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UNIVARIATE WEIBULL DISTRIBUTIONS FOR CARDIOVASCULAR ACTIVATION IN HEALTHY MEN

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ABSTRACT

In this paper we have used Univariateweibull distribution and are applied in plasma glucose, systolic blood pressure, plasma renin activity, epinephrine to find survival function and joint survival functions.Measurement of hormone concentrations revealed an enhanced release of adrenocorticotropic hormone and growth hormone and growth hormone in response to stress of hypoglycaemia in subject treated with both antidepressants used. A similar augmentation was observed in systolic blood pressure. Stress-induced prolactin release was potentiated by citalopram only. Plasma renin activity, epinephrine, norepinephrine and cortisol levels failed to be modified by antidepressants. The Present study demonstrates that (i) repeated antidepressant treatment in healthy men does not inhibit, but enhances, neuroendocrine activation during stress and (ii) such effects were observed after treatment with antidepressants having opposing actions on brain serotonin, indicating involvement of nonserotoninergic mechanisms.

Keywords: *antidepressants, blood Pressure, hormones, MSW, MO-MSW, MSP, MO-MSP distributions.*

1.INTRODUCTION

Stress is generally considered to be one of the factors involved in the pathogenesis of affective disorders [1,5]. The dominant part of the stress response is neuroendocrine activation with consequent alterations in psychosomatic function[9]. Neuroendocrine activation includes profound changes in central neurotransmitter system as well as increased release of stress hormones, such as cortisol, catecholamines, adrenocorticotropic hormone (ACTH), growth hormone, prolactin or angiotension II. Of particular importance is the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, as its disturbances have been implicated in the development of major depressionand other psychiatric disorders.

2. APPLICATION

A total of 31 healthy male volunteers, aged 20-27 years, participated in the investigation. Subjects were included if they had normal body weight (body mass index between 19-26 kg/m^2), were not currently taking any medication, and avoided alcohol and excessive physical activity at least 24 h before the study. Subjects were excluded from the study if they were suffering from any somatic or mental diseases, had a family history of psychiatric disorders or had a control blood pressure higher than 140/90 mmHg. The subjects gave their written informed consent to participate after the procedures and possible side-effects were explained to them.

Blood pressure was recorded before each blood sample. Blood was divided into two polyethylene tubes using heparin (catecholamines, glucose) or ethylenediaminetetracetic acid (ACTH, cortisol, growth hormone, prolactin, plasma renin activity) as anticoagulants.

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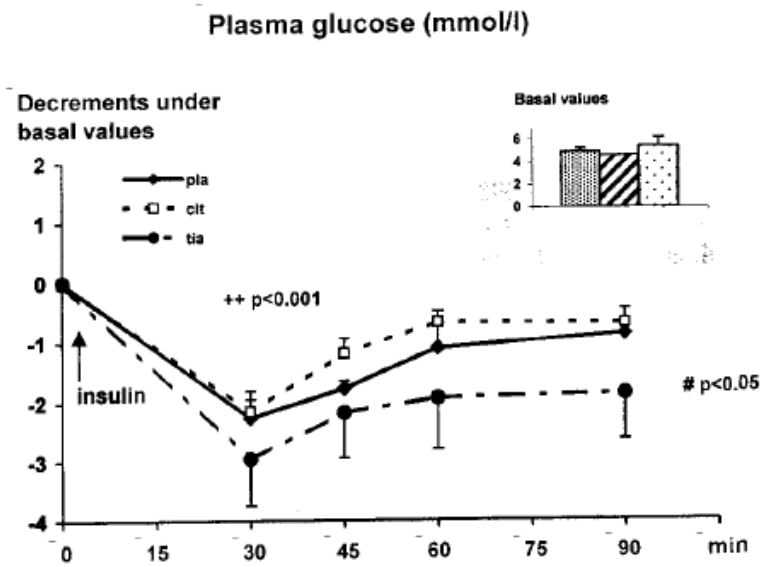

Fig.1. Decrease in plasma glucose levels induced by insulin infusion (0.1 UI/kg i.v.) in citalopram (cit), tianeptine (tia) or placebo (pla) treated subjects.

As expected, insulin administration included a decrease in blood glucose, which reached the nadir at 30 min and then returned towards the control levels (Fig. 1) No statistically significant differences in blood glucose concentrations were found between placebo and any of the antidepressant treated groups. Insulin-induced hypoglycaemia was somewhat more prolonged in subjects treated with tianeptine compared to the values in citalopram but not placebo treated group.

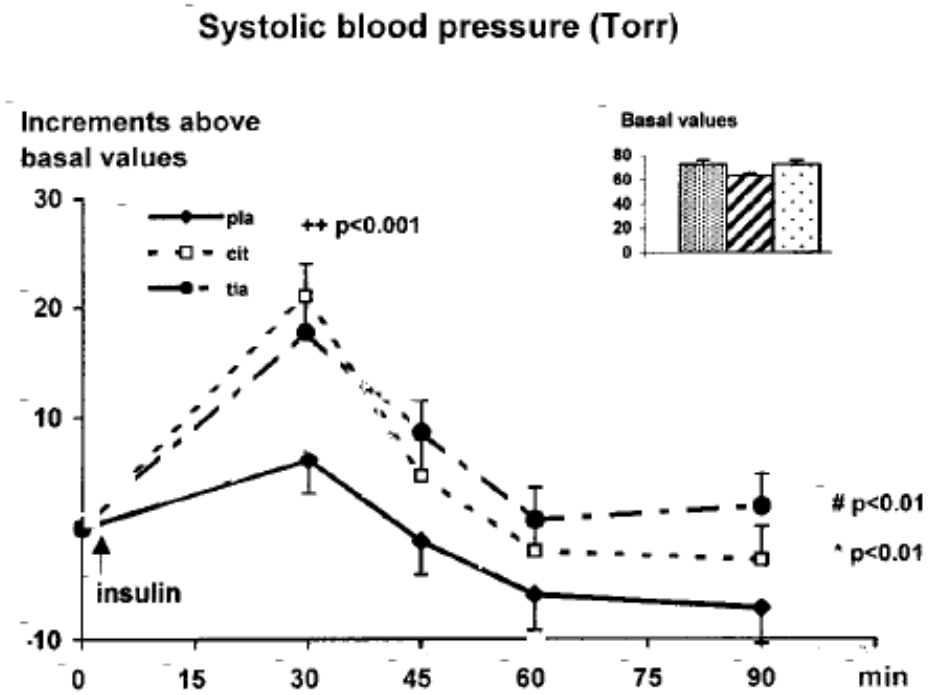

Fig.2. Enhancement of systolic blood pressure response during stress of hypoglycaemia of treatment with citalopram (cit) or tianeptine (tia) in comparison to placebo

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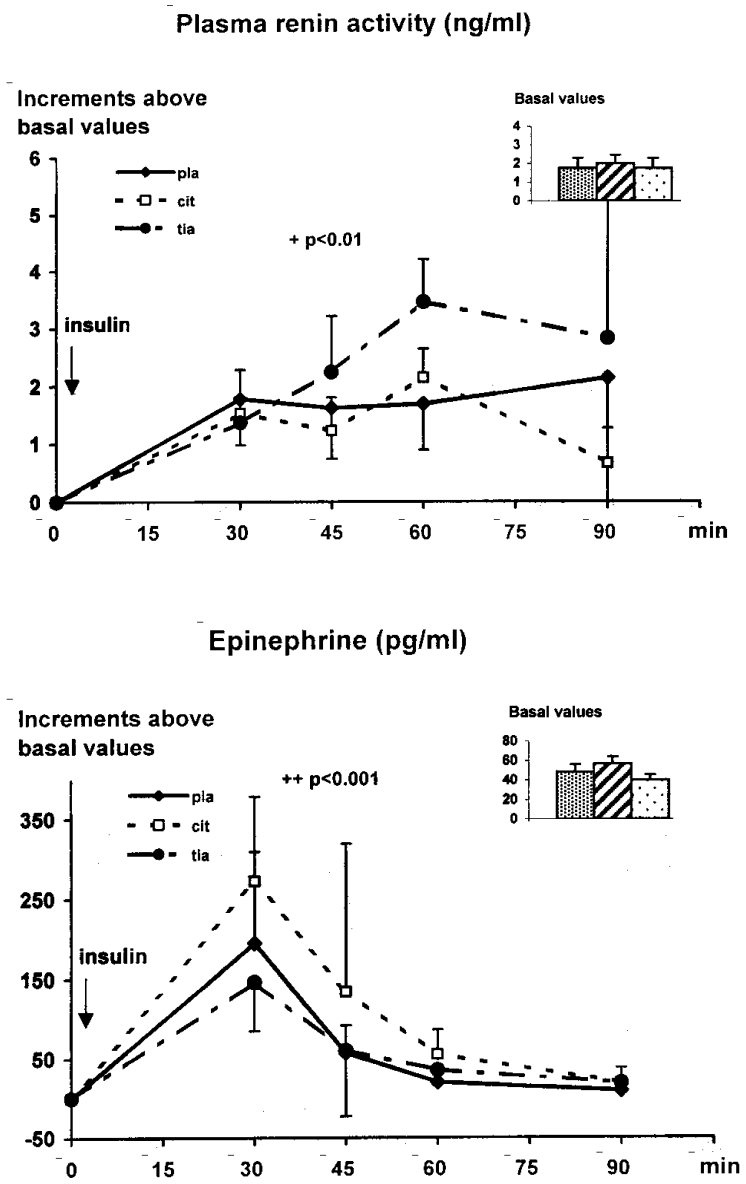

Fig.3. Increase of plasma renin activity and epinephrine levels during stress of hypoglycaemia in subjects treated with citalopram (cit), tianeptine (tia) or placebo (pla) for 7 days.

With respect to cardiovascular responses, changes in systolic blood pressure reached statistical significance for both time and treatment. Stress-induced rise in systolic blood pressure was significantly higher in the citalopram and tianeptinegroups compared to that in subjects treated with placebo (Fig.2). Diastolic blood pressure decreased in time, but no statistically significant difference among groups were observed.

Plasma renin activity rose in response to insulin-induced hypoglycaemia in all groups (Fig.3). With respect to treatment, no significant differences were observed.

The mechanism of action of antidepressants is not fully understood. The main characteristic of drugs used in the treatment of depression is their ability to enhance monoaminergic neurotransmission, particularly by inhibiting reuptake of monoamines in nerve endings in [7].

Although plasma renin activity and plasma catecholamine concentrations failed to be modified by citalopram or tianeptine, the rise in systolic blood pressure was enhanced in both treatment groups. Interestingly, increased noradrenergic function, ad evaluated by excretion of a melatonin metabolite, was observed in responders to antidepressant therapy . It was suggested that enhanced noradrenergic function might play an important role in determining in clinical response to antidepressant treatment [6].

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3. MATHEMATICAL MODELS

The general UnivariateWeibull distribution has the survival function $\bar{F}(x) = e^{-((x-\mu/\sigma)^{\alpha}}, x \geq \mu, \rightarrow(1)$ where $\mu \in \mathcal{R}, \sigma > 0, \alpha > 0$ are parameters. The importance of the univariate and multivariate Weibull distributions is evident since they are often used as reliability models for life lengths.

In [3] studies five classes of multivariate Weibull distributions. A bivariate semi-Weibull distribution is given in [10]. In[4] consider a bivariate extension of a family of distributions as follows:

Let (X,Y) be a bivatiate random vector with joint survival function $\bar{F}(x,y)$; then

$$\bar{G}(x,y) = \frac{\beta \bar{F}(x,y)}{1-(1-\beta)\bar{F}(x,y)}, \quad x,y > 0 \qquad \ldots (2)$$

is a proper survival function for all $0 < \beta \leq 1.$

In [3,4] results to the multivariate case, and constructs two more general multivariate Weibull distributions. The first is named the Marshal-Olkin multivariate semi-Weibull distribution (denoted as MO-MSW). The second is the multivariate semi-Weibull distribution (denoted by MSW). Two characterizations of the homogeneous MSW via weighted minima and marginal distributions are proved.

The univariate semi-Weibull distributions were first introduced in [8]. Some special bivariate semi-Pareto distributions and extends their results to more general case and studies many properties of the multivariate semi-Pareto distribution (denoted by MSP). A new MSP distribution is developed by the technique of [4] and its is denoted as MO-MSP; it is discerned that the MO-MSP distribution is in the multivariate minima domain of partial attraction of the MSW distribution.

3.1 Two characterization theorems for the homogeneous MSW distributions

Two characterization theorems of the homogeneous MSW $(p, \alpha\underline{1}, \underline{\sigma})$ distribution are proved in this section. Both are based on the minima order statistics. Actually, this theorem is an application of Theorem (3.1.1) of which is the characterization in terms of weighted ordered coordinates and marginal distributions.

Theorem 3.1.1

Let $\underline{X} = (X_1,..., X_k)$ be a *k*-variate random vector and let $\underline{\sigma} = (\sigma_1,....\sigma_k) > \underline{0}, \ \alpha > 0, l > 0.$ Then the following two statements are equivalent.

(1) For all $\underline{a} = (a_1,....a_k) > \underline{0}$ such that $\| a \| = \left(\sum_{i=1}^{k} a_i^{\alpha} \right)^{1/\alpha} = 1,$ the weighted minimum among the coordinates in $\underline{X}$, say $\tilde{m} = \min_{1 \leq i \leq k} \left\{ \frac{X_i}{a_i \sigma_i} \right\},$ has a univariateWeibull variable with shape parameter $\alpha l (\alpha > 0, l > 0)$ and the survival function is $P(\tilde{m} > t) = e^{-t^{\alpha l}}$ for $t > 0.$

(2) The survival function of $\underline{X}$ is $\bar{F}(\underline{x}) = e^{-\left(\sum_{i=1}^{k} \left(\frac{x_i}{\sigma_i} \right)^{\alpha} \right)^{l}}$
i.e., $\underline{X} \sim$ in [2] MW

Proof

(1) $\Rightarrow$ (2) For arbitrary $\underline{x} \geq \underline{0},$ let $t = \left\| \frac{1}{\sigma} \underline{x} \right\| \underline{\Delta} = \left(\sum_{i=1}^{k} \left(\frac{x_i}{\sigma_i} \right)^{\alpha} \right)^{1/\alpha}$, writing $a_i = \frac{x_i / \sigma_i}{t}, \ i = 1,..., k.$ With the choice of a_i, it satisfies $\| a \| = \left(\sum_{i=1}^{k} a_i^{\alpha} \right)^{1/\alpha} = 1,$ and the survival function of $\underline{X}$ is

$$\bar{F}(\underline{x}) = P(X_1 > x_i,..., X_k > x_k) = P\left(\frac{X_1}{\sigma_1} > \frac{x_1}{\sigma_1},..., \frac{X_k}{\sigma_k} > \frac{x_k}{\sigma_k} \right)$$

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$$= P\left(\frac{X_1}{a_1\sigma_1} > t,..., \frac{X_k}{a_k\sigma_k} > t\right)$$

$$= P\left(\min_{1\le i\le k}\left(\frac{X_i}{a_i\sigma_i} > t\right)\right) = e^{-t^{\alpha l}}$$

$$= e^{-\left(\sum_{i=1}^{k}\left(\frac{x_i}{\sigma_i}\right)^{\alpha}\right)^{l}}.$$

Then $\underline{X} \sim$ in [ ] MW $(\underline{\sigma}, \alpha, l)$.

To prove (2) $\Rightarrow$ (1): Suppose $\underline{X} \sim$ in [2] MW; then the survival function of $\tilde{m}$ is

$$\bar{F}_{\tilde{m}}(t) = P\left(\frac{X_1}{a_1\sigma_1} > t,..., \frac{X_k}{a_k\sigma_k} > t\right) = P(X_1 > a_1\sigma_1 t,..., X_k > a_k\sigma_k t)$$

$$= e^{-\left(\sum_{i=1}^{k}\left(\frac{a_i\sigma_i t}{\sigma_i}\right)^{\alpha}\right)^{l}} = e^{-t\alpha l\left(\sum_{i=1}^{k} a_i^{\alpha}\right)^{l}}.$$

Since $\left(\sum_{i=1}^{k} a_i^{\alpha}\right) = 1$, so $\bar{F}_{\tilde{m}}(t) = e^{-1t^{\alpha l}}$, and hence $\tilde{m} \sim$ UnivariateWeibull (αl).

Thus (2) implies (1) follows.

3.2 Minima domain of partial attraction of MSW distribution

The following theorem depicts the relationship between MO-MSP and MSW.

Theorem 3.2.1

Let $\{\underline{X}^i = (X_1^i, X_2^i,..., X_k^i\}_1^n$ be a *k*-variate sequence of non negative random vectors independently and identically distributed as MO-MSP with joint survival function

$$\bar{F}_{(\underline{x})}(\underline{x}) = \frac{1}{1+\frac{1}{\beta}\underline{\psi}(\underline{x})}, \quad \underline{x} \ge \underline{0}, \quad 0 < \beta \le 1$$

Then the normalized component wise sample minima $\underline{m}_n = ((n/\beta)^{1/\alpha_1} \min_{1\le i\le n} X_1^i, (n/\beta)^{1/\alpha_2} \min_{1\le i\le n} X_2^i, \ ..., \ (n/\beta)^{1/\alpha_k} \min_{1\le i\le n} X_k^i)$ are asymptotically distributed as an MSW distribution.

Proof

If $\underline{X}^i$ are i.i.d. as MO-MSP, then the joint survival function of $\underline{m}_n$ is

$$\bar{F}_{\underline{m}_n}(\underline{x}) = P(\underline{m}_n \le \underline{x}) = P\begin{pmatrix} X_1^1 \ge (n/\beta)^{-1/\alpha_1} x_1, ..., X_k^1 \ge (n/\beta)^{-1/\alpha_k} x_k \\ X_1^2 \ge (n/\beta)^{-1/\alpha_1} x_1, ..., X_k^2 \ge (n/\beta)^{-1/\alpha_k} x_k \\ \vdots \\ X_1^n \ge (n/\beta)^{-1/\alpha_1} x_1, ..., X_k^n \ge (n/\beta)^{-1/\alpha_k} x_k \end{pmatrix}$$

$$= \{P(\underline{X}^1 \ge (n/\beta)^{-1/\underline{\alpha}}\underline{x})\}^n = \{(\bar{F}_{\underline{x}}(n/\beta)^{-1/\underline{\alpha}}\underline{x}\}^n$$

$$= \left\{\frac{1}{1+\frac{1}{\beta}\underline{\psi}((n/\beta)^{-1/\underline{\alpha}}\underline{x}}\right\}^n = \left\{\frac{1}{1+\frac{1}{\beta}\frac{\beta}{n}\underline{\psi}(\underline{x})}\right\}^n \to e^{-\underline{\psi}(\underline{x})}. \quad \ldots (4.1)$$

The last identity holds because $0 < \beta/n < 1$, and

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$$\underline{\psi}\left(\left(\frac{n}{\beta}\right)^{-1/\underline{\alpha}}\underline{x}\right)=\underline{\psi}\left(\left(\frac{\beta}{n}\right)^{-1/\underline{\alpha}}\underline{x}\right)=\frac{\beta}{n}\underline{\psi}(\underline{x}).$$

Thus $\underline{m}_n$ has MSW as its limiting distribution.

Then the joint survival function,

$$\overline{F}_{\underline{m}_n}(\underline{x})=\left\{\overline{F}_{\underline{x}}\left(\frac{n}{p}\right)^{-1/\alpha}\underline{x}\right\}^n=\left\{\frac{1}{1+\sum_{i=1}^{k}\left(\frac{(n/p)^{-1/\alpha_i}x_i}{\sigma_i}\right)^{\alpha_i}}\right\}^n$$

$$=\left\{\frac{1}{1+\left(\frac{p}{n}\right)\sum_{i=1}^{k}\left(\frac{x_i}{\sigma_i}\right)^{\alpha_i}}\right\}^n$$

It is discerned that the limiting distribution is the multivariate Weibull distribution with independent univariateWeibull $(\alpha_i, p^{-1/\alpha_i}\sigma_i)$ marginals, and hence the result follows.

4.RESULT:

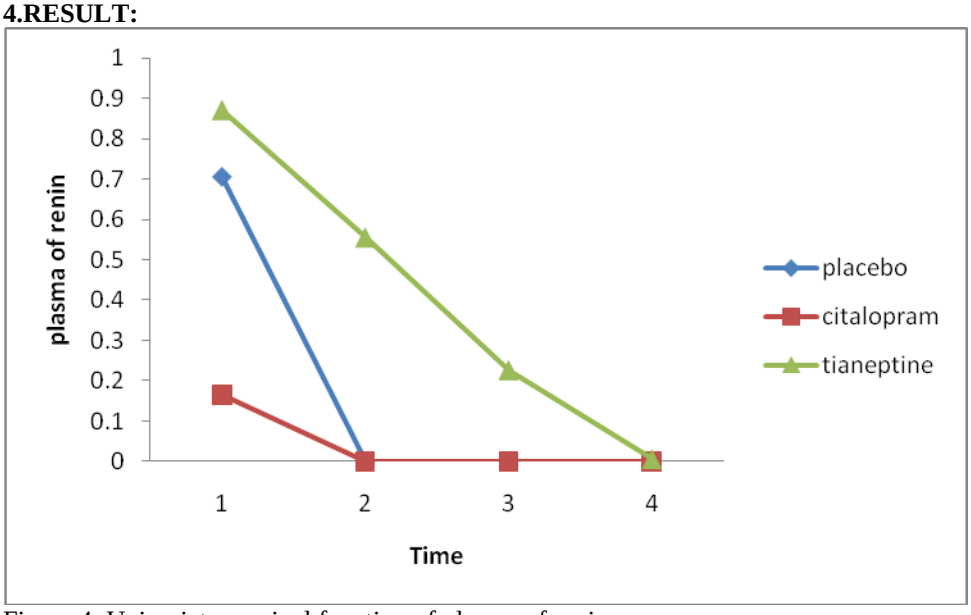

Figure 4: Univariate survival function of plasma of renin

Table 1: Univariate joint survival function of plasma of renin

Time (t=2,3,4,6)	Joint survival function
Placebo	0.2552
Citalopram	0.1463
Toaneotine	0.1868

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5. CONCLUSION

The repeated antidepressant treatment in healthy men does not inhibit, but enhances neuroendocrine activation during stress. Such effects were observed after treatment with antidepressants having opposing action on brain serotonin. Stress induces both protective and damaging effects on the body. It is suggested that an enhancement of neuroendocrine activation to acute stress stimuli may be benefit for patients with depression, in which an attenuated stress response has been reported.We found univirate survival function and jointsurvival function for plasma of renin,plasma of glucose,systolic blood pressure,Epinephrine

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