Anaphylaxis-Induced Atrial Fibrillation and Anesthesia: Pathophysiologic and Therapeutic Considerations

Abstract

Atrial fibrillation is the most common cardiac arrhythmia in western society affecting more than 35 million individuals worldwide annually. It is a common postoperative complication and may also occur spontaneously during general and local anesthesia administration. Aging, diabetes mellitus, hypertension, and cardiovascular diseases including cardiomyopathies, congenital cardiac anomalies, heart failure, myocardial ischemia, pericarditis, previous cardiac surgery, vascular disease, and valvular heart disease are some correlated factors. Beyond age, increased incidence of atrial fibrillation has been correlated to autoimmunity system activation as it is the underlying mechanism of persistent atrial fibrillation development. Current research supports an association between the complement system activation and lymphocyte-pro-inflammatory cytokines release with the cardiac conduction system and atrial fibrillation. The loss of CD28 antigen from CD4+ CD28+ T lymphocytes seems to play a major role in atrial fibrillation development and prognosis. Except atrial fibrillation, a variety of additional electrocardiographic changes, resembling those with digitalis intoxication may accompany anaphylaxis and particularly Kounis syndrome. Histamine is one well-known mediator in allergic and inflammatory conditions as physiologically regulates several cardiovascular and endothelial functions with arrhythmogenic potential. The increased oxidative stress, measured by the redox potentials of glutathione, has been correlated with atrial fibrillation incidence and prevalence. The use of antazoline, a first-generation antihistamine agent used for rapid conversion of recent-onset atrial fibrillation in patients with preserved left ventricular function and for rapid atrial fibrillation termination during accessory pathway ablation denotes that anaphylaxis-induced histamine production could be the cause of atrial fibrillation at least in some instances. The anaphylaxis diagnosis in anesthesia can be challenging owing to the absence of cutaneous manifestations such as flushing, urticaria, or angioedema. Anticoagulation for stroke prevention, rate and rhythm control medications, invasive methods such as radiofrequency ablation or cryoablation of pulmonary veins as well surgical ablation constitute the treatment basis of atrial fibrillation. Understanding the underlying mechanisms of atrial fibrillation by cardiologists, anesthesiologists and surgeons, as well as potential treatments, to optimize care is of paramount importance.

Keywords: Anaphylaxis, anesthesia, antihistamines, atrial fibrillation, histamine, Kounis syndrome

Introduction

Atrial fibrillation represents the most common complex cardiac arrhythmia with a lifetime risk in the community of 25%. It is a common complication in anesthesia and peri-postoperative period with an incidence ranging from 15 to more than 45%. Atrial fibrillation during anesthesia is related with peri-procedural complications, poor outcomes, and increased length of hospitalization. This arrhythmia is related to various risk factors such as aging, diabetes mellitus, hypertension, and cardiovascular diseases including cardiomyopathies, congenital cardiac anomalies, heart failure, myocardial ischemia, pericarditis, previous cardiac surgery, vascular disease, and valvular heart disease. Pulmonary diseases such as pneumonia, lung cancer, pulmonary embolism, and sarcoidosis may be associated with increased atrial fibrillation (AF) incidence. Additionally, obesity, obstructive sleep apnea, hyperthyroidism, subclinical hypothyroidism, excessive alcohol consumption, smoking are related with an increased risk of AF development. Especially, the corrected risk of atrial fibrillation incidence is increased by 28% corresponding to each 5 units increase of body mass index. However, the majority of atrial fibrillation episodes cannot be fully explained by predisposing factors or cardiac

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diseases.\textsuperscript{[5]} In the Gutenberg-healthy-study, there were 14.3% of patients with atrial fibrillation with no cardiovascular risk factors other than age.\textsuperscript{[8]} In addition, atrial fibrillation has been associated with immunological, allergic, psychiatric, and neurovegetative diseases.\textsuperscript{[9]} Nowadays, the increased life expectancy along with increasing atrial fibrillation incidence with age has a dramatical impact over the health care costs.\textsuperscript{[7]}

In this review, therefore, we present the pathophysiological, preventive, and therapeutic considerations of this serious arrhythmia together with its associations with anaphylaxis and anesthesia in clinical practice.

Autoimmunity and atrial fibrillation

Current research, strongly, supports an association between the complement system activation and lymphocyte pro-inflammatory cytokines release with the cardiac conduction abnormalities and atrial fibrosis/remodeling.\textsuperscript{[8]} Cluster of differentiation (CD) 4+ T lymphocytes without the surface-antigen (protein) CD28, the so-called CD4+ CD28 null T cells, are crucially involved in chronic inflammatory processes. However, for T-cell-proliferation, regulation, activation, and cell-survival a co-stimulatory CD28-receptor on CD4 T cells is needed.\textsuperscript{[9]} On the basis of longstanding inflammatory conditions, CD4+ CD28+ T lymphocytes lose their expression of the CD28 antigen, and therefore, their sensitivity for both suppression and apoptosis induction by regulatory T cells, leading to an extensive inflammatory response as well as auto-reactivity against human tissue.\textsuperscript{[10]} In fact, this T cell subset plays a major role on the development of atrial fibrillation as well as on the prognosis of patients.\textsuperscript{[8,11]}

Several community-based studies have shown that high levels of low-density lipoprotein and total cholesterol were associated with a lower risk of atrial fibrillation.\textsuperscript{[12,13]} In a recent prospective study,\textsuperscript{[14]} reverse findings supported the above paradoxical findings. It was found that in sex- and age-adjusted patients, the atrial fibrillation was associated with lower total and low density lipoprotein cholesterol levels, low serum apoB, and high sex hormone binding globulin. On the basis of the above findings, the authors suggested that Lp(a) protein and its component apoB due to high oxidative damage can be aggregated to high sex hormone binding globulin forming a complex. In fact, such complexes comprising Lp(a) have been reported in association with premature atherosclerosis in patients with rheumatoid arthritis\textsuperscript{[15]} and coronary artery disease.\textsuperscript{[16]} conditions associated with autoimmunity and inflammation. Furthermore, circulating oxLDL/beta2-glycoprotein I complexes have been detected and assessed in autoimmune-mediated atherosclerosis.\textsuperscript{[17]} The complex formation by low serum apoB and high sex hormone binding globulin, strongly support the hypothesis that autoimmune activation might be an additional underlying mechanism, beyond aging, for persistent atrial fibrillation development.

Anaphylaxis and atrial fibrillation

Anaphylaxis-induced atrial fibrillation was described for the first time in a report published nearly 50 years ago\textsuperscript{[18]} and concerned of 23 patients suffering from anaphylaxis; in 14 of whom, there were various electrocardiographic abnormalities. Specifically, fattening of the T waves, inversion of the T waves, ST-segment elevation or depression, nodal rhythm, and atrial fibrillation were observed in 6 patients. In these patients, the etiology of atrial fibrillation was attributed to a direct antigen-antibody myocardial reaction, induced by either mediator released during anaphylaxis, pharmaceutical agents such as epinephrine used for treatment, anoxia, pre-existing heart disease, or a combination of several factors.

Subsequently, the concurrence of acute coronary syndromes including coronary spasm associated with atrial fibrillation, acute myocardial infarction, and stent thrombosis, with conditions caused by mast-cell and platelet activation and involving interrelated and interacting inflammatory cells, such as macrophages and T-lymphocytes, in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid reactions was established by American and Greek authors as Kounis syndrome.\textsuperscript{[19]}

In a recent report,\textsuperscript{[20]} 3 episodes of atrial fibrillation were triggered by anaphylaxis. The first concerned a 42-year-old hyperlipidemic man who developed general discomfort, itching, facial angioedema, and tachycardia, 45 min after fresh grilled fish consumption (hake). The electrocardiogram showed atrial fibrillation with a ventricular rate of 81-160 bpm. Cutaneous symptoms disappeared in less than 30 min following anti-allergic treatment, and atrial fibrillation was reverted back to sinus rhythm with 5 mg of IV atenolol and 200 mg of oral flecainide within 24 h. Allergy workup showed a positive skin prick test with Anisakis Simplex.

Additionally, an 84-year-old patient, with a history of allergy to beta-lactams and hypertensive cardiomyopathy, developed generalized urticaria, palpebral angioedema, syncope, vomiting, and atrial fibrillation post-kiwi consumption. He was treated with 80 mg intravenous methylpredisolone, 5 mg subcutaneous dexchlorpheniramine, and intravenous metoclopramide, and 5 mg of intravenous atenolol and atrial fibrillation were reverted to sinus rhythm within 24 h. However, 3 months later, he developed generalized pruritus and hives, dizziness, and vomiting after the intake of peanuts. Again, the electrocardiogram showed atrial fibrillation that was treated with intravenous methylprednisolone, dexchlorpheniramine, and intravenous atenolol, and the arrhythmia resolved in 2 h. Allergy workup confirmed hypersensitivity to food allergy, and skin tests were positive to peanuts and kiwi.

Anaphylaxis-induced atrial fibrillation is not the only electrocardiographic sign. A variety of additional
electrocardiographic changes ranging from ST-segment elevation or depression to any degree of heart block and cardiac arrhythmias resembling digitalis intoxication are associated with the anaphylactic cardiac symptoms and signs.\cite{19}

**Anaphylaxis and histamine**

Several studies have shown an association of histamine with cardiac arrhythmias. Atrial fibrillation has been triggered during anaphylaxis from insect stings, drugs, and during venom and pollen immunotherapy. Histamine is one well-known mediator in allergic and immune-inflammatory conditions that physiologically regulates several cardiovascular and endothelial functions with arrhythmogenic potential.

Such arrhythmogenic potential has been linked to increased histamine concentrations in cellular and animal models.\cite{21} Ventricular tachycardias have been associated with depolarization of Purkinje-fibers induced by histamine.\cite{22} Paroxysmal atrial tachycardia has been induced by stimulation of the H2-receptors in the right atrium and the H1-receptors in the left atrium through spontaneous diastolic depolarization.\cite{23} There are rare cases of hyperhistaminemia that have been related with cardiac arrests or atrial fibrillation in patients with mastocytosis\cite{24} or in anaphylaxis during venom and pollen immunotherapy.\cite{25} In fact, in a recent study regarding histamine impact on atrial fibrillation, a subpopulation of 10 patients with atrial fibrillation demonstrated increased levels of histamine. The authors suggested that in patients with new-onset atrial fibrillation, clinical history should be focused on any allergic reactions during the last 24–48 h.\cite{26} Histamine intolerance, ingestion of histamine-rich foodstuffs, and any background of IgE-mediated diseases,\cite{27,28}

The relationship between atrial fibrillation and histamine levels needs to be further investigated in future studies. It has been suggested that the use of antihistamines, mast cell stabilizers, or vitamin C as a further treatment option could be considered in cases of recurrent atrial fibrillation.\cite{29} In allergic, atopic, or mastocytosis patients suffering from recurrent atrial fibrillation episodes without any other cardiac pathologies, the above treatment together with corticosteroids could be beneficial. In fact, findings from a recent meta-analysis suggested that periprocedural administration of corticosteroids during catheter ablation was associated with a reduction of early but not late recurrence of atrial fibrillation.\cite{30}

**Antihistamines and atrial fibrillation**

Antazoline is a first-generation antihistamine with quinidine-like and anticholinergic properties that induces prolongation of the action potential, increases refractory period and atrial post-repolarization refractoriness, and further increasing the interatrial conduction time. This antihistamine has been used recently for rapid conversion of recent-onset atrial fibrillation in patients with preserved left ventricular function as well as for rapid termination of atrial fibrillation during ablation of accessory pathways.\cite{31} In another single-center, double-blind, and placebo-controlled trial, the intravenous antazoline administration achieved a rapid conversion of recent-onset atrial fibrillation in patients with preserved left ventricular function.\cite{32}

In experiments with isolated and retrogradely perfused rabbit hearts, atrial fibrillation was induced by atrial burst pacing in 5 of 20 hearts under baseline conditions and was maintained with a combination of acetylcholine and isoproterenol. Concurrent infusion of antazoline resulted in complete suppression of atrial fibrillation in all inducible cases, increasing significantly atrial action potential duration, atrial effective refractory period, and consequently, atrial post-repolarization refractoriness.\cite{33}

Although the antazoline’s beneficial action is according to cardiac electrophysiologic parameters, its subsequent antihistaminic action denotes that anaphylaxis-induced histamine production could be the cause of atrial fibrillation at least in some instances.

**Oxidative stress and atrial fibrillation**

Experimental studies have shown that atrial fibrillation is associated with increased systemic oxidative stress\cite{33,34} whereas the evidence in humans remains limited.\cite{35} Oxidative stress is the result of reactive oxygen species production that counteracts with endogenous antioxidants resulting in tissue injury. The reactive oxygen species are short-lived substances that derived from many sources including mitochondria, xanthine oxidase, uncoupled nitric oxide synthases, and nicotinamide adenine dinucleotide phosphate oxidases.\cite{36} The increased oxidation can cause alterations in cellular proteins and signaling pathways leading to cell dysfunction, necrosis, or apoptosis.\cite{37} Lipid peroxidation (isoprostanes), oxidized phospholipids, malondialdehyde, nitrotyrosine, myeloperoxidase, and aminothiol compounds are stable and easily measured plasma markers in the human circulation that reflect cellular and systemic oxidative stress.\cite{38}

In a recent study, the increased oxidative stress, measured by the redox potentials of glutathione, was associated with increased prevalence and incidence of atrial fibrillation. As a result, this study suggested that potential therapies that participate in oxidative stress modulation need to be investigated to treat and prevent atrial fibrillation.\cite{39}

Oxidative stress has been implicated as a possible mechanism for postoperative atrial fibrillation. Mitochondria are the major site of cellular oxidation. Patients with atrial fibrillation demonstrate mitochondrial dysfunction at various levels that might represent appropriate targets for potential pharmacotherapy. Furthermore, the correlation
of endothelin gene polymorphism in post-coronary artery bypass grafting atrial fibrillation might elucidate the genesis of postoperative atrial fibrillation, contributing to targeted therapy development for the refractory cases.\[^{40}\]

Therefore, new concepts have emerged concerning pathophysiology, etiology prevention, and treatment of atrial fibrillation that might contribute to the individual basis management of this arrhythmia.

**Anaphylaxis and atrial fibrillation in anesthesia**

Immediate hypersensitivity and anaphylactic reactions during anesthesia constitute the most challenging medical emergencies in clinical practice. Atrial fibrillation alone or post an anaphylactic reaction may also occur spontaneously under anesthesia. Data from a recent UK snapshot survey and the UK Sixth National Audit Project (NAP6) on perioperative anaphylaxis demonstrated that the incidence of such reactions is estimated to be in the range of 1:353 to 1:18,600 procedures.\[^{41}\] Prospective studies suggest an incidence of 1:3180 from France\[^{42}\] and 1:1480 from Spain.\[^{43}\] A recent study revealed that 68% of patients experienced anaphylaxis during anesthesia had a history of atopic diathesis.\[^{44}\] Diagnosing anaphylaxis in anesthesia becomes difficult as cutaneous manifestations such as flushing, urticaria, and angioedema may be absent. Anaphylaxis from passive transfer of peanut allergen in a blood product\[^{45}\] or by fresh frozen plasma\[^{46}\] has also been described. Anaphylaxis may occur at any time during anesthesia with all potentially allergenic substances but usually occurs shortly after induction.\[^{47}\]

Several grading systems have been introduced for classification of anaphylaxis during anesthesia.\[^{48}\] According to Ring and Messmer system, which is the most quoted, the anaphylactic symptoms and signs are graded as grade I involving cutaneous-mucus signs, grade II involving mild cutaneous-mucus signs, grade III involving cutaneous-mucus signs and/or bronchospasm with cardiovascular collapse, and grade IV denoting cardiac arrest.\[^{49}\] So far, several conditions have been associated with the occurrence of anaphylaxis-associated Kounis syndrome during anesthesia such as mastocytosis, left parotid gland excision spinal anesthesia, laparoscopic ileocecal excision for cecal cancer, takotsubo syndrome, coronary artery bypass graft, and the variety of drugs used in anesthesia. Multiple causes that can induce anaphylactic reactions are encountered during anesthesia increasing the risk for the anesthetized patient. Neuromuscular blocking drugs, antibiotics, latex exposure, contrast media, hypnotic agents, opioids, colloids, apronitin, protamine, chlorhexidine, dyes, local anesthetics, and blood transfusion are some of the offenders. There are several examples of anaphylaxis complicated with atrial fibrillation following the use of drugs during anesthesia. Profound fall in blood pressure associated with atrial fibrillation, followed by the appearance of a rash, vomiting, and transient loss of consciousness occurred in a 69-year-old Caucasian male immediately after surgery.\[^{50}\] The culprit cause of the anaphylactic reaction was the diagnostic agent hexaminolevulinate hydrochloride (Hexvix) instilled into the bladder for fluorescence cystoscopy. Spinal anesthesia was established with 4 ml of plain bupivacaine 5 mg/ml. The hypotension persisted for several hours in spite intensive treatment. The reaction commenced approximately 5 h post exposure to hexaminolevulinate hydrochloride. There was an increase in serum tryptase (almost nine-fold) and a positive skin prick test to undiluted hexaminolevulinate hydrochloride.

Local anesthesia can also be associated with atrial fibrillation.\[^{51}\] Lidocaine has been widely used as a local anesthetic as well as an antiarrhythmic. Its use in epidural anesthesia is increasing, presenting new risk and a potential for harm. Atrial fibrillation, with convulsions, has been documented post transforaminal cervical epidural injection with 2 ml of 2% lidocaine (40 mg) that resolved with no long-term sequelae. The patient had a negative serum lidocaine level. The authors concluded that as cervical epidural injections consists a common treatment for radicular pain, it is important for medical providers to be aware of the various complications associated with this procedure.

**Treatment of atrial fibrillation**

The main treatment of atrial fibrillation includes anticoagulants, such as warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, for prevention of intracardiac thrombosis and subsequent cerebral strokes.\[^{52}\] If atrial fibrillation persists for more than 48 h. Bridging therapies should be considered when these patients require elective surgery, and for reversal should emergency surgery be required. Several studies have compared rate control with rhythm control in varied patient populations, with no consensus that rhythm control is superior to the rate one.\[^{53}\] Ventricular rates may be controlled with beta-blockers, nonhydroxyidine calcium-channel blockers, or digoxin. The heart rate of less than 80 beats per minute is preferable. In patients with pre-excitation syndromes, beta-blockers, calcium-channel blockers, and amiodarone should be avoided. Rhythm control can be achieved with flecainide, dofetilide, propafenone, or ibutilide, and sinus rhythm can be maintained with these medications as well as amiodarone, dronedarone, and sotalol.

Invasive treatment of atrial fibrillation includes catheter radiofrequency ablation or cryoablation of pulmonary veins with approximately 25% of late recurrence risk of atrial fibrillation (at 12 months) requiring repeat ablation.\[^{54}\] Surgical ablation for atrial fibrillation during cardiac surgery
for other reasons, or alone surgical ablation through a minimally invasive technique or through a thoracotomy is an alternative with 93% success at 1 year.[35]

Conclusion

Atrial fibrillation is frequent in perioperative care and anesthesia induction, correlating with significant morbidity increase including procedure-related complications, poor patient outcome, and increased length of hospitalization. Mechanisms and underlying causes of atrial fibrillation are complex, but continuing advances in both medical and procedural therapy reduce the burden of complications. Cardiologists, anesthesiologists, and surgeons should understand the trigger mechanisms of this arrhythmia as well as potential treatments, to optimize care.

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Conflicts of interest

There are no conflicts of interest.

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