A Mathematical Model for the Hormonal Responses During Neurally Mediated Syncope as an indication of Central Serotonergic Activity using Multivariate Normal Distribution

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Abstract:-The purpose of this study is to find a Mathematical model for the participation of central serotonergic activity in neurocardiogenic syncope by comparing cortisol and prolactin plasma levels in patients with positive and negative tilt test by using Multivariate Normal Distribution.

Keywords:-Cortisol, Multivariate Normal Distribution, Neurally Mediated Syncope, Prolactin,.

I.   INTRODUCTION

The role of central serotonergic activity in neurocardiogenic syncope has not been completely investigated especially in humans. Changes of cortisol and prolactin plasma levels are good, although indirect, indicators of the central serotonergic activity. The purpose of this study is to evaluate the participation of central serotonergic activity in neurocardiogenic syncope by comparing the cortisol and prolactin plasma levels in patients with positive and negative tilt test. In this paper the normal distribution is used for finding the joint moment generating function for the curve of central serotonergic activity during Neurally Mediated Syncope for the four variables Blood Pressure, Heart Rate, Cortisol and Prolactin.

II.   MATHEMATICAL MODEL

2.1 Bivariate and Multivariate Normal Distribution:

Two random variables (X,Y) have a bivariate normal distribution $N(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2, \rho)$ if their joint p.d.f is $f_{X,Y}(x,y) = \frac{1}{2\pi\sigma_1\sigma_2\sqrt{(1-\rho^2)}} e^{\frac{-1}{2(1-\rho^2)}\left[\left(\frac{x-\mu_1}{\sigma_1}\right)^2 - 2\rho\left(\frac{x-\mu_1}{\sigma_1}\right)\left(\frac{y-\mu_2}{\sigma_2}\right) + \left(\frac{y-\mu_2}{\sigma_2}\right)^2\right]}$;   **(2.1.1)**

for all x ,y [7, 9].

The parameters μ_1, μ_2 may be any real numbers, $\sigma_1 > 0, \sigma_2 > 0, -1 \leq \rho \leq 1$. It is convenient to rewrite **(2.1.1)** in the form $f_{X,Y}(x,y) = ce^{\frac{-1}{2}Q(x,y)}$, where c $= \frac{1}{2\pi\sigma_1\sigma_2\sqrt{(1-\rho^2)}}$ and

$$Q = (1-\rho^2)^{-1}\left[\left(\frac{x-\mu_1}{\sigma_1}\right)^2 - 2\rho\left(\frac{x-\mu_1}{\sigma_1}\right)\left(\frac{y-\mu_2}{\sigma_2}\right) + \left(\frac{y-\mu_2}{\sigma_2}\right)^2\right];$$ **(2.1.2)**

Statement:

The marginal distributions of $N(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2, \rho)$ are normal with random variables X and Y having density functions

$$f_X(x) = \frac{1}{\sqrt{2\pi}\sigma_1} e^{-\frac{(x-\mu_1)^2}{2\sigma_1^2}}, f_Y(y) = \frac{1}{\sqrt{2\pi}\sigma_2} e^{-\frac{(y-\mu_2)^2}{2\sigma_2^2}}$$

2.2   The multivariate Normal Distribution:

Using Vector and Matrix Notation:

To study the joint normal distributions of more than two random variables it is convenient to use vectors and matrices. But let us first introduce these notations for the case of two normal random variables X_1, X_2[8]. We set,

$$X = \begin{pmatrix} X_1 \\ X_2 \end{pmatrix}, x = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}, t = \begin{pmatrix} t_1 \\ t_2 \end{pmatrix}, m = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, V = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

Then m is the vector of means and V is the variance – covariance matrix.

Note that $|V| = \sigma_1^2\sigma_2^2(1-\rho^2)$ and $V^{-1} = \frac{1}{(1-\rho^2)}\begin{pmatrix} \frac{1}{\sigma_1^2} & \frac{-\rho}{\sigma_1\sigma_2} \\ \frac{-\rho}{\sigma_1\sigma_2} & \frac{1}{\sigma_2^2} \end{pmatrix}$

Hence $f_X(x) = \frac{1}{(2\pi)^{1/2}|V|^{1/2}} e^{\frac{-1}{2}(x-m)^T V^{-1}(x-m)}$ for all x. Also $M_x(t) = e^{t^T m + \frac{1}{2} t^T V t}$;　　　**(2.2.1)**

We again use matrix and vector notation, but now there are n random variables so that X, x, t and m are now n-vectors with i^{th} entries $X_i, x_i, t_i, and \mu_i$ and V is the n x n matrix with ii^{th} entry σ_i^2 and ij^{th} entry $(for i \neq j)\sigma_{ij}$. Note that V is symmetric so that $V^T = V$.

The joint p.d.f is $f_X(x) = \frac{1}{(2\pi)^{n/2}|V|^{1/2}} e^{\frac{-1}{2}(x-m)^T V^{-1}(x-m)}$ for all x.We say that $X \sim N(m, V)$.

We can find the joint m.g.f quite easily.

$M_x(t) = E[e^{t^T X}] = \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \frac{1}{(2\pi)^{n/2}|V|^{1/2}} e^{\frac{-1}{2}((x-m)^T V^{-1}(x-m)-2t^T x)} dx_1 \ldots dx_n;$ 　　　**(2.2.2)**

We do the equivalent of completing the square, i.e we write

$$(x - m)^T V^{-1}(x - m) - 2t^T x = (x - m - a)^T V^{-1}(x - m - a) + b$$

for a suitable choice of the n-vector a of constants and a constant b. Then

$M_x(t) = e^{-b/2} \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \frac{1}{(2\pi)^{n/2}|V|^{1/2}} e^{\frac{-1}{2}((x-m-a)^T V^{-1}(x-m-a))} dx_1 \ldots dx_n = e^{-b/2};$ 　　　**(2.2.3)**

We just need to find *a* and *b*. Expanding we have

$((x - m) - a)^T V^{-1}((x - m) - a) + b$
$= (x - m)^T V^{-1}(x - m) - 2a^T V^{-1}(x - m) + a^T V^{-1}a + b$
$= (x - m)^T V^{-1}(x - m) - 2a^T V^{-1}x + [2a^T V^{-1}m + a^T V^{-1}a + b]$

This has equal to $(x - m)^T V^{-1}(x - m) - 2t^T x$ for all x. Hence we need $a^T V^{-1} = t^T$ and $b = -[2a^T V^{-1}m + a^T V^{-1}a]$. Hence $a = Vt$ and $b = -[2t^T m + t^T V t]$.

Therefore $M_x(t) = e^{-b/2} = e^{t^T m + \frac{1}{2} t^T V t}$.

Results obtained using the m.g.f:

1.　Any (non-empty) subset of multivariate normal is multivariate normal. Simply put $t_j = 0$ for all j for which X_j is not in the subset.

For example $M_{X_1}(t_1) = M_{X_1, \ldots, X_n}(t_1, 0, \ldots \ldots \ldots, 0) = e^{\mu_1 t_1 + \frac{1}{2}\sigma_1^2 t_1^2}$.

Hence $X_1 \sim N(\mu_1, \sigma_1^2)$. A similar result holds for X_i. This identifies the parameters μ_i and σ_i^2 as the mean and variance of X_i. Also

$$M_{X_1, X_2}(t_1, t_2) = M_{X_1, X_2, \ldots, X_n}(t_1, t_2 0, \ldots \ldots \ldots, 0)$$
$$= e^{(\mu_1 t_1 + \mu_2 t_2) + \frac{1}{2}(\sigma_1^2 t_1^2 + 2\sigma_{12} t_1 t_2 + \sigma_2^2 t_2^2)};$$ 　　　**(2.2.4)**

Hence X_1 and X_2 have bivariate normal distribution with $\sigma_{12} = Cov(X_1, X_2)$. A similar result holds for the joint distribution of X_i and X_j for $i \neq j$. This identifies V as the variance – covariance matrix for $X_1, X_2 \ldots, X_n$.

2.　　X is a vector of independent random variables iff V is diagonal (i.e. all off-diagonal entries are zero so that $\sigma_{ij} = 0$ for $i \neq j$).

Proof:

　From the above result if the X's are independent then $t^T V t = \sum_{j=1}^{n} \sigma_j^2 t_j^2$ and hence

$$M_X(t) = e^{t^T m + \frac{1}{2} t^T V t} = \prod_{j=1}^{n} e^{\mu_j t_j + \frac{1}{2}\sigma_j^2 t_j^2/2} = \prod_{j=1}^{n} M_{X_j}(t_j);$$ 　　　**(2.2.5)**

By the uniqueness of the joint m.g.f $X_1, X_2 \ldots, X_n$ are independent.

3.　　Linearly independent linear functions of multivariate normal random variables are multivariate normal random variables. If $Y = AX + b$, where A is a n x n non-singular matrix and b is a (column) n-vector of constants, then $Y \sim N(Am + b, AVA^T)$.

Proof:

　Use the joint m.g.f

$$M_Y(t) = E[e^{t^T Y}] = E[e^{t^T AX + b}] = e^{t^T b} E[e^{(A^T t)^T X}] = e^{t^T b} M_X(A^T t)$$
$$= e^{t^T b} e^{(A^T t)^T m + \frac{1}{2}(A^T t)^T V(A^T t)} = e^{t^T(Am+b) + \frac{1}{2} t^T(AVA^T)t}$$

This is just the m.g.f for the multivariate normal distribution with vector of means Am+b and variance – covariance matrix AVA^T. Hence, from the uniqueness of the joint m.g.f $\sim N(Am + b, AVA^T)$. Note that from (2) a subset of the Y's is multivariate normal.

III.　　APPLICATION

　The role of central serotonergic activity in neurocardiogenic syncope has not been completely investigated especially in humans. Changes of cortisol and prolactin plasma levels are good, although indirect, indicators of the central serotonergic activity. The participation of the central serotonergic mechanisms in the provocation of NMS is less well established. Drugs that enhance the central serotonergic activity, like fluoxetine hydrochloride in adults [1] and sertraline in children [2] , proved to be effective in more than 50% of patients with refractory to the "classic" NMS therapy. The beneficial effects of these drugs may be attributable

to the enhancement of serotonergic transmission and the down regulation of the serotonin receptors in the CNS. The release of serotonin from projections of the raphe nuclei to the hypothalamus results in prolactin and adrenocorticotropic hormone (ACTH) secretion from the pituitary [3]. Subsequently the release of ACTH results in cortisol secretion from the adrenals. The purpose of this study was to investigate the participation of the central serotonergic activity in humans with NMS by comparing the changes of cortisol and prolactin plasma levels in patients with positive and negative tilt test.

Forty – Six patients with history of neurocardiogenic syncope underwent tilt test at 600 for 30 minutes. Blood samples for cortisol and prolactin plasma evaluation were drawn from a peripheral vein at 0 (before), 10, 20 and 30 minutes after the start of tilt test (blood samples 1, 2, 3 and 4) in case of a negative tilt test. In case of a positive tilt test the patient was returned to supine position and blood samples were drawn at 5 and 10 minutes after the development of syncope (blood samples 3 and 4).

No neurologic or cardiac disease was found in any of the patients. No patients were undergoing any medical treatment. All tilt test were performed between 11.00 and 15.00 hours. All patients had fasted for at least 12 hours. Heart rate and rhythm was continuously observed and Blood Pressure was also measured during the tilt test when symptoms were appeared.
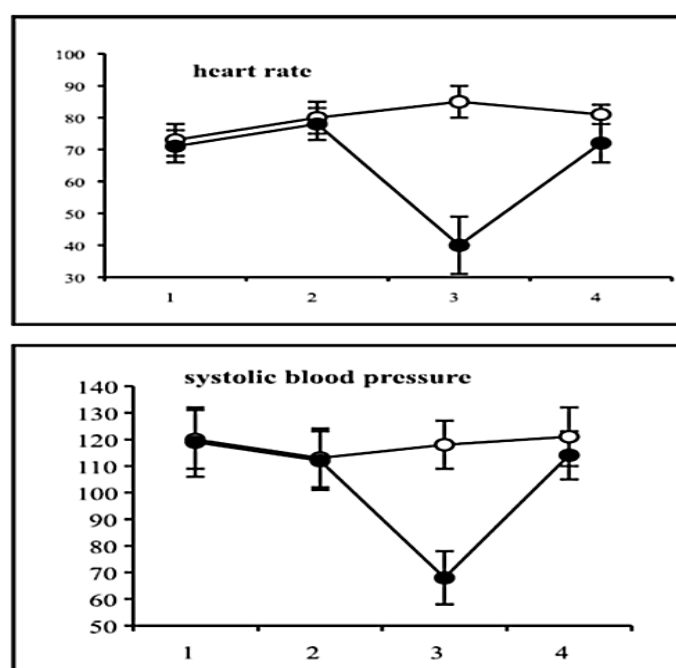

Figure 3.1

Heart rate (beats per minute) and systolic blood pressure (mm Hg) in patients with positive (filled circles) and negative (open circles) tilt test.

Thirty minutes before the tilt test, a venous cannula was inserted into a peripheral vein, in order to obtain blood samples for cortisol and prolactin plasma levels estimations and to administrate drugs or normal saline in case of syncope. The patency of the venous cannula was maintained by slow infusion of normal saline. All patients were placed in supine position for 10 minutes for baseline recordings of blood pressure and heart rate. Blood samples were collected for baseline estimations of cortisol and prolactin plasma levels.
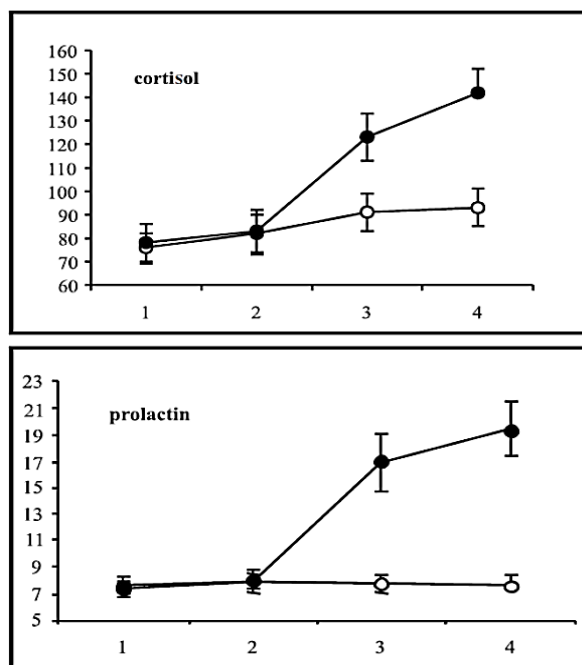
Figure 3.2

Cortisol and Prolactin plasma levels (in ng/ml, mean values ± standard error) in patients with positive (filled circles) and negative (open circles) tilt test.

Blood samples for cortisol and prolactin plasma level estimations were collected before (baseline), 10, 20 and 30 minutes after the beginning of the tilt test (samples 1, 2, 3 and 4). Eighteen of the 46 patients had a positive response at the 15 ± 4 minute of the tilt test (minimum 6th, maximum 25th minute). The remaining 28 patients completed the tilt test without symptoms. The patients of the groups (Group A with the negative tilt test and Group B with positive tilt test) were of similar ages (42 ± 17 years in Group A and 35 ± 16 years in Group B).

At baseline there were no significant differences in the mean systolic blood pressure values and heart rate between groups. Tilting until the 10th minute, provoked a similar increase in heart rate and similar drop in systolic blood pressure in the 2 groups (Fig.3.1). During syncope both variables were significantly reduced in Group B. Baseline cortisol and prolactin plasma levels were similar in the two groups. In both groups tilting caused a small increase in cortisol plasma levels. The cortisol plasma level increases were more pronounced in Group B after syncope than in Group A(Fig. 3.2).

Baseline prolactin plasma levels were similar in the 2 groups. In Group A prolactin remained stable throughout the tilt test. In Group B prolactin increased significantly after syncope. The differences in cortisol and plasma levels secretion were statistically significant. The differences become significant at the 5th and 10th minute after syncope from baseline. This hormonal profile during a positive tilt test is similar to that found in humans after administration of drugs that increase central serotonergic activity. Increases in cortisol and prolactin were observed in healthy volunteers after intravenous infusion of m − chloro − phenylpiperazine, a drug that releases serotonin and blocks its uptake [4]. Prolactin and cortisol increases were also found after administration of the specific serotonin releaser d − fenfuramine [5]. The similar hormonal response pattern of a positive tilt test to that obtained by central serotonergic agents supports the hypothesis that there is a transient activation of of the central serotonergic system that leads to 1) hypotension and 2) stimulation of pituitary hormone release like prolactin and ACTH that subsequently leads to cortisol release. Increased levels of cortisol and prolactin 5 and 10 minutes after syncope are an indication of central of central serotonergic stimulation.

CNS serotonin increased significantly enough to provoke syncope, exclusively in patients with a positive tilt test. Positive tilt test response's mean time was 15 ± 4 minutes from the beginning of the test. CNS serotonin activation beginning time differs among patients with syncope. In order to prove the central serotonergic participation in neurocardiogenic syncope, blood samples were drawn 5 and 10 minutes after syncope, associating the increase of cortisol and prolactin plasma levels with CNS activation. This participation seems to have a similar pathway between all patients with positive tilt test, but time of occurrence differs, depending on syncope's beginning.

Serotonergic mechanisms may be involved in the integrated cardiovascular and endocrine responses to central blood volume depletion during neurocardiogenic syncope in humans. The type is involved in the stimulation of cortisol and prolactin in humans at the three levels of serotonin neural activity in CNS: the raphe nuclei, the hypothalamus and the pituitary. Activation of 5HT1A serotonin receptor with the selective agonist 8 – OH – DPTA lowers blood pressure and heart rate. Although many of 5HT1A agonists exhibit affinity for a 1 adrenoreceptors, hypotension seems to result from their action on central 5HT1A receptors rather than by a 1 adrenoreceptor blockade [6]. The increased cortisol and prolactin plasma levels after syncope are an indication of increased serotonergic activity.

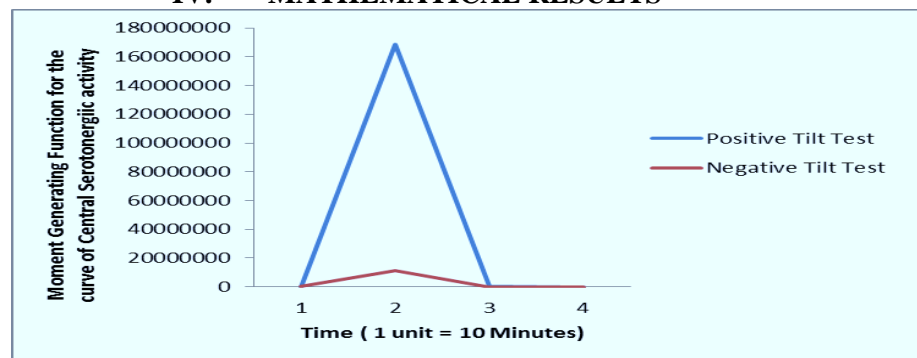## IV.   MATHEMATICAL RESULTS

Figure 4.1
Moment Generating Function for the Hormonal responses of Central Serotonergic Activity for Heart Rate, Blood Pressure, Prolactin and Cortisol with Positive and Negative Tilt Test.

V.   CONCLUSION

The joint moment generating function forthe participation of central serotonergic activity in neurocardiogenic syncope with positivetilt test is maximum and it reaches its peak value at the time period of 20th minute after syncope and it decreases suddenly after reaching its peak value and meet the baseline at 30th min, and the negative tilt test reaches a small height at the time of 20th minute and it decreases and meet the baseline at the 30th minute. In the medical conclusion they have given that the increased cortisol and prolactin plasma levels after syncope are an indication of increased serotonergic activity.

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