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Mathematical Model for Obtaining Survival Probabilities of Aldosterone-Producing Adenoma Due to Stress

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***Abstract*—In this paper the mean time to get the recoupment of organism due to stress related disease or dysfunction is obtained through shock models. Two types of non-cumulative damage shock models are considered here. Based on the distribution of damage, caused by a shock affecting a biological organ system, the intervals with small, intermediate and large damage are introduced. The initial homogeneous Poisson process is split into three homogeneous Poisson processes and studied independently. In this study we also consider the administration of Low salt & High salt diet causes a shock effects in terms of aldosterone in the human system. The study reveals the damage caused to the organ system in the sense of blood pressure. The study of data from the patients under the influence of high salt food revealed that the higher level of stress can cause permanent damage to biological organism.**

***Keywords*—Aldosterone, Stress, Poisson Process, Shock Model, Hazard rate, Laplace Transform**

***AMS Classification*— 60E05, 62N 05. 60Gxx, 62Hxx, 62Pxx**

I. INTRODUCTION

There are many mathematical models to explain how various factors influence the performance of an engineering and / or physical system. As these models are well defined the prediction obtained from these models exactly match with the real situations. A biological system is being continuously influenced by various biological, environmental and social factors. In the absence of exact information about the contributions of such factors to the biological system, developing a model which can predict exactly is difficult. The biological activities such as milk production, reproduction etc are greatly influenced by factors like heat, cold, body weight, food and other environmental stresses. As it is essential to identify the key parameters which affect the production of milk and reproduction capability, it is suggested here a mathematical model which could be used to assess the effect of key parameters on the biological activities.

Human are highly adapt in nature. They are able to fend off stresses, of course to certain limit, which poses a threat to an individual's physical and psychological well being. Some of these threats are physical in nature, such as extreme temperature or malnutrition's or deficit of water. But for most people, perceived threats to their well being often are psychological. For example insecurity of job causes mental agony that affect one's well being. Similarly a failed relationship between people triggers distress affecting smooth functioning of a biological system. Regardless of the source of the stress, the body responds by activating well-defined physiological systems that specialize in helping a person cope with the stress.

Biological organisms are usually subject to shocks, which are harmful events that occur randomly in time and magnitude, and that can cause a failure or death, respectively. Diseases, viruses, heart attack, stress or more generally, demand for energy, can be interpreted as shocks for organisms. The stochastic theory of shocks was extensively studied in reliability literature, although there are still a lot of open questions from theoretical and practical points of view. Traditionally, two basic cases – the cumulative shock model and the extreme shock model – were considered. The former means that the system fails when the cumulative shock magnitude enters some critical region. The latter means that the system breaks down as soon as the magnitude of an individual shock goes into some given critical region.

In this paper the mean time to get the recoupment of stress related disease or dysfunction is obtained through shock models. Two types of non-cumulative damage shock models are considered here. Based on the distribution of damage, caused by a shock affecting a biological organ system, the intervals with small, intermediate and large damage are introduced. The initial homogeneous Poisson process is split into three homogeneous Poisson processes and studied independently. In this paper we also consider the administration of Low salt & High salt diet causes a shock interms of aldosterone in the biological system. The study reveals the damage caused to the organ system in the sense of blood pressure. The concept of shock model and cumulative damage process has been used to determine the expected time to the failure of the biological organ system under different assumptions. One can refer the shock model approach in Gurland (1955), Bartholomew (1971), Esary, Marshall and Proschan (1973), Barlow and Proschan (1975), Bartholomew and Forbes (1979) Shanthikumar & Sumita (1983, 1985), Nakagava T, Kijima M (1989), Ross SM(1996), Lakshmi (2001), Lam & Zhang (2004) and Lakshmi & Venkatesh (2009).

II. ASSUMPTIONS OF THE MODEL

1) Stresses are events which cause perturbation to the biological system, leading to its deterioration and consequent failures or threatening.
2) The effect of stress response on the biological system is measured by damage process.
3) Stress response is the source of hormone secretion. The mineralocorticoid aldosterone is secreted from the adrenal cortex in response to stress.
4) Damages are caused by response of stress at each episode, whose inter arrival times are assumed to be i.i.d random variables.
5) If the total damage exceeds a threshold level, which is itself a random variable, the threat occurs and the biological system is recognized as stressed.
6) The random threshold is assumed due to the fact that the coping ability of stresses varies from one individual system to another.
7) The process which generates stress episode, the sequence of damages and threshold are mutually independent.

III. MATHEMATICAL MODEL

3.1 Introduction

Biological organ systems are subject to a sequence of shocks to be modeled by a stochastic point process in $[0,\infty)$. Shocks (or Stresses) are often harmful and can destroy biological system and therefore probability of survival under shock (or stress) is of the main interest in this field of biological theory. Each stress response, independent of the previous ones, causes a random damage Z with distribution function W(z). This damage is accumulated and when exceeding some given level results in failure of a system **[1, 2].** The cumulative damage process was studied in many publications **[5, 11].** Assume for simplicity that stress process is the one of the cause of biological organ system failures **[7, 12].**

In the simplest non-cumulative setting each shock independent of the previous ones and the state of a system leads to its failure with a fixed probability *p*. In this case the probability of a system's survival in [0, *t*) can be easily obtained for the Poisson process of shocks.

It is useful noting that in the alternative interpretation of the non-cumulative model a variable Z is understood not like a direct damage to a system but as a random level (shock) of a stress. The probability of a biological organ failure in this model depends on the realized value of Z.

3.2 Splitting the shock process

A non – homogeneous Poisson process with rate $h(t)$ is assumed to be our model for the process of shocks. Consider the following n regions (intervals):

$$[0, z_1), [z_1, z_2), \ldots .[z_{n-1}, \infty) \tag{1}$$

The probability that the damage does not exceed level z_i is $W(z_i)$, $0 \le i < j$; $i, j \le n$, $d_n = \infty, d_0 = 0$ is denoted by

$$P_{i,j} = W(z_j) - W(z_i)$$
$$P_j = W(z_j) - W(0) = W(z_j) \tag{2}$$

The first important step is to derive the probability $P_j(t)$ that all shocks which have occurred in $[0,t)$ had resulted in the damage not exceeding c_i. This probability can be defined as

$$P_i(t) = \exp\left\{-\int_0^t (1-p_i)h(x)dx\right\} \tag{3}$$

Consider a terminating orderly point process when each event with probability $1-p_i(t)$ where t is the time since the starts of the process terminates it. Let t_p denote the random time to termination. The conditional hazard (CH) rate $\lambda_c(t, H_t)$ can be defined as

$$\lambda_c(t, H_t)dt = \Pr\{T_p \in [t, t+dt) / H_t, T_p(H_t) > t\}$$
$$= (1-p_i(t)\lambda(t, H_t))dt \tag{4}$$

Where H_t and $\lambda(t, H_t)$ denote the history in $[0,t)$ and the complete intensity function of the point process respectively. **[14]**

The specific case of the Non Homogeneous Hazard process:

$$\lambda_z(t, H_t) = h(x)$$
$$\lambda_z(t, H_t) = (1 - p_i(t))h(t) \tag{5}$$

The probability that all shocks had resulted in damage in the interval $[z_i, z_j)$ can be defined as

$$P_{i,j}(t) = \exp\left\{-\int_0^t (1 - p_{i,j})h(x)dx\right\} \tag{6}$$

Consider the most important specific case, in practice of the three regions $[0, z_s)$, $[z_s, z_l)$, $[z_l, \infty)$ where "s" stands for "small" and "l" stands for large. In accordance with definition (3), denote probabilities of the damage in the corresponding interval as p_s, $p_{s,l}$, p_l. Then

$$P_s(t) = \exp\left\{-\int_0^t (1 - p_s)h(x)dx\right\} \tag{7}$$

$$P_{s,l}(t) = \exp\left\{-\int_0^t (1 - p_{s,l})h(x)dx\right\} \tag{8}$$

$$P_l(t) = \exp\left\{-\int_0^t (1 - p_l)h(x)dx\right\} \tag{9}$$

Here $P_s(t)$ is the probability that all shocks from the Poisson process in $[0,t)$ result in a "small" damage in $[0, z_s)$; $P_{s,l}(t)$ denote the probability that all shocks in an intermediate damage in $[z_c, z_l)$; $P_l(t)$ denote the probability that all shocks in a "large" damage in the interval $[z_l, \infty)$.

The strongest non - cumulative criterion of failure in [0, *t*) is when at least one shock had resulted in a damage exceeding z_s. This means that all shocks with damage from the first region are allowed. Then the corresponding survival function is defined by $P_s(t)$ in Eq. (7). In this stage the stress level is mild.

Let the shock process be the homogeneous Poisson process with rate *h*. Then it can be split into three independent Poisson processes with rates

$$hp_s, hp_{s,l}, hp_l \tag{10}$$

The operation of splitting **[3, 18]** is an important tool for the described approach. In accordance with the formulated criterion, the failure of our organism will occur in [0,*t*), if at least one shock from the process with rate hp_l will occur or, if more than k shocks from the process with rate $hp_{s,l}$ will occur (shocks with small damage are allowed without restrictions). These considerations lead to the following formula for the survival function:

$$P_{s,k}(t) = \exp\{-hp_l\, t\}\exp\{-hp_{s,l}\, t\}\sum_{i=0}^{k}\frac{(hp_{s,l}\, t)^i}{i} \tag{11}$$

When there is no intermediate region: $z_s = z_l$ we arrive at the formula

$$P_{s,0}(t) \equiv P_s(t) = \exp\{-hp_l\, t\} = \exp\{-h(1 - p_s)t\} \tag{12}$$

It is reasonable to assume in the absence of additional information that each shock with damage in $[z_c, z_l)$ can still be considered as harmless with some probability. This probability can be defined as

$$p_a(z)=\frac{z_l - z}{z_l - z_s},\ z\in[z_s, z_l)$$

It means that when the damage is close to z_s the probability of accepting it is close to 1 and it is close to 0 for the other margin. Integrating over all possible values of *c* gives

$$p_a=\int_{d_s}^{d_l} p_a(z)\ \ dW(z)$$

Then the probability of a system functioning without a failure in $[0,t)$ for this case

$$P_{s,a}(t)=\exp\{-hp_l t\}\exp\{-hp_{s,l}(1-p_a)t\} \tag{13}$$

Indeed, the first multiplier in the right hand side is the probability that not a single shock with damage in the third region will occur. The second multiplier defines the probability that all shocks (stresses) with damage in the second region are classified as acceptable.

3.3 Time – dependent criterion of failure

In our first interpretation of acceptable shock (stress) the biological system was competent of recovering the consequences of each shock or stress with a small damage. In a simplified version it was assumed that no time is needed for this operation. On the other hand, it is clear that the model can be more adequate, if the time needed for the system to recover after the shock is taken into consideration. It is natural to assume that it is a random variable τ with a distribution function of *R*(*t*) (different values of damage need different time of recovering and this fact is described by *R*(*t*)). Thus, if the shock occurs while the system still has not recovered from the previous one, then it is a failure (criterion of failure). **[13, 19, 20]** As previously, we want to derive the probability of a failure-free performance in [0, *t*): $P_\tau(t)$.Consider the Poisson process of shocks with rate λ . The following equation for $P_\tau(t)$ takes place:

$$P_\tau(t)=\exp\{-\lambda t\}(1+\lambda t)+\int_o^t \lambda\exp\{-\lambda x\}\times\left[\int_0^t \lambda\exp\{-\lambda y\}R(y)P_\tau^*(t-x-y)dy\right]dx \tag{14}$$

Where the first term in the right hand side is the probability that there was not more than one shock in [0,*t*) and the integrand defines the joint probability of the following events:

- the first shock occurred in $[x, x+dx)$;
- the second shock occurred in $[x+y, x+y+dy)$;
- the time between two shocks *y* is sufficient for recovering (probability *R*(*y*));
- the organ system is functioning without failures in $[x+y, t)$

By $P_\tau^*(t)$ in equation (14) we denote the probability of system's functioning without failures in [0,*t*) given that the first shock had occurred at t = 0: Thus, it differs from $P_\tau(t)$ by the initial state of the shock process. This is important because, if the first shock is fixed at *t* = 0; then the next one, occurring earlier than τ , will cause a failure. Probability $P_\tau^*(t)$ in its turn can be easily obtained from the following integral equation:

$$P_\tau^*(t)=\exp(-\lambda t)+\int_0^t \lambda\exp(-\lambda x)R(x)P_\tau^*(t-x)dx \tag{15}$$

Interpretation of equation (14) is simpler than of equation (15): the integrand defines the joint probability of the first shock occurrence in $[x, x+dx)$, this time is sufficient for recovering from the first shock at *t* = 0, and the organ system is functioning without failures in [*x*,*t*).

Equations.(14) and (15) can be easily solved by means of the Laplace transform. Denote the Laplace transforms of $P_\tau(t), P_\tau^*(t)$ by $\widetilde{P}_\tau(s)$, $\widetilde{P}_\tau^*(s)$ respectively. Applying the Laplace transform to equation (15)

$$\tilde{P}_{\tau}^{*}(s)=\frac{1}{(s+\lambda)\left[1-\lambda\tilde{R}(s+\lambda)\right]}$$

Where $\tilde{R}(s)$ denote the Laplace transform of $R(t)$. Performing the Laplace transform of both sides of equation. (14) and substituting $\tilde{P}_{\tau}^{*}(s)$.; we eventually obtain

$$\tilde{P}_{\tau}(s)=\frac{s\left[1-\lambda\tilde{R}(s+\lambda)\right]-\lambda^{2}\,\tilde{R}(s+\lambda)+2\lambda}{(s+\lambda)^{2}\left[1-\lambda\tilde{R}(s+\lambda)\right]} \tag{16}$$

Now we consider the following specific cases of practical importance.

Case 1:

Exponentially distributed τ: $R(t)=1-\exp(-\mu t)$.

Then: $\tilde{R}(s+\lambda)=\frac{\mu}{(s+\lambda)(s+\lambda+\mu)}$

and

$$\tilde{P}_{\tau}(s)=\frac{s+2\lambda+\mu}{s^{2}+s(2\lambda+\mu)+\lambda^{2}} \tag{17}$$

Performing the inverse Laplace transform

$$P_{\tau}(t)=A_{1}\exp(s_{1}t)+A_{2}\exp(s_{2}t) \tag{18}$$

Where s_1, s_2 are the roots of the denominator in equation (17)

$$s_{1,2}=\frac{-(2\lambda+\mu)\pm\sqrt{(2\lambda+\mu)^{2}-4\lambda^{2}}}{2}$$

and

$$A_{1}=\frac{s_{1}+2\lambda+\mu}{s_{1}-s_{2}} \qquad A_{2}=-\frac{s_{2}+2\lambda+\mu}{s_{1}-s_{2}}$$

Equation (18) gives an exact solution for $P_{\tau}(t)$. In practical applications it is convenient to use simple approximate formulas, showing the role of the key parameters of the problem.

Consider the following reasonable assumption:

$$\frac{1}{\lambda}>>\tilde{\tau}\equiv\int_{0}^{\infty}(1-R(x)) \tag{19}$$

Relation (19) means that the mean inter-arrival time in the shock process is much larger than the mean time of recovery, and this is often the case in practice. In the study of repairable systems the similar case is usually called the fast recoup **[7, 8]**. Using relation (19) for deriving an approximate relation for the probability $P_{\tau}(t)$ of case1 $\left(\tilde{\tau}=\mu^{-1}\right)$ we can obtain $P_{\tau}(t)\approx\exp(-\lambda^{2}t)$ as the second term in the right hand side decreases very sharply with t $(\approx\exp(-\tilde{\tau}t))$.

The corresponding time dependent error can be easily estimated as $\delta=\exp(-\lambda^{2}\tilde{\tau}t)\left[1-\exp(-2\lambda^{3}\tilde{\tau}^{2}t)\right](1+o(1))$ and is usually sufficiently small. The error arising from substitution of A_1 in Eq. (18) for case 1 is bounded by $(\lambda\tilde{\tau})^{2}$. The assumption of fast recoup is often considered for highly unfailing organ systems ($P_{\tau}(t)$ is close to 1) **[21]**. For this case: $\delta\approx 2\lambda^{3}\tilde{\tau}^{2}t$.

Case 2:

Constant time of recovery:

$$R(t)=\begin{cases}0 & 0\le t<\tilde{\tau}\\ 1 & t\ge\tilde{\tau}\end{cases}$$

General relation will turn to

$$\tilde{P}_{\tau}(s)=\frac{s\left[1-\lambda\exp\left(-(s+\lambda)\tilde{\tau}\right)\right]-\lambda^{2}\exp\left(-(s+\lambda)\tilde{\tau}\right)+2\lambda}{(s+\lambda)^{2}\left[1-\lambda\exp\left(-(s+\lambda)\tilde{\tau}\right)\right]} \tag{20}$$

Here we differentiate above equation with respect to s and setting s=0 we get the expected time to get recovery of stress related dysfunction. **[12,16]**

$$E(Z)=-\frac{d}{ds}\tilde{P}_{\tau}(s)\Big|_{s=0}=\frac{3-\lambda\exp(-\lambda\tau)(4-\lambda\tau-\lambda\exp(-\lambda\tau))}{\left[\lambda(1-\exp(-\lambda\tau))\right]^{2}} \tag{21}$$

Another and much more effective approximate approach is based on additional assumption (19): $\frac{1}{\lambda}>>\tilde{\tau}$ Indeed, applying equation similar to Eq. (3) for the specific case of this example

$$h(x)=\lambda,\ p_i\equiv q=1-\exp(-\lambda\tilde{\tau})\approx\lambda\tilde{\tau} \tag{22}$$

In the absence of recovery time (but under the assumption that each shock with probability $1-p=p$ results in the failure), according to Eq. (3), the probability of failure free performance in $[0,t)$ is exactly $\exp(-\lambda qt)$:

In the presence of a recovery time the corresponding probability can be written as

$$P_{\tau}(t)=E\left[\exp\left(-\lambda q(t-\tau_s)\right)\right] \tag{23}$$

where τ_s denote the total random time the system is in the state of recovery in $[0,t)$.

Assume that the system is highly unfailing (the probability of failure-free performance is close to 1) and relation (19) holds. Using Taylor's expansion in a series in equation (23) for $t>>E(\tau_s)$

$$\delta=\exp(-\lambda qt)-E\left[\exp\left(-\lambda q(t-\tau_s)\right)\right]$$
$$=\lambda^{2}q\tilde{\tau}\,t\left[1+\frac{\lambda q\ E(\tau^{2})}{2\tilde{\tau}}\right](1+o(1)) \tag{24}$$

Relation (24) is derived for an arbitrary $R(t)$. When $R(t)$ is a step function of Case 2, the term in square brackets can be simplified to $1+\lambda qt/2$. It can be easily seen that Eq. (20) follows from equation (24) for the exponential case. It also follows from equation (23) that the additional to relation (19) assumption for the definition of the fast recoup is: $\frac{\lambda q\ E(\tau^{2})}{2\tilde{\tau}}<<1$.This means that the second central moment of τ should be bounded. But this is the case for the usual lifetime distribution functions to be used for modeling the recovery time.

IV. APPLICATION

Effect of salt stress on biological system

In this study we consider the administration of Low salt (LS) diet & High salt (HS) diet causes a shock in terms of aldosterone in the biological system. The study reveals the damage caused to the organ system in the sense of blood pressure.

Methods

A group of patients with unilateral aldosterone-producing adenoma (APA) were feeding a LS diet for one week followed by HS diet for another week. At the end of each diet period, measurements of blood pressure (BP) at regular interval, daily aldosterone measurement and a metaclopramide (MCP) test were performed**[21].**

It was observed that the blood pressure level both systolic and diastolic were remarkably high during the day time and night time due to the administration of LS diet. Also it was observed that HS diet caused a steep increase in BP both systolic and diastolic in day time and night time. From the observations it was revealed that there was a vast difference between systolic blood pressure (SBP) level in day time due to LS diet and diastolic blood pressure (DBP) level in day time due to HS diet; but there was no significance in DBP level due to LS & HS diet. The conclusion is the HS diet causes very high level of SBP (>140 mm Hg) in a normal person due to the intake of salt diet.

Results of MCP Test

Patients diagnosed with unilateral APA were enrolled for MCP test. The patients had abnormally high ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA), ranging from 52 to 468 with a mean of 189 ± 31.

After administrating an intravenous injection of 10 mg MCP, the patients PRA was further suppressed by HS. Initially the change in PAC was marginal but after few minutes their PAC increased significantly. **[6, 22]**

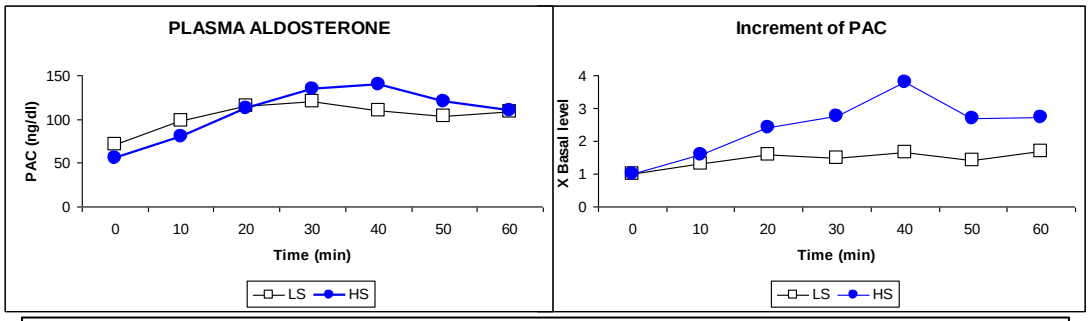

Fig. 1: **Left Panel:** Changes in PAC after a 10-mg intravenous administration of metoclopramide on low-salt and high-salt. **Right Panel:** Increment of PAC from basal on low-salt diet and high-salt diet

V. RESULTS

The mean increment of PAC at basal level is considered as shock response which is exactly fitted the Poisson Process whose rate is $h(x)=\lambda$ and $\tilde{\tau}$ is mean time of recovery for the corresponding shock response which is distributed exponentially and the realized damage level is measured as in the sense of blood pressure.

In our application let us take the parameter values $\lambda=1.45\,\&\,\bar{\tau}=0.033$ and $\lambda=2.4186\,\&\,\bar{\tau}=0.033$ we get $E(T)=2.221805\,\&\;E(T)=2.600104$ from low salt diet and high salt diet in patients with aldosterone producing adenoma respectively.

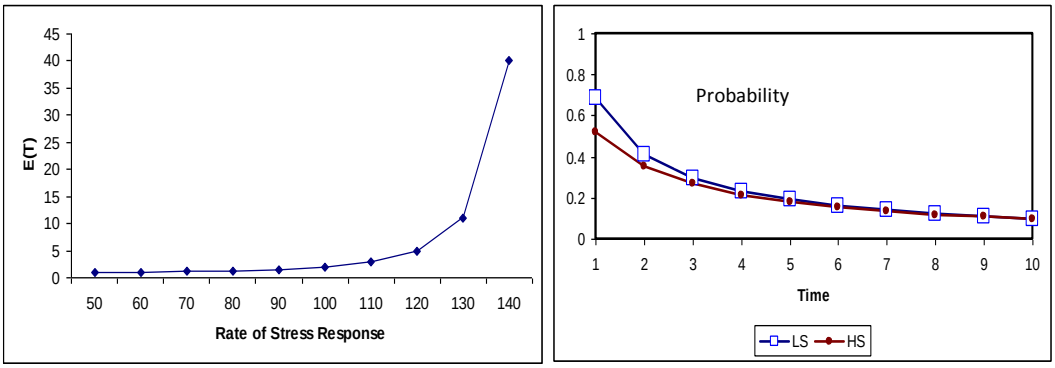

Fig.2: **Left Panel**: Mean time changes due to aldosterone concentration by using Poisson shock model. **Right Panel**: Survival probabilities of patients on salt manipulation

VI. CONCLUSION

Our mathematical model reveals that the negligible amount of stress effects does not affect the organ system immediately but if it is too long or it is too often i.e, it survives more time to stand in its positions strongly which induces the organ system to failure. In our result, the rate of stress effect between 50 and 120, it gives the small level of damage to the system which is mild and also the rate of stress effect between 120 and 130, it causes moderate level of damage to the organ system, but the rate of stress effect exceeding above 130, the system fails under this circumstances. In summary, in our application part, we defined two subtypes of patients with APA according to their responses to MCP during salt manipulation. On HS, the so-called nonsuppressible patients had higher level blood pressure.

Although different responses of aldosterone secretion to MCP in various hypertensive diseases have been reported, the significance of individual variations has not studied. In the present study, we defined two subgroups of patients APA according to their different responses of aldosterone secretion to MCP on changes of salt intake. Patients with a larger difference in the increment areas of PAC between LS and HS are thought to be more suppressible by Dopamine. Therefore, we speculate that angiotensin responsive APA may have a greater response to MCP. Although the absolute PAC after MCP was not different between LS and HS, the PAC increment was greater on HS. This indicates that changing salt intake does not alter autonomous aldosterone secretion from APA.

Finally, we discuss human systems under the influence of two different types of salt stress (LS & HS). Low salt stress does not alter PAC then the expected damage level is less than the given threshold level and expected recovery time is also negligible, but in the case, high salt induces the PAC level too high than the expected level of damage and the recovery time is also high. This paper may be extended to patients of hypokalemia due to hypertension and PRA suppression in all by increasing number of subjects and using other medical variables.

Many mathematical models have been developed for the simulation of various engineering systems such as mechanical, electrical and etc. But little progress has been made in constructing mathematical models to simulate various biological organ systems. Here we have developed a mathematical model to study the effects of stress in aldosterone. Similar approach can be adapted to analyze the effect of hypertension and PRA in patients affected by hypokalemia. Further attempts can be made to construct relationships between stresses and psychological effects of biological systems to estimate their behavior for varied stress responses.

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