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REVIEW ARTICLE

Challenges in Treatment of Inappropriate Sinus Tachycardia

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Abstract: ***Background*:** Inappropriate Sinus Tachycardia (IST) is a clinical syndrome characterized by a sinus heart rate inexplicably higher than one hundred beats per minute at rest that is associated with symptoms like palpitations, dyspnea or dizziness in the absence of primary causes of tachycardia.

The diagnosis requires exclusion of other causes of tachycardia including medications/substances (such as anti-cholinergic, beta-blocker withdrawal, caffeine, and alcohol) or medical conditions (such as panic attacks, pulmonary embolism, fever, hyperthyroidism, hypovolemia, anemia, and pain).

***Methods*:** Work up should include an EKG to differentiate other causes of tachycardia, 24 hour-Holter monitor if indicated, serum thyroid levels, hemoglobin levels and toxicology screen. Electrophysiological studies are not routinely recommended, but should be considered in certain patients in whom concurrent supraventricular tachycardia is suspected.

***Conclusion*:** The underlying pathology in IST is yet to be completely understood. However, it is thought that the causes of IST can be broadly classified into two groups; either as an intrinsic increase in sinus node automaticity or an extrinsic cause. Among extrinsic causes, there is evolving evidence that IgG anti-β receptor antibodies are found in IST causing tachycardia.

Managing patients with IST includes lifestyle modification, non-pharmacological and pharmacological interventions. Ivabradine has recently emerged as an effective treatment of IST and was shown to be superior to beta-blockers.

Keywords: Clinical syndrome, symptoms, diagnosis, tachycardia, EKG, IST, sinus, arrhythmia, tachycardia.

1. INTORODUCTION

1.1. Epidemiology

Heart rate is inversely related to age and independently related to height, physical activity and intake of stimulant (such as caffeine) in healthy individuals [1, 2]. Inappropriate Sinus Tachycardia (IST) is a clinical syndrome characterized by a sinus heart rate inexplicably higher than one hundred beats per minute (bpm) at rest that is associated with symptoms like palpitations, dyspnea or dizziness in the absence of primary causes of tachycardia [3, 4]. Therefore, individuals with sinus tachycardia without associated symptoms do not qualify for the diagnosis of IST. Diagnosis can be obtained through a 24 hour-Holter monitor, event monitor, loop recorder, or telemetry. Some publications suggest that an average heart rate of greater than ninety bpm at rest can qualify for diagnosis of IST [5].

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An Icelandic study of randomly sampled patients from insurance registries for hypertension estimated the prevalence of IST to be 1.16 % with no difference between IST and the control group in age, gender and physical activity [6].

1.2. Clinical Presentation

Patients with IST often present with non-specific symptoms including palpitations, exercise intolerance, lightheadedness, dizziness, dyspnea, syncope or weakness. Symptoms can be debilitating and vary between individuals. Symptoms are not always related to heart rate and may affect quality of life [3]. Even though the symptoms can have a profound effect on the patient, IST is generally a benign condition. Studies have not demonstrated any increase in mortality or cardiomyopathy with patients with IST [6].

1.3. Diagnosis and Differential Diagnosis

Diagnosis of IST is based on the criteria of resting heart rate greater than 100 bpm with average heart rate exceeding

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90 bpm on 24-hours Holter monitor, in symptomatic patients [3, 6]. The diagnosis requires exclusion of other causes of tachycardia including medications/substances(such as anticholinergic, beta-blockers withdrawal, caffeine, and alcohol) or medical conditions (such as panic attacks, pulmonary embolism, fever, hyperthyroidism, hypovolemia, anemia, and pain) [7]. An important distinction to make is that inappropriate sinus tachycardia must be distinguished from other forms of tachycardia including supraventricular tachycardias and atrial arrhythmias.

Work up should include an EKG to differentiate other causes of tachycardia, 24 hour-Holter monitor if indicated, serum thyroid levels, hemoglobin levels and toxicology screen. Fig. (**1**) shows 24 hours-Holter in a patient with IST, with average heart rate of 96 bpm exceeding the cutoff point for diagnosis of IST, *i.e.* 90 bpm. Electrophysiological studies are not routinely recommended, but should be considered in certain patients in whom concurrent supraventricular tachycardia is suspected.

Another condition that can mimic IST is postural tachycardia syndrome (POTS). IST and POTS can present similarly and both syndromes overlap and can affect the same individual. The key distinguishing feature is that patients with POTS have symptoms and tachycardia induced by standing and relieved by recumbence (occasionally along with blood pressure changes) while IST is mainly provoked by emotional or physiological distress [3].

1.4. Mechanism

The underlying pathology in IST is yet to be completely understood. However, it is thought that the causes of IST can be broadly classified into two groups. It can be classified either as an intrinsic increase in sinus node automaticity or an extrinsic cause (sympatho-vagal imbalance, increased sympathetic receptor sensitivity, decreased parasympathetic tone, and impaired neurohormonal modulation). Among extrinsic causes, is evolving evidence that IgG anti-β receptor antibodies are found in IST patients that triggers positive chronotropic action by inducing long lasting increment in cAMP which mediates calcium influx and depolarization causing continuous activation of the β-adrenergic receptor without desensitization. This mechanism is thought to be the similar in patients with Chagas disease, in which antibodies directed against a ribosomal P protein of Trypanosoma cruzi cross-react with and stimulate the β adrenergic receptors causing tachycardia [8, 9].

Recent evidence revealed a familial form of IST associated with a gain-of-function mutation in the HCN4 pacemaker channel causing increased sensitivity to the second messenger cAMP leading to increase sympathetic drive [9].

1.5. Treatment

Inappropriate Sinus Tachycardia is a chronic medical condition and can be associated with significant loss of quality of life. The treatment is multifaceted and remains a substantial challenge; mainly because IST is a complex syndrome and controlling heart rate doesn't always lead to elimination of symptoms. Managing patients with IST includes lifestyle modification, non-pharmacological and pharmacological interventions.

Treatment options for IST are limited. Initially it's recommended to decrease caffeine and other stimulant intake, engage in regular exercise activities and maintain adequate fluid and salt intake. The use of negative chronotropic agents such as β-adrenergic blockers is not usually effective and associated with many adverse effects [3, 10]. In a study of 20 patients, Metoprolol was compared to ivabradine, and was found to be less likely to be successful in reduction of heart rate and improvement of symptoms in patients with IST [10].

Ivabradine is a promising drug that was recently approved that acts by inhibiting the If current causing reduction in heart rate and improvement in symptoms and quality of life. Multiple studies including randomized trials have reported its efficacy, although long-term follow up is lacking [11-15]. However, the high costs of ivabradine make its use prohibitive.

Radiofrequency ablation to modify sinus node has been studied in small populations [16-18]. Primary success rates were excellent acutely, however, in many patients, tachycardia may come recur from other sites of the sinus node or from the atrioventricular junction. Both patients and physician should be aware of the high risk of such intervention which includes: requirements for permanent pacing, phrenic nerve damage or superior vena cava stenosis. Given severity of the complications and no statistically significant long term efficacy in terms of symptomatic relief, radiofrequency ablation should be reserved as a last line option for patients who

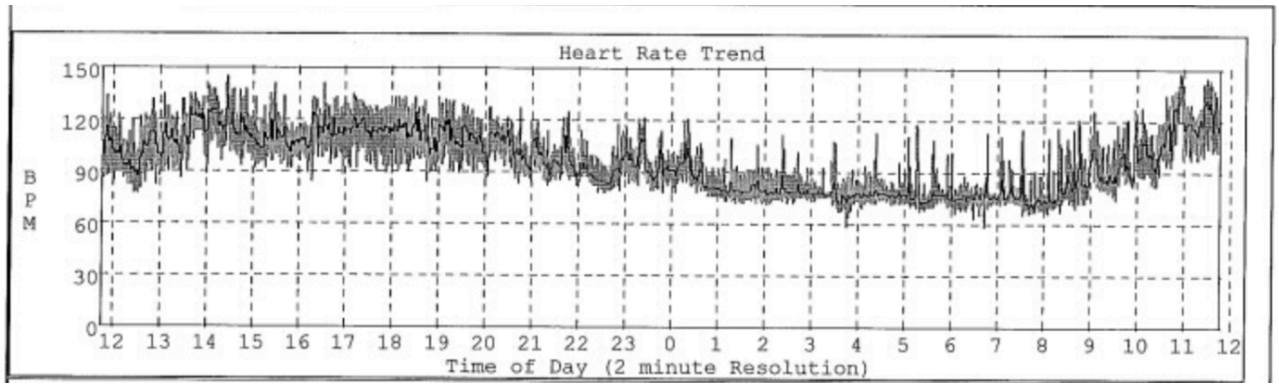

Fig. (1). 24 hours Holter monitor showing average heart rate of 96 bpm with max heart rate of 148 bpm; consistent with inappropriate sinus tachycardia.

remain severely symptomatic despite medical treatment and life style modification [3, 5].

CONCLUSION

Inappropriate sinus tachycardia is diagnosed when sinus tachycardia is inexplainable, and is associated with symptoms like palpitations, fatigue or dizziness. Pathophysiology is not completely understood but involves increased sinus node automaticity due to abnormal autonomic activation, or autoantibodies in some cases.

First line treatment strategy involves life style modifications and exercise. When pharmaceutical treatment is needed; Ivabradine was shown to be effective and tolerable.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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