Ventricular Fibrillation

Subjects: Pathology

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A perennial task is to prevent the occurrence and/or recurrence of most frequent or life-threatening cardiac arrhythmias such as atrial fibrillation (AF) and ventricular fibrillation (VF). VF may be lethal in cases without an implantable cardioverter defibrillator or with failure of this device. Incidences of AF, even the asymptomatic ones, jeopardize the patient's life due to its complication, notably the high risk of embolic stroke. Therefore, there has been a growing interest in subclinical AF screening and searching for novel electrophysiological and molecular markers. Considering the worldwide increase in cases of thyroid dysfunction and diseases, including thyroid carcinoma, we aimed to explore the implication of thyroid hormones in pro-arrhythmic signaling in the pathophysiological setting. The present review provides updated information about the impact of altered thyroid status on both the occurrence and recurrence of cardiac arrhythmias, predominantly AF. Moreover, it emphasizes the importance of both thyroid status monitoring and AF screening in the general population, as well as in patients with thyroid dysfunction and malignancies. Real-world data on early AF identification in relation to thyroid function are scarce. Even though symptomatic AF is rare in patients with thyroid malignancies, who are under thyroid suppressive therapy, clinicians should be aware of potential interaction with asymptomatic AF. It may prevent adverse consequences and improve the quality of life. This issue may be challenging for an updated registry of AF in clinical practice. Thyroid hormones should be considered a biomarker for cardiac arrhythmias screening and their tailored management because of their multifaceted cellular actions.

Keywords: thyroid diseases ; thyroid hormone signaling ; cardiac arrhythmias

1. A Brief Overview on Ventricular Fibrillation(VF)

Concerning VF, development of this life-threatening arrhythmia is similar to the development of a multifactorial AF[1][2][3]. VF is triggered by the dysfunction of ion and connexin channels along with abnormal Ca^{2+}-handling and facilitated in the presence of an arrhythmogenic structural substrate (such as myocardial hypertrophy, fibrosis, and misdistribution of connexins). All these events are influenced by the modulating factors, such an ischemia or autonomous nervous system (ANS) and hormonal imbalance, including TH. Specific QRS complex patterns, recognized due to hypertrophy, may potentially predict ventricular arrhythmias[4]. When structural abnormalities are not evident, autoimmune channelopathies have been established as a novel mechanism in cardiac arrhythmias[5][6][7][8][9][10]. In particular, proarrhythmic autoantibodies targeting calcium, potassium, or sodium channels and anti-desmosome antibodies in the heart have been identified. These autoantibodies promote conduction disturbances and induce substantial electrophysiological changes facilitating life-threatening ventricular arrhythmias.

Despite recognizing the basic mechanisms that can cause VF, the changes in the cardiac electrical properties remain poorly understood. Electrical disturbances result from the immediate operation of one or other arrhythmogenic mechanisms in different heart conditions. Accordingly, higher levels of total T_3 have been positively associated with the heart rate, QTc, and negatively associated with the PR interval and QRS duration[11].

Notably, many pathophysiological processes implicated in the development of AF and VF are linked to a mitochondrial dysfunction, which causes an altered calcium homeostasis, an excess of reactive oxygen species formation (oxidative stress), and alterations in the oxygen consumption. Mitochondria are considered to be a metabolic sink and[12] the targets for suppressing arrhythmias[13].

Despite the progress in the treatment of heart diseases and the management of arrhythmias, sudden cardiac death, occurring due to malignant ventricular arrhythmias, remains a major cause of mortality globally[3]. An implantable cardioverter defibrillator may be efficient in preventing sudden death due to VF when it occurs but cannot prevent VF development and/or its recurrence. This issue remains to be investigated to reduce the risk of an incident VF.

2. Thyroid Status Imbalance Promotes VF

In contrast to the prevalence of AF, the incidence of VF attributed solely to the hyperthyroid status is less common and registered with a frequency similar to that in the euthyroid population[14]. It is likely because VF is exceptional in those cases where TH levels are elevated but without the observation of an arrhythmogenic structural substrate or channelopathies[15]. Nevertheless, ventricular tachycardia has been registered in hyperthyroid patients suffering from Grave's disease and it has been associated with the interaction of autoantibodies of the β1-adrenergic, the M2 muscarinic, and the TSH-receptors[16]. While thyroidectomy in Graves' disease attenuates the occurrence of ventricular arrhythmias[17], it seems likely that VF may occur in individuals with an altered thyroid status when accompanied by the presence of the autoantibodies.

Autoimmunity may alter the myocardial electrical properties promoting idiopathic ventricular arrhythmias[18][19]. Recent data strongly point out the implication of autoantibodies toward the β1 and β2 adrenergic or the M2 muscarinic receptors and the myosin heavy chain in the occurrence of cardiac rhythm disturbances[20][21][22][23][24]. Anti-β adrenergic and anti-muscarinic receptor antibodies affect the myocardial electrophysiological properties and have been reported to be the independent predictors of sudden cardiac death in patients with various heart diseases[25]. The dysregulating effects of the autoantibodies against the calcium and potassium ion channels can play the basis for autoimmune phenocopies of genetic cardiac channelopathies[26]. Autoimmune cardiac channelopathies have been suggested as a novel mechanism in the development of cardiac arrhythmias[27].

Occasionally, acute thyrotoxicosis accompanied by severe hypokalemia can induce a persistent ventricular tachycardia[28]. Unlike poor evidence in humans, the impact of TH on the development of VF in experimental animals is well documented[29][30][31][32] and associated with both the genomic and non-genomic TH actions[33]. Perhaps because of high TH dose, the oxidative stress-related impairment of ion and Cx43 channels is more pronounced in animal models.

Concerning TH, the prevalence of atrial versus ventricular arrhythmias may be explained by the chamber-related differences in the expression of ion and connexin channels, the duration of the effective refractory period, conduction velocity, and local activation time[14][34][35] , as well as in numerous signaling pathways[36] and distinct tissue pro-fibrotic properties[37]. Certainly, hyperthyroidism promotes a myocardial electrical instability[38] due to an increased excitability and shortening of the repolarization, thereby facilitating triggered activity and ventricular premature beats that often initiate malignant arrhythmias in a structurally altered heart[39]. TH may also affect ventricular arrhythmogenesis via an influence of the ANS[40] as the density of the adrenergic binding sites has been shown to be enhanced by a chronic or an acute treatment with TH[41][42].

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