Adrenomedullary Response to Maximal Stress in Humans

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The most important neuroendocrine response to stress is an increase in plasma epinephrine concentration. To investigate the clinical significance of this response, plasma catecholamine levels were measured (single-isotope derivative assay) in chronic stress (severe illness; n = 22) and acute maximal stress (cardiac arrest; n = 23). The results were then compared with the values from 60 normal resting subjects: epinephrine (mean ± SEM) 0.034 ± 0.002 ng/ml; norepinephrine 0.228 ± 0.01 ng/ml. Chronic stress (intensive care unit patients) was associated with a fourfold elevation of epinephrine concentration (0.14 ± 0.06 ng/ml; range 0.01 to 1.37; p <0.01 versus normal control subjects). Acute maximal stress (resuscitation following cardiac arrest) resulted in a greater than 300-fold increase in the plasma epinephrine level (10.3 ± 2.9 ng/ml; range 0.36 to 35.9; n = 15; p <0.01). Peak plasma epinephrine levels in successfully resuscitated patients (n = 6) ranged from 0.36 to 273 ng/ml (three patients had received epinephrine therapy). The plasma norepinephrine level was increased twofold in intensive care unit patients (0.52 ± 0.06 ng/ml; p <0.01) and 32-fold after cardiac arrest (7.37 ± 1.8 ng/ml; p <0.01). During resuscitation, the correlation between the simultaneous epinephrine and norepinephrine levels was highly significant: r = 0.76; p <0.01. It is concluded that (1) chronic, severe stress produces only moderate elevations of plasma epinephrine levels (up to 1.37 ng/ml), whereas acute stress produces marked increases of plasma epinephrine that may reach the extraordinarily high level of 35.9 ng/ml, (2) the potential toxicity from the adrenomedullary response to acute stress is further exacerbated by the parallel release of norepinephrine, and (3) under close medical monitoring, it is possible to survive with plasma epinephrine concentrations as high as 273 ng/ml.

Stress may be defined as a life-threatening stimulus of endogenous or exogenous origin that elicits a characteristic, synchronized response from the neuroendocrine system. The hormonal response to stress has been studied experimentally, using the stimulus of acute hypoglycemia. Hypoglycemia, induced by the administration of insulin in a bolus injection, is followed by the release of epinephrine, cortisol, growth hormone, and prolactin [1,2]. Of these, epinephrine may be considered the most sensitive and consistent index of the stress response, since the level of this hormone is also elevated during psychologic challenges when a threat to life is not readily apparent [3], and the increase in the levels of the other stress hormones is only modest [4,5].

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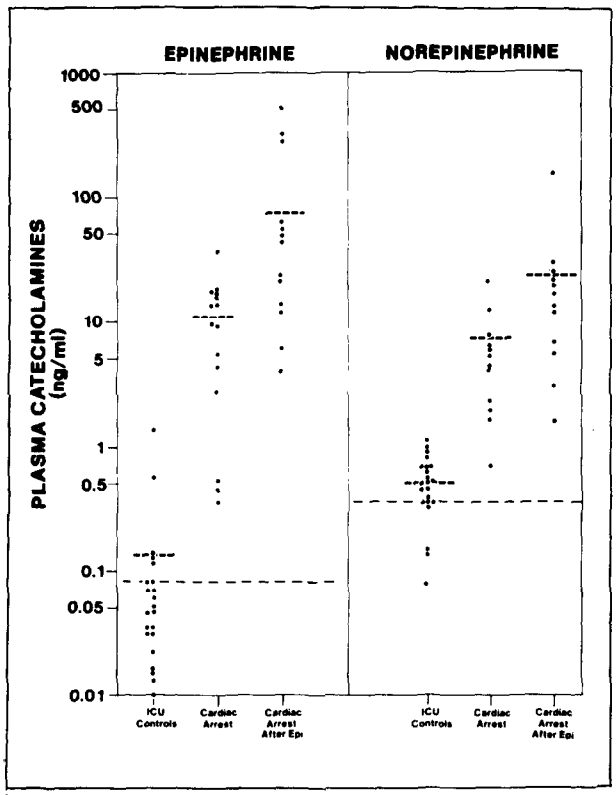

Figure 1. *Distribution of plasma catecholamine concentrations in severely ill patients. Blood samples from intensive care unit control subjects were obtained the morning following admission. The concentrations in patients with cardiac arrest represent individual peak values in the absence of, or before, epinephrine administration. Note the logarithmic scale used in the representation of plasma catecholamine concentrations. The results of statistical testing are shown in Table II. The* ***broken line*** *at the bottom of the columns represents the upper limit of normal (mean ± 2 SD) for normal resting subjects. Peak norepinephrine concentrations from three patients who received norepinephrine during resuscitation are not included in this figure.*

The adrenal medullae, like sympathetic nerves, are under direct control from the central nervous system; but the adrenomedullary hormone epinephrine is secreted directly into the bloodstream as opposed to the narrow synaptic cleft. This property, release into the circulation following adrenomedullary stimulation, e.g., during stress, would give epinephrine the advantage of rapid access to adrenergic receptors not served by a nerve terminal. We attempted to determine the clinical significance of adrenomedullary secretion during the stress by measuring plasma epinephrine concentrations in patients undergoing chronic stress (severe illness) or acute and maximal stress (imminent death from cardiac arrest).

PATIENTS AND METHODS

The clinical population comprised 23 patients who experienced cardiac arrest requiring resuscitation in an intensive care unit. No attempts were made to select specific types of patients for the study. Blood samples were obtained during the resuscitation procedure as soon as possible after cardiac arrest and at approximately one, three, five, 10, 20, and 30 minutes, and at one, two, four, 12, and 24 hours. When epinephrine was administered, it was given as a bolus intravenous or intracardiac injection. The blood specimens were placed immediately in prechilled tubes containing reduced glutathione at a final concentration of 5 m*M*. Plasma was separated in a refrigerated centrifuge at 4°C and stored at −70°C until the time of analysis. Blood samples were also obtained from a control group of 22 patients admitted consecutively to the intensive care unit who had not had a cardiac arrest. Patients in this group gave their informed consent and, the morning after admission, their blood samples were drawn simultaneously with the samples for tests requested by their attending physician. This protocol was approved by the Springfield Committee for Research on Human Subjects.

Experimental Methods. Plasma catecholamine levels were measured by a single-isotope derivative method based on the enzymatic conversion of the catecholamines to their respective metanephrines [6]. Labeled metanephrine and normetanephrine were separated by thin-layer chromatography to permit independent measurement of epinephrine and norepinephrine. This method is sensitive to less than 0.01 ng/ml of epinephrine or norepinephrine. Interassay coefficients of variation were 8.5 percent for epinephrine and 3.5 percent for norepinephrine. With the chromatographic system used in our single-isotope derivative assay, there is no detectable crossover between the norepinephrine and epinephrine derivatives with initial catecholamine concentrations up to 4 ng/ml, i.e., concentrations that span the physiologic range [2]. However, at extraordinarily high plasma catecholamine concentrations, 10 to 1,000 ng/ml, norepinephrine-to-epinephrine crossover is up to 0.6 percent and epinephrine-to-norepinephrine crossover is up to 2.5 percent.

RESULTS

Plasma epinephrine level in the control intensive care unit patients was 0.14 ± 0.06 ng/ml (mean ± SEM). This value was significantly higher than the mean concentration of 0.034 ± 0.002 ng/ml obtained in a population of 60 normal resting subjects. Cardiac arrest produced markedly elevated plasma epinephrine concentrations. The mean peak value in 15 patients, 10 who did not receive epinephrine plus five in whom samples prior to the administration of epinephrine were available, was 10.3 ± 2.9 ng/ml (**Figure 1** and **Tables I** and **II**). Evaluation of the timing of the epinephrine peak could be performed in 11 patients. The epinephrine peak appeared in the first sample in four patients (at one, nine, and 15 minutes), whereas the remaining seven had the epinephrine peak in the second or later

TABLE I Plasma Catecholamine Levels following Cardiac Arrest*

Group	Number	Plasma Epinephrine (ng/ml)	Plasma Norepinephrine (ng/ml)
Normal subjects†	60	0.034 ± 0.002	0.228 ± 0.010
Intensive care unit control patients	22	0.14 ± 0.06	0.52 ± 0.06
Cardiac arrest requiring resuscitation			
Peak concentration before epinephrine	15	10.3 ± 2.9	7.37 ± 1.8
Peak concentration after epinephrine	13	72 ± 31	22.3 ± 11

* Mean ± SEM.
† Supine, following a 30-minute resting period.

TABLE II Effect of Cardiac Arrest on Plasma Catecholamine Levels: Statistical Evaluation

Groups Compared	Epinephrine (ng/ml)	p Value	Norepinephrine (ng/ml)	p Value
1 vs. 2	0.14 vs. 10.3	0.0004	0.52 vs. 7.37	0.034
1 vs. 3	0.14 vs. 72	0.039	0.52 vs. 22.3	0.083
2 vs. 3	10.3 vs. 72	0.07	7.37 vs. 22.3	0.222

Group 1: Intensive care unit control patients.
Group 2: Cardiac arrest requiring resuscitation (levels before epinephrine administration).
Group 3: Cardiac arrest requiring resuscitation (levels after epinephrine administration).

samples (from three to 40 minutes after cardiac arrest had occurred).

The effect of epinephrine therapy upon plasma epinephrine levels was determined in a total of 13 patients; of these, eight had received the drug immediately after cardiac arrest, before baseline blood samples could be obtained. The mean peak plasma epinephrine concentration after epinephrine administration was 72 ± 31 ng/ml. The total dose of epinephrine had been 1 mg in seven patients, 2 mg in four, 3 mg in one, and 4 mg in one patient.

Only six of the 23 patients with cardiac arrest survived. Three of the survivors had not received epinephrine; their peak epinephrine levels were 0.36, 0.45, and 18.3 ng/ml. In the three survivors who did receive epinephrine, peak epinephrine levels were 3.89, 22.7, and 273 ng/ml.

Plasma norepinephrine levels in intensive care unit patients (0.52 ± 0.06 ng/ml) were slightly but significantly higher than in normal resting subjects (0.228 ± 0.010 ng/ml; $p < 0.01$). Plasma concentrations were markedly elevated following cardiac arrest, when they reached the mean peak level of 7.37 ± 1.8 ng/ml. Plasma norepinephrine levels showed a further rise after the administration of epinephrine, to a mean peak level of 22.3 ± 11 ng/ml. This latter figure does not include the results in three patients who had received norepinephrine during resuscitation, and whose peak plasma norepinephrine concentrations were 4.74, 210, and 584 ng/ml. Among the six survivors, one had received norepinephrine; in this patient, the peak recorded value for plasma norepinephrine was 210 ng/ml. In the remaining five survivors, peak norepinephrine concentrations were 1.59, 2.25, 6.45, 12.6, and 18.7 ng/ml.

There was a significant correlation between epinephrine and norepinephrine concentration in intensive care unit patients ($r = 0.47$; $p < 0.05$; $n = 22$). The same correlation, between peak plasma epinephrine and norepinephrine levels, was more significant in the patients with cardiac arrest whose samples had been obtained in the absence of epinephrine administration ($r = 0.76$; $p < 0.01$; $n = 12$). The significance of this correlation was further confirmed by two independent methods. First, all the plasma values recorded simultaneously in these patients (not just the peak levels) were computed separately in the calculation of the correlation coefficient. After logarithmic transformation of the data (**Figure 2**), the r value was 0.83 ($p < 0.01$; $n = 45$ sets of paired epinephrine and norepinephrine determinations). Second, in the patients who had a cardiac arrest and in whom two or more pairs of epinephrine and norepinephrine determinations were available ($n = 10$), the correlations were examined separately for each patient. By this type of evaluation, all the individual correlations were found to change in the same direction.

COMMENTS

The effects of epinephrine can be consistently reproduced and depend on the plasma concentration, not on the infusion rate: plasma levels of 0.05 to 0.1 ng/ml are

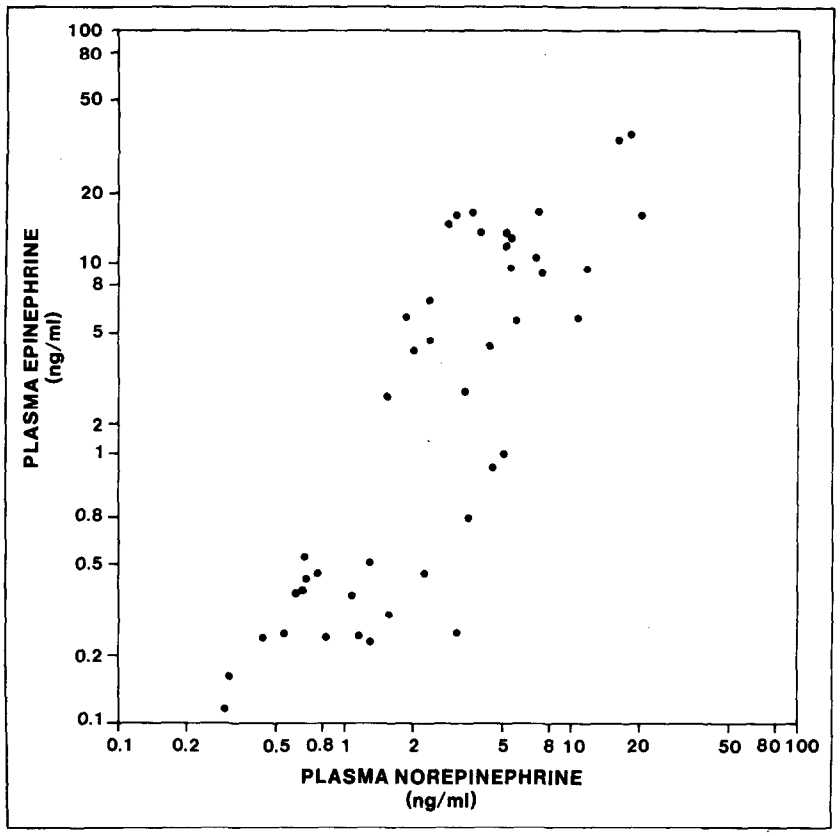

Figure 2. *Correlation between simultaneous plasma concentrations of epinephrine and norepinephrine during resuscitation after cardiac arrest. The figure includes only samples obtained in the absence of epinephrine administration. Note the logarithmic scale used in the representation of plasma catecholamine concentrations. The correlation coefficient (r) value is 0.83 ($p < 0.01$; $n = 45$).*

associated with increases in heart rate; lipolysis and systolic blood pressure elevations occur at 0.075 to 0.125 ng/ml; hyperglycemia, ketogenesis, and glycolysis occur at 0.10 to 0.2 ng/ml [7]. These concentrations are much lower than the values observed in life-threatening disorders [2]. For instance, a plasma epinephrine value of 1.58 ng/ml has been observed in severe diabetic ketoacidosis [8], and a concentration of 16 ng/ml has been noted in a patient with septicemia and shock [9].

Resuscitation after cardiac arrest is associated with the highest endogenous epinephrine concentration ever recorded: 35.6 ng/ml. This finding supports our a priori assumption that the stress of cardiac arrest produces maximal adrenomedullary stimulation. The marked variation in peak catecholamine concentration observed among these patients who experienced the same intensity of stress may be related to interindividual differences in catecholamine release due to differences in resuscitation, pre-existing illnesses, or exaggerated response to repeated adrenal stimulation (adrenal "memory" [10]); to differences in catecholamine clearance from the circulation; or to insufficient sampling.

The attainment of very high concentrations of epinephrine may be biologically beneficial, since large doses increase the survival rate in dogs subjected to acute hypoxemia or ventricular fibrillation [11] and, probably, in humans experiencing cardiac arrest [12–14]. However, the use of high doses of epinephrine is also hampered by significant toxicity; early studies in 1919 performed in dogs by Erlanger and Gasser [15] showed that the administration of epinephrine in very large doses for several days resulted in death from visceral congestion and redistribution of the intravascular blood compartment. These observations have been subsequently confirmed, and additional findings of renal damage, pulmonary insufficiency, and myocardial necrosis have been noted [16–18]. In humans, the deleterious effects of sudden, extremely high concentrations of epinephrine include serious cardiac arrhythmias and lactic acidosis. These have occurred after the self-administration of a large amount of epinephrine (20 mg) intravenously, following the spontaneous necrosis of a pheochromocytoma, and during the treatment of anaphylactic reactions [19–22].

The plasma catecholamine response to severe stress appears to differ according to the latency of the involved threat to life, i.e., immediate or delayed. These types of responses can also be evaluated from this series. The

study comprised two groups of severely ill patients: one relatively stable and under chronic stress (intensive care unit control subjects) and another with maximal stress acutely superimposed (cardiac arrest and resuscitation). The groups could be separated on the basis of clinical background and plasma epinephrine concentration. The plasma epinephrine response to acute maximal stress (following cardiac arrest) was marked (approximately 300-fold elevation over that in normal resting subjects), prompt (within 10 minutes), transient (less than 40 minutes' duration), and accompanied by elevation of the plasma norepinephrine level (approximately 32-fold). In contrast, chronic stress (intensive care unit control subjects) was associated with minimal increases in the epinephrine level (approximately fourfold over that in normal resting subjects) and only a slight elevation in the norepinephrine level (approximately twofold).

The present study could not determine the homeostatic significance of the adrenomedullary response to a cardiac arrest. Indeed, survival was observed in the absence of either epinephrine administration or spontaneously elevated plasma levels, as represented by the wide range of peak plasma concentrations among the survivors. Thus, plasma epinephrine increments of as little as 10-fold or as great as more than 8,000-fold over normal basal levels were found compatible with survival, albeit in the setting of an intensive care unit. Nevertheless, these results cannot be extrapolated to acute stress occurring in the absence of close medical supervision. It is probable that these high levels of epinephrine have major physiologic effects in otherwise healthy persons.

The elevation of plasma norepinephrine levels following cardiac arrest may represent overflow from intense stimulation of the sympathetic nervous system, adrenomedullary release, or both. The highly significant correlation between the simultaneous epinephrine and norepinephrine concentrations following cardiac arrest was similar to that observed during insulin-induced hypoglycemia, a potent stimulus to adrenomedullary catecholamine secretion in normal humans ($r = 0.83$). In contrast, in normal resting subjects, the same correlations were not significant, whether in the supine or standing position: $r = 0.11$ and $r = 0.08$, respectively (unpublished observations). Thus, acute stress stimulates adrenomedullary release of norepinephrine in addition to epinephrine, further exaggerating the risks of catecholamine toxicity, especially in the presence of increased cardiac irritability.

In conclusion, we report the concentrations of plasma catecholamines detected in severely ill patients, severely ill patients experiencing cardiac arrest and resuscitation procedures, and patients who had a cardiac arrest and were receiving epinephrine during resuscitation. We have demonstrated that acute maximal stress such as cardiac arrest is associated often, although not always, with extremely high concentrations of catecholamines; the resulting mean plasma levels of 10 ng/ml for epinephrine and 7 ng/ml for norepinephrine could produce significant cardiovascular and metabolic toxicity in otherwise healthy persons.

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