Atrial Fibrillaton in Athletes background and mechanisms

Introduction

Atrial fibrillation (AF) and atrial flutter are facilitated by atrial remodeling, atrial ectopy, and an imbalance of the autonomic nervous system. Endurance sports practice has an impact on all of these factors and may therefore act as a promoter of these arrhythmias. In an animal model, long-term intensive exercise training induced fibrosis in both atria and increased susceptibility to AF. While the prevalence of AF is low in young competitive athletes, it increases substantially in the aging athlete, which is possibly associated with an accumulation of lifetime training hours and participation in competitions. A recent meta-analysis revealed a 5-fold increased risk of AF in middle-aged endurance athletes with a striking male predominance Beside physical activity, height and absolute left atrial size are independent risk factors for lone AF and the stature of men per se may explain part of their higher risk of AF. Furthermore, for a comparable amount of training volume and performance, male non-elite athletes exhibit a higher blood pressure at rest and peak exercise, a more concentric type of left ventricular remodelling, and an altered diastolic function, possibly contributing to a more pronounced atrial remodelling. The sports cardiologist should be aware of the distinctive features of AF in athletes. Therapeutic recommendations should be given in close cooperation with an electrophysiologist. Reduction of training volume is often not desired and drug therapy not well tolerated. An early ablation strategy may be appropriate for some athletes with an impaired physical performance, especially when continuation of competitive activity is intended.

Many gaps in evidence related to epidemiology, mechanisms, and management of endurance athletes with AF persist. Clinicians must use the limited, but best available data to manage these patients. To the extent that the cardiovascular benefits of exercise are well established, all patients should be encouraged to be physically active with moderation. The evidence is conclusive that sedentary lifestyles contribute to AF development independent of sex. Physical activity in moderation decreases the risk of AF in men and women; however, men should be advised of the potentially increased risk of AF with long-term, high intensity endurance training.(1)

1. **Estes NAM 3rd, Madias C. Atrial Fibrillation in Athletes: A Lesson in the Virtue of Moderation. JACC Clin Electrophysiol. 2017 Sep;3(9):921-928. doi: 10.1016/j.jacep.2017.03.019**

Cuspid et al. sought to investigate left atrial (LA) volume, function and strain in elite athletes by a meta-analysis including echocardiographic studies that provided volumetric and strain analysis of LA phasic function. Left atrial enlargement (LAE) is a physiological adaptation to training. Elite athletes are exposed to intensive training that is associated with hemodynamic adaptation and cardiac remodeling. Most of studies have been focused on left ventricular (LV) changes induced by training. However, an important part of cardiac adjustment to increased cardiac output during effort is played by LA remodeling. There is a consensus regarding LA dilatation in athletes and large meta-analysis confirmed that LA linear dimensions, as well as LA volume, was significantly enlarged in athletes(1;2) Whether reduced LA reservoir and contractile function are adaptive changes in athletes remains to be defined. As functional remodeling of LA has been related to development of paroxysmal atrial fibrillation(PAF) in male veteran athletes and normalization of LA changes during deconditioning has been reported, evaluation of LA function by volume and strain analysis is of major importance. All studies involved in a meta-analysis by Cuspid et al (3) used GE echocardiographic machine and Echopac software for evaluation of LA strain and strain rates. However, other studies that used other vendors did not fulfilled inclusion criteria for this meta-analysis. Longitudinal investigations are needed to determine the influence of training-induced LA remodeling on cardiovascular outcome in elite athletes.

1. Iskandar A, Mujtaba MT, Thompson PD. Left atrium size in elite athletes. JACC Cardiovasc Imaging. 2015;8:753-62.
2. Gjerdalen GF, Hisdal J, Solberg EE, Andersen TE, Radunovic Z, Steine K. Atrial size and function in athletes. Int J Sports Med. 2015;36:1170-6.
3. Cuspidi C, Tadic M, Sala C, Gherbesi E, Grassi G, Mancia G.Left atrial function in elite athletes: A meta-analysis of two-dimensional speckle tracking echocardiographic studies.Clin Cardiol. 2019 May;42(5):579-587. doi: 10.1002/clc.23180

Atrial Fibrillaton in Athletes

Lone atrial fibrillaton: AF in absence of any clinical evidence of cardiac or extra cardiac fator such as latent hypertension, coronary artery disease, chronic obstructive lung disease, valvular disease, cardiomyopathy, diabetes, hyperthyroidism. obesity, metabolic syndrome, sleep apnea, alcohol consumption, endurance sports, anger, hostility, subclinical atherosclerosis, inflammation. etc

≤ 60 years AF is exceptional in children, uncommon in young adults, but 3 to 4% of subjects over 60 years of age.

Possibilites

Long-term endurance exercise

Athlete mem with AF

The proportion of sportsmen among patients with lone AF is much higher than that reported in the general population

1. lower incidence of mild hypertension
2. AF vagal mediate

Echocardiogram: greater atrial and ventricular dimension shigher ventricular mass.(**Mont 2002**)

Idiopatic, criptogenetic, essencial, primary
truly lone AF

30% of patients with paroxysmal AF

It is the effect of an underlying, 'masked' disorder.

It has a favourable prognosis

Embolic risk of 2 to 5% per year.

Genetic causes Familial genetic predisposition

Epidemiological studies have provided unequivocal evidence that the arrhythmia has a substantial heritable component.

Autosomal dominant pattern,

1. Mutations in K^+ channel genes: congenital SQTS mutations *KCNE2*, *KCNJ2*, and *KCNQ1*
2. Common AF-associated 4q25 polymorphisms (**Ritchie 2012**)
3. Brugada syndrome
4. Sinus node dysfunction (see next slide)

Atrial Fibrillation genetic mutations background: Mechanistic Sub classification of Lone Atrial Fibrillation (Robert 2010)

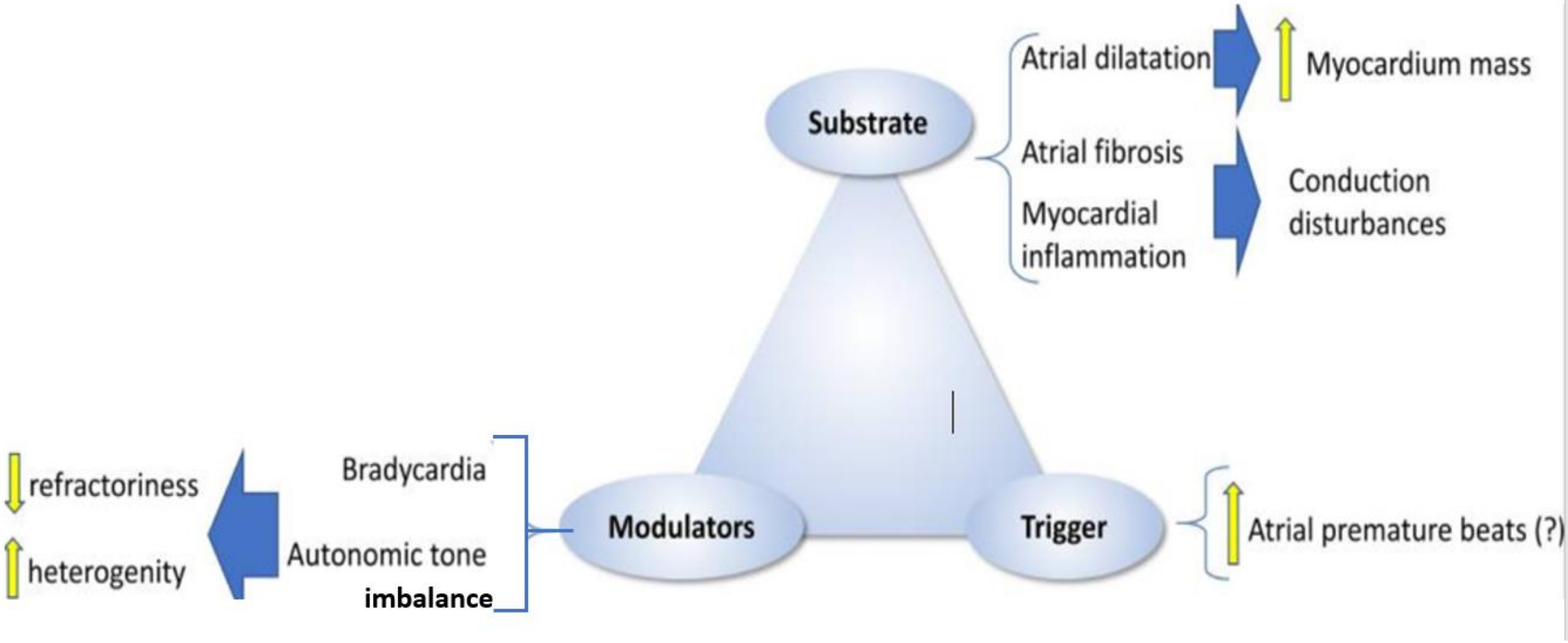
AF subclassification	Culprit Gene	Functional effect
Enhanced atrial action potential repolarization	KCNQ1 KCNE2 KCNJ2 (**Xia 2005**) KCNE5 (**Rayn 2008**)	Enhanced slow component of the delayed rectifier K+ current (Iks). Enhanced KCNQ1 (**Das 2009; Chen 2003; Lundby 2007**) -KCNE2 K+ (**Yang 2004**) current Enhanced inward rectifier current (I_{k1}) Enhabced I_{ks}
Delayed atrial action potential repolarization	KCNA5 SCN5A(**Makiyama 2008; Watanabe 2009; Darbar 2008**)	Decreased ultrarapid component of the delayed rectifier potassium current (I_{kur}). (**Yang 2009; Olson 2006**) Hiperpolarizing shift in Na, 1.5 inactivation.
Conduction velocity heterogeneity	GJA5 (**Gollob 2006**)	Decreased Gap Junction conduction (**Delmar 2000**)
Cellular hyper excitability	SCN5A (**Li 2009**)	Depolarizing shift in Na, 1.5 inactivation.
Hormonal modulation of atrial electrophysiology Adrenocholinergic stimulation (**Yamazaki 2009**)	NPPA	Increased circulating levels of mutant atrial natriuretic peptide (**Hodgson-Zingman 2008**)
Cholinergic	Unknown	Enhanced cholinergic sensitivity A greater abundance of Kir3.x channels and higher $I_{(K,ACh)}$ density in LA than RA myocytes result in greater ACh-induced speeding-up of rotors in the LA than in the RA, which explains the ACh dose-dependent changes in overall AF frequency and wavelet formation (**Sarmast 2003; Rudy 2004**).

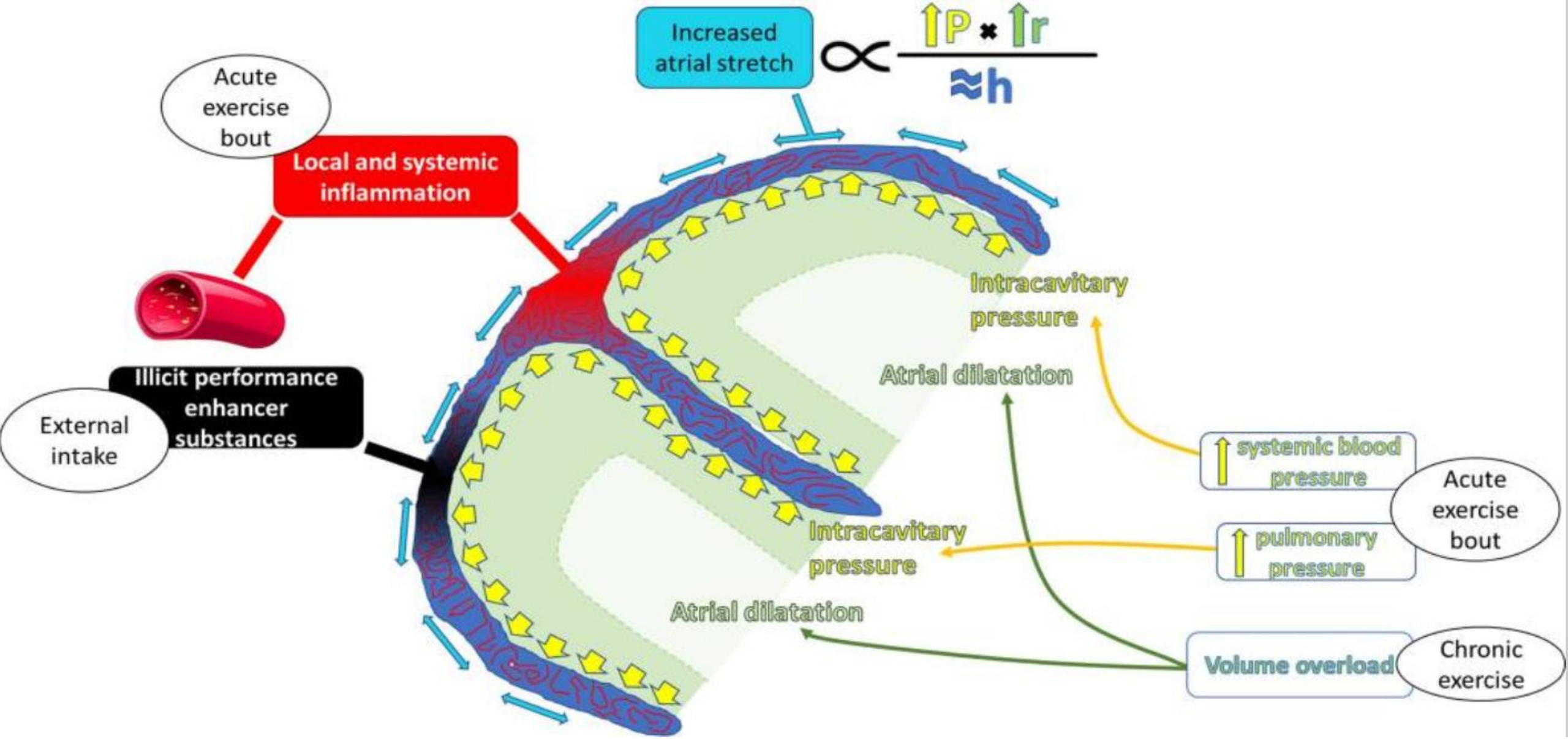
Continuation…..

AF subclassification	Culprit Gene	Functional effect
Locus on chromosome 10q22-q24 Gene Map locus on chromosome 4(4q25)	ATFB1 ATFB5 (**Gudbjartsson 2007; Benjamin 2009; Kääb 2009; Ellionor 2010; Husser 2010**)	Type 1 familial AF (**Brugada R 1997**)
Locus on chromosome 16q22	ZFHX3	(**Gudbjartsson 2009**)
ATP-binding cassette sub-family A member 1	Chromosome: 9; Location: 9q31.1 (Chen 2009)	cholesterol efflux regulatory protein
Locus on chromosome 10q22-q24 Gene Map locus on chromosome 4(4q25)	ATFB1 ATFB5 (**Gudbjartsson 2007; Benjamin 2009; Kääb 2009; Ellionor 2010; Husser 2010**)	Type 1 familial AF (**Brugada R 1997**)

1. Middle-aged males have been engaged in strenous endurance training for more than 10 years and who are otherwise healthy, are at the highest risk of developing AF caused by exercise
2. Vagal enhancement, atrial dilatation and, posibly, , atrial myocardial fibrosis are likely contributors to exercise-induced AF, but definitive evidence in athetes is still warranted.
3. Atrial fibrosis in athletes might be the consequence of increased atrial stretch, inflammation and oxidative stress during sternous exercise, that incompletely recover between bouts.
4. Large knowledge gaps in the mechanism of exercise-induced AF impedes providing evidence-based directives aiming at improving primary prevention of treatmente of AF specifically in athletes.

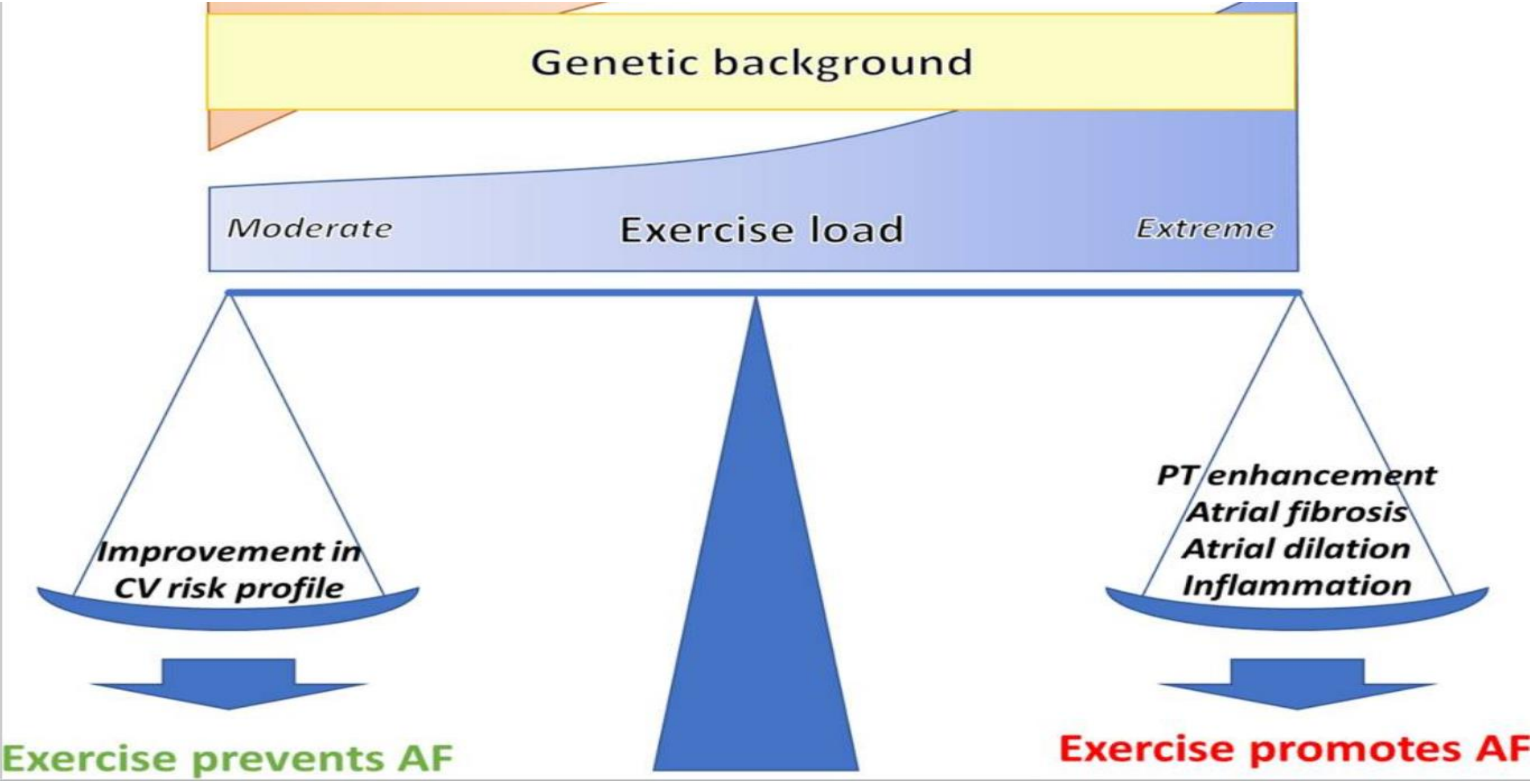
Physiopathology





Potential factors leading to a pathological atrial remodelling in athletes (atrial fibrosis). Systemic blood pressure and, particularly, pulmonary pressure promote an increase in atrial intracavitary pressure during exercise. In the presence of chronically dilated atria and limited ability to increase wall thickness, atrial wall stretch has remarkably increased, which may promote the activation of profibrotic mechanisms. A pro-inflammatory status during each exercise bout and intake of an illicit performance enhancer may also contribute. *RA* right atrium, *LA* left atrium

Factors contributing to the balance between the antiarrhythmic and the pro-arrhythmic effect of exercise



Summary of Proposed Pathophysiologic Mechanisms of atrial fibrillation in the Endurance Athlete