

Tips for management of arrhythmias in endocrine disorders from an European Heart Rhythm Association position paper

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ABSTRACT

In endocrine diseases, hormonal changes, electrolyte abnormalities, and the deterioration of heart structure can lead to various arrhythmias. In diabetic patients, hypoglycemia, hyperglycemia, and hypokalemia can trigger arrhythmias, and diabetic cardiomyopathy can also cause electrical and structural remodeling to form substrates for arrhythmias. The risk of atrial fibrillation (AF) increases in hyperthyroidism; however, the prevalence of ventricular arrhythmias in hypothyroidism is higher. Besides AF and ventricular tachycardias, bradycardias and atrioventricular blocks can also be seen in pheochromocytoma due to the desensitization of adrenergic cardiovascular receptors. The correction of metabolic and electrolyte disturbances in patients with adrenal cortex disease should be the main approach in the prevention and treatment of arrhythmias. Early initiation of treatment in patients with acromegaly seems to decrease the development of cardiac remodeling and ventricular arrhythmia. Early and late after depolarizations due to hypercalcemia in hyperparathyroidism can lead to life-threatening ventricular arrhythmias. This elegant position paper provides important recommendations regarding prevention and treatment of arrhythmias for specific endocrine disorders. (*Anatol J Cardiol* 2018; 20: 241-5)

Keywords: endocrine disorders, arrhythmias, diabetes mellitus, thyroid dysfunction

Introduction

Endocrine disorders are associated with various arrhythmias, and different mechanisms may play a role. Hormonal changes and electrolyte abnormalities can easily trigger arrhythmias in normal hearts, and some other endocrine diseases may lead to structural changes in the heart and create a substrate for arrhythmias in long term. Recognizing this close relationship between endocrine disorders and arrhythmias, the European Heart Rhythm Association (EHRA) published a position paper, with representation from Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE) (1). The authors address frequent arrhythmias that are common in endocrine disorders and provide extremely useful suggestions. In this paper, we summarize this intense document and list the recommendations in a stepwise manner for each endocrine disease to simplify it for daily clinical approach.

Initially, mechanisms and pathophysiology of cardiac arrhythmias in endocrine disorders are discussed in general. The man-

agement of arrhythmias in specific diseases is then addressed one by one.

Diabetes mellitus

Naturally, diabetes mellitus (DM) takes the largest place in the document. The risk for arrhythmias in patients with DM is closely related to the presence and severity of underlying cardiovascular diseases (2). Conversely, DM-related factors, such as hypoglycemia, hyperglycemia, and hypokalemia, could induce arrhythmias independently of cardiovascular comorbidities (3). These factors increase oxidative stress and catecholamine levels. They alter intercellular coupling and cause channel dysfunction and cardiac fibrosis. Diabetic cardiomyopathy leads to both electrical and structural remodeling. Each factor and its role in arrhythmogenesis are demonstrated in an elegant figure.

In diabetic patients, we summarize the recommended strategies for the prevention and treatment of cardiac arrhythmias in four steps:

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Step 1: Setting glycemic targets

Both hyper and hypoglycemia are associated with an increased risk of ventricular arrhythmias (4). Importantly, hypoglycemia has been associated with arrhythmic deaths in type 1 and 2 DM (5, 6). Intensive glucose lowering (target HbA1c <6.0%) has been associated with a similar incidental AF rate as using a less stringent approach (HbA1c <8.0%), but the risk of death and other cardiovascular events was higher (7). Therefore, glycemic targets in patients with DM should be defined individually. Patient age, individual risk profile, patient preferences, and life expectancy should be considered. Factors favoring less stringent HbA1c goals (i.e., 7.0%–7.9%) are listed in the document; patients with long-standing DM, extensive comorbidities, advanced micro- or macro-vascular complications, history of hypoglycemia, and limited resources should be monitored carefully for hypoglycemia. Intensive glucose control with target HbA1c of <7.0% should not be attempted in patients who are elderly and/or have high-risk DM, owing to the increased risk of severe hypoglycemia and neutral effect on all-cause mortality.

Step 2: Managing risk factors and cardiovascular disease

Intense management of cardiovascular risk factors, such as hypertension, hyperlipidemia, obesity, and obstructive sleep apnea, reduces the risk of cardiac arrhythmias by preventing the development of cardiovascular diseases. Treatment targets and strategies for each risk factor are recommended according to the relevant guidelines. Checking for thyroid disease and other autoimmune disorders is also recommended in patients with type 1 DM.

Step 3: Screening for arrhythmias

If 12 lead electrocardiograms (ECGs) are not diagnostic in patients with DM and suspected arrhythmia, 24–48-hour Holter ECG monitoring is recommended. The authors state that the monitoring period can be extended in high-risk patients (e.g., CHA2DS2-VASc ≥ 2) or highly symptomatic patients. The similarities of the risk factors for subclinical AF and stroke are previously discussed in the EHRA consensus document for screening AF (8). DM is a disease that increases the risk of AF and stroke, and long-term rhythm monitoring is advised.

Compared with the general population, patients with DM have an increased risk of sudden cardiac death (SCD) (9). Some diagnostic tests that may predict SCD in patients with DM are addressed in the document. Authors underline that none of these tests have been routinely used to stratify the risk for ventricular arrhythmias or SCD in clinical practice. Because there is no specific protocol for the screening of SCD, regular screening for cardiovascular risk factors or structural heart disease is advised for all patients.

Step 4: Treatment of arrhythmias and prevention from stroke

Treatment strategies were not detailed in the text, but two different treatment algorithms were demonstrated in a figure for

both ventricular and supraventricular arrhythmias. For atrioventricular nodal re-entrant tachycardia (AVNRT), atrioventricular re-entrant tachycardia, and atrial flutter (AFL), the arrows directly point to the catheter ablation. The reason for the recommendation of direct ablation is not mentioned in the text. However, considering higher success rate of ablation in these arrhythmias and disadvantages of polypharmacy in DM, this recommendation is reasonable.

The treatment strategy for AF should be individualized for each patient. Rate control is recommended to decrease the symptoms and to prevent tachycardiomyopathy. In patients with persistent symptoms despite adequate rate control, in those with left ventricular dysfunction attributable to poorly controlled high ventricular rate, or as per the patient's preference, rhythm control strategy is recommended. Authors mention the increased AF recurrence rates after successful cardioversion of persistent AF (10). Therefore, catheter ablation is a reasonable option for selected patients with AF to reduce the number of patients requiring antiarrhythmic drugs.

DM is a well-known risk factor for stroke in AF. It is included in the CHA2DS2-VASc risk score and is one of the parameters most closely associated with stroke (11). Stroke and bleeding risk should be assessed for each patient with diabetes, and oral anticoagulation is recommended for patients with a CHA2DS2-VASc score ≥ 1 . The authors comment that non-vitamin K antagonist oral anticoagulants could be the preferred choice in most patients. They also mention the heterogeneity of patients with AF patients and the availability of different oral anticoagulants.

In addition, authors note interesting points about the coexistence of DM and AF. For example, the duration of diabetes accentuates the stroke risk, but not the bleeding risk (12). Furthermore, the duration of DM seems to be a more important predictor of ischemic stroke than glycemic control in such patients (13). These findings indicate the presence of a progressive, inevitable substrate related to arrhythmias and stroke and explain why strict glycemic control is insufficient.

The treatment of ventricular arrhythmias depends on the presence of an underlying structural heart disease. The routine use of antiarrhythmic drugs is not recommended for ventricular premature beats in patients with structurally normal hearts. Searching for correctable factors and their treatment is sufficient. It is mandatory to check glucose regulation and prevent hypoglycemia, electrolyte imbalances, and excess adrenergic stimulation in patients with ventricular arrhythmias. Diagnostic tests that can be used to clarify suspected structural heart disease are briefly listed, but the treatment of arrhythmias in patients with structural heart disease is not mentioned.

Importantly, it is emphasized that the use of (non-selective) beta-blockers in patients with DM without coronary artery disease could be weighed against the risk of severe hypoglycemia.

In addition, diabetes is an important risk factor associated with an increased risk of infections of cardiac electrical implantable devices (CIEDs). The odds ratio for the risk of CIED infection is

between 2.3 and 3.5. However, the sub-analysis of different randomized clinical trials reveals that patients with diabetes have similar clinical benefits compared with patients without diabetes. Therefore, patients with diabetes should not be deprived of this treatment but should be more cautious regarding infections.

Thyroid dysfunction

The normal levels of thyroid hormones are necessary for the proper functioning of the electrical system of the heart. Hyperthyroidism is associated with increased automaticity and triggered activity in the atria and the ventricle, whereas hypothyroidism slows down the velocity of conduction system and prolongs the effective refractory periods (14). Authors underline the difference between tachycardia and bradyarrhythmia occurrence in hyperthyroidism and hypothyroidism. The lack of evidence on the treatment strategies is also emphasized.

The correction of thyroid dysfunction with the restoration of euthyroid state should be the primary target in the treatment of arrhythmias associated with hyperthyroidism or hypothyroidism. Clinical forms and subclinical forms of thyroid dysfunction may need to be treated if they are associated with arrhythmias. It is strongly advised to refer patients to endocrinologists for appropriate thyroid function therapy.

Hyperthyroidism is associated with an increased risk of AF (15). Fortunately, in most cases, AF reverses spontaneously to sinus rhythm once the euthyroid state is achieved, usually after 3 months of therapy. In addition, hyperthyroidism-related AF usually has a lower recurrence rate than non-hyperthyroidism-related AF after electrical cardioversion (16). Therefore, rhythm control strategy is encouraged if hyperthyroidism-related AF persists after the euthyroid condition has been achieved (>3 months of thyrostatic therapy). The history of hyperthyroidism is not an independent risk factor for thromboembolism (17).

Therefore, the decision for antithrombotic therapy should be provided like that for non-hyperthyroid-AF.

Ventricular arrhythmias are rarer than atrial arrhythmias in patients with hyperthyroidism. Associated conditions, such as coronary vasospasm, electrolyte abnormalities, early repolarization, and amiodarone toxicity, are not rare and should be taken into account, especially in patients without structural heart disease. Besides antithyroid therapy and prednisolone, beta-blockers, antiarrhythmics (caution with amiodarone), and DC cardioversion (in cases of hemodynamic compromise) can be used.

Contrary to the general belief, the prevalence of ventricular arrhythmias is higher in patients with hypothyroidism (18). VT/VF accompanying hypothyroidism associated with the long QT interval should be managed with the correction of bradycardia and electrolyte imbalance. Antiarrhythmic drugs that prolong the QT interval should be avoided.

Conduction abnormalities and bradyarrhythmias are also reported in patients with thyroid dysfunction. They may require the implantation of a temporary pacemaker, and rarely, a permanent pacemaker if AF persists after the restoration of euthyroid con-

dition (19). Importantly, hypothyroidism may lead to functional changes in the tissue and may increase pacing thresholds that are usually reversible by the correction of thyroid status (20). Therefore, thyroid dysfunction should be taken into account if atrial or ventricular pacing thresholds problems appear in patients with implanted pacemakers and ICDs.

Amiodarone-induced thyroid dysfunction

Thyroid dysfunction is a common entity during amiodarone treatment, and hyperthyroidism can be observed in about 10.3%–14.7% of patients taking amiodarone. Two different mechanisms may play a role:

1. Hyperthyroidism develops in the presence of underlying thyroid disease with excessive hormone production in response to iodide load associated with amiodarone.
2. Direct toxic effects of iodine-associated amiodarone may lead to destructive thyroiditis.

The management of amiodarone-induced thyroid dysfunction depends on the underlying mechanism. Thyroid-directed autoantibodies and ultrasonography can be used for the differential diagnosis of type 1 and type 2 amiodarone-induced hyperthyroidism. Authors recommend using antithyroid medications for type 1 and steroids for type 2 (thyroiditis), and the use of antithyroid medications and steroids in cases of coexistence of hyperthyroidism and thyroiditis. Hormone replacement therapy may be needed for amiodarone-induced hypothyroidism in later periods.

In this position paper, it is strongly recommended to weigh risk/benefit of amiodarone toxicity and consider catheter ablation to cure or modify the substrate for arrhythmias before prescribing amiodarone therapy for long-term use. The monitoring of thyroid function every 6 months and electrocardiogram follow-up in patients on amiodarone therapy is advised. If hyperthyroidism occurs during treatment with amiodarone, its discontinuation is mandatory. The drug should only be re-initiated by assessing the expected risk and benefit for each patient after the euthyroid state is achieved.

Pheochromocytoma

The prevalence of pheochromocytoma (PCC) is rare but should be kept in mind as a possible diagnosis in patients with a paroxysmal headache, hypertension, palpitations, and recurrent arrhythmia. Arrhythmia mechanisms are complex. Both tachy and bradyarrhythmias may be observed. Beta and alpha 1-adrenergic stimulation of the heart mostly leads to supraventricular arrhythmias and AF, but malignant and bidirectional VT is also reported. PCC can prolong the QTc interval and increase the risk of Torsades de Pointes. Therefore, antiarrhythmic drugs prolonging the QTc should be used with caution and only after QTc monitoring. Beta-blockers, especially esmolol, are recommended for rate control in AF and AFL. In these cases, the associated alpha blockade is mandatory to prevent hypertensive crisis.

Prolonged adrenergic stimulation results in desensitization of adrenergic cardiovascular receptors and reflex increase in vagal

tone. Some patients with PCC manifest with reflex bradycardia, asystole, sick sinus syndrome, and AV block (21).

Diseases of the adrenal cortex

Both hyperaldosteronism and adrenal insufficiency may cause variable arrhythmias. Primary hyperaldosteronism, known as Conn's disease, causes hypertension, hypokalemia, metabolic alkalosis, and renin suppression (22). The excess of aldosterone causes K^+ and Mg^{++} loss, catecholamine excess, and cardiac fibrosis, leading to arrhythmias. Naturally, the main treatment is surgical resection of the adrenal adenoma or pharmacological therapy targeting adrenal hyperplasia. The treatment of arrhythmias in this condition should focus on controlling metabolic and electrolyte disturbances.

Primary adrenal insufficiency (PAI), known as Addison's disease, is the other edge of the spectrum. Corticosteroid and mineralocorticoid deficiency leads to hyponatremia, hyperkalemia, hypoglycemia, and hyperpigmentation. Idiopathic dilated cardiomyopathy and takotsubo cardiomyopathy are associated with PAI. Different ECG abnormalities, including Brugada like-pattern, may be observed in this condition, and life treating arrhythmias, such as polymorphic ventricular tachycardia and ventricular fibrillation, are reported. The stabilization of electrolyte and metabolic disturbances is crucial. Hydrocortisone and fludrocortisone should be initiated in the setting of dilated cardiomyopathy. It should be kept in mind that fludrocortisone may lead to fluid retention and worsen the symptoms of heart failure.

Similar to diabetes, long-term treatment with chronic corticosteroids is an important risk factor for infections of CIEDs. The odds ratio for the risk of CIED infection is 9.1, and this risk should be considered during implantation.

Growth hormone dysfunction

Acromegaly is a rare disease characterized by increased growth hormone and insulin-like growth factor-1. Acromegalic cardiomyopathy is characterized by biventricular hypertrophy, progressing to diastolic and systolic dysfunction, and culminating in heart failure in 10% of patients (23). Ventricular arrhythmias are common in acromegaly due to cardiomyocyte hypertrophy, myofibrillary abnormalities, and interstitial fibrosis. The control of acromegaly in the early stages seems to decrease the development of cardiac remodeling and ventricular arrhythmia (24).

Parathyroid disease

Parathyroid hormone (PTH) plays a critical role in calcium homeostasis. Hypoparathyroidism causes hypocalcemia and may lead to QT interval prolongation and arrhythmias. The authors state that this theoretical risk is rare in real clinical life. Torsades de pointes are rare despite extreme QT prolongations. Intravenous calcium replacement is necessary in case of severe hypocalcemia, including long-term calcium and Vitamin D supplementation.

Hyperparathyroidism is more dangerous with respect to arrhythmias. Both early and delayed afterdepolarization due to

hypercalcemia are the responsible mechanisms. Every kind of arrhythmia, including life-threatening VT/VF, is observed. Although its effect on mortality is controversial, parathyroidectomy is the recommended treatment for primary hyperparathyroidism. VT storms controlled only after parathyroid surgery are reported in the literature (25).

Effects of sex hormones on arrhythmia

Although the reason has not been fully elucidated, men and women differ with respect to the risk of arrhythmia. Possible mechanisms and role of sex hormones are discussed in detail. Briefly, women have longer repolarization and QTc intervals that render them more susceptible to drug-induced Torsades de Pointes. Therefore, the authors emphasize that drugs that prolong QT should be used with caution in women, particularly in the presence of electrolyte imbalance. They recommend using web-based tools (<https://crediblemeds.org/>) to evaluate the risk of drugs regarding QT interval. In addition, women have greater arrhythmic risk than men in congenital LQTS. The risk of arrhythmias is reduced during pregnancy but increased in the postpartum period. AVNRT and inappropriate sinus tachycardia are also common in women, whereas the Brugada syndrome and AF are frequent in men.

Conclusion

This elegant position paper describes the common problems of two different medical disciplines that often intersect in clinical practice. It summarizes the underlying mechanism related to the endocrine disorders and provides important recommendations regarding the prevention and treatment of arrhythmias for each endocrine disorder.

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