

SYMPATHETIC SKIN RESPONSE AND GALVANIC SKIN RESISTANCE IN MALES WITH TYPE 2 DIABETES MELLITUS

Saravanan Mohanraj¹, Krishnamurthy Narayanan²

¹Assistant Professor, Department of Physiology, Velammal Medical College Hospital & Research Institute, Madurai.

²Professor (Retired), Department of Physiology, Pondicherry Institute of Medical Sciences, Puducherry.

ABSTRACT

BACKGROUND

Diabetes mellitus, a metabolic disorder affects the nervous system due to alteration in various metabolic pathways. As neuropathy manifests in longstanding diabetes mellitus, autonomic nervous system also gets affected. The study was started based on the hypothesis that the sweat glands innervated by autonomic nervous system will be affected in patients with type 2 diabetes mellitus patients with clinical features of neuropathy. This study was undertaken to compare the sympathetic skin response (SSR) and galvanic skin resistance (GSR) in males with type 2 diabetes mellitus and in controls.

METHODS

Thirty males in the age group of 45-55 years, known to have diabetes mellitus and having a history of neuropathic symptoms served as subjects and thirty males in the same age group with no history of diabetes mellitus and neuropathy served as controls. SSR and GSR were recorded using Recorders and Medicare Systems 4 channel polygraph in the noise and light reduced research laboratory, Department of Physiology. All the recordings were done between 10-12 noon at ambient temperature. SSR was measured by deep inspiration and the GSR was measured in the supine and standing response. Comparison of latency and amplitude of the sympathetic skin response and the percentage of decrease in galvanic skin resistance was done.

RESULT

A statistically significant delay in the latency and a reduction in the amplitude of sympathetic skin response was observed in the diabetes patients. There was a lesser percentage of decrease in GSR in the diabetic patients.

CONCLUSION

This study shows that the SSR and GSR responses are significantly reduced in diabetic individuals and can be used as a diagnostic tool in the detection of diabetic autonomic neuropathy.

KEYWORDS

Diabetic Autonomic Neuropathy, Diabetes Mellitus, Electrodermal Responses, Galvanic Skin Resistance, Sympathetic Skin Response, Skin Conductance Response.

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INTRODUCTION: Diabetes mellitus being the most common human metabolic disease affecting millions of people worldwide has great importance in early diagnosis and preventing complications. Neuropathy is a frequent complication in diabetes mellitus. Abnormality of autonomic nervous system is frequently associated with the peripheral neuropathy seen in diabetes mellitus. Symptoms of diabetic autonomic neuropathy are vague and difficult to detect with routine physical examination.¹ The autonomic control of various organ systems has opened up a whole new area of research interest with many complex interrelationships which still need to be unravelled.² Sudomotor activity refers

to the response of sweat glands to stimulation and it is a function of the autonomic nervous system.

Sudomotor dysfunction is occasionally the sole or earliest clinical feature in diabetic neuropathy.^{3,4}

Sympathetic skin response (SSR) is a change in potential recorded from the surface of the skin and represents sudomotor activity. In literature, SSR is described by several terms such as electrodermal activity, electrodermal response, psychogalvanic reflex, peripheral autonomic surface potential, endosomatic skin response. However, the most frequently used term is sympathetic skin response.⁵

The galvanic skin resistance (GSR) refers to the resistance of the skin to a very small galvanic current (5 μ A) and is caused by the activity of the sweat glands. The early detection and analysis of SSR and GSR may help to understand the impairment of the autonomic nervous system in diabetes. SSR can help to detect subclinical affection of the ANS before the appearance of symptoms or signs of neuropathy.⁶

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Corresponding Author:

Dr. Saravanan Mohanraj,

100, South Street, Aruppukottai-626101, Tamilnadu.

E-mail: saravanan_apk@rediffmail.com

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GSR which is a consequence of SSR also helps to assess the ANS dysfunction and facilitates the diagnosis of diabetic autonomic neuropathy. Jerrold S Petrofsky and Katie McLellan concluded that galvanic skin resistance at any environmental temperature may be a good means of assessing vascular damage and impaired sweat response in people with diabetes.⁷

The present study is being undertaken as the review of literature shows conflicting results regarding the concordance between SSR - GSR and sudomotor function in diabetes mellitus.

AIMS AND OBJECTIVES: Aim of the study is to assess the functional status of the sweat glands in type 2 diabetes mellitus. This is accomplished by;

1. Recording sympathetic skin response and galvanic skin resistance in males with type 2 diabetes mellitus.
2. Recording SSR and GSR in age and sex matched controls.
3. Comparing the results obtained from type 2 diabetes mellitus patients with the results from control subjects and seeking for statistical significance.

MATERIALS AND METHODS: The study was conducted in the research laboratory, Department of Physiology. Ethical clearance was obtained from the Institutional Ethics Committee. The participants were informed about the study and written consent was obtained from them before including them in the study.

Inclusion Criteria:

Cases: Type 2 diabetes mellitus male patients from the outpatient department and patient volunteers in the age group 45-55 with clinical features of peripheral neuropathy.

Control: Normal age and sex matched controls from volunteers and attendants of patients.

Exclusion Criteria: Alcoholics, smokers, patients consuming drugs acting on autonomic nervous system, patients with any dermatological disease affecting the recording procedure.

Plan of the Study: 60 male subjects were recruited for the study. All the subjects were either diabetic patients or attendants of the patients or volunteers. Among the sixty, thirty were apparently healthy men in the age group 45-55 with no clinical evidence of diabetes or neurological symptoms and the other thirty were known diabetics with neurological symptoms like numbness or tingling sensation of the digits and receiving treatment.

Preparation: The subjects reported to the Physiology Research Laboratory at 10 a.m. in the morning after a light breakfast. Prior to the study, no special instructions were given to them to change their life style, diet or drug therapy. On arrival in the laboratory, the entire experimental procedure was explained to them in the language that they

could understand and a written informed consent was taken from them.

A detailed clinical history of the subject was taken. Relevant past history, family history, personal habits like smoking, alcoholism, duration of diabetes, duration of neuropathic symptoms, details about medication, demographic details and basal vital parameters were noted. Random blood glucose (RBS) in mg/dL was estimated for all the subjects just prior to the procedure using a glucometer device (ACCU-CHEK Active, ROCHE, Germany).

The skin temperature was recorded in the non-dominant hand using a digital thermometer (range -50 to +150°C and accuracy to one decimal) placed over a non-moist area of the skin of the forearm. Right hand was dominant while the left hand was non-dominant in all the recruited subjects. The subject was asked to remove all metallic objects like watch, ornaments and cell phone from his body. The non-dominant hand was placed close to the chest and fixed in a position of adduction at the shoulder and flexion at the elbow using a sling. The sling was applied in such a way that the digits of the non-dominant hand were well exposed for easy attachment of the electrodes. The sling helped to maintain the hand in a constant position with respect to heart level both in supine and during standing posture.

The subject was made to rest for 15 minutes on the couch in supine position to adapt to the environment. The ambience of the environment and illumination were maintained during the recording of both SSR and GSR.

Measurement of SSR: A 4-channel polygraph Polyrite (Recorders and Medicare Systems, Ambala, India) was used to record SSR and GSR. Among the four channels, two AC preamplifiers were used to record SSR and Electromyogram (EMG). For SSR recording, the low frequency filter setting was 0.3 Hz while the high frequency filter was 35 Hz. The sensitivity of the graph was set to 0.5/1/2 mV depending upon the individual response. The recording was calibrated before the start of the procedure. For EMG recording, the low frequency filter was 1 Hz and high frequency filter was 75 Hz with sensitivity of 2 mV.

The recording electrodes used for the study were the Ag-AgCl surface disc electrodes of 1 cm diameter. The active surface electrode was firmly fixed to the palmar area of non-dominant hand using RMS recording paste. The reference surface electrode was firmly fixed to the dorsal aspect. Micropore plaster was used to firmly fix the electrodes and prevent it from slipping during the recording procedure. The ground electrode was firmly fixed to the pulp of the thumb. For recording the EMG, two surface electrodes were fixed in the similar manner to the nares of either side.

SSR Recording: The subject was allowed 15 minutes of rest in the supine position after the placement of the electrodes. SSR was recorded in the supine position after a deep inspiration using a sweep speed of 10 mm/sec. The sweep speed was given by a time tracing at the bottom of the recording. Since the SSR was subject to habituation, if

the record was not proper, adequate time was given before a second recording of the SSR.

The latency of the SSR was calculated by the time lag in seconds between the onset of EMG of nares (recorded in 3rd channel) and the onset of the SSR waveform (recorded in 1st channel).

The amplitude of the SSR was given by the peak to peak distance between the positive and negative waves of the SSR.

Recording of GSR: The DC amplifier was used for recording the GSR. The GSR recording was done using a high frequency filter setting of 35 Hz. The balance voltage was adjusted to 0/10/20 mV and sensitivity of the graph was set at 2 mV or 5 mV depending upon the individual response. The two electrodes were firmly fixed to the volar aspects of the index finger and middle finger.

After 15 minutes of rest in the supine position, the basal GSR was recorded using the DC amplifier of the polygraph. The calibration of the GSR amplifier was done first. Once the GSR showed a steady trace, the subject was asked to stand using his dominant hand for support. To ensure insulation, the subject was made to stand a rubber matt. During this act of standing, the change in GSR was recorded at the sweep speed set at 1 mm/sec. The sweep speed was confirmed by the time trace at the bottom of the recording. From the tracing, GSR in supine position and GSR in standing position were calculated.

RESULTS: Parametric tests were used when the data obtained was normally distributed. When the data was not uniformly distributed, non-parametric tests were used. Student's unpaired t test was used to compare the means of SSR latency, and Mann-Whitney U test was used to compare the means of SSR amplitude and the GSR percentage decrease of the diabetic and control groups. $P < 0.05$ was taken as significant. Pearson's correlation test was applied to correlate the duration of diabetes, duration of neuropathic symptoms and the RBS values to the SSR latency, SSR amplitude and percentage decrease of GSR.

The demographic details like age, height, weight, BMI of the controls and diabetic subjects were subjected to Student's unpaired t test in order to validate the comparison between the groups.

Analysis of the demographic details with Student's t test showed no significant difference between the age, height, weight and BMI of control group and that of the diabetic group ($p > 0.05$). Since no demographic differences existed between the diabetic and control groups, they were found suitable for this comparative study.

In the control group, mean age was 48.73 years and ranged between 45-55 years. Height of the control groups in the study had a range of 153-178 cm with a mean of 166.47 cm. Weight of the control group in the study had a range of 50-90 kg with a mean of 69.77 kg. Body mass index of the control group in the study had a range of 18.4-32.4 with a mean of 25.17.

In the diabetic group, mean age was 50 years and ranged between 45-55 years. Height of the diabetic group in the study had a range of 155-175 cm with a mean of 165.97 cm. Weight of the diabetic group in the study had a range of 42-84 kg with a mean of 67.70 kg. Body mass index of the diabetic group in the study had a range of 17.0-29.7 with a mean of 24.52. Duration of diabetes in the diabetic group ranged from 1-12 years with a mean of 6.6 years.

The skin temperature plays a major role in the function of sweat glands which forms the underlying mechanism for the generation of the SSR and GSR, So comparison between the skin temperatures were done between the control and diabetic groups. Skin temperature of the control group ranged between 33-37°C with a mean of 35.3°C. Skin temperature of the diabetic group ranged between 33.2-37.1°C with a mean of 35.2°C. Both the set of data were subjected to Student's unpaired t test. The p value was 0.85 ($p > 0.05$) indicating there was no statistical difference between the skin temperature recordings of the control and diabetic groups implying the sweat gland activity was comparable in these two groups.

RBS of the control group ranged between 89-149 mg/dL with a mean of 120.90 mg/dL. RBS of the diabetic group ranged between 105-268 mg/dL with a mean of 207.77 mg/dL. Even though the diabetic subjects were on treatment, most of them had elevated blood glucose levels which could be the reason for the neuropathic symptoms in the diabetics. Comparison of random blood sugar levels between the two groups by Student's unpaired t test was statistically significant ($p < 0.0001$).

SSR latency of the control group ranged between 0.5-2 seconds with a mean of 1.25 seconds. SSR latency of the diabetic group ranged between 1-2.8 seconds with a mean of 1.81 seconds. The SSR latency in diabetic group was consistently prolonged than in the control group. Comparison of SSR latencies of control and diabetic groups by Student's unpaired t test, gave a highly significant p value ($p < 0.0001$).

SSR amplitude of the control group ranged between 1.2-5.6 mV with a mean of 3.04 mV. SSR amplitude of the diabetic group ranged between 0.3-4.6 mV with a mean of 1.29 mV. The peak to peak SSR amplitude was markedly lesser in the diabetic group as compared to the control group. As the results were not normally distributed, non-parametric test was performed. By Mann-Whitney U test, this decrease in amplitude in the diabetic group was highly significant as compared to the control group ($p < 0.0001$).

GSR in the supine posture in control group ranged between 64-280 kΩ with a mean of 113.9 kΩ. GSR in the supine posture in diabetic group ranged between 76-570 kΩ with a mean of 230.2 kΩ. As the results were not normally distributed, non-parametric test was performed. By Mann-Whitney U test, the difference between the mean GSR in the control and diabetic group in supine posture was highly significant ($p < 0.0001$).

GSR in the standing posture in control group ranged between 38-185 kΩ with a mean of 70.4 kΩ. GSR in the standing posture in diabetic group ranged between 32-510 kΩ with a mean of 201.2 kΩ. As the results were not

normally distributed, non-parametric test was performed. By Mann-Whitney U test, the difference between the mean GSR in the control and diabetic group in the standing posture was highly significant ($p < 0.0001$).

The percentage decrease in GSR in the control group ranged between 10.42-66.1% with a mean of 39.1%. The percentage decrease in GSR in the diabetic group ranged between 2.50-65.22% with a mean of 14.3%. The GSR values in the supine and the standing posture in diabetics was higher than in the control group, which implies that there is greater skin resistance in the diabetics. As the results were not normally distributed, non-parametric test was performed. By Mann-Whitney U test, the percentage of fall in GSR as a response to standing was found to be significantly less in diabetics ($p < 0.0001$).

The correlation between the SSR latency with the duration of diabetes by the Pearson's correlation test gave an r value of 0.24 ($p > 0.1$). The correlation between the SSR amplitude with the duration of diabetes by the Pearson's correlation test gave an r value of -0.11 ($p > 0.1$). Both the correlation analysis showed that the duration of diabetes does not correlate with the prolongation in latency or with decrement in amplitude of the SSR. On the other hand, Pearson's correlation test applied to the decrement in percentage of GSR gave an r value of -0.39 ($p < 0.05$). This implies that greater the duration of diabetes lesser is the decrease in GSR percentage (Negative correlation).

Pearson's correlation test also showed that SSR latency, SSR amplitude and percentage decrease in GSR did not show any significant correlation with either duration of neuropathic symptoms or with random blood glucose levels.

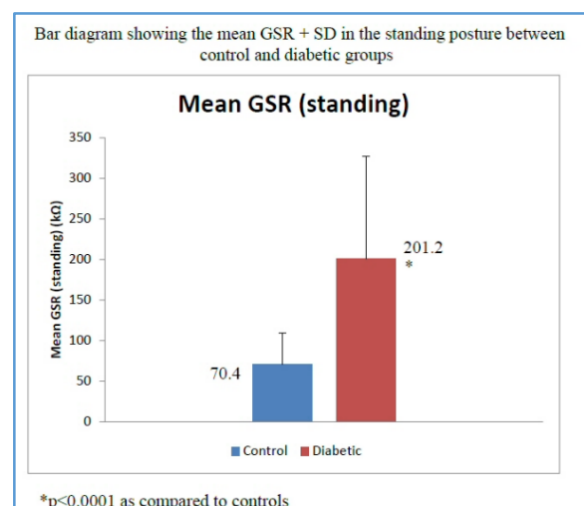
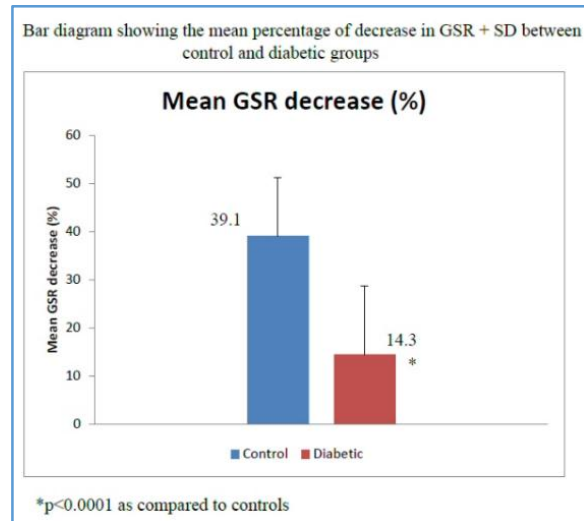
DISCUSSION: Autonomic neuropathy which can affect several organ systems is one of the disturbing and serious problems seen in diabetic neuropathy. The early symptoms and signs are minor and are often difficult to detect upon clinical examination. So a simple and non-invasive method for evaluation of autonomic functions is very essential for screening, diagnosis, evaluation and prognostic assessment of autonomic function in diabetes.

SSR being simple, non-invasive and easily performable. SSR was thought to be abnormal only if it is absent under 70 years of age.⁸ However, many studies had found the association between the variation in SSR latency and amplitude in patients with diabetic neuropathy. Our study was similar to that of others where SSR was recorded in all control groups.^{4,9-14} Niakan and Harati declared SSR to be absent in 83% of diabetic patients with neuropathy.¹⁵ Takebayashi and his colleges reported significant lowering in the SSR amplitude.¹⁶ Ayhan et al observed that SSR was absent in 14.6% of his diabetic study population.¹⁷ Our finding that SSR was present in all the subjects could be due to the fact that SSR was recorded only in the upper limb. Absent SSR is encountered in lower limb only very often. As the study was done in an ambient temperature, the response was easily picked up from all the study subjects.

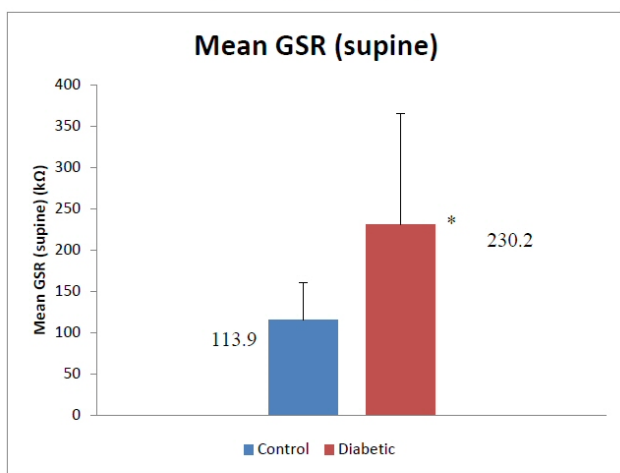
In the present study, the diabetic subjects showed a statistically significant prolongation of SSR latency. Amplitude of SSR showed a statistically significant decrease than the control group. Feriha et al found SSR tests in the

upper limbs of 22.5% of patients with more than 15 years of diabetes were pathological as compared to control group ($p < 0.02$).¹⁸ In our study, abnormal SSR was found with even lesser years of duration of diabetes. The reason being that most of the time diagnosis of diabetes is incidental finding. The actual period of diabetes would have been many years before the diagnosis and it is the neuropathic symptom that brought the disease to notification.

GSR which is a simple, non-invasive easy technique of sudomotor function on the basis of electrodermal skin resistance, not much work had been done on this. Literature showed paucity in the available studies with skin resistance. As early as 1950, Van Der Valk and Groen while working on GSR during emotional stress found the skin resistance levels of diabetic people were almost twice that of normal subjects.¹⁹ In GSR, we could find a decrease in fall of skin resistance. Autonomic neuropathy affecting the number of active sweat glands raised the basal skin resistance and decreased the fall in resistance associated with standing. Literature search did not reveal any reference describing the effect of posture on GSR.²⁰ This study shows the change in posture from supine to standing influences the value of GSR and the change can be utilised as a marker for decreased sweat response associated with diabetic autonomic neuropathy.

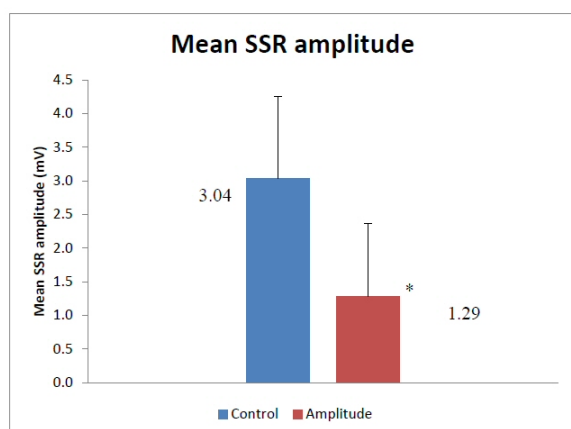


Bar diagram showing the mean GSR + SD in the supine posture between control and diabetic groups



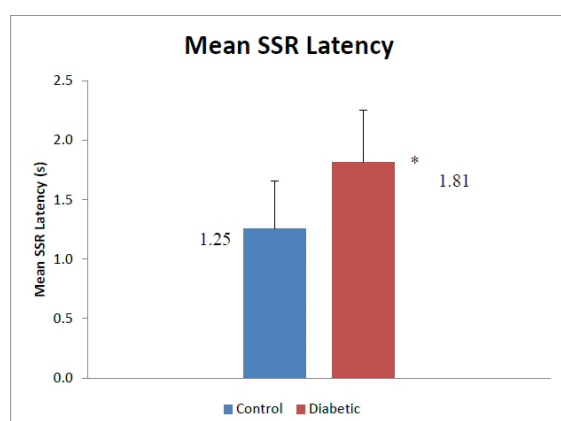
*p<0.0001 as compared to controls

Bar diagram showing the mean SSR amplitude + SD of control and diabetic groups



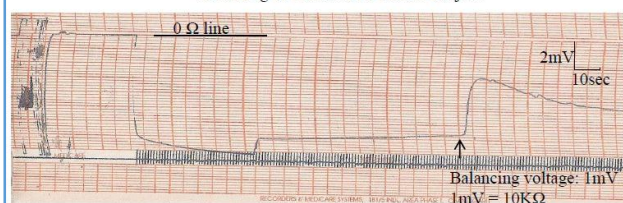
*p<0.0001 as compared to controls

Bar diagram showing the mean SSR latency + SD in the control and diabetic groups



*p<0.0001 as compared to controls

Recording of GSR from a control subject

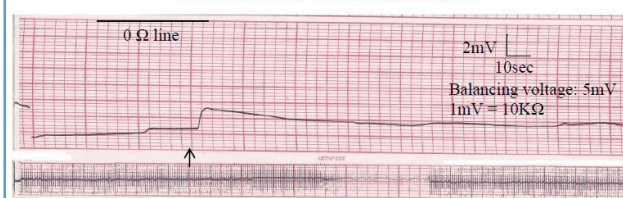


The basal GSR in supine posture was 78KΩ.

On standing, the GSR decreased to 38KΩ.

The percentage of decrease of GSR was 51.28%

Recording of GSR from a diabetic subject

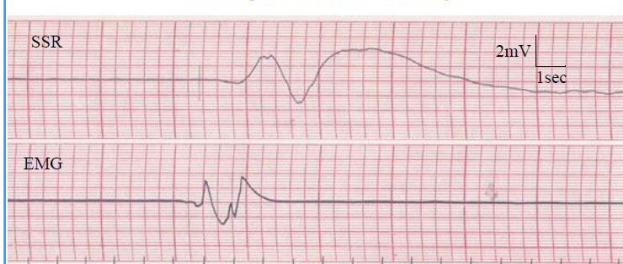


The basal GSR in supine posture was 118KΩ.

On standing, the GSR decreased to 104KΩ.

The percentage of decrease of GSR was 11.9%

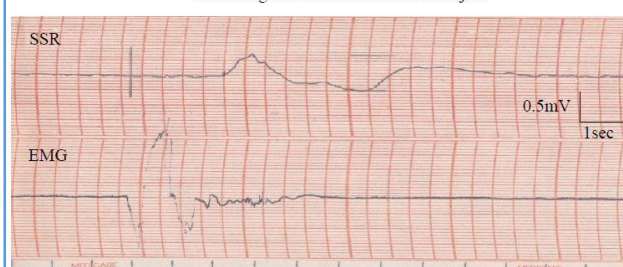
Recording of SSR from a control subject



With 10mm/sec sweep speed, the latency is 1.5 seconds.

With the sensitivity of 2mV, the peak-peak amplitude is 3.8mV.

Recording of SSR from a diabetic subject



With 10mm/sec sweep speed, the latency is 2.2 seconds.

With the sensitivity of 0.5mV, the peak-peak amplitude is 0.6mV.

CONCLUSION: The study revealed SSR latency is prolonged in cases of diabetic autonomic neuropathy. SSR amplitude is decreased in cases of diabetic autonomic neuropathy. Percentage of decrease in GSR during standing from the supine position is reduced in diabetic autonomic neuropathy. The lesser fall in GSR in diabetics showed a negative correlation with the duration of diabetes. Greater the duration of diabetes, lesser is the decrement response of GSR on standing from supine position. SSR latency, SSR amplitude do not show any correlation with duration of diabetes, duration of neuropathic symptoms and random

blood glucose levels. GSR decrease on standing from supine position does not correlate with the duration of neuropathic symptoms and random blood glucose levels.

As San Antonio Consensus Panel recommends the use of non-invasive validated measures of autonomic neural reflexes as specific markers of autonomic neuropathy, when used by properly by trained individuals, autonomic function tests are a safe and effective diagnostic tool for diagnosing and grading diabetic autonomic neuropathy. This study shows that in a diabetic individual suffering from neuropathic symptoms, SSR and GSR would be a valuable tool in establishing the diagnosis of diabetic autonomic neuropathy.

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