Вестник РУДН. Серия: МЕДИЦИНА
RUDN Journal of MEDICINE. ISSN 2313-0245 (Print). ISSN 2313-0261 (Online)
2025;29(1)
http://journals.rudn.ru/medicine

DOI 10.22363/2313-0245-2025-29-1-95-103
EDN GBJJXN

REVIEW
ОБЗОРНАЯ СТАТЬЯ

Autonomic functions testing

Kapil Gupta, Ravi Saini ✉, Naina Jangid

Sawai Man Singh medical college, *Jaipur, Rajasthan, India*
✉ sainiravi414@gmail.com

Abstract. *Relevance.* The ubiquitous nature of the sympathetic and parasympathetic nervous system has allowed detailed tests in a variety of systems, including cardiovascular, gastrointestinal, urogenital, pupillary, sudomotor, and neuroendocrine. The most important characteristics of these tests are that they should be non-invasive, sensitive, specific, repeatable, quantitative, clinically useful and time-efficient. These tests were designed to investigate the possibility of autonomic failure, measure its severity, and assess its distribution. Clinical testing and research tests are the two main categories of these examinations. Cardiovagal, sudomotor and adrenergic autonomic functions are assessed by standard laboratory tests. The sweat test based on for measurement of the thermoregulation and the quantitative sudomotor axon reflex test (QSART) can be used to assess sudomotor function. Response of blood pressure and response of heart rate to Valsalva maneuver and head tilt are used to assess adrenal function, and extended hand grip tests are effective in determining the presence of autonomic failure, its natural history, and response to treatment. The Autonomic Function Test Battery is a set of tests for autonomous functioning. The Ewing battery is commonly used, which includes several parasympathetic and sympathetic tests. *Conclusion.* Autonomic function testing has a considerable amount of diagnostic importance, which can have preventive value due to a large number of mortality due to autonomic disorders.

Keywords: cardiovagal, Ewing's battery, parasympathetic, sudomotor, sympathetic

Funding. The authors received no financial support for the research, authorship, and publication of this article.

Author contributions. Ravi Saini — literature review, writing text; Naina Jangid — collection and processing of materials; Kapil Gupta — concept and design of research. All authors have made significant contributions to the development concepts, research and manuscript preparation, read and approved final version before publication.

Conflict of interest statement. The authors declare no conflict of interest.

Ethics approval — not applicable.

Acknowledgements — not applicable.

Consent for publication — not applicable.

Received 24.04.2024. Accepted 27.05.2024.

For citation: Gupta K, Saini R, Jangid N. Autonomic functions testing. *RUDN Journal of Medicine*. 2025;29(1):95—103. doi: 10.22363/2313-0245-2025-29-1-95-103. EDN GBJJXN

Introduction and background

The need for autonomic function tests lies in the fact that patients with autonomic failure show increased mortality [1]. Initially with the development of non-invasive cardio-vascular reflex function tests, a more systematic range is now available that is optimized for the early diagnosis of autonomic neuropathy. The primary need for these tests is to be noninvasive, sensitive, specific, reproducible, quantitative, clinically relevant, and less time-consuming [2, 3]. The appropriate reach of the parasympathetic and sympathetic nervous system to every organ of the body has allowed tests to be described in various organs [4].

Indications for evaluation of autonomic nervous system

Numerous variables such as posture of body, mental condition, consumable meals, drugs, as well as additional chemicals, might impact autonomic processes. The use of caffeine and nicotine need to be resisted for no less than 3–4 hours and 8 hours, correspondingly, before testing [5]. Anticholinergic substances must be ceased for 48 hours and sympathomimetic medications between 24 to 48 hours prior assessment [6]. Different approaches for assessing autonomic functions are represented in Table 1 [7].

Table 1

Different approaches for assessing autonomic functions

Clinical examinations	Research examinations
1. Tests of cardiovagal function	1. Evaluation of baroreflex gain
2. Tests of adrenergic function	2. Pharmacologic dissection studies
3. Plasma catecholamines	3. Skin vasodilation
4. Sudomotor functioning evaluations a. Quantitative sudomotor axon reflex test (QSART) b. Sweat test based on measurement of thermoregulation	4. Microneurography
	5. Splanchnic-mesenteric blood flow
	6. Cerebral vasoregulation
	7. Cardiac innervation
	8. Vasoregulation of the veins

Set of these tests sought to examine the existence of autonomic failure, quantify its severity, and evaluate its distribution (sudomotor, adrenergic, cardiovagal) [8].

This review aims to give a general overview of the neurophysiological assessments utilized to assess autonomous dysfunction [9–11]. Clinical goals in the evaluation of autonomic function are represented in Table 2 [12].

Table 2

Clinical goals in the evaluation of autonomic function

To evaluate the severity and distribution of autonomic function
To diagnose limited autonomic neuropathy
To diagnose and evaluate orthostatic intolerance
To monitor the course of dysautonomia
To monitor response to treatment
As an instrument in research studies

Autonomous functional assessments

1. Sudomotor function test: The most commonly used methods for quantification of the sweat response are QSART, Thermoregulatory sweat test, Sympathetic skin response, and the Silastic imprinting method/sweat imprint [13,14].

a) *Thermoregulatory sweat test (TST):* In it, adequate stimulus is given for the rise of core temperature to raise blood and mean skin temperature. Modified Guttmann's quinizarin sweat test (QST) is used to conduct the TST. The sodium salt of quinizarin (2–6-sulphonic acid) is used as a color indicator. It is a red-brown dye. The composition of the mixture is commonly used is represented in Table 3.

Table 3

The composition of the mixture is commonly used

Component	Amount
Quinizarin 2–6-disulphonic acid	35 g.
Sodium carbonate (powdered)	30 g.
Rice starch	60–70g.

b) Sweating is usually induced by heat, by giving one or two cups of hot tea and 5–10 gm of aspirin before the powder is applied. The patient is then placed under a Specially designed sweating cabinet having the dimensions as follows: Length 6 ft. 9 inches, Width 3 ft. 3 inches, Height 3 ft. 9 inches used for a variable time, usually from 15 to 45 minutes, depending on the readiness with which sweating is produced. The temperature within the box is regulated by 12 electric lamp bulbs of 25 watts each of them, as well as tube warmers and carbon filaments lights installed has a chromium-platedreflectors; Wall-mounted controls on the exterior of the cabinets operate stacks of 3 carbon filament lights with a power output of 24–32 candle watts. Furthermore, four 6-foot-long tubular heaters with a 60-watt capacity per foot are installed. When the secretion of sweat commences the hydrotic The anhidrotic parts stay the same color while the skin in certain places turns a violet-blue hue and the openings of each sweating ducts appears as tiny black spots. Body temperature measurements like skin temperatures, rectum temperatures, mouth temperatures, potentiometer, and cold junction are measured [15, 16].

c) *QSART:* It quantitatively evaluates the postganglionic sympathetic sudomotor axon recorded from four sites Medial fore-arm site three-fourths of the distance from the ulnar epicondyle to the pisiform bone; proximal lateral leg, 5 cm distal to the fibular head; medial distal leg, 5 cm proximal to the medial malleolus, Proximal foot over the extensor digitorum brevis muscle [17, 18].

Acetylcholine and a constant current of 2 mA for 5 min is delivered and the responses are recorded in a compartment of a multi-compartmental sweat cell. The sweat response is measured by determining the volume of sweat with help of a sudorometer. The composite autonomic scoring scale (CASS) is 10 point scale that Permits 4 points for adrenergic insufficiency and 3 points for cardiovagal and sudomotor failure, respectively. Individuals with a CASS score of less than three have relatively modest autonomic dysfunction, those with scores of 7 to 10 have a severe failure, and those with scores between these two ranges have moderate autonomic failure [19]. Since QSART volumes vary with age and gender, CASS has used the correction of confounding effects of them. The sudomotor index is scored from 0 (no deficit) to 3 (maximal deficit) [20].

d) *Sympathetic skin response (SSR):* Skin potential recordings is able to identify sympathetic sudomotor deficit in peripheral neuropathies and central autonomic disorders [21]. It is a momentary change of the electrical potential of the skin, which can be evoked by various internal or external stimuli [22]. Following thorough cleansing of the skin's areas, electrolyte gels should be applied and Put the active electrodes in the bottom of your foot or palms. SSR may also be recorded from the forehead, the axilla, or the genitalia. The temperature of a quiet dimly lit room is normally kept at 22–24 °C or higher, with the subject supine and relaxed. Most laboratories keep the skin temperature at >32–36 °C. The stimuli might be coughing, an electrical surge, a loud noise, an inspiring gasp, or a skin stroke; flashing or cold pressor test, hypodermic «injection» and other forms of stress can also induce the SSR. Deep breathing or mixed stimuli (electric and acoustic). Because emotions differ, sweating glands produce sweat which brings a change in resistance of our body. Therefore, different changes were expected at different states of emotion in GSR, and the production of different emotional expressions was reflected whenever there is a change in autonomic activity Table 4 [23].

Table 4

Different GSR ranges

Conditions	GSR range (K ohms)
Normal	25 to 29
Fit	30 to 40
Exercise	22 to 24

As GSR value is > 25K OHMS this will indicate low arousal which means the brain is in a calm state and if < 5 K OHMS then this will indicate a high level.

e) *Silastic imprinting method/Sweat imprint (SIM):* Kennedy E. systematically measured the number and size of sweat droplets activated in response to direct chemical stimulation. Skin sites on the medial calf and foot dorsum, each measuring 2cm2 stimulated to sweat maximally by iontophoresis of 1 % pilocarpine (2 mA, 5min). The skin test sites are prepped with a 1 % iodine solution. The skin is wiped dry and immediately the camera was pressed against the skin, to begin image collection and storage. Excreted sweat from each sweat pore after coming in contact with iodine and starch, a tiny dark spot is formed. Transparent tape thinly coated with starch is attached over the lens of the Sensitive Sweat Test (SST) miniature camera. The tape prevents the formation of a drop and sweat is forced to flow centrifugally to form a flat expanding dark spot. The SST device imaged spots from > 200 sweat glands (SGs) at 1 frame/sec (area of 2 cm2) for 60 to 90 seconds, until adjacent spots coalesced [24].

2. Neuroendocrine function test.

Acute exposure to CO2 (acute hypercapnia) can be used as a biological stressor for assessing hypothalamic-pituitary-adrenal (HPA) and sympatho-adrenomedullary (SAM) axes [25]. HPA and SAM are neuroendocrine components of responses to stress. The CO_2 test involves taking a single Vital Capacity (VC) breath of four different concentrations respectively 5 %, 25 %, 35 %, 50 % [26, 27]. Physiological, psychological, and neuroendocrine responses against CO_2 exposure are measured. Alone 35 % of CO_2 can be used.

a) *Physiological measures and psychological measures:* Subjects are rested for 30 min before physiological monitoring and blood sampling. Baseline cardiovascular measures are taken at the end of the rest period with continuous monitoring starting 5 min before the CO_2 and continuing 5 min after completion of exposure. Continuous blood pressure and pulse are measured. Subjective feelings of anxiety, fear, breathlessness, relaxed are recorded by a visual analog scale, for the recording of somatic symptoms of panic similar analog scale is used with 39 point questionnaire. Questionnaire and blood samples are taken simultaneously every 15 min, starting 30 min before exposure and continuing 60 min after it [28].

b) *Biochemical measures:* Plasma cortisol, salivary cortisol, ACTH, prolactin, arginine vasopressin, FSH, LH, GH, TSH, renin, noradrenaline, and adrenaline are measures against CO_2 exposure [29–31].

3. Pupillary function test.

Pupil tests provide a convenient, simple, and non-invasive method for the evaluation of autonomic functions [32]. Balance of activity in parasympathetic

and sympathetic are standardized or controlled for the measurement of pupil size and can be used to identify parasympathetic or sympathetic deficits. All modern pupillometers are based on the principles of having an infra-red source that illuminates the iris, a video camera records the reflected light, to detect the pupil computerized image analysis techniques are used within each video frame which provides continuous measurement of pupil size, and a light stimulus to the eye by using a photostimulation.

4. Gastrointestinal function test.

Gastrointestinal scintigraphy: The accuracy and ease of quantification of radiolabeled solids and liquids had made scintigraphy the gold standard for testing gastric emptying [33–35].

5. Urogenital function test.

In these tests, urogenital autonomic functions, sexual dysfunction, and bladder dysfunction are assessed [36, 37].

a) *Urodynamic tests:* These tests observe using the urethra, sphincters, and bladder to store and release pee. The capacity of the bladder to retain pee and release it consistently fully is the primary objective of these examinations. Additionally, they demonstrate if the bladder is leaking urine due to involuntary spasms [38].

b) *Sexual dysfunction tests:* Assessing genitourinary autonomic functions erectile dysfunction (ED), retrograde ejaculation, and female sexual dysfunctions are assessed by a detailed medical history, sexual function history, medication history, assessment of glycemic control; a hormonal and psychological evaluation [39, 40].

6. Cardiovascular function tests.

Cardio vagal and adrenergic function tests

Cardio vagal functions are assessed by the Valsalva ratio and heart rate response to deep breathing or standing up and adrenergic functions are assessed by the blood pressure response to the Valsalva maneuver or Isometric handgrip test [41–50]. A number of other tests of cardiovascular reflex function have been described, the arterial blood pressure response to different stresses including mental calculation, loud noise, ice and lower-body negative pressure being used [51, 52].

a) *Mental stress test*. For two minutes, the participant is required to complete a typical arithmetic exam that involves repeatedly deducting 17 from a four-digit figure. Systolic blood pressure increases more than 10 mmHg are regarded as typical.

b) *Cold-pressor test.* The participant's hand was submerged in ice-cold (0–4 °C) water for three minutes. It is assessed how much the opposing arm's systolic blood pressure increased [53, 54]. The afferent pain and temperature fibers from the skin are activated by the cold stimulation. The nerve impulses cause the contraction of arteries elevated arterial pressure, and an accelerated heart rate as they travel along the spinothalamic tract to reach certain brain regions. A reading of > 15 mmHg is normal.

c) *Cold face test.* Participants are asked to breathe normally and to avoid breath-holding, deep breathing, or hyperventilation [55]. After resting for 15 min in the supine position, the CFT was induced by the application of three cold packs bilaterally (0.5C) at the forehead, face(excluding the eyes), and nose, for 1 min. Heart rate, blood pressure, and skin temperature should be recorded from 5 min before CFT (baseline) to 5 min after the CFT.

d) *Lower body negative pressure.* The lower body negative pressure (LBNP) test is a useful choice for individuals who are incapable to complete the Valsalva Maneuver (VM). An applied pressure of around –40 mmHg creates a blood volumetric range, identical to what happens with the VM, which leads to a reduction in venous return, a decrease in venous pooling throughout the body, and comparable changes in blood pressure and heart rate. Cardiovascular reflexes and orthostatic tolerance have been studied in relation to submerging, inaction, extended rest in bed, and weightlessness during spaceflight using LBNP [56–58]. Each supine participant positioned his lower body within the cylindrical suction chamber, which is sealed behind the sternum and has a Neoprene skirt on it. To keep people from moving, foot supports were positioned within the room [59, 60].

Baroreflex sensitivity testing

Stretching sensors called baroreceptors, found in the aorta and carotid sinus and react to artery wall expanding detects changes in blood pressure [61–63]. The brain

stem receives burst-like information about each blood pressure pulse from aortic and carotid baroreceptors via the afferent vagal and glossopharyngeal pathways. An increase in afferent input into central autonomic nuclei (nucleus tractus solitarius) is the consequence of this increase in stretching, which also causes a transient rise in blood pressure. The baroreflex's sensitivities may be understood as its reactivity to blood pressure challenges. It can be described as the level of alteration in sympathetic neural activity (SNA) for any variation in blood pressure [64, 65]. A vasoconstrictor drug (phenylephrine) can be injected to raise blood pressure, which will naturally lower heart rate (HR) and raise IBI. This will allow BRS to be assessed.Most often, natural heart rate variability (HRV) and blood pressure variability (BPV), which are derived from a continuous noninvasive finger arterial pressure measurement using the Finapress technique, may also be used to noninvasively assess BRS [66]. The theory is that there is constantly random BPV because of the resonance phenomena described above as well as breathing, which beat-to-beat regulates cardiac filling, stroke volume, and, therefore, the BP pulsations (Mayer [67–70].

Conclusion

Autonomic functions could be tested by various methods most of them noninvasive consist sympathetic and parasympathetic types of tests. Due to the pervasive nature of autonomic functions, autonomic function testing (AFT) includes a wide range of tests related to different physiological systems of the body. AFT has a considerable amount of diagnostic importance, which can have preventive value due to a large number of mortality due to autonomic disorders.

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Тестирование автономных функций

К. Гупта, Р. Саини ✉, Н. Джангид

Медицинский колледж Савай Ман Сингх, *Джайпур, г. Раджастхан, Индия*
✉ sainiravi414@gmail.com

Аннотация. *Актуальность.* Повсеместная природа симпатической и парасимпатической нервной системы позволила проводить подробные тесты в различных системах, включая сердечно-сосудистую, желудочно-кишечную, мочеполовую, зрительную, судомоторную и нейроэндокринную. Наиболее важными характеристиками этих тестов являются то, что они должны быть неинвазивными, чувствительными, специфичными, повторяемыми, количественными, клинически полезными и эффективными по времени. Эти тесты были разработаны для исследования возможности автономной недостаточности, измерения ее тяжести и оценки ее распространения. Клинические испытания и исследовательские тесты являются двумя основными категориями этих обследований. Кардиовагальные, судомоторные и адренергические автономные функции оцениваются с помощью стандартных лабораторных тестов. Тест на пот, основанный на измерении терморегуляции, и количественный тест рефлекса судомоторного аксона (QSART) можно использовать для оценки судомоторной функции. Реакция артериального давления и реакция частоты сердечных сокращений на маневр Вальсальвы и наклон головы используются для оценки функции надпочечников, а тесты с расширенным захватом руки эффективны для определения наличия автономной недостаточности, ее естественного течения и реакции на лечение. Набор тестов автономной функции представляет собой совокупность тестов для оценки автономного функционирования. Обычно используется набор Юинга, который включает несколько тестов для парасимпатической и симпатической нервной системы. *Выводы.* Тестирование функции вегетативной нервной системы имеет большое диагностическое значение, которое также может иметь и профилактическое значение ввиду большого количества смертей из-за расстройств вегетативных функций.

Ключевые слова: кардиовагальный, набор тестов Юинга, парасимпатический, судомоторный, симпатический

Информация о финансировании. Авторы не получали финансовой поддержки за исследование, авторство и публикацию этой статьи.

Вклад авторов. Рави Саини — обзор литературы, написание текста; Наина Джангид — сбор и обработка материалов; Капил Гупта — концепция и дизайн исследования. Все авторы внесли значительный вклад в разработку концепций, исследования и подготовку рукописи, прочитали и одобрили окончательную версию перед публикацией.

Информация о конфликте интересов. Авторы заявляют об отсутствии конфликта интересов.

Этическое утверждение — неприменимо.

Благодарности — неприменимо.

Информированное согласие на публикацию — неприменимо.

Поступила 24.04.2024. Принята 27.05.2024.

Для цитирования: *Gupta K., Saini R., Jangid N.* Autonomic functions testing // Вестник Российского университета дружбы народов. Серия: Медицина. 2025. Т. 29. № 1. С. 95—103. doi: 10.22363/2313-0245-2025-29-1-95-103. EDN GBJJXN

Corresponding author: Ravi Saini- PhD scholar, Department of physiology, Sawai Man Singh Medical College, 302004, Adarsh Nagar, Jaipur, Rajasthan, India. E-mail: sainiravi414@gmail.com
Gupta K. ORCID 0000-0002-6505-4216
Saini R. ORCID 0000-0001-8154-9385
Jangid N. ORCID 0009-0005-3178-6522

Ответственный за переписку: Саини Р. — аспирант, кафедра физиологии, *Медицинский колледж Савай Ман Сингх, Индия*, 302004, *Раджастхан*, Джайпур, *Адарш Нагар*, E-mail: sainiravi414@gmail.com
Гупта К. ORCID 0000-0002-6505-4216
Саини Р. ORCID 0000-0001-8154-9385
Джангид Н. ORCID 0009-0005-3178-6522