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Correlation between Circulating Catecholamine Levels and Ventricular Vulnerability during Psychological Stress in Conscious Dogs (40533)[1, 2]

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Psychologic stress has been recently shown to enhance myocardial susceptibility to ventricular fibrillation (1). In animals with ligation of a coronary artery such stresses may provoke ventricular ectopic arrhythmias (2) and even precipitate ventricular fibrillation (3). Raab (4) has shown that diverse psychologic stresses can induce myocardial necrosis. Evidence has also been presented in man linking psychologic factors with the occurrence of ventricular fibrillation, the usual mechanism for sudden cardiac death (5).

While neural pathways mediating brain–heart interactions remain to be fully defined, much attention has been focused on the sympathetic nervous system. β-Adrenergic blockade (6, 7) or stellectomy (7) significantly reduce or entirely prevent expression of psychologically initiated changes on ventricular vulnerability to fibrillation. It is suggested that the level of sympathetic tone mediates cardiac susceptibility to varying ventricular arrhythmias.

The present study aimed to determine whether alterations in circulating catecholamines occurred in animals subjected to minimal psychologic stress states and whether these correlated with changes in the ventricular vulnerable period threshold for repetitive response. Circulating norepinephrine has been suggested as a quantitative index of sympathetic tone (8). We therefore measured both norepinephrine and epinephrine levels in dogs in an aversive and tranquil environment and compared these to changes in repetitive extrasystole threshold, a marker of cardiac vulnerability to VF (9).

Material and Methods. General. Seven healthy mongrel dogs weighing between 10 and 15 kg were utilized for this study. A week before experimentation, dogs were anesthetized intravenously with sodium pentobarbital (20 mg/kg). A catheter for recording the electrocardiogram and a bipolar pacing catheter were transvenously placed at the apex of the right ventricle. An indwelling catheter for pressure monitoring and blood sampling was inserted retrograde into the aorta through an omocervical artery.

Cardiac testing. The repetitive extrasystole (RE) threshold method was used to determine the cardiac vulnerability for ventricular fibrillation (VF) (10). A Medtronic pacemaker was used to provide rectangular pulses of 2-msec duration at 273-msec intervals. This heart rate was necessary to exceed the tachycardia in the stressful environment. The pacemaker current was set at twice the mid-diastolic threshold and the distal pole of the catheter was made cathodal. An electrically isolated Grass S44 square-wave pulse generator provided constant-current test impulses of 5-msec duration. After the delivery of a test stimulus the circuitry employed shut off the pacemaker output for 3.0 sec. The RE threshold was determined with heart rate maintained at 220 beats/min. Briefly, the vulnerable period was determined as follows: Scanning for the RE threshold was commenced with a stimulus of 4-mA intensity delivered 30 msec beyond the effective refractory period. The test stimulus was delivered progressively earlier by 5-msec intervals until the refractory period was encountered. If no RE was elicited, the stimulus intensity

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was increased by 2 mA and the scanning procedure was repeated. The RE threshold was taken as the minimum current intensity at which RE occurred in two out of three trials.

Psychological environments. Two environments were employed: one deemed stressful and the other nonstressful (1, 2). The nonstressful environment was a large cage in a soundproof room where the animal was undisturbed and appeared relaxed. The stressful environment consisted of a Pavlovian sling in which the animal was restrained. The animal in the sling received a transthoracic 4-wsec shock on 3 consecutive days. On the fourth day, the dog received no further electric shocks and the perception of stress resulted from the memory of previous aversive stimuli. Determination of heart rate, blood pressure, and RE threshold and sampling of blood were carried out in both environments on the fourth day. The animals were studied only once in each setting.

Biochemical method. Five milliliters of whole blood collected via the chronic indwelling catheter was transferred to a vacutainer tube containing 100 μl of an additive solution (90 mg/ml EGTA, 60 mg/ml glutathione, pH 6.0–7.4); circulating catecholamines were measured according to a single-isotope radioenzymatic assay (10).

Statistical analyses were made using Student's paired t test. All values are expressed as mean ± SEM.

Results. When the animal was transferred from the nonstressful cage environment to the stressful sling environment, there was a significant 41% ($P < 0.01$) reduction in the RE threshold. Concomitant with the decrease in RE threshold during stress, plasma norepinephrine levels increased twofold ($P < 0.05$) and epinephrine levels increased fourfold ($P < 0.01$). The reduction of RE threshold was also accompanied by significant elevations in heart rate ($P < 0.01$) and mean arterial pressure ($P < 0.05$) (Fig. 1).

A differential release of norepinephrine and epinephrine was observed in the two environments. In the nonstressful environment norepinephrine was the predominant catecholamine in the peripheral circulation. When the animals were exposed to the stressful sling environment, there was a larger increase in epinephrine release and epinephrine became the predominant plasma catecholamine (Fig. 2). The stress-induced changes in both norepinephrine and epinephrine correlated significantly with lowering in RE threshold in the sling environment. The total

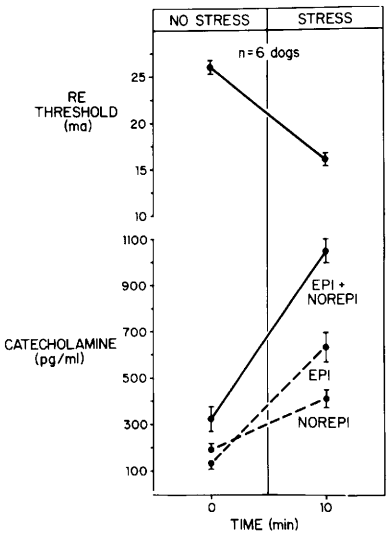

FIG. 1. Effect of aversive sling environment on repetitive extrasystole (RE) threshold and circulating plasma catecholamine level. The RE threshold decreased 41% within 10 min of placing the animals in the sling after removal from the cage. The reduction in threshold was accompanied by substantial increases in both norepinephrine and epinephrine. Values are means ± SEM.

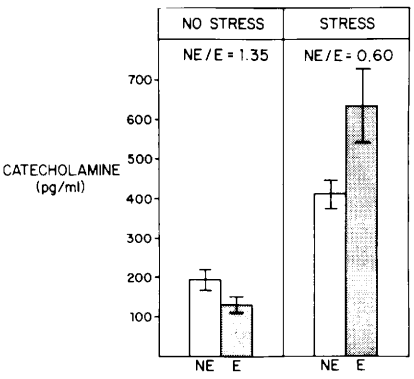

FIG. 2. Relative plasma levels of norepinephrine (NE) and epinephrine (E) in two different psychologic environments. In the nonstressful cage environment the predominant catecholamine was NE (NE/E ratio = 1.35). In comparison, in the stressful sling setting E became the prevailing catecholamine (NE/E ratio = 0.60).

plasma catecholamine levels also showed a significant positive correlation with the RE threshold changes (Table I).

Discussion. In the experimental animal, enhanced sympathetic activity, whether induced by electrical stimulation of the posterior hypothalamus (12) or the stellate ganglia (13), predisposes the myocardium to ventricular fibrillation. Cardiac sympathectomy (14) or β-adrenergic blockade (15) prevents the stimulation-induced increase in ventricular vulnerability. Infusion of subpressor doses of norepinephrine produces significant reduction in ventricular fibrillation threshold (16). These findings indicate that norepinephrine released at the sympathetic nerve endings increases cardiac vulnerability to ventricular fibrillation.

In the present study the animals were not subjected to physically noxious stimulation beyond 3 days. The sling environment was merely evocative of remembered aversive situation; thus one could surmise that it constituted a psychologic stress. Indeed there was a substantial rise in blood catecholamine concentrations indicative of enhanced sympathetic neural activity as well as adrenal medullary discharge. Concomitant with the changes in circulating adrenergic neurohumoral agents there was a significant decrease in the ventricular vulnerable threshold. These observations in conjunction with the findings that changes in ventricular RE response resulting from diverse psychologic stresses can be annulled by such β-adrenergic blocking drugs as tolamolol (6) or propranolol (7) indicate that these psychologically induced electrophysiologic alterations are mediated largely by the sympathetic nervous system.

In the present study the animals were exposed first to the stressful and then to the nonstressful environment. It is therefore relevant to question whether reversing the conditioning sequence might have yielded different results. A previous study carried out in our laboratory, however, indicates that the order in which the animals were exposed to the stressful and nonstressful environments is not crucial to the magnitude and direction of the RE threshold changes (17).

Recent studies in man (18) support the hypothesis first formulated by Funkenstein (19) that aggressive emotions induce a predominant release of norepinephrine, whereas anxiety elicits a preferential release of epinephrine. Car racing was associated primarily with augmented circulating norepinephrine; whereas fear and anxiety evoked by the first experience in parachute jumping induced epinephrine release (18). It is not known which type of psychologic stress (aggression or anxiety) is more conducive to enhanced ventricular vulnerability to fibrillation. Our investigations show that the type of stress associated with the sling-cage paradigm is characterized by the release of predominantly epinephrine. One would speculate that the sling environment wherein the animal perceives itself threatened with noxious stimuli would induce a behavioral response consistent with anxiety. But as in man, the sympathetic nervous system reaction is not restricted to augmented adrenal medullary response. The relative contribution of each of the catecholamines to the altered vulnerable period threshold remains to be determined.

TABLE I. RELATIONSHIP BETWEEN INCREASE IN PLASMA CATECHOLAMINE CONCENTRATION AND DECREASE IN RE THRESHOLD DURING STRESS

	Correlation coefficient	*P* value
Norepinephrine	0.91	<0.02
Epinephrine	0.81	<0.05
Norepinephrine and epinephrine	0.84	<0.05

Summary. The correlation between circulating catecholamines and ventricular vulnerability during psychologic stress was examined in conscious dogs. The repetitive extrasystole (RE) threshold was used to assess vulnerability to ventricular fibrillation. Exposure of the animals to a stressful sling environment compared to that of nonstressful cage setting resulted in a significant 41% ($P < 0.01$) reduction in the RE threshold. Plasma levels of norepinephrine and epinephrine increased twofold ($P < 0.05$) and fourfold ($P < 0.01$), respectively. It is concluded that the elevation in circulating catecholamine levels correlates closely with enhanced ventricular vulnerability during psychologic stress and that the model for psychologic stress employed results in substantial increases in plasma catecholamine levels which is in large part due to release of epinephrine from the adrenal medulla.

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