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CLINICAL REPORT

Cardiovascular Reactivity to Experimental Stress in Psoriasis: a Controlled Investigation

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A defective response of psoriatic skin to β-adrenergic stimulation has been implicated in the pathophysiology of psoriasis. A psychophysiological study was planned to investigate whether the β-adrenergic receptor hyporesponsiveness found in psoriatic skin can also be detected in other systems. Twenty-five psoriatic patients and 50 healthy controls were submitted to a standardized stressful procedure (mental arithmetic and the Stroop Colour-Word Naming Test) to trigger the activation of the sympathetic nervous system, and their haemodynamic responses were compared. While there were no differences between groups in perceived stress, a blunted increase in heart rate and a sharper increase in diastolic blood pressure was observed in psoriasis patients compared with controls. The psychophysiological reaction pattern observed in psoriatic patients might be explained by lower reactivity of heart β1-adrenergic receptors and arteriolar walls β2-adrenergic receptors. While this study suggests that β-adrenergic receptor hyporesponsiveness might have a systemic expression in psoriatic patients, it needs support from future studies exploring β-adrenergic function in psoriatic patients more directly.
Key words: psoriasis; stress; heart rate; blood pressure; sympathetic nervous system; beta-adrenergic receptor.

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Psoriasis is a common, chronic inflammatory disease characterized by altered differentiation, epidermal hyperproliferation, and cutaneous inflammation. Although our knowledge of the psoriatic process has grown substantially over the last two decades, the aetiology and pathogenesis of the disease are still partially unclear. Several factors, including genetic determinants, racial and regional variation, injury and infection, cigarette smoking, alcohol, and diet, have been identified as associated either with causation of psoriasis or with triggering exacerbations of the disease (1, 2). Psychosomatic factors, particularly emotional stress, social support, and personality factors involved in emotion regulation are also believed to play a role (3–6).

Abnormalities in a range of intracellular "second messenger" signalling pathways have been documented in psoriatic patients. In particular, one study found decreased levels of cyclic AMP-dependent protein kinase activities, which play a pivotal role in the modulation of an array of cellular processes, ranging from proliferation to secretion and to gene expression (7). Such a signalling defect has been demonstrated in human fibroblasts (8) and erythrocytes (9), as well as in psoriatic epidermis. In this regard, lesional keratinocytes have been found to have reduced "resting" levels of cAMP, along with a diminished response to β-adrenergic agonists (10) (Fig. 1). Some findings suggest a link between reduced catecholamine-dependent cAMP output and a defective transcription of β_2-adrenergic receptor-mRNA at lesional level (11). The importance of such an anomaly in the wide range of vascular, neural and immune processes involved in psoriatic disease has yet to be fully elucidated. However, a further, indirect support of the pathogenic role possibly played by a defective response of psoriatic skin to β-adrenergic stimulation may derive from the fairly common clinical observation of patients with psoriasis occurring or worsening under beta-blocker therapy (12). The exact mechanism involved in these cases is at present under debate. However, one of the most credited hypotheses suggests a role of decreased

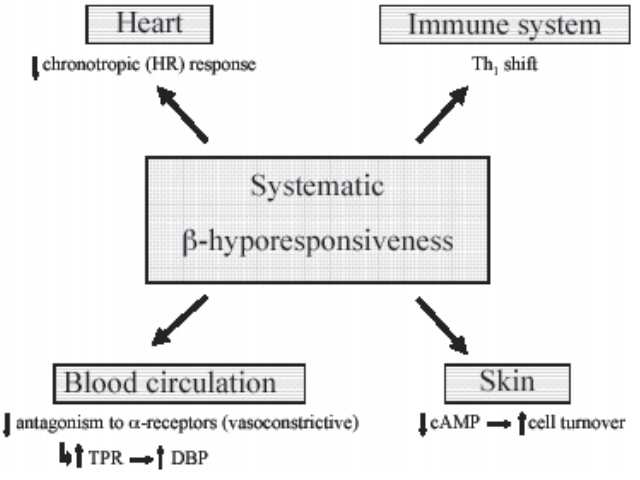

Fig. 1. Holistic hypothetical framework based on a systemic β-hyporesponsiveness in psoriatic patients. HR, heart rate; TPR, total peripheral resistance; DBP, diastolic blood pressure; Th_1, T helper.

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intra-epidermal cAMP, resulting from keratinocyte β-receptor blockade and leading to increased epidermal cell turnover (13, 14).

In this study, we tested the functionality of cardiovascular β-receptors in psoriatic patients, with the aim of investigating whether the β-adrenergic receptor hyporesponsiveness found in psoriatic skin can also be detected at systemic level. Patients with psoriasis and healthy controls were submitted to a standardized stressful procedure able to trigger the activation of the sympathetic nervous system, and their haemodynamic responses were compared.

METHODS

Participants

Twenty-five patients (11 men and 14 women; mean age 40.9 ± 10.7) with psoriasis were recruited at the outpatient clinic of the Department of Dermatology of the University Hospital "Ospedali Riuniti" located in Foggia, Bari, Italy. All consecutive admissions for psoriasis were considered for inclusion in the study according to the following criteria: age 18–65 years; at least 5 years of education; diagnosis of chronic psoriasis of mild to moderate severity with a Psoriasis Area Severity Index (PASI) score between 15 and 30; no local or systemic steroid treatment for at least 3 months before the study; absence of other clinically relevant medical diseases or mental disorders; no past or present history of drug or alcohol abuse or dependence. Participants had a mean PASI score of 17.6 ± 3.1 and they had no lesions on visible body parts such as the head, neck and hand. Nine patients were being treated with phototherapy, 7 with topical vitamin D3 derivatives, 4 with keratolytic ointments, 1 with emollients, while 4 were not receiving treatment at the time of the study.

Controls were 50 healthy subjects (22 men and 28 women; mean age 39.8 ± 10.6) matched for age, sex, educational level, smoking habits and use of oral contraceptives.

To determine eligibility, all potential participants were administered a self-report questionnaire collecting information on sociodemographic and health characteristics.

The study protocol was reviewed and approved by the institutional ethical committee. All participants gave their written informed consent to participate in the study.

Procedure

The study was conducted in a room, located in the Department of Dermatology, which was furnished to resemble a living room. The environment had incandescent lighting and the temperature was maintained at between 20 and 24°C. Stress procedures (described subsequently) were always administered by the same researcher (AB), who was masked to case-control status. In order to increase the "psychosocial pressure" to perform well and thus enhance the effectiveness of the stressful scenario, an "observer" was also present together with the experimenter, with the explicitly stated aim of monitoring participants' performance. The experimenter displayed a standardized pattern of behaviour for each subject. He was very friendly when greeting each participant to minimize apprehension regarding their participation in the experiment. However, throughout administration of the stress procedures, it was important for the experimenter to seem as aloof as possible in order to: (*i*) minimize feedback to participants; (*ii*) create an atmosphere in which the experimenter controlled the testing session; and (*iii*) ensure that the participants felt that failure on either of the tasks represented some threat to their self-esteem. These three ingredients are likely to be essential to produce reliable sympathetic activation from an experimental stress protocol. Moreover, immediately upon completing the challenging tasks, the experimenter once again became as friendly as possible to facilitate the participants' return to baseline conditions.

All experimental sessions were run between 14.30h and 15.30h. Participants had been instructed to refrain from heavy exercise, using tobacco, eating, and consuming alcoholic drinks for at least one hour before the start of the study. Upon their arrival, the participants were introduced to the experimenter who gave them full standardized instructions for the two tasks they would be required to perform. The experimenter also informed the participants that their responses to the psychological challenge would be scored according to how accurately they could perform without making any errors, and gave them detailed information on the devices utilized to obtain heart rate and blood pressure measurements. Following these instructions, the participants were given an opportunity to ask questions regarding any aspect of the experimental procedure, and then they were told that the study would start with a 5-min relaxation period.

The phases and timing of the experimental procedure are summarized in Fig. 2. After the initial relaxation period, two standardized stressful procedures were administered sequentially. Firstly, a timed, mental arithmetic task, in which each participant was asked to count backwards, out loud, from 1022 in intervals of 13, as fast and as accurately as possible for 5 min. On every mistake, the participant had to start over again from the first subtraction. Then, the Stroop Colour-Word Naming Test (15), lasting a further 5 min, was performed, during which the participant was asked to identify as rapidly as possible the colours in which a series of words were printed on a table (e.g. the word "yellow" printed in red, the correct response being "red"). The validated Italian version of the test was used (O.S., Organizzazioni Speciali, Italy). Both these stressful procedures were chosen in view of their capacity to consistently elicit mental effort and mobilize active coping strategies which, in turn, predominantly involve sympathetic (primary β adrenergic) activation (16).

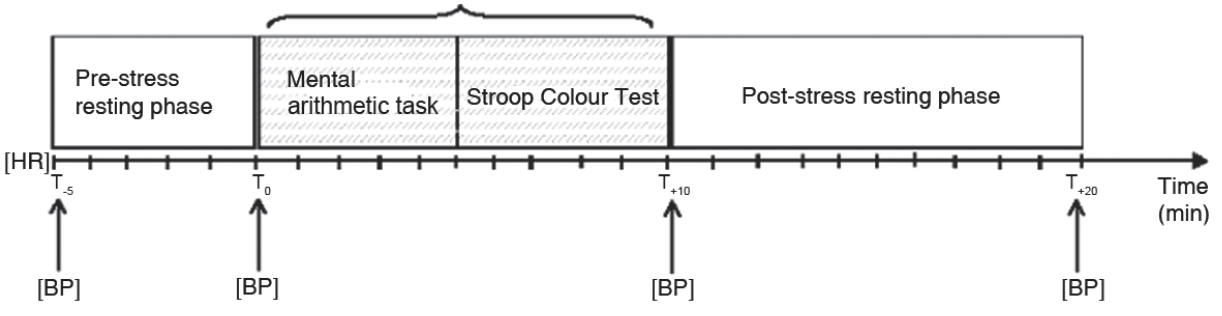

Fig. 2. Phases and timings of the experimental procedure. BP: Blood pressure; HR: Heart rate.

The physiological response to such a stress procedure can be summarized as follows. The presence of an internal or external force that may disrupt the homeostatic balance of any organism is perceived as a stressor and triggers a quite stereotyped, complex behavioural response pattern, called alerting reaction (AR) or "fight-or-flight" response, reflecting the attempt to restore the threatened homeostasis. The AR involves several physiological responses that originate in the cerebral cortex and are driven to the peripheral target organs through corticohypothalamic pathways. This adaptive reaction eventually gives raise to a number of physical effects, including heightened awareness, pupillary dilation, increased skeletal muscle tension, and global activation of the cardiovascular apparatus. More specifically, the cardiovascular component of the AR is driven by a general increase in sympathetic nervous system (SNS) activity, which culminates in increased blood pressure (BP) and improvement of the heart pumping abilities. All these effects are driven by activation of the vascular α-adrenergic receptors, which cause blood vessel constriction and increased total peripheral resistance, and of the cardiac β_1-adrenergic receptors, which increase heart rate (chronotropic effect), rate of action potential conduction (dromotropic effect) and contractile ability of the cardiac muscle (inotropic effect). Moreover, under stressful conditions, activation of the SNS is accompanied by release of catecholamines by the adrenal glands, resulting in increased plasma levels of adrenaline and noradrenaline. In general, the cardiovascular effects of high levels of circulating catecholamines parallel the direct effects of sympathetic activation, as both adrenaline and noradrenaline activate cardiac β_1-adrenergic receptors to increase heart rate (HR) and myocardial contractility, and activate vascular α-adrenergic receptors to cause vasoconstriction and an increase in BP.

HR was taken at 1-min intervals, utilizing a wireless signal transmission device (Polar Instruments, Germany) which was fitted to the subject's chest. Systolic and diastolic BP measurements were carried out at the beginning of the pre-stress 5-min phase (T_{-5}), just before the beginning of the stress procedure (T_0), at the end of the stress procedure (T_{+10}), and after a 10-min post-stress phase (T_{+20}), utilizing a fully automatic monitor device (Omron, UK).

At the end, all participants completed a 9-point visual analogue scale (VAS) measuring the perceived stressfulness of the experimental session, and ranging from 1 ("not at all stressful") to 9 ("awfully stressful").

Data reduction and statistical analysis

The first five HR measurements were averaged to yield a pre-test value. Given that the HR declined rapidly after the Strop test and then remained fairly constant over time in each group, the last 10 measurements were also averaged to yield a post-test measure. Mean BP values were obtained by averaging the diastolic and systolic pressure values at each time point.

Student's *t*-test was used to test for differences between groups in baseline values of BP and HR. Then, group-by-time repeated measures analysis of variance was used to examine changes in HR and in systolic, diastolic, and mean BP over time. The Greenhouse-Geisser correction was used to adjust the degrees of freedom for all F-tests if the Mauchly's test of sphericity indicated heterogeneity of covariance. All analyses were run under SPSS, version 9.0 for Windows.

RESULTS

Patients with psoriasis and controls did not significantly differ on the two baseline values (at T_{-5} and T_0) of systolic, diastolic, and mean BP or on the pre-test HR. The stress procedure induced a significant increase in HR and in systolic, diastolic, and mean BP ($p < 0.001$ for all variables). With regard to systolic (Fig. 3 top) and mean BP, the trend was similar in patients and controls and no group-by-time interaction was found.

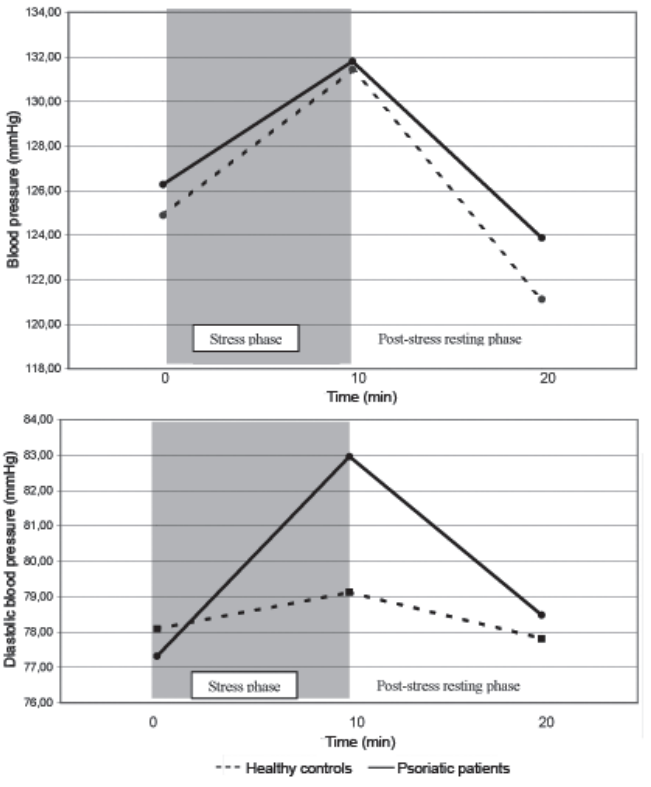

Fig. 3. Systolic (top) and diastolic (bottom) blood pressure response to the stress procedure

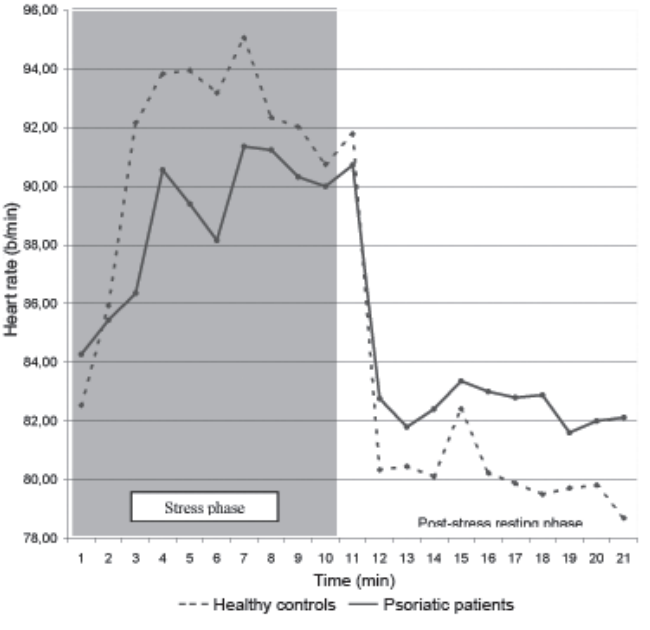

Fig. 4. Heart rate response to the stress procedure.

However, a significant group-by-time interaction was found for diastolic BP ($p = 0.01$) (Fig. 3 bottom) and HR ($p = 0.004$) (Fig. 4), in patients with psoriasis showing a blunted increase in HR and a sharper increase in diastolic BP compared with controls.

The perceived stressfulness of the experimental session as measured by the VAS was strikingly similar in the two groups, with mean values of 7.14 ± 1.07 in the psoriasis group and 7.16 ± 1.07 in the control group.

DISCUSSION

In psoriatic patients we observed an unusual, biphasic pattern of cardiovascular response to the stress procedure. Compared with controls, in these patients the stress-triggered rise in sympathetic nervous activity induced a blunted cardiac reactivity in terms of HR fluctuations, which was coupled with a sharper increase in diastolic BP.

This finding is consistent with the few pioneer psychophysiological studies performed to date which have shown altered psychophysiological reactivity to stress in at least some patients with psoriasis (17–20). As psoriatic patients did not report a greater level of stress than controls, our findings are not likely to be accounted for by differences in the perceived stressfulness of the experimental procedure. Rather, they seem to indicate differences in the psychophysiological reaction pattern.

In our view, these differences might be explained by hypothesizing the existence, on one hand, of a reduced reactivity of heart β_1-adrenergic receptors (which normally drive the chronotropic effect under stressful conditions, as seen above), and on the other hand, of a hyporesponsiveness of the β_2 sub-class of adrenergic receptors which are found on arteriolar walls (21). Activation of this class of receptors promotes vasodilation, and hence counteracts the effect of α-adrenergic receptors activation, which mediates vasoconstriction. In this context, considering that most current evidence suggests that levels of diastolic BP relate more closely to vascular resistance than to cardiac function (22), one may speculate that in psoriatic patients defective β_2-receptors may not have adequately counterbalanced the effect of the stress-triggered action of the SNS on vascular α-adrenoceptors, with over-boosted peripheral vasoconstriction, significant increase of total peripheral resistance and, lastly, the observed sharper rise in diastolic BP.

Overall, our findings are consistent with the frequent clinical observation of psoriasis occurring or worsening under beta-blocker therapy (12) in pointing to a defective responsiveness of psoriatic skin to β-adrenergic stimulation, and they support the hypothesis that such an anomaly might have a much more systemic expression in psoriatic patients (Fig. 1). Indeed, a substantial body of evidence suggests that immune and inflammatory responses are influenced by the SNS. Sympathetic/noradrenergic nerve fibres are detectable in the parenchyma of primary and secondary lymphoid organs. These fibres are located adjacently to and along the blood vessels; hence, it is likely that the SNS plays a role in controlling blood flow in these organs and lymphocyte trafficking and circulation within their vessels. Moreover, noradrenergic fibres that are not associated with blood vessels are also present in lymphoid tissues, where noradrenaline release may exert immunomodulatory effects by altering the activity of local leukocytes (23). In this regard, it has been demonstrated that Th_1/Th_2 cell differentiation balance is consistently affected by catecholamines, which have been found to be able to drive a Th_2 shift at both antigen-presenting cells and Th_1 cells level. Given that these effects are completely abolished by propranolol, a well-known β-adrenoreceptor antagonist, they are likely mediated by stimulation of β_2-adrenoreceptors (24). To our knowledge, an impaired reactivity (or decreased expression) of β-adrenoceptors on antigen-presenting cells and lymphocytes has not yet been documented in psoriatic patients. However, a defective response of the immune system to adrenergic stimuli might help explain, at least in part, the preponderance in psoriasis of Th_1 cells and type-1 pro-inflammatory cytokines (IFN-γ, IL-2 and TNF-α) secretion.

In designing this study, we made efforts to minimize possible confounding by factors that may affect cardiovascular reactivity, such as age, gender, tobacco or alcohol consumption, recent physical exercise, use of oral contraceptives or other drugs acting on the cardiovascular system, and presence of clinically relevant mental disorders or medical diseases other than psoriasis. Given that cognitive tasks were administered as part of the stress procedure, we also controlled for education level. Furthermore, the absence of psoriatic lesions on exposed body parts allowed us to mask the experimenter to patient-control status in order to prevent bias. However, some limitations of our study should be acknowledged. Firstly, the sample size was relatively small. In spite of the statistical significance of our findings, the small number of subjects involved would nevertheless suggest caution and dictate the need of a replication. Secondly, only patients with mild to moderate severity were involved. While this inclusion criterion was used to rule out possible confounding due to substantial differences in clinical severity between patients, whether our findings generalize to patients with very mild or severe psoriasis is to be verified. Lastly, our interpretation of the results is mainly inferential and needs to be substantiated by studies exploring β-adrenergic function in psoriatic patients more directly.

Future studies of β-adrenoceptor responsiveness in psoriatic patients, both in the skin and at systemic level, including lymphocytes and antigen-presenting cells, are

mandatory. The possible role of psoriatic phenotype as a risk factor for future development of blood hypertension might be another subject of fruitful investigation. It is hoped that an improved understanding of this issue might permit advances in the treatment of a disease such as psoriasis, that takes a heavy toll on patients, is associated with substantial physical and psychosocial disability, and deeply affects emotional wellbeing and quality of life (25–28).

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