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(71) Applicant *(for all designated States except US)*: **STRESSMETER A/S** [DK/DK]; Lemchesvej 1, DK-2900 Hellerup (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BALLEGAARD, Søren** [DK/DK]; c/o Stressmeter A/S, Lemchesvej 1, DK-2900 Hellerup (DK). **MAGNUSSON, Gisli** [IS/DK]; c/o Ballegaards Akupunkturcenter ApS, Lemchesvej 1, DK-2900 Hellerup (DK).

(74) Agent: **INSPICOS A/S**; Bøge Allé 5, P.O. Box 45, DK-2970 Hørsholm (DK).

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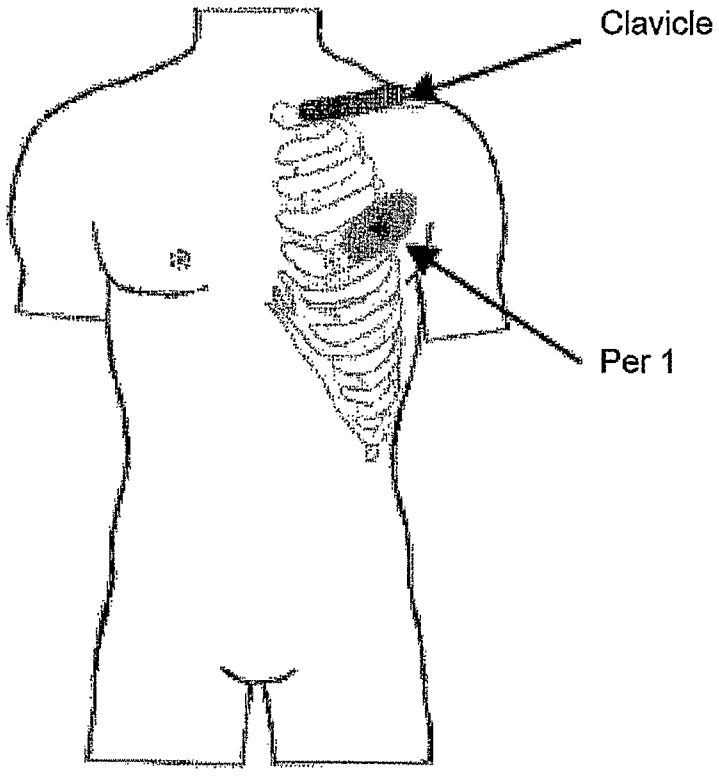
(54) Title: EVALUATION OF SYMPATHETIC TONE



(57) Abstract: The invention relates to a method of determining the sympathetic tone Including the steps of: measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value in one or more sympathetic tone-dependent points. The invention further relates to a system for applying and measuring a stimulation, and the use of a system for applying and measuring a stimulation for determining the sympathetic tone including the steps of: measuring an applied stimulation at a threshold value of the stimulation at one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value of the stimulation at one or more sympathetic tone-dependent points.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

EVALUATION OF SYMPATHETIC TONE

Technical Field

The invention relates to a method of here-and-now determination of the sympathetic tone and a system for measurement thereof. As the method provides the person with a here-and-now determination of the sympathetic tone it is applicable for determining healthy individuals' level of potential for performing optimally both physically and mentally. The invention further relates to use of the system according to the invention for determining the sympathetic tone and use of measuring of the nociception for determining the sympathetic tone.

Background Art

In mammals the nervous system is functionally divided into a somatic nervous system and an autonomic nervous system. The autonomic nervous system functions automatically and reflectory. The autonomic nervous system can further be divided into the counteracting sympathetic and parasympathetic systems. The sympathetic and parasympathetic nerves have opposite effects.

The sympathetic nervous system mobilizes the resources in the organism in a so-called "stress phase" such that an immediate dangerous situation/a challenge is handled in the optimum manner. This means that mentally the person thinks faster and more clearly at the same time as sharpening the ability to focus his/her thoughts. For supporting this purpose, irrelevant sense impressions are effectively impeded. Physically the body responds by lowering the response time, increasing the muscle strength, sharpening the senses, and optimizing the coordination between thought and motor skills.

In conclusion, the above entails that the "stress phase" is a positive physiological phenomenon, when it manifests itself in the right amount and in the right balance with the necessary recovery, which as described below is effected when the parasympathetic nervous system dominates.

The parasympathetic nervous system restores and builds up the organism's resources and thereby ensures that the necessary resources are available when they are to be mobilized in an acute stress situation.

Physiologically, simulation via the sympathetic nerves increases the pulse and the blood pressure and inhibits the secretion formation in the glands, etc., whereas the

parasympathetic nerves *Inter alia* lower the heart rate and the blood pressure and stimulate glands to secrete. During stress and in dangerous situations the sympathetic nervous system is activated.

Stress is a condition in which the resources of the organism are activated with a view to handling a situation which is perceived as dangerous or potentially dangerous by the brain. If the person has the necessary resources available, the situation is perceived in a positive manner. If the situation represents a state in which the strain exceeds the resources of the body, the organism's resources become taxed and long-term and intense stress will impair the person's performance. This state is called chronic or negative stress.

In its mildest form chronic stress manifests itself as moderate bodily symptoms such as muscle tension, fatigue or headache. In a more severe degree of stress additional symptoms are experienced in form of for instance memory problems, lack of concentration and distress from the internal organs (eg. palpitations, stomach ache, decreased libido). In an even more serious stress state, social ability is also impaired, eg reduced tolerance, irritability and uncontrolled bursts of anger. In the latter case, untreated chronic stress may lead to illness whereby the working capacity is lost for a period of time.

The body's reaction to the above strain is controlled by the hypothalamic-pituitary-adrenal system which activates the release of steroid hormones (glycocorticoids½) including cortisol. Additionally, other hormones are released among others catecholamines including dopamine, noradrenaline and adrenaline. As a result, a set of physiological reactions are created which in combination is called the response phase. Substantially all the systems of the body are affected including the brain, the cardiovascular system, the immune system, the respiratory system and the digestive system.

When the physical and mental dangers/challenges/strains have passed, the body's response thereto is inactivated and the recovery phase begins.

The stress reactions are not activated by purely physical or psychological threats, but also by our thoughts. A number of everyday-life situations inter alia rush for time, worries, personal relationship problems and financial worries, activates the response phase without the person being threatened. It is the accumulated effect of these minor but daily strains that lead to chronic stress.

As a part of avoiding that the stress condition develops and thus leads to negative implications, the determination of a person's acute or accumulated stress level is vital to allow for actions to be initiated which can reduce or completely remove the strains causing

the stress or the person's readiness to handle these strains can be increased such that the negative stress-related consequences - both personal and social - may be averted and/or prevented. Stress cannot per se be considered an illness, but accumulated stress can make a person more susceptible to impacts which may develop into an illness.

A number of methods are known for determining the sympathetic tone (the activity of the sympathetic nervous system) as a measure of a person's stress level including measuring of cortisol in saliva, measuring of catecholamines (adrenaline and/or noradrenaline) and cortisol in serum as well as measuring of catecholamines in urine (Ekman R. and Lindstedt. G.: "Molekyler på liv og død" (molecules in life and death), in Ekman R. and Arnetz B. (red) "Stress; Molekylerne, Individen, Organisationen, Samhället" (stress; molecules, the individual, organisation and society), Libers publishing firm, Stockholm 2002, pages 77-89; Hansen A.M., Garde A.H., Christensen J.M., Eller N.H. & Nettestrøm B. "Evaluation of a radioimmunoassay and establishment of a reference interval for salivary cortisol in healthy subjects in Denmark", Scand J Lab Invest 2003; 63: 303-10.) "Måling af hudtemperatur" (measurement of skin temperature) (Normell LA, Wallin BG. "Sympathetic skin nerve activity and skin temperature changes in man". Acta Physiol Scand 1974; 91: 417-26) and sweat secretion are other known method for measuring stress.

The known methods of determining stress and sympathetic tone are encumbered by the drawbacks that either complicated technical analyses involving delays, communication and expenses are required or the methods are not unsusceptible to impacts/influences from the physical environment. Serum determination of for instance cortisol requires a laboratory analysis. Additionally one drawback of such a determination is that a change in the serum concentration of cortisol may rely on other causes than an increased level of stress. The sweat secretion determination is encumbered by the drawback that this determination may be highly unreliable, especially on a hot day where sweat secretion increases regardless of the person's level of stress.

A need thus exists for a fast, reliable and inexpensive method of determining the sympathetic tone as a measure of a person's potential to perform optimally both physically and mentally.

Description of the Invention

The present invention provides a method of determining the sympathetic tone. It is fast, simple, reliable and inexpensive and can be used as a measure of a person's acute and accumulated level of stress.

The invention further provides a system for carrying out the method.

In a first aspect, the invention relates to a method of determining the sympathetic tone and/or the level of stress in a subject, including the steps of: measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value in one or more sympathetic tone-dependent points, or measuring an applied stimulation at a threshold value in one or more sympathetic tone-dependent points and optionally comparing said threshold value to a predetermined or pre-established calibration threshold value.In a second aspect, the invention relates to a method of quantitative and/or qualitative determination of sympathetic tone and/or level of stress in a human, said method including:

a) storage of a calibration threshold value and a stimulation threshold value, the calibration threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-neutral point on a human body and the stimulation threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-dependent point on the human body, and subsequently;

b) calculation of an indication value of sympathetic tone by comparing the stimulation threshold value with the calibration threshold value, whereby the indication value of sympathetic tone is a measure of the sympathetic tone in the human being.

Further aspects of the invention relate to various practical implementations of the inventive methods set forth above, where these implementations aim at optimizing treatments and programmes the efficacy or compliance of which are dependent on stress-level and/or sympathetic tone in the individual subjected to the treatment or programme. For instance, the invention relates to a method for controlling the progress of a patient's therapeutic regimen, wherein the efficacy and/or patient compliance of said regimen is dependent on sympathetic tone and/or stress level in said patient, comprising

i) determining one or more times during the course of the therapeutic regimen the sympathetic tone and/or level of stress in said patient, and

ii) adjusting the therapeutic regimen based on an integrated measure of the patient's benefit from the therapeutic regimen and the sympathetic tone and/or level of stress determination is step i.

Related to these aspects, is a method of the invention which includes an intervention possibility in the event the level of stress and/or sympathetic tone is deemed to high by the above-referenced methods. More precisely, the present invention also relates to a method for prevention of undesired or unproductive stress, the method comprising

a) determination of sympathetic tone and/or the stress level in a patient by using the herein-described methods for such determination,

and if the determination in step a indicates an elevated sympathetic tone and/or level of stress, subjecting a sympathetic tone dependent point to a stimulation having a lower intensity than the stimulation threshold value for a period of time.

Also embraced by the present invention is a method of prognosis of a disease in a patient, comprising

1) determining the sympathetic tone and/or level of stress in the patient, and subsequently

2) providing a prognosis for the patient with respect to the disease by incorporating in the determination of the prognosis the result of the determination in step 1, a determination in step 1 indicating a low sympathetic tone and/or level of stress being indicative of a better prognosis than a determination in step 1 of a higher sympathetic tone and/or level of stress.

The invention also relates to a method for determining whether an interview-based evaluation of stress level in a subject provides a true indication of stress, comprising,

a) in parallel to the interview, determining the sympathetic tone and/or level of stress in the patient by utilising the method determination methods described herein, and

b) ascertaining whether the interview-based evaluation provides a result that correlates positively with the determination in step a, a positive correlation indicating that the interview-based evaluation provides a true indication.

In a third aspect, the invention relates to a system for measuring the sympathetic tone in a human being, said system including:

a) Memory means for storing a nociception calibration threshold value determined in a sympathetic tone-neutral point on the human body and for storing a nociception stimulation threshold value determined in a sympathetic tone-dependent point on the human body;

b) An electronic circuit programmed to data process the nociception calibration threshold value and the nociception stimulation threshold value so as to obtain the measurement.

The calibration threshold value may be a predetermined or pre-established value, which is stored permanently, e.g. the value zero.

In a fourth aspect, the invention relates to a system for measuring the sympathetic tone in a human being, said system including a pressure base with a contact face adapted to exert an outer compressive force on the human body, a sensor for measuring the compressive force exerted by the pressure base on the body, an electronic circuit adapted to store a first measured compressive force and a second measured compressive force, respectively, and to calculate a read-out value as an expression of the ratio between the first measured

compressive force and the second measured compressive force, and wherein the system includes a read-out unit for displaying the read-out value.

In a fifth aspect, the invention relates to use of a system according to the invention for applying and measuring a stimulation for determining the sympathetic tone including the steps of measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value of the stimulation in one or more sympathetic tone-dependent points.

In a sixth aspect, the invention relates to use of measuring nociception for determining the sympathetic tone.

In a further aspect, the invention relates to a kit of elements for assembling the system of the invention, comprising a plurality of exchangeable pressure bases having different characteristics, such as different degrees of hardness, colour, shape or surface texture.

Brief Description of the Drawings

The invention is explained in detail below with reference to the drawings, in which

Fig. 1 shows the position of the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, and the position of the sympathetic tone-dependent point, Per 1, the grey-shaded area, between the nipple and the anterior axillary fold, the black dot in the grey-shaded area indicating the most frequently used point within Per 1 according to the invention.

Fig. 2 shows the position of the sympathetic tone-neutral point posteriorly on the spinal column, more precisely at TH 10-11 and the position of the sympathetic tone-dependent point posteriorly corresponding to TH 3-6 in the area between the shoulder blades.

Fig. 3 shows the position of the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, and the position of the sympathetic tone-dependent point, C.V. 17, the grey-shaded area, in the middle of the sternum, the black dot in the grey-shaded area indicating the most frequently used point within C.V. 17 according to the present invention.

Fig. 4 shows the position of the sympathetic tone-neutral point, anteriorly, on the upper side of the clavicle, and the position of the sympathetic tone-dependent point, St 18, the grey-

shaded area, between two ribs below the nipple, the black dot in the grey-shaded area indicating the most frequently used point within St 18 according to the invention.

Fig. 5 shows a system according to the invention, the parts of the system being shown as integrated in one and the same apparatus. The apparatus includes a pressure base with a contact face adapted to exert an outer compressive force on a human's body, a sensor for measuring the compressive force exerted on the body by the pressure base. The apparatus includes a read-out unit for displaying the read-out value.

Fig. 6 shows an end portion of an apparatus of a system according to the invention, the end portion comprising a contact face adapted to exert a force on a human's body and a sensor for measuring the force exerted on the body.

Best Mode(s) for carrying out the Invention

Definitions

Prior to a detailed description of the invention, specific phrases relating to the aspects of the inventions are defined:

The phrase "stress" denotes a strain condition in which the strain exceeds the resources of the body. Stress has physical and emotional implications and may have positive and negative effects. An increased level of stress is expressed as an increased sympathetic tone.

The phrase "sympathetic tone" denotes the level of activity in the sympathetic part of the nervous system and is a measure of a person's potential to perform optimally both physically and mentally.

The phrase "acute stress" denotes a condition in which a person over a short period of time, typically hours/days, has experienced situations which have caused an increased activity in the sympathetic nervous system.

The phrase "accumulated stress" denotes a condition in which a person over a long period of time, typical weeks/months/years, has experienced situations which have caused an increased activity in the sympathetic nervous system.

The phrase "clinical stress" denotes a condition in which stress triggers clinical symptoms.

The phrase "physiological stress" denotes the determination of sympathetic tone.

The phrase "stimulation" denotes any type of stimulation which activates the skin's mechanoreceptors, thermoreceptor and/or nociceptive receptors. Stimulation may be provided as mechanical, thermal, radiation and/or chemical stimuli. A mechanical stimulation may for instance be provided by means of a compressive force. A thermal stimulation may for instance be provided by means of cold and/or heat. Radiation stimulation may for instance be provided by means of an applied infrared, visible and/or ultraviolet light or combined spectra thereof, eg. a laser, light-emitting diode, infrared, ultraviolet and/or white light source. Chemical stimulation may be provided by means of an organic and/or an inorganic compound.

The phrase "sympathetic tone-neutral point" denotes a point on the body in which the sensitivity to an applied stimulation is independent of the activity level of the sympathetic nervous system and/or to the level of acute stress. Also covered by the expression is a point on the body where increased sympathetic tone and/or level of stress causes a higher threshold for sensitivity or nociception in said point.

The phrase "sympathetic tone-dependent point" denotes a point on the body in which the sensitivity to an applied stimulation is dependent on the activity level of the sympathetic nervous system, in the sense that increased sympathetic tone or an increased level of stress causes the point to exhibit a lowered threshold for sensitivity and/or nociception.

The phrase "threshold value of the simulation" denotes at which intensity the applied stimulation is to be applied to a given point in order for the person to perceive the applied stimulation as not pleasant, more specifically as unpleasant or as pain.

The phrase "threshold value of pressure sensitivity" denotes at which intensity the applied pressure is to be applied to a given point in order for a person to perceive the applied pressure as not pleasant, more specifically as unpleasant or as pain.

The phrase "nociception threshold value" denotes the threshold at which the person in the respective point perceives a stimulation as nociceptive, ie. as tissue-damaging. The expression also includes stimulation which is perceived as uncomfortable by the person.

The phrase "substantially at the same time" denotes that the measurings, eg. of the calibration threshold value and the stimulation threshold value, are performed within a period of a few minutes, eg. one minute, two minutes, three minutes, five minutes, ten minutes, fifteen minutes.

The phrase "significantly lower" means that the nociception threshold value in a sympathetic tone-dependent point is no more than 85%, particularly no more than 80%, and most particularly no more than 75%, of the threshold value in a sympathetic tone-neutral point.

The phrase "system for applying and measuring a stimulation" denotes a system, eg an apparatus or several apparatuses, which are able to apply and measure a stimulation.

The phrase "pressure-sensitive apparatus" denotes an apparatus which is able to apply and measure a pressure.

The phrase "marker" denotes a means marking a measuring point.

The phrase "measuring point" denotes a point whose threshold value of the stimulation at an applied stimulation is either neutral or dependent on the sympathetic tone.

The expressions "C.V. 17", "Per 1" and "St 18" denote meridian points pursuant to conventional Chinese theory (Beijing College of Traditional Chinese Medicine: Essentials of Chinese Acupuncture, Beijing Foreign Languages Press, 1980). C.V. is a conception vessel; Per is the pericardium and St is the stomach. The C.V. 17 point, the grey-shaded area, is shown in Fig. 3, where the most frequently used point according to the present invention within C.V. 17 in the grey-shaded area is indicated by the black dot. The Per 1 point, the grey-shaded area, is shown in Fig. 1, where the most frequently used point according to the present invention within Per 1 in the grey-shaded area is indicated by means of the black dot. The St 18 point, the grey-shaded area, is shown in Fig. 4, where the most frequently used point within St 18, in the grey-shaded area, is indicated by means of the black dot. The described points, C.V. 17, Per 1 and St 18, are well-defined according to their Chinese names and are in form of points on the surface of the body. In Figs. 1, 3 and 4 grey-shaded areas are provided to mark that an actual area is to be examined and that the point merely is defined by its quality as being the most sore point when stimulated. This also means that the point may be outside the grey-shaded area marked on the drawings. In reality, the point may be at any position within the portion of the skin corresponding to the nerve supply to the heart of the sympathetic nervous system (as for instance stated in the following references: Rutherford J.D., Braunwald E. & Cohn P.F., "Chronic heart disease"; Braunwald E., ed. "Heart Disease. A textbook of Cardiovascular Medicine". Philadelphia: W.B. Saunders Company, 1988; 1314-67; Williams P.L., Warwich R., Dyson M. & Bannister L.H., eds. Gray´s Anatomy. New York: Churchill Livingstone, 1989; 723-1168; Mann, F., "Textbook of acupuncture", William Heinemann medical books, London 1987; 57-64).

The expressions "TH 3-6" and "TH 10-11" denote the spinous processes 3-6 and the spinous processes 10-11, respectively, on the thoracic vertebrae of the same numbers. The spinous processes are the parts of the spinal column which feel like hard projections. The spinous processes 3-6 and the spinous processes 10-11 are shown in Fig. 2, the spinous processes 3-6 being the uppermost four black dots on the spinal column and the spinous processes 10-11 being the two lowermost dots on the spinal column.

For ensuring the optimum utilization of a person's total resources, in a given stress-evoking situation it is vital that this can be ensured by measuring the functional level of the nervous system at any given time.

The method according to the invention provides humans with such a tool in form of a method of determining the immediate (here-and-now) activity level of the sympathetic nervous system:

1) A low measured value denotes a low activity level in the sympathetic nervous system and is thus the best possible base for coping optimally with a future stressful situation.

2) A single high value provides the user with the information that the person - physiologically speaking - has mobilised the resources of the organism in a so-called "stress phase" with a view to coping with a situation which the brain perceives as dangerous or potentially dangerous.

3) Repetitive high measurements provide the user with the information that the person is in a prolonged "stress phase", which in the long run may tax the resources of the organism and provide a basis for a reduced functional level mentally, physically, emotionally and socially.

4) Varying high and low measurements provide the user with the information that the person is in situations in which the" stress phase" alternately is activated and inactivated. As a result a possibility for learning and awareness exists.

In a specific embodiment, the method is thus linked to special tools and educational programmes which based on the actual measurement can teach the person how to prevent and treat negative stress and teach the person what specifically increases/reduces the stress level in him/her.

The present invention is the result of intensive research in methods for determining the activity level of the sympathetic nervous system and thus a person's potential to perform optimally both physically and mentally and neatly solves the problems of the known methods of determining the sympathetic tone, which is precisely a measure of the activity level of the sympathetic nervous system, here referred to as physiological stress.

According to the present invention, it has surprisingly been found that points on the body exist, whose threshold value of a stimulation when this is applied to the point is sympathetic tone-neutral or even capable of reacting by analgesia, while other points are sympathetic tone-dependent, cf. the definition above. In other words, certain points exist, where the sensitivity to an applied stimulation is independent of the activity level of the sympathetic nervous system or where an increased sympathetic tone/level of stress induces analgesia, while there are other points, where the sensitivity to an applied stimulation is dependent on the activity level of the sympathetic nervous system in the sense that these points can become hyperalgesic in response to an increased sympathetic tone and/or level of stress. Hence, according to the invention, a person's sensitivity to the applied stimulation in a sympathetic tone-dependent point increases when the activity level of the sympathetic nervous system also increases. This realization is surprising in that it has previously been described that stress and thus increased sympathetic tone generally increases the tolerance to pain (Amit and Galina, Physiol. Rev. 66: 1091-1120, 1986). The identified sympathetic tone-dependent points thus respond differently than what is known for the body in general. In fact, the identified sympahthetic tone dependent points are those where stress and/or increased sympathetic tone can be demonstrated to effect a hyperalgesia (*i.e.* increased sensitivity or increased nociception), something which is in contrast to the previously demonstrated analgesia induced by stress or increased sympathetic tone.

By measuring which intensity of an applied stimulation is necessary to obtain a threshold value of the stimulation in a sympathetic tone-neutral point and comparing this with the necessary intensity of an applied stimulation to obtain the same threshold value of the stimulation in a sympathetic tone-dependent point, a physiological measure of the sympathetic tone and thus of the person's physiological stress or immediate stress level is obtained. The measurement may be considered as a here-and-now determination of the activity level of the sympathetic nervous system.

When using the method according to the invention to determine the chronic, immediate or acute stress level, the method provides the person with a tool for adjusting the stress state and thereby optimizing his/her performance. An acute increase in the activity level of the sympathetic nervous system may have a beneficial effect on the person's performance. It is thus well known that an increased adrenaline level may be beneficial for optimising the

performance. The method according to the invention is thus used to adjust the sympathetic tone such that an increased activity level of the sympathetic nervous system is obtained resulting in a beneficial effect.

A method of determining the immediate activity level of the sympathetic nervous system and/or of the level of stress is thus provided, said activity level being significant to the person's ability or potential to perform optimally. The method may be of a diagnostic nature and have diagnostic value, but it may also be described as a prognostic method in that it provides the person with a prognosis of the person's immediate potential to perform optimally. As mentioned in the introduction, the sympathetic nervous system mobilises the resources of the organism in a so-called "stress phase" such that an actual dangerous situation/challenge is handled in the best possible manner. This means that mentally the person thinks faster and more clearly at the same time as the ability to focus his/her thoughts is increased. For supporting this purpose, irrelevant sense impressions are effectively impeded. Physically the body responds by lowering the response time, increasing the muscle strength, sharpening the senses, and optimizing the coordination between thought and motor skills.

A test among healthy randomly selected persons reveals that half of the persons which are heavily stressed, ie. in a stress group level 3 as defined below, perceive themselves as being unstressed. As a result, the present method and measuring tool are of great practical value by providing the person with vital information to which the person otherwise would not have access.

The method according to the invention may also be used to record the activity level of the sympathetic nervous system on a long-term basis and may thus be effective for preventing in time that such a state lead to stress-related complications. Such recordings may for instance be forwarded to a central register/data centre monitoring the data of the individual person and in time sends a warning back to the person, whereby the said complications can be avoided.

According to the invention the stimulation sensitivity in the points may vary highly from one person to the next and a single determination of the sympathetic tone for a given person cannot necessarily be related to the actual stress state of the person unless the person's normal state is known. It may thus be necessary to supplement the determination of the sympathetic tone with additional information. A low activity level of the sympathetic nervous system (ie. small difference between the two determinations) thus indicates an optimum prognostic utilization of the person's resources. A high activity level (ie. large difference between the two determinations) is, however, not unambiguous, but requires additional

information. A situation, where a high activity level is determined by means of the method, may thus occur, while an additional analysis by means of a stress form (questionnaire) reveals that the person displays no sign of clinical stress. In this case the measurement reflects acute stress and not chronic stress.

Nevertheless, for many practical purposes it is convenient to determine calibration threshold values representing various levels in a population, since this provides for the possibility of ascertaining the stress level and/or sympathetic tone in an individual by performing one single measurement of the stimulation threshold value, thus rendering the need for the measurement of a calibration threshold value unnecessary.

Thus, the calibration threshold value may, instead of being a value obtained from a measurement, be a predetermined or preestablished value, *i.e.* a value based on previous observations from one person or a large group of persons.

According to the invention a stimulation may be any type of stimulation activating the skin's mechanoreceptors, thermoreceptor and/or nociceptive receptors. Stimuli may be provided as mechanical, thermal, radiation and/or chemical stimulus. A mechanical stimulation may for instance be provided by means of a compressive force. A thermal stimulation may for instance be provided by means of cold and/or heat. Radiation stimulation may for instance be provided by means of an applied infrared, visible and/or ultraviolet light or combined spectra thereof, eg. a laser, light-emitting diode, infrared, ultraviolet and/or white light source. Chemical stimulation may be provided by means of an organic and/or an inorganic compound.

The recorded physiological measure of the sympathetic tone is a total measure of the sum of the person's acute stress level and the person's accumulated stress level. The method according to the invention also allows for the recordal of the effect of any intervention/stress-reducing initiatives.

The threshold value of the stimulation is obtained when the person, to whom a stimulation is applied to a specific point no longer perceives the applied stimulation as comfortable, more specifically when the person perceives the applied stimulation as unpleasant or as pain.

Sympathetic tone-neutral points may also be denoted as calibration points. These points may be located anteriorly on the upper side of the clavicle and posteriorly on the spinal column, specifically denoted as TH 10-11. The points may also be located anywhere on a finger or a toe, although preferably on the dorsal side of a finger or a toe.

Sympathetic tone-dependent points may also be denoted as recording points. These points may be located anywhere on the skin which innervationally correspond to the nerve supply of the sympathetic nervous system to the heart, eg. anteriorly, to which three points are connected: C.V. 17 in the middle of the sternum, ST 18 between two ribs below the nipple and Per 1 between the nipple and the anterior axillary fold and posteriorly corresponding to TH 3-6 in the area between the shoulder blades. According to an embodiment the most sore point of the said points is preferably chosen, such a point rendering the most accurate representation of the activity level.

The present invention allows for an overall measure of a person's acute stress over a short period of time, eg. hours/days, as well as of the accumulated stress over a long period of time, eg months/years.

The distinction between acute and accumulated stress may be carried out by means techniques known to the person skilled in the art. These techniques include without being limited thereto: conversations about the person's physical and mental state or other manners in which the state can be elucidated optionally by filling in a stress form (questionnaire). Furthermore, the causes of stress can be found by means of techniques which are known to the person skilled in the art. These techniques include without being limited thereto: a conversation about the person's physical and mental state or other manners in which the state can be elucidated optionally by filling out a stress/resource balance sheet. This is briefly discussed above as supplement of additional information to the determination according to the invention.

The first clinical signs of chronic stress are fatigue and increased muscle tension in the muscles of the motor apparatus. It can manifest itself as for instance headache and back, shoulder and neck pains. This state is harmless and is experienced in many of the situations which are perceived as positive stress.

In case of prolonged stress loads, additional symptoms are triggered in the portions of the nervous system which are not under the power of the will, viz. the autonomic nervous system. These symptoms may for instance manifest themselves as moodiness, stomach ache, palpitations and lack of concentration.

If the stress load is further exacerbated, additional symptoms to the above symptoms are triggered in the portions of the nervous system which are under the power of the will. A person is for instance no longer able to control his/her anger or irritability and the social behaviour is negatively affected.

The measuring of which intensity of an applied stimulation is necessary to obtain a threshold value of the stimulation can be determined by using a system capable of measuring the intensity of the applied stimulation. One example of such a system for measuring an applied stimulation is a system capable of measuring an applied mechanical stimulus, an applied thermal stimulus, an applied radiation stimulus and/or a chemical stimulus. A system for measuring an applied mechanical stimulus may for instance be an apparatus for measuring an applied compressive force, said apparatus for instance being a manometer. After tests with for instance an apparatus capable of measuring an applied compressive force, the measuring of which intensity of an applied compressive force is necessary to obtain a threshold value of the pressure sensitivity can be performed with a finger.

The method according to the invention may furthermore be used as a measure of the effect of various initiatives. These initiatives, which may or may not be related to professional health treatment, may for instance include initiatives corresponding to the situations perceived as stress-evoking.

The method according to the invention may be carried out by a person other than the person being measured or by the person being measured. The most accurate measurement is obtained when the person himself/herself performs the determination.

Comprehensive studies have now revealed that the levels of activity of the sympathetic nervous system (Level 0-3) can be correlated in the following manner to which stimulation in form of an applied compressive force is necessary to obtain a threshold value of the pressure sensitivity in a sympathetic tone-neutral in relation to which stimulation in form of an applied compressive force is necessary to obtain the same threshold value of the pressure sensitivity in a sympathetic tone-dependent point:

Level 0: When the applied compressive force at a threshold value of the pressure sensitivity in a sympathetic tone-dependent point exceeds or is equal to 80% of the applied compressive force at the same threshold value of the pressure sensitivity in a sympathetic tone-neutral point.

Level 1: When the applied compressive force at a threshold value of the pressure sensitivity in a sympathetic tone-dependent point is between 55% and less than 80% of the applied compressive force at the same threshold value of the pressure sensitivity in a sympathetic tone-neutral point.

Level 2: When the applied compressive force at a threshold value of the pressure sensitivity in a sympathetic tone-dependent point is between 30% and less than 55% of the applied

compressive force at the same threshold value of the pressure sensitivity in a sympathetic tone-neutral point.

Level 3: When the applied compressive force at a threshold value of the pressure sensitivity in a sympathetic tone-dependent point is less than 30% or the applied compressive force at the same threshold value of the pressure sensitivity in a sympathetic tone-neutral point.

The above ratios between the level of activity of the sympathetic nervous system and the applied compressive force at a threshold value of the pressure sensitivity in a sympathetic tone-dependent point in relation to the applied compressive force at the same threshold value of the pressure sensitivity in a sympathetic tone-neutral point may vary from one person to the next. In a few cases the variation may be up to about 90 %.

In the same person, the measurements may furthermore vary between the different sympathetic tone-dependent points and between the different sympathetic tone-neutral points. In order to obtain the most accurate determination of the activity level of the sympathetic nervous system it is thus vital to choose a sympathetic tone-neutral point, which is not sensitive due to other factors.

The above correlation between which applied compressive force is necessary to obtain a threshold value of the pressure sensitivity in a sympathetic tone-neutral point in relation to which applied compressive force is necessary to obtain the same threshold value of the pressure sensitivity in a sympathetic tone-dependent point has also been found to apply when a thermal, radiation or chemical stimulus is used. As an example it has been found that when an applied compressive force is used, a sympathetic tone-dependent point is more sensitive to for instance heat and cold, the heat for instance being transferred by heat conduction or by radiation, said point also being more sensitive to influences from organic and/or inorganic compounds than a sympathetic tone-neutral point.

Any sympathetic tone-neutral point can be used with any sympathetic tone-dependent point. The use of sets of a sympathetic tone-neutral point and a sympathetic tone-dependent point either anteriorly or posteriorly is preferred. As an example, it is preferable to use the sympathetic tone-neutral point anteriorly on the upper side of the clavicle in combination with the sympathetic tone-dependent points C.V. 17 or St 18 or Per 1 or preferable to use the sympathetic tone-neutral point TH 10-11 in combination with the sympathetic tone-dependent point TH 3-6.

The invention thus relates to a method of determining the sympathetic tone and/or the level of stress in a subject, including the steps of: measuring an applied stimulation at a threshold

value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value in one or more sympathetic tone-dependent points, or measuring an applied stimulation at a threshold value in one or more sympathetic tone-dependent points and optionally comparing said threshold value to a predetermined or pre-established calibration threshold value. Typically, the threshold value of said stimulation is the stimulation's nociception threshold value in the relevant point of stimulation.

According to a particular embodiment of the invention, an applied stimulation may be provided by an applied mechanical, thermal, radiation and/or chemical stimulus.

According to a particular embodiment of the invention a mechanical stimulus may be provided by an applied compressive force.

According to a particular embodiment of the invention, a thermal stimulus may be provided by an applied heat or cold source.

According to a particular embodiment a radiation stimulus may be provided by means of an applied infrared, visible and/or ultraviolet light or combined spectra thereof, eg. a laser, light-emitting diode, infrared, ultraviolet and/or white light source.

According to a particular embodiment of the invention a chemical stimulus may be provided by an applied organic and/or inorganic compound.

According to a particular embodiment of the invention, the determination of an applied stimulation at a threshold value of the stimulation may be carried out by means of a system for measuring the applied stimulation.

According to a particular embodiment of the invention, the measuring of the applied stimulation at a threshold value of the stimulation in a sympathetic tone-neutral point may be performed anteriorly on the upper side of the clavicle and/or posteriorly on the spinal column corresponding to TH 10-11 and/or on a finger and/or on a toe; in the latter two cases, the applied stimulation is preferably performed on the dorsal side of the finger/toe.

According to a particular embodiment of the invention, the measuring of the applied stimulation at a threshold value of the stimulation in a sympathetic tone-dependent point may be carried out at one or more locations on the skin which innervationally correspond to the nerve supply of the sympathetic nervous system to the heart, eg. in one or more of the anterior points to which three locations are connected: C.V. 17 in the middle of the sternum, ST 18 between two ribs below the nipple and Per 1 between the nipple and the anterior

axillary fold and posteriorly corresponding to TH 3-6 in the area between the shoulder blades, where the most sore of the said points is chosen.

According to a particular embodiment of the invention it relates to a method of quantitative and/or qualitative determination of sympathetic tone and/or level of stress in a human, said method including:

a) storage of a calibration threshold value and a stimulation threshold value, the calibration threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-neutral point on a human body and the stimulation threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-dependent point on the human body, and subsequently;

b) calculation of an indication value of sympathetic tone by comparing the stimulation threshold value with the calibration threshold value, whereby the indication value of sympathetic tone is a measure of the sympathetic tone in the human being.

In an embodiment, the calibration threshold value and the stimulation threshold value are measured substantially simultaneously. The calibration threshold value may, however, also represent a historic mean value obtained on the basis of previous measurements or a predetermined value such as a constant which for instance may represent an average value of a number of different persons. In certain embodiments, the calibration threshold value is set to zero.

When using pre-established or predetermined calibration threshold values, this is primarily done in order to facilitate a user-friendly approach to the methods of the invention, since it will only be necessary to perform one single measurement in order to obtain a simple and readily accessible indication of the level of stress and/or sympathetic tone.

At any rate, the indication value of the sympathetic tone/level of stress is a preferably a mathematical combination of the calibration threshold value and the stimulation threshold value. This is to mean, that the read-out of the method is a value (or other alpha-numerical indication such as a colour code, a tone etc.) which is obtained by mathematically combining the stimulation threshold value and the calibration threshold value. Typically, the mathematical combination is a mathematical function of the ratio between the calibration threshold value and the stimulation threshold value (*i.e.* a function of the calibration threshold value divided by the stimulation threshold value). However, the mathematical combination may also be a function of the difference between the two values.

It should be noted that even though it is practical to do so according to the invention, these two threshold values *need* not be measured using the same unit of measure, and it is even conceivable (although not highly practical) that the two threshold values are threshold values for different types of stimulation.

The present invention has surprisingly been demonstrated to be capable of distinguishing between chronic and acute stress. The basis for this realization is the following findings:

a) acute stress may lead to stress-induced analgesia, which can be observed on virtually any part of the surface on the human body (except or significantly less pronounced in the sympathetic tone-dependent points discussed herein),

b) acute as well as chronic stress lead to stress-induced hyperalgesia in specific point of the surface of the skin (*i.e.* in the sympathetic tone dependent points), and

c) chronic stress leads to a decrease in "elasticity" of the autonomic nerve system in response to a standard intervention (*i.e.* the methods described herein but also acupuncture) having the effect to decrease sympathetic tone and/or the stress level.

Hence, in one embodiment of the invention a general elevation of the calibration threshold value in combination with a reduction of the stimulation threshold value is an indication of stress, and also a normal level of the calibration threshold value and a reduction of the stimulation threshold value is an indication of stress. The determination of whether or not a general elevation or reduction of threshold values is typically based on historical data, preferably obtained from a large population.

Further, it has according to the invention been found that a stimulation threshold value of more than 80% of the (measured or pre-established or predetermined) calibration threshold value indicates that there is no significant level of stress in the human,
- a stimulation threshold value of between more than 55% and at most 80% of the (measured or pre-established or predetermined) calibration threshold value indicates that there is a low but significant level of stress in the human,
- a stimulation threshold value of between more than 30% and at most 55% of the (measured or pre-established or predetermined) calibration threshold value indicates that there a intermediate and significant level of stress in the human, and
- a stimulation threshold value of at most 30% of the (measured or pre-established or predetermined) calibration threshold value indicates that there is a high and significant level of stress in the human.

In order to determine whether or not the low, intermediate or high stress level includes acute, acute/chronic or chronic elements, it has been found that a combination of
1) a stimulation threshold value of at most 80% of the calibration threshold value (thus indicating some level of stress) and
2) a sum of the values of the calibration threshold and the stimulation threshold, which is significantly above average,
indicates that the low, intermediate or high level of stress is predominantly acute.

Further, a combination of
1) a stimulation threshold value of at most 80% of the calibration threshold value and
2) a sum of the values of the calibration threshold and the stimulation threshold, which is about average,
indicates that the low, intermediate or high level of stress is of both acute and chronic nature.

Finally, a combination of
1) a stimulation threshold value of at most 80% of the calibration threshold value and
2) a sum of the values of the calibration threshold and the stimulation threshold, which is significantly below average
indicates that the low, intermediate or high level of stress is of predominantly chronic.

Thus, the "average" value of the sum of values is determined from previous measurements according to the present invention in an established stressed population which is known to include individuals that are both chronically and acutely stressed. State of the art methods for such determinations of stress are used (*i.a.* the interview techniques referred to above).

The above can be simply illustrated by the following exemplification

A) measurement of the calibration threshold value, e.g in on the index finger); B1) measurement of the stimulation threshold value in a point referred to herein; and B2) A Standard Intervention (SI) with a known sympaticus decreasing effect is introduced to the patient (such treatment data exists presently concerning the use of acupuncture and acupressure in the hands of a professional). After the intervention has had sufficient time to induce the effect (for instance 1 minute for acupressure and 3 minutes for acupuncture according to pressent information, but the optimum times are still being investigated), the measurement in the sympaticus hyperalgesic point is repeated.

Situation a)
A/B1 < 1.25 indicate stress level of no clinical signifance

Situation b)

A/B1 > 1.25 indicate stress level *of* clinical signifance.

Situation c)

A/B1 > 1.25 and A+B1 = high value (value > 15 based on historical and clinical data): acute stress dominates the measure of elevated stress level.

Situation d)

A/B1 > 1.25 and A+B1 = intermediate value (10.0 < value < 15): acute and chronic stress contribute both in a significant aspect to the measure of the elevated stress level.

Situation e)

A/B1 > 1.25 and A+B1 = low value (value < 10.0): chronic stress dominates the measure of elevated stress level.

Situation f)

A/B1 > 1.25 and A+B1 = low value; if the effect from acupressure provides less than an 18% decrease in a subsequent measurement according to the inventin or if the effect from acupuncture is less than a 40% decrease, it is concluded that chronic stress dominates the level of stress – and additional treatments/efforts are important to re-establish normal "elasticity" in the nervous system (the professional may, however, consider that the patient has received an insufficient dose of stimulation –and thus repeate stimulation before communicating the conclusion to the patient or prescribing further treatment). If, on the other hand, the effect is less than the lower 95% confidence limits of the expected effect, then it is concluded that chronic stress dominates the level of stress. However, the accumulation of chronic stress has not reached a level in which the elasticity of the nervous system has been impaired.

As will be noted, the above exemplification also includes an intervention step – this will be detailed below.

In an embodiment nociception is induced by means of a exposure to compressive force, heat, cold, radiation, chemical stimulus or combinations thereof.

According to an embodiment, a significantly lower nociception threshold value in a sympathetic tone-dependent point than in a sympathetic tone-neutral point indicates that a person has increased sympathetic tone.

The determined indication values of the sympathetic tone can be recorded either here-and-now or over a lengthy period of time. A particular embodiment thus relates to a method in which the indication value of the sympathetic tone is compared to at least one previously determined indication value of the sympathetic tone, said previous value indicating sympathetic tone at a earlier point in time.

Various uses of the method of the invention

Since the methods referred to above are capable of providing a quantitative and/or qualitative measure of sympathetic tone and/or level of stress, it is possible to utilise the methods in connection with a large number of treatments (medical and non-medical) where the efficacy of the treatment is to some extent dependent on the sympathetic tone and/or level of stress in the patient being subjected to the particular treatment.

Numerous disease states are associated with changes in sympathetic tone, which may either contribute directly to the pathogenesis of the disease (e.g., ischemic heart disease, hypertension) or be a consequence of the primary disease (e.g., pain, endocrinological disorders, psychological disorders). In either case, the method of the invention may be used to accurately monitor the influence of any pharmacological intervention prescribed to either treat the primary disease or to alleviate symptoms that are associated with major dyscomfort. To the patient and/or practitioner, this measure provides a measurable read-out that allows the patient to monitor efficacy of the pharmacological treatment and if necessary to effect a change of the therapy in order to provide an optimization thereof.

So, the present invention provides for a method for controlling the progress of a patient's therapeutic regimen (medicinal, surgical or by other means), wherein the efficacy and/or patient compliance of said regimen is dependent on sympathetic tone and/or stress level in said patient, comprising

i) determining one or more times during the course of the therapeutic regimen the sympathetic tone and/or level of stress in said patient, and

ii) adjusting the therapeutic regimen based on an integrated measure of the patient's benefit from the therapeutic regimen and the sympathetic tone and/or level of stress determination is step i. Preferably, step i is performed by one of the methods for determing sympathetic tone and/or level of stress described herein.

The term "integrated measure of the patient's benefit from the therapeutic regimen and/or level of stress determination" denotes a combination of information concerning the general and/or specific medical status of the patient, the patient's stress/resource balance and the stress level measurement disclosed herein together with information which gauges to what

extent the patient has in fact followed or been subjected to the therapeutic regimen. In other words, the presently disclosed methods for determination of sympathetic tone and/or stress level are used together with more traditional means and measures for evaluating effect or compliance of a therapeutic regimen in order to arrive at a more accurate evaluation of said efficacy and/or compliance.

Examples of pharmacological compliance enhancement is expected during therapy with the following non-limiting group of therapeutic regimens: insulin-treatment in diabetes, nicotine substitution used as adjuvant therapy in smoking cessation, hormonal therapy in postmenopausal syndromes, antiinflammatory therapy in acute and chronic inflammation, antiinfective therapy in infectious diseases, treatment of hypo- or hyperthyroid conditions, treatment of diseases in heart, vessels, and kidney using cardiovascular drugs, treatment of ulcers, irritable bowel syndrome, malabsorption, nausea, and other symptoms using gastrointestinal drugs, pharmacological treatment with body weight lowering drugs, exercise programmes, relaxation programmes, diet programmes, counseling or coaching, stress-management programs, personal development programmes, personal performance programmes, and self-care programmes.

As discussed above, it is also possible to utilise the methods for stress-determination of the present invention with a view to intervention. Thus, the invention also relates to a method for prevention of undesired or unproductive stress, the method comprising

a) determination of sympathetic tone and/or the stress level in a patient by means of the methods disclosed herein,

and if the determination in step a indicates an elevated sympathetic tone and/or level of stress, then subjecting a sympathetic tone dependent point on the patient to a stimulation having a lower intensity than the stimulation threshold value for a period of time.

This particular intervention can e.g. be used to treat a patient which suffers heavily from stress and is in a situation where immediate treatment is necessary. However, it is also possible to use a more long-term treatment regimen in less critical cases, where the above method further comprises, after step a,

b) a determination of sympathetic tone and/or the stress level in a patientvia the methods disclosed herein, and if this new determination does not indicate a less elevated sympathetic tone and/or level of stress, then subjecting a sympathetic tone dependent point to a stimulation having a lower intensity than the stimulation threshold value for a period of time which is different (preferably longer) from the period of time in step a, and

c) repeating step b until the determination indicates a less elevated sympathetic tone and/or level of stress than the determination in step a. Conveniently, and especially practical in cases where the intervention is not performed by a skilled practitioner, the subjection of the

sympathetic tone dependent point.to the lower stimulation intensity may be controlled by indicating a correct stimulation intensity by means of a visible or audible indication – in this way, it is avoided that the stimulation becomes insufficient or too forceful. Of course, this embodiment requires that a system or appatus including means for sensing the intensity of the stimulation is used by either the patient himself or a practitioner.

It has been found that a combination
- where, in step a, the stimulation threshold value is at most 80% of the calibration threshold value and the sum of the values of the calibration threshold and the stimulation threshold is significantly below average, and
- where the determination in step b reveals a decrease in stimulation threshold value which is less than the lower 95% confidence limit of the expected decrease after stimulation,
then this is an indication of chronic stress of a prolonged nature, which requires several subsequent repetitions in step c.

It is also possible to use the present invention prognostically in a method comprising
1) determining the sympathetic tone and/or level of stress in the patient, and subsequently
2) providing a prognosis for the patient with respect to the disease by incorporating in the determination of the prognosis the result of the determination in step 1, a determination in step 1 indicating a low sympathetic tone and/or level of stress being indicative of a better prognosis than a determination in step 1 of a higher sympathetic tone and/or level of stress. Also here, it is preferred that the determination in step 1 is performed by methods disclosed herein.

The disease is preferably selected from the group consisting of
an acute, subacute or chronic inflammatory condition;
a condition in which immunological reactions cause harm to human organs or in which insufficient function of the immunological system cause impaired function and/or disease;
an acute, subacute and chronic infectious disease;
a cardiovascular disturbance, which is affected by sympathetic tone, such as circulatory shock, atheriosclerosis, thrombosis, an ischemic condition, infarction, cardiac arrhythmia, hypertension;
a neoplastic growth disturbance;
an aquired metabolic disturbance;
a poisining or physical damage due to mechanic, termal, electrical or radiation energy;
a psychological, mental or behavioral disturbance, which are influenced by sympathetic tone, such as depression or other mood disorders, an addiction or dependence disorder of any kind, a neurosis, a suicidal behaviour; a sleep disturbance, fatique, astress-related complain of psychological and/or mental character;

a fertility decrease in both female and male;
a gynecological disturbance, which is influenced by sympathetic tone, such as premenstrual syndrome, dysmenorhea, menopause problems, hyperemesis gravidarum, preeclampsia and eclampsia, premature labor, situs invertus, induction of Labor, postpartum hemorhage;
an otolaryngological disturbance, which is influenced by sympathetic tone, such as tinnitus and presbyacusis;
a dermatological disturbance, which is influenced by sympathetic tone such as pruritus;
a gastrointestinal disease with stress-sensitive clinical signs and symptoms, such as gastric and duodenal ulcer, irritable bowel syndrome, malabsorption, diarrhea, constipation, nausea, and vomiting;
a neurological disturbance, such as tension headache, migraine, concussion, Parkinson's disease, Alzheimer's disease, intracranial traumas, and neuropathies
an endocrinological disorder, such as diabetes, hypothyroidism, hyperthyroidism, an adrenocortical disorder, adrenomedullary disorder, a hypothamic disorders, a pituitary disorder, and polycystic ovary syndrome;
a allergy, such as one with reactions in skin, bronchi, and the gastrointestinal tract;
a pulmonary diseases with impaired gas exchange, such as bronchitis and emphysema;
a disease in joints and bone, such as, acute or chronic arthritis and osteoporosis;
a disorder related to changes in body weight composition, such as obesity, weight loss, cachexia;
a sodium and water-retaining disease state, such as heart failure, kidney failure, liver failure; and
pain.

One of the important findings leading to the present invention is that the methods of determining sympathetic tone and/or level of stress disclosed herein provide for an objective evaluation of stress-level. It thus becomes possible to utilise the methods as a quality control of other methods for determining stress in subjects.

Questionaires for the use of measure level of stress is today regarded as evidence-based and used all over the world. However, in patients with chronic stress – such as for example women with breast cancer – the present inventors have found that the correlation between stress level measured by questionnaires and stress hormone in the blood is negative, indication that psychological neglect is present. It has, however, been found that the present technique has the ability to identify this negative correlation – and thus providing an objective (and non-invasive) control for the use of questionnaires in the measurement of clinical stress

Hence, the present invention relates to a method for determining whether an interview-based evaluation of stress level in a subject provides a true indication of stress, comprising,
a) in parallel to the interview, determining the sympathetic tone and/or level of stress in the patient by utilising any one of the methods disclosed herein, and
b) ascertaining whether the interview-based evaluation provides a result that correlates positively with the determination in step a, a positive correlation indicating that the interview-based evaluation provides a true indication.

The above thus allows for correct design of interview studies of stress.

Systems of the invention

The invention also relates to a system for measuring the sympathetic tone in a human being, said system including:

a) Memory means for storing a nociception calibration threshold value determined at a sympathetic tone-neutral point on the human body and for storing a nociception stimulation threshold value in a sympathetic tone-dependent point on the human body;

b) An electronic circuit programmed to data process the nociception calibration threshold value and the nociception stimulation threshold value so as to obtain the measurement.

In an embodiment, the system according to the invention may further include user-operated means for applying a discomfort-inducing stimulus to the surface of the human body and user-operated storage means adapted to store the nociception calibration threshold value resulting from a first user operation.;

The system may further, or alternatively, include user-operated means for applying a discomfort-inducing stimulus to the surface of the human body and user-operated storage means adapted to store the nociception stimulation threshold value resulting from a second user operation.

The means for applying a discomfort-evoking stimulus may be contained in a first unit and said electronic circuit may be contained in another unit. For obtaining the necessary data transfer between the first and second units the units may for instance be provided with means for wireless communication. In a so-called "distributed system" the first unit may for instance be a hand-held unit, which the user easily can bring with him/her, while the other unit may be a central computer at a doctor or hospital, said computer collecting data from a number of different users which each has a hand-held unit. Optionally the computer may be

placed in the home of the user. In a distributed system a mobile phone may advantageously be used as communications means for transferring data from the hand-held unit to the computer, the hand-held unit for instance wirelessly transmitting data to the computer via a conventional mobile phone signal. This signal may be forwarded by a mobile phone provider to the computer via the internet. Optionally the second unit may be formed of a programmed mobile phone for instance communicating with the first unit via Bluetooth™, in which case a system utilizing the computing strength and memory storage of the mobile phone is used instead of a distributed system.

In a second embodiment, the means for applying a discomfort-evoking stimulus and the said electronic circuit are integrated in one and the same apparatus.

In an embodiment, the means for applying a discomfort-provoking stimulus are adapted to apply a stimulus which is gradually increased, the storage means being adapted to store a stimulation level at a moment in time corresponding to the first and second user operation, respectively.

In an embodiment the invention relates to a system in which the applied discomfort-evoking stimulus includes exposure to compressive force, heat, cold, radiation, chemical stimulus or combinations thereof.

In an embodiment the pressure may be applied by means of a pressure base or a clamp.

In a particular embodiment of the system, the applied discomfort-inducing stimulus is stopped at the time of the first or the second user operation.

The contact face of the pressure base is resilient in a particular embodiment.

In further embodiment the pressure base contains a liquid, a gel and optionally gas-filled bubbles.

In a particular embodiment the contact face on the pressure base is less than 4 cm^2, preferably between 1 and 2 cm^2.

The invention further relates to a system for applying and measuring a stimulation to determine the sympathetic tone, said system including a measuring unit and a read-out unit displaying the applied stimulation.

According to a particular embodiment of the invention, the system includes a marker for marking the measuring points such that it can be established where the stimulation was applied.

According to a particular embodiment of the invention, the system is provided with a scale divided into at least two zones, particularly four zones, which each for instance relates to the above levels of stress 0, 1, 2 and 3.

According to a particular embodiment of the invention these zones may have different colours, patterns or other distinctive marks which make them distinguishable from each other.

The system according to the invention includes a pressure base with a contact face adapted to exert an outer compressive force on the human body, a sensor for measuring the compressive force exerted by the pressure base on the body, an electronic circuit adapted to store a first measured compressive force and a second measured compressive force, respectively, and to calculate a read-out value as an expression of the ratio between the first measured compressive force and the second measured compressive force, the system also including a read-out unit for displaying the read-out value. If the first measured compressive force is the measuring performed in a sympathetic tone-neutral point and the second measured compressive force is the measuring performed in a sympathetic tone-dependent point, the level of activity of the sympathetic nervous system is displayed as the read-out value.

The contact face of the pressure base may be resilient. As a result a more accurate measurement is obtained, the contact face being adaptable to uneven areas on the body and provides a uniform pressure. The pressure thus corresponds to the applied force divided by the area of the contact face.

The pressure base may contain a liquid, a gel and optionally gas-filled bubbles, whereby a particularly snug fit to the surface of the body is obtained in the measuring point.

According to an embodiment the area of contact face on the pressure base may be less than 4 cm^2, such as between 1 and 2 cm^2, or less than 1 cm^2, such as between 0.5 and 1 cm^2.

The sensor may include a piezoresistive force sensor.

The system may be integrated in an apparatus preferably being hand-held and power-supplied by one or more batteries. As a result the user may bring the apparatus along on travels.

The read-out unit is an electronic display.

The electronic circuit may be adapted to determine the read-out value as one of a number, eg. four, discrete read-out values (0, 1, 2, 3), the ratio between the first measured value and the second measured value being rounded off to or allocated a discrete read-out value (0, 1, 2, 3) displayed on the read-out unit.

The discrete read-out value (0, 1, 2, 3) may be non-proportional to the ratio between the first measured value and the second measured value. The apparatus may thus be accommodated to a lacking proportionality or linearity between the measuring results and the level of activity of the sympathetic nervous system. The level 0 may thus correspond to the second measured compressive force being 80 % or more of the first measured compressive force, level 1 may correspond to the second compressive force being 55-80% of the first compressive force, level 2 may correspond to the second measure compressive force being 30-55% of the first compressive force, and level 3 may correspond to the second measure compressive force being 30% or less than the first compressive force.

The electronic circuit may be adapted to calculate the first measured value as an average of a number of measured values and calculate the second measured value as an average of a number of measured values. A more reliable measurement of the person's stress level is thus obtained, the error indication of the read-out value caused by measurement uncertainty at the individual measurings being reduced.

Fig. 5 shows a system according to the invention, the system being shown as integrated in one and the same apparatus for reason of clarity. The apparatus is hand-held and includes a housing 7, an electronic display 8, a control button 9 and a pressure base 5 extending from one end of the housing 7. The free end of the pressure base 5 has a contact face 6. Inside the apparatus the pressure base 5 abuts a force sensor or pressure sensor 7 connected to a not-shown electronic circuit. The electronic circuit is capable of storing the force or pressure measurements detected by the sensor 7. The circuit 7 is further capable of making calculations and transmitting a read-out value to the electronic display 8. A not-shown battery supplies the circuit with power.

In use, the person holds the apparatus in his/her hand and exerts an increasing pressure on a sympathetic tone-neutral point on the body until the threshold value of discomfort has been

reached. The electronic circuit records the maximum compressive force detected by the sensor. The person pushes the control button 9 and then exerts an increasing pressure on a sympathetic tone-dependent point on the body until the threshold value of discomfort is reached. The electronic circuit records the maximum compressive force. When the control button 9 has been pushed, the circuit calculates a read-out value as an expression of the ratio between the first measured compressive force and the second measured compressive force. In this example, the read-out value is 0, 1, 2 or 3, if the second measured compressive force is more than 80 %, 55-80 %, 30-55 %, respectively, or less than 30 % of the first compressive force. The apparatus may optionally be adapted to determine a mean value of a number of measurements of the first compressive force and a mean value of a number of measurements of the second compressive force, the read-out value being determined on the basis of these mean values. Fig. 5 shows a measuring in which the activity level of the sympathetic nervous system is 2 corresponding to the compressive force on the sympathetic tone-dependent point at discomfort being between 30% and 55% of the compressive force on the sympathetic tone-neutral point.

Fig. 6 illustrates a detail of a contact face 16 for applying a pressure force to a human's body. The contact face 16 includes a relatively soft convex member 18 made from a resilient material, such as a rubber material. The member 18 constitutes a distal end of a device embodying the system of the present invention. The relatively soft member 18 is supported by a relatively hard supporting member 19 made from, e.g., a plastics or rubber material or steel and defining a central protrusion into the relatively soft member 18. Accordingly, a center portion of the contact face 16 is less resilient than a peripheral, outer portion thereof. The relatively soft member 18 may ensure that the contact face is capable of adapting its shape to uneven surfaces of the human's body. On the other hand, the relatively hard supporting member 19 may ensure that the force applied by the user is appropriately transferred to the body. The relatively hard supporting member 19 is supported by a pressure sensor 17, e.g. a piezoelectric sensor, mounted to or accommodated in a housing 20 of the device.

Whereas the contact face 16 is illustrated as a cylindrical member with a convex end portion in Fig. 6, it should be understood that alternative forms are envisaged. For example, it may be conical with a flat or convex end portion.

It will be appreciated that the system of the present invention may include means for applying a further stimulus to the surface of the human body, the further stimulus having a lower intensity than the stimulation threshold value, e.g. for purposes of treatment and/or stress relieve. For example, such means may be provided as a second, separate pressure base or they may be constituted by the pressure base also used for the purpose of

measurement as described above. The first and second pressure bases may be provided at a free end of a hand-held unit, e.g. a pen-shaped unit. In one embodiment, the first pressure base is exchangeable with the second one, in which case the system of the invention preferably includes one pressure-base mounting spot only. In other embodiment, the system may accommodate the first and second pressure bases simultaneously, e.g. at opposite surface portions of a hand-held unit, for example at opposite ends thereof.

The contact face or pressure base of the device may be exchangeable, so as to allow the user or physician to choose a pressure base best suitable for a particular purpose or a particular patient. A plurality of pressure bases may be provided in a kit of elements together with e.g. a hand-held device incorporating other features of the system of the invention, e.g. pressure sensor, electronic control ciruit, memory means and display.

A sound-emitting device may be provided for providing an acoustic signal to the user indicative of application of a desired force during treatment or stress relieve. Alternatively, an optical, vibratory or other signal emitter may be provided. The sound-emitting device is preferably connected to an electronic control circuit of the device, which receives input from the pressure sensor 7 or 17, so that a characteristic of the sound may be varied in dependence of the applied force. For example, the sound level, frequency, or the duration of intervals of silence between sound fragments or the duration of the sound fragments may be varied. In one embodiment, no sound is emitted, when the user applies a force, which is too low, whereas a sound having a first characteristic, e.g. a low frequency sound signal is applied, when the applied force is appropriate. If the force applied exceeds a predetermined threshold level, a high frequency alarm signal is emitted. Other embodiments are envisaged, including embodiments providing optical signals in a display of the device or by means of light-emitting diodes.

According to a particular embodiment of the invention, the system may apply and measure a thermal stimulus, eg heat or cold.

According to a particular embodiment of the invention, said system may apply and measure a radiation, eg. an infrared, visible and/or ultraviolet light or combined spectra thereof, provided as an example by means of a laser, light-emitting diode, infrared, ultraviolet and/or white light source.

According to a particular embodiment of the invention, said system may apply and measure a chemical stimulus, eg. an organic or inorganic compound.

The invention further relates to the use of a system for applying and measuring a stimulation for determining the sympathetic tone including the steps of: measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value of the stimulation in one or more sympathetic tone-dependent points.

According to a particular embodiment of the invention, a system is used for applying and measuring a stimulation for determining sympathetic tone, the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points being performed anteriorly on the upper side of the clavicle and/or posteriorly on the spinal column corresponding to TH 10-11.

In an embodiment, the invention relates to use of a system for applying and measuring a stimulation for determining sympathetic tone, the measurement of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-dependent points being performed at one or more locations on the skin which innervationally (ie relating to the nerve supply) correspond to the nerve supply of the sympathetic nervous system to the heart, eg. in one or more of the points contained in the areas: C.V. 17 in the middle of the sternum, ST 18 between two ribs below the nipple and Per 1 between the nipple and the anterior axillary fold and on the back corresponding to TH 3-6 in the area between the shoulder blades, where the most sore of the said points is chosen.

According to a particular embodiment of the invention a system is used which is capable of applying and measuring a mechanical stimulus such as a compressive force.

According to a particular embodiment of the invention a system is used which is capable of applying and measuring a thermal stimulus such as heat or cold.

According to a particular embodiment of the invention, a system is used which is capable of applying and measuring radiation, eg. infrared, visible and/or ultraviolet light or combined spectra thereof, provided as an example in form of a laser, light-emitting diode, infrared, ultraviolet and/or white light source.

According to a particular embodiment of the invention a system is used which is capable of applying and measuring a chemical stimulus such as an organic or inorganic compound.

The invention is further illustrated in the following examples:

Examples.

Unit in all measurements in the examples when measuring an applied compressive force by means of a manometer is British pounds (lbs)/cm^2, in the following referred to as lbs.

Units in all measurements in the examples when measuring a compressive force applied with a finger at the threshold value of the pressure sensitivity are: 0, +, ++, +++, where 0 is the applied compressive force at a threshold value of the pressure sensitivity in a sympathetic tone-neutral point, and where =, +, ++, +++ is the compressive force applied with a finger at the same threshold value of the pressure sensitivity in a sympathetic tone-dependent point, where 0 equals the applied compressive force in a sympathetic tone-neutral point, and +, ++, +++ is the relatively lower applied compressive force.

Example 1

Example 1a

The sympathetic tone of a person was determined in the following manner: By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 13.8 lbs. Then the applied compressive force was measured to 13.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point C.V. 17. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 94% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 0 stress. The person then filled-in a questionnaire about the person's stress level, said questionnaire confirming that the person displayed no signs of clinical stress.

Example 1b

The sympathetic tone of another person was determined in the following manner. By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 14.3 lbs. Then the applied compressive force was measured to 11.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point C.V. 17. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 77% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 1 stress.

Example 1c

The sympathetic tone of a third person was determined in the following manner. By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 10.0 lbs. Then the applied compressive force was measured to 7.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point Per 1. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 70% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 1 stress.

Example 1d

The sympathetic tone of a fourth person was determined in the following manner: By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point posteriorly on the spinal column corresponding to TH-10-11 the applied compressive force was measured to 24.0 lbs. The the applied compressive force at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point posteriorly on the spinal column corresponding to TH 3-6 was measured to 22.5 lbs. At the same threshold of the pressure sensitivity in the sympathetic tone-dependent point, the applied compressive force was thus 94% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 0 stress. The person then filled-in a questionnaire about the person's stress level, said questionnaire confirming that the person displayed no signs of clinical stress.

Example 2

Example 2a

The sympathetic tone of a person was determined in the following manner: By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 17 lbs. Then the applied compressive force was measured to 8.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point C.V. 17. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 47% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 2 stress.

Example 2b

The sympathetic tone of another person was determined in the following manner. By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 10.5 lbs. Then the applied compressive force was measured to 5.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point St. 18. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 48% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 2 stress.

Example 2c

The sympathetic tone of another person was determined in the following manner. By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 14.0 lbs. Then the applied compressive force was measured to 5.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point, Per 1, and to 5.5 lbs in the sympathetic tone-dependent point St. 18. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent points the applied compressive force was thus 36% and 39 %, respectively, of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 2 stress.

Example 3

The sympathetic tone of a person was determined in the following manner: By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 9.0 lbs. Then the applied compressive force was measured to 2.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point C.V. 17. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 22% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 3 stress.

Example 4

The person mentioned in example 3 was given a personally calibrated system according to the invention for measuring an applied compressive force for determining the sympathetic tone, said system including a measuring device and a scale, which in this example was divided into four zones corresponding to the four levels of stress, said system displaying the applied compressive force and provided with a marker for marking of one or more measuring points. By using the supplied system according to the invention, the person was able to determine his/her sympathetic tone at any convenient time. As a result the person was subsequently able to determine the sympathetic tone by observing to which zone an applied compressive force corresponded at the threshold value of the pressure sensitivity in a sympathetic tone-dependent point. One zone corresponds to less than 30 % (Level 3); another zone corresponds to between 30% and less than 55% (Level 2); a third zone corresponds to between 55% and less than 80%; and a fourth zone corresponds to more than or equal to 80% of the applied compressive force at the threshold value of the pressure sensitivity in a sympathetic tone-neutral point.

Example 5

The sympathetic tone of a person was determined in the following manner: By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 9.0 lbs. Then the applied compressive force was measured to 2.0 lbs at the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point C.V. 17. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 22% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 3 stress. The person then filled-in a questionnaire about the person's stress level, said questionnaire showing that that the person displayed symptoms of chronic accumulated stress.

The threshold value of the pressure sensitivity was determined to "+++" by using a finger.

Four weeks later - after suitable intervention - the same measurings were repeated for the person.

By means of a manometer at a threshold value of the pressure sensitivity in the sympathetic tone-neutral point anteriorly on the upper side of the clavicle, the applied compressive force was measured to 10.0 lbs. Then the applied compressive force was measured to 9.5 lbs at

the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point C.V. 17. At the same threshold value of the pressure sensitivity in the sympathetic tone-dependent point the applied compressive force was thus 95% of the applied compressive force in the sympathetic tone-neutral point. According to the present invention this corresponds to Level 0 stress. The threshold value of the pressure sensitivity was determined to "0" by using a finger.

At the same time, the person advised that the previously recorded clinical signs of stress had passed.

Example 6

At a test with 250 randomly selected persons, the correlation between physiological stress and clinical stress was examined. The 250 randomly selected persons were told to fill out a questionnaire to ascertain whether they had experienced some specific situations within the last four weeks. There were 35 questions in total which represented different clinical signs of stress.

The persons were then instructed to examine themselves - in plenum - by initially identifying the upper side of the clavicle and there to register which intensity of an applied pressure was necessary to obtain the threshold value of the pressure sensitivity. With this as a starting point, the persons were instructed to locate C.V. 17 and based on the same procedure used on the upper side of the clavicle to determine the relative applied compressive force necessary to obtain the same threshold value of the pressure sensitivity on a four-point scale: 0, +, ++, +++.

All of the questionnaires were then collected and analysed.

The correlation between the applied compressive force to obtain the threshold value on the upper side of the clavicle in relation to C.V. 17 was significant ($p < 0.001$), ie. the more stress symptoms experienced by the individual person within the last four weeks the less compressive force was to be applied to the thorax in the point C.V. 17 in relation to the upper side of the clavicle.

Example 7. (Prognostic use of the method/system)

A completely healthy person, eg. a musician or conductor, employs the method and system each morning to ensure a low measurement, which prognostically gives an optimum utilization of his/her resources when music is to be played/conducted later in the day.

If one morning the measurement is high, the measurement allow for initiation of stress-reducing activities, such as exercise/relaxation. When the activity has been completed, the person can measure whether this has had a sufficient effect, ie. a low measurement is obtained. If the desired goal has not been met, the procedure may be repeated.

Example 8. (Daily stimulation with a preventive effect).

As in example 7, the system in this example, however, also being used for performing the following actions:

By means of the system such a strong continuous pressure is maintained in a sympathetic tone-dependent point that the pressure is felt without the stimulation causing pain. After 20-40 seconds the person registers that the subjacent soreness has decreased.

By means of the system this can be recorded as a 50% increased pain threshold; The pain threshold may thus increase from 40% to 60% of the threshold value in the sympathetic tone-neutral point.

Physiologically, this entails that the "stress phase" has passed and the restitution phase is activated.

This action may contribute to preventing negative stress.

Example 9. (Ad hoc stimulation for immediate relief of stress).

As example 7, in this example, however, the user registers a high value and immediately performs the action as described in example 8. At a correctly performed action, the user will be able to register a likely 50% improvement in the measured value after 20-40 seconds.

Example 10. (Measuring for learning)

As the method and system provide a here-and-now measurement of the stress level, ie. the activity in the sympathetic nervous system, a person is able known his/her "morning value" and repeat the measurings during the day so as to identify specific situations affecting the stress level (eg. a conversation, an order, a phone message, a task).

As the stress phase is activated within a few second and passes again within 20-40 seconds, the method and system provide completely new possibility for learning how different daily situations affect the stress level - both in negative and positive direction.

In the long view, the method is thus able to tell the person whether for instance a holiday has had the desired relaxing effect.

CLAIMS

1. Method of determining the sympathetic tone and/or the level of stress in a subject, including the steps of: measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value in one or more sympathetic tone-dependent points, or measuring an applied stimulation at a threshold value in one or more sympathetic tone-dependent points and optionally comparing said threshold value to a predetermined or pre-established calibration threshold value.

2. The method according to claim 1, wherein the threshold value of the stimulation is the stimulation's nociception threshold value.

3. Method according to claim 1 or 2, wherein the applied stimulation is provided by means of an applied mechanical stimulation.

4. Method according to claim 3, wherein the applied mechanical stimulation is provided by means of an applied compressive force.

5. Method according to claim 1 or 2, wherein the applied stimulation is provided by means of an applied thermal stimulation.

6. Method according to claim 5, wherein the applied thermal stimulation is provided by means of an applied heat or cold source.

7. Method according to claim 1 or 2, wherein the applied stimulation is provided by means of an applied radiation.

8. Method according to claim 7, wherein the applied radiation is provided by means of an applied infrared, visible and/or ultraviolet light or combined spectra thereof.

9. Method according to claim 1 or 2, wherein the applied stimulation is provided by means of an applied chemical stimulation.

10. Method according to claim 8, wherein the applied chemical stimulation is provided by means of an applied organic or inorganic compound.

11. Method according to any one of the preceding claims, wherein the determination is performed by means of a system for measuring the applied stimulation.

12. Method according to any one of the preceding claims, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points is carried out anteriorly on the upper side of the clavicle and/or posteriorly on the spinal column corresponding to TH 10-11 and/or on a finger and/or on a toe.

13. Method according to any one of the preceding claims, wherein the measuring of an applied stimulation at a threshold value of the stimulation is carried out in one or more sympathetic tone-dependent points at one or more locations on the skin which innervationally correspond to the nerve supply to the heart of the sympathetic nervous system.

14. Method according to any one of the preceding claims, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-dependent points is carried out in one or more of the points: C.V. 17 in the middle of the sternum and/or St 18 between two ribs below the nipple and/or Per 1 between the nipple and the anterior axillary fold and/or on the spinal column corresponding to TH 3-6, where the most sore point of the said points are chosen.

15. Method of quantitative and/or qualitative determination of sympathetic tone and/or level of stress in a human, said method including:

a) storage of a calibration threshold value and a stimulation threshold value, the calibration threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-neutral point on a human body and the stimulation threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-dependent point on the human body, and subsequently;

b) calculation of an indication value of sympathetic tone and/or level of stress by comparing the stimulation threshold value with the calibration threshold value, whereby the indication value of sympathetic tone is a measure of the sympathetic tone and/or level of stress in the human being.

16. The method according to claim 15, wherein the calibration threshold value is a pre-determined or pre-established constant value which is stored permanently.

17. The method according to claim 15 or 16, wherein the calibration threshold value is zero, whereby the indication value is identical to the stimulation threshold value or is a function of the stimulation threshold value.

18. Method according to claim 15, wherein the calibration threshold value and the stimulation threshold value are measured substantially simultaneously.

19. The method according to claim 18, wherein the indication value of the sympathetic tone is a mathematical combination of the calibration threshold value and the stimulation threshold value.

20. The method according to claim 18, wherein the indication value is a function of the ratio between the calibration threshold value and the stimulation threshold value.

21. The method according to claim 18, wherein the indication value is a function of the difference between the calibration threshold value and the stimulation threshold value.

22. The method according to any one of claims 19-21, wherein a general elevation of the calibration threshold value in combination with a reduction of the stimulation threshold value is an indication of stress.

23. The method according to any one of claims 19-21, wherein a normal level of the calibration threshold value and a reduction of the stimulation threshold value is an indication of stress.

24. The method according to any one of claims 19-21, wherein
- a stimulation threshold value of more than 80% of the calibration threshold value indicates that there is no significant level of stress in the human,
- a stimulation threshold value of between more than 55% and at most 80% of the calibration threshold value indicates that there is a low but significant level of stress in the human,
- a stimulation threshold value of between more than 30% and at most 55% of the calibration threshold value indicates that there a intermediate and significant level of stress in the human, and
- a stimulation threshold value of at most 30% of the calibration threshold value indicates that there is a high and significant level of stress in the human.

25. The method according to claim 24, wherein a combination of
1) a stimulation threshold value of at most 80% of the calibration threshold value and
2) a sum of the values of the calibration threshold and the stimulation threshold, which is significantly above average,
indicates that the low, intermediate or high level of stress is predominantly acute.

26. The method according to claim 24, wherein a combination of
1) a stimulation threshold value of at most 80% of the calibration threshold value and
2) a sum of the values of the calibration threshold and the stimulation threshold, which is about average,
indicates that the low, intermediate or high level of stress is of both acute and chronic nature.

27. The method according to claim 24, wherein a combination of
1) a stimulation threshold value of at most 80% of the calibration threshold value and
2) a sum of the values of the calibration threshold and the stimulation threshold, which is significantly below average
indicates that the low, intermediate or high level of stress is of predominantly chronic.

28. Method according to any one of claims 15-27, wherein nociception is induced by means of exposure to compressive force, heat, cold, radiation, chemical stimulation or any combination thereof.

29. Method according to any one of the claims 15-28, wherein a significantly lower nociception threshold value being obtained in a sympathetic tone-dependent point than in a sympathetic tone-neutral point indicates that a person has increased sympathetic tone and/or an increased level of stress.

30. Method according to any one or the claims 15-29, wherein the indication value of the sympathetic tone and/or level of stress is compared to at least one previously determined indication value of sympathetic tone and/or level of stress, said previous value indicating sympathetic tone and/or level of stress at an earlier point in time and/or a result of said value.

31. A method for controlling the progress of a patient's therapeutic regimen, wherein the efficacy and/or patient compliance of said regimen is dependent on sympathetic tone and/or stress level in said patient, comprising
i) determining one or more times during the course of the therapeutic regimen the sympathetic tone and/or level of stress in said patient, and
ii) adjusting the therapeutic regimen based on an integrated measure of the patient's benefit from the therapeutic regimen and the sympathetic tone and/or level of stress determination is step i.

32. The method according to claim 31, wherein the determination in step i is performed according to the method according to any one of claims 1-30.

33. The method according to claim 31 or 32, wherein the therapeutic regimen is selected from the group consisting of Insulin-treatment in diabetes, nicotine substitution used as adjuvant therapy in smoking cessation, hormonal therapy in postmenopausal syndromes, antiinflammatory therapy in acute and chronic inflammation, antiinfective therapy in infectious diseases, treatment of hypo- or hyperthyroid conditions, treatment of diseases in heart, vessels, and kidney using cardiovascular drugs, treatment of ulcers, irritable bowel syndrome, malabsorption, nausea, and other symptoms using gastrointestinal drugs, pharmacological treatment with body weight lowering drugs, exercise programmes, relaxation programmes, diet programmes, counseling or coaching, stress-management programs, personal development programmes, personal performance programmes and self-care programmes.

34. A method for prevention of undesired or unproductive stress, the method comprising
a) determination of sympathetic tone and/or the stress level in a patient according to any one of claims 1-30, and if the determination in step a indicates an elevated sympathetic tone and/or level of stress, subjecting a sympathetic tone dependent point to a stimulation having a lower intensity than the stimulation threshold value for a period of time.

35. The method according to claim 34, further comprising, after step a
b) determination of sympathetic tone and/or the stress level in a patient according to any one of claims 1-30, and if the determination does not indicate a less elevated sympathetic tone and/or level of stress, subjecting a sympathetic tone dependent point to a stimulation having a lower intensity than the stimulation threshold value for a period of time which is different from the period of time in step a, and
c) repeating step b until the determination indicates a less elevated sympathetic tone and/or level of stress than the determination in step a.

36. The method of claim 34 or 35, wherein subjection of the sympathetic tone dependent point to the lower stimulation intensity is controlled by indicating a correct stimulation intensity by means of a visible or audible indication.

37. The method according to claim 35 or 36, wherein a combination
- that, in step a, the stimulation threshold value is at most 80% of the calibration threshold value and the sum of the values of the calibration threshold and the stimulation threshold is significantly below average, and
- that the determination in step b reveals a decrease in stimulation threshold value which is less than the lower 95% confidence limit of the expected decrease after stimulation is an indication of chronic stress of a prolonged nature, which requires several subsequent repetitions in step c.

38. A method for prognosis of a disease in a patient, comprising
1) determining the sympathetic tone and/or level of stress in the patient, and subsequently
2) providing a prognosis for the patient with respect to the disease by incorporating in the determination of the prognosis the result of the determination in step 1, a determination in step 1 indicating a low sympathetic tone and/or level of stress being indicative of a better prognosis than a determination in step 1 of a higher sympathetic tone and/or level of stress.

39. The method according to claim 38, wherein the determination in step 1 is performed according to the method according to any one of claims 1-30.

40. The method according to claim 38 or 39, wherein the disease is selected from the group consisting of
an acute, subacute or chronic inflammatory condition;
a condition in which immunological reactions cause harm to human organs or in which insufficient function of the immunological system cause impaired function and/or disease;
an acute, subacute and chronic infectious disease;
a cardiovascular disturbance, which is affected by sympathetic tone, such as circulatory shock, atheriosclerosis, thrombosis, an ischemic condition, infarction, cardiac arrhythmia, hypertension;
a neoplastic growth disturbance;
an aquired metabolic disturbance;
a poisining or physical damage due to mechanic, termal, electrical or radiation energy;
a psychological, mental or behavioral disturbance, which are influenced by sympathetic tone, such as depression or other mood disorders, an addiction or dependence disorder of any kind, a neurosis, a suicidal behaviour, a sleep disturbance, fatique, astress-related complain of psychological and/or mental character;
a fertility decrease in both female and male;
a gynecological disturbance, which is influenced by sympathetic tone, such as premenstrual syndrome, dysmenorhea, menopause problems, hyperemesis gravidarum, preeclampsia and eclampsia, premature labor, situs invertus, induction of Labor, postpartum hemorhage;
an otolaryngological disturbance, which is influenced by sympathetic tone, such as tinnitus and presbyacusis;
a dermatological disturbance, which is influenced by sympathetic tone such as pruritus;
a gastrointestinal disease with stress-sensitive clinical signs and symptoms, such as gastric and duodenal ulcer, irritable bowel syndrome, malabsorption, diarrhea, constipation, nausea, and vomiting;
a neurological disturbance, such as tension headache, migraine, concussion, Parkinson's disease, Alzheimer's disease, intracranial traumas, and neuropathies
an endocrinological disorder, such as diabetes, hypothyroidism, hyperthyroidism, an

adrenocortical disorder, adrenomedullary disorder, a hypothamic disorders, a pituitary disorder, and polycystic ovary syndrome;
a allergy, such as one with reactions in skin, bronchi, and the gastrointestinal tract;
a pulmonary diseases with impaired gas exchange, such as bronchitis and emphysema;
a disease in joints and bone, such as, acute or chronic arthritis and osteoporosis;
a disorder related to changes in body weight composition, such as obesity, weight loss, cachexia;
a sodium and water-retaining disease state, such as heart failure, kidney failure, liver failure; and
pain.

41. A method for determining whether an interview-based evaluation of stress level in a subject provides a true indication of stress, comprising,
a) in parallel to the interview, determining the sympathetic tone and/or level of stress in the patient by utilising the method according to any one of claims 1-30, and
b) ascertaining whether the interview-based evaluation provides a result that correlates positively with the determination in step a, a positive correlation indicating that the interview-based evaluation provides a true indication.

42. System for measuring the sympathetic tone and/or level of stress in a human being, said system including:
a) Memory means for storing a nociception calibration threshold value determined in a sympathetic tone-neutral point on the human body and for storing a nociception stimulation threshold value determined in a sympathetic tone-dependent point on the human body;
b) An electronic circuit programmed to data process the nociception calibration threshold value and the nociception stimulation threshold value so as to obtain the measurement.

43. System according to claim 42, wherein the calibration threshold value is a pre-determined or pre-established constant value which is stored permanently.

44. System according to claim 42, wherein the calibration threshold value is zero.

45. System according to claim 42 and which further includes user-operated means for applying a discomfort-evoking stimulus to the surface of the human body and user-operated storage means adapted to store the nociception calibration threshold value resulting from a first user operation.

46. System according to any one of claims 42-45, which further includes user-operated means for applying a discomfort-evoking stimulus to the surface of the human body and

user-operated storage means adapted to store the nociception stimulation threshold value resulting from a second user operation.

47. System according to claim 45 or 46, wherein the means for applying a discomfort-evoking stimulus is contained in a first unit and where the said electronic circuit is contained in a second unit.

48. System according to claim 47, wherein the first and the second units are adapted to allow wireless communication between the first unit and the second units.

49. System according to claim 45 or 46, wherein the means for applying a discomfort-evoking stimulus and the said electronic circuit are integrated in one and the same apparatus.

50. System according to any one of the claims 42-49, wherein the means for applying a discomfort-evoking stimulation are adapted to apply a stimulus which is gradually increased, the storage means being adapted to store a stimulation level at a moment in time corresponding to the first and the second user operation, respectively.

51. System according to claim 50, wherein the applied discomfort-evoking stimulus includes an exposure to compressive force, heat, cold, radiation, chemical stimulation or combinations thereof.

52. System according to claim 51, wherein the compressive force is applied by means of a first pressure base (5) or a clamp.

53. System according to any of the claims 42-44, wherein the applied discomfort-evoking stimulus is discontinued at the time of the first or second user operation.

54. System according to any of claims 42-53, comprising means for applying a further stimulus to the surface of the human body, said further stimulus having a lower intensity than the stimulation threshold value.

55. System according to claim 52 or 54, wherein the means for applying said further stimulus are selected from said first pressure base and a second pressure base.

56. System according to any one of claims 52-55, wherein the first and/or second pressure base (5) contains a liquid, a gel and optionally gas-filled bubbles.

57. System according to any one of the claims 52-56, wherein the area of a contact face (6) of the first/and second pressure base is less than 4 cm^2, such as between 1 and 2 cm^2, or less than 1 cm^2, such as between 0.5 and 1 cm^2.

58. System according to any of claims 53-56, wherein the first and/or second pressure base (5) has a resilient contact face (6).

59. System according to claim 58, wherein an inner center portion of the contact face (6) is less resilient than an outer portion of the contact face (6).

60. System according to claim 59, wherein the first and/or second pressure base (5) comprises a relatively hard supporting member defining a first end surface with a protruding center portion, said first end surface being covered by a relatively soft member, an end surface of which constitutes said resilient contact face.

61. System according to claim 60, further comprising a pressure sensor arranged on a second end surface of the relatively hard supporting member.

62. System according to any of claims 58-61, wherein the contact face (6) is convex.

63. System according to any of claims 58-62, wherein the first and/or second pressure based is essentially conical.

64. System according to any of claims 42-63, further comprising a sound-emitting device for providing an acoustic signal to the user, the sound-emitting device being controllable to vary a characteristic of the acoustic signal in dependence of said measurement.

65. System according to any of claims 55-64, wherein said first and second pressure bases are detachably mountable to a pressure-base receiving portion of a hand-held unit of the system, whereby either one of said pressure bases is exchangeable with the other one.66. System according to any of claims 55-64, wherein the first and second pressure bases are mountable or mounted at separate pressure-base receiving portions of a hand-held unit of the system.

67. A kit of elements for assembling a system according to any one of claims 42-66, wherein said first and/or second pressure base comprises a plurality of pressure bases having different characteristics.

68. System (4) for measuring the sympathetic tone in a human being, said system including a pressure base (5) with a contact face (6) adapted to exert an outer compressive force on the human body, a sensor (7) for measuring the compressive force exerted by the pressure base (5) on the body, an electronic circuit adapted to store a first measured compressive force and a second measured compressive force, respectively, and to calculate a read-out value as an expression of the ratio between the first measured compressive force and the second measured compressive force and wherein the system includes a read-out unit (8) for displaying the read-out value.

69. System according to claim 68, wherein the pressure base (5) and the sensor (7) are integrated in a first unit and wherein the said electronic circuit is integrated in a second unit.

70. System according to claim 69, wherein the first and the second units are adapted such to allow wireless communication between the first unit and the second unit.

71. System according to claim 68, wherein the pressure base (5), the sensor (7) and the said electronic circuit are integrated in one and the same apparatus.

72. System according to any one of the claims 68-71, wherein the contact face (6) of the pressure base (5) is resilient.

73. System according to claim 72, wherein the pressure base (5) contains a liquid, a gel and optionally gas-filled bubbles.

74. System according to any one of the claims 68-73, wherein the area of the contact face (6) is less than 4 cm^2, preferably between 1 and 2 cm^2.

75. System according to one of the claims 68-74, wherein the sensor (7) is a piezoresistive force sensor.

76. System according to one of the claims 68-75, said system being hand-held and supplied with power by one or more batteries.

77. System according to one of the claims 68-76, wherein the read-out unit is an electronic display (8).

78. System according to one of the claims 68-77, wherein the electronic circuit is adapted to determine the read-out value as one of a number, eg. four, discrete read-out values (0, 1, 2,

3), the ratio between the first measured value and the second measured value being allocated a discrete read-out value (0, 1, 3, 4) displayed on the read-out unit (8).

79. System according to claim 78, wherein the discrete read-out value (0, 1, 2, 3) is non-proportional to the ratio between the first measured value and the second measured value.

80. System according to one of the claims 68-79, wherein the electronic circuit is adapted to calculate the first measured value as an average of a number of measured values and calculate the second measured value as an average of a number of measured values.

81. Use of a system for applying and measuring a stimulation for determining the sympathetic tone including the steps of: measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value of the stimulation in one or more sympathetic tone-dependent points.

82. Use according to claim 81, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points is carried out on the upper side of the clavicle and/or on the spinal column corresponding to TH 10-11 and/or on a finger and/or on a toe.

83. Use according to claim 81 or 82, wherein the measuring of an applied stimulation at a threshold value of the stimulation is carried out at one or more points on the skin, said points innervationally corresponding to the nerve supply to the heart from the sympathetic nervous system.

84. Use according to any one of the claims 81-83, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-dependent points is carried out in one or more of the points: C.V. 17 in the middle of the sternum and/or St 18 between two ribs below the nipple and/or Per 1 between the nipple and the anterior requirement and/or on the spinal column corresponding to TH 3-6, where the most sore point of the said points is chosen.

85. Use of measurement of increased nociception (hyperalgesia) for determining the sympathetic tone and/or level of stress.

86. Use according to claim 85, wherein the increased nociception is measured in a sympathetic tone-dependent point.

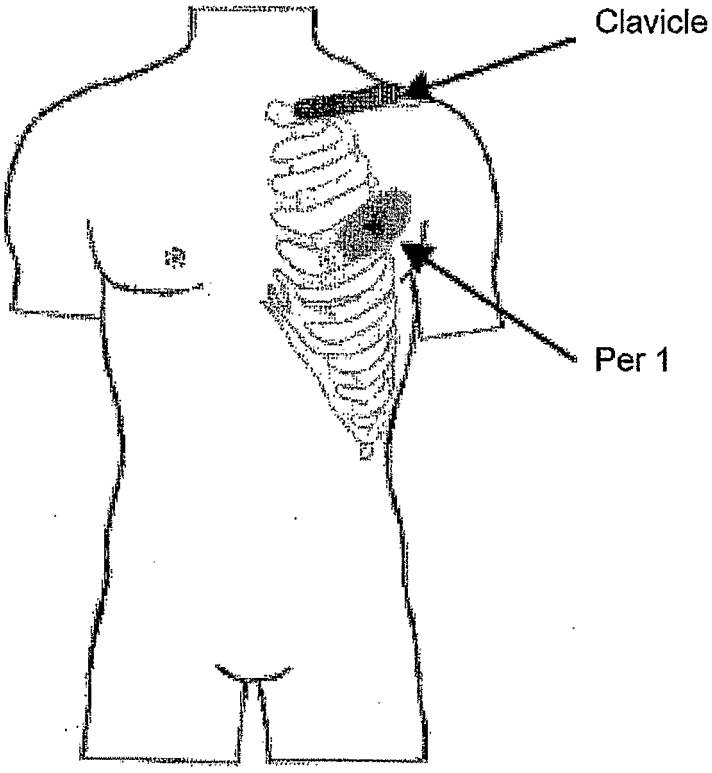

Fig. 1

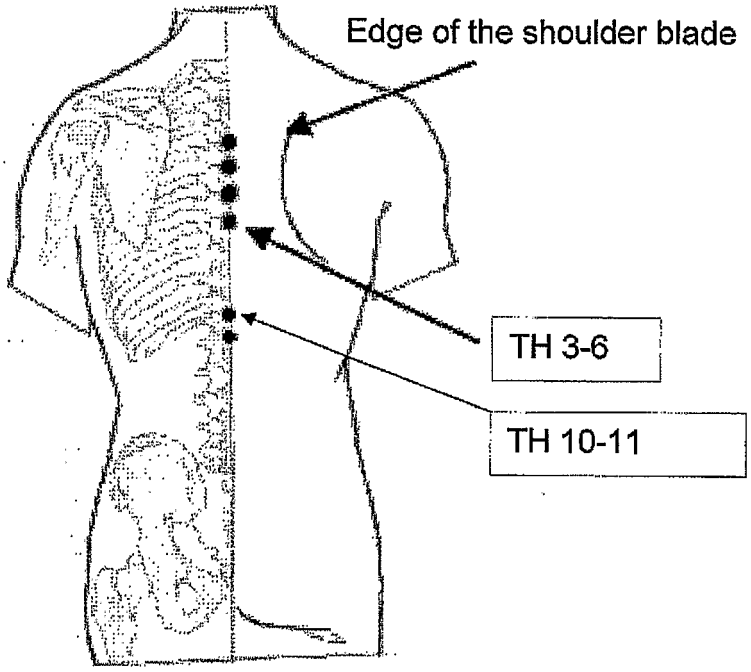

Fig. 2

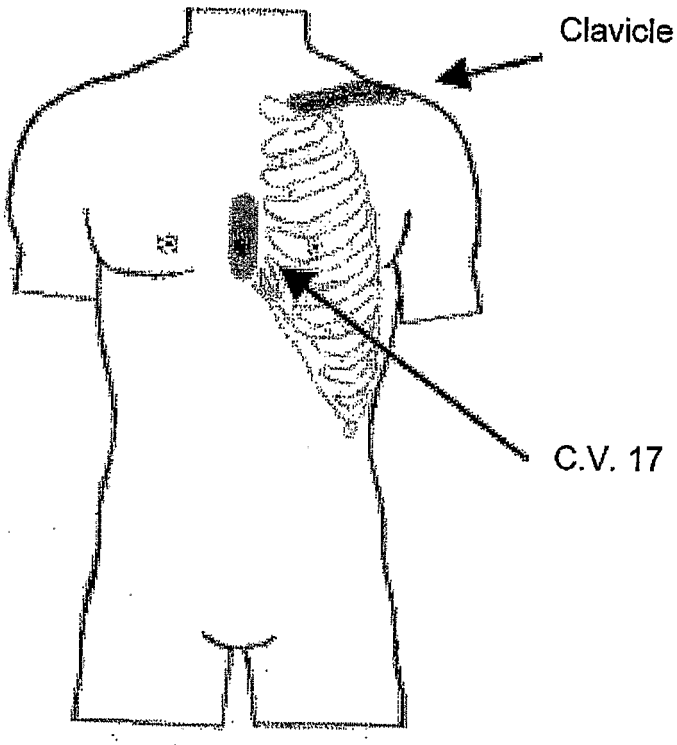

Fig. 3

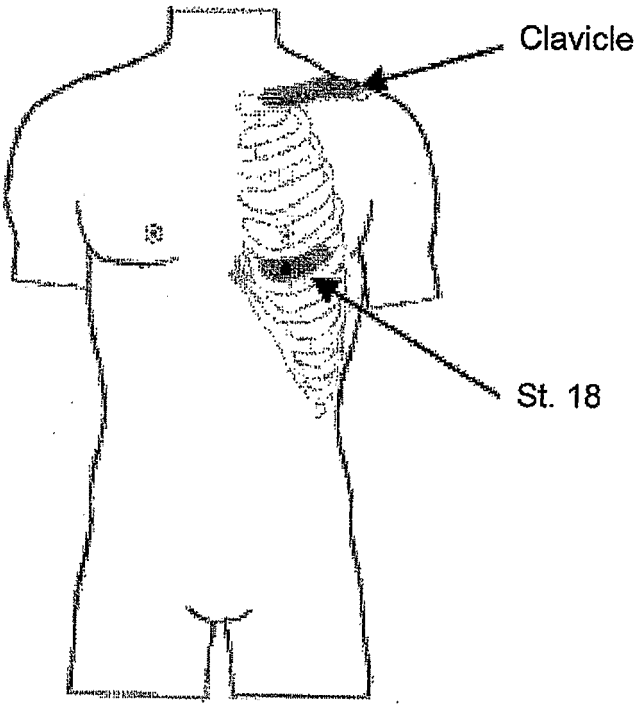

Fig. 4

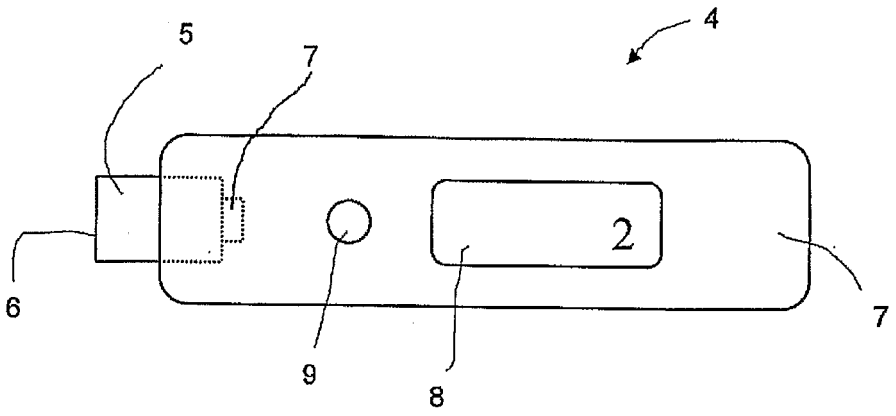

Fig. 5

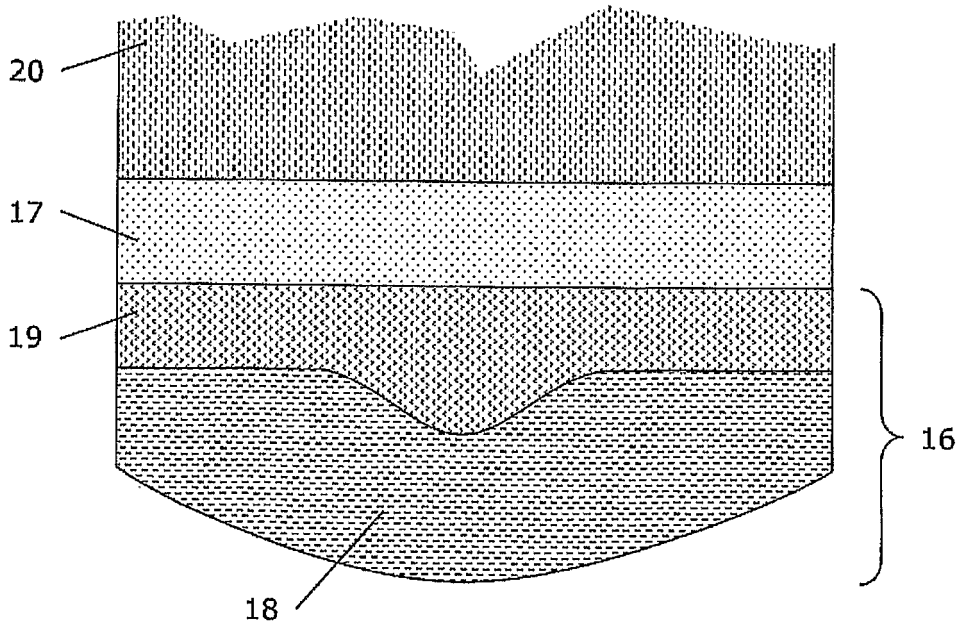

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2006/000128

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B18/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 571 124 B1 (STORM HANNE) 27 May 2003 (2003-05-27)	85
A	column 6, line 54 - column 7, line 2	42
X	EP 0 236 513 A (BARSA, JOHN E) 16 September 1987 (1987-09-16)	85
A	page 5, line 30 - line 33 page 6, line 15 - line 18 page 9, line 14 - line 35 page 9, line 51 - page 10, line 4 page 10, line 37 - line 44 page 11, line 20 - line 23 page 12, line 1 - line 18 page 12, line 42 - page 13, line 7 page 14, line 1 - line 23 page 15, line 43 - page 16, line 38	42

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2006	28/06/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Martelli, L

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2006/000128

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 673 708 A (ATHANASIOU ET AL) 7 October 1997 (1997-10-07) column 10, lines 31-47 column 12, lines 34-40 column 13, line 26 - column 14, line 58 figures 5-8	68-71, 74-78,80
A	US 5 038 795 A (ROUSH ET AL) 13 August 1991 (1991-08-13) column 7, line 65 - column 8, line 34	68
A	US 5 922 018 A (SARVAZYAN ET AL) 13 July 1999 (1999-07-13) column 9, line 66 - column 10, line 27	68
P,X	WO 2005/084529 A (STRESSMETER A/S; BALLEGAARD, SOEREN) 15 September 2005 (2005-09-15) page 16, lines 8-17 page 18, lines 1-19 page 21, lines 4-21 page 23, lines 21-23 page 24, lines 23-26	15,18, 19, 28-30, 41,42, 45-58, 68-80

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2006/000128

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-14,31-33,38-40,81-84
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 15-30, 34-37, 41, 42-67, 85-86

   System including means for processing nociception threshold values to evaluate sympathetic tone

   ---

2. claims: 68-80

   System including sensor of compression exerted by pressure base on the human body

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-14,31-33,38-40,81-84

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery. All the claims include the step of "measuring an applied stimulation at a threshold value of the stimulation", whereas such a stimulation brings about "discomfort" in the person under examination (see the description, page 9, lines 9-11 and page 15, lines 17-20).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/DK2006/000128

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6571124 B1	27-05-2003	AT 275871 T	15-10-2004
		AU 5115100 A	18-12-2000
		DE 60013828 D1	21-10-2004
		DE 60013828 T2	22-09-2005
		EP 1191879 A1	03-04-2002
		JP 2003500149 T	07-01-2003
		NO 992635 A	04-12-2000
		WO 0072751 A1	07-12-2000
EP 0236513 A	16-09-1987	NONE	
US 5673708 A	07-10-1997	NONE	
US 5038795 A	13-08-1991	NONE	
US 5922018 A	13-07-1999	US 5836894 A	17-11-1998
WO 2005084529 A	15-09-2005	NONE	

专利名称(译)	评价交感神经张力		
公开(公告)号	EP1895890A1	公开(公告)日	2008-03-12
申请号	EP2006706099	申请日	2006-03-02
申请(专利权)人(译)	应力计A / S		
当前申请(专利权)人(译)	ULL METER A / S		
[标]发明人	BALLEGAARD SREN MAGNUSSON GISLI		
发明人	BALLEGAARD, SØREN MAGNUSSON, GISLI		
IPC分类号	A61B5/00 A61B18/14		
CPC分类号	A61B5/4035 A61B5/00 A61B5/0048 A61B5/411 A61B5/4824 A61B2562/164 A61B2562/168		
优先权	200501291 2005-09-15 DK 60/716922 2005-09-15 US PCT/DK2005/000146 2005-03-03 WO		
其他公开文献	EP1895890B1		
外部链接	Espacenet		

摘要(译)

本发明涉及一种确定交感神经张力的方法，包括以下步骤：在一个或多个交感神经张力中性点测量刺激阈值的施加刺激，并在一个或多个相同阈值下测量施加刺激交感神经张力依赖点。本发明还涉及一种用于施加和测量刺激的系统，以及用于施加和测量用于确定交感神经张力的刺激的系统的使用，包括以下步骤：在一个或多个处测量刺激阈值处的施加刺激。更多交感神经张力中性点，并在一个或多个交感神经张力依赖点处以相同的刺激阈值测量所施加的刺激。