voltage than grater electrodes in order to obtain the same ablative effect. Electrode orientation in according to cardiac fibers orientation of the target area is another important factor for the ablation result with PFA. For spherical cells, which do not include cardiomyocytes, a stronger electroporation effect occurs when the electric field is delivered parallel to tissue fibers rather than when the same field is perpendicular. Therefor, in a complex anatomical area such as pulmonary vein (PV)/left atrium (LA) junction where there are a lot of bundles organized in multiple positions (primarily circular and secondarily longitudinal and oblique), a definite and irreversibly electroporated lesion could be dependent on cardiomyocytes fibers orientation [12–17]. Finally, PEF can be applied to the targeted tissue through two main ways: unipolar versus bipolar. Unipolar method allows a deeper lesion formation with lower energy delivery than bipolar method. However, monopolar configuration is less controlled, determining also skeletal muscle contraction and significant pain without general anesthesia. Therefore, bipolar method is the preferred method for approved PFA catheters [17]. Finally, the contact force seems a less important factor for PFA than cryoballoon ablation because PFA creates lesions also in absence of a good direct contact with the targeted area due to the high conductivity of blood [12–17], although recent papers have highlighted the importance of contact even for PFA [18–20].

2.2.2. Thermal Effect: Is It Possible?

When the electric field is applied, heating occurs. Although PEF has been considered a non-thermal energy, temperature rising is reported at least in the range of 1-10 °C, regardless of the electric field strength and period of exposition. When the temperature reaches the range of 43-45°C the thermal damage is established after hours whereas when the temperature exceeds 50° it occurs after seconds. Actual PFA systems are deprived of any feedback loop for temperature monitoring. Nowadays, a multielectrode device, Globe PF Pulsed Field Mapping and Ablation System (Kardium Inc.), whose last version allows for PFA delivery, measuring contact force and temperature, is subjected to clinical trials. Therefore, further research is necessary to better evaluate the thermal potential and avoid unwanted thermal injury [12,20].

3. Are There Predictive Parameters of Success?

3.1. With CBA …

There are some parameters which are markers of acute or chronic PVI through CBA. These factors are time to isolation (TTI), time to reach target temperature (- 40°C), thawing speed, coldest nadir temperature achieved, PV occlusion grade and PV capture [21]. TTI is the time required from the beginning of freezing to the last recording of PV potentials. It is also the most studied parameter which has demonstrated a strong relationship with CBA effectiveness and is an important and independent pointer of both acute and chronic PVI. In particular, a lower TTI is linked to a more efficient PVI in both short and long term follow up. However, CBA carried out up to TTI (TTI-based CBA) is associated with a reduced duration of the procedure, without providing more advantage than a more prolonged approach. To overcome this, according to a recent metanalysis, less frequent atrial arrhythmias subsequent to AF PFA occur when TTI-based CBA is followed by extended (longer than 2 minutes) cryoablation post-TTI [21]. As TTI, time to target temperature of -40°C is an independent factor of durable PVI. Specifically, if the time to reach this temperature is not higher than 60 s, PVI is more effective in both short and long times. This novel parameter is the result of the relationship between freezing curve slope and isolation durability. This correlation is due specifically to two events. First, progressive freezing below -40°C leads to intracellular ice crystals formation, which allows catheter adherence to the tissue during CBA. Therefore, in this way the brushing effect,

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which is verified during rocking heart movements and respiratory variations, is eliminated because of a strong catheter adherence to the selected area. For the second, the coldest nadir temperature is usually reached within 60 s; indeed, after this period of time, the curve slope enters a plateau [21–23]. The thawing phase is another important CBA phase which provides useful information about PVI durability. This stage is composed of three subphases: initial thawing (IT), which occurs from the end of freezing to 0°C, thawing plateau (TP), which happens from 0° C to 10° C and late warming (LW), which happens from 10°C to 20°C, when cryoballoon becomes flat [21]. Thawing time of ≥25 s between −30°C and +15°C and IT time higher than 10 s seem to be associated with a permanent PV isolation. In a recent retrospective study, TP has been considered as the greatest biophysical predictor among other factors. Indeed, TP gives information about quantity of frozen tissue and includes a subphase of recrystallization, which increases cell osmotic trauma. This explains also the relationship between TP time and troponin T (TnT) [24]. Given that TnT quantifies the extension of myocardial injury, the higher the TP time, the greater the elevation of TnT after CBA. Moreover, according to the same retrospective study, after 1 cryoenergy delivery, if TP time is less than 15 s, it is necessary to perform an extra application while if TP time is higher than 25 s, it is unnecessary. Therefore, TP time could be visualized in the future and subsequently used in the decision whether to carry out or not another CBA application [24]. Other predictor parameters of long-term success are the coldest nadir temperature reached and PV occlusion grade during CBA [21]. Finally, loss of PV capture is a parameter associated with strong long- term success in patients with both PAF and PeAF. In details, PV capture is a marker that identifies patients with PeAF in whom PVI is sufficient as the initial CBA approach and for an eventual subsequent CBA in case of recurrence of PeAF. This factor provides more information about PeAF ablation because of the absence of an established optimal lesion set for treating this condition [21,25] (Table 1).

Table 1. Predictors of success of PVI by CBA [21–25]. They factors are markers of acute or chronic PVI through CBA and are time to isolation (TTI), time to reach target temperature (- 40°C), thawing speed, coldest nadir temperature achieved, PV occlusion grade and PV capture.

Success Predictors	Independent or dependent?	Linking to extension of myocardial injury
TTI [21]	Independent	None
Time of reaching of target temperature (-40°C) [22,23]	Independent	None
thawing speed [24]	Dependent	Thawing plateau prolongation correlates with TnT levels [24]
Coldest nadir temperature achieved [21–24]	Dependent	None
PV occlusion grade [21]	Independent	None
PV capture [25]	Independent	None

3.2. With PFA …

Currently, PFA is being thoroughly evaluated with the aim of identifying some predictive parameters of success for AF ablation. According to a recent clinical trial, the inspIRE study, a number of PFA applications equal to or higher than 48 total (equal to or higher than 12 for each PV) with a novel 3-dimensional mapping integrated circular loop catheter (the Varipulse catheter) is a strong parameter of long-term success for drug-refractory PAF, resulting in a 1-year success rate of 80% after AF ablation [26]. Recently, failure of class I/III antiarrhythmic drugs prior to PFA is associated with improved outcome in patients with PAF [27]. Moreover, PFA has also been studied preclinically for ventricular ablation; specifically, in a recent preclinical study it has been demonstrated that epicardial unipolar electrograms after pulsed-field energy delivery differ within thirty minutes when a reversible electroporation becomes irreversible (28) (Table 2). Nowadays, the estimate of long-term

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success of PFA continues to be almost exclusively linked to follow-ups of patients subjected to this procedure. This means that the biophysical mechanism behind PFA has to be still clarified and understood in greater details.

Table 2. Predictors of success of PFA [26–28]. PFA is being thoroughly evaluated with the aim of identifying some predictive parameters of success for AF ablation.

Success Predictors	Is it related to only particular PFA catheter?	Applications in AF ablations
Number of applications of PFA >= 12 for PV [26]	Varipulse	Yes
Failure of class I/III antiarrhythmic drugs prior to PFA [27]	Farapulse	Yes
Different epicardial unipolar electrograms after 30 minutes of PFA [28]	Monopolar focal catheter	No, in ventricular ablations

4. Cardiac and Neuronal Biomarkers: PFA versus CBA

In every cardiac ablation the injury myocardial markers represent the amount of tissue ablated; in particular, high sensitivity TnT (hsTnT) is the most specific marker of any myocardial damage. According to a recent study, after PFA hsTnT delivery is 1,9 times higher in comparison with CBA. Although TnT is strongly linked to lesion extension, it is currently unclear if PVI performed by CBA or PFA is associated with a different lesion size and morphology. Moreover, clinical studies are currently needed to evaluate if the more pronounced increase of hsTnT after PFA could influence the success rate or safety of the procedure compared to CBA [29]. The neuronal damage is another factor to consider in PVI by CBA or PFA. It's evaluated by a neuron-specific marker (S100B), which is expressed by glial cells next to the autonomic nerves and ganglionated plexi of the heart. According to recent clinical trials and owing to the strong selectivity of electroporation, PVI by PFA causes lower delivery of S100B than PVI by CBA. This is correlated to a particular effect noticed after PVI with cryoenergy. Specifically, resting heart rate rises after PVI by CBA while it is not modified after PFA. Therefore, this is very probably linked to the reduced neuronal injury testified by a lower S100B delivery with PFA. Unfortunately, these last laboratory observations are very limited because they are the result of not randomized clinical trials [30].

5. Database Research and Selection Criteria of Patients

This review is based on inclusive search of the databases, as Pubmed, Embase and Cochrane Library, analyzing important studies published before he August 2025. The keywords used are: "atrial fibrillation ablation", "one-shot devices", cryoballoon ablation" and "pulsed-field ablation". The literary resources chosen for this review were randomized or not randomized clinical trials or meta-analyses which compare outcomes between CBA and PFA; reporting the results of this comparation; reviews of novel ablative techniques for atrial fibrillation. Case reports and case series have been excluded. This review compares CBA and PFA in patients with PAF or PeAF submitted to AF ablation for the first time, with one or more cardiovascular risk factor, such as hypertension, dyslipidemia, diabetes mellitus and transient ischemic attack (TIA)/stroke.

6. Acute and long-Term Efficacy

Acute and long-term efficacy is evaluated by recent meta-analyses of randomized or not randomized clinical trials or recent single randomized or not randomized clinical trials of patients with PAF or PeAF subjected to PVI for the first time. The acute efficacy is evaluated by absence or persistence of PV potentials after ablation while the long-term results are evaluated by freedom from

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AF recurrence after ablation. According to a recent randomized, single-bind, non-inferiority trial, ADVENT trial, PVI by PFA, performed through catheter FARAWAVE, was not inferior to PVI by conventional thermal ablation (both CBA and RFA) in 706 patients with symptomatic PAF refractory to antiarrhythmic drugs, regarding the primary efficacy composite endpoint of freedom from index procedure failure, occurrence of atrial tachyarrhythmias after a 3-month blanking period, arrhythmic drugs use, need of cardioversion or repeated ablation [31]. Moreover, according to a recent meta-analysis of 400 patients with PAF or PeAF, Urbanek et al. evaluated 200 patients treated with PVI by second-generation Arctic Front System and 200 patients by FARAPULSE. In details, acute PVI was similar (98% in CBA and 100% in PFA); time procedure was shorter in PFA patients than CBA patients while fluoroscopy time was similar. 1-year freedom from AF recurrence was slightly in favor of CBA (CBA in PAF : 83,1% vs PFA in PAF: 80,3%; CBA in PeAF: 71% vs PFA in PeAF: 66,8%) [32]. A relatively new cryoballoon, POLARx, showed similar efficacy and safety profiles with respect to Arctic Front CBA system, exhibiting lower procedural time and fluoroscopy time than the Arctic Front system [33]. Regardless of PV variant anatomy, POLARx system is associated with good long-term efficacy and safety in patients with PAF and PeAF, similarly to Arctic Front System and FARAPULSE [33,34]. Moreover, in a not randomized clinical trial Badertscher et al. compared PVI by CBA with last generation POLARx system and PVI by PFA with FARAPULSE in patients with PAF and PeAF. An acute success rate of almost 100% was reported in both groups. Overall, 1-year freedom from AF recurrence was slightly in favour of PFA compared to CBA (76% for PFA and 70% for CBA) [36]. Subsequently, in other meta-analysis Zhang et al. demonstrated that PVI by PFA with FARAPULSE is more tissue-specific and permits shorter procedures than PVI by CBA with Arctic Front or POLARx Systems, with a slightly greater efficacy in favour of PFA in more than 1500 patients with PAF. Indeed, acute procedural success is 99,6% in CBA and 99,9 % in PFA and 1 year freedom from AF recurrence is 75% in CBA patients and 79,6 % in PFA patients [36]. In a successive meta-analysis, Rudolph et al. compared PVI by CBA and PVI by PFA with FARAPULSE in 3805 patients principally with PAF. Specifically, arrhythmia recurrence appeared lower with PFA than CBA (odds ratio= 0,73, 95% CI = 0,54-0,98). Moreover, procedural time and radiation dose were shorter with PFA than CBA while fluoroscopy time resulted similar [37]. In a systematic review and meta-analysis, Vetta et al. compared PVI by CBA with Arctic Front and POLARx Systems and PVI by PFA with FARAPULSE in patients with PAF or PeAF, showing similar acute success (CBA: 99,9% vs PFA: 99,1%), while long-term success was slightly favorable to PFA with respect to CBA (CBA: 80,3% ±1,7% vs PFA: 82,3% ±1,4%). Moreover, a higher number of patients with PeAF was included in PFA group because FARAWAVE catheter allowed to provide not only PVI but also left atrium posterior wall isolation and posterior mitral line ablation [38].

Regarding patients with only PeAF there are fewer studies . Baderstcher et al. considered a population of 181 patients referred for either AF PFA or CBA, of whom 35% had PeAF. Both the tecnhiques showed similar results after a one year follow up, with an insignificant advantage for PFA and a similar very low complications incidence. The ADVANTAGE AF TRIAL was conducted on 255 patients in PeAF treated with PVI and posterior wall ablation (PWA) with PFA, with a subpopulation of 141 subjects (66%) also receiving CTI ablation. All patients enrolled underwent continuous rhythm monitoring with an insertable device. After a one year follow up, the procedural effectiveness was around 70%, considering the atrial arrhythmias recurrence threshold a burden > 0.1% and episodes duration lasting more than one hour. The CRALAL randomized clinical trial enrolled 289 patients suffering from PeAF who were randomly assigned in a 1:1 fashion to two groups treated with only CBA or with CBA plus right atrial linear ablations. Success was higher in the group with biatrial approach, with a recurrence rate after a one year follow up based on repeated ECGs and holter monitoring of 37% vs 53%, with very few complications in both [40]. Hence, basing on the results of these two last studies we might hypothesize that CBA and PFA, especially if accompanied by adjunctive right atrial ablations, offer a valid treatment also to PeAF patients. Unfortunately, they did not compare the two different techniques and the slight superiority exhibited by PFA - success at one year 70% vs 67% - does not reflect an ojective outcome since the additional lesions set differed in the

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two populations [39,40]. Finally, Isenegger et al. compared the results of CBA and PFA in a population of 220 patients divided in two almost equal groups (107 vs 113 subjects). After a mean follow up of one year, PFA demonstrated a higher success rate, although not significant (72% vs 60%). Interestingly, in the PFA group they noticed a greater tendency of PeAF to transform in PAF than in the other group.

PFA has also been studied with other systems, as PulseSelect and Varipulse Systems, which have showed acutely comparable efficacy and safety profile with respect to FARAPULSE System. In details, FARAWAVE catheter and PulseSelect catheter have the same acute success efficacy and exhibited the same safety, even though greater clinical trials are needed to compare long-term outcomes between these different systems [42]. Unfortunately, the majority of these studies have considerable limitations in the absence of continuous rhythm monitoring after AF ablation because follow-up data were very often collected with serial 24- to 72-hour Holter ECG or periodic 12-lead ECG recordings. Therefore, this practice may cause an underestimation of the real AF burden during follow-up. However, a very recent randomized clinical trial conducted on two arms of 105 patients each, (SINGLE SHOT CHAMPION), providing continuous rhythm monitoring through implantable cardiac monitors (ICMs) during a one year follow-up in all its participants, considering the first three months as the blanking period. In details, SINGLE SHOT CHAMPION is the first randomized controlled trial with ICM use during follow-up to compare PVI with PFA by FARAPULSE system and PV with CBA using the new. fourth-generation Arctic Front cryoballoon in patients with PAF [43,44]. In details, this important trial has demonstrated that PFA was non-inferior to CBA in terms of atrial tachyarrhythmias recurrence incidence, as assessed by continuous rhythm monitoring, exhibiting, on the contrary, a slight superior efficacy (37 recurrences vs 53, p=0.046) [43,44]. Subsequently, there will be clinical trials that will include other novel systems, such as PulseSelect and Varipulse, with thermal ablation with cryoenergy.

Finally, basing on this comprehensive analysis it seems reasonable that PVI by PFA is slightly more effective than PVI by CBA in patients with PAF or PeAF submitted to one of these procedures for the first time.

6.1. PVs' Reconnection After CBA or PFA: Where Is the Truth?

In a retrospective study Della Rocca et al. demonstrated that CBA was associated with a higher PVs reconnection rate than PFA in patients with PAF or PeAF referred to redo procedures (CBA: 27,5% vs PFA 19,1%) [8]. Despite this, in a very recent MANIFEST-REDO study comprising 427 patients submitted to a redo procedure owing to recurrence of AF or atrial tachyarrhythmias, Scherr et al. (45) showed that PVs reconnection after PFA was not uncommon since a discrete proportion of the enrolled patients (55%) had at least one PV reconnected and the rate of reconnection was similar - around 30% - among the different veins, while the remaining 45% exhibited persistent isolation of all 4 PVs, considering that its rate for each PV was around 30%. Interestingly, in this study 140 of the patients enrolled who had undergone also posterior wall isolation in the index procedure exhibited the same proportion of reconnection as for the PVs. After the redo procedure, in a one year follow-up, considering the first three months as the blanking period, freedom from any recurrence of atrial tachiarrhythmias regarded a discrete proportion of patients (65%) and the complications rate was reasonably low (2.8%). In terms of rate of reconnection, similar results were demonstrated in a very recent study involving 1330 referred for CBA of AF (73% paroxysmal) [46]. After a very long follow up of at least 5 years, recurrence rate of any atrial tachyarrhythmia was 52.5%, with a PVs reconnection incidence in those patients (15.7%) who underwent a redo procedure of 55% despite a mean number of 3 veins still disconnected, with the remaining 45% of the entire group of redo patients with all 4 PVs persistently isolated [46].

7. Safety and Adverse Effects

The safety is valued through the same recent meta-analyses and the various clinical trials used to compare the efficacy and durability in obtaining PVI by PFA and by CBA. The ADVENT trial

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shows that PFA has the same 1-year safety than thermal ablation (both CBA and RFA) [31]. Urbanek et al. demonstrated that CBA by second generation Arctic Front System was overall slightly less safe than PFA by FARAPULSE in their meta-analysis of 400 patient with PAF and PeAF. Among these patients, this slight difference was strongly linked to damages of the surrounding tissues observed in the CBA group, as phrenic nerve palsy (PNP) (1,5%), esophageal injury (0,5%) and hemoptysis (0,5%) while the only case of cardiac tamponade occurred in the PFA group [32]. Subsequently, Badertscher et al. shows that CBA by last generation POLARx System was equally safe with respect to FARAPULSE in 181 patients with PAF or PeAF. In details, three PNPs were found only in CBA group (two after CBA of right superior PV and one after CBA of right inferior PV) while two cardiac tamponades were observed only in PFA group. In particular, all PNPs recovered during follow-up [35]. Moreover, Zhang et al., in their meta-analysis of more than 1500 patients with PAF, confirmed that CBA by Arctic Front and POLARx Systems were more frequently associated with PNP than PFA by FARAPULSE (CBA: 2,3 % vs PFA 0,1%) while cardiac tamponade was found only in PFA patients (CBA: 0% vs PFA: 1,3%) [36]. Subsequently, Rudolph et al. demonstrated that periprocedural complications were lower in FARAPULSE group than CBA group (odds ratio = 0,62, 95% CI =0,4-0,96) in 3805 patients predominantly with PAF. In details, PNPs and esophageal injuries (EI) were more frequent in CBA group than PFA (PNPs: 2,2 % vs 0,2%; EI: 2% vs 0,7%) while cardiac tamponades resulted more related to PFA than CBA (PFA:1% vs CBA: 0,2%). However, more recent evidences support an uncommon, but possible role of PFA on causing phrenic nerve injury (PNI) [47–49]. Chehirlian et al. in a study conducted on 64 subjects referred for PFA of AF, monitoring phrenic nerve function during the procedure, noted a 40.6% (26 patients) incidence of acute PNI that was still present in 6 (24%) at discharge, with only one case of persistent dysfunction at three months [47]. In an animal model Howard et al. confirmed PNI as a possible rare complication of PFA and highlighted its possible dose-dependence [48]. Another important observation was made by Oda et al. who reported a case of persistent PNI after PFA and attributed it to high intensity ablation of the anterior wall of the right superior PV, underlining the importance of checking the position of all the electrodes [49].

Finally, there were not particular differences in vascular access complications and TIA/stroke [37]. Afterwards, Vetta et al. demonstrated that FARAPULSE System led to a lower number of periprocedural complications than Arctic Front and POLARx Systems (CBA: 5,6% vs PFA: 3,1%). In particular, PNP was confirmed to be more common in CBA than in PFA (1,84% vs 0,01%) while cardiac tamponade continued to be more frequent in PFA than in CBA (0,8% vs : 0,4%). ST-elevation caused by coronary spasm or air embolism occurred more frequently in PFA group (PFA: 0,85% vs CBA: 0,33%). The differences between vascular complications and TIA/stroke were similar, as in previous meta-analysis [38].

Moreover, in a great study of 17 thousand patients with AF, MANIFEST-17K, acute kidney injury (AKI) due to intravascular hemolysis was another complication mentioned after PFA ablation (0,03%) and seem to be dependent on the number of PFA applications. In particular, less than 100 energy deliveries is recommended to avoid severe hemolysis and a hydration protocol could be actuated after PFA to reduce kidney failure risk [50,51].

The risk of kidney damage due to PFA emerged also from the NEMESIS-PFA Study , in which several hemolysis markers revealed greater red cell destruction in the PFA group with respect to the patients treated with radiofrequency (RF). In the same study the authors underlined also a dramatically higher TnT release with respect to the RF group, with a clear dose response relationship. This greater myocardial injury provoked by PFA might explain also the finding of a contextual major impairment of left atrial function recorded in the same patients [52]. An impairment of left atrial function was also reported in a very recent study that enrolled 59 patients divided in two groups, according to the energy adopted for PVI (RF, 28 pts, or PFA, 31 pts) [53]. All the patients underwent left atrial (LA) speckle tracking analysis at baseline, in the acute and chronic post-procedure phase. Only the group submitted to PFA developped a significant and persistent reduction at distance of LA contraction strain, while the LA reservoir strain decreased only immediately after the intervention

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[53]. These observations appear to be concordant with the finding of more extended left atrial lesions discovered with cardiac MRI with LGE after PFA and CBA in comparison with those obtained with RF [52], which in turn, allowed to achieve a higher proportion of complete encircling of the PVs performing more contiguous lesions [52]. CBA, however, does not seem to affect left atrial function neither acutely, nor at distance - one and three months after the procedure [54–56].

In conclusions it seems to be quite clear that PVI by PFA is slightly safer than PVI by CBA in patients with PAF or PeAF referred to these procedures for the first time as far as PNP is concerned, that however also in CBA appears to be a very uncommon complication. Despite that, we should not neglect that very rare adverse events such as cardiac tamponades and AKI by hemolysis result more frequent in patents treated with PFA.

8. Versatility

CBA and PFA have other therapeutic options besides PVI in patients with AF. In details, CBA of the LA roof and posterior wall is one of the target of AF ablation once PVI has been achieved in order to have total conduction block of the LA roof and posterior wall isolation in patients with PAF or PeAF [57–60]. As for PFA, ablation of the LA roof and posterior wall is a possible adjunctive target during redo procedures, especially in patients with PeAF [61–63]. However, utilizing either CBA or PFA for treating other substrates in the LA in addition to the PVs still remains a matter of debate despite in PeAF recent findings seem to favour the treatment of adjunctive substrates [57–63].

9. Costs

As for the economic aspects, if we estimate that in a country like Italy every year 10000 AF ablations are performed and we suppose to divide this number in 5000 PVIs by CBAs and 5000 PVIs by PFAs, we can imagine the following hypothetical results. Given that the average cost of the CBA and PFA kits in Italy are respectively approximately 4500 and 5500 euros [64], the Italian Health Care System would spend 22,5 million euros for 5000 CBAs and 27,5 million euros for 5000 PFAs. Therefore, a difference in cost of 5 million euros would emerge between the two procedures. Even admitting a slightly better short and long-term efficacy of PVI by PFA , although not definitely proven, in terms of freedom from AF recurrence after the first procedure (PFA: 75% vs CBA: 72%, considering an approximate average value of effectiveness of the main studies and meta-analyses), in these two hypothetical groups 3750 patients would be effectively treated with PFA while 3600 patients with CBA, resulting in a difference of 150 patients in favour of PFA with however an adjunctive expense of 5 million euros. Each of these 150 patients would therefore imply an additional cost of more than 33000 euros (5 million euros/150 patients). This cost for a single patient is much greater than the average cost for a CBA (4500 euros) or PFA kit (5500 euros). On the other hand, if we destined the adjunctive expense of 5 millions euros to acquire more CBA kits in order to treat other patients with PVI for the first time, approximately further 1100 patients could be treated with CBA, with about 790 patients successfully ablated. Estimating a long-term success rate with CBA of 72%; if the overmentioned difference of 5 millions euros was used to acquire PFA kits at the average cost of 5500 euros, this would allow to treat 909 patients with PFA, ensuing in approximately 682 patients successfully ablated, admitting a success rate of 75% as previously outlined. In summary, at the actual average costs in Italy if we considered to perform 10000 procedures of CBA, the expense would be 45 millions euros with 7200 patients successfully treated. On the other hand, the same amount of money would enable to acquire only 8200 PFA kits, resulting in the achievement of an effective cure for only 6150 individuals (Table 3). Currently, the debate on the difference in costs between CBA and PFA is still very controversial because of the reported subtle difference in effectiveness and safety between these two procedures. Finally, we should not overlook that PFA procedures require general anesthesia or deep sedation and therefore, at least in Italy, according to our current rules, the mandatory presence of the anesthesiologist, whose availability is not always granted and involves a further cost.

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Table 3. Economics aspects of PFA and CBA [51]. The debate on the difference in costs between CBA and PFA is still very controversial but it is undeniable that actual cost/benefit ratio may be in favour of CBA.

	Single procedure average cost	Expected number of patients successfully treated out of 5000 procedures	Global cost of 5000 procedures	Expected number of patients successfully treated with 5 million euros expense	Expected number of patients successfully treated with 5 million euros expense
PFA	5500 euros	3750	27,5 million euros	682	6150
CBA	4500 euros	3600	22,5 million euros	790	7200
Difference between PFA and CBA	1000 euros	150	5 million euros	-108	-1050

Our assumptions about the cost-benefit ratio of choosing one-single shot technology rather than another are based on their current market price for the Italian healthcare system. However, we should not ignore that financial strategies related to production costs and market requests dictated by physicians preferences may induce the biomedical companies to promote one technology rather than the other, decreasing its sale price.

10. Conclusions

Currently, one-shot devices for AF ablation are increasingly used in many countries and a lot of randomized clinical trials or meta-analyses are ongoing to optimize the efficacy and safety of CBA and PFA. For example, recently Jungen et al. have showed that overweight and obese patients subjected to PVI by PFA had lower contrast-dye volume with respect to patients undergoing PVI by CBA; therefore, overweight and obesity have been associated with increased radiation exposure in PVI by PFA. For these reasons, PVI by CBA is usually preferred in overweight and obese patients compared to PFA [65]. Nowadays, the comparison between CBA and PFA is constantly evolving and the actual situation is summarized in Table 4. According to this review, PVI by PFA seems to be slightly more effective than PVI by CBA in patients submitted to AF ablation for the first time, keeping also an insignificantly higher general safety profile than CBA itself for most of the complications, with the exception of cardiac tamponade. Finally, the debate on the difference in costs between CBA and PFA is still very controversial but it is undeniable that actual cost/benefit ratio may be in favour of CBA. Unfortunately, the majority of studies conducted to investigate the effectiveness of these procedures exhibit a great limitation, I.e. the lack of continuous rhythm monitoring during follow-up after AF ablation. However, as it was just said, some clinical trials are ongoing to overcome this limit. However, according to the data collected, it is still difficult to evaluate whether and how it is possible to establish which one of these two technologies is more suitable for a given patient.

Table 4. Head-to-head comparison between CBA and PFA.

Procedural time	↓	↑
Costs of ablation kit	↑	↓
Cost/Benefit ratio	↓	↑
Cardiomyocyte specific damage	↑	↓
Neuronal specific damage	↓	↑
Necessity of sedation	↑ ↑	↑
Complete PVI at first shot	↑ ↑	↑

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At 1 year AF recurrence freedom after ablation	↑	↑	↑
Phrenic nerve and exophagus damage	↓		↑

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