Behavioral, psycho-physiological and salivary cortisol modifications after short-term alprazolam treatment in patients with recent myocardial infarction

Carlo Pruneti, Mariarosa Giusti, Adriano Boem*, Michele Luisi**

*Clinical Psychology Center, Children and Adolescents Neuropsychiatric Department, *Department of Cardiovascular Medicine, S. Chiara University Hospital, **Pathophysiological and Endocrine Research Unit of the Italian National Research Council, Department of Obstetrics and Gynecology, S. Chiara University Hospital, Pisa, Italy*

Key words:
Acute myocardial infarction; Adrenergic activity; Psychophysiology.

Background. **The aim of this study was to determine the behavioral and physiological effects of the central nervous system depressant alprazolam on a group of cardiac patients.**

Methods. **Immediately after hospital discharge, the Crown and Crisp Experiential Index (CCEI) was administered, the salivary cortisol was detected and a psycho-physiological profile was recorded in 52 subjects who had suffered from myocardial infarction. Half of the subjects represented the experimental group and the remaining 26 individuals acted as a control group not undergoing treatment. The benzodiazepine alprazolam (0.25 mg) was administered twice daily to the treated group only. With the exception of the administration of the drug, all recruited subjects underwent the same clinical evaluation.**

Results. **The CCEI data of the treated group showed significant decreases for the following scales: free floating anxiety ($p < 0.001$), phobic anxiety ($p < 0.01$), somatic complaints ($p < 0.05$), and depression ($p < 0.01$). In the same group, with regard to the physiological parameters, the skin conductance response significantly decreased during the baseline phase ($p < 0.01$), and almost all parameters showed decreased values during mental stress test administration. Cortisol levels also decreased during the recovery phase of the psycho-physiological profile assessment.**

Conclusions. **Alprazolam seems to be able to reduce sympathetic discharge and some stress-related behavioral and physiological responses. This could be of benefit for selected cardiac patients for whom increases in sympathetic tone may constitute a risk factor.**

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Address:

Prof. Carlo Pruneti

Dipartimento di Psicologia Università degli Studi Borgo Carissimi, 10 43100 Parma E-mail: carlo.pruneti@unipr.it

Introduction

The degree of expression or repression of one's feelings together with the consequent autonomic response may facilitate the development of specific pathological events. It follows that the designing of multidisciplinary therapeutic strategies for the treatment of stress disorders requires that one takes into account both the lifestyle habits and the behavior favoring pathological events as well as the corresponding physiological reactions, such as neurovegetative and neurohormonal changes[1-7]. Fluctuations in body cortisol levels are taken as an index of various degrees of stress-related activation of the adrenal cortex depending upon the impact of stressful stimulation. Psychological variables, in fact, do represent the most powerful trigger capable of activating the adrenal cortex, thereby prompting the secretion of this hormone[8-15].

The use of situational stimuli inducing long lasting neurovegetative activation is widespread within the field of psychophysiological research. One of the mental stress tests (MST) employed in psychophysiological studies includes the Raven's Progressive Matrices 47 Colored (CPM 47)[16]. A computerized version of this test has been developed and its application to patients with cardiovascular diseases and healthy subjects supports the hypothesis that it is capable of significantly increasing some physiological parameters[17,18]. As following adrenergic nervous system activation, physiological response fluctuations may be observed in patients with myocardial infarction during the acute phase of the illness, evaluation of these parameters could turn out to be extremely important for the prevention of relapses and of negative consequences[15,19-24]. Indeed, despite the fact that increases in the adrenergic tone may be helpful in main-

taining arterial functionality, excessive adrenergic activation, by augmenting cardiac activity, may cause myocardial ischemia or ventricular arrhythmia. It follows that a decreased catecholaminergic response to stress is desirable in ischemic patients, especially those with infarction.

Several studies have shown that the central nervous system-inhibiting benzodiazepine, alprazolam, can decrease catecholaminergic plasma levels in normal subjects exposed to stress, e.g. at a dosage of 0.5 mg 3 times daily. Furthermore, this benzodiazepine is able to alter the epinephrine and norepinephrine plasma levels in normal subjects. More generally, it has an overall inhibiting effect on adrenergic activity[25-28]. The well-known benefits of β-blockade in patients with coronary heart disease suggest a centrally mediated reduction in sympathetic flow. Moreover, if inhibition of sympathetic activity reflects a secondary effect of the benzodiazepine therapy and if it is found to occur in patients with cardiovascular disease, this could turn out to be clinically beneficial for the management of cardiac stress-related disorders.

In the light of the aforementioned observations and in order to verify the impact of benzodiazepine therapy on both behavioral and psycho-physiological parameters as well as on daily cortisol fluctuations, alprazolam was administered for a limited period to patients who had had their first myocardial infarction during the previous 6 months.

Methods

Patients who had had a first episode of myocardial infarction were randomly assigned to two groups: treated and non-treated. Indeed, in spite of the great evidence presented in the literature on obvious intersubjective diversities relative to psycho-physiological parameter levels and fluctuations, following Student's t-test computations no significant differences between the two subject groups were found.

The treated group consisted of 26 subjects (6 females and 20 males) aged 39 to 66 years (mean age 54.3 ± 6.4 years). All the subjects were consecutively examined at the Clinical Psychology Center of the Children and Adolescents Neuropsychiatric Department of the S. Chiara University Hospital in Pisa. They were here attending for an outpatient examination following their discharge from the Department of Cardiovascular Medicine to which, owing to a first episode of acute myocardial infarction, they had been admitted for a period lasting between 7 to 16 days (mean 9.54 ± 1.9 days). All patients were debriefed regarding the need to evaluate the psycho-social aspects of stress and the individual resistance to the same in ischemic disease. Subsequently, each subject was encouraged to ask questions about the to-be-adopted-behavior, and, more generally, about typical problems such as those related to social life, work and family reintegration, ageing effects, diet, etc., that subjects with a previous infarction have to face.

The psychologist and the cardiologist conducted the interview together. Benzodiazepine drug therapy was then proposed to the treated group only. It was emphasized that it represented only one kind of intervention and, therefore, that it should be regarded not as a substitute for, but rather as a supplement to their treatment. All the patients also received weekly data collection forms (diary) to be filled in daily. Furthermore, the patients were encouraged to contact the cardiovascular medicine center or the clinical psychology facility whenever they felt it was necessary. Because the patients had to repeat the cardiovascular control examination after about 30 days, the administration period of the drug was chosen to last for 1 month. The initial dosage prescribed was 1 mg twice daily since it allowed drug assumption at breakfast and dinner. This dosage, however, proved to be excessive for the first 3 patients, who complained of various side effects, such as dizziness, drowsiness, and loss/lack of appetite. The dosage was therefore reduced in the next 4 recruited subjects, first to 0.5 mg 3 times daily and then to 0.5 mg 2 times daily. It proved to be optimal for our sample, as it did not provoke significant side effects in the remaining 26 patients whose results will be discussed in the present study.

A second group of 26 patients (9 females and 17 males) with the same characteristics as the treated group and aged 44 to 65 years (mean 55.6 ± 4.6 years), formed the control group of non-treated patients. All control subjects underwent the same cardiological and psychological examinations as the treated subjects. All patients were asked for written informed consent prior to recruitment in the study.

Inclusion/exclusion criteria. No changes to the subjects' previous pharmacological therapies were made, but those receiving hormonal and antihypertensive therapy were excluded. Furthermore, none of the subjects reported signs of either primary or secondary adrenal under- or over-functioning (Addison or Cushing disease), hyperthyroidism, obesity, or had been treated for depressive disorders.

Behavioral evaluation. The Crown and Crisp Experiential Index (CCEI) was administered after the first interview and on occasion of the last visit. The obtained scores were pooled in 6 scales: free floating anxiety, phobic anxiety, obsessive behaviors, somatic complaints, depression, poor emotional control and hysterical behavior. In addition, the total score was calculated. This is usually regarded as a reliable index for neuroticism[29-32].

Psycho-physiological evaluation. The pre- and post-treatment psycho-physiological profiles were obtained at 4.00 p.m. by means of the following procedure:

adaptation phase (5-7 min), baseline (8 min), stressor presentation (8 min), recovery (6 min).

• Adaptation: having explained the procedure and placed all the electrodes and devices, the medical operator waits for the patient's physiological values to become steady (5-7 min). During this period of time the values are monitored but not recorded.

• Baseline: monitoring of the psycho-physiological parameters at rest (8 min).

• Stress presentation: presentation of MST (8 min).

• Recovery: during this phase it is assessed whether the values return to baseline levels; the resulting pattern is then monitored and recorded (6 min).

The psycho-physiological profile procedure was performed using an 8 channel device Biolab PT 104 C, PT 711 (manufactured by Satem, Rome) interfaced to an IBM compatible personal computer.

The following parameters were continuously monitored:

• the skin conductance response, measured at the fingertips of the dominant hand (index and ring fingers or middle and little fingers) by means of gold plated sensors with a measuring surface area of 1 cm^2;

• the electromyogram of the frontal muscles, measured by means of three electrodes, 14 mm in diameter and made of unchanging metal (two active and one connecting the patient to the device mass), placed 4.5 cm from one another on the patients' forehead, with the mass electrode placed between the two active electrodes;

• the peripheral temperature measured by means of an integrated circuit and a sensor (calibrated by the manufacturer's trimmer) placed just over the thenar eminence of the dominant hand and monitoring temperature variations in the range of 0.01°C;

• the heart rate taken by means of an optoreflector picking up superficial skin variations related to the sphygmic wave;

• the respiratory rate measured by means of a small rubber belt correctly tensioned around the patients' abdomen or chest.

All the patients were examined in a semi-recumbent position in a room at a temperature between 18 and 22°C and a humidity not exceeding 50%.

Mental stress test. A computer-based version of CPM 47 was used. In this version, a time limit (30 s) for the presentation of each picture was established and a series of visual and acoustic stimuli were introduced as distractors.

These procedures served to increase the difficulty of the proposed task, thus enhancing the attention level needed. Indeed, at specific times the subject had to take into account at least 6 stimuli simultaneously[33].

Cortisol evaluation. In order to obtain the daily profile of cortisol secretion, saliva samples for hormone assay were taken at 8.00 a.m. (zenith), at 4.00 p.m. (three samples according to the three phases: baseline, stress presentation, recovery) and at 11.00 p.m. (nadir).

All saliva samples were stored at -20°C prior to analysis. The assay procedures were performed according to the manufacturer's instructions: 25 ml of the 7 standards (containing 0, 10, 50, 100, 200, 500, 800 mg/l cortisol), 25 ml of the quality control standard, and 100 ml of the cortisol samples were fractionated in tubes coated with a specific antiserum anticortisol. Subsequently, 1 ml of 125-iodinate cortisol was added to all the tubes. These were centrifuged and left at room temperature for 90 min. The liquid phase was then aspirated and the cortisol fraction which was bound to the antibody coating the tubes was counted for 1 min in a gamma counter. In order to minimize the variability of results, all samples from each individual were analyzed in a single assay. A radioimmunological dosage designed for the quantitative determination of human cortisol was used for the assay of cortisol in saliva.

After approximately 5 weeks (mean 36.2 days, range 33-42 days), all patients underwent the same evaluation procedure, repeating the CCEI, the psycho-physiological and the salivary cortisol evaluation.

Statistical analysis. The mean values and SD for all data obtained in the various tests are presented in table I. Several ANOVA analyses were computed in order to assess for significant differences between groups for each of the parameters taken into account. This proce-

Table I. Crown and Crisp Experiential Index before and after treatment.

	Treated group				Non-treated group			
	Before	After	F	p	Before	After	F	p
A	7.78 ± 3.29	3.89 ± 1.72	20.91	< 0.001	8.18 ± 3.14	5.77 ± 2.13	7.23	< 0.05
P	6.62 ± 2.24	3.84 ± 2.16	8.35	< 0.01	5.3 ± 2.7	4.9 ± 1.75	4.02	NS
O	9.52 ± 2.03	6.94 ± 2.41	6.57	< 0.05	9.78 ± 3.4	9.89 ± 2.5	1.97	NS
S	7.84 ± 3.46	3.97 ± 2.18	8.40	< 0.05	8.1 ± 2.9	8.8 ± 2.1	4.66	NS
D	6.78 ± 2.52	3.57 ± 1.26	24.51	< 0.01	7.96 ± 3.01	6.8 ± 2.2	2.33	NS
H	5.1 ± 2.49	4.63 ± 2.06	1.73	NS	4.41 ± 1.83	5.78 ± 2.01	2.87	NS
TOT	42.88 ± 10.84	29.63 ± 6.52	6.38	< 0.05	43.52 ± 7.94	41.37 ± 6.6	3.37	NS

A = free floating anxiety; D = depression; H = hysteria; O = obsessiveness; P = phobia; S = somatic complaints; TOT = total score.

dure was carried out both for the pre- and post-treatment measures for each of the parameters as well as for the treated vs non-treated group comparison *per se*.

Results

Crown and Crisp Experiential Index. Table I shows the mean values and respective SD of the CCEI scores obtained before and after alprazolam treatment.

In the treated group, the post-treatment scores (both mean and SD values) were considerably lower than the pre-treatment ones. This last finding can be interpreted as a general increase in the homogeneity of the scores obtained after treatment (reduction of the interindividual variance) especially for anxiety and depression-related symptoms.

The analysis of variance confirmed that with regard to the treated subjects, the scores of 4 out of 6 CCEI scales and the total score significantly decrease after treatment, with a high significance value precisely in scales which represent anxiety and depression ($p < 0.001$). In the control group, on the other hand, albeit decreasing, the anxiety scale reached only a poor level of significance ($p < 0.05$). All the other scales scores remained steadily elevated.

The main effect of treatment is further illustrated in figure 1. The graph clearly shows that in the treated group, after treatment, symptoms presented by patients such as anxiety, phobia, depression, and somatic complaints almost return to the scores obtained by Crisp in the general population. In other words, the scores "normalize".

Psycho-physiological profile. Table II shows the treated group data. Treated subjects presented a significant decrease in the skin conductance response ($F = 30.67$, $p < 0.01$), with the frontal electromyogram and respiratory rate also somewhat decreasing. A slight increase in both the peripheral temperature and heart rate was also observed. Furthermore, significant decreases in the skin conductance response ($F = 24.19$, $p < 0.01$), frontal electromyogram ($F = 8.66$, $p < 0.01$) and heart rate ($F = 7.62$, $p < 0.05$) were revealed during the MST phase relative to the pre- and post-treatment values. This indicates that the drug intervention allowed for a decrease in the aforementioned parameter. The respiratory rate mean value remained substantially stable, while the peripheral temperature mean score increased significantly ($F = 6.79$, $p < 0.05$).

Table III presents the non-treated subjects' results. As can be easily discriminated, none of the parameters were subject to great alterations. Within the same phase, pre-and post-treatment values remained approximately the same. As expected, values tended to increase between the baseline and MST phases. The only

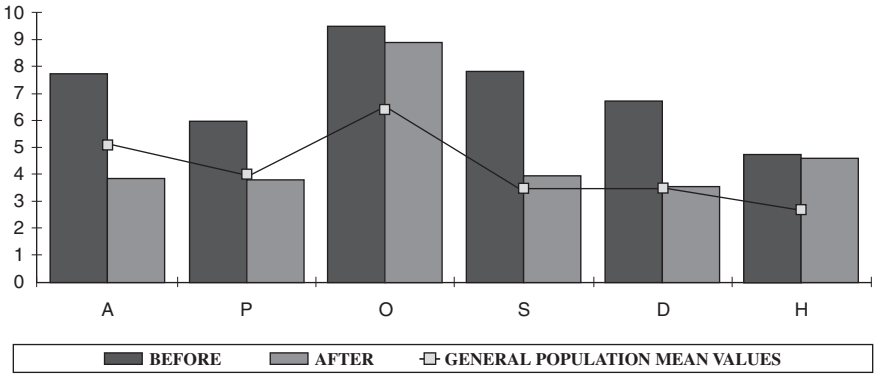

Figure 1. *Crown and Crisp Experiential Index: comparison before and after treatment in the treated group. A = free floating anxiety; D = depression; H = hysteria; O = obsessiveness; P = phobia; S = somatic complaints.*

Table II. Psycho-physiological profile at baseline and during stress presentation in the treated group before and after 30 days of treatment.

	Baseline				Stress presentation			
	Before	After	F	p	Before	After	F	p
SCR	13.12 ± 6.48	7.18 ± 3.01	30.67	< 0.01	19.33 ± 6.83	13.45 ± 3.77	24.19	< 0.01
EMG	5.11 ± 1.76	4.18 ± 1.20	2.89	NS	8.99 ± 2.31	7.18 ± 2.43	8.66	< 0.01
PT	32.2 ± 0.86	33.05 ± 0.55	1.8	NS	30.70 ± 0.81	31.88 ± 0.67	6.79	< 0.05
HR	67.31 ± 6.56	68.47 ± 3.74	4.36	NS	86.15 ± 10.72	80.12 ± 6.14	7.62	< 0.05
RR	1.75 ± 0.45	1.65 ± 0.28	4.08	NS	2.58 ± 0.53	2.20 ± 0.39	3.18	NS

EMG = frontal electromyogram; HR = heart rate; PT = peripheral temperature; RR = respiration rate; SCR = skin conductance response.

Table III. Psycho-physiological profile at baseline and during stress presentation in the non-treated group before and after 30 days of treatment.

	Baseline				Stress presentation			
	Before	After	F	p	Before	After	F	p
SCR	12.23 ± 5.64	11.48 ± 6.59	0.207	NS	18.48 ± 2.12	18.08 ± 5.84	0.187	NS
EMG	4.57 ± 1.73	4.14 ± 2.61	1.67	NS	7.14 ± 1.74	6.84 ± 2.76	0.812	NS
PT	32.15 ± 0.92	32.57 ± 0.99	0.219	NS	30.57 ± 1.08	30.19 ± 0.84	2.989	NS
HR	66.84 ± 4.91	62.5 ± 9.03	0.430	NS	82.57 ± 6.27	84.57 ± 8.6	1.368	NS
RR	1.96 ± 1.96	1.74 ± 0.73	1.135	NS	2.72 ± 0.91	2.66 ± 2.32	0.578	NS

Abbreviations as in table II.

parameter which did not follow this pattern was the peripheral temperature. As demonstrated by the relative mean score, the latter parameter, in fact, tended to decrease. Altogether then, in the non-treated group, no significant differences in the mean values were found either for the measure at rest or for that taken during stress.

No significant differences were found in the recovery phase of the psycho-physiological profile in the same comparison for either group.

Salivary cortisol. The evaluation of the results obtained in assaying the salivary cortisol appears more complex, since the great interindividual variability renders the reporting of the mean trend difficult and more uncertain. Data in table IV show a clear and statistically significant decrease in cortisol secretion during the recovery phase of the psycho-physiological profile relative to the treated group only. This extremely important result will be thoroughly explained in the discussion section.

Discussion

The present study attempted to evaluate the behavioral, psycho-physiological and endocrine variables linked to stress in a sample of subjects who had recently suffered from a myocardial infarction. These variables were evaluated by analyzing several parameters, both before and after benzodiazepine treatment in order to monitor the impact of the drug on the same. In order to attain reliable data, a control group was compared to the treated group. Patients in the latter group were submitted to benzodiazepine therapy for 30 days. Significant decreases in psycho-physiological parameter levels relative to the treated group between pre- and post-treatment data were evidence in favor of the beneficial effect of alprazolam therapy.

With regard to the behavioral data, results clearly demonstrate a significant decrease in anxious-depressive signs and somatic symptoms relative to the treated group. With regard to the psycho-physiological profile, the skin conductance response proved to be the most sensitive index for the evaluation of the effects of treatment ($F = 30.67$, $p < 0.01$). Considering that the skin conductance response measures peripheral vasoconstriction levels, it represents one of the clearest indexes of adrenergic hyperactivity. These data allow one to conclude, therefore, that a lower level of autonomic arousal, i.e. of physiological signs of chronic stress, is achieved after treatment.

However the decrease, during the induced arousal phase (stress session), in heart rate and frontal electromyogram should not be disregarded, even though it seems difficult to interpret these latter findings as anything other than a side effect of tension, effort and stress while performing a task. On the other hand, the slight increase in peripheral temperature values together with the skin conductance response, can be in-

Table IV. Salivary cortisol (μg/l) before and after treatment.

	Treated group				Non-treated group			
	Before	After	F	p	Before	After	F	p
Zenit	9.34 ± 6.52	8.11 ± 4.89	2.65	NS	10.66 ± 6.91	10.38 ± 4.66	11.97	NS
Adaptation (PPP)	4.59 ± 5.42	4.67 ± 4.4	9.21	NS	5.32 ± 4.46	4.86 ± 4.59	7.39	NS
Baseline (PPP)	4.24 ± 5.64	3.4 ± 2.72	4.32	NS	4.91 ± 5.01	4.2 ± 3.57	3.55	NS
Stress (PPP)	7.6 ± 5.71	6.18 ± 2.87	6.82	NS	8.18 ± 4.84	6.93 ± 2.79	0.57	NS
Recovery (PPP)	7.54 ± 7.57	5.03 ± 2.23	16.37	< 0.01	6.59 ± 3.96	6.05 ± 2.79	7.44	NS
Nadir	3.51 ± 6.09	2.62 ± 3.87	6.57	NS	2.5 ± 3.77	2.94 ± 1.98	2.17	NS

PPP = psycho-physiological profile.

terpreted as indexes of a lower level of peripheral vasoconstriction.

As already said, given the wide range of increases measured, it is difficult to interpret data obtained from cortisol evaluation. However, it is precisely for this reason that its significant decrease during the recovery phase is so interesting. It is in fact well known that, in every physiological function, the absence or the lack of recovery, i.e. the return to baseline values, is one of the most important pathognomonic signs of chronic stress. With regard to this point, a significant decrease in stress hormone serum levels precisely during the recovery phase, could be a further index of a lower adrenergic arousal.

More specifically, it is well known that one of the crucial factors of the psycho-physiological profile assessment is the revealed difference in parameter levels relative to the three phases, namely baseline, stress and recovery. The latter evaluates the subject's ability to return to baseline values, i.e., values observed before the presentation of the MST. A lack in activation may indicate post-stress fatigue and depression. A lack in recovery, on the other hand, may be indicative of the presence of chronic stress. This can be measured not only by means of autonomic variables, but also via all those processes controlled and mediated by the hypothalamus-adrenal axis such as the increase in cortisol levels. It is crucially important, therefore, that treated subjects showed a significant inhibition of cortisol secretion during the recovery phase of the psycho-physiological profile. With cortisol serum levels being an extremely fluctuating parameter, this result highlights the potential of alprazolam to positively influence chronic stress management.

The present study shows that the benzodiazepine alprazolam helped to significantly reduce some behavioral, psycho-physiological and hormonal signs of stress, both at baseline as well as during the administration of the MST in a group of subjects who had recently suffered from a myocardial infarction. Altogether, then, these results suggest a general decrease in stress levels for these subjects as well as a general lowering of adrenergic arousal. However, as the present study was not conducted under double blind conditions, it presents some shortcomings that should be taken into account. Firstly, data concerning the possible and probable placebo effect, both of the drug itself and of the influences on its efficacy favored by the psychologically comfortable and reassuring setting that was created, are not available. Secondly, such a small sample certainly does not warrant the widespread applicability of the data of the present study. Nevertheless, as the inhibiting effects of the benzodiazepine alprazolam at the adrenergic arousal level have been already determined, this is an important result within a clinical and experimental setting and should encourage further research including follow-up studies in order to assess for longitudinal results.

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