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MATHEMATICAL MODEL FOR THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN PATIENTS

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Abstract:

In this paper we use mathematical model for the application of The Renin-Angiotensin-Aldosterone system the difference of sleep related activity of the RAAS between depressed patients and healthy controls. We studied the nocturnal plasma concentration of ACTH, cortisol, renin and aldosterone, and sleep EEG in 7 medication free patients with depression. The huge increase in aldosterone in depressed subjects compared to controls and the unchanged cross correlation between the time course of nocturnal hormone secretion, especially between ACTH with cortisol and aldosterone and the lack of a correlation between renin and aldosterone independent of presence or absence of depression.

Key Words: ACTH, RAAS, ABAO & AGAN

Introduction:

The natural ligand of mineral corticoid Receptors (MR) is aldosterone. The peripheral concentration of aldosterone is regulated by the rennin angiotensin-aldosterone system (RAAS). Several links between the regulation of RAAS and the HPA system exist. 1. ACTH is a common stimulus for cortisol, but also for aldosterone at the adrenal cortex. 2. Spironolactone, an MR antagonist, increases the cortisol concentration in humans and another MR antagonist, canrenoate, reduces the sleep related inhibition of ACTH release induced by an intravenous bolus of CRH. These findings suggest an activating action of MR blockade on HPA system. The aldosterone agonist deoxicorticosterone accordingly suppresses plasma cortisol in humans 3. Angiotensin II (AT II) has a direct stimulating action on CRH and vasopressin release from the hypothalamus. 4. A polymorphism in the angiotensin converting enzyme gene seems to be related to HPA axis changes in depression.

Besides endocrine changes, sleep is markedly changed indepression. A bidirectional interaction exists between sleep and endocrine systems, especially the RAAS. Renin and aldosterone secretion increase during sleep and are synchronized to the non REM-REM cycle. On the other hand the aldosterone antagonistcanrenoate reduced slow wave sleep (SWS), where as the MR agonist deoxicorticosterone did not influence sleep when given shortly before sleep onset.

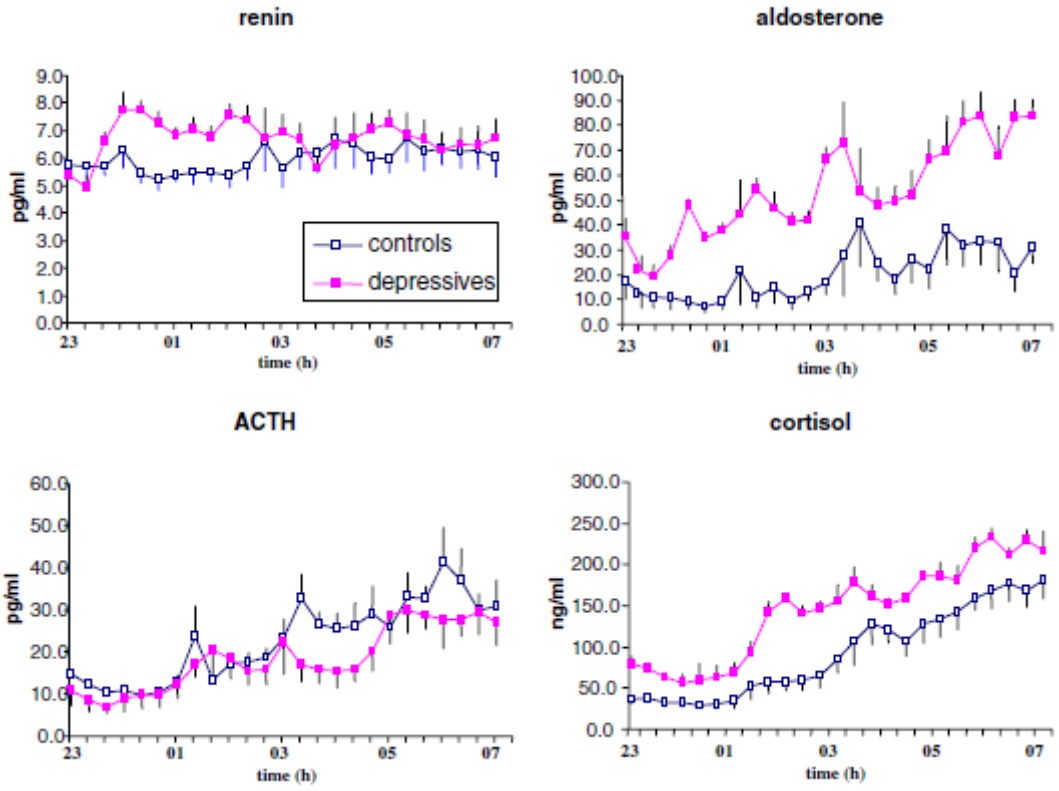
The first study period consisted of an adaptation night, when EEG electrodes were attached without recording an EEG, followed by the examination night. For this the subjects arrived at the sleep laboratory at 19.00 h. An intravenous catheter was fixed at 19.30 h in the forearm, which was connected via a tube through the wall with the adjacent room. Therefore, it was possible to get blood samples without relevant disturbance of the subjects. The venous catheter was perfused with 0.9% saline containing 200 I.E.heparin per liter to keep the catheter patent in a constant rate of 30 ml per hour. Hormone samples were collected every 30 minutes between 20.00 h and 22.00 h and every20 minutes between 22.00 h and 7.00 h. The first 5ml drawn from the catheter were removed and the subsequent10 ml used for analysis. Blood was

centrifuged immediately after it was taken and the serum distributed in 3 containers, which were immediately frozen at -20°C for the rest of examination night and stored in a -80°Cfreezer by the next morning. The hormone analysis took place between 3 and 6 month after the examination. Only the data for the duration between 23.00 h and 7.00 h were used for analysis. The earlier data served as a control for the stress reaction by administering the catheter. Before lights out the subjects were allowed to read or spoke with the technicians and were observed via video monitoring. After 22.00 h the subjects stayed in bed aside from rest room visits. The light was turned off at 23.00h and the subjects were allowed to sleep until 7.00 h. At this time a polysomnography was performed.

The analysis of the serum levels cortisol, ACTH, renin and aldosterone were done by radio immunoassay with a coefficient of variation < 10 % for each hormone.

Depressed patients compared to controls did not show any univariate difference of the sleep EEG parameters compared to controls.

The same is true for the parameters of the first and the second half of the night. Four of the patients and 2 of the controls had to interrupt the bed rest due to rest room visits, which took between 2.5 and 8 minutes. Concerning endocrine parameters, for the first half of the night there was a trend to an increase in cortisol ($p<0.06$) and a significant increase in aldosterone ($p < 0.05$), but no change in ACTH or renin secretion. In the second half of the night, a pronounced increase in aldosterone occurred ($p < 0.01$), but no significant change in the other hormones. This endocrine change was not accompanied by changes in serum electrolyte concentrations assessed some days before the sleep-endocrine examination, controls (n = 5) vs. depressed patients (n =7).



Mathematical Model:

Some important industrial systems (like nuclear power plants, planes, trains) come to the end of their planned life, but they seem to be still in normal working conditions. To extend their functioning life, one must justify some reliability

requirements. One way to do it is to take into account the effect of repair actions or corrective maintenance. Repair is carried out after a failure and intends to put the system into a state in which it can perform its function again. Modelling the effect of these repair actions is of great practical interest and is the first step in order to be able to assess maintenance efficiency.

The basic assumptions on repair efficiency are known as minimal repair or AsBad as Old (ABAO) and perfect repair or As Good As New (AGAN). In the ABAO case, each repair leaves the system in the same state as it was before failure. In the AGAN case, each repair is perfect and leaves the system as if it were new. Obviously, reality is between these two extreme cases: standard maintenance reduces failure intensity but does not leave the system as good as new. This is sometimes known as imperfect or better-than-minimal repair.

Assumptions:

The distribution of these processes is completely given by the failure intensity defined as:

T_i - be the time of stress effect.
N_t - be the number of stress effect in time t.
H_t - be the past stress effect in time t.

$$\forall t \geq 0, \quad \lambda_t = \lim_{dt \to 0} \frac{1}{dt} P(N_{t+dt} - N_t = 1 | \mathcal{H}_t)$$

We assume that before the first failure, the failure intensity is a deterministic and continuous function of time λ(t) called the initial intensity. In addition, the considered system is supposed to wear out continuously, so the initial intensity is strictly increasing.

For any stochastic point process $\{E_t\}_{t \geq 0}$ we define E_{Ti}^+ (resp. E_{Ti}^-) as the left (resp. right) limit, if it exists, of E_t when t tends to T_i.

Definition:

For a model with failure intensity λt, the minimal wear intensity is, if it exists, the deterministic function λmin(t) defined as:

$$\forall t \in I\!R^+, \; P(\lambda_t \geq \lambda_{min}(t)) = 1$$

$$\forall \epsilon > 0, \; \forall t \in I\!R^+, \; P(\lambda_t \leq \lambda_{min}(t) + \epsilon) > 0$$

(2) means that λ_t is greater than $\lambda_{min}(t)$and (3) means that λ_t can be as close as possible to $\lambda_{min}(t)$.The minimal wear intensity can be viewed as the maximal lower bound for failure intensity. The wear out of all system with failure intensity λ_t is greater than that of a system with failure intensity $\lambda_{min}(t)$.

The Non Homogeneous Poisson Process:

The most simple model is obtained by assuming that repair leaves the system as it was before failure. The corresponding random process is the Non Homogeneous Poisson Process (NHPP) and its failure intensity is a continuous function of time:

$$\lambda_t = \lambda(t)$$

If the failure intensity is a constant, ∀t, λ(t) = λ, then the times between failures X_i are independent and exponentially distributed with parameter λ, So there is no wear out. The failure process is then called an Homogeneous Poisson Process (HPP).

The most usual NHPP is the Power Law Process (PLP), with a failure intensity defined as a power of time:

$$\lambda(t) = \alpha\beta t^{\beta-1}, \quad \alpha > 0, \beta > 0$$

The Renewal Process:

Another simple assumption is that repair is perfect that is to say, each repair restores the system as if it were brand new. The system is said to be As Good As New (AGAN). Then, the times between failures are independent and have the same distribution. The failure process is called a Renewal Process (RP), and its failure intensity is of the form

$$\lambda_t = \lambda(t - T_{N_t})$$

Consider the repair actions cannot reduce the global wear of the system, but only the relative wear since the last repair. This assumption leads to:

$$\lambda_{T_i^+} = \lambda_{T_i^-} - \rho[\lambda_{T_i^-} - \lambda_{T_{i-1}^+}]$$

The corresponding model will be called the Arithmetic Reduction of Intensity with memory one (ARI_1) model. Its failure intensity is:

$$\lambda_t = \lambda(t) - \rho\lambda(T_{N_t})$$

$$\begin{aligned}\lambda_{T_{i+1}^+} &= (1-\rho)\lambda_{T_{i+1}^-} + \rho\lambda_{T_i^+} \\ &= (1-\rho)[\lambda(T_{i+1}) - \rho\lambda(T_i)] + \rho(1-\rho)\lambda(T_i) \\ &= (1-\rho)\lambda(T_{i+1}) \\ &= \lambda(T_{i+1}) - \rho\lambda(T_{i+1})\end{aligned}$$

The minimal wear intensity of this model is:

$$\lambda_{min}(t) = (1-\rho)\lambda(t)$$

Property:

The minimal wear intensity of the ARI_m model is:

$$\lambda_{min}(t) = (1-\rho)^m\lambda(t)$$

Proof:

Since λ is an increasing function:

$$\forall j \leq N_t - 1, \quad \lambda(T_{N_t-j}) \leq \lambda(t)$$

Then,

$$\lambda_t \geq \lambda(t) - \rho \sum_{j=0}^{Min(m-1,N_t-1)} (1-\rho)^j\lambda(t)$$

$$\geq \lambda(t)[1 - \rho\sum_{j=0}^{m-1}(1-\rho)^j] = (1-\rho)^m\lambda(t)$$

So,

$$P(\lambda_t \geq (1-\rho)^m\lambda(t)) = 1.$$

Now we have to prove the second part of the definition of the minimal wear intensity. Let t $\epsilon\mathbb{R}_*^+$(the result is obvious when t = 0). The idea of the proof is that, at time t, failure intensity is excessively close to $(1 - p)^m$ λ(t) if there have been m failures between t - ϵ and t for a small ϵ. As λ is an increasing function and 0 ≤ρ≤1, for all $\epsilon\tilde{}\epsilon\ \mathbb{R}_*^+$ we have:

$$P(\lambda_t \leq \lambda(t) - (1-(1-\rho)^m)\lambda(t-\tilde{\epsilon}))$$

$$= P(\lambda_t \leq \lambda(t) - \rho\sum_{j=0}^{m-1}(1-\rho)^j\lambda(t-\tilde{\epsilon}))$$

$$= P\Big(\sum_{j=0}^{Min(m-1,N_t-1)} (1-\rho)^j \lambda(T_{N_t-j}) \geq \sum_{j=0}^{m-1} (1-\rho)^j \lambda(t-\tilde{\epsilon})\Big)$$

$$\geq P\left(\left[\sum_{j=0}^{m-1} (1-\rho)^j \lambda(T_{N_t-j}) \geq \sum_{j=0}^{m-1} (1-\rho)^j \lambda(t-\tilde{\epsilon})\right] \cap [N_t \geq m]\right)$$

$$\geq P([T_{N_t} \geq ... \geq T_{N_t-m+1} \geq t-\tilde{\epsilon}] \cap [N_t \geq m])$$

$$\geq P(\text{“There are } m \text{ failures between } t-\tilde{\epsilon} \text{ and } t\text{”})$$

Since λ_t is not equal to zero everywhere between $t-\tilde{\epsilon}$ and t, then:

$$P(\text{“There are } m \text{ failures between } t-\tilde{\epsilon} \text{ and } t\text{”}) > 0$$

And so we have:

$$P(\lambda_t \leq \lambda(t) - (1-(1-\rho)^m)\lambda(t-\tilde{\epsilon})) > 0$$

In addition, because λ is continuous:

$$\forall \epsilon' \in I\!R_*^+, \ \exists \eta \in I\!R_*^+, \ \forall \tilde{\epsilon} \in [0, \eta[,$$

$$\lambda(t) - \lambda(t-\tilde{\epsilon}) \leq \epsilon'$$

or

$$\lambda(t) - \epsilon' \leq \lambda(t-\tilde{\epsilon})$$

So,

$$\lambda(t) - (1-(1-\rho)^m)\lambda(t-\tilde{\epsilon}) \leq \lambda(t) - (1-(1-\rho)^m)(\lambda(t)-\epsilon').$$

By using equation we deduce that:

$$P(\lambda_t \leq \lambda(t) - (1-(1-\rho)^m)(\lambda(t)-\epsilon')) > 0$$

Or

$$P(\lambda_t \leq (1-\rho)^m \lambda(t) + (1-(1-\rho)^m)\epsilon')) > 0$$

By letting $\epsilon = (1-(1-\rho)^m)\epsilon'$, we obtain for all $\epsilon \in I\!R_*^+$:

$$P(\lambda_t \leq (1-\rho)^m \lambda(t) + \epsilon) > 0$$

So finally,

$$P(\lambda_t \leq \lambda_{min}(t) + \epsilon) > 0$$

Conclusion:

Time coures of nocturnal hormone secretion in patients with depression compared to controls. Cortisol is increased by trend in patients with depression compared to controls in the first half of the night (23.00 h – 3. 00 h) where asaldosterone is significantly increased in the first and second half of the night. ACTH and renin show no difference. Hyperaldosteronism could be a sensitive marker for depression. Also found mathematical model for the stress effect is characterized by the change induced on the Renin level before and after stress effect in patients with depression.

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