

## Vacuum-assisted Breast Biopsy: Insight into Stress-induced Endocrine Events

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**Abstract.** *Background:* Stereotactic vacuum-assisted breast biopsy (VABB) is used for the assessment of non-palpable mammographic lesions. This study aims to evaluate stress- and anxiety-related endocrine responses during VABB. *Materials and Methods:* VABB (11 G, Fischer's table) was performed on 22 women. Serum adrenaline, noradrenaline, prolactin, cortisol, growth hormone, glucose and insulin were measured prior to, during (at 10 and 30 minutes), at the end of and one hour after VABB. *Results:* Baseline serum adrenaline and noradrenaline were above the normal range in 14/22 and 13/22 patients, respectively. Baseline serum growth hormone, insulin, prolactin, cortisol were above the normal range in <10% of patients. At all time points, serum prolactin and cortisol exhibited a significant increase from baseline values. Serum noradrenaline and growth hormone were found elevated at the end of and one hour after VABB. *Conclusion:* Immediately before VABB, women are frequently stressed expecting the forthcoming biopsy. The further hormone increase which follows VABB may be attributed to surgical trauma.

Stereotactic vacuum breast biopsy (VABB) on a Fischer's table is a safe and effective technique for the assessment of non-palpable mammographic lesions (microcalcifications, solid lesions, asymmetric density) (1-4). Many authors have acknowledged its superior performance to that of stereotactic automated core biopsy, due to more accurate targeting and superior calcification retrieval, the ability to obtain multiple cores *via* a single needle insertion and the high specificity, sensitivity and positive predictive value of

the method (5-8). VABB is performed in the outpatient setting under local anesthesia. Despite its ever-growing use in the clinical practice, the stress experienced during the procedure has not yet been extensively evaluated.

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 (9, 10). In response to stressogenic stimuli, neuroendocrine events, including the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, ensue (11). The hypothalamic stimulation of the sympathetic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of noradrenaline (9, 12). HPA axis activation, i.e. the well-established pathway of corticotrophin-releasing hormone (CRH) – adrenocorticotrophic hormone (ACTH) – glucocorticoid release from the adrenal cortex, accounts for the increased circulating levels of cortisol. Stimulation of the hypothalamus by stressful conditions also triggers the release of growth hormone (hGH) and prolactin (13). The increased secretion of catecholamines, cortisol and growth hormone, as part of the stress response, results in elevated blood glucose levels (hyperglycaemia). Consequently, synthesis and release of insulin is stimulated to maintain glucose levels within the normal range (12).

As far as VABB is concerned, different approaches, such as medication, relaxation techniques and self-hypnosis have been discussed (14, 15). All these approaches have been evaluated by psychometric measurements, such as the State-Trait Anxiety Inventory (STAI), or the visual analogue scale for anxiety or pain, and no insight into the underlying molecular mechanisms has been provided.

On the other hand, a recently published study demonstrated cytokine dysregulation and immune system alterations one month after the stereotactic breast biopsy procedure (16). Apart from this medium-term effect, it would be of great interest to evaluate the stress response *during* VABB. In the present study, for the first time to our knowledge, stress- and anxiety-related endocrine responses

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were evaluated during VABB. More specifically, this study focused on serum adrenaline, noradrenaline, prolactin, cortisol, growth hormone, glucose and insulin, so as to depict as many aspects of the stress response as possible.

**Materials and Methods**

*Study population.* The population of this study consisted of 22 VABB procedures performed between January and February 2006 in our Unit on women with a median age of 53 years (range 32-60 years) for non-palpable BI-RADS 4 mammographic breast lesions. Amongst the twenty-two women, nineteen were subsequently found to have benign lesions (mostly fibrocystic changes and fibroadenomas) whereas a malignant lesion was revealed in three of them.

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 the study period, VABB was performed by a surgeon and a radiologist who was present to assist in the targeting in all instances. All women were informed about the procedure by the surgeon performing the intervention. VABB (Ethicon Endo-Surgery, Johnson & Johnson, Livingston, UK) was performed on a digital prone table (Mammotest, Fischer Imaging, Denver, CO, USA), using 11-gauge vacuum probes, under local anesthesia (local lidocaine). More than 24 cores were obtained in all cases. A clip was placed in the biopsy site. After VABB, a mammogram on the women confirmed the excision of the suspicious non-palpable lesion, showing the cavitation in the suspicious area. The biopsies were performed between noon (12.00) and 14.00.

The Institutional Research Committee approved the protocol before the study started. Written informed consent was obtained by all patients 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, 30 minutes), at the end of the procedure (56±14 minutes) and one hour after the end of the procedure. Serum and plasma samples were isolated from whole blood by centrifugation according to standard protocols (17).

Prolactin and cortisol serum levels were measured using the immunochemistry auto-analyzer Immuno-1 (Bayer, Tarrytown, New York, USA). Plasma adrenaline and noradrenaline were quantitatively determined 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, Nivelles, Belgium). Serum glucose levels were assessed by reflecting photometry in Olympus AU640 monitoring system (Olympus America Inc, Center Valley, PA, USA).

The range of normal values was defined as follows: adrenaline: 18.0-120.0 pg/ml, noradrenaline: 120.0-700.0 pg/ml; growth hormone <0.2-10 µIU/ml; insulin: 5.0-19.0 µIU/ml; serum glucose: 65.0-110.0 mg/dl; prolactin: 3.0-19.0 ng/ml; cortisol: 3.0-17.3 µg/dl.

*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, TX, USA).

Table I. Baseline values, prior to the onset of the procedure.

	Proportion of patients above normal range
Adrenaline (pg/ml)	14/22
Noradrenaline (pg/ml)	13/22
Growth hormone (µIU/ml)	0/22
Insulin (µIU/ml)	2/22
Serum glucose (mg/dl)	14/22
Prolactin (ng/ml)	1/22
Cortisol (µg/dl)	2/22

Given the small sample size, trends with borderline statistical significance are also provided (0.1<p<0.05), since they might become significant in the context of a larger sample.

**Results**

The percentage of patients exhibiting values above the normal range are shown in Table I. Table II presents in detail the measured parameters at all selected time points. All p-values in Table II are derived from Wilcoxon matched-pairs signed-ranks test (each value was compared with the respective baseline value).

**Discussion**

Anxiety before and during VABB is a rather neglected issue in the current literature. Although it has been recognized as a problem (18), the cascade of anxiety-related endocrine events during VABB remains still elusive. The present study unravels two constituents of anxiety and stress in the context of VABB: the background anxiety (phase prior to the procedure) and the physical/psychological stress imposed during biopsy.

Women frequently begin VABB with elevated plasma catecholamine (adrenaline and noradrenaline) levels, reflecting the sympathetic activity (19) and the stress vis-à-vis of the forthcoming biopsy. Interestingly enough, noradrenaline displays an additional increase at the end of VABB, which becomes more pronounced one hour after the end of VABB. Despite the limitations due to the peripheral venous sampling (20, 21), it is tempting to speculate that the changes in noradrenaline levels reflect the well-established, multivalent modulating role of the latter on the experience of pain (22). Indeed, pain is a non-negligible aspect of VABB (3), and its effects on hormone synthesis have not been yet studied at the context of VABB.

With respect to the pituitary hormones prolactin, hGH and the final result of HPA axis activation (cortisol), all three exhibit a significant increase as the procedure

Table II. Serum levels (mean±S.D) of all measured molecules.

	Prior to the procedure	During the procedure		End of the procedure	One hour after the end
		10th minute	30th minute		
Adrenaline (pg/ml)	259.7±235.8	NS 260.0±166.6	NS 313.3±337.5	NS 272.4±184.7	NS 268.6±190.5
Noradrenaline (pg/ml)	1082.1±718.9	NS 1215.6±799.2	NS 1225.4±893.4	<i>p</i> =0.062 1363.2±1001.9	<i>p</i> =0.008 1487.4±1000.0
Growth hormone (μIU/ml)	0.8±1.9	NS 0.4±1.0	NS 0.2±0.5	<i>p</i> =0.044 1.9±2.8	<i>p</i> =0.058 1.8±2.6
Insulin (μIU/ml)	11.0±7.0	NS 10.9±5.5	NS 10.0±5.0	NS 9.9±5.4	NS 12.6±13.7
Serum glucose (mg/dl)	113.1±12.9	NS 110.7±13.7	NS 117.2±11.1	NS 111.1±14.1	NS 111.5±14.0
Prolactin (ng/ml)	7.4±5.9	<i>p</i> =0.008 8.9±8.6	<i>p</i> =0.055 13.5±17.9	<i>p</i> =0.003 20.1±20.4	<i>p</i> =0.004 13.6±11.2
Cortisol (μg/dl)	11.3±3.7	<i>p</i> =0.036 13.9±6.3	<i>p</i> =0.041 14.5±7.7	<i>p</i> =0.002 17.7±9.5	<i>p</i> =0.076 16.2±10.7

NS: not significant.

progresses without a background, baseline elevation. Prolactin demonstrates a gradual increase during the procedure, exhibiting a peak at the end of the procedure. hGH demonstrates an approximate 2-fold increase also at the end of the procedure while cortisol exhibits a nearly 50% increase at the same time point. This profile seems rational, since all three have been linked with surgical trauma (23, 24). It is fairly surprising that a minor interventional procedure, such as VABB, is capable of significantly stimulating release of the three molecules. In any case, the rapid induction of these molecules may not seem intriguing, as it reflects their biological half-life, which for prolactin and hGH is approximately 15-20 min and for cortisol about 90 min (25-27).

Of notice, the diptych insulin/serum glucose did not exhibit any significant changes during VABB in our sample. The observed hyperglycemia prior to the procedure cannot be fully attributed to stress, as women had received a light meal (breakfast) in the morning. Since blood glucose levels have been shown to be related to the intensity of surgical injury (9), the lack of any significant dysregulation in the diptych insulin/glucose may be due to the minimally invasive character of the procedure.

In conclusion, this study provides the first insight into anxiety- and stress-related endocrine events during VABB. Women frequently begin VABB with elevated plasma catecholamine levels, putatively due to anxiety

vis-à-vis the forthcoming biopsy. Prolactin, hGH and cortisol increase as the procedure progresses, possibly reflecting a response to the surgical trauma. The documented events are significant, and efforts should be made to minimize or even prevent them, if possible. It remains to be assessed whether interventions proposed in the literature, such as oral medication or self-relaxation, also exert significant effects on the molecular events studied herein. Furthermore, studies adopting additional time points and examining putative longer-term phenomena regarding these molecules might be of particular interest in the context of VABB and other breast biopsy techniques.

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