Pharmacological treatment of atrial fibrillation and the underlying substrate

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THE ROLE OF ANGIOTENSIN CONVERTING ENZYME-INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS IN THE MANAGEMENT OF ARRHYTHMIAS AND ATRIAL FIBRILLATION

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Atrial fibrillation is a major medical problem due to its complications, like systemic embolism and reduction of the cardiac output[1]. Lately the management of this arrhythmia has been very aggressive with procedures like ablation of the atrial myocardium and pulmonary veins[2]. This monograph will deal with the management of arrhythmias, including atrial fibrillation, especially its prevention with angiotensin converting enzyme (ACE)-inhibitors and angiotensin II receptor blockers. This management is beyond the basic treatment of atrial fibrillation with digitalis, other antiarrhythmic agents and anticoagulants[1]. This brings the importance of the renin-angiotensin system in the physiology and hemodynamics of the cardiovascular system, but also in the electrophysiologic properties of the heart[3-8].

Electrophysiology of angiotensin converting enzyme-inhibitors and angiotensin II receptor blockers

It has been reported that vascular smooth muscle cells and myocytes have the enzyme involved in the conversion of angiotensin I to angiotensin II. Suppression of reperfusion arrhythmias by ACE-inhibitors indicates that these inhibitors can alter the electrical properties of the heart muscle. Other investigators have also shown that these drugs reduce the incidence of ventricular arrhythmias due to ventricular remodeling, reduction of left ventricular mass and reduction of the left ventricular conduction delay in hypertensive patients with left ventricular hypertrophy[1-9].

The basic mechanisms how these drugs reduce arrhythmias are described in table I. We will discuss the mechanisms involved in these processes.

Table I. Antiarrhythmic properties of ACE-inhibitors and angiotensin II receptor blockers.

Enalapril increases junctional gap conduction
Enalapril increases cardiac refractoriness
Enalapril reduces intracellular resistance and conduction velocity
Losartan reduces gap junction conductance reduction induced by angiotensin II

Junction gap function

Heart cells are connected through low resistance junction connections (junction gaps). Junctional conductance has an important role in the electrical and mechanical synchronization of heart cells (atrium-ventricle) as well as in the generation of cardiac arrhythmias. Gap junction conductance is implicated in normal and abnormal impulse conduction in cardiac muscle. Factors involved in junctional conductance are calcium ions, intracellular pH and cyclic adenosine monophosphate.

De Mello and Altieri[4] reported that in isolated heart cells and myocytes enalapril (1 μg/ml) increases conductance by 106 ± 3.1% and that angiotensin II (1 μg/ml) reduces conductance by 55%. These observations point out that an intrinsic cellular renin-angiotensin system exists and has an influence in junction gap function. A reduction of gap junction conductance (as seen with angiotensin II) increases the incidence

of reentry phenomena in the ventricles and atrium inducing ventricular and atrial arrhythmias like atrial fibrillation and ventricular arrhythmias.

Cardiac refractoriness

In clinical trials, such as CONSENSUS and SAVE, the incidence of ventricular arrhythmias and sudden death was reduced. Besides the improvement of junction gap by enalapril, De Mello et al.[5] reported that ACE-inhibitors increase refractoriness of the heart reducing the incidence of ventricular and atrial arrhythmias.

Effect on intracellular resistance and conduction velocity

The incidence of arrhythmias is increased by angiotensin II by increasing electrical conduction resistance across the myocardium. This is due to the fact that angiotensin II increases junction gap resistance increasing reentry. Enalapril and losartan (angiotensin II receptor blocker) will decrease junction gap resistance producing a reduction of arrhythmias by reducing reentry. The effect of angiotensin II is by activating protein kinase C stausporine a blocker of protein kinase C that will block the effect of angiotensin II[6].

Causes of atrial fibrillation

The pathophysiology of atrial fibrillation is multifactorial. Several patients have intermittent atrial fibrillation without any pathology (idiopathic). Alcohol intake is a primary reason in the induction of atrial fibrillation. The reason for this is sinus and atrioventricular node dysfunction reported by our group several years ago. Other causes are hyperthyroidism[1], apoptosis necrosis of the atrial muscle induced by angiotensin II[9,10], mitochondrial disease due to aging[11], atherosclerosis of the sinus node producing ischemia of the atrium. Also dilation of the left atrium seen in hypertensive patients[12].

Treatment of atrial fibrillation

This consists in controlling the heart rate using digoxin and cbonic anticoagulation with coumadin[1]. To avoid recurrence, the use of propaphenone, amiodarone, and β-blockers is standard treatment, but there is a new trend in using ACE-inhibitors and angiotensin II receptor blockers in the prevention of these arrhythmias. This is based in the electrophysiologic changes induced by this drug[1-9] (Table I) and the interesting observation of the reduction of the oxidative stress in myocytes and mitochondria induced by losartan (angiotensin II receptor blocker)[10,11]. Also the invasive management of this arrhythmia by pulmonary vein and atrial ablation of the ectopic foci.

Conclusions

In hypertensive patients the left ventricle will develop hypertrophy and left atrial enlargement[12]. This will induce an environment prone to arrhythmias (ventricular-atrial). A reduction of this will reduce the incidence of arrhythmias.

Angiotensin II receptor blockers will reduce reentry arrhythmias by increasing junction gap conduction. This will reduce reentry including ventricular and atrial arrhythmias. Also, by reducing ventricular mass and remodeling which will improve left ventricular function a reduction of arrhythmias will be seen[8]. These drugs are extremely important by stabilizing the electrical status of the heart and also stabilizing the myocardium by reducing the damage done by oxidative stress in the myocardial cells and in this way reducing reentry.

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DO ANTI-ISCHEMIC AGENTS REDUCE THE ATRIAL FIBRILLATION BURDEN?

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About 1% of the population is suffering from the most common cardiac arrhythmia, atrial fibrillation (AF). Our understanding of pathophysiology of AF has evolved greatly over the past 10 years but it remains incomplete, thus limiting the efficacy of therapeutic approaches.

A number of risk factors have been associated with AF, such as age, acute or chronic hemodynamic, metabolic, neuro-hormonal or inflammatory stressors. Though AF and coronary artery disease (CAD) share most of pathogenetic mechanisms, studies on ischemic origin of AF are lacking. Ischemia may not only induce and promote progression, but it may be a factor for persistence of arrhythmia[1]. Angina is a common symptom during AF[2], but the prevalence of AF among patients with proven CAD has been reported as extremely low, varying from 0.2 to 5%[3-6]. Normal coronary anatomy is found in 34 to 98% of patients with AF undergoing coronary arteriography[4,6]. Congestive heart failure, an obvious potential mediator between CAD and AF, appears to be present in only a minority of patients with AF and CAD[7]. Changes in atrial electrophysiology accompanying chronic atrial dilation during congestive heart failure (shortening of action potential duration and increased spatial dispersion of repolarization) facilitate the formation of multiple reentrant circuits and therefore AF. However, the finding of a greater atrial size in patients with AF cannot help to a better understanding of what comes first: AF or atrial enlargement. In addition, although the incidence is declining, AF remains a common complication of acute myocardial infarction[8].

On the other hand, epidemiologic studies have reported a high prevalence of CAD in patients with AF[7,9,10] but a causal relation between them was not proved yet[11]. Subjects who develop AF are usually elderly, more likely than age-matched controls to have diabetes, left ventricular hypertrophy, echocardiographic abnormalities, CAD, valvular heart disease and heart failure. About 30% of men and half as many women have history of myocardial infarction, and about 25% of both sexes have heart failure. In the Framingham study[9], taking other risk factors and cardiac conditions into account, myocardial infarction was significantly associated with AF only in men, increasing their risk by 40%. Adjusting only for age, cigarette smoking in women, diabetes, hypertension and electrocardiographically demonstrated left ventricular hypertrophy (ECG-LVH) in both sexes were significant AF predictors. Women who smoked were 40% more likely to develop AF; those who were diabetic had a 2-fold increased risk; those with hypertension had a 70% greater risk; and those with ECG-LVH had almost a 4-fold increased risk. In men, diabetes increased risk by 70%, hypertension by 80%, and ECG-LVH by 3-fold. After adjusting for other associated conditions, as well as age and sex, diabetes and hypertension remained significant predictors of AF, but with somewhat decreased odds ratios.

In most of the intervention trials of ischemic heart disease, AF is not included in the primary or secondary endpoints. Therefore, it is impossible to know its incidence and the effects of any anti-ischemic agent in this large subset of patients. This lack of attention might be due to the pathophysiology of AF itself, which is a complex interplay of direct and indirect mechanical and electrical factors. Being considered a pure electrical problem, for a long time the research and the therapy of AF focused on antiarrhythmic drugs; as the result of volume and/or pressure overload associated with heart failure, AF has been treated correcting the hemodynamic and mechanical derangements. The challenge of identifying and separating a pure ischemic mechanism, apparently has hampered any effort for a better understanding of a possible isolated ischemic origin of this arrhythmia.

The importance of AF in the setting of acute ischemia has been recently documented by the analysis of the data from patients with an acute coronary syndrome (ACS) enrolled in the Global Registry of Acute Coronary Events (GRACE)[12]. In these unselected patients a history of AF is not uncommon in patients with ACS. Furthermore, the results of the registry demonstrate that new-onset AF frequently complicated an acute coronary event (AF was present in approximately 1 of every 7 patients). Most in-hospital complications were higher in patients with ACS with any AF than in those without any AF, including higher mortality. When stratified by the time of onset, all complications were higher in patients with ACS with new-onset AF than in those with previous AF. New-onset AF remained an important independent association of most in-hospital outcomes after adjustment for baseline differences in clinical characteristics. In contrast, a multivariate adjustment markedly attenuated the association of previous AF with any in-hospital outcomes. These results extend the findings from previous reports of the common occurrence and poor in-hospital outcomes of AF complicating acute myocardial infarction. The actual incidence of AF in these patients might have been underestimated as non-ST-elevation myocardial infarction or unstable angina was the more frequent presentation of ACS in patients

with previous cardiac surgery or myocardial infarction, already on effective cardiac therapies for the secondary prevention such as β-blockers and angiotensin-converting enzyme-inhibitors that might decrease the risk for the development of AF. However, the observation from the GRACE does not unable to establish a temporal relation between new-onset AF and the occurrence of in-hospital complications, and only the association between AF and these complications, rather than cause and effect relation, can be inferred. Moreover, as the proportion of patients with new-onset AF who remained in AF at the time of hospital discharge and those who later reverted to normal sinus rhythm (paroxysmal AF) is not reported, we cannot evaluate the effect of treatment and the differences between these two groups of patients.

Atrial ischemia, either acute, or chronic, or both, may contribute to development of AF by slowing and fractionating conduction, slowing action potential upstroke, and decreasing action potential duration[13]. However, acute atrial ischemia *per se* is rarely considered as a direct contributor to AF. Recently, it has been shown that isolated atrial ischemia strongly promotes the persistence of AF in the dog[14]. Atrial ischemia had relatively little effect on refractoriness but caused strong conduction slowing in the ischemic zone, which may stabilize atrial reentry that maintains AF. The strong local atrial conduction slowing and unchanged atrial effective refractory period observed with acute atrial ischemia are consistent with previous observations at the ventricular level. Thus, reentrant mechanisms most likely played a predominant role in the substrate for atrial tachyarrhythmia. Lammers et al.[15] evaluated the effects of hypoxia on isolated superfused rabbit atrial preparations. They observed a transient increase in effective refractory period over 15 min, along with a sustained decrease in conduction velocity. Conduction properties became more heterogeneous, and premature stimuli readily induced reentry around arcs of functional conduction block. The effects of homogeneous hypoxia on isolated superfused atrial preparations *in vitro* cannot be extrapolated directly to the effects of ischemia (which includes the consequences of hypoxia, substrate, and oxygen deprivation, as well as reduced metabolite removal) on intact atria *in situ*. Nevertheless, many of the phenomena observed by Lammers et al. are quite similar to the changes observed as a result of isolated atrial ischemia *in vivo* by Sinno et al.[14]. Jayachandran et al.[16] showed that proximal right coronary artery occlusion, which causes both posterior left ventricular and left atrial ischemia, reduces atrial effective refractory period after several hours, an effect not altered by the adenosine triphosphate (ATP)-dependent K^+-channel blocker glibenclamide. Atrial arrhythmias were not reported.

There is extensive indirect evidence for a significant clinical role of atrial ischemia in AF associated with acute myocardial infarction. Several studies have suggested that atrial infarction is relatively common, observed in up to 17% of autopsy-proven cases of myocardial infarction, with > 20% of cases constituting isolated atrial infarction[17,18]. Isolated atrial infarction is difficult but possible to diagnose clinically and atrial tachyarrhythmia is a characteristic manifestation[19,20]. The pathophysiological role of acute atrial ischemia underlying paroxysmal AF has recently been highlighted by a patient with infero-posterior infarction in whom mechanical reperfusion of occluded atrial coronary branches led to spontaneous termination of AF[21].

Atrial ischemia as a result of inadequate cardioplegic protection or compromised atrial coronary arterial supply has been suggested as a causative mechanism of AF occurring after cardiac surgery[22,23]. In addition, stenosis of the sino-atrial nodal artery, supplying an important atrial territory, is an important contributor[23,24]. Thus, there is substantial circumstantial evidence for a role of atrial ischemia in AF after coronary artery bypass surgery.

It remains to be determined whether less severe forms of atrial ischemia, as might complicate chronic CAD, could also promote atrial arrhythmogenesis and contribute to the increased prevalence of AF associated with chronic CAD. Recently Budeus et al.[25] evaluated the incidence of atrial late potentials in patients with a proximal stenosis of the right coronary artery and new-onset AF and studied the effect of mechanical revascularization. Preexistent atrial late potentials were found among 15 out of 23 patients before percutaneous transluminal coronary angioplasty (PTCA) of the right coronary artery. After successful PTCA only 3 out of 15 patients were affected ($p < 0.0004$) after 1 day, as well as after 1 month. All patients with a history of AF did not suffer from an arrhythmic recurrence within the following 6 months after successful PTCA.

The role of healed prior atrial infarction as a potential atrial arrhythmogenic factor also remains to be examined. The involvement of atrial ischemia in particular cases of AF might have therapeutic implications, given the specific responses of arrhythmias related to acute myocardial ischemia and infarction to pharmacological interventions.

Chronic AF is likely to be associated with cell death and fibrosis that would be expected to be the results of prolonged ischemia and/or necrosis. These changes might contribute to atrial mechanical dysfunction and persistence of the arrhythmia[26,27]. Atrial remodeling is characterized by a shortening of the action potential, down-regulation of several ion channels, alteration of the morphological structure of the atria, activation of several neurohormones and accumulation of intracellular calcium. During atrial remodeling, the expression of proteins involved in intracellular calcium homeostasis, such as the sarcoplasmic reticulum calcium ATPase (SERCA2a) and the ryanodine receptor[28,29] is reduced. Interestingly, it has also been shown that expression of the inositol 1,4,5 trisphosphate IP3 receptor, which also serves to regulate the intracellular calcium concentration, is upregulated in chronic AF[30]. Taken together these data suggest that the atrial remodeling process is very similar to that underlying ischemia, and might be prevented by strategies aimed at minimizing calcium overload.

Among these strategies, calcium channel antagonists – by reducing the amount of calcium entering into the cell at any given time – could prevent atrial electrical remodeling. Some studies have demonstrated that verapamil could attenuate short-term (≤ 24 hours) tachycardia-induced shortening and maladaptation of atrial effective refractory period and reduce the inducibility of AF[31]. However, it has been reported that the voltage-dependent L-type calcium channel antagonist verapamil, which is believed to be effective in preventing short-term atrial remodeling, can increase the incidence of AF in the long term[32,33]. Indeed, in an experimental model, verapamil could not prevent long-term (1 and 6 weeks, respectively) tachycardia-induced changes of atrial electrophysiological properties and increased the duration of AF in the dogs either before or after long-term rapid atrial pacing[32]. Verapamil was evaluated as a prophylactic agent using a daily oral dose of 320 mg administered after cardiac surgery by Davison et al.[34]. Although verapamil decreased the incidence of AF compared to placebo, it was associated with a 20% withdrawal rate and significant complications like hypotension and pulmonary edema (13 vs 1% in placebo, $p < 0.001$).

In contrast, it seems that the inhibition of T-type calcium channels with mibefradil could be of benefit and would better prevent the electrophysiological remodeling[35]. This would suggest a predominant role for the T-type voltage-dependent calcium channel in a pathological situation such as chronic AF. However, further studies are necessary to confirm this hypothesis, which is based on a pharmacological approach using mibefradil. It has recently been shown that the cardiovascular action of mibefradil could be explained by the effect of this compound on the L-type calcium channel as well as the T-type calcium channel[36].

Trials with newer generation calcium channel blockers (like amlodipine and felodipine) are unavailable.

Tedisamil is an unusual antifibrillatory compound that has a novel mechanism of action by inhibiting the transient outward current and the repolarizing potassium currents in the sino-atrial node. Tedisamil works acutely against AF. Importantly, AF is often caused by or related to cardiac ischemia, and conversely, ischemia is caused by the increased oxygen demand of AF. Hence, the double properties of tedisamil as a drug that both inhibits AF and acts in an anti-ischemic mode are an attractive basis for future clinical research[37].

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ATRIAL FIBRILLATION AND ILLICIT DRUGS IN ATHLETES

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Atrial fibrillation (AF) in competitive athletes performing long-term vigorous sport practice is one of the most frequent causes of long-lasting palpitations. The present management of athletes with AF is complicated by the problem of illicit drug assumption. Most of the illicit drugs included in the International Olympic Committee World Anti-Doping Agency 2004 list, taken to improve athletic performance or as masking agents (for instance stimulants, cannabinoids, alcohol, anabolic androgenic steroids, combination of different prohibited substances), may induce AF through a direct or indirect arrhythmogenic effect. That may happen both in healthy subjects and in presence of a latent underlying arrhythmogenic heart disease, including some forms related to the assumption of illicit drugs.

Atrial fibrillation (AF) is one of the most frequent causes of prolonged palpitations[1-6] in young competitive athletes, including elite type. It can occur frequently during training, competition, in the post-exercise recovery period, rarely at rest.

Recurrences of paroxysmal AF in young competitive athletes may interfere with competitive professional activity, particularly if they are at a high ventricular rate and exercise-related, and may be a cause of non-eligibility for athletic sports activity. AF in competitive athletes (with intact heart) seems to be due to adrenergic or vagal mechanisms in "susceptible" subjects with neurohormonal imbalance related to a prolonged athletic training[1-8]. An interesting animal model of AF can be found in racehorses that have a combination of a large heart (including the atria), high vagal tone and episodes of extreme exercise that cause stimulation of the atria by epinephrine release[9] (Bove AA. Looking for atrial fibrillation. June 2, 2003, 3-4: www.cardiosource.com). The role of a long-term vigorous and regular sports practice in favoring AF occurrence is supported by the higher prevalence of AF/atrial flutter in "master" than in younger (less < 35 years) athletes and in the general population[10,11].

Also the "lone" form is the most frequent manifestation of AF and can be the first sign of an underlying heart disease (i.e. myocarditis, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia, ischemic heart disease). A well identified initiation mechanism (atrioventricular nodal reentrant tachycardia, concealed form of Wolff-Parkinson-White syndrome, focal atrial tachycardia), besides left atrial ectopic beats, may be found.

The current management of competitive athletes with AF is complicated by the widespread use of illicit drugs taken both by professional and non-professional athletes of any age.

We suggest the term "illicit drugs"[12] rather than "doping", in that they comprise both drugs taken as true doping or performance enhancing drugs and "masking agents", i.e. drugs taken to the aim of masking the presence of other specific drugs in tests for doping control.

Almost all illicit drugs, banned by the International Olympic Committee (IOC) and yearly updated (since 1999) by the World Anti-Doping Agency (WADA),

may cause, through a direct or indirect arrhythmogenic effect, in a short, medium or long term, a wide range of cardiac arrhythmias (focal or reentry type, supraventricular and/or ventricular), lethal or not, even in healthy subjects with no previous history of cardiac diseases. In subjects with preexisting health problems, particularly latent arrhythmogenic substrate or primary arrhythmic disorders including some inherited cardiomyopathies at risk of sudden cardiac death, the illicit drug assumption could be the cause of many types of arrhythmic manifestations including severe forms leading to life-threatening arrhythmias, cardiac arrest and sudden cardiac death. The 2004 IOC list of the "Prohibited classes of substances" (www.wada-ama.org - WADA Code - Valid January 1, 2004, updated November 25, 2003) includes: S1) stimulants, S2) narcotics, S3) cannabinoids (e.g. hasish, marijuana), S4) anabolic agents (androgenic steroids and other anabolic), S5) peptide hormones (including their mimetics and analogues), S6) beta$_2$-agonist, S7) agents with an antioestrogenic activity, S8) masking agents, S9) glucocorticosteroids. The IOC list of "Prohibited methods" includes: M1) enhancement of oxygen transfer (blood doping and oxygen carriers), M2) pharmacological, chemical and physical manipulation, M3) gene doping.

Atrial fibrillation and illicit drugs in athletes

AF is quite possible in athletes assuming illicit drugs like:

• stimulants. They may easily provoke AF also in the general population and in athletes they frequently induce AF during physical activity. In fact, blood catecholamine levels are directly proportional to the intensity of exercise[13] and elevated levels of epinephrine appear to induce AF combining their action with the arrhythmogenic effect of stimulant assumption.

The list of stimulants includes cocaine, substance for which the relationship between sport and arrhythmogenic effect is well established[14]. This alkaloid may cause different kinds of focal or reentrant supraventricular and ventricular arrhythmias such as ectopic beats, AF, atrioventricular nodal reentrant tachycardia, Wolff-Parkinson-White arrhythmias, non-sustained and sustained ventricular tachycardia and fibrillation. The association of the sympathomimetic effects of physical exertion with cocaine addiction may play an important role in the genesis of these arrhythmias[15,16].

In the long term, the abuse of stimulants may cause dilated cardiomyopathy and related arrhythmias, AF included.

The 2004 prohibited list of stimulants (S1) – WADA Code – is the following: "adrafinil, amfepramone, amiphenazole, amphetamine, amphetaminil, benzphetamine, bromantan, carphedon, cathine, clobenzorex, cocaine, dimethylamphetamine, ephedrine, ethylamphetamine, ethylefrine, fencamfamin, fenetylline, fenfluramine, fenproporex, furenorex, mefenorex, mephentermine, mesocarb, methamphetamine, methylamphetamine, methylenedioxyamphetamine, methylenedioxymethamphetamine, methylephedrine, methylphenidate, modafinil, nikethamide, norfenfluramine, parahydroxyamphetamine, pemoline, phendimetrazine, phentermine, phenmetrazine, prolintane, selegiline, strychnine and other substances with similar chemical structure or similar pharmacological effects".

The following stimulants are placed on the 2004 Monitoring Program and not considered as prohibited substances (WADA Code 4.5): "in competition only: caffeine, phenylephrine, phenylpropanolamine, pipradol, pseudoephedrine, synephrine";

• beta$_2$-agonists (S6) may induce effort-related AF[17,18] as well as focal and reentrant arrhythmias, supraventricular and ventricular, especially in subjects with underlying cardiomyopathies and in case of concomitant administration with other drugs. The arrhythmogenic effect of these drugs is related both to their direct beta$_2$ stimulant action (particularly when inhaled) and, in the long term, to their anabolic action. "All beta$_2$-agonists, including their D- and L-isomers, are prohibited except that formoterol, salbutamol, salmeterol and terbutaline are permitted by inhalation only to prevent and/or treat asthma and exercise-induced asthma/bronchoconstriction" (WADA Code 2004);

• alcohol, included in the classes of prohibited substances in particular sports (and in competition only), may be a cause of AF like in the "holiday heart syndrome"[19] related to ethanol intake. Also it may provoke a late occurrence of alcoholic cardiomyopathy with AF;

• cannabinoids. They include marijuana and hashish and can induce exercise-related AF in athletes;

• sport performance supplements often contain caffeine and ephedrine as performance enhancing drugs and cause AF[20];

• anabolic androgenic steroids. The arrhythmias most frequently reported during treatment with anabolic steroids are: AF[21], supraventricular and ventricular ectopic beats, sustained and non-sustained ventricular tachycardia, ventricular fibrillation. QT prolongation may also occur, particularly in genetically predisposed subjects[14]. Arrhythmias, including AF, often occur during physical activity and result from different cardiac abnormalities induced by anabolic steroids through different mechanisms and frequently due to combination of different illicit drugs. In fact, anabolic steroids are often administered along and at high dosages with masking agents such as diuretics, tamoxifen (to reduce gynecomastia), chorionic gonadotropin (which increases endogenous testosterone levels), thyroid hormones (to increase metabolic activity), growth hormone and insulin-like growth factor-I for their well-known anabolic effects, together with recreational substances such as cannabinoids and alcohol.

The 2004 prohibited list of anabolic androgenic steroids (S4) – WADA Code – is the following:
"a) exogenous anabolic androgenic steroids including but not limited to: androstenedione, bolasterone, boldenone, boldione, clostebol, danazol, dehydrochlormethyltestosterone, delta1-androstene-3,17-dione, drostanolone, drostanediol, fluoxymesterone, formebolone, formoterol, gestrinone, 4-hydroxytestosterone, 4-hydroxy-19-nortestosterone, mestanolone, mesterolone, methandienone, metenolone, methandriol, methyltestosterone, mibolerone, nandrolone, 19-norandrostenediol, 19-norandrostenedione, norbolethone, norethandrolone, oxabolone, oxandrolone, oxymesterone, oxymetholone, quinbolone, stanzolol, stenbolone, 1-testosterone (delta1-dihydro-testosterone), trenbolone and their anologues;
b) endogenous anabolic androgenic steroids including but not limited to: androstenediol, androstenoedione, dehydroepiandrosterone, dihydrotestosterone, testosterone and their analogues.
c) other anabolic agents: clenbuterol, zerenol".

AF in athletes may be secondary to some forms of hypertrophic or dilated cardiomyopathy, coronary artery disease, and myocarditis due to the prolonged assumption of several illicit drugs such as stimulants including cocaine, narcotics and many types of anabolic agents.

Conclusions

AF in competitive athletes performing long-term vigorous sports practice is one of the most frequent causes of long-lasting palpitations. The present management of athletes with AF is complicated by the problem of illicit drug assumption. In fact, most of the illicit drugs (sometimes more than one type) included in the IOC list, taken to improve athletic performance or as masking agents, may induce AF through a direct or indirect arrhythmogenic effect. That may happen both in healthy subjects with no previous history of arrhythmias and in presence of a latent underlying arrhythmogenic heart disease, including some forms related to a long-term assumption of illicit drugs.

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