Atrial Fibrillation in the Perioperative Period

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Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population. Its incidence increases with age so that in next years the number of subjects affected is likely to grow due to the elongation of average life expectancy. AF is an arrhythmia that poses major health problems because it is associated with greater incidence of arterial thromboembolism, stroke, heart failure, and higher overall mortality [1–6].

5.1 Epidemiology and Classification

A recent study has shown that AF has a prevalence of 1.8% in the Italian population over 15 years of age. Similar percentages, around 2%, were detected in England, Germany, and Sweden. In the USA, this arrhythmia affects 3–6% of hospitalized patients. Prevalence is higher in Caucasians and increases in the presence of congestive heart failure, valvulopathies, arterial hypertension, atrial tachyarrhythmias (returning nodal tachycardia, WPW syndrome), various thoracic diseases, sepsis, and conditions that increase the cardiovascular risk (diabetes mellitus, obesity, smoking).

AF is classified as: (a) persistent, if it lasts for longer than 7 days; (b) paroxysmal, if it reoccurs in less than seven days after being resolved, spontaneously or as a result of a therapeutic intervention; (c) long-standing persistent, if it lasts more than 12 months; (d) permanent, if the doctor and the patient decide to stop the attempts to resolve the arrhythmia. Valvular AF refers to patients with mitral stenosis or

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artificial heart valves; North American guidelines include valve repair in this group. In comparison with non-valvular ones, valvular AF may be associated with a higher risk of stroke and needs a specific prophylactic approach.

5.2 Etiology and Pathogenesis

AF pathogenesis is complex and not yet completely clarified. At the basis of this arrhythmia, there are some electrical alterations of the atrial myocardium. They include inhomogeneities of the refractory period that facilitate the onset of re-entry mechanisms; after-depolarizations (oscillations) that intervene during early or late reuptake phases, promoting the onset of extrasystoles; ectopic focal depolarizations, which often originate from pulmonary vein confluence areas in the left atrium. Finally, some studies have shown a correlation between the incidence of postoperative AF and the duration of P wave on the ECG.

The abovementioned electrical alterations can be induced by different factors. Genetic abnormalities are often the basis of isolated AF that is not associated with other cardiac disorders and occurs in subjects less than 60 years old. In most cases, however, the onset of AF is the consequence of structural alterations of the atria, which include fibrosis, dilation, hypertrophy, ischemia, and infiltration. Fibrosis, which manifests itself with an increase in the amount of collagen, is a process that progresses with age and is considered to be the primary responsible for the high incidence of AF in the elderly. Atrial dilation occurs during the natural history of mitral valvulopathy and left ventricular dysfunction. In the intra- and post-operative period, the atria may dilate acutely, for fluid mobilization or excessive intake; in addition, atriotomy performed in cardiac surgery represents an important mechanism of stimulation. In the perioperative period, the hyperactivity of the autonomic nervous system and the increased levels of mediators of inflammation, and oxidizing agents have a marked influence on atrial activity, favoring the onset of AF. Sympathetic hyperactivity also facilitates the occurrence of ectopic outbreaks and re-entry circuits, and shortens the refractory period. As a result, pain, agitation, and in general all factors that stimulate sympathetic activity may favor the onset of AF. A similar effect may be caused by the reduction of parasympathetic tone, while parasympathomimetic drugs as opioids may have a protective action.

5.3 Presentation and Diagnosis

The onset of AF is often felt by the patient for heart rate irregularity. In some cases, the arrhythmia manifests itself directly with an embolic episode. At clinical examination, AF can be suspected for irregularities of the arterial pulse and cardiac tones. Diagnosis is confirmed by the electrocardiographic detection of an absolute irregularity of the RR intervals, of the absence of the P wave or of an atrial cycle duration (when visible) irregular and less than 200 ms (corresponding to a frequency higher than 300 bpm). In the case of paroxysmal AF, which alternates with sinus rhythm periods, it is often necessary to resort to Holter monitoring.

Predisposing causes should be recognized and, if possible, treated. Electrocardiogram can show the presence of various electrical abnormalities, left ventricular hypertrophy, branch blocks, signs of myocardial infarction. Ashman's phenomenon consists in an aberrant intraventricular conduction (broad QRS complexes) in beats associated with a short RR cycle preceded by a longer RR one; it originates from the prolongation of the refractory period that follows long RR cycles. Transthoracic echocardiography (TTE) allows to evaluate valve function, contractility, chamber dimensions and wall thickness; systolic pulmonary pressure can often be estimated and the presence of endocavitary thrombi assessed. On this purpose, however, transesophageal echocardiogram (TEE) is more effective. AF is sometimes associated with thoracic diseases that can be diagnosed or suspected based on chest X-ray. The presence of extra cardiac diseases associated with a higher incidence of AF, as hyper- or hypothyroidism, should also be investigated.

5.4 Treatment

5.4.1 Prevention of Atrial Thrombosis and Thromboembolism

Three classes of drugs are used: vitamin K inhibitors, new oral anticoagulants, and platelet antiaggregates [7–10]:

1. *Sodium warfarin* (Coumadin®) and *acenocoumarol* (Sintrom®), known as vitamin K inhibitors or dicumarolics, hinder the hepatic synthesis of coagulation factors II, VII, IX, and X, and of proteins C and S. Vitamin K inhibitors are the gold standard for prevention of thromboembolism, but their narrow therapeutic range requires frequent controls of coagulation parameters and entails a greater risk of hemorrhagic complications. Their anticoagulant effect is assessed with the International Normalized Ratio (INR), the ratio between the prothrombin time of the patient and that of standard plasma blends. INR should be maintained between 2 and 3 or between 2.5 and 3.5 depending on the thrombogenic risk that characterizes the patient. The activity of this class of drugs is influenced by liver function, but not by renal function; besides, it can be influenced by the intake of numerous drugs and certain foods. In the initial phase of the therapy, INR should be dosed at least once a week; successively, dosages can be performed once a month. In the case of overdose or of the need to restore normal coagulation, the anticoagulant effect can be inhibited by the administration of vitamin K (Konakion®, 5–25 mg intravenously, possible allergic reactions) or, in urgent cases, of fresh frozen plasma (15 mL/kg) or concentrated prothrombin complex (30–50 units/kg).
2. *New oral anticoagulants* are the direct thrombin inhibitor dabigatran (Pradaxa®), and the two factor X inhibitors, apixaban (Eliquis®) and rivaroxaban (Xarelto®). Dabigatran is a competitive thrombin inhibitor and prevents the conversion of fibrinogen to fibrin. Apixaban and rivaroxaban are selective inhibitors of factor Xa. This factor intervenes at the point of convergence between intrinsic and extrinsic pathways of coagulation; its inhibition blocks the conversion of prothrombin

Table 5.1 CHA2DS2-VASc score utilized to quantify the risk of thromboembolism in patients affected by AF

C	**C**ongestive Heart Failure History	1
H	Arterial **H**ypertension History	1
A_2	Age ≥75 years	2
D	Diabetes	1
S_2	Stroke/TIA/Thromboembolism History	2
V	**V**ascular Diseases History (i.e., obliterating arteriopathy, myocardial infarctum, coronary artery disease)	1
A	**A**ge 65–74 years	1
Sc	Female **S**ex	1

The final score is obtained by adding partial scores. The zero value corresponds to low-risk; the value of one corresponds to low-moderate risk; values of two or greater correspond to moderate-high risk (modified from [2])

into thrombin. Unlike vitamin K inhibitors, these drugs do not require routine monitoring of coagulation parameters. Their blood levels increase in the presence of kidney failure which, when severe, contraindicates their use. Moderate renal function impairment requires a reduction in dosage. The relatively short half-life, 12–17 h for dabigatran, 5–9 h for rivaroxaban, and 12 h for apixaban, is the basis of the risk of thromboembolic episodes shortly after the acute suspension of these drugs. If dabigatran is to be discontinued and substituted with vitamin K inhibitors, the latter should be initiated 3 days before the last dose of dabigatran. In case of severe bleeding, the suspension of these drugs is recommended as well as the administration of coagulation factors, in particular, prothrombin complex concentrates. Specific antidotes for this class of drugs are now available. Idarucizumab is a humanized mouse monoclonal antibody fragment that reverses the effects of dabigatran and Andexanet alfa is a recombinant modified human factor Xa decoy protein that binds factor X inhibitors.

3. *Platelet antiaggregants* like acetylsalicylic acid, ticlopidine, and clopidogrel are relatively safe drugs, but their efficacy on thromboembolism is definitely lower than that of anticoagulants.

Prophylaxis of thromboembolism should be performed regardless of the type of AF, paroxysmal, persistent or permanent, but does not eliminate the risk of thrombosis. Vitamin K inhibitors, which provide the greatest protection, assure a reduction in embolic episodes of 60–70%. Of note, not all patients with AF have the same degree of risk of thromboembolism. Numerous indices expressing the risk of thromboembolism are available; CHA2DS2-VASc is the one suggested by the American Heart Association guidelines (Table 5.1). The score obtained with this index varies from 1 to 10. A value of zero is associated with a very low-risk and requires no therapy or, at most, the administration of platelet antiaggregates. A value of one suggests the need of platelet antiaggregates. Scores of two or more indicate the use of new oral anticoagulants or dicumarolics. The choice of prophylaxis modalities also depends on which heart disease is associated to AF. In patients affected by valvulopathies, only dicumarolics are indicated for the particularly high risk of thromboembolism. In cases where dicumarolic therapy is indicated, anticoagulation

should be initiated as soon as possible with unfractionated heparin (an initial bolus of 80 UI/kg, followed by the infusion of 18 UI/kg/h, titrated to obtain an aPTT of 45–60 s) or with low molecular weight heparin (100 UI to 1 mg/kg every 12 h).

5.4.2 Rate Control vs Rhythm Control Strategies

Apart from the thromboembolic risk, AF poses two main problems: the loss of the atrial pump to ventricular filling and the onset of too high or low ventricular rates. These alterations are particularly damaging in patients with left ventricle diastolic dysfunction or mitral stenosis. The therapeutic goal can be limited to maintain ventricular rate within an acceptable range (rate control) or aimed to restore sinus rhythm (rhythm control). Although the second approach may appear as the best one, it should be considered that 50% of recent-onset AFs spontaneously convert to the sinus rhythm and that from the point of view of survival and morbidity, no significant difference has been observed between the two strategies.

5.4.2.1 Rate Control

In AF, the average ventricular rate depends on the length of the refractory period of the atrioventricular node, which blocks most of the electrical impulses that arrive from the atria at a frequency greater than 300 bpm. A too high rate may compromise ventricular filling and cause myocardial ischemia. On the other hand, bradycardia can interfere with the function of the left ventricle both in systolic and diastolic dysfunction. In the former, tachycardia represents a compensation mechanism; in the latter, diastolic stiffness limits the volume of blood that the left ventricle can accept in diastole. The rate control strategy aims to keep the average ventricular rate at rest below 80 bpm. In acute cases with good hemodynamic compensation, an initial goal may be to maintain the rate below 110 bpm. In order to control ventricular rate, the refractory period of the atrioventricular node is increased to reduce the number of atrial excitations transmitted through the conduction system. For this purpose, some drugs can be used:

- Beta-blockers act by reducing the effects of sympathetic hyperactivity; furthermore, they are particularly effective to prevent myocardial ischemia. Their prophylactic activity against AF has been proved in at least two conditions: paroxysmal AF induced by sympathetic hyperactivity and postoperative AF that occurs in 30% of patients after cardiac surgery. Main contraindications are the severe systolic dysfunction of the left ventricle and bronchial obstruction. Several molecules are used, including atenolol, bisoprolol, carvedilol, metoprolol, nadolol, propranolol, and timolol. Metoprolol is administered acutely at the dosage of 2.5–5 mg every 5 min up to 10–15 mg; oral dosage varies from 25 to 100 mg every 12 h. A special role is played by esmolol, which is particularly valuable in critically ill patients because of its short half-life of about 10 min. The dosage is 0.05–0.2 mg/kg/min after an initial bolus of 0.5 mg/kg.
- Non-dihydropyridine calcium antagonists (verapamil, diltiazem) prolong atrioventricular node conduction and refractory period. They have negative inotropic

and vasodilator effects, which contraindicate their use in ventricular systolic dysfunction and in arterial hypotension. They should also be avoided in patients with Wolff–Parkinson–White (WPW) syndrome. Verapamil can be administered intravenously as a bolus, 5–20 mg, and in rare cases as an infusion, at a rate of 5–10 mg/h. Orally, the dosage is 40–80 mg every 8 h.

- Amiodarone is a class III antiarrhythmic drug (K channel blockers) according to Vaughan Williams classification, and is effective both to reduce mean ventricular rate and to restore sinus rhythm. This drug is particularly useful in patients with cardiovascular instability and/or systolic dysfunction because of its modest negative inotropic effect; the vasodilator effect is also mild and is clinically apparent only during rapid intravenous infusion. Amiodarone may cause phlebitis and prolongation of QT with potential induction of polymorphic ventricular tachycardia (torsades de pointes); it is also contraindicated in WPW syndrome. Intravenously, an initial injection of 300 mg is given as a slow injection in 10 min (risk of hypotension by vasodilatation) or as an infusion in 2 h, followed by a 5-h infusion at a rate of 75 mg/h, and finally by a constant-rate infusion at 18 mg/h. Orally, the dosage is 200–400 mg daily.
- Digitalis slows down the average ventricular rate in the presence of AF because it increases the parasympathetic tone. For this reason, it may be ineffective in conditions characterized by an increased activity of sympathetic hyperactivity, as is often the case in the perioperative period. Digoxin is contraindicated in WPW syndrome. In the attack phase, the loading dose is 0.5–1 mg iv, followed by a maintenance dose of 0.25 mg orally.

The choice of the drugs to be used for heart rate control is partly based on associated pathologies. For instance, beta-blockers and calcium antagonists are indicated for the presence of coronary heart disease and arterial hypertension, digitalis in the presence of heart failure. A particular case is that of patients with WPW syndrome. Drugs such as calcium antagonists, amiodarone, and digitalis increase the refractory period of the atrioventricular node. In case the refractory period of the accessory bundle is shorter than the atrioventricular node, electric impulses can be transmitted from the atria to the ventricles through the former and high ventricular rates can occur. In patients with WPW, rate control approach is therefore based on the administration of beta-blockers, but rhythm control is recommended.

5.4.2.2 Rhythm Control

The decision to pursue AF conversion to sinus rhythm in emergency conditions is generally based on the presence of hemodynamic instability, too high or low ventricular rates, and myocardial ischemia. Otherwise, it is reasonable to follow the rate control strategy and to shift to the rhythm control only after a few days, when a spontaneous cardioversion becomes unlikely. The sinus rhythm can be restored by an electrical or pharmacological cardioversion. The former is recommended in patients with WPW syndrome.

- Electrical cardioversion. Its main advantage is the very high percentage of success, even in persistent AFs. Disadvantages are the need for sedation, the

risk of thromboembolism, the proarrhythmic effect, possible skin lesions, and potential interference with medical devices, such as pacemakers and Implantable Cardioverter Defibrillators.

In electrical cardioversion, a monophasic or biphasic, synchronous shock is applied with an initial current intensity of 100–200 J. The classic position of the plates is that the sternal one is placed to the right of the sternal margin and immediately below the collarbone, while the apex one is positioned at the height of the left nipple at the midaxillary line. In cases of failure, in addition to testing for greater current intensity, the plates can be positioned in the antero-posterior position (left parasternal, left subscapular), which would favor the passage of a larger amount of current through the atria. The success of cardioversion depends on the amount of current that crosses the heart. A high body mass index (BMI) reduces the chances of success. The contact between the plate and the skin is particularly important because the air is an electrical insulator. In addition to the use of conductive pastes, gels, or adhesive plates, it is useful to exert pressure on the plates themselves. Some authors suggest to reduce electrical impedance by performing a trichotomy in areas where plates will be applied. The shock should be administered during exhalation when the chest impedance is lower. Furthermore, a second electric shock has more chances of success after an ineffective result because the electric impedance is reduced; the optimum lapse of time would be around 3 min.

Administration of some antiarrhythmic drugs influences the success of the attempt of electric cardioversion. Atropine given immediately before the electric shock could increase the rate of success. Verapamil, amiodarone, quinidine, and propafenone may be effective in preventing a new onset of AF after efficacious cardioversion. The incidence of recurrences is greater in AFs that last for more than a year and in those associated with not well-controlled hyperthyroidism, mitral valve diseases, congestive heart failure, and generally with an enlargement of the left atrium (diameter greater than 5 cm).

- Pharmacological cardioversion does not require sedation and, in case of failure, can facilitate the success of electrical cardioversion. On the other hand, it may require hospitalization and cardiovascular monitoring; it is proarrhythmic, involves the risk of thromboembolism, and is characterized by limited success rates for long-term AFs. Pharmacological cardioversion is indeed more effective in recent atrial fibrillations. In those less than seven days old, the percentage of success within 24 h from the beginning of antiarrhythmic therapy varies from 34 to 95%. Over seven days, the percentage falls below 40%, and often it is necessary to resort to electrical cardioversion.

Various antiarrhythmics may be used, including flecainamide 2 mg iv or 200–300 mg/os, propafenone 2 mg iv or 450–600 mg/os, amiodarone at the dosage reported above, ibutilide, dofetilide. Flecainamide and propafenone can sometimes convert AF into flutter and therefore require calcium antagonists or beta-blockers to slow the pulse transmission at the atrioventricular node level. In the patient who develops AF after surgery, the classic choice is that of amiodarone, especially when

there is a basic heart disease. Vernakalant is a new antiarrhythmic agent indicated for the treatment of AF that occurs in the postoperative period after cardiac surgery. Given within three days from the onset of arrhythmia, the drug is administered intravenously at a dose of 3 mg/kg over 10 min and has a 50% success rate within 90 min from the administration (far greater than that of amiodarone). It is contraindicated in case of bradycardia, hypotension, marked prolongation of QT, severe valvulopathies, congestive heart failure.

5.4.2.3 Anticoagulant Therapy and Cardioversion

Whether cardioversion is performed electrically or pharmacologically, it exposes the patient to the risk of mobilization of any thrombi formed within the atria. In addition, even after sinus rhythm restoration, there is a temporary risk of formation of thrombi due to the persistence of transient atrial dyskinesias and generally to the risk of AF recurrence. In accordance with current guidelines, the prevention of these complications should be based on the time elapsed from the onset of arrhythmia:

(a) Patients in AF for less than 48 h:
   - High embolic risk: cardioversion is followed by anticoagulation for at least 4 weeks, started with unfractionated heparin or low molecular weight heparin and continued with dicumarolics.
   - Low embolic risk: cardioversion is followed by one options among heparin, low molecular weight heparin, new oral anticoagulant (dabigatran, rivaroxaban, or apixaban), or no therapy.

(b) Patients in AF for 48 h or more or for an unknown time period:
   - Non-urgent cardioversion: anticoagulation with dicumarolics (INR from 2 to 3) is performed three weeks before and 4 weeks later; new oral anticoagulants (dabigatran, rivaroxaban, or apixaban) can also be utilized. Alternatively, it is reasonable to proceed to cardioversion if transesophageal echocardiography excludes the presence of thrombi in the left atrium (particularly in the auricula) provided that anticoagulation is achieved before cardioversion.
   - Urgent cardioversion: electrical cardioversion and anticoagulation for the next four weeks initiated as soon as possible (low molecular weight heparin or heparin followed by dicumarolics)

5.5 Some Further Points

During the perioperative period, the anesthetist is called, in collaboration with other specialists and in particular with the cardiologist, to handle three main issues.

In patients affected by AF, the anticoagulant treatment should be discontinued during surgery and in the immediate postoperative period. After the interruption of oral anticoagulants, the recovery of an INR <1.5 is expected after at least 4–5 days. In the case of dabigatran, suspension should occur 1 or 2 days before surgery in patients with normal renal function and up to 4 days before in patients with creatinine clearance between 30 and 50 mL/min and undergoing high-risk hemorrhagic surgery.

In the lapse of time from the end of oral anticoagulants to surgery, treatment depends on the degree of thromboembolic risk assessed by the above-described scores:

- In patients with high thromboembolic risk, non-fractionated heparin or low molecular weight heparin is administered at therapeutic doses up to 12 h before surgery
- In patients with moderate thromboembolic risk, non-fractionated heparin or low molecular weight heparin is administered at therapeutic or prophylactic doses
- In patients with low-thromboembolic risk, low-molecular-weight heparin is given at prophylactic doses or not at all.

In patients who develop AF during the perioperative period, the treatment is based on the choice between rate control and rhythm control strategies. In cardiac or thoracic surgery, where the incidence of AF in the postoperative period is around 30–40%, high ventricular frequency should be preferably treated with beta blockers, provided there are no contraindications to their use. If the ventricular rate is not adequately controlled, a non-dihydropyridine calcium antagonist (verapamil, diltiazem) should be associated. Sinus rhythm restorative attempts can be performed with ibutilide or with cardioversion if AF persists. Anticoagulant therapy should be initiated and maintained according to the criteria used in non-surgical patients. Some drugs have prophylactic action against perioperative AF, and their use should therefore be considered in high-risk subjects. Beta-blockers could reduce the incidence of AF to 19% in cardiac surgery. Other therapeutic options are amiodarone and sotalol; colchicine is used because of its anti-inflammatory action.

During trans-catheter ablation, anesthesia support for patient sedation/anesthesia is often required. The procedure involves electrical separation of the entry point of the pulmonary veins from the rest of the atrium. This separation is obtained by causing an atrial wall injury by application of low temperatures (cryoablation) or radiolabel, resulting into the formation of a fibrous scar. In last few years, radio anatomic mapping systems have been introduced to create a three-dimensional representation of the atrium and the areas under ablation during the procedure. Such systems have considerably increased the effectiveness of ablation procedures, but have also prolonged the duration. Moreover, they are extremely sensitive to patient movements. It is therefore generally necessary to perform the procedure under sedation (usually midazolam and fentanyl), deep sedation (usually propofol and fentanyl), or general anesthesia. Each technique has advantages and disadvantages. General anesthesia and deep sedation ensure the patient's immobility even for long periods, but may in part hinder the recognition of some complications. These include perforation of the atrial wall which results in hemopericardium, onset of conduction blocks, formation of atrio-esophageal fistulas, paralysis of the phrenic nerve. In the last case, for example, the use of myorelaxants inhibits the detection of diaphragmatic contractions, which result from nerve stimulation and precede nerve damage. Similarly, general anesthesia abolishes the feeling of intense pain that often precedes atrial wall perforation.

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