

## **Psychological, psychophysiological and salivary cortisol assessment in patients with recent heart attacks being treated with Alprazolam.**

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### *Introduction*

In humanity's current historical and cultural situation, stress is commonly recognized as having an important role in the origin and continuation of disorders and illnesses. In everyday terms stress means both the set of potentially harmful external forces that produce a series of biochemical, somatic and visceral reactions in the organism, as well as the reaction, whether or not it is behavioural, resulting from or in defence against the stress itself.

In fact, the word stress would have no meaning if the organism's reaction to potentially harmful stimuli were considered; therefore the reactions are highly individualized and coherent according to the psychobiological uniqueness of each personality, and the way an individual perceives the meaning of an event is extremely variable.

The definition of the term is different in the scientific domain: here stress means only the human organism's reaction to one of more events (stressors) which alter the homeostatic equilibrium. Every kind of stimulus is presented as a request for a modification of the homeostasis which, independently from the source, whether it is characterised by a physical, chemical or psychosocial stimulus, is always associated and mediated by emotive reactions. From this point of view, then, it can be said that stress is the expression of an effort made by the organism when faced with any request for modification of its homeostasis. Moreover, stress must always be seen as a complex psychophysiological reaction concerning the whole personality.

In itself, the term "stress" should not have a negative or positive meaning, since its harmfulness is tied to different variables such as the type of stressor, frequency, intensity, conditions of the system, the personality, the context, etc., however in psychosomatics, stress is usually considered as at least a potentially pathological element or anyway one with negative nuances.

In actual fact, when it was first formulated (Selye, 1970), stress was defined as "the organism's aspecific response to every request made upon it". For Selye the intensity of stress can be measured only by assessing the size of the organism's reaction, and the numerous changes produced by stress constitute what he called "General Adaptation Syndrome" (G.A.S.). With its reaction the organism tries to adapt to different conditions of disequilibrium, trying to overcome them or tolerate them. The G.A.S works in three phases:

a) alarm reaction, the response of arousal of the Vegetative Nervous System of Cannon (1932) in which essentially biochemical-hormonal modifications are manifested.

b) resistance phase of adaptation to the stimulus with arousal of the Neuroendocrinal and Immune Nervous System in which the organism organizes its defences c) exhaustion phase in which there is the incapacity to further adapt to the stressors.

Therefore for Selye, stress is to be considered adaptive insofar as it enables the organism, before a stressor of various kinds, to implement physiological responses that try to re-establish the homeostatic equilibrium. Selye later described two separate models of stress based on the effect produced at every level of the organism; he in fact called the pleasant, desirable and adaptive after-effect, "eustress", and the disadaptive, harmful, unpleasant effect, "distress" (Selye, 1970).

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For this reason we can talk about a positive role of stress in the sense of eustress and about the need to avoid or control distress. It should be noted that according to Cousins (1991), the experience of eustress can prevent or balance the negative effects of distress.

Again, Selye was the first to underline that the stress response was essentially characterized from the physiological viewpoint by an arousal of the cortex and medulla of the suprarenal glands with the consequent production of substances that he called "stress hormones".

Lastly, Selye suggested the possibility that the stress reaction was directly triggered by emotional stimuli.

But the emotional reaction, in turn, is not triggered by just any stimulus, only by those that manage to penetrate a sort of filter that can be called "cognitive assessment" (Biondi, Pancheri & Cotugno, 1987). The obvious consequence of this is that it is precisely the cognitive factors that are ultimately the source of stress, and this is true above all in man, in whom memories, fantasies and interpersonal relations, represent the predominant part of his psychic activity.

It should be underlined at this point that for stress to play an important role in the onset of some illnesses, as well as being intense enough to trigger the biochemical processes involved in the various kinds of response, it must be able to produce, through the organism's automatic control mechanisms, a model of chronic reaction.

In man, a decisive role is played by psycho-social stimuli. In any kind of human society, in fact, but above all in the western world, the complexity of interpersonal relations at times means that the stress they cause cannot be neutralised. Moreover, in some cases, the agent mainly responsible for stress may not be easily identifiable; in yet other cases, the cognitive assessment of the situation can lead the immediate neutralization of the stress to cause even worse consequences later, so it may be decided to delay the implementation of behavioural patterns designed to immediately reduce stress. Lastly, the stressing situation may not be external, but internal to the individual. As far as emotions and feelings go, it should be pointed out that the physiological indexes in emotional arousal do not change according to whether the emotional stimulus is positive or negative. In other words, the heart "beats fast" both out of anger and out of fear and out of love; in all these cases, in fact, after a situation of initial, acute stress, for the positive emotions there is a relatively rapid recovery, or a return to the pre-stress base values, while for negative emotions, there is the risk of the disadaptive response becoming chronic with the consequent prolonging of the state of hyperarousal.

It follows that in man, especially in western countries where these behavioural reactions of avoidance or repression are dominant, the risk of chronic stress are extremely high.

Moreover, the role of stress and the emotional arousal connected to it is variable in the aetiology of certain illnesses. It is in fact possible that it is the principle cause, or only a contributing cause, or an accessory element of factors predisposing the subject to the illness. The response to stress, lastly, is different from person to person: stimuli with the same stress power do not necessarily cause the same reaction in different individuals, just as different degrees of stressfulness may lead to the same reaction in different individuals. It is therefore possible that stress that is easily tolerated by some individuals may become pathogenous in others and cause disorders or illnesses of various kinds; the opposite however may happen, that is, the effect of a highly stressful stimulus for some, may be easily tolerated by others thanks to greater "constitutional" resistance and/or the acquiring of suitable techniques of self-control (non repressive).

This means that the organism, while responding to stress according to a predetermined biological scheme, is capable of modulating the size and degree of the reaction to the stress it is repeatedly exposed to (Timio, 1980).

The differentiated pathological effect of stress, intensity and duration being equal, is therefore a function of conditioning factors that can heighten or block the reaction to stress, whether it is represented by internal factors (constitution, genetic predisposition, personality, age, sex) or external factors (medications, diet, smoking, etc.).

The organism's response is therefore always multimodal, involving various mechanisms both at the physiological and the behavioural level.

The reaction to stress is therefore now known to be one of the main culprits, not only of cardiovascular disease but also of numerous other disorders, so recognising early signs such as a sort of natural or constitutional predisposition to show this complex psychophysiological reaction becomes more and more important for the work of prevention, diagnosis and rehabilitation therapy in most organic and psychic disorders and illnesses.

The literature on the subject is increasingly in agreement in saying that the early identification of some typical behaviours, lifestyles and corresponding physiological patterns, such as neurovegetative and neuro-hormonal modifications, is very important for the development of multidisciplinary therapeutic strategies.

It is now well-known that some behaviours, habits and lifestyles, as well as some personality traits, can have an influence on the development and on the continuation of serious disorders and illnesses, through a particular pattern of response to stress. For this reason, the early identification of typical behaviours, lifestyles or corresponding physiological patterns, is very important for establishing multidisciplinary therapeutic strategies to reduce the risk of serious pathological events (Selye, 1970; Timio, 1980; Mertens, 1986; Carney et al., 1987). The way each individual controls his emotions therefore seems to play a specific role in the aetiology of many psychosomatic disorders and organic illnesses. Perspective and retrospective studies so far carried out indicate that the degree of expression or repression of one's feelings can facilitate the development of specific pathological events (Rosenman & Friedman, 1977; De Faire & Theorell, 1977; Friedman, 1977; Massing & Angermeyer, 1985). Particular attention has also been paid to the physiological responses elicited by stressful situations, which, like those of a behavioural kind, seem to indicate the presence of specific models of physiological reaction. In the literature today we find a number of research projects designed to identify the profile of psychophysiological response to stress, which offer numerous tests believed to be capable of eliciting significant reactions of neurovegetative arousal. This is also made possible by the use of sophisticated methods of measurement for the assessment of the reaction pattern, such as the level of skin conduction, the peripheric temperature, respiratory rate, etc., or the variation, before and after the presentation of the various stressors, of hormones like PRL, Cortisol, etc. (Stratton & Halter, 1985; Bohnen, Houx, Nicolson & Jolles, 1990).

A valid tool for the measurement of the individual's physiological reactions, which seems to offer a certain scientific guarantee, is still the psychophysiological profile (Fuller, 1979). This method allows us, using equipment for physiological recording interfaced with a personal computer and placed in controlled environments, to record some parameters thanks to which clinicians can acquire information on various reaction patterns and to assess the stability or lability of physiological activity at rest and in conditions of moderate stress.

Usually the physiological parameters recorded during the various phases of the profile (rest, relaxation, stress, recovery) are: skin conduction, muscular activity, peripheric temperature, heart rate, respiratory rate and reactivity. At the end, one thus obtains a complete measurement which will not only make it possible to assess the individual's physiological self-regulation situation, and how important this is in the onset of the disorder, but also in the event the assessment shows the need for Biofeedback training, to choose which physiological parameter the patient must learn to control. The assessment of the psychophysiological profile therefore lets us know the subject's level of arousal and the subtypes of the different patterns of reaction to stressful stimuli.

The psychophysiological profile should not be seen as a useful procedure for a descriptive diagnosis that in general in the diagnostic field does not present great difficulties, but rather, an essential tool to interpret the current dynamic equilibrium of the patient's systems of knowledge and of information elaboration, both at a tacit (or emotional) level, and at an explicit (or cognitive) level (Reda, Demontis & Blanco, 1988).

Muscular activity is studied in psychophysiology as a peripheral indicator of psychological processes that require or are expressed through muscular contractions: the response to a signal, the expression in facial muscles of emotive states and of disorders due to stress, etc. The set of techniques for the measurement and recording of the variations of electric

potential sparked off by muscular contractions is called electromyography. The electromyographic tracing (electromyogram, EMG) represents the recording in a given time span of the potentials of muscular action; in psychophysiology research a surface recording is generally used, placing the electrodes on the epidermis (surface electromyography).

These electrodes, placed at the level of forehead muscles since these reflect the total body tension, are positioned a certain distance apart so as to record the difference of electric potential produced between them in the underlying and remote muscle tissue. Therefore the EMG activity of the frontal region correlates with anxiety and tension and has been aetiologically linked to tension headache.

Subjects suffering from disorders typically due to stress present high levels of arousal of the nervous system. This implies an increase in the tension of forehead muscles, heart beat, blood pressure, sweating and cooling of the hands (vasoconstriction), breathing irregularity and other reactions like increased blood sugar.

As well as an index of arousal levels, the EMG has been used as an index of specific cognitive and emotive processes (Cacioppo & Petty, 1981; Pruneti, Giusti, Boem & Luisi, 2002; Pruneti, 2005).

The technique of EMG biofeedback offers the therapist the widest range of clinical uses, in fact, besides being used in the treatment of psychosomatic disorders, it is used in anxiety neuroses, phobia and as a support technique in Systematic Desensitization.

As skin conduction is a variable of electrodermic activity linked to the working of the sudoriparous glands innervated by the sympathetic branch of the ANS, it is a direct indicator of the affective and emotive processes (of emotional arousal). The electrodermic reaction is now universally recognised as a parameter that provides significant indications of an individual's emotional state: so a rapid increase from the base level, which instead provides information on the general state of consciousness, is a reliable index of an anxiety reaction.

In psychophysiological research, the most common measurements of modifications in the characteristics of the skin are skin electrical resistance and its counterpart, skin conductivity; a recent addition is skin potential.

The first two measurements are obtained by applying a continuous electric current of low intensity to two places on the subject's skin and measuring the variation of voltage occurring after various stimulations. The resistance varies with the activity of the sudoriferous glands: the more the sweating, the lower the resistance and vice versa. It is possible to take two measurements of the skin's electric resistance. The first is the basic resistance, or level of skin resistance, while the second is the skin resistance response, also known as galvanic skin reaction (GSR). A second method of assessing skin neurovegetative activity is by measuring the variations in the skin's electric potential manifested periodically and spontaneously between the skin and the inside of the body. This measurement, called SPR (Skin Potential Response), is more physiological than the previous one in that it does not depend on a current applied externally, but poses greater technical problems which makes it less commonly used than the GSR. As in the case of skin resistance, it is possible to obtain two measurements: the number of responses of skin potential and a measurement of the basic level.

It seems useful in fact to distinguish between a basic activity (tonic component) and a response to discrete stimuli (basic component). For tonic activity, the expressions used are skin conduction level or skin potential level depending on whether the recording is exogenous or endogenous. To refer to phasic activity, the expressions used are skin conduction response and skin potential response.

Conduction, the counterpart of resistance, is expressed in *mho*, the graphic inversion of the unit measuring resistance, the *ohm*.

One of the most highly studied parameters among the cardiocirculatory vegetative responses is heart rate, both due to the relative simplicity of the measurement techniques, but above all due to the important psychophysiological and psychosomatic implications associated with it. For some time it has already been shown to be a sensitive indicator of the relations between

the cerebrospinal system and the VNS and therefore of relations between behaviour, vegetative reactions and stimuli from the outside environment.

An increase in the diameter of the blood vessels that serve a certain organ (vasodilation) produces an increase in the flow of blood in the organ itself, while a reduction of the diameter of the vessels (vasoconstriction) reduces the amount of blood available to the organ. Vasoconstriction and vasodilatation also produce modifications in skin temperature, the first causing a drop, the second causing a rise (Plutchick, 1956).

The heart rate is the result of a series of physiological mechanisms linked to the Sympathetic (arouser) and the Parasympathetic System (inhibitor) and is therefore greatly influenced by stress, by physical activity or by muscular tension, by personality structure, motivation, emotional state as well as the great variety of organic pathologies.

High levels of physiological arousal, of anticipatory anxiety and muscular tension are closely connected to the increase in activity and heart rate.

Changes in the heart rate are generally recorded by means of an electrocardiograph (ECG), which provides a tracing of the electrical activity of the heart muscles. There are 5 phases of the cardiac cycle visible in a ECG tracing, indicated respectively with the letters P, Q, R, S, T, each of which represents a positive or negative deviation from the base line, and the R wave shows heart contraction. Although the respiratory rate is not a cardiovascular measure, when the heart rate is recorded, a note is also made of the respiratory variations; this is due to the fact that in some cases variations in the heart rate may be due to respiratory changes linked to inhaling and exhaling. Skin temperature responds to changes in the outside temperature through a mechanism of thermoregulation characterised by a dilation and contraction of the smooth muscles of the peripheral blood vessels. The increase in sympathetic activity of the peripheral vessels causes a vasoconstriction which in turn produces a lowering of the temperature in those parts, a reduction in the blood flow and a reduction in peripheral blood pressure.

In normal subjects, the values of the EMG and GSR, both during base-line and training, have a positive correlation. This means that a drop in skin conduction responds to a reduction in muscular tension, considered the index of autonomic arousal. In fact the electrodermic response is now universally recognised as the parameter providing significant indications of the individual's emotional state: so its rapid rise above the base level, which gives information about the general state of consciousness, is a reliable index of an anxiety response. With reference to the normal group, when there is a relaxation response, there is a rise in temperature (EMG-TEMP correlate negatively) and with a fall in the electrodermic activity, there is a rise in temperature (GSR-TEMP correlate inversely). In fact with a decrease in muscle tone there is a lowering of the electrodermic activity due to the greater vasodilation, and an increase in peripheral temperature.

During all the phases making up the P.P.F. the values of the physiological parameters are constantly recorded. In this way one obtains a complete measurement that will make it possible to assess how far the capacities of physiological self-regulation are compromised.

### *Method*

The patients that had had a first episode of heart attack were randomly assigned to two groups: treated and untreated. In actual fact, in contrast to what is reported in the literature about the obvious intersubjective diversity related to the levels and fluctuations of the psychophysiological parameters, no significant differences were found between the two groups following the calculation of Student's t.

The treated group was composed of 26 subjects (F=6 and M=20) aged between 39 and 66 (average age  $54,3 \pm 6,4$ ).

All the subjects were consecutively examined at the Clinical Psychology centre of the department of Child Neuropsychiatry of the 'Santa Chiara' University Hospital in Pisa. The same subjects, released from the division of Cardiovascular Medicine where they had been

admitted for a period lasting from seven to 16 days, were undergoing routine checkups in this department.

**All the patients were counselled about the need to assess the psychosocial aspects of stress and to test the individual risk factors for the ischemic pathology.**

Every subject was encouraged to ask questions about how to behave generally in their social life, on the return to their work and family settings, as regards the effects of aging, diets etc., all factors that the heart attack victim has to deal with.

A psychologist and a cardiologist conducted the interview together. The therapy based on Benzodiazepine was then presented only to the untreated group, who were told it was just a supplementary aspect of the basic treatment.

All the patients were given diaries that they were to compile daily and they were encouraged to contact the centre for Cardiovascular Medicine or that of Clinical Psychology whenever they felt it necessary.

As the subjects had to repeat the cardiovascular tests after 30 days, it was decided that the period of administration of the medication would have the same duration.

Benzodiazepine was administered to every patient twice a day with a dosage of 0.5mg.

The control group (Untreated subjects) was made up of 26 patients (F=9 and M=17) with the same characteristics as the experimental group, aged between 44 and 65 (average age  $55.6 \pm 4.6$ ).

All the subjects present in the control sample did the same Psychological and Cardiological tests as the members of the experimental group.

**Criteria of Inclusion and Exclusion.** The subjects receiving hormonal and anti-hypertension therapies were excluded from both samples.

Moreover, none of the subjects could show signs of hypo or hyper-arousal (Addison's disease or Cushing's syndrome), of hyperthyroidism, obesity or be on medication for depressive syndromes.

**Psychological Assessment of Current State.** The Crown and Crisp Experiential index (CCEI) was administered after a first interview and at the time of the last interview. The score obtained was divided into six scales (free floating anxiety, phobic anxiety, obsessive behaviour, somatic symptoms, depression, lack of emotive control) plus a total score, which is usually considered a good indicator of general neuroticism.

**Psychophysiological Assessment.** Psychophysiological profiles were recorded pre and post treatment and were done at four in the afternoon with the following procedure: adaptation phase (5-7 minutes), rest (8 min), presentation of stress (8 min), recovery (6 min). Adaptation: after explaining the procedure and positioning all the electrodes, the operator waits for the physiological values to stabilize (5-7 min). During this period, the values are monitored but not recorded.

Base line: monitoring of all the psychophysiological parameters at rest (8min)

Presentation of the stress: presentation of the MST (8 min)

Recovery: during this phase the operator waits for the values of all the parameters to return to Base-line levels; the resulting patterns are then monitored and recorded (6 min).

The Psychophysiological recording was done using a machine with 8 output channels Biolab 104 C,PT 711 (Produced by SATEM, ROMA), interfaced with an IBM compatible PC.

The following parameters were constantly monitored:

- Skin Conduction (CC): measured on the dominant hand using gold plated electrodes with a surface of 1 square cm placed on the index and ring finger.
- Electromyograph of the frontal muscle (EMG): using three electrodes of 14mm in diameter made of unalterable metal. The electrodes are placed 4.5 cm apart, the one representing

the mass is placed between the two active sensors, in the centre of the patient's forehead.

- Peripheric temperature (TP) was measured thanks to the use of an integrated circuit and of an electrode placed just above the thenar of the dominant hand for the monitoring of temperature variations in a range of 0.01°C.
- Heart Rate (FC): was measured with an optoreфлектор placed on the surface of the skin, able to pick up the variations of sphygmic flow.
- Respiratory rate (FR): measured with the use of a thin tourniquet, carefully placed around the Patient's abdomen or hips.

All the patients were examined in a semi-prone position, the recording was done in a room with a temperature between 18 and 22 degrees Centigrade and not over 50% humidity.

**Mental stress test:** a computerized version of the CPM47 was used. In this version a time limit of 30 seconds was set for the presentation of each figure and a series of visual and acoustic stimuli were introduced as distracters.

This particular procedure, requiring a higher level of concentration, was carried out so as to increase the difficulty of the test; in fact, the subjects had to pay attention to six stimuli simultaneously.

**Measurement of cortisol:** to obtain a daily measurement of the secretion of cortisol, the saliva sample for measuring this hormone was taken at 8 a.m., at 4p.m. (three saliva samples in three phases: base line, stress presentation, recovery) and lastly, at 11p.m. Before being analysed, the saliva samples were kept at a temperature of -20°C.

The testing procedure in the Kit instructions were followed: 25 ml of the 7 standard solutions (containing 0, 10, 50, 100, 200, 500, 800 mg/l of cortisol), 25 ml for the standard quality control and 100 ml of hormone were mixed in a vial containing a contrast liquid for cortisol.

Later, one ml of cortisol was added to each test-tube and after being mixed, it was left in a room with a suitable temperature for 90 minutes.

Lastly, the liquid was aspirated while the portion of cortisol remaining on the bottom of the test-tube along with the antibody was deposited for one minute in a special container.

To minimize the risk of variability of the results, all the samples for each subject were analysed at once.

The radioimmunological dosage designated to determine the amount of cortisol in man was used for the assessment of the salivary cortisol.

After about 5 weeks (an average of 36.2, in a range of 33-42 days) all the patients underwent the same assessment procedure, the Crown Crisp Experiential Index (CCEI) was administered again, they did a psychophysiological recording and a salivary cortisol assessment.

**Statistical Analysis:** the analysis of the descriptive Statistics (average values and Standard Deviations) for all the scores obtained in the various tests is shown in Table 1.

The analysis of the variance (ANOVA) served to find the significant differences between the treated group of patients and the untreated group as regards the parameters considered.

The analysis procedure was used to compare the values measured before and after the treatment with Alprazolam for all the variables measured and also to compare the experimental group (treated) with the control group (untreated).

## *Results*

**Crown and Crisp Experiential Index:** Table 1 shows the average values and the related Standard Deviations obtained for the CCEI scores before and after treatment with Alprazolam.

In the experimental group the scores obtained after treatment (average values and Standard Deviations) are considerably lower than those obtained before treatment.

The latter consideration can be interpreted as a general shift towards the homogeneity of the scores obtained after the administration of the drug (reduction of interindividual variability) especially as regards the scores related to anxiety and symptoms correlating to Depression.

The analysis of the variance confirmed that the scores related to four of the six scales belonging to the CCEI along with the total score significantly decrease after treatment and it is also possible to see a very significant reduction ( $p < 0.001$ ) in the values shown in the Anxiety and Depression scales in the same test.

In the control group, instead, there is a significant reduction ( $p < 0.05$ ) only as regards the Anxiety score while on all the other scales the values remain too high.

The effect of the treatment is visible in Figure 1. The graph clearly shows that the patients who were part of the experimental group, after the pharmacological treatment, showed values for Anxiety, Depression, Phobia and Somatic Syndromes typical of a normal population to whom the same psychodiagnostic reagent has been administered.

In other words: "Normal Scores".

**Table 1: Crown and Crisp Experiential Index : Average values (Standard deviations) and ANOVA (between conditions) before and after treatment**

	Treated			Untreated		
	Before	After	F	Before	After	F
A	7.78 ( $\pm 3.29$ )	3.89 ( $\pm 1.72$ )	20.91***	8.18 ( $\pm 3.14$ )	5.77 ( $\pm 2.13$ )	7.23*
F	6.62 ( $\pm 2.24$ )	3.84 ( $\pm 2.16$ )	8.35**	5.3 ( $\pm 2.7$ )	4.9 ( $\pm 1.75$ )	4.02
O	9.52 ( $\pm 2.03$ )	6.94 ( $\pm 2.41$ )	6.57*	9.78 ( $\pm 3.4$ )	9.89 ( $\pm 2.5$ )	1.97
S	7.84 ( $\pm 3.46$ )	3.97 ( $\pm 2.18$ )	8.40 *	8.1 ( $\pm 2.9$ )	8.8 ( $\pm 2.1$ )	4.66
D	6.78 ( $\pm 2.52$ )	3.57 ( $\pm 1.26$ )	24.51**	7.96 ( $\pm 3.01$ )	6.8 ( $\pm 2.2$ )	2.33
E	5.1 ( $\pm 2.49$ )	4.63 ( $\pm 2.06$ )	1.73	4.41 ( $\pm 1.83$ )	5.78 ( $\pm 2.01$ )	2.87
TOT	42.88 ( $\pm 10.84$ )	29.63 ( $\pm 6.52$ )	6.38*	43.52 ( $\pm 7.94$ )	41.37 ( $\pm 6.6$ )	3.37

Legend: A = Free Floating Anxiety; F = Phobic Anxiety; O = Obsession  
S = Somatic Symptoms; D = Depression; E = Expressed Emotivity; TOT = Total Score  
\*p<.05 \*\* p<.01 \*\*\*p<.001

Legend: A=Free Floating Anxiety; F=Phobia; O=Obsession; S=Somatic Symptoms; D=Depression; E=Emotivity (lack of control).

**Psychophysiological Profile.** Table 2 shows the data for the group of treated subjects who, during Baseline, present a significant decrease in skin conduction ( $F=30.67$ ,  $p < 0.01$ ), with a similar tendency, though milder, in forehead muscle tension and in respiratory rate, while



both the peripheric temperature and the heart rate show a slight increase. As regards the values recorded during the stress presentation phase, there is a significant drop, comparing the pre- and post- treatment values, in skin conduction ( $F=24.19$ ,  $p<0.01$ ), in the electromyograph of the frontal muscle ( $F=8.66$ ,  $p<0.01$ ) and in the heart rate ( $F=7.62$ ,  $p<0.01$ ). This might suggest that the pharmacological intervention favours a reduction in these parameters. The respiratory rate remains substantially stable, while the average value of peripheric temperature increases in a significant manner ( $F=6.79$ ,  $p<0.05$ ).

Table 3 shows the data concerning the group of untreated subjects. As can easily be seen, none of the parameters of the Baseline showed great changes between pre- and post-treatment. As was expected, the values tend to increase in the stress phase, the only parameter which, however, undergoes a decrease is peripheric temperature.

In the control group no significant differences were found as regards the rest phase or the stress phase.

In the comparison between the groups, there were no significant differences in the recovery phase.

**Table 2: Psychophysiological profile during Baseline: Average values (Standard deviation) and ANOVA (between conditions) Before and after 30 days' treatment.**

	Treated Group			Untreated group		
	Average ( $\pm$ DS)		F	Average ( $\pm$ DS)		F
	Before	After		Before	After	
<i>SCR</i>	13,12 ( $\pm$ 6.48)	7.18 ( $\pm$ 3.01)	30.67**	12.23 ( $\pm$ 5.64)	11.48 ( $\pm$ 6.59)	.207
<i>EMG</i>	5.11 ( $\pm$ 1.76)	4.18 ( $\pm$ 1.20)	2.89	4.57 ( $\pm$ 1.73)	4.14 ( $\pm$ 2.61)	1.67
<i>PT</i>	32.2 ( $\pm$ .86)	33.05 ( $\pm$ .55)	1.8	32.15 ( $\pm$ .92)	32.57 ( $\pm$ .99)	.219
<i>HR</i>	67.31 ( $\pm$ 6.56)	68.47 ( $\pm$ 3.74)	4.36	66.84 ( $\pm$ 4.91)	62.5 ( $\pm$ 9.03)	.430
<i>RR</i>	1.75 ( $\pm$ .45)	1.65 ( $\pm$ .28)	4.08	1.96 ( $\pm$ 1.96)	1.74 ( $\pm$ .73)	1.135

Legend: SCR = Skin Conduction Response; EMG = Muscle Tension; PT= Peripherical Skin Temperature; HR = Heart Rate; RR = Respiratory Rate  
\* $p<.05$  \*\* $p.<.01$

**Table 3: Psychophysiological profile during Stress Presentation: Average values (Standard deviation) and ANOVA (between conditions) Before and after 30 days' treatment.**

	Treated Group			Untreated group		
	Average ( $\pm$ DS)		F	Average ( $\pm$ DS)		F
	Before	After		Before	After	
<i>SCR</i>	19.33 ( $\pm$ 6.83)	13.45 ( $\pm$ 3.77)	24.19**	18.48 ( $\pm$ 2.12)	18.08 ( $\pm$ 5.84)	.187
<i>EMG</i>	8.99 ( $\pm$ 2.31)	7.18 ( $\pm$ 2.43)	8.66**	7.14 ( $\pm$ 1.74)	6.84 ( $\pm$ 2.76)	.812
<i>PT</i>	30.70 ( $\pm$ .81)	31.88 ( $\pm$ .67)	6.79*	30.57 ( $\pm$ 1.08)	30.19 ( $\pm$ .84)	2.989
<i>HR</i>	86.15 ( $\pm$ 10.72)	80.12 ( $\pm$ 6.14)	7.62*	82.57 ( $\pm$ 6.27)	84.57 ( $\pm$ 8.6)	1.368
<i>RR</i>	2.58 ( $\pm$ .53)	2.20 ( $\pm$ .39)	3.18	2.72 ( $\pm$ 0.91)	2.66 ( $\pm$ 2.32)	.578

**Legend:** SCR = Skin Conduction Response; EMG = Muscle Tension; PT= Peripheric Skin Temperature; HR = Heart Rate; RR = Respiratory Rate  
 \* p<.05 \*\*p<.01

Salivary Cortisol. The evaluation of the results obtained appears very complex because of the great interindividual variability of the results observed. The data in Table 4 shows a statistically significant reduction in cortisol during the recovery phase, measured by the PPF in relation to the untreated group. This result, so clear and important, will be clarified and commented on in the Discussion section.

**Table 4: Salivary Cortisol (µg/l) – Average values (Standard deviation) and ANOVA (between conditions) Before and After treatment.**

	Treated Group			Gruppo Untreated		
	Average (±DS)		F	Media (±DS)		F
	Before	After		Before	After	
<i>Zenit</i>	9.34 (±6.52)	8.11 (±4.89)	2.65	10.66 (±6.91)	10.38 (±4.66)	11.97
<i>Adattamento</i>	4.59 (±5.42)	4.67 (±4.4)	9.21	5.32 (±4.46)	4.86 (±4.59)	7.39
<i>Baseline</i>	4.24 (±5.64)	3.4 (±2.72)	4.32	4.91(±5.01)	4.2 (±3.57)	3.55
<i>Stress</i>	7.6 (±5.71)	6.18 (±2.87)	6.82	8.18 (±4.84)	6.93 (±2.79)	.57
<i>Recupero</i>	7.54 (±7.57)	5.03 (±2.23)	16.37**	6.59 (±3.96)	6.05 (±2.79)	7.44
<i>Nadir</i>	3.51 (±6.09)	2.62 (±3.87)	6.57	2.5 (±3.77)	2.94 (±1.98)	2.17

\*\*p<.01

### Discussion

This study tried to assess the behaviour, the psychophysiological parameters, and the stress-related endocrinal responses in a group of subjects recently affected by heart attack. These variables were assessed by analysing multiple parameters before and after treatment with benzodiazepine, so as to monitor the impact of the drug on the same. To obtain more reliable data a control group was introduced to compare with the group treated. The patients in the experimental group were subjected to treatment with benzodiazepine for 30 days. In these subjects a significant lowering of the psychophysiological parameters was observed between the pre and post treatment phase, in confirmation of the beneficial effect of the therapy of benzodiazepine.

As far as the behavioural data is concerned, the results of the untreated group clearly show a considerable reduction in the anxiety-depressive and somatic symptoms indexes. As regards the PPF, skin conduction was shown to be the most sensitive physiological parameter for the assessment of the effects of treatment (F=30.67, p<0.01). Considering that skin conduction correlates to the levels of peripheric vasoconstriction, it is one of the clearest indicators of adrenergic hyperactivity.

This data therefore lets us conclude that after the treatment, a lower level of autonomic arousal was reached, which therefore signals chronic stress.

However, one must not underestimate the importance of the reduction in heart rate and frontal muscle tension during the stress phase, even though it seems difficult to interpret this fact exclusively as a secondary effect of the tension, the effort and the stress while the subject carries out the task. On the other hand, also the slight increase in peripheric

temperature, along with the trend of skin conduction, can be interpreted as an index of a lower level of peripheral vasoconstriction.

As we have already said, the data related to cortisolemia is difficult to interpret because of the wide range of values found and it is precisely for this reason that the relative decrease is so interesting. It is a well known fact that in every physiological function, an insufficient or even non-existent return to the values at rest can be considered one of the signs most indicative of chronic stress; a significant reduction in the stress hormone during the recovery phase could be interpreted as a further indicator of lower adrenergic arousal. One of the crucial factors in assessment using the psychophysiological profile is the differences in the level of each parameter in the three phases (Baseline-Stress-Recovery). This could be measured not only thanks to autonomic variables but also by monitoring the processes controlled and mediated by the adreno-hypothalamic axis as well as by an increase in the cortisol levels. It is absolutely important to notice that the subjects treated show a significant inhibition of the secretion of cortisol during the recovery phase of the PPF. These results, especially in relation to the extreme interindividual variability of the levels of serum cortisol, emphasise the positive influence the basic benzodiazepine therapy has on the management of chronic stress. The present study shows that the benzodiazepines help to significantly reduce some behaviours, some signals of psychophysiological and hormonal stress, both in the Baseline phase and during the MST in a group of subjects who have recently suffered a heart attack. These results show a general reduction in the stress levels of these subjects as well as a general lowering of adrenergic arousal. However, although the present study was not conducted in double blind, it presents some limits that must be kept in mind: first of all, there is no data available on a possible placebo effect due both to the drug itself and due to a setting that is psychologically comforting and reassuring; secondly, such a small sample of subjects cannot guarantee the generalizability of the results obtained in the present study. In spite of this, since the inhibiting effect of the benzodiazepine on levels of adrenergic arousal has already been demonstrated in previous studies, this is an important result because it was obtained in an experimental clinical setting which should encourage further research including follow up studies to confirm these results in a longitudinal manner.

## References

- Avis, N.E., McKinlay, J.B. & Smith, K. W. (1990). Is cardiovascular risk factor knowledge sufficient to influence behavior?. *American Journal of Preventive Medicine*; 6: suppl., 3:137-144.
- Biondi, M., Pancheri, P. & Cotugno, A. (1987). Personalità e coping styles nella risposta immunitaria dei linfociti T in condizioni di stress emozionale. *Rivista di Psichiatria*, 22 (1), 1-10.
- Bohnen, N., Houx, P., Nicolson, N. & Jolles, J. (1990). Cortisol reactivity and cognitive performance in a continuous mental task paradigm. *Biological Psychology* 31, 107-116.
- Brambilla, F., Bellodi, L., Perna, G. & Garberi, A. (1993). Psychoneuroendocrine aspects of panic disorder, a stress - like disease. *Journal Of Endocrinological Investigation* ; 16, Suppl. 1: 52- 67.
- Cacioppo, J.T. & Petty, R.E. (1981). Electromyograms as measures of extent and affectivity of information processing, *American Psychologist*, 36(5), 441-456.
- Carney, R. M., Rich, M. W., Tevelde, A., Saini, J., Klark, K., Jaffe, A. S. (1987). Major depressive disorder in coronary artery disease. *American Journal of Cardiology*, 60,1273 -1275.
- Cousins, N. (1991). Anatomy of an illness (as perceived by the patient). In A. Monat & R.S. Lazarus (Eds), *Stress and coping: An anthology (3rd ed.)* (pp. 48-61). New York, NY, US: Columbia University Press.

- Crisp, A.H., Priest, R.G. (1971). Psychoneurotic profiles in middle age. *Brit. J. Psychiat.*, 21: 119-128.
- Crown, S. & Crisp, A.H. (1970). *Manual of the Middlesex Hospital Questionnaire (MHQ)*. Psychological Test Publications; Barnstaple: Devon, 67-91.
- Crown, S., Duncan, K.P. & Howell, R.W. (1970). Further evaluation of the Middlesex Hospital Questionnaire (MHQ). *Brit. J. Psychiat.*, 31, 116-118.
- Crown, S., Lucas, C.J. & Supramaniam, S. (1973). Delineation and measurement of study difficulty in students. *Brit. J. Psychiat.*, 33, 123-129.
- De Faire, U. & Theorell, T. (1977). Life changes and myocardial infarction. *Preventive Medicine*, 6, 302-311.
- Delle Chiaie, R., Carmenini, G., Seripa, S., et al. (1992). Stress psicologico e modificazioni di pressione arteriosa, frequenza cardiaca ed elettrocardiografiche in un gruppo di cardio-pazienti funzionali: uno studio controllato. *Medicina Psicosomatica*, 27, 29-49.
- Fisher, L. A. (1989). Corticotropin-releasing factor: endocrine and autonomic integration of responses to stress. *Tips*, 10, 189-194.
- Frank, C. & Smith, S. (1990). Stress and the heart: biobehavioral aspects of sudden cardiac death. *Psychosomatics*, 31(3), 255-263.
- Friedman, M. (1977). Some pathophysiologic phenomena observed in subjects exhibiting type A behaviour. In: T. Mason (Ed.), *Advancement Heart disease* (111-143), New York: Grune & Stratton.
- Fuller, G.D. (1979). *Biofeedback methods and procedures in clinical practice*. San Francisco: Biofeedback Press.
- Galeazzi, A., Castelli, G. & Saccomani, M. V. (1979). Contributo alla taratura italiana delle PM 47 per soggetti in età dai 4 agli 11 anni (forma ad incastro e forma a quaderno). *Bollettino Di Psicologia Applicata*, 152, 79-81.
- Hubert, W. Jong & Meyer, R. (1990). Autonomic, neuroendocrine, and subjective responses to emotion-inducing film stimuli. *International Journal Of Psychophysiology*, 11, 131-140.
- Hubert, W., Jong & Meyer, R. (1992). Saliva cortisol responses to unpleasant film stimuli differ between high and low trait anxious subjects. *Neuropsychobiology*, 25, 115-120.
- Kirschbaum, C., Steyer, R., Eid, M., Patalla, U., Schwenkmezger, P., & Hellhammer, D. H. (1990). Cortisol and behavior: 2. application of a latent state - trait model to salivary cortisol. *Psychoneuroendocrinology*, 15(4), 297-307.
- Kirschbaum, C., Strasburger, C. J., Jammers, W. & Hellhammer, D. H. (1989). *Cortisol and behavior: adaptation of a radioimmunoassay kit for reliable and inexpensive salivary cortisol determination*. *Pharmacology Biochemistry & Behavior*, 34, 747-751.
- Lehnert, H., Beyer, J., Walger, P., Murison, R., Kirschbaum, C. & Hellhammer, D. H. (1989). Salivary cortisol in normal men: the effects of corticotropin-releasing factor and different psychological stimuli. In H. Weiner, I. Florin, *Frontiers Of Stress Research*.
- Lehnert, H., Rohrer, T., Richthofen, V., Shulz, C., & Beyer, J. (1993). Effects of the triazolobenzodiazepine alprazolam on the stress and crh induced activation of the pituitary-adrenal axis. *Journal Of Endocrinological Investigation*, 16: Suppl. 1. 8, 22: 100-111.
- Manhem, K., Jern, C., Pilhall, M., Shanks, G. & Jern, S. (1991). Haemodynamic responses to psychosocial stress during the menstrual cycle. *Clinical Science*, 81, 17-22.

- Massing, W. & Angermeyer, M. C. (1985). Myocardial infarction on various days of the week. *Psychological Medicine*, 15, 851-857.
- McLeod, D.R., Hoehn-Saric, R., Porges, S.W. & Zimmerli, W.D. (1992). Effects of alprazolam and imipramine on parasympathetic cardiac control in patients with generalized anxiety disorder. *Psychopharmacology*, 107, 535-540.
- Mertens, C. (1986). Psychological etiology in cardiovascular disorders. Basic findings and new trends. *Acta Psychiatrica Belgica*, 86, 5-21.
- Nardella, R. (1979). *Un questionario di personalità a scale cliniche: il Middlesex Hospital Questionnaire (M.H.Q.)*. Firenze: O.S. pp. 26-29.
- Pruneti C. A., Giusti M., Boem A. & Luisi M., (2002). Behavioral, psycho-physiological and salivary cortisol modifications after short-term alprazolam treatment in patients with recent myocardial infarction, *Italian heart journal: official journal of the Italian Federation of Cardiology*, 3(1), 53-9.
- Pruneti C.A., L'Abbate A. & Steptoe A. (1993). Personality and Behavioral changes, in patients after myocardial infarction. Research Communications in Psychology, *Psychiatry and Behavior*, 18, 37-51.
- Pruneti, C. (2005). *Manuale di Diagnostica e Clinica Psicologica*. Parma: Ed. Santa Croce.
- Pruneti, C. A., Vogele, C. & Steptoe, A. (1991). Stress e disturbi cardiovascolari. Problemi metodologici nell' utilizzo della tecnica dello stress mentale (Mental Stress Test). *Medicina Psicosomatica*, 36, 343-356.
- Pruneti, C.A. (1985). Dati normativi del test PM 47 coloured su un campione di bambini italiani. *Bollettino Di Psicologia Applicata*, 176, 27-35.
- Pruneti, C.A. (1994). Presentazione e valutazione psicofisiologica di una nuova versione computerizzata del test PM 47 Coloured di Raven. *Bollettino Di Psicologia Applicata*, 210, 41-48.
- Pruneti, C.A. (1995). Psychophysiological response in healthy subjects and in patients after myocardial infarction elicited by a new computerized version of the Raven Coloured PM 47 as mental stress test. *Functional Neurology*, X, 4-5: 195-201.
- Pruneti, C.A., Mazzei, M.G., L' Abbate, A. & Baracchini-Muratorio, G. (1988). Aspetti psicopatologici nel paziente cardiovascolare: possibile ruolo prognostico di alcune caratteristiche della personalità. *Annali di Neurologia e Psichiatria*, 82, 1-17.
- Raven, J. C. (1940). Matrix test. *Mental Health*, 1, 27-34.
- Raven, J. C. (1956). *Guide to using the coloured progressive matrices, sets A, Ab and B*. London: H. K. Lewis Publisher; 45-62.
- Reda M.A., Demontis D., Blanco S. (1988, October). *Profili psicofisiologici e organizzazioni cognitive*. Paper presented at 5° Congresso Nazionale A.I.A.M.C.: Salute e stile di vita, Treviso.
- Rosenman, R. H. & Friedman, M. (1977). Modifying type A behaviour pattern. *Journal of Psychosomatics Research*, 21, 323-233.
- Ruddel, H., Langewitz, W., Schachinger, H., Schmieder, R. & Schulte, W. (1988). Hemodynamic response patterns to mental stress: diagnostic and therapeutic implications. *American Heart Journal*, 116(2), 617-627.
- Sbandi, M. (1958). Taratura delle progressive matrices 1947 di J. C. Raven. *Bollettino Di Psicologia Applicata*, 25-30, 185-198.

- Selye, H. (1970). The evaluation of stress concept. Stress and cardiovascular disease. *American Journal of Cardiology*, 26, 289- 299.
- Step toe, A. & Voge le, C. (1991). Mental stress test is an effective inducer of vasospastic angina pectoris: comparison with cold pressor, hyperventilation and master two-step exercise test. *International Journal of Cardiology*. 70(2),155-163.
- Step toe, A. & Wardle, J. (1988). Emotional fainting and the psychophysiological response to blood and injury: autonomic mechanisms and coping strategies. *Psychosomatic Medicine*, 50, 402-417.
- Stratton, J. R. & Halter, J. B. (1985). Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. *American Journal Of Cardiology*, 56, 136-139.
- Stupnicki, R. & Obminski, Z. (1992). Glucocorticoid response to exercise as measured by serum and salivary cortisol. *European Journal Of Applied Physiology*. 65, 546-549.
- Suarez, E. C. & Willians, R. B. Jr. (1989). Situational determinants of cardiovascular and emotional reactivity in high and low hostile men. *Psychosomatic Medicine*. 51, 404-418.
- Tavazzi, L., Mazzuero, G., Giordano, A., Zotti, A.M. & Bertolotti, G. (1984). Hemodynamic characterization of different mental stress tests. Breakdown in human adaptation to stress. Nijoff Publishers, Commission Of European Comunity, Bruxelles: pp.923-934.
- Taylor, C. B., Hayward, C., King, R., et al (1990). Cardiovascular and symptomatic reduction effects of alprazolam and imipramine in patients with panic disorders results of a double - blind placebo controlled trial. *Journal Of Clinical Psychopharmacology*, 10,112-118.
- Timio, M. (1980). *Stress e cardiopatie*. Roma: Lombardo Editore.
- Widgren, B.R., Wikstrand, J., Berglund, G. & Andersson, O.K., (1992). Increased response to physical and mental stress in men with hypertensive parents. *Hypertension*, 205, 606-611.
- Wittling, W. & Pfluger, M. (1990). Neuroendocrine hemisphere asymmetries: salivary cortisol secretion during lateralized viewing of emotion - related and neutral films. *Brain And Cognition*, 14, 243-265.
- Zotti, A.M., Bettinardi, O., Soffiantino,F., Tavazzi, L. & Steptoe, A. (1991). Psychophysiological stress testing in postinfarction patients. psychological correlates of cardiovascular arousal and abnormal cardiac responses. *Circulation*, 83, Supplement II 4, 25-35.