

## Excisional Breast Biopsy Under Local Anesthesia: Stress-related Neuroendocrine, Metabolic and Immune Reactions During the Procedure

GEORGE C. ZOGRAFOS<sup>1</sup>, FLORA ZAGOURI<sup>1</sup>, THEODOROS N. SERGENTANIS<sup>1</sup>,  
GEORGIA GIANNAKOPOULOU<sup>1</sup>, XENI PROVATOPOULOU<sup>2</sup>, ELENI KALOGERA<sup>2</sup>,  
CHRISTOS PAPADIMITRIOU<sup>3</sup>, GEORGE FILIPPAKIS<sup>1</sup>, ALEXANDROS SAGKRIOTIS<sup>2</sup>,  
JOHN BRAMIS<sup>1</sup> and ANTONIA GOUNARIS<sup>2</sup>

<sup>1</sup>Breast Unit, First Department of Propaedeutic Surgery, Hippokratia Hospital,  
School of Medicine, University of Athens;

<sup>2</sup>Research Center, Hellenic Anticancer Institute, Athens;

<sup>3</sup>Alexandra Hospital, Department of Clinical Therapeutics, University of Athens, Athens, Greece

**Abstract.** *Aim: The aim of this study was to evaluate three axes: the sympathetic system (adrenaline and noradrenaline), surgical stress-related endocrine factors (prolactin, cortisol, insulin, glucose and growth hormone) and inflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$  and IL-6) during excisional breast biopsy under local anesthesia (EBBLA). Patients and Methods: On 14 women undergoing EBBLA, all the aforementioned molecules were measured in peripheral venous blood samples prior (baseline), during (at 10 and 30 minutes), at the end of EBBLA (46 $\pm$ 9 minutes) and one hour after its end. Results: Serum growth hormone glucose and cortisol were found elevated at the 10th and 30th minute and at the end of EBBLA. Serum prolactin increased only at the 30th minute. Of notice, none of the measured parameters was found elevated one hour after the end of biopsy. Concerning adrenaline, noradrenaline and interleukins, no significant changes were documented. Conclusion: During EBBLA, significant stress-related endocrine events arise. However, no significant sympathetic / cytokine triggering was noted.*

Tissue sampling is required for the establishment of breast cancer diagnosis. Tissue can be obtained by open surgical biopsy or core needle biopsy; despite the gradual decline of excisional biopsy in the clinical practice, the latter can be still considered the gold standard for the evaluation of

palpable breast masses (1, 2). In the absence of malignant or highly suspicious preoperative findings, excisional breast biopsy can be performed under local anesthesia: it is a safe and more economical procedure in terms of medical costs, surgeon's time and patients' anxiety (3). Excisional or core needle breast biopsy represents a challenging experience for patients. Anxiety (2, 4-6), pain (7), distress associated with the threat of cancer (6, 8) or with the operative procedure *per se* (9), and long-lasting psychologic stress (10), have all been recognized as phenomena accompanying breast biopsy.

Stress response is defined as the hormonal and metabolic changes that accompany injury and trauma and encompasses a variety of endocrinological, immunological and haematological events (11, 12). In response to stress, neuroendocrine events are induced, including the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (13). The hypothalamic stimulation of the sympathetic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of noradrenaline (11, 14). In parallel, the stress response involves the HPA axis [corticotrophin releasing hormone (CRH) – adrenocortico-trophic hormone (ACTH)-cortisol], and the release of growth hormone (hGH) and prolactin (15). The circulating catecholamines, cortisol and growth hormone, as part of the stress response, result in elevated blood glucose levels (hyperglycaemia). Consequently, synthesis and release of insulin is stimulated to maintain glucose levels within the normal range (14). Cytokines are produced as an early response to tissue injury. They mediate inflammation and immunity, and initiate the acute phase response. Surgical tissue damage results in the release of the cytokines IL-1, IL-6 and TNF- $\alpha$ , mainly. Initially, IL-1 and TNF- $\alpha$  are released from activated

*Correspondence to:* George C. Zografos, Associate Professor of Surgery; University of Athens, 101, Vas Sofias Ave, Ampelokipi, Athens 11521, Greece. Tel: +30 2106426390 Fax: +30 2106426390, e-mail: gzografo@med.uoa.gr

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macrophages and monocytes in the damaged tissue, further stimulating the production and release of IL-6 (16).

As mentioned above, excisional breast biopsy under local anesthesia has been widely used. It is quite impressive, however, that there is a scarcity of data as far as the stress-, anxiety- and early inflammation-related events are concerned. Physicians performing biopsies may be unaware of the levels of stress patients experience (17). Studies examining stress related reactions have been conducted in minimally invasive breast biopsy procedures (18).

In the present study, a spherical knowledge about the above events is sought. Three putatively important axes are thus evaluated: the sympathetic system (adrenaline and noradrenaline), a selection of endocrine factors (prolactin, cortisol, insulin, glucose and growth hormone) and a selection of inflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$  and IL-6). The molecules were measured prior to, during and shortly after the procedure.

## Patients and Methods

*Population of the study.* The material of this study consisted of 14 consecutive women who underwent excisional breast biopsy under local anesthesia from January 2006 to March 2006 at the Hippokratio Hospital. The median age was 51 (range 31-61) years. All these women had a palpable breast lesion 1-2 cm in diameter. In these women, the inflammatory and stress-related hormonal responses were evaluated, quantified and compared during and shortly after the biopsy.

Patients with endocrine or metabolic disorders, diabetes, obesity (Body Mass Index >30 kg/m<sup>2</sup>), history of CNS diseases and patients under current or recent medication affecting the sympathetic response or the hormonal secretion were excluded from the study.

*Biopsy.* During this period of time, the biopsy was performed by two surgeons, who informed the women about the procedure. Local lidocaine was used to establish local anesthesia. The biopsies were performed between noon (12.00 a.m.) and 2.00 p.m.

Institutional Research Committee approved the protocol before the study started. The study was explained to prospective patients and written informed consent was obtained prior to study entry.

*Sample analysis.* Venous samples were collected peripherally, from an antecubital vein of the arm contralateral to the biopsy, with a small catheter. For each patient, peripheral blood samples were collected at five time points: prior, during (at 10 and 30 minutes), at the end of the procedure (46 $\pm$ 9 minutes from commencement) and one hour after the end of the procedure. Serum and plasma samples were isolated from whole blood by centrifugation according to standard protocols (19).

Prolactin and cortisol serum levels were measured using an immunochemistry Analyzer (Bayer, Germany). Plasma adrenaline and noradrenaline were measured by enzyme-linked immunosorbent assay (Biosource, Nivelles, Belgium). Enzyme-linked immunosorbent assays were also used for the determination of serum levels of hGH and insulin (Biosource), and interleukins IL-1 $\alpha$ , IL-1 $\beta$  and IL-6 (R&D Systems, Minneapolis, MN USA). Serum glucose levels were assessed by reflecting photometry in Olympus AU640 monitoring system (Olympus America Inc, Center Valley, PA, USA).

*Statistical analysis.* All time points were compared with the respective initial value with the use of the Wilcoxon matched-pairs signed-ranks test. The statistical analysis was carried out with STATA 8.0 statistical software (Stata Corporation, Texas, USA).

## Results

Table I presents in detail the measured parameters at all selected time points. All *p*-values in Table I are derived from Wilcoxon matched-pairs signed-ranks test (each value was compared with the respective baseline value). Serum growth hormone, glucose and cortisol exhibited statistically significant increase at the 10th and 30th minute, as well as at the end of the procedure. An increase in prolactin was noted at the 30th minute of the procedure. On the other hand, insulin, interleukin-1 $\alpha$  and interleukin-1 $\beta$ , interleukin-6, adrenaline and noradrenaline displayed no significant changes.

## Discussion

The present study assesses three potentially important axes during excisional biopsy under local anesthesia: catecholamines, endocrine response and inflammatory cytokines. Of the three axes, the most important one seems to be the stress-related endocrine response.

Growth hormone and cortisol exhibited the most striking elevations at all time points during and at the end of the procedure. Prolactin displayed only an occasional peak at the 30th minute. The documented endocrine pattern may not seem surprising since the above hormones have been linked with surgical trauma (20, 21). Additionally, the relatively rapid increase in their serum levels is in line with their biological half-life, which is equal to 15-20 minutes (22, 23) for GH and prolactin and 90 minutes for cortisol (24).

In parallel, the observed hyperglycemia during the procedure is in agreement with previous studies having documented the association between blood glucose levels and surgical injury. (11) Noteworthy, however, the changes in serum glucose have not been reflected upon insulin levels and might indeed be insulin-independent.

Plasma catecholamine levels, reflecting the sympathetic activity (25), did not present any significant changes before, during or after the procedure. In any case, the limitations due to the peripheral venous sampling should be kept in mind (26, 27); peripheral sampling may not always be a reliable index of the "sympathetic tone". Independently, larger samples, with greater statistical power, may be needed for the documentation of putative existing patterns concerning catecholamines during excisional biopsy.

Similarly, no significant effects existed regarding IL-1 $\alpha$ , IL-1 $\beta$  and IL-6. This is of particular interest, since

Table I. Serum levels (mean±S.D) of all measured molecules in serum.

	Prior to the procedure	10th minute	30th minute	End of the procedure	One hour after the end
Growth hormone (μU/mL)		<i>p</i> =0.006	<i>p</i> =0.006	<i>p</i> =0.002	NS
	0.91±1.23	1.85±2.05	2.62±2.75	5.09±4.28	0.84±0.51
Insulin (μIU/mL)		NS	NS	NS	NS
	11.2±2.6	10.6±2.6	10.6±4.5	10.3±4.0	10.1±4.3
Serum glucose (mg/dL)		<i>p</i> =0.047	<i>p</i> =0.002	<i>p</i> =0.002	NS
	101.1±14.4	104.4±13.5	110.8±12.5	116.1±11.1	103.3±16.8
Prolactin (ng/mL)		NS	<i>p</i> =0.023	NS	NS
	8.53±3.51	8.83±4.52	9.87±3.70	8.24±3.43	6.88±2.00
Cortisol (μg/dL)		<i>p</i> =0.022	<i>p</i> =0.009	<i>p</i> =0.006	NS
	13.8±2.9	16.3±4.3	20.1±7.9	19.2±6.6	12.7±4.3
Interleukin-1α (pg/mL)		NS	NS	NS	NS
	0.79±0.12	0.83±0.32	0.92±0.28	0.77±0.10	0.89±0.23
Interleukin-1β (pg/mL)		NS	NS	NS	NS
	0.94±0.22	0.90±0.26	0.95±0.22	0.87±0.15	0.89±0.19
Interleukin-6 (pg/mL)		NS	NS	NS	NS
	1.07±0.87	1.05±0.52	0.95±0.53	1.07±0.52	1.78±1.40
Adrenaline (pg/mL)		NS	NS	NS	NS
	56.2±51.6	85.8±87.4	110.0±107.6	116.1±124.6	66.2±56.2
Noradrenaline (pg/mL)		NS	NS	NS	NS
	973.8±678.9	627.1±207.1	748.9±422.6	875.2±435.9	1414.8±611.9

<sup>a</sup>NS: not significant.

interleukin up-regulation has been documented following various other, putatively more severe, types of breast surgery, such as segmental resection, simple mastectomy (28) and breast reconstruction after mastectomy (29).

Focusing on the last time point, *i.e.* one hour after the end of the procedure, it is interesting that no significant changes were observed for any of the measured molecules. The lack of any carry-over effect may imply a relief of the patient after excisional biopsy; the feeling of relief may predominate over the concern about the biopsy results.

This study provides the first detailed insight into anxiety- and stress-related phenomena during excisional breast biopsy under local anesthesia. The importance of endocrine events is clearly documented. Additional studies comparing various settings, incorporating larger samples and more stress-related molecules, seem indispensable for the further evaluation and expansion of the present findings. It would be of interest to envisage studies examining interventions which might limit the observed endocrine events.

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