An approach to an acute emotional stress reference scale

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Introduction. The clinical diagnosis aims to identify the degree of affectation of the psycho-physical state of the patient as a guide to therapeutic intervention. In stress, the lack of a measurement tool based on a reference makes it difficult to quantitatively assess this degree of affectation.

Aim. To define and perform a primary assessment of a standard reference in order to measure acute emotional stress from the markers identified as indicators of the degree.

Subjects and methods. Psychometric tests and biochemical variables are, in general, the most accepted stress measurements by the scientific community. Each one of them probably responds to different and complementary processes related to the reaction to a stress stimulus. The reference that is proposed is a weighted mean of these indicators by assigning them relative weights in accordance with a principal components analysis.

Results. An experimental study was conducted on 40 healthy young people subjected to the psychosocial stress stimulus of the Trier Social Stress Test in order to perform a primary assessment and consistency check of the proposed reference. The proposed scale clearly differentiates between the induced relax and stress states.

Conclusions. Accepting the subjectivity of the definition and the lack of a subsequent validation with new experimental data, the proposed standard differentiates between a relax state and an emotional stress state triggered by a moderate stress stimulus, as it is the Trier Social Stress Test. The scale is robust. Although the variations in the percentage composition slightly affect the score, but they do not affect the valid differentiation between states.

Key words. Electro-physiological, biochemical, and psychometric parameters. Emotional stress. Multivariable biomarker. Quantification of stress level. Reference standard.

Introduction

The clinical diagnosis consists of the identification of the disease or disorder, and its degree of affectation. In terms of medical practice, the diagnosis is a clinical judgement aiming to assess and to inform the psycho-physical state of the individual. As a guide towards an appropriate therapeutic intervention. In the field of stress, with the exception of the post-traumatic stress disorder described in DSM-5 [1] and in ICD-10 [2], the diagnosis is usually limited to the identification, while the degree of affectation is relegated to the experience of the professional. In any case, it introduces a component of subjectivity that always makes the follow-up difficult [3].

Stress is the body adaptive reaction to a stimuli that threaten its integrity (real or potential). In a given moment this reaction may be transformed into a clinical condition and act as a pathogenic agent. The presence of a pathogenic stress state has been associated with both negative psychic and physical repercussions on health [4]. However, the level and/or duration that is necessary to lead to a transformation into a pathogenic agent is still unknown, which would be of great clinical utility.

Having an established standard is indispensable to make a comparisons, for communicating with others in an unambiguous way, as well as for documenting the evolution and facilitating the follow-up. This was understood by Knaus et al and his team from the intensive care unit of the University Hospital of George Washington University in 1981, when quantifying the severity of critically ill patients through the APACHE (Acute Physiology and Chronic Health Evaluation) index [5,6] based on an objective evaluating a certain number of parameters. APACHE continues today with some modifications and adaptations that configure a third version that takes into account a score of parameters.

In the same way as assessing the seriousness, the measurement of the level of a complicated process as stress cannot rest on the assessment of one particular aspect, and for this reason we propose to include a group of measurements in the reference scale that should take into account the possible af-

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fectation at various levels: psychological, biological, and physiological.

The general aim of this work that is sustained in this article is to define a reference standard for the measurement of acute emotional stress. Since there is no general consensus on the definition of stress, we develop an operating definition from the parameters clearly defined in the literature as indicators of the level of stress: free cortisol in saliva [7], plasma levels of prolactin [8] and copeptin [9], state psychometric tests [10], trait psychometric tests [11], and the experience of the group in the planning, development, and interpretation of several pilot studies along this line [12-15]. We expect that this first step in the measurement of stress will be significant, with the time and support of the professionals of the sector, the beginning of a path towards a quantitative approach in other aspects of neuropsychiatry.

Subjects and methods

In general, medicine has indicators of 'biological status', which are known as biomarkers and are used to objectively measure a biological process or a pathological state. From this point of view, it is clear that we would go towards solving the problem raised if the biomarkers/s of stress are discovered.

A stress biomarker must: (1) have the capacity to reflect the intensity of the stress stimulus (not necessarily in a linear), (2) be specific, that is, discriminate between a natural adapting reaction and a pathological one, (3) have sufficient temporal resolution, in such a way that through a 'continuous' measurement, we will be able to 'monitor' the phenomenon by reflecting the immediate response, the plateau, and the subsequent relaxation. And finally, (4) the measurement should be able to be made non-invasively, easy to apply, and be low cost for acquisition and process, if we wish to use the biomarker to perform screening or systematic measurements on large populations at risk.

Three large groups of potential markers are highlighted in the extensive literature on stress: psychometric tests [16] , biochemical variables [17], and electro-physiological signals [18,19]. However, none of the indicators included in these groups satisfy the conditions to be considered as stress marker. Furthermore, to search a set of biomarkers for the objective measurement of stress is even more difficult due to the almost non-existence of studies using the same stress stimulus and taking into account indicators of the three groups.

Analyzing each of the three groups of markers, it can be seen that the physiological signals are non-invasive, low-cost, and have a good temporal resolution, but are non-specific, and it is still not clear that they reflect the intensity of the stimulus. The most common parameters are computed from the electrocardiogram, the photoplethysmography [20], the electromyogram [21], the temperature [22], and the skin conductance [23]. Despite their low specificity, they have a high potential for providing information still not completely known or exploited, and scarcely documented regarding the topic. This potential has mainly been studied by engineering and biomedicine groups that currently focus on 'wearable' solutions, integrating sensors that are steadily decreasing in size and price [24,25] or in even less invasive solutions, still in their initial stages, analyzing, for example, speech and voice [26].

Psychometric tests are non-invasive, inexpensive, and have been specifically designed to be used as markers by the professionals. They can even indicate the predisposition (trait) of the individual to respond with higher or lower intensity to a stress stimulus. However, their temporal resolution is low and may be altered by repeated administering. Some of the most used tests that give information on the state and on the trait are: the Perceived Stress Scale (PSS) [27], Visual Analog Scale (VAS) [28], and the State-Trait Anxiety Inventory (STAI) [29], which has two groups of questions, one that measures the trait or general tendency to increase anxiety in stress situations (STAI-t) and another that measures the state of the subject in the specific situation (STAI-s).

In this last group the selected biochemical signals are included that possess an acceptable level of specificity as regards stress, as well as data that suggest that their levels are proportional to the intensity of stressful situations. Their temporal response is lower than the electro-physiological measurement, but better than the psychometric tests. Cortisol and prolactin are the most used as indicators of emotional stress, while copeptin is used mainly as an indicator of physical stress. In any case, for the moment the measurement of the majority of the biochemical variables is invasive, and in general, the process is expensive. It is the case, for example, of cortisol in blood, although the invasive aspect can be resolved by repeated measurements in saliva. However, the fact of having to recur to a one-off measurement at a particular time makes an exact and dynamic assessment difficult.

In summary, a considerable number of markers are available, for which the value will change due to

Figure 1. PCA variances: biomarkers.

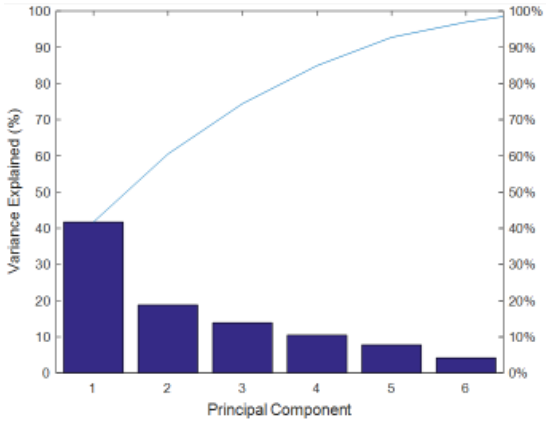


Table I. PCA coefficients: biomarkers.

	Comp. 1	Comp. 2	Comp. 3	Comp. 4	Comp. 5	Comp. 6	Comp. 7
STAI-s	0.6160	0.0249	−0.0089	0.0003	0.0227	−0.5075	0.6014
VAS	0.7067	0.0757	−0.3436	−0.0197	0.2240	0.4239	−0.3828
STAI-t	0.2899	−0.2987	0.7684	−0.3900	−0.2003	0.1718	−0.1205
PSS	0.0227	−0.1235	0.4257	0.6295	0.6332	−0.0366	−0.0669
Cortisol	0.0575	0.0078	0.0493	0.4709	−0.4163	0.6122	0.4736
Copeptin	0.0384	0.9387	0.3283	0.0020	−0.0505	−0.0137	−0.0830
Prolactin	0.1782	−0.0894	0.0024	0.4790	−0.5765	−0.3961	−0.4915
Variability explained	42%	19%	14%	10%	8%	4%	3%

PSS: Perceived Stress Scale; STAI: State-Trait Anxiety Inventory; VAS: Visual Analog Scale.

the action of a stress stimulus. In some cases, it is even possible to associate the magnitude of the changes with the intensity of the stress stimulus. However, the inverse is not true, It is possible to observe changes in these markets that are not related to any stress agent, and being able to a large number of possible causes a priori virtually inextricable.

The proposed alternative that is under development in ES3 Project [12] is to try to find a multivariable marker in such a way that the set of values of some selected variables within the three groups may be able to determine univocally not only if there is stress, but also discriminate the degree of affectation of the individual in five or seven levels depending on the severity of the affectation. Definitely, it will be a sort of discreet 'measurement' of the level of stress that would be related with the response of the individual and only in an indirect way with the intensity of the stress stimulus. However the assignment of the descriptors (or a numeric classification) may be useful, and therefore not totally subjective or arbitrary, a reference standard needs to be defined. Only in this way we will have the certainty to understand exactly the significance of the diagnosis of a particular case by another professional.

Results

The difficulty of evaluating the individual response to stress is due to the diversity of factors, mechanisms involved and the complexity of the relationships between them. However, given the need to detect it, we propose a reference scale limited to the type of stress and population detailed below. This reference scale is based on a weighted average between psychometric tests and biochemical variables as more solid and accepted measures by the scientific community, which we have verified in a specific experimental test. With this, we are leaving aside the electro-physiological signals to focus on those mostly described and validated in different studies reported in the literature.

The response to stress is a complex phenomenon involving conscious and unconscious processes that also vary dynamically. The changes at the psychological or biological level that can be observed are precisely the result of these complex processes, hence a qualitative analysis already suggests that the stress response is hardly comprehensible by the measurement of a single variable. As a consequence, for the determination of the stress level we propose to use in the first approximation the group of variables most commonly accepted in this field, assigning to each of them a weight obtained from the principal component analysis (PCA) [30]. This technique allows to group multiple variables around orthogonal axes that are assumed to represent the underlying theoretical construct.

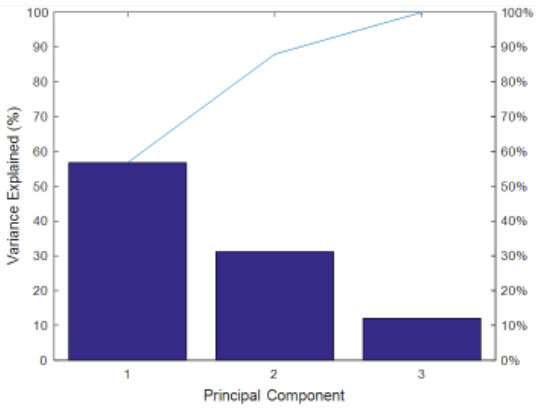
The concretion and verification of the proposed scale was performed as part of the experimental trial designed and executed under the ES3 Project [12] described in Garzón-Rey et al [13], with a sample of 40 healthy youngsters. In the first session the individual is relaxed and taken to a state we name

Table II. PCA coefficients: psychometric tests.

	Comp. 1	Comp. 2	Comp. 3	Comp. 4
STAI-s	0.6239	−0.0191	0.0467	0.7799
VAS	0.7218	−0.3414	0.1081	−0.5922
STAI-t	0.2991	0.8392	−0.4105	−0.1941
PSS	0.0173	0.4228	0.9042	−0.0576
Variability explained	60%	21%	14%	5%

PSS: Perceived Stress Scale; STAI: State-Trait Anxiety Inventory; VAS: Visual Analog Scale.

Figure 2. PCA variances: psychometric tests.



relax state (RS). In the second session stress is induced by applying the stressful stimulus typified as Trier Social Stress Test (TSST) [31] with a slight modification. At the end of the second session the individual reaches the highest stress state we call stress state (SS). At the end of each session, the psychometric tests are administered and the blood and saliva samples are taken for analysis.

For draw up of the reference scale, we propose to include VAS and STAI-s in the psychometric tests section, since both are statistically different in both the RS state (VAS: 27.3 ± 22.5; STAI-s: 15.8 ± 9.4) and the SS state (VAS: 52.3 ± 25.1; STAI-s: 26.7 ± 14.1). Likewise, we propose to include the STAI-t and the PSS as they can reflect the stable predisposition (trait) of the individual to respond to stress situations, but not on the current state of the subject. Once again, following the indications provided by the literature and our own experience, we propose to use cortisol, prolactin, and copeptin in the group of biochemical variables, dismissing others such as glucose or α-amylase, which in the experiment carried out, did not show statistically significant differences in the RS and SS states.

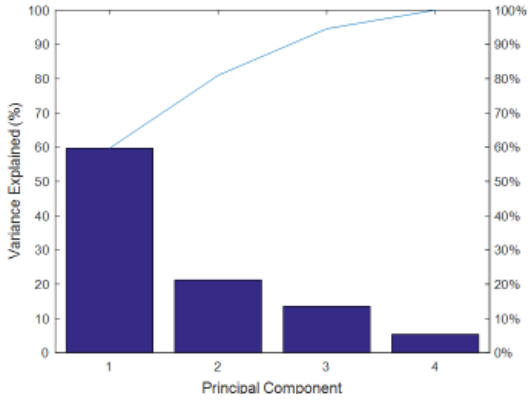
Table I and figure 1 show the results of the PCA regarding the variables that we propose to include in the reference scale. The coefficients that can be observed in table I indicate the existing correlation between each variable and each one of the components. The last row of the table corresponds to the explained variability or variability of the set of data included in each one of the components.

On first inspection, none of the components have sufficiently high correlations with all the variables sensitive to stress to conclude that any of them mainly reflects the concept of stress. This is in agreement with the fact that the response of the body to the stress phenomenon is expressed in many and distinct forms. That is to say, the response to a stress stimulus is multimodal. The first component (Comp. 1) correlated in particular with the state anxiety psychometric tests (STAI-s and VAS). The second component is highly associated exclusively with copeptin. The third one is highly or moderately associated with the trait psychometric tests and with copeptin, respectively. Finally, the fourth component correlates with PSS, cortisol and prolactin. The last three components (Comp. 5-7) together only explain 15% of the explained variability, a low enough percentage to discard them, assuming that they offer information on the variability caused by systematic errors common to the experimental design.

It is observed that the first and third components are associated with the psychometric tests, and the second and fourth components to the biochemical variables. We conclude that the Explained variability for the psychometric tests is 56% and for the biochemical variables it is 34%. And therefore, in order to propose a weighted measurement of these variables for a stress reference scale, the psychometric tests should have an approximate weight of 60% and the biochemical variables a weight of 40%.

To check the validity of the PCA results with all the variables, a new PCA analysis was performed for the psychometric tests and the biochemical variables separately. Table II and figure 2 show the results of the analysis of the psychometric tests. The first component resulting from the PCA assigns a higher weight to the tests that make reference to the state than to the trait of the subject,

Figure 3. PCA variances: biochemical variables.



with the STAI-s and VAS tests obtaining similar coefficients. The second component only has positive coefficients for the trait test, taking the PSS a value lower than that of the STAI-t. As was expected, the first component explained a much higher percentage (60%) than the second component (21%). It is interesting to observe that component three correlates highly with PSS and moderately, but negative, with STAI-t, which suggests that PSS and STAI-t evaluate different psychological aspects.

Table III and figure 3 show the PCA as regards the biochemical variable. As regards these, it confirms the previous overall analysis that included all the variables, in such a way that copeptin and the other stress hormones are situated in different components. The first component of the PCA correlates highly and practically exclusively with copeptin. The opposite situation to the second component where cortisol and prolactin have similar values between them, and there is practically no correlation with copeptin. Component 3, although it explains a smaller part of the variance, is interesting on showing a positive correlation with cortisol and a negative one with prolactin.

Assuming that the overall results of the PCA give us an overall idea of the relationship of all the variables with the response to stress, although the different variables evaluate distinct aspects of the stress, we propose as scale in which the variables that are considered important have a weight proportional to the explained variability by the component where they are situated. The percentages distribution is explained in figure 4, and in another format in table IV. The assignment of percentages to the scale is approximate given that it may change

Table III. PCA coefficients: biochemical variables.

	Comp. 1	Comp. 2	Comp. 3
Cortisol	0.0195	0.6024	0.7979
Copeptin	0.9965	0.0527	–0.0642
Prolactin	–0.0807	0.7964	–0.5993
Variability explained	57%	31%	12%

slightly depending on the particular population studied and the experimental errors.

Once the composition of the reference scale is fixed with the percentages indicated, the values for the level of stress are calculated for the RS and SS in the aforementioned study [13]. The results obtained, which we see as a first evaluation of the scale, are shown in table V. The statistically significant difference is clearly seen in the RS and SS at the end of the baseline session and stress session. On the other hand, they also show the results discriminate by sex and self-perception of stress by the individuals themselves shown to be subjected to due to other circumstances. That is to say, the reference scale differentiates between the values in RS and in SS without including the sex, or on whether or not the individual shows to be subjected to stress due to other circumstances.

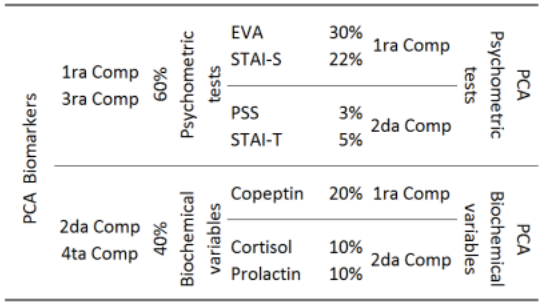
If the weights assigned to each component vary, they change, accordingly, the values corresponding to the level achieved in the BS and SS as regards the reference scale. Table VII shows the results obtained for the composition of the reference scale that is shown in table VI, in which a weighting of 75% is given to the tests, and 25% to the biochemical variables.

From the comparison of tables V and VII it is inferred that the proposed scale is robust. Although the scale may have been determined from the PCA, variations in its composition may only result in variations in the distance between both states, but the groupings remaining statistically significant. The participation of the different components enables stressful effects to be detected that may not even be perceived psychologically by the individual and that, in turn, if they have a physiological impact.

Discussion

The importance of the objective assessment of the level of stress to which an individual is subjected at

Figure 4. Composition of the reference scale proposed from the PCA analysis.



a given moment is clear, and it is demonstrated by the efforts dedicated to this up until now, although satisfactory solutions may have not been found. The difficulty of performing an objective assessment has an effect, for example, on the difficulty to rapidly evaluate the efficacy of a treatment destined to reduce stress or its consequences, and also in the difficulty in objectifying stress situations, minimizing the subjective perception or the more or less conscious attempts of deception in fictitious disorders. From another perspective, in risk professions (e.g. pilots, air-traffic controller, public transport or heavy goods vehicle drivers, surgeons), it would be important to objectively determine the stress conditions in which personal performance falls below the minimum in order to replace the individual affected. A suitable treatment and follow-up would prevent the emergence or aggravation of disease such as diabetes, depression, or the appearance of a stroke, which some authors directly associate with stress [32].

It is obvious that the same stress stimulus will trigger different responses in different individuals in the same way that a same physical force applied in the same point of the body causes different levels of pain in different individuals. Like pain, stress has an important subjective component, with the added problem of being a much more complex phenomenon. For this reason, it is important to have an objective measurement available on this subjective effect on the individual, and a reference scale or standard is needed for this purpose. The reference scale proposed is based on objective measurements of a group of biomarkers that may form part of the taking of systematic data in the hospital setting. The markers taken into account for the preparation of the scale are widely studied and universally accepted as stress indicators. The psychometrics incorporate into the scale, information on the conscious psychological response, whilst the biochemical markers incorporate information on the physiological response (to a great extent, more automatic and unconscious.

We may conclude from the results of the PCA that there is no component that we can identify as a stress response. On the other hand, the variables studied are distributed among several components, which probably reflects that the response construct to stress is multimodal. As regards the relative participation of the psychometric and biochemical tests, the first idea was to give them both the same score in analog form in the same way as all the questions in a type of examination are evaluated. However, on analyzing the contribution of the different components of this construct, it is obvious that psychometric tests that evaluate anxiety have a predominant effect on the scale. This confirms, as is well-known by the professionals, that the verbalization of our perception of the state used to be accurate, particularly when there were no causes that lead to its magnification. It is interesting that there may be a contribution of anxiety trait and the stress scale perceived that may be independent of anxiety state, which could represent, to a certain extent, individual vulnerability and deserves to be studied in the future.

Based on the PCA results, it seems that biochemical variables contribute to a lesser extent than the psychometric ones to the construct. The result are surprising considering that cortisol and also the prolactin, are used extensively as stress markers in humans and animals. However, it is possible that this minor contribution may be a result of the lower sensitivity of the biochemical variables in response to situations of moderate stress, as is used in the TSST model. It is of great interest that copeptin is associated with different components than those of cortisol and prolactin. The variations in cortisol and prolactin were sex dependent, with the response of cortisol being significant in the males, whilst it was prolactin in females. This fact could explain its lower overall contribution. Since the literature references on copeptin are much less and much more recent (probably due to the inherent difficulty of its analysis technique), our data open a great opportunity for the study of this hormone, which in reality is a reflection of vasopressin release (it forms part of the precursor peptide of vasopressin), but is more stable in blood than the latter.

Once the standard is defined, that is, once specific percentages of the contributions of each one

Table IV. Scale weights 60-40%.

Component	Weight	Component	Weight
PSS	3%	Cortisol	10%
STAI-t	5%	Prolactin	10%
VAS	30%	Copeptin	20%
STAI-s	22%	Total	100%

PSS: Perceived Stress Scale; STAI: State-Trait Anxiety Inventory; VAS: Visual Analog Scale.

Table V. Stress reference scale results 60-40%.

	Basal state	Stress estate
All	34.31 (9.2)	49.21 (10.1)
Female	33.39 (8.4)	48.28 (10.3)
Male	35.47 (10.3)	54.79 (9.9)
No under stress	29.43(5.4)	45.72 (10.9)
Under stress	38.65 (9.8)	52.16 (8.5)

t-test; $p < 0.001$.

Table VI. Scale weights 75-25%.

Component	Weight	Component	Weight
PSS	4%	Cortisol	6%
STAI-t	6%	Prolactin	6%
VAS	38%	Copeptin	13%
STAI-s	28%	Total	100%

PSS: Perceived Stress Scale; STAI: State-Trait Anxiety Inventory; VAS: Visual Analog Scale.

Table VII. Stress reference scale results 75-25%.

	Basal state	Stress state
All	44.24 (14.7)	65.99 (16.3)
Female	44.33 (14.8)	66.27 (15.9)
Male	44.12 (14.9)	65.62 (17.4)
No under stress	36.4 (7.9)	60.64 (17.9)
Under stress	51.21 (15.9)	70.5 (14.3)

t-test; $p < 0.001$.

of the markers are fixed to the reference scale, the quantification of the level of stress of each individual is immediate: The combination of values of each one of the biochemical markers directly provide an estimation of its affectation. The sample taken into consideration up until now, confirms that a higher score in the proposed scale effectively corresponds to a higher level of affectation and vice versa. On the other hand, despite the subjectivity inherent to the scale definition form itself, the scale is robust in the sense that is qualitatively independent of its quantitative composition. That is, a variation on the percentage of the scale only has an impact in the score obtained by each individual, but the distinction between the two states is always maintained, and of course without reversing their positions. Thus, moderate changes in the percentages assigned, derived from the results that could follow new studies with other populations, should not affect the provisional value of the scale.

A significant difference is seen in the RS and SS scores, regardless of whether the participants show to be stressed for other reasons. This difference is maintained even if the sample is separated by sex. Therefore, the capacity of the reference scale to differentiate the distinct stress levels is not affected by sociodemographic variables, such as sex or self-perception of stress.

The scale proposed here, although being restricted to the case of acute emotional stress, must be taken as a first approach to the problem of measuring stress, which must be validated and modified, if necessary, in the future when other studies are considered, and other populations in different clinical environments and stress situations of different intensity. Work has already started in these aspects in collaboration with other centers.

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Aproximación a una escala de referencia de estrés emocional agudo

Introducción. El diagnóstico clínico persigue identificar el grado de afectación del estado psicofísico del paciente como orientación hacia la intervención terapéutica. En el estrés, la falta de un instrumento de medición por comparación con una referencia dificulta la valoración cuantitativa del nivel de afectación.

Objetivo. Definir y hacer una primera validación de un patrón de referencia para la medida del estrés emocional agudo a partir de marcadores identificados como indicadores del nivel.

Sujetos y métodos. En general, las medidas más sólidas y aceptadas de estrés por la comunidad científica son los test psicométricos y las variables bioquímicas. Cada uno de ellos responde probablemente a procesos distintos y complementarios de la reacción frente a un estímulo estresante. La referencia que se propone es una media ponderada de estos indicadores, asignándoles pesos relativos de acuerdo con un análisis de componentes principales.

Resultados. Para una primera aproximación y verificación de coherencia de la referencia propuesta, se ha utilizado un estudio experimental con una muestra de 40 jóvenes sanos sometidos al estímulo estresante psicosocial del *Trier Social Stress Test*. La escala propuesta diferencia netamente entre los dos estados con distintos niveles de estrés inducido.

Conclusiones. Aceptando la subjetividad de la definición, y a falta de una validación posterior con nuevos datos experimentales, el patrón propuesto diferencia entre un estado de relax y uno de estrés emocional generados con un estímulo estresante moderado, como es el *Trier Social Stress Test.* La escala es robusta, ya que variaciones en la composición porcentual repercuten ligeramente en la puntuación, pero no en la diferenciación válida entre estados.

Palabras clave. Biomarcador multivariable. Cuantificación del nivel de estrés. Estrés emocional. Parámetros electrofisiológicos, bioquímicos y psicométricos. Patrón de referencia.