Autonomic Nervous System Indices in Patients with Systemic Sclerosis without Overt Cardiac Disease

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ABSTRAC. **Background:** Systemic sclerosis (SSc) is a connective tissue disease that may affect the heart and the autonomic nervous system (ANS). There is little knowledge regarding the degree of ANS involvement in SSc patients with unknown cardiac disease.
Objectives: To evaluate cardiac and pupillary autonomic functions in patients before cardiac involvement has emerged.
Methods: The study comprised 19 patients with SSc and 29 healthy controls. Heart rate variability (HRV) analysis for time and frequency domains, as well as deep breathing test and Ewing maneuvers, were performed in all patients. Automated pupillometry for the evaluation of pupillary diameter and pupillary light reflex was completed in 8 SSc patients and 21 controls.
Results: Both groups had similar characteristics, except for medications that were more commonly or solely prescribed for SSc patients. Compared with control subjects, the SSc patients had significantly lower HRV parameters of NN50 (15.8 ± 24.4 vs. 33.9 ± 33.1, $P = 0.03$), pNN50 (4.9 ± 7.4% vs.10.8 ± 10.8%, $P = 0.03$), and HRV triangular index (11.7 ± 3.4 vs. 15.7 ± 5.8, $P = 0.02$). Abnormal adaptive responses in heart rate changes were recorded during deep breathing tests and Ewing maneuvers. There was no significant difference in any of the pupillometric indices or other HRV parameters within groups.
Conclusions: SSc patients may manifest cardiac autonomic dysfunction, while their autonomic pupillary function is seemingly spared. The role of certain medications, the significance of differential organ involvement, as well as the prognostic value of our findings should be evaluated in future studies.

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Systemic sclerosis (SSc) is a connective tissue disease characterized by small vessel vasculopathy, autoantibody production, and excessive collagen deposition in the skin and internal organs. Nervous system dysfunction, mainly of the peripheral and autonomic divisions, is increasingly recognized in scleroderma [1], appearing early in the course of the disease and importantly, preceding the development of irreversible fibrosis [2,3].

According to a comprehensive, systematic review regarding neurologic involvement in scleroderma, the prevalence of autonomic nervous system (ANS) involvement ranged from 14.28% to 79% and affected either just the sympathetic and parasympathetic systems or both branches simultaneously [4]. Common clinical features of scleroderma such as esophageal dysmotility, gastrointestinal dysfunction [1,5], and Raynaud's phenomenon [6] are increasingly ascribed to ANS dysfunction.

Autonomic dysfunction of the cardiovascular system, presenting as disturbances in cardiac rhythm and rate, is well-documented among scleroderma patients. While these may frequently go unnoticed, they may be associated with increased risk for cardiovascular mortality, life-threatening arrhythmias and sudden cardiac death. Unfortunately, ANS dysfunction is more commonly found in patients with advanced scleroderma, while it may be latent in patients with early disease [7].

Heart rate variability (HRV) has been proposed as a simple, non-invasive tool for evaluating the autonomic control of the heart. It reflects in its entirety the integrity of the cardiac ANS. Impaired HRV may serve as a marker for poor prognosis in patients with congestive heart failure and diabetes mellitus, as well as in patients after myocardial infarction. Since low HRV is associated with an increased risk for arrhythmic complications, assessment of HRV among patients with SSc might aid in early detection of potential cardiac problems [8].

HRV has been assessed in patients with SSc [9-12] and demonstrated impairment of either one or both branches of the ANS [13]. Interestingly, one study reported a positive correlation between disease duration and digital ulcers with increased

root mean square of the successive RR differences (RMSSD), a marker for autonomic hyperactivity [6], whereas another study reported that HRV parameters are within normal limits in most SSc patients [14]. However, HRV analysis may be insufficient for the study of the complete ANS as it may not correlate with other measures of ANS, such as response to autonomic tests, pupillometric parameters, and sudomotor functions. There is also limited information as to the response of heart rate to deep breathing test (DBT) and to postural change (e.g. Ewing maneuver) [14].

Pupillary function is also dependent on the integrity of the ANS and was found to be impaired in some rheumatic diseases [15]. Studies addressing pupillary autonomic dysfunctions in scleroderma are scant and inconsistent regarding the mechanisms used to assess neurologic impairments [4]. Interestingly, several studies found both pupillary dysfunction and impaired HRV in the same individuals [16,17]. Yet, they were performed over 20 years ago and evaluated only a few pupillometric parameters with a fixed degree of illumination. We aimed to fill this gap by conducting advanced pupillometry and pupillary light reflex (PLR) measurements, as well as HRV, DBT, and Ewing maneuvers to comprehensively evaluate ANS function among patients with SSc. Specifically, the study focused on SSc patients who had not developed overt cardiac disease.

PATIENTS AND METHODS

STUDY DESIGN

A comparative case-control design was implemented. The research protocol was approved by the institutional review board. All participants gave written informed consent.

PARTICIPANTS

Nineteen patients with SSc were recruited from the rheumatology outpatient clinic. The diagnosis of SSc was based on the American College of Rheumatology/European League against Rheumatism criteria [18]. A control group was comprised of 29 healthy age- and sex-matched individuals. Volunteers were recruited from the hospital staff and their family members. Exclusion criteria included cardiac or ophthalmic disease, use of drugs known to affect pupil diameter, acute illness in the 2 weeks prior to the tests, and/or pregnancy. Cardiac disease was excluded based on absence of physical findings suggesting heart disease and normal transthoracic echocardiographic scan (in SSc patients) or by individual statements (control subjects). Pharmacologically balanced mild dyslipidemia and anti-depressant intake were not considered exclusion criteria.

ASSESSMENT OF HEART RATE VARIABILITY

The HRV test was conducted between 9:00 and 12:00 to avoid the circadian influence on heart rate and ANS function. Participants were asked not to smoke or drink caffeinated beverages and to avoid strenuous exercise for 24 hours before the test. Introduction of new medications or dose changes were not allowed in the 4 weeks prior to the assessments.

To prevent sympathetic over-activity, subjects were requested to empty their bladder and lie motionless for 10 minutes in a room where temperature was maintained at 21–23ºC. ECG electrodes were placed on the limbs, according to standard procedure, and recordings were made for 5 minutes at a sampling rate of 2000 Hz. Data were saved in binary format and processed using a commercial computer software (PC-ECG, HRV ver. 5.514, Norav Medical, Yokne'am, Israel), which was validated and tested for reproducibility according to accepted standards [19]. RR intervals were measured between two consecutive beats.

To quantify the HRV time domain, the following variables were calculated in the supine position: standard deviation of RR intervals (SDNN), reflecting the cyclic variability of the heart rate during the recording period; and RMSSD, reflecting the average change in RR intervals between beats; number of intervals differing by > 50 ms from the preceding interval NN50 as well as pNN50, which was calculated by dividing NN50 by the total number of RR intervals. HRV triangular index measurement is the integral of the density distribution, that is, the number of all RR intervals, divided by the height of the density distribution. Power spectral analysis using the nonparametric fast Fourier transform was performed and integral calculations of the area beneath the power spectral density curve for frequency range were made in absolute values of power (ms^2). The spectral components were divided into very low frequency (VLF, 0.0033–0.04 Hz) low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz) components.

PUPILLOMETRY

The right horizontal pupil diameter was measured using a NeurOptics PLR-200 pupillometer (Irvine, CA, USA) and then videographed using the infrared function after 5 minutes dark adaptation at < 0.3 lux ambient illumination, according to standard protocol [20]. To avoid pupil meiosis by accommodation, patients were asked to fix their gaze on a target at least 3 meters away, with the opposite eye. Stimuli consisted of pulses of light at an intensity of 1 microwatt/cm^2 and 180 microwatts/cm^2. Flash duration was 180 milliseconds for all measurements. Visual light stimuli were generated from white light emitting diodes. Pupil size measurements were sampled at a frequency of 32-frames/s and for up to 5s following pupillary illumination; thus, allowing full or partial recovery of the pupil size after light constriction. PLR of the eye was measured twice, at an interval of 30 seconds and averaged data were used. The following parameters were computed: maximum pupillary diameter (PDmax), the percentage of pupillary constriction compared with maximum diameter (CON), average constriction velocity (ACV), maximum constriction velocity (MCV), and average

dilatation velocity (ADV). Measurements were repeated if a participant blinked during the study. Data of participants who failed to complete the study without blinking or gazing forward were excluded.

DEEP BREATHING TEST

The subjects were asked to remain supine and to breathe deeply in and out 6 times. Maximum heart rate during expiration (E) and minimum HR during inspiration (I) were measured, and the difference between the two calculated (maximum HR – minimum HR= ΔE-I). The standard deviation of the RR interval and RMSSD were computed for the DB period. The E/I ratio was calculated by dividing the longest RR interval during expiration by the shortest RR interval during inspiration. Values higher than 1.2 in young individuals are considered within the normal range [21].

EWING MANEUVER

Participants were requested to move from supine position directly to upright standing position. The sudden active standing causes a decrease in blood pressure and elevation in heart rate after approximately 15 seconds. After 30 seconds, blood pressure and heart rate usually normalize. The ratio between the highest RR interval length after 30 seconds and the lowest RR interval length after 15 seconds is referred to as the 30/15 ratio and reflects the orthostatic cardiac response. Values above 1.04 are usually considered normal [21].

STATISTICAL ANALYSIS

Data were analyzed using JMP version 15.0 (SAS Institute, Cary, NC, USA). Results are presented as mean and standard deviation. Abnormal results were defined as more than 2 standard deviations from the normal range. Findings were compared between the groups with the Kruskal-Wallis one-way analysis test and the Fisher's Exact Test. $P < 0.05$ was considered statistically significant. The power of the sample was calculated with the online ClinCalc tool (https://clincalc.com/stats/power.aspx), assuming that autonomic abnormalities were found in at least 50% of SSc patients (as reported by some studies [4]) and in none of the control group. A type I/II error rate alpha of 0.05 was allowed and a study power > 80% was considered methodologically acceptable. The association between modified Rodnan skin score (mRSS) and autonomic indices was evaluated with Pearson's correlation test.

RESULTS

Nineteen SSc patients and 29 healthy controls were included in the study. The mean time from diagnosis was 9.1 ± 9.2 years. One patient was diagnosed with limited cutaneous SSc and 18 had diffuse scleroderma. The main demographic and clinical parameters of both groups are shown in Table 1. There was no significant difference between the groups in age, sex, body mass index (BMI), smoking status, and prevalence of diabetes mellitus, family history of ischemic heart disease, hypertension, or dyslipidemia. Treatment with angiotensin-converting-enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and immunosuppressive therapy was prescribed exclusively to scleroderma patients. None of the patients was prescribed with cyclophosphamide. Among the SSc patients, 73.7% had gastrointestinal involvement, and 68.4% had pulmonary involvement. Renal involvement was recognized in 10.5% of patients, and the mean mRSS was 19.6 ± 14.9.

Table 1. Baseline characteristics of the study groups

Variable	SSc (n=19)	Controls (n=29)	*P* value
Age (years)	44.5 ± 11.7	38.8 ± 12.9	NS
Sex (Female / Male)	17 / 2	22 / 7	NS
BMI (kg/m2)	22.3 ± 5.0	22.7 ± 2.2	NS
Active smoker (%)	26.3	17.2	NS
Former smokers (%)	10.5	6.9	NS
Family history of IHD (%)	63.1	48.3	NS
Diabetes mellitus (%)	5.3	0	NS
Hypertension (%)	5.3	0	NS
Dyslipidemia (%)	15.8	6.9	NS
Hypothyroidism (%)	5.3	0	NS
Aspirin intake (%)	5.3	0	NS
Plavix intake (%)	10.5	0	NS
ACEI or ARBs intake (%)	31.6	0	< 0.01
CCBs intake (%)	26.3	0	< 0.01
BB intake (%)	10.5	0	NS
Statins intake (%)	10.5	3.5	NS
Fibrates intake (%)	0	0	NS
Insulin intake (%)	5.3	0	NS
Other anti-diabetic drugs (%)	5.3	0	NS
Anti-depressants intake (%)	10.5	3.5	NS
Levothyroxine intake (%)	5.3	0	NS
Immunosuppressive therapy (%)	36.8	0	< 0.01
Prostacyclin therapy (%)	10.5	0	NS

ACEI = angiotensin-converting-enzyme inhibitors, ARBs = angiotensin II receptor blockers, BB = beta blockers, BMI = body mass index, CCBs = calcium channel blockers, IHD = ischemic heart disease, NS = non-significant, SSc = systemic sclerosis

All SSc patients and controls completed the HRV study. Results of the HRV analysis are shown in Table 2. Compared with controls, the SSc patients showed significantly lower values of NN50 (15.8 ± 24.4 vs. 33.9 ± 33.1, $P = 0.03$) and pNN50 (4.9 ± 7.4% vs. 10.8 ± 10.8%, $P = 0.03$). Also, HRV triangular index values were significantly lower in SSc compared with controls (11.7 ± 3.4 vs. 15.7 ± 5.8, $P < 0.01$). No significant difference was

Table 2. HRV results in SSc patients and in controls

Variable	SSc (n=19)	Controls (n=29)	*P* value
Maximum RR (ms)	1141.2 ± 315.1	1084.0 ± 179.3	NS
Minimum RR (ms)	686.8 ± 171.3	740.6 ± 138.6	NS
Average RR (ms)	853.4 ± 120.6	907.3 ± 137.9	NS
SDNN (ms)	42.9 ± 15.6	52.0 ± 21.0	NS
RMSSD (ms)	42.5 ± 22.7	45.5 ± 26.2	NS
HRV triangular index	11.7 ± 3.4	15.7 ± 5.8	< 0.01
NN50	15.8 ± 24.4	33.9 ± 33.1	0.03
pNN50	4.9 ± 7.4	10.8 ± 10.8	0.03
VLF (ms^2)	172.8 ± 76.4	194.0 ± 105.0	NS
LF (ms^2)	166.8 ± 95.4	147.9 ± 58.1	NS
HF (ms^2)	176.6 ± 65.3	160.2 ± 95.5	NS
Total power (ms^2)	538.6 ± 111.9	559.4 ± 107.5	NS
LF/HF ratio	1.21 ± 1.45	1.37 ± 1.04	NS

HRV = heart rate variability, HF = high frequency, LF = low frequency, NS = non-significant, NN50 = number of NN intervals differing by > 50 ms from the preceding interval, pNN50 = NN50 divided by the total number of RR intervals, RMSSD = square root of the mean squared differences of successive RR intervals, SDNN = standard deviation of the RR interval, SSc = systemic sclerosis, VLF = very low frequency

Table 3. Pupillometry results in SSc patients and in controls*

	Variable	SSc (n=8)	Controls (n=21)	*P* value
A	PDmax (mm)	6.2 ± 0.7	6.7 ± 1.0	NS
	CON (%)	20.5 ± 2.7	17.3 ± 7.4	NS
	ACV (mm/s)	2.9 ± 0.4	2.6 ± 0.8	NS
	MCV (mm/s)	3.8 ± 0.6	3.6 ± 0.9	NS
	ADV (mm/s)	0.64 ± 0.13	0.70 ± 0.16	NS
B	PDmax (mm)	5.8 ± 0.6	6.6 ± 1.0	NS
	CON (%)	32.3 ± 6.4	26.7 ± 10.1	NS
	ACV (mm/s)	3.3 ± 0.6	3.1 ± 0.5	NS
	MCV (mm/s)	4.8 ± 0.8	4.3 ± 0.7	NS
	ADV (mm/s)	0.52 ± 0.27	0.71 ± 0.27	NS

*Stimuli consisted of pulses of light at an intensity of 1 microwatt/cm^2 (A) and 180 microwatts/cm^2 (B)

ACV = average constriction velocity, ADV = average dilatation velocity, CON = the percentage of pupillary constriction (compared with maximal diameter), MCV = maximal constriction velocity, NS = non-significant, PDmax = maximal pupillary diameter, SSc = systemic sclerosis

noted in any of the frequency domains between the two groups.

Pupillometry was successfully assessed in 8 SSc patients and 21 controls (calculated study power of 89.3% according to a post hoc analysis). Some pupillometry measurements were excluded due to inability to complete the pupillometry test without blinking. A separate analysis of the demographic parameters and medication intake in patients who successfully completed the pupillometry test was similar to the proportions presented in Table 1, suggesting that the cohort evaluated is a representative sample of the entire SSc group. Accordingly, the rates of ACEI or ARBs, CCBs, and immunosuppressive therapy were higher in the SSc patients who completed the pupillometry test. The results of the pupillometry analysis are shown in Table 3. The pupillometry indices in the control and the SSc groups were statistically similar.

The DBT and the Ewing maneuver results are summarized in Table 4. DBT was performed in all patients. Ewing test results from three patients from each group were excluded from analysis due to technical difficulties. Following the DBT, SSc patients had lower SDNN values than controls did (74.5 ± 34.6 ms vs. 102.9 ± 43.4 ms, $P = 0.02$). Also, ΔE-I results were lower for the SSc group compared to the control group (26.7 ± 12.4 beats per minute [bpm] vs. 33.4 ± 11.7 bpm, $P = 0.04$). Despite similar minimum RR values recorded after 15 seconds of active standing, SSc patients had lower maximum RR after 30 s of standing (804.2 ± 140.8 ms vs. 904.2 ± 137.5 ms, $P = 0.03$). Accordingly, SSc patients had lower 30/15 ratio compared with controls (1.22 ± 0.18 vs. 1.49 ± 0.26, $P < 0.01$). No significant correlation was found between mRSS and any of the indices found to be abnormal in patients with SSc.

DISCUSSION

We evaluated ANS in SSc patients without overt cardiac disease by using HRV. As HRV is an insufficient marker of the whole spectrum of ANS dysfunction, ancillary autonomic tests have been proposed. We used HRV in conjunction with testing the heart rate response to several autonomic maneuvers, and pupillometry test, and showed that cardiac autonomic imbalance is prevalent in this subset of SSc patients. Specifically, we found several indications of reduced parasympathetic modulation of cardiac activity at rest, including significantly decreased values of HRV triangular index, NN50 and pNN50, as compared to controls. Also, we found blunted autonomic response to deep breathing and assuming an upright position, manifested as lower values of SDNN, ΔE-I, and lower 30/15 ratio. Frequency domain variables representing disturbed sympathetic activity, such as decreased VLF and LF or increased LF/HF ratio [19] were comparable among the SSc and control groups. We also found that ANS impairment in SSc patients preceding the development of overt cardiac manifestations might be organ specific. While some cardiac HRV parameters were abnormally low, the pupillary autonomic control was seemingly unaffected. Decreased HRV and heart rate response to autonomic maneuvers may reflect sinus node autonomic denervation, sympathetic overactivity [1], and/or reduced cardiac conduction system re-

Table 4. Test results in SSc patients and in controls

Variable	SSc (n=19)	Controls (n=29)	*P* value
Deep breathing			
Maximal RR (ms)	1017.2 ± 156.8	1088.2 ± 198.5	NS
Minimal RR (ms)	698.5 ± 87.8	679.3 ± 115.9	NS
SDNN (ms)	74.5 ± 34.6	102.9 ± 43.4	0.02
ΔE–I (bpm)	26.7 ± 12.4	33.4 ± 11.7	0.04
E/I ratio	1.47 ± 0.30	1.62 ± 0.28	NS
RMSSD (ms)	52.0 ± 30.7	71.8 ± 41.8	NS
VLF (ms^2)	111.1 ± 78.6	77.4 ± 64.3	NS
LF (ms^2)	386.9 ± 80.7	426.0 ± 93.2	NS
HF (ms^2)	90.4 ± 46.1	83.2 ± 35.4	NS
Total power (ms^2)	596.5 ± 68.1	593.5 ± 87.3	NS
Ewing maneuver			
Minimum RR after 15s (ms)	665.4 ± 119.1	617.3 ± 112.2	NS
Maximum RR after 30s (ms)	804.2 ± 140.8	904.2 ± 137.5	0.03
30/15 ratio	1.22 ± 0.18	1.49 ± 0.26	< 0.01

bpm = beats per minutes, E = maximal expiratory heart rate, I = minimal inspiratory heart rate, HF = high frequency, LF = low frequency, RMSSD = square root of the mean squared differences of successive RR intervals, SDNN = standard deviation of the RR interval, SSc = systemic sclerosis, VLF = very low frequency

sponsiveness to autonomic modulation. Regardless of the cause, abnormal HRV was found to be associated with reduced survival in several patient populations [19].

Other than three studies that found HRV parameters in SSc patients to be normal [14,22] or increased [6], most researchers agree with our results [8-12], confirming ANS imbalance. Our results differ from those of Bajocchi et al. [14], who reported that DBT results were within normal limits in most SSc patients. The discrepancy between the various studies could be attributed to different measurement methodologies, sample size or cohort characteristics. Supporting decreased HRV in SSc is the finding that HRV decline is associated with cardiac remodeling [9-11], esophageal dysmotility [17], extensive skin fibrosis, and anti-SCL70 antibody [8].

Medications may also affect the ANS and HRV indices. ACEI or ARBs were suggested to decrease sympathetic activity in hypertensive patients and enhance parasympathetic activity, although this effect is debatable [23]. Our finding of decreased HRV triangular index, NN50, and pNN50 despite possible anti-sympathetic activity caused by ACEI or ARBs further substantiates our results that cardiac autonomic control is abnormal in SSc. However, CCB were reported to increase or decrease sympathetic drive [24], further complicating interpretation of the current results. Among the antidepressants, the tricyclic antidepressants are associated with reduction in HRV, leading to lower SDNN and frequency domain, while the selective serotonin reuptake inhibitors give mixed results and are generally considered as having a weaker effect on HRV compared to tricyclic antidepressants [25]. Thus, in SSc patients, cardiac autonomic dysfunction might be driven by scleroderma factors as well as by drugs administered for co-morbidities.

Pupil reactivity to light of SSc patients was comparable to that of the control group. This finding is supported by the autonomic dysfunction COMPASS-31 questionnaire, which found similar pupillomotor function scores in SSc (1.6 ± 1.1) and in healthy controls (1.2 ± 0.8) [5]. In addition, no relationship was found between gastrointestinal autonomic symptoms and pupillomotor function [5], suggesting that the ANS is affected differentially in various organs of SSc patients. Our finding of intact pupillary autonomic function in patients with no overt cardiac manifestations does not exclude a possible occurrence of pupillary autonomic dysfunction at a more advanced stage of the disease.

Several small pupillometry studies found PLR alterations among SSc patients. Using automatic pupillometry studies, Straub et al. found that both pupillary response latency (reflecting parasympathetic control) and maximum pupillary area (under sympathetic control) were impaired in SSc patients, suggesting impairment of both divisions of the ANS [16]. In comparison, Bertinotti et al. [15] found decreased baseline pupillary diameter (comparable to PD max) and miosis response to substance P (a member of the tachykinin neuropeptide family, directly acting on the iris sphincter) in SSc patients, strengthening the suggestion that both sympathetic and parasympathetic pupil control are disturbed in SSc. Although our study used a fully automated pupillometer and more sensitive indices of pupillary dysfunction, we were unable to detect pupillary autonomic impairment. This difference may stem from different patient characteristics, better pharmacotherapies currently available, and from the use of different methodology for pupillometric evaluation. A larger scale study in patients without overt cardiac involvement and with long-term follow-up is needed to validate our findings and their role in predicting unwanted cardiac events.

LIMITATIONS

Our observation of cardiac autonomic dysfunction in SSc patients without overt cardiac involvement, utilizing HRV and pupillary parameters should be cautiously interpreted considering the small number of patients in the study (due to low prevalence of SSc and poor patient corporation), the heterogeneity of the patient population, and possible effects of the medications used.

CONCLUSIONS

Despite frequent use of ACEI and ARBs by patients with SSc, which may increase parasympathetic tone, some HRV parameters and indices reflective of heart rate response to autonomic maneuvers, were found to be relatively decreased in SSc, imply-

ing ANS impairment in SSc even before overt cardiac involvement is diagnosed. In contrast to the abnormal cardiac autonomic responses found in this population, pupillary autonomic function seemed to be spared. The prognostic implications of our results and the ANS involvement in pupillary function in more advanced SSc and the effect of drugs on our findings should be determined in future studies.

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Capsule

Emergence and expansion of SARS-CoV-2 B.1.526 after identification in New York

Annavajhala et al. reported the emergence of the variant lineage B.1.526 (also known as the Iota variant), which contains E484K, and its rise to dominance in New York City in early 2021. This variant is partially or completely resistant to two therapeutic monoclonal antibodies that are in clinical use and is less susceptible to neutralization by plasma from individuals who had recovered from SARS-CoV-2 infection or serum from vaccinated individuals, posing a modest antigenic challenge. The presence of the B.1.526 lineage has now been reported in all 50 states in the United States and in many other countries. B.1.526 rapidly replaced earlier lineages in New York, with an estimated transmission advantage of 35%. These transmission dynamics, together with the relative antibody resistance of its E484K sub-lineage, are likely to have contributed to the sharp rise and rapid spread of B.1.526. Although SARS-CoV-2 B.1.526 initially outpaced B.1.1.7 in the region, its growth subsequently slowed concurrently with the rise of B.1.1.7 and ensuing variants.

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