Cardiac Performance in Experimental Adrenal Insufficiency in Cats

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ABSTRACT

Cardiac function was evaluated by ventricular function curves during the cardiovascular collapse observed in acute and chronic adrenal insufficiency. A progressive decline in peak cardiac work was observed in the acutely adrenalectomized cat (30% decrease at 1.8 hours and 50% at 3.5 hours after adrenalectomy). This impairment in cardiac work paralleled the decrease in mean arterial blood pressure which reached 50 mm Hg 3.5 hours after adrenalectomy. Cortisol and d-aldosterone, and the volume-expander, dextran, prevented a significant fall in mean arterial blood pressure and in peak cardiac work. When the mean arterial blood pressure of nonadrenalectomized cats was adjusted to follow the changes seen in adrenalectomized cats, a 49% depression in cardiac work resulted 3.5 hours after the initial decline in arterial blood pressure. The data suggest that the time course of the hypotension and presumed reduction in coronary perfusion pressure is sufficient to account for the large impairment in peak cardiac work observed. Cardiac work was reduced 56% in chronically adrenalectomized cats 8 to 10 days after adrenalectomy. Dexamethasone and deoxycorticosterone acetate, administered separately, prevented significant myocardial impairment. Since the mean arterial blood pressure of conscious, chronically adrenalectomized cats was normal, the myocardial depression was not secondary to inadequate coronary perfusion in chronic adrenal insufficiency and thus represents direct impairment of myocardial performance.

ADDITIONAL KEY WORDS   ventricular function   cardiac work
cortisol   adrenalectomy   aldosterone   circulatory collapse

■ Adrenal insufficiency is characterized by circulatory collapse in which hypotension and decreased cardiac output are prominent features (1-4). The precise cause of the collapse seen after adrenalectomy is not known. Presumably a deficiency of corticosteroids is the major contributing factor, but the site and mechanism of action of corticosteroids in the circulatory collapse is not defined. Thus, it is not known whether impaired myocardial performance occurs in this situation, since only indirect evidence is available (1-5). Since acute adrenal insufficiency results in a differ-

ent circulatory disturbance than does chronic adrenal insufficiency (5), both must be investigated. The purposes of the present study were to evaluate cardiac performance in acute and chronic adrenal insufficiency using a direct technique, to determine the relative efficacy of glucocorticoids and mineralocorticoids in protecting against post-adrenalectomy circulatory collapse, and to determine whether any observed changes in ventricular performance are independent of changes in systemic arterial pressure.

Methods

One hundred and twenty-four mongrel cats of both sexes and of mean weight 2.71 kg (1.9 to 3.8 kg) were studied. The control cats were anesthetized with 30 mg/kg of sodium pentobarbital, but the adrenalectomized cats without steroid support required only 15 mg/kg.

A carotid artery, a femoral vein, and a jugular vein were cannulated with polyethylene tubing. The femoral vein cannula was advanced cephalad into the inferior vena cava and served as the route of infusion for the blood or Krebs-Henseleit solution. A midline sternotomy was performed, and the chest was left open throughout the experiment. A fourth cannula was placed in the left atrial appendage. The carotid arterial and atrial cannulas were connected to Statham P-23 pressure transducers for monitoring arterial blood pressure and left atrial pressure. Heart rate was measured continuously with a Beckman type 9853 cardiotachometer coupler. A noncannulating electromagnetic flow transducer (5 or 6 mm in diameter, In Vivo Metric Systems) was placed around the root of the aorta. Both mean and phasic flow were recorded with a Statham Model M-4001 electromagnetic flowmeter. The diastolic plateau was taken as the zero flow reference level, and the phase was repeatedly checked during the experiment using a Tektronix 502A oscilloscope. The transducer calibration factors were checked periodically between experiments by placing the transducer around an excised aorta through which isotonic saline was driven by a variable-height hydrostatic column of the saline solution. Calibration with saline yielded a 2 to 5% higher value than with blood. All recordings were made on a six-channel Beckman Type R Dynograph recorder.

LEFT VENTRICULAR FUNCTION TECHNIQUE

Two modifications of a basic technique for evaluating myocardial function by ventricular function curves were employed in this study. The first type of ventricular performance test was similar to that introduced by Bishop and associates (6) and was designed to test the maximal or reserve capacity of the heart. The cats were bilaterally vagotomized at the time of the cannulations, the animals were not bled prior to infusion (except for the bleedout groups), and Krebs-Henseleit solution instead of blood was infused. Krebs-Henseleit solution was rapidly infused at a rate of 50 ml/min until the aortic flow reached a constant peak value despite further increases in left atrial pressure (i.e., until a plateau in the ventricular output was reached). The plateau was usually attained after infusion of 50 to 70 ml. Thus, the emphasis was placed on testing the maximal work capacity of the heart. Two infusion tests were made in each animal in the acute series of experiments. The first (or control infusion) was made shortly after the completion of chest surgery, and the work values obtained served as a reference for the second (or test infusion) which was made following an experimental procedure such as adrenalectomy. Thus, ventricular performance before and after

adrenalectomy could be compared in the same animals. However, in cats with chronic and sham adrenalectomies only a single ventricular performance test was made. A second technique was used to compare blood as an infusion fluid and also to determine whether a submaximal infusion challenged the corticosteroid deficient myocardium.

The second type of function test employed was similar to that used by Gomez and Hamilton (7). The animals were heparinized (1000 units/ kg of Liquaemin, Organon) just prior to the ventricular function test, and the arterial blood pressure was then adjusted to 50–55 mm Hg by rapid bleeding for three to four minutes. About 50 ml of blood was drawn from cats with intact adrenals and about 10 ml from adrenalectomized cats. Adrenalectomized cats were infused with blood from adrenalectomized donors. The blood (50 ml) was warmed to body temperature and then rapidly infused into the inferior vena cava through the femoral cannula at the rate of 72 ml/ min with a Harvard infusion pump. A single ventricular function curve was obtained from the control cats.

In both types of infusion tests the increase in the rate of cardiac work in g-m/sec resulting from the massive volume infusion was calculated by the following formula:

$$W = F \frac{(AP - LAP)}{100},$$

where $W =$ left ventricular work in g-m/sec, $F =$ aortic flow in ml/sec, $AP =$ arterial pressure in cm H_2O, and $LAP =$ left atrial pressure in cm H_2O. Left ventricular function curves were then obtained by plotting cardiac work in g-m/sec on the ordinate against left atrial pressure in cm H_2O (as an index of left ventricular filling pressure) on the abscissa. Cardiac performance was tested in this way in two groups of acutely adrenalectomized animals. One group, called early acute adrenalectomized cats, was tested when the blood pressure had spontaneously declined to 65–75 mm Hg, usually about 1.8 hours after adrenalectomy. Another group, called late acutely adrenalectomized cats, was tested when the pressure had reached 55 mm Hg, at an average of 3.5 hours after adrenalectomy. The work values of both of these groups were then compared with those obtained from cats with intact adrenals tested after a comparable post-operative period.

ADDITIONAL EXPERIMENTAL PROCEDURES
Acute Series

The glucocorticoid-treated group of acutely adrenalectomized cats was given a priming dose of hydrocortisone, 1 mg i.p., prior to thoracic

surgery. An intravenous infusion of hydrocortisone (cortisol, 100 μg/min) was started prior to adrenalectomy (just after the control run) and was continued to the time of the second or test run, 210 minutes later. The mineralocorticoid-treated group was given a priming dose of 100 μg of d-aldosterone (Ciba). An intravenous infusion of aldosterone, 100 μg/hour, was started prior to the adrenalectomy and continued for 210 minutes after adrenalectomy.

In one group of acutely adrenalectomized cats, dextran (Cutter, clinical 6% dextran in normal saline, 50 to 70 ml) was substituted for Krebs-Henseleit solution in the control run. To examine the effect of hypotension in cats with intact adrenal glands, the cats were bled in two different ways, and cardiac function was tested by the ventricular plateau technique. In the first protocol, the cats were rapidly bled to an arterial blood pressure of 50 to 55 mm Hg for a period of 30 minutes, two hours after laparotomy. The pattern of arterial blood pressure decline which was observed in the late acute adrenalectomized cat was duplicated in a second group of intact cats by bleeding every 30 minutes to adjust the mean arterial blood pressure to that seen in adrenalectomized cats at the same time after adrenalectomy.

The serum concentration of free cortisol was determined in several acutely and chronically adrenalectomized cats by the technique of plasma fluorometry (8) modified for cortisol, to provide a check on the presence of accessory adrenal tissue and the rate of disappearance of cortisol from plasma.

Chronic Series

In the chronic experiments, the cats were bilaterally adrenalectomized through a ventral midline incision under sterile conditions. On the day of surgery these cats were given 4 mg of dexamethasone (Decadron; Merck, Sharp and Dohme) intramuscularly. The dexamethasone dose was reduced to 2 mg and then to 1 mg on the 2nd and 3rd postoperative days, respectively. All drug support was then discontinued and ventricular function was tested on the 10th to 12th day after adrenalectomy. In one series, called the glucocorticoid-supported group, dexamethasone therapy, 2 mg/day, was reinstituted on the 10th day after adrenalectomy for 4 days before ventricular function tests were made.

The mineralocorticoid-supported group was given 4 mg dexamethasone on the day of surgery. On the following day 1 mg of desoxycorticosterone acetate (DOCA; Percorten, Ciba) was added to the regimen. On subsequent days, DOCA, 1 mg/day, alone was administered for 10 to 12 days at which time cardiac function was tested. All groups of adrenalectomized ani-

mals were given 0.9% sodium chloride to drink instead of tap water. The sham-operated animals were subjected to a midline incision and their adrenal glands were then exposed.

In some additional cats, heparin-filled cannulas were chronically implanted in a carotid artery and exteriorized at the back of the neck. This permitted the daily measurement of mean arterial blood pressure in the conscious state.

Results

ACUTE EXPERIMENTS

Figure 1 depicts a pair of ventricular function curves before and after acute adrenalectomy. The upper curve was obtained 60 minutes after thoracic surgery. Ten to twenty minutes later a bilateral adrenalectomy was performed. The lower curve was obtained 210 minutes later and shows a 52% decrease in peak work.

A series of experiments was then performed in a variety of groups in an attempt to determine the reasons for this decrease in peak cardiac work after adrenalectomy, and to
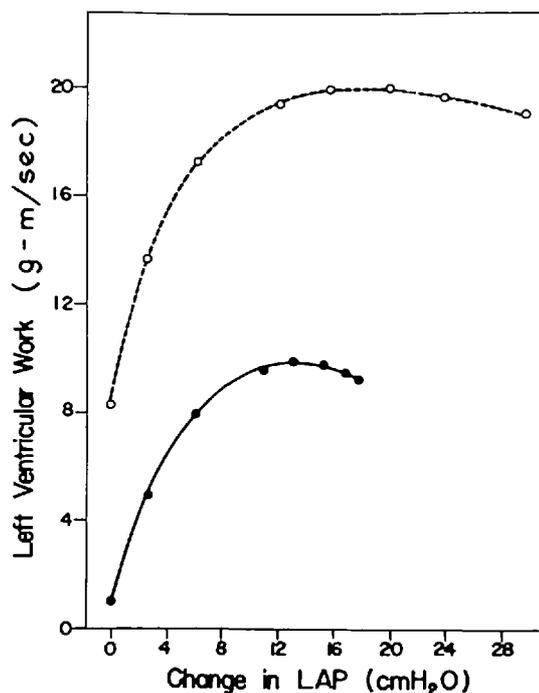

FIGURE 1

Ventricular function curves before and after acute adrenalectomy from a cat weighing 2.72 kg. LAP = left atrial pressure. See text for details.
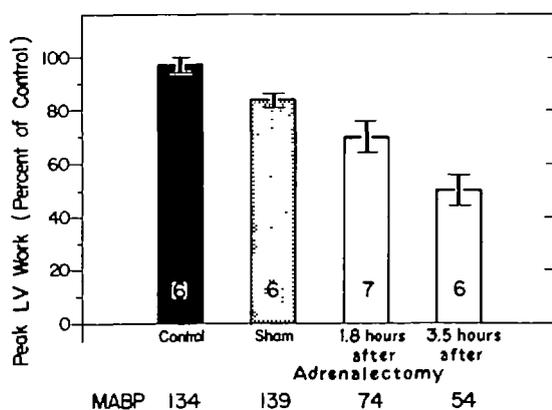
FIGURE 2

The progressive decline in cardiac work performance following acute adrenalectomy. The peak work is given on the ordinate as a percent of the control or first infusion test. The mean arterial blood pressure (MABP) in mm Hg at the time of the test is given below each graph. The bars represent means ± SEM. The numbers inside the bars represent the number of animals in each group.

determine means of preventing this decrease in work performance. Figure 2 summarizes some of these experiments showing that the impairment of cardiac performance is a progressive phenomenon, decreasing 30% 1.8 hours after adrenalectomy, and 50% 3.5 hours after adrenalectomy. The impairment of cardiac work paralleled the decline in perfusion pressure. The 50% decrease in peak

work was expressed as an equal reduction between diminished peak perfusion pressure (28.3% lower) and peak cardiac output (28.1% lower). Furthermore, laparotomy and sham adrenalectomy only resulted in a 16% reduction in cardiac work observed 3.5 hours later, probably reflecting operative trauma.

Figure 3 summarizes the results of a further series of experiments designed to ascertain whether the impairment of cardiac work was due to the decreased arterial blood pressure, and a consequent reduction in coronary perfusion pressure. The mean arterial blood pressure just prior to the second infusion test closely correlated with the peak left ventricular work obtained during the second infusion. Both cortisol and aldosterone maintained systemic pressure within normal limits, and both steroids protected against the decline in cardiac work seen 3.5 hours after acute adrenalectomy. In addition to these corticosteroids, dextran was also effective in maintaining systemic pressure and in preventing the decline in peak cardiac work. Thus, volume support as well as corticosteroids prevented the circulatory collapse seen after acute adrenalectomy.

In another series of cats, sham adrenalectomy was performed, and the animals were observed for 2 hours. At this time, these animals were bled until a mean arterial blood pressure of 66 mm Hg was reached; this

TABLE 1

Hemodynamic Status of Cats Studied After the First Test Infusion and just Prior to the Second Test Infusion

Group	N	Mean arterial BP (mm Hg)	Cardiac output (ml/min)	Total peripheral resistance (mm Hg/ml/min/kg)
Control (3.5 hours)	G	134 ± 18	242 ± 30	1.52 ± 0.23
Sham-adrenalectomized (3.5 hours)	6	139 ± 21	294 ± 56	1.29 ± 0.17
Adrenalectomized (1.8 hours)	7	66 ± 6*	190 ± 27**	1.07 ± 0.17
Adrenalectomized (3.5 hours)	6	55 ± 4*	141 ± 17*	1.13 ± 0.09
Adrenalectomy + cortisol (3.5 hours)	6	133 ± 6†	233 ± 28	1.67 ± 0.15†
Adrenalectomy + aldosterone (3.5 hours)	7	107 ± 10†	240 ± 28†	1.13 ± 0.08
Adrenalectomy + dextran (3.5 hours)	6	123 ± 10†	329 ± 38†	0.99 ± 0.08
Sham + rapid bleeding (2.0 hours)	4	70 ± 7*	179 ± 34**	1.13 ± 0.26
Sham + slow bleeding (3.5 hours)	4	55 ± 4*	162 ± 47**	0.92 ± 0.28

All values are means ± SEM. N = number of cats. Times refer to time after the first test infusion of Krebs-Henseleit solution. *$P < 0.01$ from control cats. **$P < 0.05$ from control cats. †$P < 0.01$ from adrenalectomized cats.
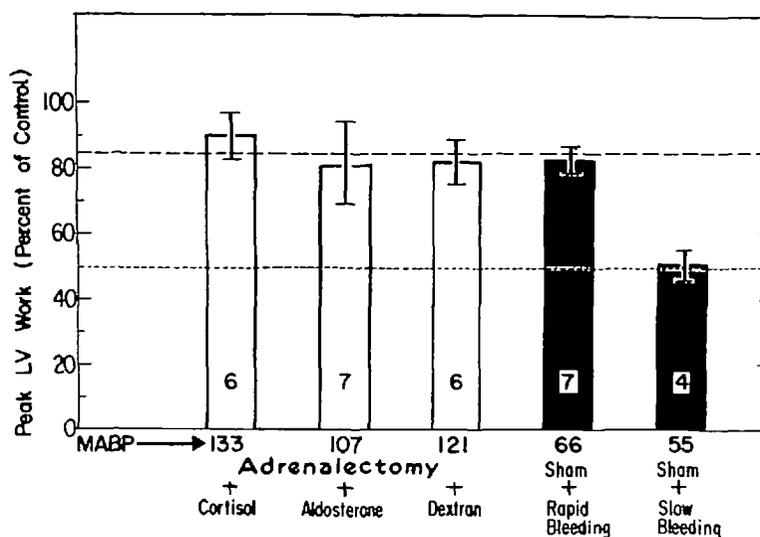
FIGURE 3

Support of the acutely adrenalectomized cat by various agents. The mean arterial blood pressure (MABP) just prior to the test infusion is given below each bar and the percent decrease in peak left ventricular work is given on the ordinate. For reference purposes, the degree of cardiac work impairment of the sham-adrenalectomy group (86% of control) is given by the horizontal dashed (upper) line, and the dotted (lower) line (50% of control) represents the reference line for acutely adrenalectomized cats 3.5 hours after adrenalectomy. The cortisol-, aldosterone- and Dextran-supported adrenalectomized groups were not significantly depressed from the sham-adrenelectomized group (P < 0.01). The sham-adrenalectomized animals which were bled for a brief period (i.e., maintained at 66 mm Hg for 15 minutes) were also not significantly depressed. However, the sham-adrenalectomized cats which were bled so as to follow the changes in mean arterial blood pressure of the adrenalectomized group showed a 49% depression. The bars represent means ± sEM. The numbers inside the bars represent the number of animals in each group.

pressure was slightly lower than that spontaneously attained in adrenalectomized cats two hours after adrenalectomy. The mean arterial blood pressure was maintained at 66 mm Hg for about 15 minutes, and then a second test infusion was performed. Despite this brief exposure to hypotension and the two-hour post-laparotomy period, peak cardiac work was not significantly different from the sham-adrenalectomized group not subjected to bleeding (Fig. 3). An attempt was then made to determine whether prolonged hypotension is an important factor in the development of the impairment of cardiac function. Sham adrenalectomy was performed, and the arterial pressure of these cats was reduced by bleeding to match the changes in average mean arterial blood pres-

sure of the adrenalectomized cats during the 3.5 hours after adrenalectomy. Cardiac work values obtained at this time were decreased 49% compared with a 50% reduction for the adrenalectomized cats; both groups had a mean arterial blood pressure of 55 mm Hg at this time. Thus, it appears that the prolonged hypotension experienced by the adrenalectomized cat can account for the large impairment in cardiac performance observed after acute adrenalectomy.

In addition to the hypotension, a reduced cardiac output and an increased total peripheral resistance occurred after acute adrenalectomy. Heart rate and left atrial pressure were not significantly changed 3.5 hours after adrenalectomy. Table 1 shows the hemodynamic values of all the groups in the acute

series. Sham adrenalectomy resulted in a slightly elevated cardiac output and a slightly reduced total peripheral resistance. In adrenalectomized cats, cortisol maintained the mean arterial blood pressure and cardiac output and also significantly ($P < 0.001$) elevated the total peripheral resistance above pre-adrenalectomy values. Aldosterone fully maintained cardiac output and partially maintained mean arterial blood pressure, but the total peripheral resistance was slightly decreased. Dextran maintained the mean arterial blood pressure and greatly elevated cardiac output in adrenalectomized cats so that the total peripheral resistance was reduced. The sham adrenalectomized cats which had been bled slowly and whose mean arterial blood pressure was matched closely to that of the adrenalectomized cats, showed values similar to those of the adrenalectomized cats for cardiac output and total peripheral resistance after 3.5 hours. Only the cortisol-treated adrenalectomized cats showed an increase above the pre-adrenalectomy control value. No other group showed a significant change from the adrenalectomized or sham-adrenalectomized groups.

The plasma cortisol concentration declined to virtually undetectable levels two hours after adrenalectomy, definitely preceding the circulatory collapse. These low concentrations (0.3 ± 0.5 μg/100 ml plasma, in six cats) are not significantly different from zero, which was the plasma free cortisol concentration seven to nine days after adrenalectomy.

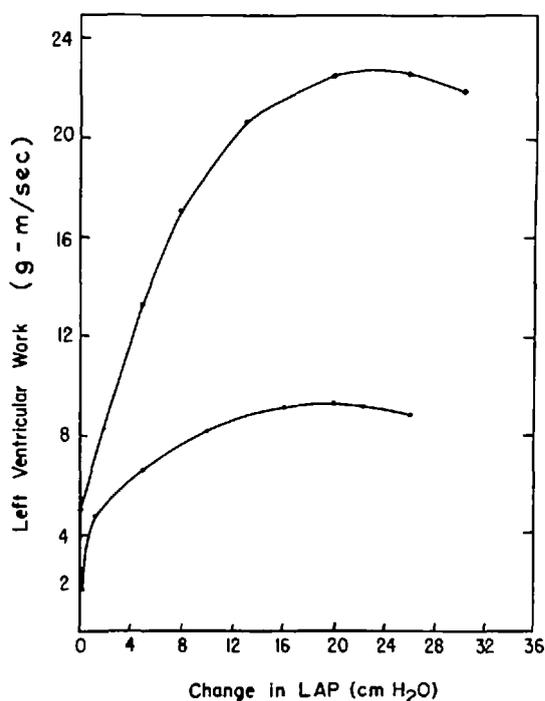In the protocol just discussed, the acutely

FIGURE 4

Comparison of a ventricular function curve obtained from a sham-adrenalectomized cat (upper curve) with that of an adrenalectomized cat seven days after termination of corticosteroid therapy (lower curve). The chronic adrenalectomized cat exhibited a 56% reduction in peak work capacity compared with the sham-adrenalectomized cat.

adrenalectomized animals functioned from a lower baseline mean arterial blood pressure and cardiac output than did the control animals. Therefore, a second protocol was used in which all animals were bled to 50 mm Hg

TABLE 2

Effect of Submaximal Rapid Infusion of Blood on Peak Cardiac Work in Adrenalectomized Cats Bled to 50 mm Hg just Prior to the Infusion of Blood

Group	N	Peak cardiac work (g-m/sec)	% Change from control	P value compared to control
Control	9	9.7 ± 0.4		
Acutely adrenalectomized (1.8 hours after adrenalectomy)	6	7.9 ± 0.5	-18.6	$P < 0.02$
Acutely adrenalectomized (3.5 hours after adrenalectomy)	6	6.3 ± 0.2	-35.1	$P < 0.001$

All values are means $\pm$ SEM. N = number of cats. Adrenalectomized cats 3.5 hours after adrenalectomy required little or no bleeding.

15 minutes prior to the infusion test, to set the baseline conditions for the infusion test at an equal point. Results obtained with this protocol shown in Table 2 were similar to those obtained with the first protocol. This protocol also demonstrated a progressive impairment of cardiac performance with time after acute adrenalectomy.

CHRONIC EXPERIMENTS

To determine whether impairment of cardiac performance exists several days after adrenalectomy, a series of chronically adrenalectomized cats was studied using the maximal infusion protocol of Bishop et al. (6). In this series, only one infusion was performed. Figure 4 shows left ventricular function curves plotted from two typical experiments (sham-adrenalectomized and adrenalectomized cats). Ventricular function was assessed nine days after sterile surgery in both cats. The adrenalectomized cat exhibited a marked impairment of work performance,

showing a 56% reduction in peak work compared with the sham-operated cat.

Figure 5 shows a summary of the data obtained in chronically operated cats. Control (unoperated cats observed for 8 to 10 days) exhibited a mean cardiac work of 19.2 g-m/sec, a value which is very similar to the 19 to 20 g-m/sec value obtained for most of the first infusion tests in the acute series. Sham-operated cats did not differ significantly from unoperated control cats in their peak work capacity. Chronically adrenalectomized cats, studied eight to ten days postoperatively, exhibited a marked reduction in peak work (49% decreased from values obtained in sham-operated cats, $P < 0.001$). Daily maintenance doses of both dexamethasone and DOCA were effective in preventing the decrease in work performance observed after chronic adrenalectomy.

The mean arterial blood pressure of conscious cats was reasonably stable from day to day, not varying more than 15 to 20 mm Hg
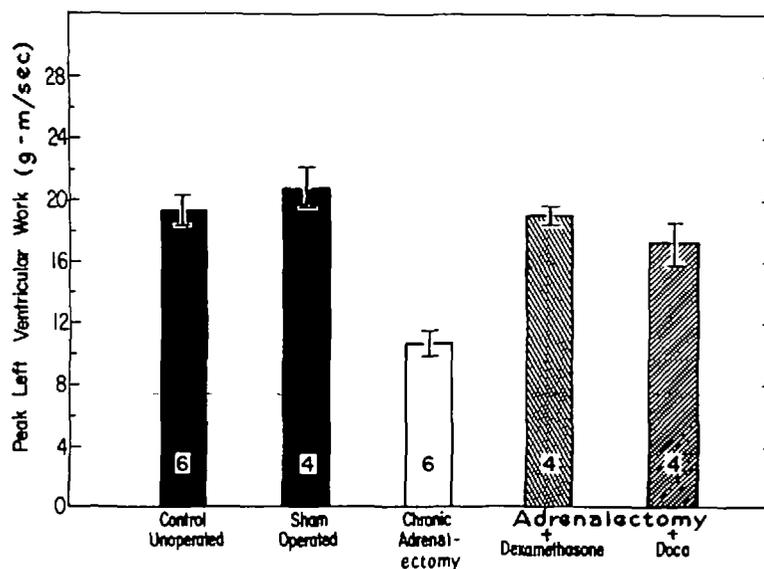

FIGURE 5

Summary of the peak work capacity of chronically adrenalectomized cats. Both the dexamethasone- and deoxycorticosterone acetate (DOCA)-treated cats were protected against any statistically significant reduction in peak cardiac work. The sham-operated cats were also not significantly different from unoperated controls. Only the chronically adrenalectomized cats exhibited a marked reduction (49%) in peak work. All values are means ± SEM. The numbers inside the bars represent the number of animals in each group.

over the entire eight- to ten- day observation period. The mean arterial blood pressure of six conscious adrenalectomized cats was 94 ± 3.1 mm Hg. This compares closely with the value of 100 mm Hg obtained in anesthetized cats eight to ten days after adrenalectomy. Administration of pentobarbital to the conscious adrenalectomized cats while the mean arterial blood pressure was recorded, showed only a 10 to 15 mm Hg rise after induction of a surgical plane of anesthesia. Five cats which were unoperated except for the chronic carotid artery cannula showed mean arterial blood pressures of 110 ± 4.5 mm Hg after eight to ten days. Although the chronic adrenalectomized cats exhibit a significantly lower mean arterial blood pressure ($P < 0.02$), it seems unlikely that diminished arterial blood pressure is a major contributory factor in the impairment of cardiac work observed in chronically adrenalectomized cats, since cardiac work decreased 49% in the face of only a 15% decline in mean arterial blood pressure.

Discussion

Circulatory collapse is a prominent feature of chronic adrenal insufficiency, i. e., four to ten days after adrenalectomy with no steroid support (1, 3, 4, 9). The data presented in this study show direct evidence for an impairment of myocardial performance in chronically adrenalectomized cats. The severity of the cardiac impairment also suggests that this is a major mechanism for the circulatory collapse which is evident several days after termination of corticosteroid therapy in adrenalectomized cats. This finding is in agreement with that of Webb et al. (10) who found cardiac depression in adrenalectomized dogs, and of Lefer (11) who showed a reduction in the reserve capacity of papillary muscles isolated from adrenalectomized rats. Furthermore, there is anatomical evidence for altered myocardial function in adrenal insufficiency. Suzuki (12) observed disrupted and fragmented mitochondria, edema and fragmented myofibrils in the myocardium of rats 5 to 13 days after adrenalectomy.

Circulatory collapse also occurs two to four hours after acute bilateral adrenalectomy in the dog (13-16). The cat exhibits a similar time course of collapse after acute adrenalectomy, declining to a mean arterial blood pressure of 50 to 55 mm Hg, 3.5 hours after adrenalectomy (17). Although left ventricular function curves obtained at this time indicate an impaired myocardial performance, the impairment appears to be secondary to the reduced systemic blood pressure. Furthermore, the severity of the apparent cardiac depression parallels the fall in arterial blood pressure. Prolonged hypotension, as produced in the sham-adrenalectomized cats with slow bleeding, resulted in an impairment of cardiac work, whereas a brief period of hypotension did not. This observation supports the finding that prolonged hemorrhagic hypotension impairs the mechanical performance of isolated cat papillary muscles (18) and confirms the finding of Gomez and Hamilton (7) that impairment of ventricular function occurs 90 to 150 minutes after termination of hemorrhagic hypotension. This impairment could be explained by cardiac damage due to coronary insufficiency during the hypotensive period and/or production of cardiotoxic materials during hypotension which are released into the blood (7).

The finding of a reduced cardiac work capacity in acutely adrenalectomized cats was demonstrated and verified using two types of ventricular function tests termed maximal and submaximal infusion tests. Within each protocol, peak left atrial pressure during rapid infusion was similar in all groups; 21 to 24 cm H_2O in the maximal infusion test (first protocol), and 10 to 11 cm H_2O in the second infusion protocol.

Since bilateral vagotomy was performed, heart rate changes were less than 10 beats/min at the peak of the infusion. Furthermore, heart rate was not significantly altered in any of the acute groups in the 210-minute period between the two infusions. Therefore, heart rate changes cannot account for the observed effects in myocardial performance.

Increased peripheral resistance limits ventricular performance, such that a 30% increase in outflow resistance results in an 11% decrease in maximum cardiac output (19), and a decrease in resistance of 50% would increase the maximum cardiac output by 10%. In the acutely adrenalectomized cats, 210 minutes after adrenalectomy, total peripheral resistance was only slightly decreased which by itself would tend to slightly increase the peak cardiac output. Therefore, the observed decreases in ventricular function in acutely adrenalectomized cats is not due to alterations in peripheral resistance.

Two hours after adrenalectomy, the plasma cortisol concentration was extremely low, about 3% of pre-adrenalectomy values, at a time when mean arterial blood pressure was reduced to approximately 75 mm Hg. At this time, cardiac work capacity was found to be reduced by 30%. Ninety minutes later, the corticosteroid level was undetectable, the mean arterial blood pressure had fallen to 50 mm Hg, and cardiac work capacity was 50% of its pre-adrenalectomy value. Thus, corticosteroid disappearance actually preceded impairment of work performance. The lack of corticosteroids in the presence of elevated catecholamine concentrations and excessive sympathetic nervous activity has been thought to compromise the integrity of the small blood vessels leading to a state of hypotension (4, 13, 20, 21). In this regard, the glucocorticoids are viewed as agents which are essential for normal vasomotor regulation, and in their absence, catecholamines are presumed to exert deleterious effects on the unprotected vasculature (20).

In the acutely adrenalectomized animal, plasma catecholamine concentrations rise shortly after adrenalectomy but are decreased three hours after adrenalectomy (13). However, the fact that maintenance of systemic blood pressure by Dextran prevents the decrease in work performance, argues against decreased circulating catecholamines as a cause of the impairment in ventricular performance. Cardiac and plasma catecholamine levels are normal in adrenalectomized dogs

three weeks after adrenalectomy (22), so this is not a factor in impairment of ventricular performance seen in the chronically adrenalectomized cats in this study. If the increased sympathetic activity postulated in adrenal insufficiency were to influence myocardial performance, it would presumably enhance ventricular function. No evidence of this was seen. Therefore, either (a) the cardiac sympathetics are not involved in this post-adrenalectomy sympathetic discharge, (b) the enhanced cardiac activity occurs earlier than 3.5 hours after adrenalectomy, or (c) it is masked by the apparent decrease in myocardial performance. It is also possible that increased sympathetic activity does not occur after adrenalectomy. In any event, sympathetic activity does not appear to significantly influence myocardial performance after adrenalectomy.

It is of considerable interest that both a glucocorticoid (cortisol) and a mineralocorticoid (aldosterone) prevented circulatory collapse in the acutely adrenalectomized cat. These hormones may exert this protective effect via different mechanisms. Cortisol may act on the small blood vessels and protect their functional integrity during the acute stress of adrenalectomy (23). The fact that cortisol was the only agent which increased total peripheral resistance suggests some effect on peripheral vascular tone. Cortisol may also protect against circulatory collapse via its effects on carbohydrate metabolism. In this regard, hypoglycemia is known to occur soon after acute adrenalectomy in fasted dogs (13). Furthermore, glucocorticoid administration prevents the reduction in cardiac glycogen after adrenalectomy (24). A third possible mechanism of protection by glucocorticoids which would be effective acutely is their possible action as an α-adrenergic blocking agent. This has been suggested by Lillehei et al. (25) in various forms of shock. However, this alleged effect requires much higher concentrations of cortisol than used in this study.

Mineralocorticoids, on the other hand, might exert beneficial effects acutely through

their positive inotropic effects (26). Another possibility is the retention of sodium and thus conservation of plasma volume. The fact that dextran was also effective acutely in protecting against the post-adrenalectomy circulatory collapse as well as against the impairment of cardiac performance is consistent with the latter possibility. However, a purely metabolic effect of dextran unrelated to its volume-supporting effect cannot be ruled out (27). Neither aldosterone nor dextran increased total peripheral resistance above pre-adrenalectomy values, so that their protective effects are probably not through alterations in vascular tone.

The impairment of cardiac work in chronically adrenalectomized cats appears to be a direct result of adrenal insufficiency rather than to a diminished arterial blood pressure, since arterial blood pressure was 100 mm Hg in these animals soon after anesthetization. Furthermore, in a series of conscious, adrenalectomized cats in which the arterial blood pressure was recorded daily, the mean arterial blood pressure decreased to only 94 mm Hg, eight to ten days after adrenalectomy (six to nine days after discontinuation of steroid support). In view of the low cardiac oxygen requirements due to the reduced pressure and the large vasodilator capacity of the coronary vessels, it is unlikely that the decreased myocardial work performance is caused by impairment of coronary blood flow. However, this possibility cannot be unequivocally eliminated in this study. If the decreased cardiac work capacity of adrenalectomized cats is indeed a primary event, it suggests a major defect in the heart which could explain the gradual circulatory collapse seen in chronically adrenalectomized animals. It also suggests that the myocardium is ultimately dependent upon corticosteroids for maintenance of its functional integrity.

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