

## Invited Editorial / Davetli Editöryal Yorum

### Inappropriate sinus tachycardia: Time to consider new therapeutic options

#### Uygunsuz sinüs taşikardisi: Yeni tedavileri gözden geçirme zamanı

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Heart rate is inversely related to age and independently related to height, physical activity and intake of stimulant (such as caffeine) in healthy individuals.<sup>[1]</sup> IST is a clinical syndrome characterized by a sinus heart rate inexplicably higher than 100 bpm at rest that is associated with symptoms in the absence of primary causes of tachycardia. 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.<sup>[2]</sup> Although distinct underlying pathophysiological mechanisms of IST have not been well understood, several responsible causes were defined. Increased sinus node automaticity, or autonomic factors have been thought to be responsible for IST.

Cardiac autonomic system plays a critical role for the development of various cardiac arrhythmias. Parasympathetic over-activity or an imbalance between sympathetic and parasympathetic systems is the underlying cause of particular clinical conditions such as vasovagal syncope, functional atrioventricular block, and some forms of sinus node dysfunction.<sup>[3]</sup> On the contrary, sympathetic over-activity or imbalance in the favor of sympathetic system may cause IST, and some forms of ventricular tachycardia.

Additionally, IgG anti- $\beta$  receptor antibodies are found in IST patients that trigger positive chronotropic

action by inducing long lasting increment in cAMP which mediates calcium influx

and depolarization causing continuous activation of the  $\beta$ -adrenergic receptor without desensitization.<sup>[4]</sup> 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 an increase in sympathetic drive.<sup>[5]</sup>

In this issue of TSCA journal, Dr. Şimşek and co-workers published their experience on inappropriate sinus tachycardia.<sup>[6]</sup> In this interesting study authors reported that prevalence of inappropriate sinus tachycardia prevalence in symptomatic patients who underwent 24-hour Holter monitoring was nearly 5%. This prevalence seems to be higher than previously reported<sup>[7]</sup> and most probably due to narrow indication for Holter monitoring or in other words highly symptomatic patient population of the study. In the present study, patients with IST were generally young (mean age was  $39.6 \pm 17.3$  years) and mostly female (60%).

These findings support the importance of demographic characteristics in differentiating symptomatic patients with IST from other healthy individuals or

#### Abbreviations:

cAMP	Cyclic adenosine 3',5'-monophosphate
GP	Ganglionated plexi
IST	Inappropriate sinus tachycardia

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patients with atypical or non-cardiac symptoms.

Treatment of IST can be challenging and it is a chronic medical condition and can be associated with significant loss of quality of life. Correct diagnosis and exclusion of secondary causes of sinus tachycardia is the most critical step. Exclusion of sinus node reentry is also important, as it is purely amenable for catheter ablation. Conventional treatment such as reduction of caffeine and stimulant intake, encouraging regular exercise and optimization of salt and fluid intake should be advised.<sup>[2]</sup> Decrease of heart rate cannot resolve symptoms all the time. Thus, IST is a complex clinical syndrome with limited treatment options. Beta-blockers are not very effective and unfortunately have many side effects. 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.<sup>[8]</sup> Ivabradine is a promising drug that can limit symptoms and decrease heart rate,<sup>[9]</sup> and is tolerated better than beta-blockers. However, cost is still an issue in the case of ivabradine therapy. Radiofrequency modification of sinus node can be considered in selective patients<sup>[10]</sup> but optimal end-points of the procedure have not been well defined. More data is needed for identification of underlying causes and pathophysiology of IST to develop better treatment options. In the study by Dr. Şimşek and coworkers, heart rate variability patterns were also investigated and compared to matched controls to better understand pathophysiological mechanisms of IST. Time domain HRV parameters (SDNN, SDANN and RMSSD) were found to be decreased in the IST group. Present study demonstrated that IST patients had reduced values of all frequency domain parameters; UF, VLF, LF, and HF, which suggests a possible decrease in parasympathetic activity. LF/HF ratio which may show sympatho-vagal balance was found to be similar in IST and control groups, which is a rather unexpected finding. It should be stressed that this may be related to this parameters association with baroreceptor activity. Skin sympathetic nerve activity could be added this cohort to identify sympathetic system tonus.

There are recent developments in managing cardiac autonomic system mediated arrhythmic syndromes. Ablation of ganglionated plexi (GP) around the heart has been shown to be effective for vagally

mediated arrhythmias.<sup>[11]</sup> The intrinsic cardiac nervous system forms a complex neural network composed of GP, concentrated within distinct epicardial fat pads around atria, and contain a heterogeneous population of neurons those include both parasympathetic and sympathetic neurons.<sup>[12]</sup> Therefore, it can be speculated that achievement of a denervation on the sympathetic system as well as on the parasympathetic system might be possible after CNA. A recent study has identified durable irreversible damage of post-ganglionic nerve fibers of sympathetic system similar to effects on parasympathetic neuronal bodies was claimed.<sup>[13]</sup> Despite provoking data, we are aware of need for more research to get new indications of CNA for sympathetic system driven arrhythmias.

In conclusion IST is not a fully understood clinical syndrome mostly due to sinus node hypersensitivity or cardiac autonomic imbalance. There is unfortunately no exact treatment option additional to conventional recommendations. Ivabradine can be useful to control symptoms. Interventional therapies targeting sympathetic system may help treatment in the near future.

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