Circadian Rhythms of Serum Aldosterone, Cortisol and Plasma Renin Activity in Burn Injuries

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ABSTRACT

Circadian rhythm of serum aldosterone and cortisol concentrations and of plasma renin activity (PRA) were measured by radioimmunoassay in 10 adults with thermal injuries. The determinations were begun 6 to 48 hours after the injury and continued for five consecutive days four times a day. In all patients, the normal pattern of the circadian rhythm for all three hormones disappeared and values remained quite high at any time of the day or the night. Four patients developed an hypertensive crisis with quite elevated levels of aldosterone, cortisol and plasma renin activity. The same hormones were also found very elevated in two hypotensive patients with 80 percent or more of injured body surface who were in agonal conditions and succumbed to the injury.

Introduction

It has been reported that about 30 percent to 50 percent of thermally injured children and 25 percent of thermally injured adults develop an hypertensive crisis after burns. This crisis usually begins after an initial period of two days to as long as three to four weeks from the date of the injury, and it lasts for an average of four to six days with a range of two to eight days.

The pathogenesis of the crisis is still unclear. Several hormones of the adrenal glands, such as aldosterone, cortisol, catecholamines, and of the pituitary (corticotropin) were found in abnormally high concentrations in the blood and urine of burned hypertensive subjects; however, the same hormones were found elevated and in similarly abnormal levels in normotensive thermally injured individuals. Plasma renin activity (PRA) and plasma angiotensin-2 concen-
tations were also found elevated during the hypertensive crisis\(^5\) often, as recently reported by us, coincident with a decrease in serum sodium levels.\(^4\) Severe hyperreninemia, however, is present not only in hypertensive but also in normotensive or hypotensive burn patients, especially in agonal conditions.\(^3\) These contradictory results could possibly be explained by the fact that thus far only "spot" measurements of these hormones were performed, usually in the morning, in the thermally injured patients studied. These "spot" measurements do not represent the daily cycle of the hormones which may differ from their circadian rhythm in normal subjects.

Nowaczynski et al\(^1\) have reported that the circadian rhythm of aldosterone is altered in patients with benign essential hypertension (BEH). In normal subjects, these and other authors\(^2,7\) have found that the highest peak of aldosterone or cortisol is in the morning with a lower level at 20 hours and a minimum level at midnight. This decline in evening and midnight concentrations of aldosterone does not appear in patients with BEH so the values remain practically unchanged during the whole 24-hour cycle. This different rhythm of hormonal secretion could alter the homeostatic control of fluids and electrolytes with consequent sodium retention and hypertension.

The circadian rhythm of aldosterone and PRA has not been measured in thermally injured patients. In this study are reported the results of determinations of circadian rhythm of these two hormones and cortisol in an attempt to correlate these variations with possible changes of the blood pressure.

Materials and Methods

Serum aldosterone, cortisol concentration and PRA were measured by radioimmunoassay (RIA) techniques in 10 patients admitted to the Burn Center of Loyola University Stritch School of Medicine, Foster McGaw Hospital. An average interval of 6 to 48 hours occurred between the time of injury and the beginning of the study because of the occasional transfer of a patient from another hospital. Blood was collected simultaneously for the three RIA's four times a day for five consecutive days. Collection time was at 6, 12, 18 and 24 hours with an approximation of about 60 minutes from the scheduled time, owing to the technical problems of blood collection and the patient's condition. There were seven male and three female patients. Of these, seven were Caucasian, two were Negro and one was Oriental with an age range of 21 to 65 years and a mean age of 36.8 ± 5.2\(^*\) years. The mean percent of the total body surface injured was 37.3 ± 9.6 (range 3 percent [with severe smoke inhalation] to 90 percent). The mean hospital stay was 37.6 ± 13.0 days (range = 5 to 144 days). Seven patients were at complete bed rest, two were partially ambulatory and one was totally ambulatory. Blood was collected from the ambulatory patients 30 minutes after rest in a supine position. Blood pressure was measured usually 30 minutes before the collection of the serum specimens, and routine laboratory chemistries were performed as on all the other patients at the Center.

Systemic antibiotic administration consisted of penicillin (I.V. or I.M., 1,200,000 units every six hours for five days). Topical treatment consisted of application of Silvadene cream with dressing change once or twice a day. In patients with 20 percent or more burned body surface, resuscitation consisted of intravenous administration of Ringer's lactate solution (4 ml per kg of body weight per percent of burned body surface). An elemental diet was added to the general treatment in the same group. No steroids were used.

* Standard error of the mean.
Results

Mean values of serum aldosterone and cortisol were both above normal levels at the beginning of the study and remained elevated up to the fourth day (figures 1 and 2). (Using our RIA methods, we considered abnormal elevations of serum aldosterone to be above 125 pg per ml and serum cortisol above 20 ug per 100 ml.) It is also evident from figures 1 and 2 that these high concentrations persisted, practically without change through the day and not showing the expected decline seen in normal individuals at 1800 hours and midnight. There was therefore a disappearance of the regular circadian rhythm for at least three days, as it is seen in normal subjects. Toward the fourth and fifth days, a slight decrease in concentration of both hormones with a decline, particularly evident at midnight, became apparent, thus indicating a return of a trend toward normalcy. Mean values of PRA
were within normal limits (less than 8 ng per ml per hour of incubation) at day 1. They rose markedly and progressively up to day 4. There was an alteration of the circadian rhythm as for aldosterone and cortisol with the highest values being seen at midnight, the time when they should be at the lowest level (figure 3).

The mean values for systolic and diastolic blood pressure are shown in figure 4. As a whole, the population did not become hypertensive, even if an increase of 20 and 15 mmHg in the systolic and diastolic blood pressure, respectively, was evident at the highest peak (18 hours on the fourth day). Hypertensive crises (blood pressure above 160/90 mmHg) were seen in four of the ten patients, two males and two females, respectively, of 21, 25, 33, and 52 years of age. No previous history of hypertension was recorded in three patients while the fourth, a 52-
year-old Caucasian female, had a poorly defined history of cardiopathy and coronary heart disease. All of them had abnormally high aldosterone levels. The three youngest patients had higher than normal PRA and cortisol levels. Moreover, the circadian rhythm of the three hormones was abnormal with persistently high values at 18 hours and midnight.

All of the patients recovered from the crisis. Renal function damage was not found. A modest decline in serum sodium levels became evident the day preceding or coincident with the crisis. Six patients did not become hypertensive and they were divided into two subgroups. Group one consisted of two young adults with burns over 80 percent to 90 percent of their body surface. Both of them succumbed within eight days of the injury. Aldosterone, cortisol and PRA levels were extremely high in both patients for the entire five days. For most of the determinations, the aldosterone levels ranged between 600 to 900 pg per ml (normal less than 125 pg per ml), while cortisols were above 30 μg per 100 L (normals < 20), and PRA above 80 and 100 ng per ml per hour of incubation (normals < 8 ng per ml per hour). From the fourth day on, serum creatinine and BUN were quite elevated while serum sodium levels were in the lower range of normalcy.

The second subgroup (four patients) had normal aldosterone, cortisol, and PRA levels, although even in these patients the circadian rhythm of the three hormones were altered with high values at 18 hours and midnight. Two of the younger patients (ages 24 and 29 years) with about 15 percent of burned body surface recovered well, while the remaining two older patients (ages 61 and 65 years) with similar burn injury died of complications several weeks after the injury (44 and 35 days, respectively). No changes were seen in serum sodium concentrations.

Discussion

Determination of the circadian rhythm of serum aldosterone, cortisol and PRA in normal human adults had thus far yielded somewhat discordant results. Most of the reports in the literature underline a peak concentration of the three hormones during the mid-morning (6 to 9 hours) and a decline to the lowest levels in the late afternoon and a night (18 to 24 hours). Another group of investigators noted peak levels of these hormones during the first hours of sleep, and they described this pattern as always being coincident with sleep regardless of when it would occur.

From our observations in burn patients, the circadian rhythm of all three hormones is altered and the cycle observed in normal human adults of high peaks and depression is modified toward rather sustained levels for the whole 24 hours. This modification is similar to that reported in subjects with essential hypertension, renovascular hypertension, primary hyperaldosteronism, Cushing's disease, chronic glomerulonephritis, and hyperthyroidism. The alteration of the circadian rhythm was seen in all 10 burn subjects whether they were normotensive, hypotensive or developed an hypertensive crisis and independently of serum concentrations of aldosterone, cortisol and PRA.

The incidence of patients with hypertensive crisis, 4/10 (40 percent) is somewhat higher than previously reported. The difference is probably related to the number of patients included in the study and the severity of the injury in these patients. Certainly of interest are similar modifications in the circadian rhythm of the measured parameters in burned human subjects with those present in individuals with definite pathology of the renovascular system, the adrenal cortex, and the thyroid gland, thereby confirming the severe involvement of all these organs following thermal injury. The severe hyperreninemia associated with severe hyperaldosteronism and hypercortisolism in preagonal patients with burn injury above 80 percent confirmed the finding of Bozovic, et al. It is quite likely that in these conditions, the normal feedback mechanisms controlling the renin-angio-
tensin-aldosterone system as well as the pituitary-adrenal axis are deranged and the findings of very high levels of these hormones without a rise in the patient’s blood pressure may be of prognostic value.

Summary

In conclusion, our study has confirmed the occurrence of the hypertensive crisis in thermally injured patients and has indicated the existence of a correlation of the changes in blood pressure with an increase of PRA, aldosterone and cortisol, and a derangement of their circadian rhythm. It also indicates that the circadian rhythm of these hormones is altered after thermal injury, even in patients who do not develop the hypertensive crisis. Furthermore, the most severe alterations of the hormonal levels were seen in patients in preagonal conditions. There are components of the renin-angiotensin system and of the pituitary adrenal axis which have not yet been fully studied in thermally injured patients. For some of them, such as the angiotensin-1-converting enzyme, an important role in the pathogenesis of few experimental types of hypertension is emerging. The study of these other components would be necessary in order to explain why hypertensive crisis sustained by hyperreninemia and hypercorticism occur in a large percentage but not in all burned subjects. Moreover, studies in a larger population of thermally injured subjects would better define even statistically the various subgroups encountered by us, thus contributing to a better understanding of the problem.

References