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STATE-OF-THE-ART PAPER

Drug-Induced Atrial Fibrillation

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Atrial fibrillation (AF) is the most common sustained rhythm disorder observed in clinical practice and predominantly associated with cardiovascular disorders such as coronary heart disease and hypertension. However, several classes of drugs may induce AF in patients without apparent heart disease or may precipitate the onset of AF in patients with preexisting heart disease. We reviewed the literature on drug-induced AF, using the PubMed/Medline and Micromedex databases and lateral references. Successively, we discuss the potential role in the onset of AF of cardiovascular drugs, respiratory system drugs, cytostatics, central nervous system drugs, genitourinary system drugs, and some miscellaneous agents. Drug-induced AF may play a role in only a minority of the patients presenting with AF. Nevertheless, it is important to recognize drugs or other agents as a potential cause, especially in the elderly, because increasing age is associated with multiple drug use and a high incidence of AF. This may contribute to timely diagnosis and management of drug-induced AF. (J Am Coll Cardiol 2004;44:2117-24) © 2004 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained rhythm disorder observed in clinical practice. Its clinical importance is highlighted by a high prevalence and serious clinical consequences such as hemodynamic impairment and ischemic stroke. The prevalence increases with age, up to 4% in people over the age of 60 years and approximately 9% in people over the age of 80 years (1). Atrial fibrillation is associated with a four- to five-fold higher risk of ischemic stroke than the risk in the unaffected population (1-3). Multicenter studies have addressed the fact that not only permanent AF, but also paroxysmal AF, could predispose patients to systemic embolism (4-6).

Although AF can occur without detectable disease ("lone AF"), it is often associated with heart disease (7). Increasing age, heart failure, smoking, diabetes mellitus, hypertension, male sex, left ventricular hypertrophy, myocardial infarction, valvular heart diseases, pulmonary diseases, and hyperthyroidism are risk factors for AF (8). Acute, temporary causes of AF include alcohol intake, stress, coffee in excess, surgery, peri-/myocarditis, and pulmonary embolism (7).

Also, drugs have been associated with the induction of AF in case reports and clinical trials. In this review, we will discuss these drugs and what is known about their potential mechanisms to induce AF. First, we will discuss shortly what is known about the etiology and mechanisms of AF to better understand the potential mechanisms of drugs to induce AF.

ETIOLOGY AND MECHANISMS OF AF

Atrial fibrillation is associated with morphologic changes in the atrial myocardium. This may result from AF itself or from other underlying disease processes; however, it may also be general manifestations of the physiologic aging process. Changes in the autonomic innervation of the atrial myocardium and sinus and atrioventricular nodes are part of the normal aging process. Underlying disease may cause enlargement and structural changes of the atrial myocardium; vascular changes of sinus and atrioventricular nodes; acute and chronic inflammatory changes with necrosis, cellular infiltration, fatty metamorphosis, fibrosis, and calcification. These changes in the atrial myocardium lead to the electrophysiologic abnormalities that result in the mechanisms responsible for the occurrence of AF (9). Electrophysiologic effects in the atrium leading to AF can also be caused or triggered by physiologic processes such as adrenergic or vagal stimulation, metabolic or electrolyte disturbances, or by certain drugs or agents (10). Table 1 gives an overview of the most important conditions related to AF. As AF is often associated with other supraventricular tachycardias (SVT), these conditions may also induce other SVT.

Review of the etiologic factors discussed above suggests that a common pathway exists among the many diverse causes of AF. It is postulated that the onset of AF requires a trigger, such as an acute myocardial infarction or an intense neurological input to the atrium, or a drug, but that a substrate is also required for the onset and maintenance of the arrhythmia (11). After cardiac surgery, for instance, increasing age is the most powerful predictive factor for AF. Superimposed upon the age-related atrial changes are the triggers of adrenergic stimulation and perioperative pericar-

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Abbreviations and Acronyms

- AF = atrial fibrillation
- CABG = coronary artery bypass graft
- SLE = systemic lupus erythematosus
- SR = sinus rhythm
- SVT = supraventricular tachycardia

ditis and/or atrial ischemia. The importance of adrenergic triggers is emphasized by the effect that beta blockade has in decreasing the occurrence of AF after a coronary artery bypass graft (CABG). That this trigger-substrate relation is a critical partnership in arrhythmia production is apparent from the fact that AF usually resolves spontaneously within a few weeks after CABG (11). Similarly, if a drug is stopped that triggers AF, the arrhythmia will often resolve.

Another postulated proarrhythmic mechanism (12) that fits the trigger-substrate relation is based on experiences in antiarrhythmic therapy and explained in Figure 1. In reality, for arrhythmias due to re-entry, the mechanisms by which drugs cause arrhythmia are more complex than the model discussed in the legend of Figure 1. We describe this model only for basic understanding.

METHODS

We reviewed published reports on drug-induced AF in English from January 1974 to February 2003 using the PubMed/Medline and Micromedex (Drugdex) (13) databases and lateral references. We used the key words “atrial fibrillation” combined with “drug-induced,” “chemically induced,” “associated with drug,” “as cause of drug,” and “as side effect.” Case reports with a very weak and uncertain association were excluded.

REVIEW OF DRUG-INDUCED AF

It is of clinical importance to recognize drugs or other agents as a potential cause or trigger of AF, especially in the elderly, because increasing age is associated with multiple

Table 1. Conditions Related to AF

Cardiovascular conditions
Hypertension
Valvular disease
Cardiomyopathy
Coronary heart disease: acute myocardial ischemia and infarction
Peri-/myocarditis
Sick sinus syndrome
Cardiac surgery
Congenital heart disease
Noncardiovascular conditions
Pulmonary disease/embolism
Electrolyte abnormalities: e.g., hypokalemia, hyperkalemia
Adrenergic stimulation: hyperthyroidism, pheochromocytoma, fever, stress, alcohol, caffeine, drugs, neurogenic
Vagal stimulation: neurogenic, drugs
Idiopathic (“lone AF”)

AF = atrial fibrillation.

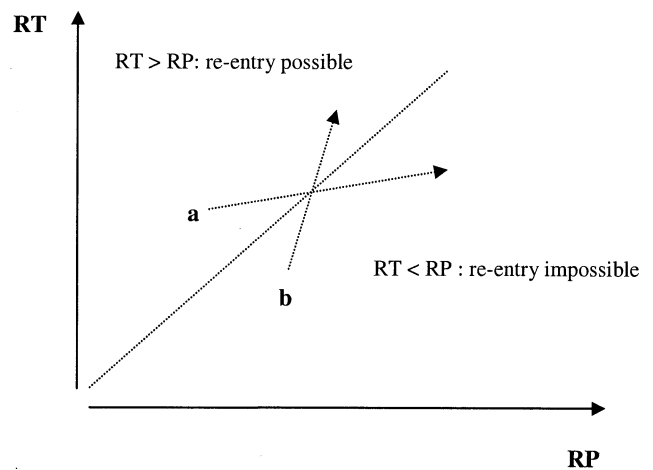


Figure 1. Antiarrhythmic drugs have diverse electrophysiologic effects on conduction, refractoriness, and automaticity in the heart. As an example we might consider the simplest form of atrial fibrillation (AF) due to re-entry around one or more obstacles (i.e., scars) that might be found in a patient with AF due to prior myocardial infarction. As a re-entry wave front circulates around an obstacle, it leaves in its wake a region of tissue that is refractory. In order for re-entry to be sustained around such an obstacle, the revolution time (RT) around the circuit must exceed the refractory period (RP) (i.e., $RT > RP$). Otherwise, the wave front would begin to encounter tissue that was still refractory, thereby preventing or extinguishing the re-entry. If $RT < RP$, re-entry is not possible, but when a (antiarrhythmic) drug slows conduction velocity more than it prolongs the RP, this drug could initiate re-entry ($RT > RP$), and the drug would be judged as proarrhythmic (arrow b). If a drug prolongs the RP to a greater degree than it slows conduction velocity, it will prevent re-entry and acts as antiarrhythmic (arrow a).

drug use and a high incidence of AF. Much has been published about severe proarrhythmic adverse effects of (antiarrhythmic) drugs, especially life-threatening drug-induced ventricular tachycardias and conduction disorders. It is not our aim to review these drug-induced arrhythmias, but to focus on drug-induced AF. Atrial fibrillation is usually not an immediately life-threatening arrhythmia, but it produces substantial discomfort and morbidity, is a major determinant of stroke (4–6), and may increase mortality, particularly in patients with structural heart disease (10). Drugs may induce different types of SVT and possibly with a similar mechanism. In this review, however, we will focus on AF because this supraventricular arrhythmia is the most common in clinical practice and known for its serious complications and potential permanent character.

Table 2 gives an overview of drugs that may induce AF and their potential mechanisms, according to published reports. In this table can be seen that almost all drug-induced AF is reported to have the following main mechanisms: adrenergic or vagal stimulation, direct cardiotoxicity, changing atrial conduction, refractoriness or automaticity, coronary vasoconstriction/ischemia, and (local) electrolyte disturbances. A distinction has been made between agents reported in case reports to be associated with AF and agents mentioned in Micromedex to be able to induce AF. As far as we could retrieve, no studies have been published on drug-induced AF besides case reports.

Table 2. Drugs* Reported to Potentially Induce AF

Drug Group	Drug	Mechanism
Cardiovascular		
Cardiac stimulants	Dopamine, dobutamine, dopexamine, arbutamine	Adrenergic stimulation
Vasodilators†	Flosequin, isosorbide mononitrate, losartan	Hypotension → adrenergic reflex?
Antiarrhythmics	Adenosine, verapamil, diltiazem, digoxin, atenolol	Changing atrial electrical properties
Cardiac ultrasound contrast agents†	Perflerane, perflurobutane	Local stimulation?
Cholinergics	Acetylcholine	Vagal stimulation
Diuretics	Thiazides	Hypokalemia
Respiratory system		
Sympathomimetic inhalants		
Alpha agonists	Pseudoephedrine	Adrenergic stimulation
Beta agonists	Albuterol‡	Adrenergic stimulation
Xanthines	Aminophylline‡	Adrenergic stimulation
Corticosteroids	Methylprednisolone (high dose)	Local potassium efflux
Cytostatics	Gemcitabine‡, melphalan, cisplatin‡, docetaxel, 5-FU, etoposide, ifosfamide†	Several, cardiotoxicity
Cytokines and immunomodulators†	Interferon-gamma, interleukin-3, interleukin-6	Not reported
Photosensitizing agents†	Porfimer, verteporfin	Not reported
Central nervous system		
Cholinergics	Physostigmine, donepezil	Vagal stimulation
Anticholinergics	Atropine	Adrenergic stimulation
Dopamine agonists	Apomorphine	Vagal activity
Antidepressants	Fluoxetine‡	Serotonin?
	Tranlycypromine, trazodone	Not reported
Antipsychotics	Clozapine‡	Not reported
Antimigraine	Sumatriptan‡	Coronary spasm → ischemia
Anesthetics	Bupivacaine	Increasing cardiac automaticity
Genitourinary system		
Drugs for erectile dysfunction	Sildenafil‡	Hypotension → adrenergic reflex?
Drugs for premature labor	Hexoprenalin, terbutaline	Adrenergic stimulation
	Magnesium sulphate	Changing atrial conduction
Miscellaneous	Nicotine, anabolic steroids, fluorescein, etanercept, azathioprine	Several
Antithrombotic agents†	Anagrelide, clopidogrel	Not reported
Antiemetics†	Alizapride, benzquinamide	Not reported
Miscellaneous†	Amifostine, disulfiram, etretinate, flupirtine, gallium nitrate, levocarnitine, nesiritide, niacin, zalcitabine, amphotericin B, pentagastrin, calcium	Not reported

*Grouped by Anatomical Therapeutic Chemical code; †micromedex (product information/clinical trials) (13); ‡causal relationship confirmed by recurrence of AF after re-challenge.

AF = atrial fibrillation; 5-FU = 5-fluorouracil.

CARDIOVASCULAR DRUGS

Cardiac stimulants. Several cardiac stimulants are known for their potential to induce SVT. This can be attributed to their adrenergic properties. Atrial fibrillation has been reported with the use of dobutamine and arbutamine stress echocardiography (14,15). Dopamine and dopexamine have been associated with AF when used for acute cardiac failure or hypotension after open-heart surgery. Some cases converted spontaneously to sinus rhythm (SR), others needed treatment (16,17). In one case report, an older patient with left atrial enlargement developed sustained AF after dobutamine stress echocardiography (14).

Antiarrhythmics. It is well known that antiarrhythmics can have proarrhythmic adverse effects, including AF and atrial flutter (12,18,19). A possible mechanism is previously described and is shown in Figure 1. It is not surprising that antiarrhythmic drugs can cause arrhythmia in view of the diverse electrophysiologic effects on conduction, refractoriness, and automaticity these agents have in the heart. In

single cases it has been described that persons treated for AF by class IA and IC drugs developed atrial flutter with 2:1 or 1:1 atrioventricular conduction (19,20). We will focus now on the specific drugs associated with AF in published reports.

Adenosine can induce AF by the shortening of atrial action potential duration while it is used for terminating atrioventricular re-entry tachycardia. Most patients convert to SR within a few minutes (21–23), but also a case has been documented that needed electrical cardioversion (24). Case reports and experiments suggest that the calcium-channel blockers verapamil (25–27) and diltiazem (28) may aggravate or induce AF in susceptible patients. The mechanism is unknown. If AF develops in patients given verapamil or diltiazem for other indications, physicians should consider the drug as a possible cause of the arrhythmia. Digoxin can cause all sorts of arrhythmias and conduction disturbances, including AF (29). Mostly this is a sign of intoxication. If digoxin is prescribed for heart failure and, after a while, AF

and/or other arrhythmias develop, this may result from absolute or relative digoxin overdose. When digoxin is prescribed to convert AF to SR and AF reoccurs, it may be difficult to assess its causation. In a study of the electrophysiologic effects of atenolol, researchers made the observation that acute use of atenolol could facilitate the induction of AF in patients with a high incidence of paroxysmal AF and conduction abnormalities. The underlying mechanism is unclear (30).

Diuretics. Thiazide diuretics are especially known for hypokalemia as a potential side effect. Via this mechanism, arrhythmia can be induced, and also AF has been reported (31,32). Therefore, regular electrolyte monitoring of patients using diuretics is essential, and adding potassium-conserving diuretics can be helpful in patients susceptible to hypokalemia.

Cholinergics. Cholinergic drugs stimulate the vagal nervous system. Paroxysmal AF is a relatively common complication of coronary artery spasm provocation tests using intracoronary injection of acetylcholine, especially in patients with ischemic heart disease (33). In a study of 740 patients, of the patients who developed AF during spasm provocation testing (n = 116), 28.4% needed antiarrhythmic agents for conversion to SR again. The potential mechanism is thought to be vagal stimulation by acetylcholine (33).

Some other cardiovascular drugs have been associated with AF in clinical trials, such as the vasodilators flosequinan and isosorbide mononitrate and the echocardiography contrast agents perflorane and perflorobutane. Potential mechanisms were not reported (13,34).

RESPIRATORY SYSTEM DRUGS

Sympathomimetic inhalants. Alpha and beta sympathomimetic inhalants are prescribed to induce bronchodilation in lung patients. They are known for their potential to cause cardiovascular adverse effects, such as sinus tachycardia and exacerbation of existing arrhythmia. Atrial fibrillation has been reported in infants <1 year of age after excessive therapeutic doses of pseudoephedrine (>4 mg/kg/day) (35). Albuterol treatment using a spacer device was reported to induce AF with a positive re-challenge in a healthy young man. The authors think that the high dose administered through the spacer triggered the AF, because the man did not have complaints using a metered dose inhaler without the spacer device (36).

Xanthines. The positive-inotropic, arrhythmogenic, and chronotropic effects of xanthines are well known (37-39). Atrial fibrillation associated with intravenous aminophylline has been reported in three patients without underlying cardiac disease. Re-challenge was positive in one patient (39). Conversion to SR occurred 9 to 14 h after cessation of the drug in all three patients.

Corticosteroids. High doses of corticosteroids are standard treatment for a wide array of medical disorders. There are

several case reports of AF after pulse methylprednisolone therapy: in two patients with multiple sclerosis (40,41), two children with nephrotic syndrome (one of them having systemic lupus erythematosus [SLE]) (42), in a man with SLE (43), and in a woman with rheumatoid arthritis (44). Fujimoto et al. (45) postulated that methylprednisolone mediates potassium efflux via a direct effect on the cell membrane. Local potassium efflux may, in turn, influence arrhythmogenesis.

CYTOSTATICS

The pathophysiology of chemically induced arrhythmias by cytotoxic agents remains to be clarified. The hypotheses are multiple and include direct and indirect effects. The sinus node may be influenced by several stimuli, and a hyperstimulation of the parasympathic as well as of the sympathetic system may cause abnormal function of the sinus node and abnormal intraatrial or atrioventricular conduction (46,47). Anthracyclines are associated with cardiac toxicity and brady- or tachyarrhythmias. Cisplatin, 5-fluorouracil, and etoposide have most frequently been associated with AF (47). In cases of cisplatin-induced AF, a positive re-challenge confirmed a causal relationship. The authors attributed this to direct myocardial toxicity (48). Gemcitabine has been reported to induce AF with a positive re-challenge in a patient who had a history of a single brief paroxysm of AF (47). The authors suggested a direct toxic effect of gemcitabine on the sinus node and/or the supraventricular conduction system. Ciotti et al. (49) describe another possible mechanism. They reported a case of severe cardiopulmonary toxicity (acute respiratory distress syndrome and AF) after gemcitabine infusion and suggest an inflammatory pathogenetic mechanism mediated by cytokine release resulting in myofibroblast proliferation and collagen deposits in lung and atrium.

Atrial fibrillation after high-dose melphalan has been described in several cases without a history of structural heart disease or any other condition potentially causing AF such as fever, septicemia, or electrolyte imbalance (50). A possible mechanism is not discussed. The authors speak of acute conduction cardiotoxicity.

Docetaxel-induced AF was recently described in a woman without any risk factors for AF (51). The authors conclude that this is probably a rare adverse effect of docetaxel.

In all cases mentioned previously, SR was reestablished by antiarrhythmic drug therapy.

CENTRAL NERVOUS SYSTEM DRUGS

(Anti)cholinergics. Cardiac dysrhythmias are among the major adverse reactions of the *anticholinergic* and vagal inhibitory agent atropine. Ophthalmic atropine eye drops after glaucoma surgery have been associated with AF. Two cases have been described, and AF resolved after antiarrhythmic treatment (52).

The *cholinergic* agent physostigmine, a cholinesterase inhibitor and vagal stimulator, is commonly used to treat the central anticholinergic syndrome or post-anesthetic depression caused by a large number of drugs. One case report describes the occurrence of AF directly after the administration of physostigmine (53). The mechanism is thought to be due to severe depression of both the sinoatrial and atrioventricular nodes due to vagal tone. This allows a latent re-entry focus to emerge within the atrial myocardium.

Also, donepezil, a cholinesterase inhibitor used in Alzheimer's disease, has been associated with AF in clinical trials (13).

Dopamine agonists. Apomorphine, a dopamine receptor agonist used in Parkinson's disease, has been associated with AF in a man without cardiovascular disease (54). Five minutes after a subcutaneous bolus of apomorphine, the man developed AF and was converted to SR after medical treatment. Other possible causes for AF were excluded. Subcutaneous apomorphine injection has been reported to cause postural hypotension and vasovagal response in 10% of patients with Parkinsonism (55). The authors state that AF in this patient may have been induced by an imbalance of autonomic tone with increased vagal activity.

Antidepressants/antipsychotics. The selective serotonin reuptake inhibitor fluoxetine has been reported to provoke AF and a recurrence on re-challenge in an elderly woman with a history of mild stable angina, but no history of arrhythmia or myocardial infarction (56). Because serotonin has an important role in the homeostatic control of the cardiovascular system, selective serotonin reuptake inhibitors can be expected to cause hemodynamic changes (57). The authors state that, in this woman with (mild) preexisting heart disease, the cardiovascular effects of fluoxetine may have been able to trigger the onset of AF.

Similarly, the occurrence of AF after the use of the monoamine oxidase inhibitor tranylcypromine has been described in a young man without cardiovascular past but a history of alcohol abuse. A possible mechanism mentioned in this report is stimulation of cardiac catecholamine receptors by a decreased catabolism of tranylcypromine in an alcohol-damaged liver (58). The atypical antidepressant trazodone has been associated with AF in a patient with underlying heart disease (59).

The atypical antipsychotic clozapine has been reported to induce AF with a positive re-challenge in a man without cardiovascular history. Antiarrhythmic therapy was needed to convert to SR again. A potential mechanism is not described. Other side effects of clozapine such as orthostatic hypotension, sinus tachycardia, heart failure, and electrocardiogram changes are well known (60).

Antimigraine drugs. The antimigraine drug sumatriptan, a serotonin-1 agonist, has frequently been associated with chest pain and myocardial infarction (61-64). This is presumed to be due to vasoconstriction of the coronary arteries. Atrial fibrillation associated with sumatriptan is uncommon, but several cases have been reported, also with

positive re-challenge (65). The authors suggest that myocardial ischemia secondary to coronary vasospasms could be a trigger for AF. This mechanism is also postulated by Hung et al. (66). Hung et al. (66) described a patient who regularly developed paroxysmal AF after early morning chest tightness. Medical history only mentioned well-controlled hypertension. Coronary artery spasm provocation with methylergonovine was performed to test whether AF was the result of coronary artery spasm. The patient indeed developed AF during the provocation test. Sueda et al. (33) reported that paroxysmal AF often occurred during spasm provocation tests with acetylcholine, especially in patients with ischemic heart disease. They suggested that vagal stimulation by acetylcholine triggered the onset of AF in susceptible patients. However, the mechanism may also be myocardial ischemia secondary to coronary vasospasms, as described previously.

Anesthetics. Atrial fibrillation has been described during epidural anesthesia with bupivacaine in a man with a history of stable angina pectoris but no arrhythmias (67). The AF persisted despite treatment during the period of epidural blockade. Only after the anesthesia was terminated, reversion to SR occurred. The reporters suggest that bupivacaine inhibits the Na⁺ K⁺ pump, hence reducing the resting cell membrane potential. This may increase cardiac automaticity, especially in cardiac fibers already partially depolarized because of ischemic heart disease. The authors postulate that bupivacaine acted as a trigger for the onset of AF.

GENITOURINARY SYSTEM

Drugs for erectile dysfunction. Three case reports describe AF after taking sildenafil (68-70). One occurred in a healthy young man who interrupted coitus because he felt light-headed and had palpitations that were followed by a brief syncopal episode (68). He failed chemical conversion twice, but converted spontaneously to SR two days later. It was suggested that sildenafil caused profound hypotension leading to syncope and reflex tachycardia via catecholamine excess. Another report describes a 50-year-old man with a hypertrophic cardiomyopathy who developed AF with dizziness and converted to SR after medical treatment (70). This man had a positive re-challenge several weeks later. A third report describes AF and hypotension in a man 1 h after taking sildenafil (69). He was diagnosed with a Wolff-Parkinson-White syndrome 12 years before. Four hours later, he returned to SR spontaneously. The authors speculate that AF was caused by increased sympathetic activity due to hypotension, which may be provoked by sildenafil.

DRUGS FOR PREMATURE LABOR

Hexoprenaline is a beta-adrenergic agonist used for treatment of premature labor. Atrial fibrillation has been reported in a young woman without cardiovascular disease during intravenous treatment with hexoprenaline (71); 8 h

after cessation of the drug, the heart rate spontaneously converted to SR. The authors state that it is reasonable to expect that arrhythmias and other adrenergic adverse effects may occasionally be produced by this drug.

Oral use of terbutaline, also a beta-sympathomimetic drug, has been associated with AF in a healthy pregnant woman with preterm labor. After several attempts of medical antiarrhythmic treatment, she converted to SR (72).

Magnesium sulfate has widespread use in pregnancy both in preeclampsia as an anticonvulsant drug and as a tocolytic drug. In a woman with preeclampsia and without history of cardiac disease, AF occurred during treatment with magnesium sulphate and resolved spontaneously after discontinuation. This drug has antiarrhythmic properties by slowing the conduction in the atrioventricular node, but in this case probably induced AF. Serum levels were within therapeutic range (73).

MISCELLANEOUS

Apart from the categories of drugs discussed in the previous paragraphs, various other agents have been associated with the occurrence of AF.

Nicotine is widely used as an aid to smoking withdrawal. There are several reports of nicotine induced AF (74-76). Nicotine overdose taken as chewing gum or nasal inhalator can result in increased heart rate and can be a potential danger for developing AF, even in individuals without a history of cardiac disease. Atrial fibrillation has also been described in a patient with mild cardiovascular disease taking the usual amount of nicotine gum (75).

High doses of anabolic steroids have been reported in association with AF (77), as with hypertension, ischemic heart disease, hypertrophic cardiomyopathy, and sudden death. A healthy 22-year-old male bodybuilder developed symptomatic AF after taking high doses of anabolic steroids for five weeks. An echocardiogram showed some left atrial hypertrophy and septal hypokinesis, but it remained unclear if this was caused by the steroids. He was hospitalized and converted spontaneously to SR after two days of stopping the intake of the steroids. Atrial fibrillation did not recur after discharge.

Intravenous fluorescein has been associated with AF. A 56-year-old man with negative cardiac history developed AF just after administration of fluorescein during ankle surgery. Cardioversion was eventually required to restore SR. Adverse reactions to fluorescein are not rare and frequently take the form of an allergic reaction. The authors suggest that nonspecific histamine-releasing mechanisms can explain the onset of AF in this patient, because histamine has long been known to have effects on cardiac rhythm through several different mechanisms (78,79).

A patient without risk factors for AF has been reported developing AF after a combination of etanercept and methotrexate for rheumatoid arthritis (80). The authors speculate that blocking tumor necrosis factor-alpha recep-

tors with etanercept could cause increased intracellular calcium in the myocyte and perhaps make the myocyte more excitable.

Azathioprine, an immunosuppressive agent used in severe psoriasis, has been associated with AF, but one of the reported patients abused alcohol and developed high fever while using azathioprine. Such factors could also have been responsible for triggering AF (81,82). The other reported, also speculative, case had no comorbidity and developed AF after four weeks of use. Other known possible causes for AF were excluded, and AF persisted for at least one year.

DISCUSSION

There are different pathways to the initiation of AF. Therefore, it is not surprising that several categories of drugs with different mechanisms of action have been associated with the onset of AF. Evidence associating drugs with AF is scanty and largely based on individual case histories. Even in cases in which a close temporal relationship between drug intake and initiation of AF exists, this may be a chance finding or be caused by the underlying condition ("confounding by indication"). Nevertheless, in several cases recurrence of AF after re-challenge confirmed a causal relationship. Such proof is not very common, however, as re-challenge is only ethical when it concerns a drug that is essential for the treatment of the patient and when a causal role of the drug is still inconclusive. However, if other known possible causes for AF are excluded and a plausible mechanism is available, the likelihood of a causal relationship increases. Pathophysiologically, drugs that increase or decrease adrenergic or vagal activity, such as sympathicomimetics, parasympathomimetics, and their inhibitors, may be able to cause AF, especially in susceptible patients with a history of cardiovascular disease (disease is the substrate, drug is the trigger), but also in "healthy" patients. These drugs represent a substantial part of cardiovascular, respiratory, and central nervous system medications. Antiarrhythmic drugs can paradoxically induce dysrhythmias as well, including AF and atrial flutter, by influencing the electrical properties of the atrial myocardium. Coronary spasm induced by certain drugs, such as acetylcholine and sumatriptan, may cause AF via myocardial ischemia. Cytostatics seem to have a more direct toxic effect on the heart, potentially initiating AF. The underlying disease and drug together can play an important role in the induction of AF (substrate-trigger relation), especially in thorax or lung carcinoma.

Most of the time it is not difficult to diagnose drug-induced AF because there is a direct time relationship between the administration of the drug and the onset of AF. However, if a patient presents with new-onset AF, it should be routine to review, besides the medical history, what medication or other agents the patient is using that may be able to induce AF. If there is suspected drug-induced AF after exclusion of other causes, the suspected drug/agent

should be stopped and AF treated if it persists after discontinuation. It may be important to have an idea about the underlying cause or mechanism, and, if overdose is not the issue, it may be advisable to find an alternative drug or treatment for the condition the drug was given for. If the drug is necessary for the patient, it may be advised to restart the drug in a lower dose and monitor the patient adequately for recurrence of AF. If AF recurs, continuous treatment to control AF is needed.

Much has been published, including observational studies, about severe proarrhythmic side effects of drugs, especially life-threatening drug-induced ventricular arrhythmias frequently associated with QT interval prolongation. Epidemiologic studies to quantify the relation between certain drugs and AF have not been performed yet, although AF is a very common arrhythmia with substantial morbidity and potentially serious complications. We think more research is needed, such as experimental and observational studies, to get more insight into the effect of drugs on the development of AF.

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