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Přehledový článek | Review article

Oral anticoagulation during atrial fibrillation ablation: Facts and controversies

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ABSTRACT

On the background of population ageing atrial fibrillation (AF) has reached epidemic dimensions in developed countries. This condition is associated with major cardiovascular morbidity and mortality mainly due to its thrombo-embolic and heart failure related complications. Left atrial (LA) catheter ablation has emerged as a suitable alternative to antiarrhythmic drugs for sinus rhythm maintenance at least for paroxysmal atrial fibrillation in the settings of no/mild LA dilatation. Chronic oral anticoagulation (OAC) is helpful to prevent AF thromboembolic complications in high-risk patients. OAC is also protective around ablation procedures in patients with or without an indication for long-term OAC therapy, emphasizing a slight increase in periprocedural risk of stroke. Due to the potential catastrophic hemorrhagic complications during trans-septal LA instrumentation, traditional approach on LA ablations involved warfarin discontinuation with periprocedural heparin bridging. Recent observational data suggests that radiofrequency (RF) catheter ablation of AF under therapeutic OAC (mainly vitamin K antagonists [VKA]) may reduce the periprocedural risk of complications, mainly thromboembolic events (possibly including silent strokes). Uninterrupted OAC has been acknowledged as an alternative to heparin bridging by the recently published consensus and guidelines update on AF ablation. Currently the recommended therapeutic level of OAC during ablation is low (such as an INR of 2–2.5). In the general AF settings new OAC (NOAC) have shown non-inferiority compared to VKA for stroke prevention, with better safety. Rapidly acting NOAC seem a tempting alternative to VKA at least for the patients taken off OAC before the ablation, possibly avoiding any post-procedural heparin bridging. However, limited experience with periprocedural use of NOAC (mainly dabigatran) suggests an increased risk of bleeding or thromboembolic complications compared with VKA.

SOUHRN

Vzhledem ke stárnutí populace dosáhla ve vyspělých zemích světa incidence fibrilace síní (FS) rozměrů epidemie. Toto onemocnění je spojeno s významnou kardiovaskulární morbiditou a mortalitou, hlavně v důsledku následných tromboembolických komplikací a komplikací v souvislosti se srdečním selháním. Vhodnou alternativou podávání antiarytmik pro udržení sinusového rytmu alespoň při paroxysmální FS v případech bez dilatace LS nebo pouze s mírnou dilatací se stala katetrizační ablace v levé síni (LS). Chronická perorální antikoagulace (PAK) pomáhá u vysoce rizikových pacientů zabránit tromboembolickým komplikacím FS. U pacientů indikovaných i neindikovaných k dlouhodobé léčbě pomocí PAK tato léčba rovněž poskytuje ochranu v období kolem ablačních výkonů, což mírně zvyšuje periprocedurální riziko rozvoje cévní mozkové příhody. Vzhledem k potenciálně katastrofálním krvácivým komplikacím během transseptální ablace v levé síni se při tradičním způsobu provádění ablací v levé síni přerušovala léčba warfarinem a periprocedurální období

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se překlenovalo podáváním heparinu. Údaje z observačních studií z poslední doby naznačují, že periprocedurální riziko komplikací, hlavně tromboembolických příhod (případně včetně němých cévních mozkových příhod) by mohla snížit radiofrekvenční (RF) katetrizační ablace FS při současném použití PAK (hlavně antagonistů vitaminu K [VKA]). Nedávno publikovaný konsensuální dokument a aktualizované doporučené postupy pro ablaci FS uznávají nepřerušovanou PAK jako alternativu k podávání heparinu pro překlenutí výše uvedeného období. V současnosti je doporučená hodnota PAK během ablace nízká (jako např. INR 2–2,5). Při léčbě běžných případů FS se ukázalo, že nové formy PAK (NPAK) nejsou o nic méně účinné než VKA, přitom jsou bezpečnější. Rychle účinkující NPAK představují lákavou alternativu VKA, přinejmenším u pacientů s vysazením PAK před ablací; pravděpodobně by se tak odstranila nutnost podávání heparinu po výkonu. Podle zatím omezeného množství zkušeností s periprocedurálním použitím NPAK (hlavně dabigatranu) se však lze domnívat, že se tak oproti VKA zvyšuje riziko krvácivých nebo tromboembolických komplikací.

Klíčová slova:
Antagonista vitaminu K
Fibrilace síní
Heparin
Katetrizační ablace
Perorální antikoagulancia

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, reaching epidemic dimensions in the developed world due to population ageing, with an overall prevalence of approximately 1.5–2% [1–3]. The arrhythmia is associated with a significant increase in mortality, morbidity and hospitalization mainly due to its thromboembolic complications and uncontrolled ventricular rate, with a five-fold risk of stroke and a three-fold incidence of congestive heart failure [4]. The two principal targets of therapy are the prevention of stroke and the alleviation of symptoms through rhythm or rate control. To accomplish the former, most patients with AF will require an oral anticoagulant (OAC). Left atrial (LA) catheter ablation has emerged as a rhythm-control alternative to antiarrhythmic drugs (AAD). Catheter ablation procedures are indicated for patients with medically refractory/recurrent, symptomatic AF. Recent consensus and guideline update assigned it a class IA indication for first-line treatment in selected patients with paroxysmal AF and no/minimal structural heart disease [5–7]. These procedures comprise ablation in the systemic circulation, often with conversion from AF to sinus rhythm and are associated with a significant risk of thromboembolism. Strategies have been developed to reduce the risk of intra-procedural stroke, like real-time detection of the newly formed thrombi (transesophageal or intracardiac echocardiography) or thrombus prevention (irrigated tip catheters, aggressive anticoagulation). However, under the settings of heavy anticoagulation, inadvertent transseptal puncture, pericardial effusions as well as LA perforations are potentially catastrophic complications.

Thromboembolic risk during atrial fibrillation ablation

During LA catheterization, catheter manipulation can result in dislodgement of the previously formed thrombus. Preablation transesophageal echocardiography can detect LA/LAA definitive thrombi as well as pre-thrombosis states (sludge) [8] and prevent this type of embolism, many centers performing it routinely prior to ablation. However, the risk seems significant and warrants this pre-procedural screening only in patients with non-paroxysmal AF as well as in patients with paroxysmal AF and high or intermediate $CHADS_2$ score (≥ 1), especially if they are in AF at the time of procedure [9,10]. Predictors of sludge/thrombus are $CHADS_2$ score ≥ 1, dilated LA (> 45 mm transverse diameter?) and/or depressed LA function (reduced LAA empting velocities) and previous CHF/LV dysfunction (LVEF < 35%) [9,10]. The occurrence of a clot/sludge in low risk patients ($CHADS_2$ 0) is rare (< 1%), indicating a relative safety of atrial fibrillation ablation in this subset of patients [10]. The role of spontaneous echo-contrast is less clear. Although its incidence parallels $CHADS_2$ score it still can be found in approximately one quarter of low risk patients ($CHADS_2$ = 0 and normal LVEF) [10]. During radiofrequency (RF) ablation embolism to the cerebral circulation or less commonly to the limbs or other organs may be produced by charing (hard coagulum produced by tissue heating, denaturation, and aggregation on the tissue or catheter surface) and/or thrombus formation [11]. The risk of stroke due to charing and/or thrombus formation is also higher in patients with previous cerebrovascular events or higher than 2 $CHADS_2$ score [12]. Overall the risk of a thromboembolic complication during atrial fibrillation ablation ranges from 0.5 to 5.0% with stroke occurrence of 0.23% and transient ischemic attack (TIA) of 0.71% [11–13]. Cerebral emboli result usually in transient neurological deficits (which resolve typically in less than 1 month) and less commonly produce permanent neurological sequels [13]. However, silent periprocedural cerebral thromboembolism detected on MRI seems to be much more common (more than 14%!), especially when activated clotting time (ACT) is lower than 250 s and/or when electrical/pharmacological cardioversion is performed during procedure [14]. Silent cerebral embolism is also significantly more frequent during non-irrigated tip RF ablations then during open-irrigated tip RF ablations or during cryoballoon ablations [15,16]. High flow perfusion with heparinized saline of the transseptal sheaths [17] as well as their withdrawal in the right atrium during ablation (a very popular approach into the electrophysiologists community) might reduce the risk of thrombus formation and therefore the risk of cerebral embolism, although the latter was never investigated.

Hemorrhagic risk during atrial fibrillation ablation

In order to minimize the embolic risk and in accordance with current guidelines anticoagulants or antiplatelet

agents are indicated preprocedural as well as during the ablation procedure, with the cost increased bleeding risk. Hemorrhagic complications are actually the most common complication of atrial fibrillation ablation, which overall occur in 2–3% of the procedures [13,18]. More frequent (1–2% of patients) bleeding occurs at the venous and/or arterial access sites [13,18,19]. Bleeding severity ranges from a simple hematoma that can be treated conservatively to complications that may require vascular repair like pseudoaneurysm or arterovenous fistula formation. Massive, life-threatening bleedings as retroperitoneal or rectus sheath hemorrhages might evolve discretely (like unexplained drop in hemoglobin level) or with signs of acute severe anemia, but fortunately they are rarely seen [19].

A not so rare and serious hemorrhagic potentially life-threatening complication is cardiac tamponade due to cardiac perforation, which has an overall incidence of 0.5 to more than 1.3% [13,18], with 1 out of 30 cases being fatal [20]. Cardiac tamponade seems more frequent during ablations in non-paroxysmal AF (which usually are more extensive) and in early-experience and/or low-volume centers [21]. Usually pericardiocentesis, reversal of anticoagulation, and holding oral anticoagulation for a week manage conservatively this complication. However, open-heart surgical repair may be required if more than 500–1000 ml blood is drained, or if drainage continues over 2 h [19]. Recent research suggests that acute and transitory pericardial effusion without cardiac tamponade occurs quite commonly (up to 22%!), significantly more frequent in patients with persistent atrial fibrillation versus other types (35% vs 10%) [22].

Standard anticoagulation strategies to minimize ablation risks

Ideally, periablation anticoagulation should minimize/eliminate the risk of thromboembolic events without significant increase in bleeding complications. Currently there are several possible strategies to accomplish this target, all of them involving intraprocedural heparin.

Intraprocedural heparin

Optimal anticoagulation with heparin to maintain therapeutic levels during the ablation is important. Thrombi can form on the transseptal sheath and/or catheters almost immediately after crossing the septum [11], therefore unfractionated heparin (UH, a loading dose of 100–150 U/kg followed by standard infusion) is usually administered prior to or immediately following transseptal puncture during AF ablation procedures and adjusted to achieve and maintain the recommended activated clotting time (ACT) of more than 300–350 s [6], especially in patients with spontaneous echo-contrast or significant atrial enlargement. The recommended frequency with which ACT levels should be monitored is 10–15-minute intervals until therapeutic anticoagulation is achieved and then at 15–30-minute intervals for the duration of the procedure.

The bridging strategy

Standard periablation strategy still largely used and supported by the current guidelines is preprocedural discontinuation of VKA for 3 to 5 days and intraprocedural intravenous UH, with pre- and postprocedural 'bridging' with intravenous UH or subcutaneous low molecular weight heparin (LMWH) till effective post-procedural OAC is resumed [5–7]. LMWH (e.g. enoxaparin 1 mg/kg b.i.d., or dalteparin 200 IU/kg once daily) is initiated 2 days ahead of procedure with none given in the morning of the procedure, and postprocedural resumption in the same evening after access sheath removal or next morning. Unfortunately, this approach was associated with a high rate of bleeding complications, especially at vascular access site [23–25]. Most centers switched to half-dose LMWH and saw less bleeding, without a higher risk of stroke [26]. Post procedure, warfarin is restarted the night of the procedure, often using a double dose for the first 2 days and titrated to an INR of 2–3.

Alternative strategy to minimize ablation risk: continuos OAC

The paradigm that for patients undergoing invasive procedures normal coagulation properties are mandatory has been challenged recently. It has been demonstrated that several cardiac procedures, including device implantation [27,28], coronary interventions [29], or even CABG surgery [30] can be performed safely with continuous OAC (cOAC).

Vitamin K antagonists

Several studies demonstrated that at least in experienced centers left atrial ablation is safe when performed in patients taking therapeutic VKA. This strategy offers the advantage of greater simplicity for both patients and physicians with possibly a lower risk of bleeding compared with LMWH. VKA therapy is continued the whole periablation period at a low therapeutic INR (ideally 2.0–2.5, preferably with INRs drawn weekly). The comparison of continuous therapeutic VKA (INR 2–3.5) with full-dose and respectively half-dose LMWH bridging in 355 patients undergoing LA catheter ablation for persistent AF showed that cOAC vs. LMWH-bridging is at least as effective in stroke prevention and superior in terms of minor or major bleeding complications (actually there was only 1 patient with pericardial effusion but without tamponade in the cOAC group) [26]. The same group reported latter in larger cohort of 3027 consecutive patients with LA ablation for AF that continuous VKA (with INR > 1.8) has a lower incidence of hemorrhagic complications (1.1%), pericardial effusion (0.29%), cardiac tamponade (0.16%) and fewer ischemic strokes (0.098%) [31] versus traditional bridging strategy [32]. We noticed that in our center in the last 2 years since we started to perform AF ablations on cOAC, the cognitive score of patients the day after ablation is significantly higher by comparison with patients with bridging therapy (unpublished observations Dr. Vatasescu), possibly related to reduction/elimination of silent cerebral embolism. Two recent single center data showed conflicting data on periprocedural silent embolism as detected by MRI, with one suggesting that silent embolism is not reduced during ablation on cOAC (i.e. incidence 12%) [33] and the other showing a 50%

reduction (i.e. incidence < 7%) [34]. However, both studies found non-paroxysmal AF, complex and prolonged ablations and dilated LA as predictors of silent cerebral embolism [33,34].

Continuous OAC seem to add benefit versus bridging therapy even on top of open-tip heparinized-saline irrigated catheters. In a large study on 6454 patients [35], 2488 underwent ablation with an 8-mm ablation catheter and preprocedural VKA discontinuation (group 1), 1348 underwent ablation with an open irrigated catheter and preprocedural VKA discontinuation (group 2), and 2618 underwent ablation with an open irrigated catheter with cOAC (group 3). Ablation with a therapeutic INR (2.0–2.5) resulted in a reduction of periprocedural thromboembolic events (odds ratio [OR] 0.54; 95% confidence interval [CI] 0.32–0.89; P 1⁄4 0.017) compared to the traditional bridging approach. Major bleeding complications (i.e. bleeding requiring transfusions, hemopericardium, hemothorax, and retroperitoneal bleeding) and pericardial effusion in patients on cOAC were also lower (0.8% vs. 1.1% in patients with bridging) as well as emergent surgical exploration. Moreover, if pericardial tamponade occurs in the presence of therapeutic OAC, it can be managed conservatively by percutaneous drainage in all patients and it seems not to be more severe than in patients with bridging therapy [36]. In the case of persistent bleeding or cardiac tamponade warfarin reversal is possible with fresh frozen plasma, prothrombin complex concentrates (PCC: Factors II, VII, IX, and X) or recombinant activated factor VII (rFVIIa) [37]. Another advantage of AF ablation on VKA treatment is that at therapeutic INR VKA do not affect clinical significance of ACT, patients on cOAC usually have a more stable therapeutic ACT (> 300–350 s), after a standard intravenous bolus of UH and necessitate smaller amounts of intraprocedural UH [38].

These favorable results can be criticized due to the fact that studies were done in large volume experienced centers and assisted by intracardiac echocardiography, which add extra-safety but is not always available and has significant extra-costs. Recent data from medium volume centers proved that transseptal puncture and LA ablation can be safely done without intracardiac echocardiography guidance [39–41]. Furthermore, some researchers advocate that the frequent and uncomfortable ACT dozing during AF ablation might not be necessary at all in patients with therapeutic INR at the time of the procedure after the initial standard bolus of UH [41].

Finally, analysis of pooled data from published studies comparing cOAC (6400 patients) with heparin-bridging (21,000 patients) during AF catheter ablation confirmed that uninterrupted VKA treatment reduces the risk of thromboembolic complications without increasing the risk of bleeding [42].

The consistence of data supporting cOAC during AF ablation is acknowledged by the most recent practice consensus and guidelines [5–7] and is reflected in significant change in practice across the European centers [43,44].

Novel oral anticoagulants

Recently new OAC (NOAC) like dabigatran (DG) or rivaroxaban (RX) proved superior efficacy and safety by comparison with warfarin in stroke prevention in patients with non-valvular AF [45,46]. Moreover, patients treated with DG seem to have similar rates of bleeding and stroke during invasive procedures (as pacemaker/defibrillator insertion, dental procedures, diagnostic procedures, cataract removal, colonoscopy, and joint replacement) versus patients on VKA [47]. However, management of periprocedural anticoagulation during AF ablation in patients on DG is currently not clear. A recent study in 8 high-volume centers found a higher incidence of bleeding and pericardial effusions and no benefit in thromboembolism prevention in patients treated with DG compared with warfarin [48]. Although these results are contra intuitive in the light of previous data in the general AF settings [45], there are several possible explanations. DG was stopped only in the morning of the procedure and was restarted 3 h after the procedure, which is nearly equivalent to uninterrupted DG. Due to its half-life of 14–17 h, manufacturer's recommendations are to stop it at least 1 day before invasive procedures in patients with normal renal function (or even longer when complete hemostasis is required). Another possible explanation is the well known unpredictable interaction of DG with ACT [49,50], which makes ACT unstable during procedure and quantity of necessary UH difficult to estimate [51]. A safer anticoagulation approach would be to use smaller DG doses or to hold the DG for 1–2 days before the ablation and resume it the following morning. In one study of 211 consecutive patients who underwent AF ablation, of whom 110 received 110 mg DG twice daily (stopped in the morning of procedure and resumed next day), there was no difference in embolic rate (including silent stroke on MRI) and less bleedings by comparison with 111 patients on therapeutic continuous warfarin (INR 2–3) [52]. A recent nonrandomized study in 34 patients with periprocedural NOAC discontinued DG for 36 h before the procedure and restarted it 22 h after the procedure, bridging with half-dose LMWH after the procedure [53]. There were no preprocedural or intraprocedural thromboembolic episodes or bleeding. Other options include using newer oral anticoagulants other than DG, such as RX [46], which has a shorter half-life and might be reversible with PCC if bleeding or tamponade were to occur [54].

Infrequent strategies: antiplatelets alone

Very limited data suggests that if preablation TEE can rule out LA/LAA clot/sludge, aspirin alone can be used to prevent periprocedural thromboembolism either pre-ablation [55] or even after ablation [56] in relatively low risk patients (i.e. paroxysmal atrial fibrillation and $CHADS_2$ score of ≤ 1). Probably this type of strategy might be strictly limited to young patients with $CHADS_2$ 0, no structural heart disease and relatively limited LA lesions during ablation.

Conclusions

Ablation for atrial fibrillation is a pertinent and possibly a lasting treatment alternative to antiarrhythmic drugs for prevention of recurrences in symptomatic patients. Bleeding and embolism remained a significant risk in standard periprocedural bridging anticoagulation strategy. There is convincing data that clearly demonstrates the efficacy and safety of LA catheter ablation on continuous

VKA. Continuation of therapeutic warfarin during ablation of AF may be the best strategy, especially in patients with nonparoxysmal AF, patients with higher thromboembolic risk scores, and patients who require extensive LA ablation. The role of new oral anticoagulants as replacements for warfarin in AF ablation protocols is the subject of ongoing research.

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