# “Inappropriate Sinus Tachycardia: A Retrospective Analysis of a Single Center Large Cohort Yielding Novel Clinical Diagnostic Criteria”

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**ABSTRACT**

**Research Question**: Limited data currently exists to characterize and predict the clinical phenotype of inappropriate sinus tachycardia (IST), with few large cohort analyses available. To determine if any demographic or clinical history data may predict IST, we have designed this research to answer two specific questions: 1) Can we determine specific diagnostic criteria using Holter monitor data to identify patients suspected to have IST? and 2) Are there any consistent demographics or components of a patient's history that exist within this clinical cohort to help clinicians predict or identify diagnosis of IST in patients that fit the clinical picture?

**Background, Significance, and Rationale**: Patients with IST reportedly have an unexplained upregulation of resting heart rate (HR) to over 100 beats per minute (bpm), with an average HR of at least 90 bpm over a 24-hour period. The tachycardia is often accompanied by distressing symptoms that can greatly impact patients' quality of life. IST is a diagnosis of exclusion, for patients with no discernable cause of secondary tachycardia. While literature surrounding clinical presentation and epidemiology is growing, there are currently few large cohort studies that have been performed to analyze trends in cardiac rhythm over time. Furthermore, a knowledge gap currently exists regarding the potential for patient history or demographics that could help predict or diagnose IST in patients with this presentation.

**Materials and Methods**: This is a retrospective cohort chart review study in which patients found to meet the inclusion criteria for IST had their clinical documents reviewed and that data compiled. While the clinical cohort analyzed was over 500 patients, the study population of patients meeting inclusion and exclusion criteria was narrowed to 205 patients. Using the electronic medical record at Consultants in Cardiovascular Medicine and Science (CCMS), each patient identified to have the IST diagnosis had their Holter monitor results analyzed. Additionally, demographics and certain comorbidities were collected and analyzed as well.

**Results:** Of the patients in the study cohort, 82% were female, with an average age of 49 and an average body mass index (BMI) of 30.4. For race and ethnicity, 82% of patients were White, 9% were Black, and 8% were Hispanic. For history and comorbidities, 24% had a history of tobacco use, 18% had diabetes, 28% had hyperlipidemia, and 44% had hypertension; 25% were being effectively treated with ivabradine. For Holter results, the mean average HR was 87 bpm, mean maximum HR was 146 bpm, mean minimum HR was 58 bpm, mean daytime HR was 93 bpm, mean nighttime HR was 83 bpm, mean % of time in sinus tachycardia was 22%, mean PVC burden was 0.55%, and mean PAC burden was 0.78%.

**Conclusions:** This study confirms that IST mostly affects females and suggests that IST may affect middle-aged patients more commonly than previously reported. It found that obesity and common major comorbidities may be more prevalent in IST patients than other studies suggest. Our cohort results suggest that the upregulation of HR in IST patients may not be as dramatic as previously thought, which should lead future studies to reconsider the most popular diagnostic criteria for IST.

## RESEARCH QUESTIONS

This project will undergo the task of addressing the following questions related to diagnostic criteria and demographic analysis of patients with IST. Studying a cohort of 205 patients with the IST diagnosis, the following questions will drive the research and data collection process:

1) Can we determine specific diagnostic criteria using Holter monitor data to identify patients suspected to have IST?

2) Are there any consistent demographics or components of a patient's history that exist within this clinical cohort to help clinicians predict or identify diagnosis of IST in patients that fit the clinical picture?

## HYPOTHESES

Based on previous studies suggesting diagnostic criteria for IST, it is anticipated that patients in this cohort will reliably have Holter monitor results that show a consistent upregulation of resting HR over time, likely to or above 90 bpm. Although limited literature exists investigating the demographic profile of patients with IST, based on clinical experience of the investigators and existing literature, it is predicted that patients in this cohort will most often be healthy, relatively young, female patients with few major comorbidities.

## BACKGROUND, SIGNIFICANCE, AND RATIONALE

In IST, patients experience an unexplained upregulation of resting HR. Based on existing literature, this upregulated HR is reported to be over 100 bpm, with an average HR of at least 90 bpm over a specified 24-hour period [1,2]. Though some patients report no additional symptoms besides tachycardia, it is more often accompanied by distressing symptoms such as palpitations, lightheadedness, chest discomfort, weakness, shortness of breath, presyncope, and syncope that can greatly impact patients' quality of life [1-3]. Although symptom severity often correlates with the level of tachycardia, it is not uncommon for the patients' symptoms to be out of proportion to the severity of tachycardia [2]. IST is a relatively newly recognized condition, as patients with a similar phenotype may have historically been misdiagnosed or presumed to be suffering from a psychosomatic condition [2,4]. IST is a diagnosis of exclusion, reserved for patients with no discernable cause of secondary tachycardia [5]. Its novelty can account for the relative lack of published literature regarding the epidemiological data of IST, however some studies estimate that the prevalence in middle-aged adults is about 1.2%, with a mean age of onset of 35, and almost 90% of those suffering being female patients [3,5]. Other studies have proposed generally that it most frequently affects females of relatively younger age, primarily ages 15-45, with 4 times greater prevalence in females than males[2]. The large single-site cohort studies in existing literature report a female prevalence of 60% and 92%, respectively, with an average age of 39 and 32, respectively [6,7]. Though there are a number of studies that report age and sex specifications associated with IST patients, a large, single-site cohort of unrelated IST patients like we present here has tremendous value to add to the existing body of literature. For that reason, we chose to take advantage of this large cohort and investigate their own data when it comes to sex and age statistics for these IST patients.

After an extensive search of current literature, we determined that there are no easily accessible studies that have investigated the prevalence of IST in certain races or ethnicities. For that reason, we found it important to collect and analyze the documented race and/or ethnicity of each patient diagnosed with IST in this study cohort, as knowing who exactly is most likely to develop IST could be vitally important to future diagnostic and treatment considerations.

Similarly, while tobacco has been proposed as a possible trigger or inciting factor for IST [1], we were unable to find existing literature looking at more specific links between tobacco use and

the development of the IST symptom profile. Nicotine and other constituents contained in tobacco products, however, have been proposed to be arrhythmogenic in a general sense [8]. Although it is thought to be implicated in human pathologic arrythmia development, most of the studies related to this idea have been done in animals rather than humans, and human studies were done on other cardiac arrhythmias besides IST [8]. For that reason, we chose to analyze patients' history of tobacco use in this study cohort of IST patients to see if any relevant conclusions could be drawn related to predicting IST diagnosis or prevention of developing IST in the first place.

Although there are few studies in current literature that report clinical data on large, single-site cohorts of IST patients, a review of existing research revealed a couple such studies. A cohort of 305 patients diagnosed with IST at the Mayo Clinic were studied to establish epidemiologic data in these patients, who were compared to a matched control group with atrioventricular nodal reentry tachycardia [7]. Their study reported that 92.1% of the IST patients were female, the mean age was 33.2 years old, and the mean body mass index (BMI) was 27.8 [7]. Although they did not report BMI, another similar study of 63 patients with IST reported that 60.3% of the IST patients were female and the mean age was 39.6 [6]. Much like these studies, we felt it was necessary to analyze age, sex, and BMI to compare to existing literature and contribute to the current body of information regarding demographics most commonly afflicted with IST. We anticipate that the data for age, sex, and BMI will be similar for this study as what has been reported in currently published research.

The previously mentioned Mayo Clinic study also tried to identify precipitating factors of IST and found that pregnancy and infectious disease were the most common, at 7.9% and 5.9%, respectively [7]. After looking into a number of comorbidities in the IST patients, anxiety and depression were found to be the most common, at 24.6% and 25.6%, respectively; however, other comorbidities were also analyzed, with diabetes at 8.2%, hypertension at 14.8%, and hyperlipidemia at 17.0% [7]. Although we chose not to re-analyze anxiety and depression, we felt that it was necessary to analyze and report data on major, common comorbidities of diabetes, hypertension, and hyperlipidemia, as those have been the most common in this cohort of patients at this particular clinical site. Reporting and documentation of psychiatric conditions like anxiety and depression is less frequent and therefore less consistent at this clinical site, a local cardiology clinic, and therefore was chosen to be excluded to eliminate the risk of poor data quality.

Although pathophysiologic mechanisms and therapeutic interventions for IST are still not widely agreed upon in the current literature, there have certainly been some breakthroughs when it comes to symptomatic treatment of these patients. Non-pharmacologic interventions like exercise therapy, trigger avoidance, and reduction of daily stimulant use have been shown to have some symptomatic improvement for some IST patients [9]. Back in 2015, the Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of IST suggested that the therapeutic drug ivabradine was beginning to show promising results in studies of IST patients [5]. This drug blocks the "funny current" ($I_f$), a cardiac pacemaker current that uses sodium-potassium ion currents to control spontaneous depolarization of the sinoatrial node. While beta blockers have traditionally been used to treat IST patients, recent studies have reported that ivabradine use is more effective at treating both tachycardia and distressing symptoms than beta blockers alone [9]. For refractory symptoms of IST unresponsive to all pharmacologic and non-pharmacologic therapies, invasive ablation procedures are potentially helpful but should be reserved as a last resort [9]. Physicians at this particular clinical site have been prescribing ivabradine to many of their IST patients and have anecdotally been seeing promising responses. As such, we wanted to compile data to report how many of the patients in the study cohort are successfully being treated with ivabradine and what regimen they are on.

While all the demographic and historical considerations discussed above are relevant to this study and present a promising way to contribute to existing literature, another important aim is to compare the study cohort patients' HR statistics and variability to that of currently proposed diagnostic criteria. When looking at the upregulated HR of patients suspected to have IST, the pattern of upregulation is not always consistent or predictable. For some patients, the tachycardia is a persistent and predictable sinus rate, while another subset of IST patients has paroxysmal episodes underlined by a relatively normal HR at baseline [2]. For that reason, it can be difficult to evaluate the presence and severity of IST with a simple electrocardiogram (ECG), like would often be administered in an office or emergency department setting. Rather, it is standard practice for patients to undergo rhythm analysis with a continuous ambulatory electrocardiogram monitoring device (Holter) for at least 24 hours [9].

As discussed above, the general consensus for diagnostic criteria of IST in current literature is an upregulated HR over 100 bpm, with an average HR of at least 90 bpm over a specified 24-hour period [1,2]. However, while many studies investigating IST have adopted these criteria, there is ambiguity when it comes to very specifically defining IST in clinical practice, compared to other tachyarrhythmias. For example, one systematic review published in 2022 undertook the

task of analyzing all English language articles related to IST published in several large databases from 1970 to 2020 to assess for consistency when it comes to defining IST with diagnostic criteria [10]. After thoroughly analyzing the qualifying 138 publications about IST, it found that only 83% of those articles gave a definition at all. Of the articles using distinct HR thresholds in definitions, the most common primary HR threshold was 100 bpm at rest (81.5%); of the 51% of those articles that used a secondary definition, a HR threshold of 90 bpm average over at least 24 hours was most common [10]. Therefore, while some degree of consistency has begun to emerge in IST definition and diagnosis, the HR statistics and variability data collected via Holter monitor for this study cohort of IST patients has important value to add to the greater conversation surrounding IST.

There are few existing studies that have reported on Holter data and HR statistics of a large, unrelated cohort of IST patients. The previously mentioned study from the Mayo clinic was one such study, as it analyzed 212 patients' 24-hour Holter monitor results at their time of diagnosis with IST [7]. The only Holter data reported in that study was the average HR over 24 hours (99.6 bpm), average minimum HR (70.4 bpm), and average maximum HR (153.3 bpm) [7]. This data is a tremendously valuable contribution to IST research and leads future studies, such as this one, to further investigate potential trends and diagnostic data from Holter monitors in these patients. Therefore, in addition to average HR, minimum HR, and maximum HR, we decided to take the opportunity to collect data on several other metrics as well. These include average HR during daytime vs nighttime hours, % of recorded time spent in sinus tachycardia (> 100 bpm), and the burden of premature ventricular contractions (PVCs) and premature atrial contractions (PACs). Since the Holter monitor results report these statistics, we chose to collect and analyze this data in hopes that trends or averages would emerge that may help inform future diagnostic criteria.

Although IST is thought to have been first described in 1939 [1], it has only begun to receive more attention in the medical research world over the last 30 years or so, making it a relatively new and novel clinical conditions compared to other well-studied arrythmias. As such, there is still much to be discovered when it comes to studying IST in general, and this particular study will endeavor to contribute to the deficit of empiric clinical data in the field. Specifically, we hope that this study cohort's demographic and medical history trends, as well as Holter monitor results of HR statistics and variability data will help clinicians to predict, diagnose, and treat IST in the future.

## MATERIALS AND METHODS APPROACH

To investigate the diagnostic criteria, demographics, and comorbidities of patients with IST, a retrospective cohort chart review study was executed, analyzing patients who met criteria below to be involved in the study:

**Inclusion**: Patients at least 18 years of age with an IST diagnosis from the practice of Consultants in Cardiovascular Medicine and Science – Fort Worth, PLLC (CCMS-FW).

**Exclusion**: Patients with IST will be excluded from enrollment in the study if they have been diagnosed with any active thyroid disorder, have been hospitalized in the last month, have had major surgery in the last 3 months, are actively using steroids, stimulants, or multiple psychotropic medications, or are currently pregnant. These considerations can change resting HR and may affect the quality of data collected on these patients, when looking specifically into IST. Additionally, any patient with diagnosed cardiac disease will be excluded and would not have received the diagnosis of IST to begin with, as it is a diagnosis of exclusion.

**Determination of Subjects**: Analysis of the CCMS electronic medical record (EMR) database was performed to determine the number of patients that match the criteria and have received a diagnosis code that corresponds to IST. These patients had been assigned this diagnosis based on the clinical judgement of the treating physician, who determined that their presentation and symptom profile, in addition to Holter monitor results, was indicative of IST. After initial analysis, there were over 500 patients that had been assigned this diagnosis code; an initial cohort of this number is far beyond the size of any single-site study is existing literature. Doing chart-by-chart analysis of clinical data in the EMR, the following metrics were collected for each patient: sex, age, race, ethnicity, body mass index (BMI), history of tobacco use, presence of existing common comorbidities (diabetes, hyperlipidemia, hypertension), use of ivabradine therapeutically, and presence of Holter monitor results.

From the original cohort of over 500 patients, the exclusion criteria were applied, which reduced the number of patients meeting criteria down to 352 patients (**Figure 1**). From there, patients were determined to be excluded from this study if they did not have documentation of important relevant clinical data, such as sufficient Holter monitor results or past medical history, that could be accessed in the EMR; this brought the cohort size down to 205 patients, which is the final number of patients that were analyzed in this study.

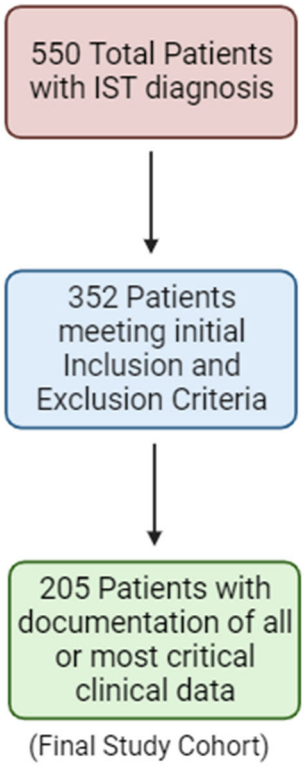


**Figure 1**. Visual display of process used to determine final study cohort from initial group of total IST patients at CCMS.

**Methods**:

This project was executed in collaboration with CCMS-FW, and all materials and methods of the project were developed in conjunction with their clinical and administrative staff members. After developing a methodical plan for this project, secure access to the EMRs associated with CCMS was granted to investigators. Having recently transitioned from an EMR that was used in the past, we spent time analyzing patient records from two EMRs and reconciling clinical data between the two. Throughout this study, all patient information and collected data were de-identified and kept in a password protected and secure spreadsheet saved to a physical hard drive that was stored securely, in order to protect the privacy and confidentiality of every patient involved.

A database analysis of both EMRs was performed to search for and identify all patients who had been given a documented diagnosis of IST, as demonstrated by the ICD10 codes associated with the condition. As mentioned above, this initial search revealed that CCMS has over 500 patients who have been given this diagnosis. While this size cohort is unprecedented in current literature for a single-site study, we chose to apply stringent exclusion criteria. As such, to arrive at a final study group size, each patient had to be thoroughly investigated in the EMR to assess whether they meet criteria and whether they have the necessary clinical data documented and available.

To ensure that each patient was thoroughly analyzed, a systematic approach to chart review was used and documented into a secure spreadsheet database for further analysis. Each of the initial 500 patients had the following data gathered from the EMR:

- Sex
- Age
- Race and Ethnicity
- BMI
- History of tobacco use
- Presence or absence of major common comorbidities
- Use of Ivabradine as a therapeutic
- Holter Monitor results

For our patient population, male and female sex were documented for each patient; an important demographic to investigate, as previous literature describing IST has identified a higher prevalence in females [2,3,5].

The age of each patient at the time of Holter monitor analysis was documented for each patient. Age is also a vital demographic for this study, as previous literature has reported IST to occur most frequently in young to middle aged adults [2,3,5].

Although limited data exists in current literature regarding prevalence of IST in people of certain races or ethnicities, we found this large cohort of unrelated patients with IST to be a unique opportunity to explore this possibility. For our cohort of 500, we found patients of “White” and “Black” documented race, with some patients choosing not to disclose their race. For this same initial cohort, we found patients of “Hispanic or Latino” or “Not Hispanic or Latino” documented ethnicity, with some patients choosing not to disclose their ethnicity. For purposes of this study, any patient who had documentation showing that they chose not to disclose their race or ethnicity was listed as “Unknown” for the associated category in our clinical analysis spreadsheet. In the initial cohort of 500 patients, we found none that reported to identify with a race or ethnicity associated with Asian, Native American, Middle Eastern, or any other racial or ethnic descent other than those listed above.

With this uniquely large cohort of IST patients, we saw an opportunity to look into the past medical history and associated contributing factors of each patient in a way that has not been clearly reported on in current literature. Although BMI does not directly assess an individual patient’s health and overall body fat percentage, it is the only consistently documented value used to assess for obesity in patients. Each patient’s BMI at the time of Holter monitor analysis was recorded as a numerical value for further analysis.

Similarly, we performed a thorough chart review to assess whether each patient has a history of tobacco use; this was recorded as either Yes or No. For the purposes of this study, any type of reported tobacco use was sufficient to receive a Yes designation, including cigarettes, electronic cigarettes, and smokeless tobacco.

Although BMI and tobacco use are both potential markers of overall health and wellness, we decided to dive deeper into the past medical history of each patient. Before clinical data collection began, we decided that each patient’s medical history would be thoroughly searched in the EMR and the following major, common comorbidities would be recorded: Diabetes, Hyperlipidemia, and Hypertension. For each of the initial 500 patients, a designation of Yes or No was recorded for each of these comorbidities, according to whether the patient had documentation of each diagnosis.

As described above, one of the few therapeutics that has been shown to give symptomatic relief to some patients with IST is the medication ivabradine. For each of the 500 patients, we recorded whether they are taking ivabradine and what dose they are taking. If they had never taken the medication or had previously been on ivabradine but stopped the medication due to ineffectiveness or adverse reaction, this was recorded as “Not taking.”

Finally, to investigate diagnostic criteria as described above, each patient’s chart was searched for Holter monitor results. If the patient did not have Holter results, this was recorded and used to help exclude that patient from the final study cohort. If Holter results were documented in the EMR, a number of objective metrics were recorded from that. Each Holter study recorded for use in this research was worn by the patient for a duration of 24 hours to 14 days. Although a duration of 24 hours would be sufficient to assess for IST, the prolonged duration of these ambulatory Holter studies makes their results even more reliably indicative of what the patient is experiencing from day to day. It also allows us to notice trends and patterns in HR variability. Although different devices produce slightly different specific results, the following categories were collected for each Holter result, if available:

- Average HR over duration of study
- Maximum HR recorded during study
- Minimum HR recorded during study
- Average HR during daytime hours (9 am – 9 pm) and average HR during nighttime hours (9 pm – 9 am)
- % of total study time spent in sinus tachycardia (defined as >100 bpm)
- Premature ventricular contraction (PVC) burden (% of total beats recorded)
- Premature atrial contraction (PAC) burden (% of total beats recorded)

Once we collected all the data described above for each of the initial 500 patients diagnosed with IST, we began narrowing down this cohort using the exclusion criteria. Once these criteria, as described above, were applied to each patient, it was found that the remaining patients who met criteria were 352 patients. A thorough review of each patient’s past medical history, medication list, and recent major surgeries or hospitalizations was necessary to investigate the satisfaction of the established criteria. The most common exclusion criteria to be met were thyroid disorder, psychotropic medication use, and current pregnancy.

It would have been ideal to have all 352 patients that met criteria be included in our final study cohort, however many of these patients were found to be missing one or more key clinical

metrics, causing them to be removed from consideration. The most common reason to be removed was not having documented Holter results. Similarly, if a patient's past medical history was not found to be reported or documented well in the charts, they were also removed for that. These insufficiencies were secondary to practice, EMR, and medical record transitions and we plan future effort in identifying these records to perform a new analysis. Once we analyzed each patient's collected data and determined it to be either sufficient or insufficient to remain in the study cohort, the number of patients remaining was 205. This is the population used to calculate any results and any conclusions made from this study are in reference to this final study cohort of 205 patients.

## RESULTS

As an investigational cohort analysis, this study does not have the traditional aim of comparing our cohort group to a healthy control group, and therefore the main findings will be reported as direct observations from our cohort.

Looking at the sex of these 205 patients, 169 were female patients (82.44%) and 36 were male patients (17.56%). A numeric representation of the sex of study cohort patients can be seen in **Table 1**.

For age, the average age of all 205 patients in the study cohort at the time of Holter monitor analysis was 49.1 years of age. Of the 205, 39 patients were ages 18-30 (19.02%); 73 patients were ages 31-50 (35.61%); 66 patients were ages 51-70 (32.20%); and 27 patients were ages 71-100 (13.17%). A graphic representation of these ages can be seen in **Table 1**. A range of ages from 18-86 were found in these 205 patients.

For race and ethnicity, 17 of the 205 patients in the study cohort chose not to disclose their race and ethnicity in the EMR. Of the remaining 188 patients, they all self-identified as either Black, White, or Hispanic/Latino, as recorded in the EMR; 17 patients identified as Black (9.04%); 15 patients identified as Hispanic or Latino (7.98%); and 156 patients identified as White (82.98%). A graphic representation of the breakdown of race and ethnicity in the study cohort can be seen in **Table 1**.

For BMI, of the 205 patients in the study cohort, 6 patients did not have a documented BMI in the EMR at the time of Holter analysis. Of the remaining 199 patients with documented values, the average BMI at the time of Holter analysis was 30.37. Of the remaining 199 patients, 7 had a BMI less than 20.0 (3.52%); 49 patients had a BMI between 20.0-25.0 (24.62%); 52 patients had a BMI between 25.1-30.0 (26.13%); 51 patients had a BMI between 30.1-35.0 (25.63%); 21 patients had a BMI between 35.1-40.0 (10.55%); and 19 patients had a BMI greater than 40.0 (9.55%). A graphic representation of the BMI data can be seen in **Table 1**. A range of BMI from 17.1-71.4 were found in the 199 patients with a documented value.

Tobacco use documentation was not easily obtained in the EMR, as many of the patients' past social history was recorded on paper charts back before the implementation of the new EMRs at CCMS. For that reason, 150 of the 205 patients in our study cohort did not have a documented tobacco use history in the EMR. Of the remaining 55 patients, 42 had no history of tobacco use (76.36%) and 13 had some history of tobacco use (23.64%). A graphic representation of the

presence or absence of a history of tobacco use in these 55 patients with documented history can be found in **Table 1**.

With regard to major medical comorbidities, diabetes was the first one to be analyzed. Of the 205 patients in the study cohort, 36 patients had a documented diagnosis of diabetes in their past medical history (17.56%), while 169 patients did not (82.44%). Another major, common comorbidity analyzed was hyperlipidemia. Of the 205 patients in the study cohort, 58 patients had a documented diagnosis of hyperlipidemia or dyslipidemia in their past medical history (28.29%), while 147 patients did not (71.71%). Finally, when looking at hypertension, of the 205 patients in the study cohort, 91 patients had a documented diagnosis of hypertension in their past medical history (44.39%), while another 114 patients did not (55.61%). A graphic representation of the breakdown of these major, common comorbidities can be found in **Table 1**.

For ivabradine use, patients documented to be currently taking this pharmacologic agent were doing so because the drug has been effective for them at either treating their symptoms or lowering their HR, or both. For those not taking the drug, this could have been due to not being eligible (pregnancy, or alternative medication interaction), poor efficacy in prior trial, or due to patient preference to refuse the medication. Of the 205 patients in the study cohort, 153 patients were not taking ivabradine at the time of chart review (74.63%), while 52 patients were taking ivabradine at the time of chart review (25.37%). Of the 52 patients currently taking ivabradine, 47 were on an effective regimen of 5.0 mg twice daily (90.38%), while the other 5 patients were on an effective regimen of 7.5 mg twice daily (9.62%). A graphic representation of ivabradine use in the study cohort can be seen in **Table 1**.

Holter monitor results were available for each of the 205 patients in the study cohort, allowing us to analyze this data. As reported above, the duration of Holter monitoring reported ranged from 72 hours to 14 days, and the specific data collected could be slightly different depending on which brand of device was used. The Holter results for all 205 patients reported an average HR over the duration of the study, and the overall mean of average HR across the 205 patients was 86.8 bpm. When breaking down each patient's average Holter HR into categories, 28 patients had an average HR less than 75 bpm (13.66%); 108 patients had an average HR between 75-90 bpm (52.68%); 58 patients had an average HR between 91-105 bpm (28.29%); and 11 patients had an average HR greater than 105 bpm (5.37%). The overall range of average HR across the 205 patients was 67-124 bpm. A graphic representation of the average Holter HR data can be found in **Table 2**.

| **Sex (n=205)** | | | **Age (n=205)** | | | **Race (n=188)** | | | |
|---|---|---|---|---|---|---|---|---|---|
| Male | 17.56% | | Avg | 49.12 | | Black | 9.04% | | |
| Female | 82.44% | | 18-30 | 19.02% | | Hispanic | 7.98% | | |
| | | | 31-50 | 35.61% | | White | 82.98% | | |
| | | | 51-70 | 32.20% | | | | | |
| | | | 71-100 | 13.17% | | | | | |
| | | | | | | | | | |
| **BMI (n=199)** | | | **Tobacco Use (n=55)** | | | **Comorbidities (n=205)** | (YES) | (NO) | |
| Avg | 30.37 | | Yes | 23.64% | | Diabetes | 17.56% | 82.44% | |
| < 20 | 3.52% | | No | 76.36% | | Hyperlipidemia | 28.29% | 71.71% | |
| 20-25.0 | 24.62% | | | | | Hypertension | 44.39% | 55.61% | |
| 25.1-30 | 26.13% | | | | | | | | |
| 30.1-35 | 25.63% | | | | | | | | |
| 35.1-40 | 10.55% | | | | | | | | |
| > 40 | 9.55% | | | | | | | | |
| | | | | | | | | | |
| **Ivabradine Use (n=205)** | | | **Ivabradine Dose (n=52)** | | | | | | |
| Yes | 25.37% | | 5.0 mg BID | 90.38% | | | | | |
| No | 74.63% | | 7.5 mg BID | 9.62% | | | | | |

**Table 1**. Demographic data including Sex, Age, Race, BMI, Tobacco Use, and Comorbidities.

The Holter results for all 205 patients reported a maximum HR during the duration of the study, and the overall mean of maximum HR across the 205 patients was 146.4 bpm. When delineating maximum Holter HR into categories, 37 patients had a maximum HR less than 125 bpm (18.05%); 81 patients had a maximum HR between 125-150 bpm (39.51%); 67 patients had a maximum HR between 151-175 bpm (32.68%); and 20 patients had a maximum HR greater than 175 bpm (9.76%). The overall range of maximum HR across the 205 patients was 91-194 bpm. A graphic representation of the maximum Holter HR data can be found in **Table 2**.

The Holter results for all 205 patients reported a minimum HR during the duration of the study, and the overall mean of minimum HR across the 205 patients was 58.23 bpm. When delineating minimum Holter HR into categories, 15 patients had a minimum HR less than 45 bpm (7.32%); 116 patients had a minimum HR between 45-60 bpm (56.59%); 61 patients had a minimum HR between 61-75 bpm (29.76%); and 13 patients had a minimum HR greater than 75 bpm

(6.34%). The overall range of minimum HR across the 205 patients was 36-95 bpm. A graphic representation of the minimum Holter HR data can be found in **Table 2**.

For daytime and nighttime HR data as described above, only a certain brand of device recorded this information, so these specific results were calculated from the Holter data of only 37 of the 205 patients in the study cohort. For those 37 patients, the overall mean of average daytime HR was 92.86 bpm, with the a range from 67.9-119 bpm. For those same 37 patients, the overall mean of average nighttime HR was 82.67 bpm, with a range from 59.1-108.7 bpm. A graphic representation of this data can be found in **Table 2**.

For % of total Holter time spent in sinus tachycardia (> 100 bpm), some brands of Holter did not record this, so these specific results were calculated from the Holter data of 167 of the 205 patients in the study cohort. For those 167 patients, the overall average % of total recorded Holter time spent in sinus tachycardia was 22.11%. The range of % tachycardia was from 0-95%. A graphic representation of this data can be found in **Table 2**.

For PVC burden, this was calculated as the % of PVC beats out of the total number of beats analyzed by Holter. Out of the 205 patients in the study cohort, 197 patients had PVC data reported on their Holter results. For those 197 patients, the overall average PVC burden was calculated to be 0.55%, with a range of PVC burdens between 0-12.8%. A graphic representation of this data can be found in **Table 2**.

For PAC burden, this was calculated as the % of PAC beats out of the total number of beats analyzed by Holter. Out of the 205 patients in the study cohort, 193 patients had PAC data reported on their Holter results. For those 193 patients, the overall average PAC burden was calculated to be 0.78%, with a range of PAC burdens between 0-26.6%. A graphic representation of this data can be found in **Table 2**.

| **Average HR (n=205)** | | | **Maximum HR (n=205)** | | | **Minimum HR (n=205)** | |
|---|---|---|---|---|---|---|---|
| Avg | 86.8 | | Avg | 146.39 | | Avg | 58.23 |
| <75 | 13.66% | | < 125 | 18.05% | | < 45 | 7.32% |
| 75-90 | 52.68% | | 125-150 | 39.51% | | 45-60 | 56.59% |
| 91-105 | 28.29% | | 151-175 | 32.68% | | 61-75 | 29.76% |
| > 105 | 5.37% | | > 175 | 9.76% | | > 75 | 6.34% |
| | | | | | | | |
| **Daytime HR (n=37)** | | | **% Time in ST (n=167)** | | | **PVC Burden% (n=197)** | |
| Avg | 92.86 | | Avg | 22.11% | | Avg | 0.55% |
| | | | | | | | |
| **Nighttime HR (n=37)** | | | | | | **PAC Burden% (n=193)** | |
| Avg | 82.67 | | | | | Avg | 0.78% |

**Table 2**. Holter data including Average HR, Maximum HR, Minimum HR, Daytime and Nighttime HR, % Time in Sinus Tachycardia, and the Burden of PVCs and PACs.

## DISCUSSION

As mentioned previously, IST is a relatively newly described disorder that has only recently begun to receive proper attention and recognition as a distressing and life-altering problem for patients, particularly women. While the novelty of IST makes it an exciting new field of study with many possibilities, it also leaves a large gap in knowledge and understanding that can be felt by those who endure its effects daily. Particularly, there are few large cohort studies in current literature that report on demographics of IST patients, beyond large review papers that have observed a propensity in women and younger aged adults. To help fill that gap in knowledge, we used this large cohort of unrelated IST patients to report our findings, add to current data, and compare our results with those in existing literature.

As has been widely reported in existing published articles, this study confirms that IST most commonly affects females, as over 82% of this cohort were female, however there was a larger number of male patients in this cohort than previously reported in some studies [5,7].

A notable percentage of the IST patients studied here are young and middle aged. Perhaps unexpectedly, the average age of this study cohort seemed to trend a bit older than those reported elsewhere, as the average patient age in this study was 49, whereas others have reported a slightly younger age, such as 33 or 35 [3,5,7]. Though the exact reason for this discrepancy is not known for certain, we suspect this is more than likely a result of CCMS-FW serving a slightly older population of patients, which may have allowed the average age to increase a bit.

When it comes to analyzing race and ethnicity of IST patients in this cohort, our results demonstrate a largely White patient demographic (82.98%), with the remaining balance distributed between Black (9.04%) or Hispanic (7.98%) patients. No existing studies report racial or ethnic distribution in IST patients, and we strongly suspect that our data are secondary to practice referral patterns and composition, and not reflective in any way of a meaningful physiologic signal.

For BMI, this study found that a very small percentage of IST patients were considered underweight (3.52%), much like a small percentage were found to be severely obese (9.55%). However, using a BMI of 30 as the lower cutoff for obesity, this study shows that 45.73% of IST patients in this cohort were obese at the time of their Holter monitor results, a higher percentage than found in other studies (21.3%) [7]. This indicates that the majority of these IST patients (50.75%) were under the threshold for obesity and fell in the 20-30 BMI range, making them

normal weight or overweight. Comparing the average BMI of the 205 patients in this study cohort (30.37), it was slightly higher than the average BMI reported by the large cohort study performed at the Mayo Clinic (27.8) [7].

Since no existing studies were found that investigate a correlation between tobacco use and IST, we thought it important to report on these statistics. For this study cohort, only 55 of the 205 patients had documentation of their tobacco use history, though we concluded a large portion of this may be due to incomplete data as we discussed in sections above. Examining those with reported history, it found that tobacco use is not a particularly common piece of history shared by these IST patients, as over 76% had no history of using tobacco products of any kind. As such, it can reasonably be concluded that tobacco use is not a common instigating factor or a common contributing factor to the development of IST.

This study found a higher incidence of the common comorbidities diabetes (17.56%), hyperlipidemia (28.29%), and hypertension (44.39%) compared to similar existing studies [7]. Considering the referenced study already reported a significantly higher number of IST patients with diabetes and hypertension when compared to a control group with a different arrhythmia, these results seem to support those prior findings. This new data suggests that although healthy young to middle-aged females still seem to be the most susceptible to developing IST, clinicians should not exclude IST as a possible diagnosis in patients being treated for these common, but potentially serious comorbidities.

When discussing the statistics related to ivabradine use in this study cohort, it is important to realize that physicians at CCMS-FW have only prescribed ivabradine to patients that present with a highly symptomatic profile, do not have any contraindications or medication interactions, and who are not breast feeding, pregnant or planning to become pregnant, out of an abundance of professional caution [2]. Similarly, they have only kept patients on continuous regimen of ivabradine if the drug has proved to be effective for them. Therefore, although only a quarter of patients in this study cohort were actively taking ivabradine at the time of chart review, that section of the cohort has received notable benefits from taking it, including symptom relief and/or HR control. The doses used here in clinical practice and their impressive efficacy at improving the lives of IST patients confirm the regimen and results reported in existing literature [2,5]. We were surprised by this initial dataset and will be probing the database further, as we expected a significantly higher proportion of patients to be treated with ivabradine, which has been prescribed for many patients with IST at CCMS-TX since its FDA approval in 2015. This is especially surprising within the current EMR system, which went into effect in 2022.

Based on the Holter monitor statistics collected here, this cohort of IST patients has a slightly lower average HR (86.8 bpm) over the duration of their device analysis than similar large cohorts in other studies [6,7]. Using the widely accepted definition of IST discussed in the introduction above [1,2], some would argue that many of the patients included in this cohort may not meet the diagnostic criteria for an official diagnosis of IST. We would push back on that and challenge readers and experts in the field to reconsider the diagnostic criteria for IST, as the patients included in this study cohort certainly meet the symptom profile and overall clinical presentation of patients with IST. Another consideration that could affect the numbers reported here is the duration of Holter monitor study. The existing studies that investigate Holter statistics for IST patients report that they are exclusively using 24-hour Holter monitor analysis, while the study duration for patients in this cohort was anywhere from 24 hours to 14 days. While that is a wide range of study duration, the longer ambulatory study time only improves the realistic accuracy of the electrocardiographic data collected from day to day, which applies to the rest of the reported Holter statistics here. We propose that it may be more appropriate for the diagnostic criteria of IST to be an upregulated HR over 100 bpm, with an average HR of at least 85 bpm (rather than 90 bpm) over a specified 24-hour period. This new definition of IST would be more inclusive and could lead to more suffering patients receiving the effective management that they need for symptom relief.

The average maximum HR of the study cohort patients collected here (146 bpm) is similar to and only slightly lower than what was reported in the large Mayo Clinic study (153 bpm) [7]. The average minimum HR of the study cohort collected here (58 bpm) was notably lower than that reported by the same Mayo Clinic study (70 bpm) [7]. Again, while this could be due to the longer duration of Holter study, it is also possible that the previously accepted diagnostic criteria has prevented some IST patients from qualifying for the diagnosis.

Although only 37 of the 205 patients in this cohort had Holter results that reported on daytime and nighttime HR statistics as defined above, we still believe that this data is valuable in understanding the HR variability that IST patients may be experiencing is an ambulatory setting. That is especially true since no existing studies were found that report on this. Since the average daytime HR (92.86 bpm) was notably higher than the average nighttime HR (82.67), it is reasonable to conclude that the physical activity and psychological stress associated with waking hours is partially contributing to the IST presentation and upregulated HR in these patients.

For % of time in sinus tachycardia, PVC burden, and PAC burden results, as reported above, it is difficult to assess what these statistics mean without a matched control group or an existing study to compare it to. We are hopeful that the raw Holter data reported in these three categories may be useful for future studies to compare.

## FUTURE DIRECTIONS

While the literature surrounding clinical presentation and epidemiology is quickly revealing promising data to help us understand IST, the underlying pathophysiological mechanism of IST is proving to be much more challenging to elucidate, though there have been several theories proposed. Future research should focus on trying to better understand what causes IST, as that would likely help to develop detection, prevention, and treatment strategies. One study by Baruscotti et al identified a gain-of-function mutation in the HCN4 gene in a specific family in Italy that correlated to the IST phenotype [11]. The HCN4 gene codes for an ion channel that is involved in the “funny current” of cardiac electrophysiology and modulates HR; when mutated, these channels have an elevated cAMP sensitivity and elevated level of activity, which could explain the IST phenotype [11]. Though this discovery is promising, the small sample size and isolated incidence demand that this gene be investigated further.

Another gene that has been implicated in IST is the caveolin-3 (cav-3) gene, which codes for a plasma membrane protein that modulates the functional properties of several ion channels in cardiomyocytes, including the HCN4 channels [12]. A specific variant of the cav-3 gene (T78M) was detected at a rate of 4.35% in a study of IST patients, compared to a rate of 0.3% in a database of the general population [12]. Demonstrated in this study, the cav-3 gene could have an affect on cardiac membrane excitability, as seen in IST.

Additionally, large-conductance Ca2+- and voltage-activated K+ (BK) channels have been shown to play a role in regulating cardiomyocyte excitability. These channels are coded by the KCNMA1 gene; mutations of this gene have been characterized in some seizure and movement disorders [13]. An in vivo study with mice also demonstrated how BK channels in the plasma membrane of sinoatrial node cells are novel modulators of cardiac automaticity in mice. In that study, Lai et al showed that pharmacologic inhibition of BK channels slowed cardiac pacing and KCNMA1 gene knockout mice conferred a lower intrinsic sinoatrial node cell firing rate [14]. The role of BK channels in cardiac cell automaticity makes it another excellent player with potential

involvement in the inappropriate automaticity seen in IST, as a gain-of-function mutation in this gene could increase cardiac pacing.

In addition to channelopathies, autoantibodies have also been proposed as a potential player in IST development. While autoantibodies have been studied in relation to atrial tachyarrhythmias previously [15], one study found that 52% of patients with IST in their study had circulating immunoglobulin G anti-β-receptor autoantibodies present that induced an elevated cAMP and tachycardia, in contrast to their healthy volunteers [16]. A detection of both β-1 and β-2 receptor autoantibodies should be performed in a study of IST patients to further identify a possible role in the pathogenesis of the disease.

Supporting the idea of autoantibody implication, Li et al immunized New Zealand white rabbits with β-2 adrenergic receptor-inducing peptides to raise the titer of autoantibodies against these peptides. In immunized rabbits with increased titers, burst pacing induced 6 episodes of sustained tachyarrhythmia out of 20 events, compared to zero episodes in 20 events in preimmunized rabbits with undetectable titers [15]. A wide survey of autoantibodies in cardiac arrythmias showed that several autoantibodies are involved in atrial fibrillation, another form of atrial tachycardia, and detection of these autoantibodies in IST patients should be performed as well, in hopes of identifying another potential immunological mechanism. These autoantibodies include anti-myosin heavy chain, anti-Na/K-ATPase, anti-M2 receptor, and anti-HSP65 autoantibodies [17].

Finally, one study looked into the autoimmunological mechanism underlying Postural Orthostatic Tachycardia Syndrome (POTS), a clinical tachycardic disorder very similar to IST [18]. In addition to the previously noted autoantibodies against β-1, β-2, and M2 receptors, Gunning et al also identified a significant number of POTS patients with elevated levels of autoantibodies against adrenergic α-1 receptors (89%) and against muscarinic M4 receptors (53%). Although the study found lower levels of autoantibodies against M1, M2, M3, M5, and α-2 receptors, these autoantibodies were still present in some patients and worth exploring in IST patients as well [18].

While mechanisms discussed above provide a solid base of knowledge to progress from, there is still a significant gap in understanding when it comes to an accepted, well-defined pathophysiologic cause for the phenotype seen in IST. Should future students in this lab choose to pursue this avenue of study, our key resource is this large cohort of unrelated patients all of who meet criteria for IST. This heterogeneous sample affords us the unique opportunity to determine if there are co-localized genomic markers present in these patients. A future study

has the potential to be broadly applicable, as the patient population is derived from unrelated patients who all meet criteria for IST and are treated with similar therapeutic algorithm approaches. As such, within this large patient population, if a future study identifies genes noted above to have similar SNPs that could explain the IST pathology, or if these patients share autoantibodies, it will have contributed to furthering the mechanistic basis for IST in a heterogenous, broad population. It is hopeful that a future study like this would then result in the development of novel therapeutics or diagnostic understanding to further effective treatment and screening for this challenging clinical condition. With a better understanding of the underlying mechanism of IST, therapy could be directed at neutralizing specific autoantibodies or at using specific genetic variants as a potential screening method to promote early detection and intervention.

As members of the Sathyamoorthy Lab have spent time designing a future study in preparation for this study, a potential framework for this future study will be proposed. There would essentially be two parts to this study that could occur simultaneously. Once the IST patients in the study cohort submitted written informed consent to be enrolled in the study, those patients would undergo sample collection of both whole blood and saliva samples. The whole blood would be used to detect autoantibodies, while the saliva samples would serve as a source of DNA for targeted genetic sequencing. The genetic sequencing data and autoantibody levels would be compared to a control group of healthy donor volunteers. This control group would need to be similar to the study group in both demographics and size, in order to ensure the most realistic comparison.

Though there are a handful of studies that investigate the mechanism of IST, the current research is relatively scarce and has left much room for future discovery. It is hopeful that future studies will help to fill that gap in understanding and shed light on the underlying mechanism that causes this mysterious disorder. Although there have been recent signs of potentially more effective treatment options, it is unlikely that superior diagnostic and treatment modalities will continue to develop without an improved fundamental understanding of what really causes IST.

The studies mentioned previously have effectively set a framework from which future studies could build. The sparse scattering of literature looking into channelopathies, specific genetic variants, altered proteins, and the presence of autoantibodies are the inspiration for future studies, which could attempt to analyze several of those potential mechanisms more thoroughly, while also revealing new causes. In addition to re-analyzing some of the genes noted in previous studies, new potential genetic players could be selected based on thoughtful

consideration of genes and their respective proteins that are involved in cardiac electrophysiology. Similarly, while the autoantibodies previously identified should be re-analyzed, the new potential autoantibodies should be chosen based on studies of similar disorders and an understanding of these receptors' role in regulating cardiac function.

## CONCLUSIONS

IST is a relatively novel tachyarrhythmia that has proven to be somewhat mysterious in its mechanism, etiology, presentation, and treatment, despite gaining more attention in recent years. This study confirms that IST most commonly affects females and suggests that IST may affect middle-aged and older patients more commonly than previously reported. Similarly, it found that while healthy females (not obese, no comorbidities) make up the majority of IST patients, obesity and common major comorbidities may be more prevalent in this patient population than other studies suggest. The Holter results reported here suggest that the upregulation of HR may not be as dramatic as previously thought. This should lead future studies to reconsider the most popular diagnostic criteria for IST, as they may be leading to some patients being excluded from a diagnosis of IST and not receiving proper treatment for their symptoms.

## COMPLIANCE

This study received approval from the Institutional Review Board (IRB) through the TCU IRB. On their website, the TCU IRB states: “Oversees human subjects research at TCU and plays a key role in promoting adherence to ethical principles, professional standards, and applicable law related to human subjects research. The IRB reports to Research Compliance with open lines of communication to the Associate Provost of Research and Institutional Official.” The protection of human subjects is based on U.S. federal law and key principles defined in the Belmont Report.

## **REFERENCES**:


1. Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. *Europace.* 2019;21(2):194-207.
2. Ahmed A, Pothineni NVK, Charate R, et al. Inappropriate Sinus Tachycardia: Etiology, Pathophysiology, and Management: JACC Review Topic of the Week. *J Am Coll Cardiol.* 2022;79(24):2450-2462.
3. Sossalla S, Vollmann D. [Inappropriate sinus tachycardia]. *Dtsch Med Wochenschr.* 2015;140(8):603-607.
4. Masumoto A, Takemoto M, Mito T, et al. Inappropriate Sinus Tachycardia Diagnosed and Treated as Depression Successfully Treated by Radiofrequency Catheter Ablation. *Intern Med.* 2017;56(5):523-526.
5. Sheldon RS, Grubb BP, 2nd, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm.* 2015;12(6):e41-63.
6. Şimşek E, Ozbay B, Mutlu I, et al. Prevalence of inappropriate sinus tachycardia and the comparison of the heart rate variability characteristics with propensity score-matched controls. *Turk Kardiyol Dern Ars.* 2020;48(2):96-102.
7. Shabtaie SA, Witt CM, Asirvatham SJ. Natural history and clinical outcomes of inappropriate sinus tachycardia. *J Cardiovasc Electrophysiol.* 2020;31(1):137-143.
8. D'Alessandro A, Boeckelmann I, Hammwhöner M, Goette A. Nicotine, cigarette smoking and cardiac arrhythmia: an overview. *Eur J Prev Cardiol.* 2012;19(3):297-305.
9. Ali M, Haji AQ, Kichloo A, Grubb BP, Kanjwal K. Inappropriate sinus tachycardia: a review. *Rev Cardiovasc Med.* 2021;22(4):1331-1339.
10. Hou CR, Olshansky B, Cortez D, Duval S, Benditt DG. Inappropriate sinus tachycardia: an examination of existing definitions. *Europace.* 2022;24(10):1655-1664.
11. Baruscotti M, Bucchi A, Milanesi R, et al. A gain-of-function mutation in the cardiac pacemaker HCN4 channel increasing cAMP sensitivity is associated with familial Inappropriate Sinus Tachycardia. *Eur Heart J.* 2017;38(4):280-288.
12. Campostrini G, Bonzanni M, Lissoni A, et al. The expression of the rare caveolin-3 variant T78M alters cardiac ion channels function and membrane excitability. *Cardiovasc Res.* 2017;113(10):1256-1265.
13. Bailey CS, Moldenhauer HJ, Park SM, Keros S, Meredith AL. KCNMA1-linked channelopathy. *J Gen Physiol.* 2019;151(10):1173-1189.
14. Lai MH, Wu Y, Gao Z, Anderson ME, Dalziel JE, Meredith AL. BK channels regulate sinoatrial node firing rate and cardiac pacing in vivo. *Am J Physiol Heart Circ Physiol.* 2014;307(9):H1327-1338.
15. Li H, Scherlag BJ, Kem DC, et al. Atrial tachycardia provoked in the presence of activating autoantibodies to β2-adrenergic receptor in the rabbit. *Heart Rhythm.* 2013;10(3):436-441.
16. Chiale PA, Garro HA, Schmidberg J, et al. Inappropriate sinus tachycardia may be related to an immunologic disorder involving cardiac beta andrenergic receptors. *Heart Rhythm.* 2006;3(10):1182-1186.
17. Lee HC, Huang KT, Wang XL, Shen WK. Autoantibodies and cardiac arrhythmias. *Heart Rhythm.* 2011;8(11):1788-1795.
18. Gunning WT, 3rd, Kvale H, Kramer PM, Karabin BL, Grubb BP. Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies. *J Am Heart Assoc.* 2019;8(18):e013602.