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Stellate ganglion block and cardiac sympathetic denervation in patients with inappropriate sinus tachycardia

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Abstract

Background: Inappropriate sinus tachycardia (IST) remains a clinical challenge because patients often are highly symptomatic and not responsive to medical therapy.

Objective: To study the safety and efficacy of stellate ganglion (SG) block and cardiac sympathetic denervation (CSD) in patients with IST.

Methods: Twelve consecutive patients who had drug-refractory IST (10 women) were studied. According to a prospectively initiated protocol, five patients underwent an electrophysiologic study before and after SG block (electrophysiology study group). The subsequent seven patients had ambulatory Holter monitoring before and after SG block (ambulatory group). All patients underwent SG block on the right side first, and then on the left side. Selected patients who had heart rate reduction ≥15 beats per minute (bpm) were recommended to consider CSD.

Results: The mean (SD) baseline heart rate (HR) was 106 (21) bpm. The HR significantly decreased to 93 (20) bpm ($P = .02$) at 10 minutes after right SG block and remained significantly slower at 97(19) bpm at 60 minutes. Left SG block reduced HR from 99 (21) to 87(16) bpm ($P = .02$) at 60 minutes. SG block had no significant effect on blood pressure or HR response to isoproterenol or exercise (all $P > .05$). Five patients underwent right (n = 4) or bilateral (n = 1) CSD. The clinical outcomes were heterogeneous: one patient had complete and two had partial symptomatic relief, and two did not have improvement.

Conclusion: SG blockade modestly reduces resting HR but has no significant effect on HR during exercise. Permanent CSD may have a modest role in alleviating symptoms in selected patients with IST.

Abbreviations: CSD, cardiac sympathetic denervation; ECG, electrocardiography; EPS, electrophysiology study; HR, heart rate; IST, inappropriate sinus tachycardia; SG, stellate ganglion.

KEYWORDS
cardiac sympathetic denervation, heart rate, inappropriate sinus tachycardia, stellate ganglion blockade

1 | INTRODUCTION

The syndrome of inappropriate sinus tachycardia (IST) is a sinus heart rate (HR) of more than 100 beats per minute (bpm) at rest or average HR of 90 or more bpm by 24-hour Holter monitoring and is associated with distressing symptoms of palpitations not due to secondary causes of sinus tachycardia.[1,2] The clinical manifestations of this syndrome are diverse and variable but include palpitations, dizziness, chest pain and a constellation of symptoms related to orthostatic intolerance. IST affects approximately 1% of the population and it most often affects young women.[3] Pharmacologic therapy to suppress sympathetic activity for IST has not been effective and has had poor long-term tolerance.[4-6] Despite the success of ablation for other arrhythmias, the long-term outcomes of catheter ablation for IST remain disappointing.[7-11]

Cardiac sympathetic denervation (CSD) has been considered as an alternative therapy for medically refractory arrhythmias that are driven by the sympathetic tone in patients with long QT syndrome, catecholamine polymorphic ventricular tachycardia, and structural heart disease.[12,13] Stellate ganglion (SG) block or permanent CSD might be an alternative therapy for IST when medical therapy fails.[14,15]

Mayo Clinic is a referral center for patients with IST who have exhausted medical therapy. Ivabradine was not available as an alternative pharmacological agent at the time of this study. Therefore, we proposed a prospective clinical practice protocol to perform SG block and to observe its acute sympatholytic effects. We then selected patients who have had temporal HR reduction to undergo surgical CSD. The aim of this study was to investigate the short-term effect by SG block and long-term outcomes by CSD.

2 | METHODS

2.1 | Study patients

The study included 12 consecutive patients with a diagnosis of IST between July 2012 and May 2015 at Mayo Clinic, Rochester, MN. According to 2015 Heart Rhythm Society Expert Consensus Statement on the diagnosis and treatment of postural tachycardia syndrome, IST, and vasovagal syncope, all patients met the criteria for IST: the syndrome of IST is defined as a sinus rate >100 bpm at rest (with a mean 24-hour HR >90 bpm not due to primary causes) and is associated with distressing symptoms of palpitations.[2] In these patients, one or more medications, including β-blocker and calcium channel blocker had failed. Exclusion criteria included postural orthostatic tachycardia syndrome, vasovagal syncope, and sinus tachycardia with a treatable cause, including hyperthyroidism, anemia, infectious disease, pulmonary emboli, myocardial ischemia, pericardial effusion, hypoxia, hypovolemia, pheochromocytoma, and heart failure. The study protocol was approved by the Clinical Practice Committee and the Mayo Clinic Institutional Review Board.

2.2 | Baseline clinical evaluation

All patients underwent a thorough baseline evaluation, including (a) complete blood count and renal function, liver function, and thyroid function tests, (b) 24-hour urine test for catecholamine level, (c) 12-lead ECG, (d) 24-hour Holter monitoring, (e) transthoracic echocardiography, (f) treadmill exercise test, (g) autonomic reflex screen (HR response during Valsalva maneuver and deep breathing, quantitative axon reflex sweat test, blood pressure and HR response to a 10-minute tilt at 70 degrees angle), (h) thermoregulatory sweat test, (i) psychiatry consultation, if needed, and (j) tilt study. We excluded patients with vasovagal syncope, primary or secondary autonomic neuropathy, and any secondary cause of sinus tachycardia associated with cardiac or systemic diseases. History of medication use, including specific drugs being administered to control IST, was recorded.

2.3 | Electrophysiology study group

Of 12 patients, five patients underwent SG block and an electrophysiologic study (EPS) to exclude potential supraventricular tachycardia in the EP lab. Two quadripolar catheters were placed in the right atrium and high ventricular septum to record atrial and His electrograms through the femoral approach. Atrial decremental pacing and programmed stimulation with single and double extrastimuli were performed to assess sinus node recovery time and right atrial and ventricular effective refractory period and to exclude sinus node reentry and ectopic atrial tachycardia. Isoproterenol infusion was then given at 2 mcg/min to evaluate the response in HR. After the EPS, cervical SG block was performed on the right side by the anesthesiologist. The EPS and isoproterenol test were repeated. HR and cuff blood pressure were continuously monitored. On the next day, the EPS and left SG block were performed using the same protocol as in the previous day (induction of atrial tachycardia was omitted). Transient Horner's sign was observed following each SG block procedure.

2.4 | Ambulatory study group

As the first five patients did not have inducible atrial tachycardia amenable to catheter ablation. Due to scheduling challenges with performing SG blocks in the EP laboratory, the other seven consecutive patients with IST had SG blocks performed in an outpatient procedure room (Figure 1). The SG block technique and procedural monitoring were identical at the two procedural sites—EP lab and an outpatient procedure room. At the Mayo Clinic, the outpatient SG block is a protocolized procedure performed by pain medicine using image guidance, utilizing fluoroscopy, and ultrasound in a sterilized procedure room. Evaluation of the effect from the SG blockade was undertaken in the ambulatory setting. A right SG block was performed on the first day, and a left SG block was performed on the next day. This

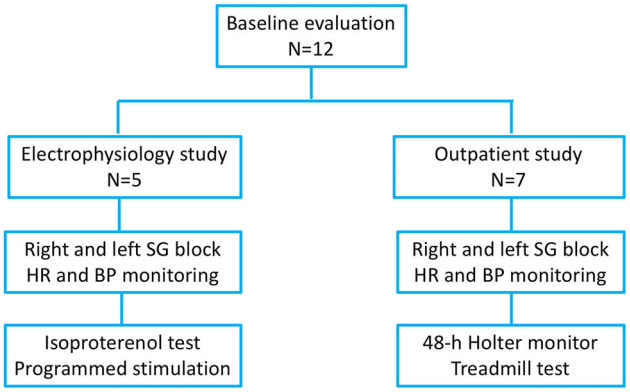

FIGURE 1 Twelve study patients who had stellate ganglion blocks underwent either electrophysiology study in the EP lab (N = 5) or outpatient study. Five of them had permanent sympathetic denervation. BP, blood pressure; HR, heart rate; SG, stellate ganglion

group had continuous 48-hour Holter monitors placed before the SG blocks to assess the short-term HR responses following the first day right SG block and the next day left SG block. The maximal, minimal, and average HRs were reported hourly. All patients had a baseline treadmill study as per protocol. After the right SG block on day 1 and left SG block on day 2, treadmill tests were repeated to assess the effect of the SG blocks on HR response to exercise. Treadmill testing was performed within 2 hours of the SG blocks.

2.5 | SG block procedure

Temporary pharmacologic block of the right and then the left SG was performed to assess the short-term effect on HR. For the patients who had SG blocks performed in the EP laboratory or in an outpatient procedure room, the right and left SG blocks were performed separately on two consecutive days. The patients were not receiving anticoagulants or clopidogrel. No sedatives were given before the procedures. The operative field was sterilely prepared and draped in the usual sterile fashion. The skin and subcutaneous tissue were anesthetized with 0.5% lidocaine. Chemical blockade of the SG was performed using image guidance, fluoroscopy or a combination of fluoroscopy and ultrasound. From an anterior oblique angle, a 25-g spinal needle was advanced to contact the ventral surface of either the C6 or the C7 transverse process at the junction with the vertebral body, just inferior to the uncinate process. Proper needle placement was confirmed using multiple views. After negative aspiration through the needle, 1 to 2 mL of radiopaque contrast agent was injected to ensure the adequate spread of injection in the region of the SG and to ensure the absence of any vascular or neuraxial spread (Figure 2A,B). Next, a total volume of 7 to 10 mL of a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine was injected slowly and incrementally. The injection site approximates the middle cervical sympathetic ganglia and contrast-confirmation was used to ensure that the local anesthetic mixture spread inferiorly to provide blockade of the upper thoracic sympathetic ganglia. HR and blood pressure were monitored and recorded at

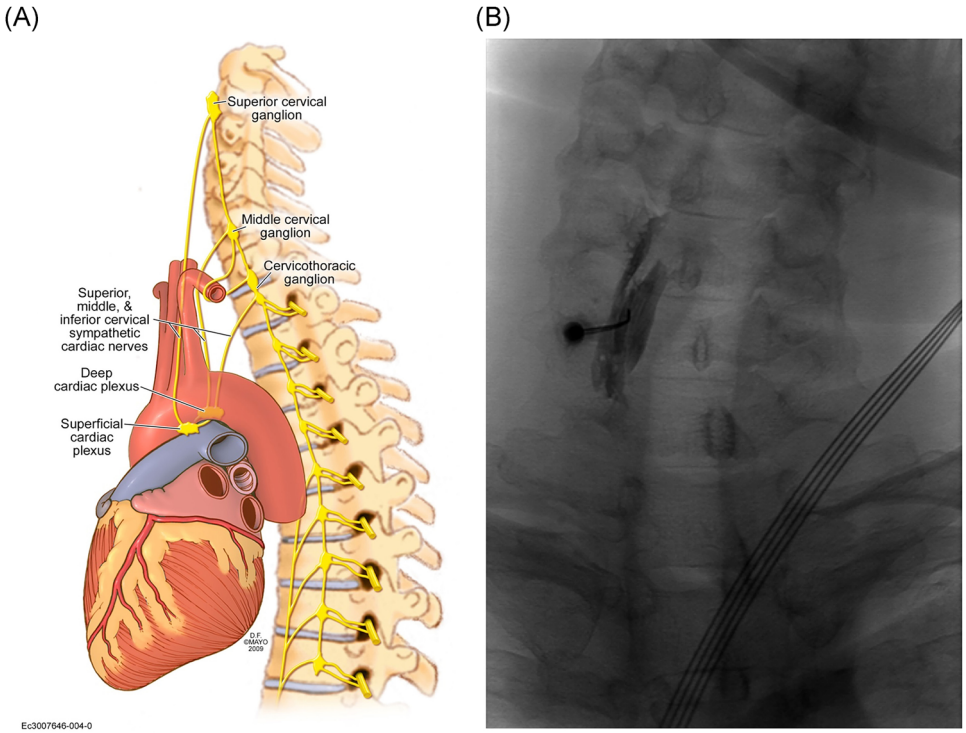

FIGURE 2 Stellate ganglion block: anatomy and procedure. A, Left stellate ganglion located anterior to transverse process of the C7 vertebra. It is bordered medially by the longus colli and laterally by the anterior scalene muscles. B, Contrast injection at the cervical sympathetic chain to ensure adequate spread of injectate in the region of the stellate ganglion and no vascular or neuraxial spread guided by fluoroscopy

baseline and every 5 minutes after the SG block for a total of 30 minutes. Hand skin temperatures were monitored and recorded before the procedure and 15 minutes after the procedure. Evidence of SG block was an ipsilateral Horner sign and an increase in the hand skin temperature of more than 1°C.

2.6 | Permanent CSD

Patients who had an effect of HR reduction of more than 15 bpm in response to SG block were referred for consideration of permanent CSD. After the informed consent process, right or bilateral CSD was performed by a thoracic surgeon under general anesthesia. After anesthetic induction, the left bronchus was selectively intubated and the right lung collapsed. Right CSD was performed using video-assisted thoracic surgery. Three small midaxillary incisions were made in the right chest wall for the insertion of the camera and scissors. With the videoscopic transthoracic approach, the sympathetic ganglia were identified through the pleura, which was then divided to expose the right-sided sympathetic chain. The lower half of the SG, together with the T2-4 sympathetic chain, was resected. The dissected materials were sent for frozen section to ensure that nerve and ganglia had been removed. For CSD, the left CSD was performed following the right side denervation with the right bronchus was selectively intubated and the left lung collapsed.

2.7 | Follow-up

All patients but one subsequently returned. For patients who had permanent CSD, the follow-up evaluation included (a) recurrent or new symptoms, (b) medication use, (c) 12-lead ECG, (d) 24-hour Holter monitoring, and (e) any complications from the denervation procedure.

2.8 | Statistical analysis

Continuous variables are expressed as mean ± SD or SEM and were compared with the the Student *t* test or with a paired *t* test. The Holter reports on the maximal, minimal, and mean HR for the first 6 hours after SG block were analyzed hourly. The mean value of maximal, minimal, and mean HR from 6 AM to the procedure time was considered the baseline to assess the effect of SG block on HR. *P* values less than .05 were considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

All 12 patients had debilitating IST with no evidence of other identifiable causes responsible for this arrhythmia. The duration of symptoms attributable to IST was 3.1 to 11.8 years. The mean age was 34 (12) years; 10 patients were female. The baseline characteristics are shown in Table 1. All patients complained of daily palpitations, three patients had presyncope and four patients had chest pain. Five patients reported dyspnea, three had fatigue and six had anxiety. In all patients, two or more HR slowing drugs had failed. Two patients had diabetes, and three had hypertension. The mean left ventricular ejection fraction was 63.0% ± 2.7%.

TABLE 1 Baseline demographic and clinical characteristics of patients with inappropriate sinus tachycardia

Characteristic	Value[a]
Age, y	34 (12.1)
Female	10
Symptoms	
Palpitations	12
Presyncope	3
Chest pain	4
Dyspnea	5
Fatigue	3
Anxiety	6
Smoking	1
Hypertension	3
Hypercholesterolemia	2
Diabetes	2
Echocardiographic results	
Left ventricular end-diastolic diameter, mm	45 (5.4)
Left ventricular ejection fraction, %	63 (2.7)
Septal wall thickness, mm	9.3 (0.9)
Posterior wall thickness, mm	9.3 (0.9)
Hemoglobin, g/dL	13.2 (1.8)
Creatinine, mg/dL	0.8 (0.2)
Thyrotropin, mIU/L	1.3 (0.8)
Thyroxine, ng/dL	1.2 (0.1)

[a]Continuous data are expressed as mean (SD); categorical data are number of patients.

3.2 | HR and blood pressure changes immediately after SG block

In all 12 patients, the periprocedural vital signs were monitored every 5 minutes either in the EP lab for the EPS group or in the pain clinic outpatient procedure room for the ambulatory group. The mean baseline HR was 106 (21) bpm. The HR significantly decreased at 5, 10, and 20 minutes after right SG block (all *P* value < .01; Figure 3). HR was not significantly reduced after the left SG block. Figure 4 shows the HR change from baseline 139 bpm to 89 bpm after right SG block in a patient who underwent EPS. Both systolic and diastolic blood pressures did not change significantly after left or right SG block (Figure 3).

3.3 | Acute effects of SG block on EPS group

Five patients underwent an EPS in the electrophysiology laboratory. Transient Horner's sign was observed following each SG block procedure. Isoproterenol shortened QT and RR intervals before (*P* = .036 and 0.019) and after SG block (*P* = .034 and .018) compared to baseline. However, There were no significant changes in the PR,

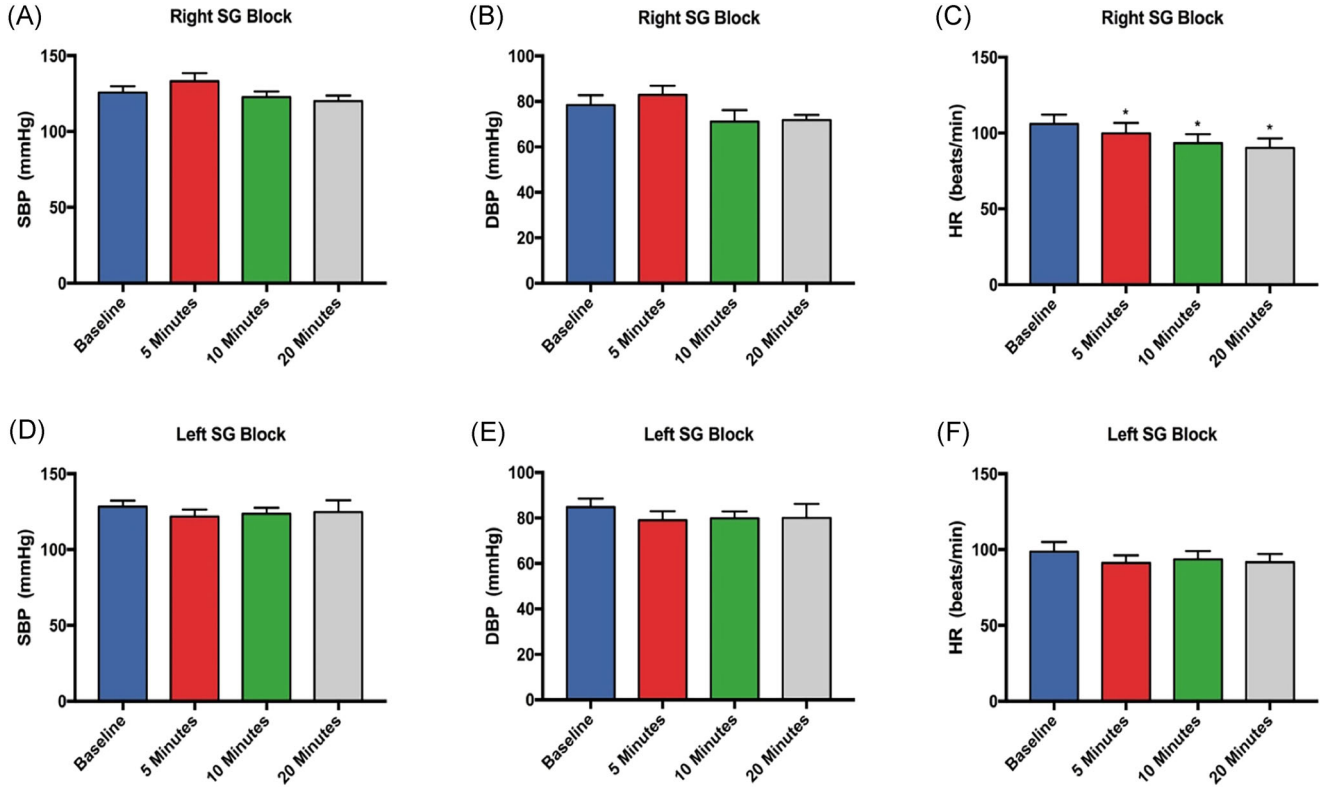

FIGURE 3 Acute effect of stellate ganglion block on heart rate and blood pressure. The systolic blood pressure (A), diastolic blood pressure (B), and heart rate (C) changed after right SG block. The systolic blood pressure (E), diastolic blood pressure (F), and heart rate (G) changed after left SG block. Values are presented mean ± SEM.*$P < .01$ compared with baseline. SG, stellate ganglion

QRS, QT, or RR intervals or atrial effective refractory period by SG block without (Figure 5A) and with (Figure 5B) isoproterenol infusion. There was no inducible supraventricular tachycardia amenable to catheter ablation.

3.4 | HR changes on holter monitoring and treadmill exercise after SG block (ambulatory group)

Six patients completed continuous Holter monitoring through the right SG block on day 1 and 3 of them also had Holter recording through the left SG block on day 2. The maximal, minimal, and average HRs after right SG block and left SG block were significantly decreased compared with the baseline HR (Figure 6). HR was significantly reduced for the first 2 hours after the block and gradually returned to baseline after 5 hours.

Seven patients underwent treadmill tests before and after the right and left SG blocks. There were no statistically significant changes in resting and peak exercise HR. The resting systolic and diastolic blood pressures, and peak exercise systolic and diastolic blood pressures were unchanged before and after SG block (Table 2). The right and left SG blocks had no significant impact on the metabolic equivalent task, a measure of exercise intensity.

3.5 | Effect of permanent CSD

In seven patients, HR was reduced by more than 15 bpm in response to the SG block. Five of them underwent permanent CSD after a thorough discussion between physician and patient (right CSD in four and bilateral CSD in one). The potential benefits and adverse effects related to the denervation were carefully reviewed. In four patients who had right sympathectomy, one had persistent substantial symptomatic improvement, one had moderate symptomatic improvement (one of these two patients required ivabradine and one required propranolol to facilitate symptom control). Remaining one patient who had right CSD and one had bilateral CSD had initial alleviation of symptoms after the surgery but began having recurrent sinus tachycardia in 2 and 6 months, with severity similar to before the denervation. The patient with bilateral CSD subsequently underwent atrioventricular junction ablation and implantation of a pacemaker (pacing mode VVIR). Besides, one patient with fatigue and dyspnea, and the other two patients with fatigue improved after CSD.

3.6 | Procedure complications

There were no documented complications associated with SG block in the 12 study patients. Of the five patients who underwent CSD, right hemothorax developed in one patient.

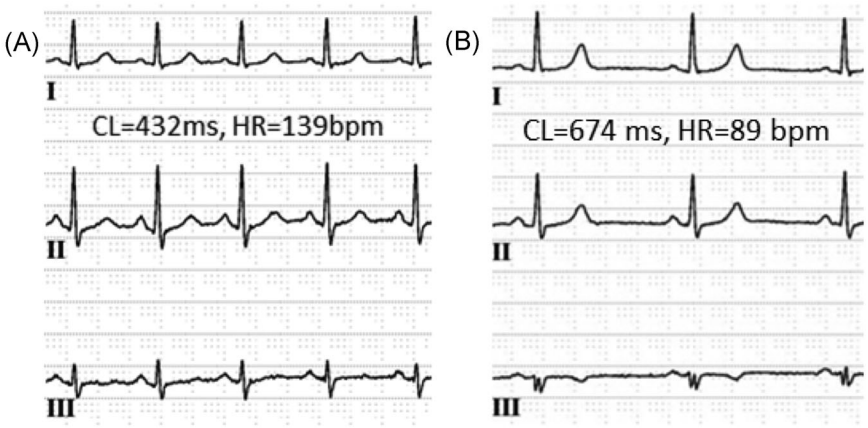

FIGURE 4 Reduction of heart rate in response to left stellate ganglion block of inappropriate sinus tachycardia. Shown are leads I, II, and III at the procedure. A, Baseline sinus cycle length (CL) was 432 ms (heart rate, 139). B, After left stellate ganglion block, the cycle length increased to 674 ms (heart rate, 89 beats per minute)

4 | DISCUSSION

4.1 | Main findings

This is the first sympathetic modulation pilot study for patients with drug-refractory and highly symptomatic sinus tachycardia found that (a) either left or right SG block with a mixture of 1% lidocaine and 0.5% bupivacaine was associated with a significant, but modest, acute HR reduction; (b) SG block had no significant effect on blood pressure, electrophysiologic parameters or HR response to exercise; and (c) permanent CSD reduced symptoms in some of the patients, but the response was heterogeneous and the majority of patients required continued medical management.

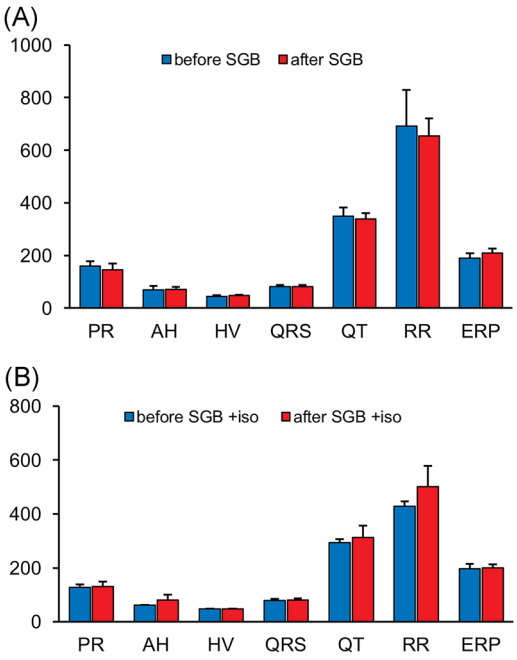

FIGURE 5 Electrophysiologic study and isoproterenol test before and after stellate ganglion block. There were no significant changes in the PR, QRS, QT, and RR intervals (ms) or atrial Effective Refractory Period after stellate ganglion block without (A) and with isoproterenol infusion (B)

4.2 | Temporal effect of SG block on IST

SG block has been used to diagnose and manage various vascular disorders and sympathetically mediated pain in the upper extremity, head, and neck. Sympathetic block has also been used to treat posttraumatic stress disorder to relieve sympathetic hyperactivity.[16-18]

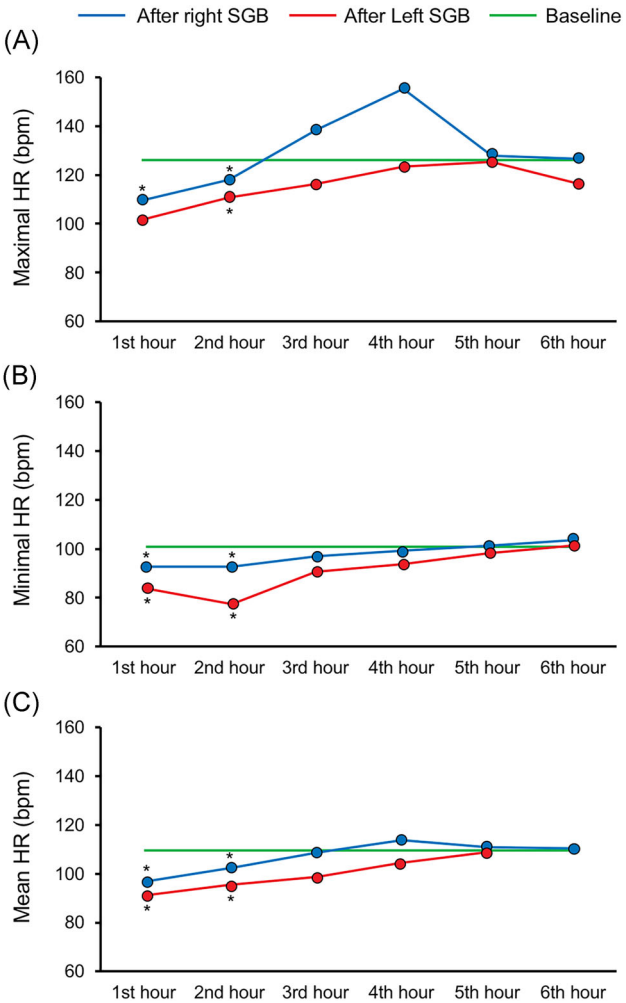

FIGURE 6 Heart rate change after right and left stellate ganglion block. A, Maximal heart rate. B, Minimal heart rate. C, Average heart rate. Values are presented as mean ± SD $^{*}P < .05$ compared with baseline. HR, heart rate

TABLE 2 Effect of stellate ganglion block on treadmill exercise

SG block	Before SGB (n = 7)	After SGB (n = 7)	*P* Value
Right			
MET	7.7 ± 1.4	9.1 ± 1.9	.32
Resting			
HR, beats/min	107 ± 21.7	99 ± 18.5	.47
SBP, mm Hg	123 ± 14.1	128 ± 21.1	.48
DBP, mm Hg	77 ± 11.6	79 ± 14.4	.35
Peak exercise			
HR, beats/min	180 ± 17.39	170 ± 11.9	.34
SBP, mm Hg	159 ± 16.1	152 ± 14.8	.59
DSP, mm Hg	64 ± 9.3	65 ± 7.5	.18
Left			
MET	7.7 ± 1.4	8.8 ± 1.8	.41
Resting			
HR, beats/min	107 ± 21.7	98 ± 16.5	.50
SBP, mm Hg	123 ± 14.1	129 ± 22.1	.58
DBP, mm Hg	77 ± 11.6	77 ± 12.4	.33
Peak exercise			
HR, beats/min	180 ± 17.39	174 ± 11.6	.26
SBP, mm Hg	159 ± 16.1	162 ± 13.1	.79
DBP, mm Hg	64 ± 9.3	61 ± 6.5	.11

Note: Continuous data are expressed as mean (SD).
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; METs, metabolic equivalent tasks; SBP, systolic blood pressure; SG, stellate ganglion.

The underlying pathophysiology of IST may be associated with an increased sympathetic tone, β-receptor hypersensitivity, α-receptor hyposensitivity, and altered sympathovagal balance.[4,19-22] Baruscotti et a[23] reported that a gain-of-function mutation in the cardiac pacemaker HCN4 channel increasing cAMP sensitivity is associated with familial IST. Studies have shown that sympathetic stimulation and block affect the sinus rate significantly.[4,24,25] In a case report, renal sympathetic denervation reduced HR in a patient with drug-refractory IST.[26]

In view of the beneficial effects of sympatholysis for treating various conditions related to sympathetic hyperactivity and lack of effective medical therapy for IST, we proposed a clinical practice protocol and collected the data carefully. Our study clearly showed in the procedure room, an acute temporal effect of SG block on sinus rate reduction within 20 minutes after right SG block by 16 bpm, although the modest HR change after left SG block did not reach statistical significance. In the ambulatory group who had continuous HR monitoring, the modest HR slowing after the SG block lasted for 2 hours, and the HR gradually returned to baseline in 5 hours after either right or left SG block. This finding appeared to be different from other studies in which right SG manipulation had a greater effect on HR than left SG manipulation as SG block was done in patients with normal HR and was in two independent patient groups rather than sequential SG block in the same patient group.[27,28]

4.3 | Effect of SG block on exercise

Neither left nor right SG block significantly reduced exercise HR. Patients had a baseline HR slightly higher than 100 bpm, which increased to 180 at peak exercise and is age-appropriate for this group of patients. Possibly, the enhanced sympathetic drive during exercise cannot be blunted by blocking the sympathetic efferent output. Catecholamine release by the hormonal axis may affect HR and blood pressure modulation, aside from the sympathetic nerve axis, during intense physical activity.

4.4 | Effects of SG block on electrophysiology and hemodynamics

SG block had no significant effects on PR, QRS, or QT intervals. This finding suggests that the sympathetic block is not strongly associated with manipulation of the atrioventricular node, His-Purkinje conduction, myocardial depolarization, and repolarization. This finding is in keeping with the observation in our animal study.[26] In that study, QRS intervals were not significantly changed during SG stimulation or after SG removal, despite the fact that HR was significantly regulated by the same maneuver. Furthermore, the left or right SG block had no significant effect on systolic and diastolic pressures.

4.5 | Effects of permanent CSD

In our study, patients who were recommended to undergo SG block had medically refractory debilitating symptoms. These symptoms remarkably affected their lifestyle and quality of life. At the time of the study, ivabradine was not available in the US market. Therefore, for patients who had an acute effect of HR reduction by more than 15 bpm in response to SG block, permanent CSD was reviewed as a therapeutic option and accepted by five patients. The outcomes were heterogeneous. Three patients who had unilateral right SG block had symptomatic improvement to different extents, and two of them still required medical therapy. The other two patients with right or bilateral CSD had an initial response but had severe recurrent symptoms after a few months of denervation. Previous studies have indicated right-sided predominance for innervation of the autonomic nerve of the sinus node.[29-32] The inconsistent and lack of long-term denervating effect may be partly explained by the fact that the superior and middle cervical and thoracic sympathetic nerve bundles bypass the SG and innervate the heart. Central system and hormonal regulation may also be involved in the pathogenesis of IST. Hoover et al[33] reported that human intrinsic cardiac ganglia have a complex neural network containing both cholinergic and noradrenergic phenotypes. It is plausible that CSD with intention to diminish sympathetic output may also attenuate vagal counterpart. The sympathovagal imbalance in IST may not be simply corrected by CSD.[34] Furthermore, recurrent tachycardia after bilateral CSD could represent a compensatory response. The autonomic system could go through an "autonomic-remodeling," as occurs in patients with heart transplants in whom IST may develop.[35] Because of the inconsistent efficacy of CSD for IST in our small group of patients, this approach may be considered with individualization in patients with highly symptomatic, debilitating symptoms in whom other available therapies have failed. The pathophysiology of IST remains unclear

and possibly associates with a mix of multiple disease processes. Thus, progress on finding the right neuromodulatory therapy will depend on first clarifying the basic mechanisms.

4.6 | Limitations of study

This study has potential limitations. First, it included a relatively small number of patients. Yet, drug-refractory IST is not a very common disorder and enrolling a large sample size is difficult. Second, the side and sequence of the SG block were not randomized, which may impact the result interpretation. As the right SG block was performed first, the effect of the left SG block may have represented accumulated effects from both sides. Third, whether five patients who underwent CSD developed lack of sweating or the function of sweating recovered in those who had recurrent sinus tachycardia was not well documented.

5 | CONCLUSION

SG block has a modest effect on resting HR reduction but no significant effect on HR control during exercise or isoproterenol challenge. Permanent CSD resulted in at least partial symptom relief in more than half of patients, but most required continued medical management.

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