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Catheter ablation for the treatment of atrial fibrillation – development of various technical modalities

Zdravljenje atrijske fibrilacije s katetrsko ablacijo – razvoj različnih tehničnih možnosti

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Abstract

Treatment of atrial fibrillation (AF) remains a rapidly developing field of cardiology characterized by continuous technological improvements and a multidisciplinary approach to problem solving. In addition to searching for improved ablation methods for effective and safe pulmonary vein isolation, the efforts are also dedicated to upgrade the understanding of apparently chaotic mechanisms of action potential propagation during AF. The mechanisms of clinical AF can be explained by the hypothesis of triggers and drivers. According to this hypothesis, AF is triggered by premature beats originating mostly from the pulmonary veins and is maintained (driven) by local regions with slow action potential propagation located predominantly in the atrial wall where pulmonary veins enter the left atrium. Pulmonary vein isolation thus remains a corner stone of invasive treatment of AF.

Izvleček

Zdravljenje atrijske fibrilacije (AF) je hitro razvijajoče se področje kardiologije, pri katerem smo priča stalnemu razvoju različnih oblik tehničnih izboljšav in multidisciplinarnega pristopa. Poleg iskanja najprimernejšega ablacijskega načina za učinkovito in varno izoliranje pljučnih ven poskušamo razumeti navidezno kaotičen mehanizem prevajanja akcijskega potenciala med samo aritmijo. Pri razumevanju nastanka AF se je uveljavila predvsem hipoteza o sprožilcih in vzdrževalcih AF. AF sprožajo prezgodnji utripi, ki večinoma izvirajo iz pljučnih ven, vzdržujejo pa jo lokalna področja z upočasnjenim prevajanjem akcijskega potenciala, ki se pretežno nahajajo na področju izraščanja pljučnih ven iz levega preddvora. Kljub številnim novim pristopom pa je izoliranje pljučnih ven s katetrsko ablacijo še vedno temelj invazivnega zdravljenja AF.

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Key words: atrial fibrillation; pulmonary vein isolation; radiofrequency ablation; balloon cryoablation; irreversible electroporation; wide antral circumferential ablation

Ključne besede: atrijska fibrilacija; izoliranje pljučnih ven; radiofrekvenčna ablacija; balonska krioablacija; ireverzibilna elektroporacija; široka obkrožitvena antralna ablacija

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1 Introduction

Among arrhythmias, atrial fibrillation (AF) is the most common. In Slovenia, according to the prevalence in comparable countries, it is estimated that there are 15,000–30,000 patients with AF. In the ECG, the absence of a P wave (an organized atrial depolarization is absent) and irregular QRS complexes (irregular ventricular repolarization) are characteristic of AF. AF is a chronic disease in which the degree of progression is assessed according to the duration of the arrhythmia. It is divided into 5 groups: first detected AF; paroxysmal AF, in which an episode of arrhythmia with spontaneous terminations lasts a maximum of 7 days; persistent AF, in which an episode of arrhythmia lasts more than 7 days; long-standing persistent AF, which lasts more than 1 year; and permanent AF. For the efficient pumping of blood, atrial and ventricular action need to be coordinated; in normal sinus rhythm, the atria contract approximately 200 ms before the ventricles. During AF, electrical activity and thus atrial contraction are entirely irregular, which leads to blood stasis, in particular in the left auricle. During blood stasis, blood clots can form, which makes AF the main risk factor for stroke (1,2). Additionally, AF causes various symptoms that negatively affect the quality of life and worsens preexisting heart failure (3). For these reasons, treatment of AF consists of anticoagulants, which prevent blood clot formation, and drugs to prevent AF or keep patients in sinus rhythm for as long as possible. In AF treatment, two main strategies have been established: rate control and rhythm control. In most cases, antiarrhythmic drugs are prescribed to limit the rapid response of the ventricles, and in permanent AF, catheter ablation can be used to sever the electrical connection between the atria and ventricles; this also requires the insertion of a permanent cardiac pacemaker. Maintaining sinus rhythm is indicated in paroxysmal and both forms of persistent AF, with treatment success depending on AF progression. Paroxysmal AF has the best prognosis. According to the 2020 European guidelines (4), if treatment with antiarrhythmic drugs (Class I, Level of Evidence A) fails, catheter ablation is indicated (2). In Slovenia, a little over 300 patients with AF are treated with catheter ablation each year, which places us in the middle among the European Society of Cardiology (ESC) members in terms of the number of treatments per million inhabitants (5).

2 Radiofrequency ablation for the treatment of AF

Catheter ablation or radiofrequency ablation (RFA) is the most widespread minimally invasive method of AF treatment, in which a high-frequency alternating electric current is supplied to the target tissue through the tip of the ablation catheter. Due to the small surface area of the ablation electrode and thus a high current density, energy in the form of heat is released on contact with the myocardial tissue, which at a temperature higher than 50°C causes a permanent lesion, which then permanently terminates the action potential conduction in the ablated area (6). RFA causes punctiform damage at the contact of the catheter with the myocardial wall at the depth of 3–4 mm (Figure 1; E) (7). This is sufficient to damage all layers of the myocardial wall from the endocardium to the epicardium in the wall of the left atrium (i.e. transmural lesion). The closed loop of the electrical circuit in RFA is enabled by a dispersive electrode placed on the patient's back, which with its large surface area ensures that the current density there is small enough and that there is no heating of the skin or other significant biological effects. The main drawback of RFA is the comparatively narrow temperature window between 37°C, which enables a physiological tissue state, and 50°C, which can cause permanent injury. The lesion always spreads from the higher temperature area with the highest current density to the lower temperature area. Two possible side effects of ablation can occur: insufficient (temporary) tissue injury instead of the desired permanent injury, and unwanted damage to the surrounding tissue, such as the oesophagus, which is located very close to the left atrium. To prevent unwanted myocardial and surrounding tissue injury, all ablation catheters are now equipped with temperature sensors which automatically adjust the supplied electrical power according to the measured temperature at the catheter tip.

2.1 Pulmonary vein isolation with radiofrequency ablation

The main goal of RFA is pulmonary vein isolation, which is considered to be the most common site of AF triggers. Anatomically speaking, two pulmonary veins exit from the left and two from the right of the

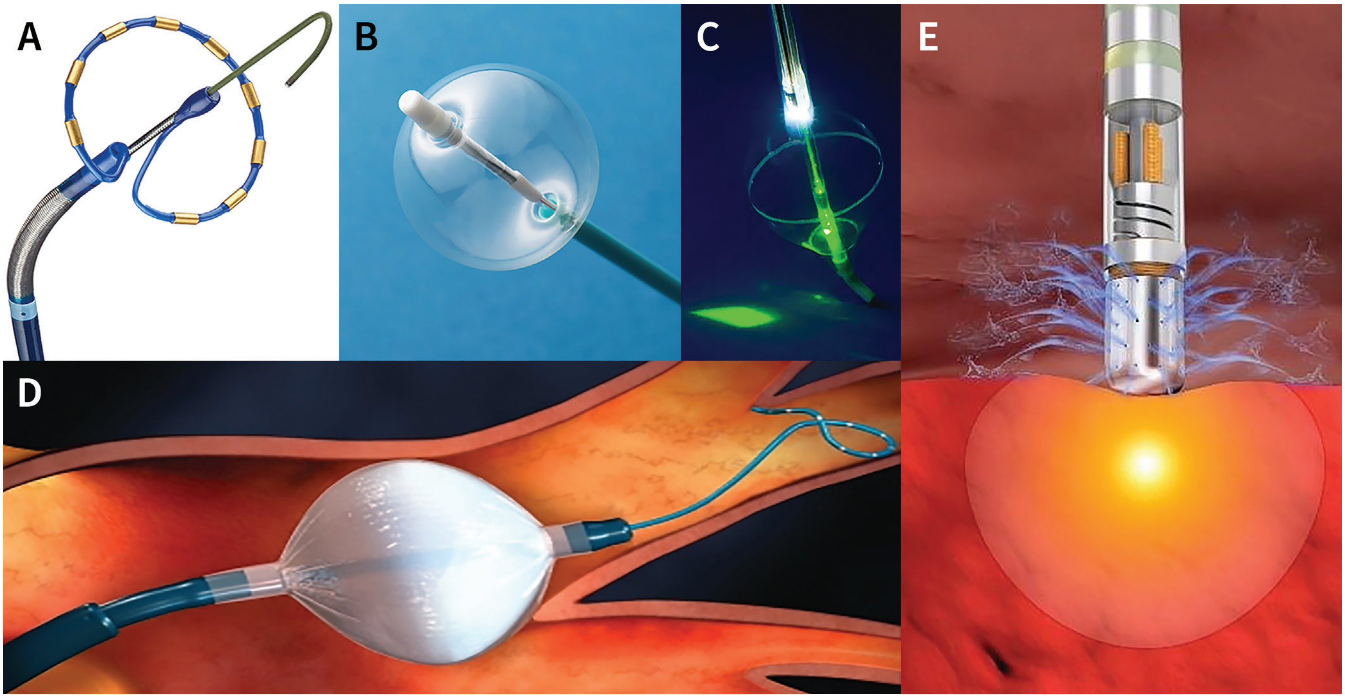

Figure 1: Multi-electrode PVAC GOLD catheter (A), hot balloon catheter (B), laser ablation balloon (C), cryoablation balloon in the pulmonary vein ostium (D). Schematic representation of the ablation catheter, used in the WACA procedure (see text for explanation) with a lesion cross section, also showing rinsing with saline (E) (8-12).

left atrium posterior wall. The tissue characteristics of the junction between the pulmonary veins and the left atrium is complex and different to other areas of the heart. Individual muscle fibres in this area are capable of spontaneous depolarization, thus causing premature beats, which can act as AF triggers. Slow action potential propagation is also characteristic for the junction between the pulmonary veins and the left atrium, which enables the depolarization wave to circle inside the local myocardial area and acts as a driver of AF (13). Over 20 years ago, Haïssaguerre et al. found that in patients with paroxysmal AF, the triggers of spontaneous premature beats are located in the pulmonary veins in 94%. With targeted RFA they tried to destroy the triggers in the pulmonary veins themselves, which they succeeded in doing in only 38 out of 45 patients (84%), despite numerous repeat attempts. Although trigger ablation was not highly effective, the recurrence of AF withing 8 months was prevented in 62% of patients after the procedure, indicating the promise of this method (14). The procedure was safe with only a few cases of cough and occasional severe pain during ablation, and one case of a small left atrial clot, confirmed by angiography, being reported. After the discovery that AF triggers are located in the pulmonary veins, pulmonary vein isolation (PVI) was established as a cornerstone of AF treatment with catheter ablation. During the PVI procedure, a circular mapping catheter (the so-called LASSO catheter, Figure 2; A) was inserted into the pulmonary vein. After the ablation around the pulmonary vein ostia, it was used to check whether complete absence of intracardiac electrical signals was achieved in the pulmonary veins, as pulmonary vein isolation is the main goal of the procedure (Figure 2; B). By using the LASSO catheter, very rapid AF triggers from the pulmonary veins were detected, confirming the hypothesis that states that spontaneous pulmonary vein electrical activity can drive AF. At the beginning of the method's development, the PVI procedure was used by targeting areas with earliest activation at the pulmonary vein ostia with ablation, achieving isolation (15); the procedure was named segmental ostial PVI. It has been used since 2003 at the University Medical Centre Ljubljana. The long-term results of the procedure on 126 patients (68% with paroxysmal AF, 32% with persistent AF) were published in 2013 (16). With repeated procedures in the 36-month follow-up period, symptomatic improvement was achieved in 73% (84% in paroxysmal AF, 48% in persistent AF) with rare complications (5.5%). These results are comparable to the data in the literature (17).

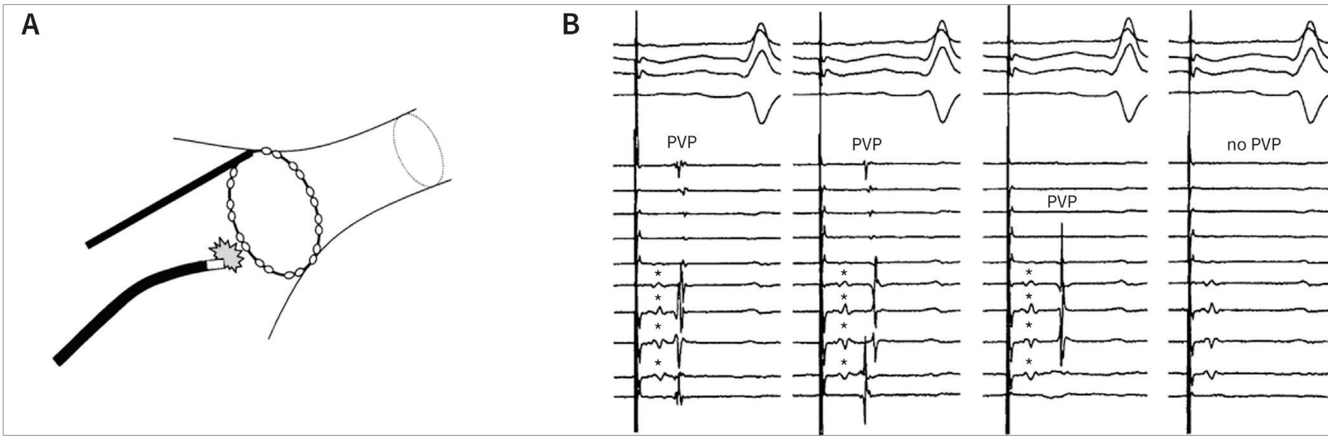

Figure 2: Schematic representation of the LASSO catheter at the pulmonary vein ostium and point-by-point ablation (A). Representation of pulmonary vein potentials (PVP) covered with a 20-electrode LASSO catheter (B). Electrical activity (PVP) can clearly be seen in the first three beats, while the last beat shows successful isolation of the pulmonary vein (no PVP). Intracardiac signals from distant locations are marked with an asterisk (*) and remain unchanged despite successful pulmonary vein isolation (18). Permission to use the images has been obtained.

2.2 Wide antral circumferential ablation

An important breakthrough in AF treatment with RFA was achieved with the development of the electrical anatomical mapping system (EAM), which enables a traceable continuous sequence of punctate lesions around the pulmonary veins ostia (Figure 3). The basic idea of the method is to guarantee a continuous isolation line (in contrast to the segmental ostial PVI, in which ablation lines are not continuous), which, in addition to pulmonary veins triggers, also covers the area of pulmonary veins exits from the left atrium and thus isolates potential AF drivers, mostly located in this area. The procedure is named wide antral circumferential ablation (WACA). As early as 2014, a review of 12 studies demonstrated the greater effectiveness of this procedure in maintaining sinus rhythm compared to segmental ostial PVI (19). Despite the high effectiveness with almost 100% achieved pulmonary vein isolation during the procedure, permanent isolation of the pulmonary veins remains a challenge, as the re-establishment of the electrical connection between the left atrium and at least one pulmonary vein in as much as 62.5% within two months after the procedure has been described (20).

Permanent isolation of the pulmonary veins strongly depends on the sufficient depth of each of the point lesions and the continuity of the isolation line (21), and acute pulmonary vein isolation (achieved during the

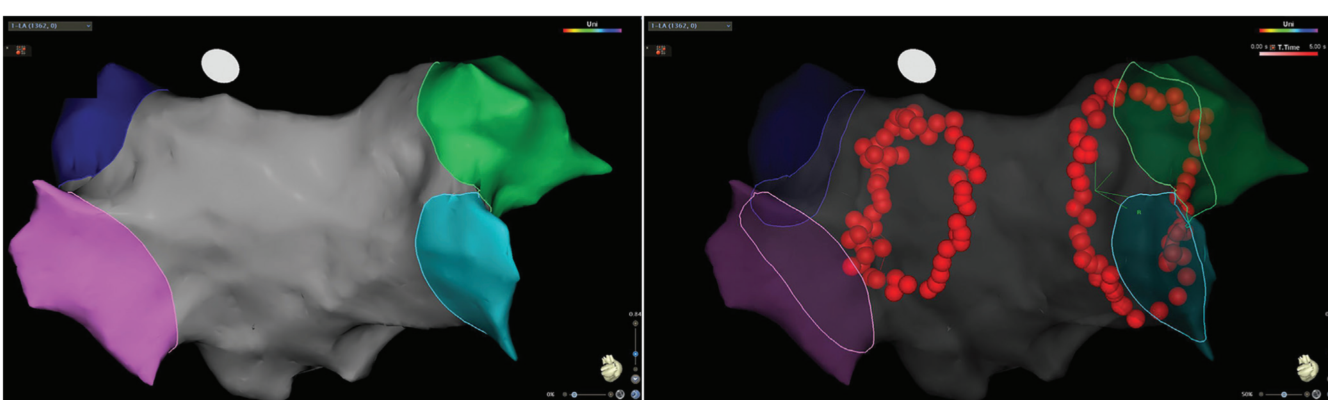

Figure 3: Example of a finished WACA procedure (see text for explanation). Red dots represent single-point RFA ablation lesions in two antral isolation lines around the exit points of the left and right pulmonary veins. The posterior view of the left atrium anatomy with coloured pulmonary veins (dark blue: left superior pulmonary vein, pink: left inferior pulmonary vein, green: right superior pulmonary vein, light blue: right inferior pulmonary vein). Image is from our own archive.

procedure) does not have a reliable predictive value for permanent pulmonary vein isolation (13,21). The lesion depth with a constant supply of electrical power is proportional to the quality of contact of the ablation catheter with the target myocardial tissue, with an increase in catheter tip temperature and a drop in ablation circuit impedance being good indicators of contact quality (22). As the WACA procedure uses cooled ablation catheters to prevent clot formation at the catheter tip, catheter tip temperature measurements are not adequate to assess the lesion depth. Therefore, circuit impedance monitoring during RFA has gained validity. A preclinical study has shown that a drop in circuit impedance of more than 15 Ω means that good contact of the ablation electrode with cardiovascular tissue has been established, but a drop in circuit impedance greater than 20 Ω predicts the risk of target tissue explosion due to heating above the boiling point of water (22). Steam pop is a frequent side effect during RFA and can cause cardiac perforation and pericardial bleeding, leading to cardiac tamponade, a life-threatening complication. There is a lack of clearly established guidelines for monitoring the drop in circuit impedance during the WACA procedure. In clinical practice, a relative drop in circuit impedance of approximately 10% has been shown as an indicator of good contact between the ablation catheter and target myocardial tissue. In one of the first clinical studies to target a 10% drop in circuit impedance with each lesion made during the WACA procedure, permanent pulmonary vein isolation was confirmed in 92% during a repeated procedure after 163 ± 133 days (median ± SD) (21). Contact quality between the ablation catheter and target myocardial tissue can be monitored by using intracardiac echocardiography (ICE) with probes up to 3 mm thick, which are inserted via guidewires through the femoral vein into the heart. The use of EAM and ICE systems enables the safe and effective use of the WACA procedure without radiography, which was shown in 144 consecutive patients with paroxysmal AF in Slovenia, among the first in the world (23).

2.3 Pulmonary vein isolation with contact force measuring technology

At the University Medical Centre Ljubljana, as at the majority of large world centre, the WACA procedure remains the first and most common method of AF treatment due to various technological improvements. One of the key improvements enables the measuring of the contact force (CF) between the ablation catheter tip and target tissue. Based on the data on the contact force during the procedure, we can estimate the depth of each individual ablation lesion. Currently, the most sophisticated protocol that exploits the technological potential of CF ablation catheters and is supported by excellent clinical results has been named CLOSE-guided WACA (24). Based on clinical experience, the authors of the CLOSE-guided WACA procedure have defined the minimum criteria for assessing the quality of lesions, summarized in the form of an ablation index (AI). It is based on an empirical equation, which, in addition to the contact force (gram), also takes into account the input power (watt) and ablation time (second). The AI value to assess the transmural lesions is adjusted to different areas in the left atrium. For example, a value of 400 is enough to achieve a transmural lesion in the thinner posterior left atrial wall, while the same is true for a value of 550 in the thickened anterior wall. The continuity of the isolation line around the pulmonary veins, achieved with an even sequence of lesions with a maximal interlesion distance of 6 mm, is also important. One of the most important findings of the method's authors was that not only the average contact force (gram) is crucial for the quality of the planned lesion, but above all the stability of the contact, which must be greater than 4 g at least 30% of the ablation time. The most impressive result of their studywas a 98% rate of pulmonary vein isolation with the establishment of an isolation line around the pulmonary veins during the procedure without the need for additional ablations. The importance of meeting the criteria of the CLOSE-guided WACA protocol was further demonstrated in three patients who had to have the procedure repeated due to AF recurrence. During the repeated procedure, they were able to identify discontinuous segments in the antral isolation line on which not all CLOSE-guided WACA criteria were met in the original procedure (24). Despite the high effectiveness of the CLOSE-guided WACA protocol, no significant complications were detected in the study, indicating the safety of the method. As the AI value provides a very reliable predictive value of the lesion's transmurality, it is possible to more accurately evaluate other parameters that predict the quality of change with the AI value; a drop in the RFA circuit impedance, reduction of signal amplitude after the ablation and a change of the signal form after the ablation. Of all the above, only the drop in RF ablation circuit impedance by 18.3 ± 1.1 Ω (mean ± SD), a reduction of approximately 12% from baseline before the start of each RFA, has an equivalent predictive value of the transmurality of an individual lesion as AI (25).

2.4 Possible complications of radiofrequency ablation

Threatening complications can appear in 2–3 % of procedures (2). They are divided into early complications, appearing during or immediately (up to 24 hours) after the procedure, or late, appearing up to 2 months after the procedure. The procedure mortality is very low at less than 0.1% (26).

During the procedure itself, due to the application of RF energy, cough can appear, a consequence of vascular tissue heating in the pulmonary vein, signalling an inappropriate ablation location outside the isolation line around the pulmonary veins. Rarely, severe chest pain can appear during the procedure, indicating thermal damage to the pericardium or pleura. When such pain appears during ablation at the posterior left atrial wall, it can be the consequence of oesophageal heating due to its location directly posterior to the left atrium. Pericardial effusion, which can lead to cardiac tamponade, and embolic stroke are also among the early complications. To prevent clot formation and stroke, therapeutic doses of heparin should be used. Ablation catheters with cooled tips can also be used, in which the tip is continuously rinsed through small holes by heparinized saline (Figure 1; E).

An atrio-oesophageal fistula, a consequence of collateral thermal injury of the oesophageal wall, also counts among the late complications. It is one of the most dangerous complications of invasive AF treatment with a high mortality rate (27). It is a rare complication, appearing in less than 0.5% (26).

3 Methods for pulmonary vein isolation with single-shot techniques

Despite the effectiveness of the WACA procedure, the tracing of punctate lesions is a relatively lengthy procedure; the average duration of the procedure is stated to be up to 284 minutes (28). In addition to the duration of the procedure, a disadvantage is also its complexity, which requires long-term training of a cardiologist (28,29). Therefore, such treatment of AF is normally available only in tertiary medical institutions. Various customized technological solutions have emerged in the search for the simplification of the procedure and ensuring wider availability of AF ablation treatment. Simplicity is common to all of them, based on single-shot techniques: multi-electrode RFA, balloon cryoablation, balloon laser ablation and hot balloon ablation (28).

The only clinically available multi-electrode RFA catheter (PVAC Gold, Figure 1; A) has 9 gold electrodes, enabling the simultaneous supply of RFA energy. The widespread use of this catheter was prevented by the extremely high incidence (20%) of otherwise asymptomatic cerebral embolisms. This complication was not detected with a standard RFA catheter with a cooled tip used in the WACA procedure (28). With normal left atrium anatomy with four separate pulmonary veins, the use of different balloon catheters is also possible. All technologies have the common goal of isolating the pulmonary vein with only one application. The hot balloon catheter (Figure 1; B) has an adaptable size from 25 mm to 35 mm and is entirely filled with a mixture of normal saline and contrast for radiography visualization. The balloon can be heated to 75°C with an RF coil, enabling vein isolation in 3 minutes and an average procedure duration of less than 2 hours (30). Due to frequent thermal oesophageal injury, oesophageal cooling with cooled liquids is recommended during each application, which necessitates the use of general anaesthesia. The currently published results are comparable in effectiveness to the WACA procedure, although the first randomized clinical study has yet to appear. The balloon for laser ablation (Figure 1; C) is interesting because it is the only one that allows for the visualization of the anatomy and quality of contact of the balloon with the target myocardial tissue via a built-in endoscopic camera. We are still waiting for the first randomized clinical study to evaluate the effectiveness of laser ablation balloon. According to the currently published results, the procedure duration is even longer than the WACA procedure, making the technology less likely to achieve widespread use (28).

The effectiveness of balloon cryoablation, in which contact between the cryoballoon catheter (Figure 1; D) and the target tissue is cooled with liquid nitrous oxide (laughing gas) up to – 60°C, was confirmed by a randomized study performed in 16 centres (29). Clinical equivalence with the WACA procedure was proved. As the study was performed in centres with a large procedure volume where only 141 minutes were required on average for the WACA procedure, the duration of the balloon cryoablation procedure was only 17 minutes shorter. Balloon cryoablation also has a safety profile comparable to the WACA procedure apart from the possible temporary phrenic nerve injury (2.7%), which was not detected in the WACA procedure. Due to its relative simplicity when compared to the WACA procedure, balloon cryoablation enabled the opening of new AF ablation treatment centres and became the method of choice in some smaller centres. In terms of the number of procedures in some European countries, such as Spain, balloon cryoablation is already approaching the scope of WACA (31).

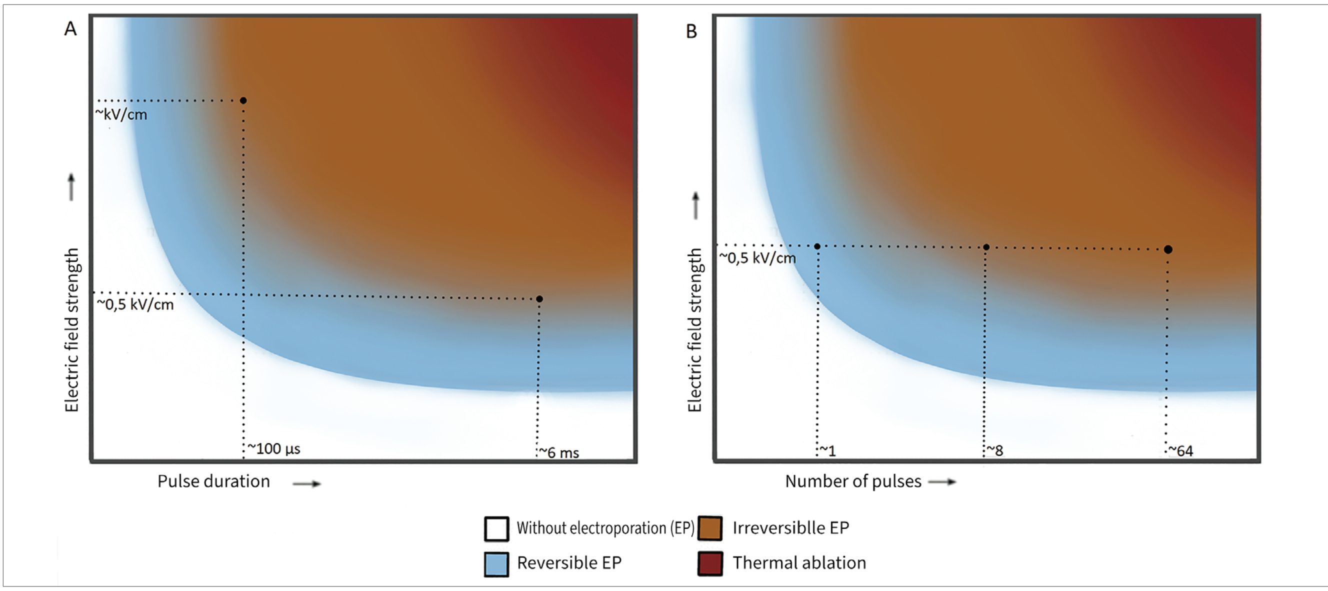

Figure 4: A: Type of electroporation depending on the strength of the electric field and the duration of each pulse. B: Type of electroporation depending on the strength of the electric field and the number of pulses (pulse duration 100 µs). (Source: The Laboratory for Biocybernetics of the Faculty of Electrical Engineering, University of Ljubljana).

4 Prospects for the development of a pulmonary vein isolation method with irreversible electroporation

In clinical practice, various sources of ablation energy are used. In all, the mechanism of tissue injury is thermal, by heating or cooling tissue. The possibility of collateral tissue damage in the immediate vicinity of the target tissue is present and comparable in both heating and cooling. A short while ago, a new method for non-thermal target ablation of myocardial tissue, based on electroporation, was introduced (32-35). Electroporation is a phenomenon by which the permeability of the cell membrane is greatly increased due to forced transmembrane voltage by exposing cells to short high-voltage electric pulses. The phenomenon is also called electropermeabilization, as it also allows molecules for which the cell membrane is otherwise impermeable to cross the cell membrane. Electroporation can be reversible if the cell membrane returns to the original state after a certain time after exposure to electric pulses. The exposed cells thus maintain homeostatic balance and retain their function, enabling them to survive. Irreversible electroporation (IRE) occurs when the cell injury becomes irreversible, leading to cell death (36). Reversible electroporation is an established method in oncology with electrochemotherapy, where electroporation is used to locally increase the influx of cytostatics into the tumour cells, thus increasing their effectiveness (37-39). In oncology, IRE is also established for the treatment of surgically or RFA-inaccessible tumours (40,41). Whether electroporation will be reversible or irreversible is most influenced by the strength of the electric field and the duration and number of pulses applied (Figure 4) (42).

More than a decade of preclinical and clinical studies points to the safety and effectiveness of the IRE ablation method. Despite the extraordinary variety of ablation catheters used and the parameters of the supplied electrical pulses, no study has detected the typical complications that otherwise accompany all thermal cardiac ablation methods (34,35,43,44,45,46). The advantage of IRE is also in the extremely short time needed to perform the ablation (only a few ms, Figure 5; C) when compared to the established thermal methods (46). In the interim report of the first clinical study on the use of IRE for the treatment of AF with catheter ablation, PVI required a third less time than other ablation methods. By optimizing the IRE protocol, they were the first to confirm a 100% permanent pulmonary vein isolation in a repeat electrophysiological procedure after 3 months (47). In addition to the already described safety and speed, ablation with irreversible electroporation enables better achievement of transmural lesions with an appropriate choice of electric pulse parameters, catheter and ablation protocol (Figure 5) (48,49). However, the development of this promising method is still in its infancy, despite much evidence of efficacy and safety.

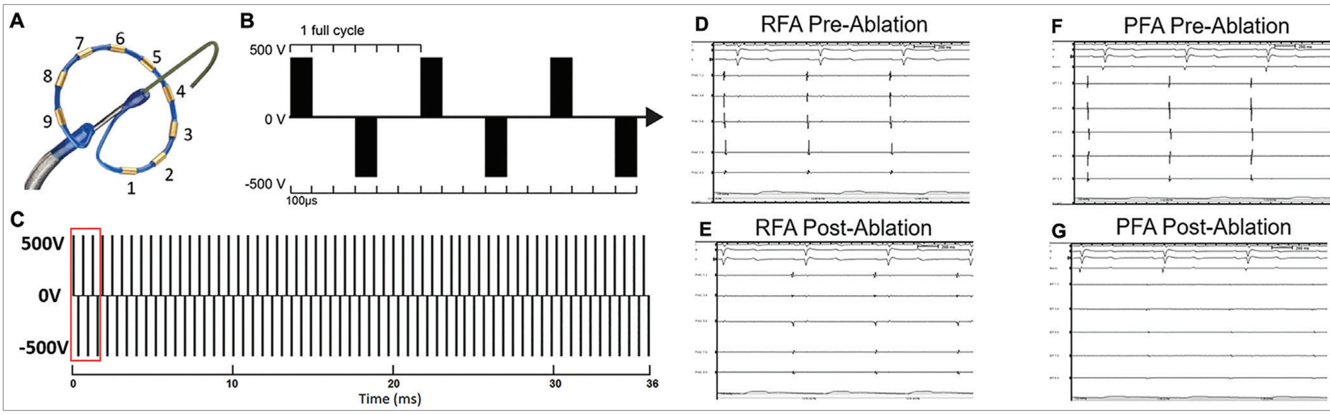

Figure 5: Multi-electrode PVAC GOLD catheter, used to supply IRE pulses (A). A schematic representation of the amplitude and duration of supplied biphasic pulses (B). Display of the duration of one ablation, composed of 60 biphasic pulse cycles (C). Display of intracardiac electric signals in a pulmonary vein before (D, F) and after (E, G) ablation with irreversible electroporation (46). Permission to use the images has been obtained.

We still expect that further technological improvements will lead to the rapid establishment of the method in clinical practice. Not long ago, the company Medtronic announced the start of a study to obtain a licence to use the PulseSelectTM system, enabling treatment of AF with irreversible electroporation in everyday clinical practice (50). The Laboratory for Biocybernetics of the Faculty of Electrical Engineering, University of Ljubljana, has also contributed its rich experience in the field of electroporation in the development of this system.

5 Conclusion

Catheter ablation with pulmonary vein isolation is currently the most effective method of AF treatment. With technological advancements, we can expect improvements and new approaches to increase the availability and safety of this invasive AF treatment.

Conflict of interest

None declared.

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