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Acute Cardiovascular Response to a Single Large Intravenous Dose of Methylprednisolone and Its Effects on the Responses to Norepinephrine and Isoproterenol (41653)

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Abstract. The cardiovascular actions of single 10-μg/kg iv doses of norepinephrine (NE) and isoproteronol (ISO), before and after the administration of a single 30-mg/kg iv dose of the glucocorticoid methylprednisolone (MP) (sodium succinate ester), were compared in adult cats. Methylprednisolone increased both systolic and diastolic pressures as well as the pulse pressure by approximately 50%. These steroid effects persisted unabated for the duration of the experiment (40 min). Heart rate was unaffected by MP. MP treatment significantly reduced the increase in systolic and diastolic pressures caused by NE. This MP effect was unrelated to the higher baselines for these two parameters caused by the steroid. The systolic blood pressure and positive chronotropic effects of ISO were also significantly blunted by MP. These observations suggest that a single large dose of MP may cause a depression of cardiovascular α- and β-1-receptor sensitivity. The results are discussed in relation to the actions of massive dose glucocorticoid administration in certain shock states and central nervous system trauma and stroke.

High-dose administration of glucocorticoid, and particularly methylprednisolone (MP), has been demonstrated to promote survival in various forms of experimentally induced shock (1–6). The general mechanism of this protective action is thought to be due to an improved maintenance of organ blood flow secondary to a decrease in peripheral vascular resistance (5), a stabilization of lysosomal membranes within the vascular endothelium (6), and a restoration of reticuloendothelial system phagocytic function (5).

In addition to the importance of such actions in shock, another intriguing aspect of the cardiovascular response to large doses of glucocorticoids concerns its potential mechanistic relationship to steroid efficacy in experimental CNS injury (7–10) and possibly stroke (11, 12). Clearly, in both instances, a glucocorticoid effect to antagonize the decrease in CNS blood flow associated with mechanical trauma (13) or infarction would constitute a beneficial action. Indeed, recent studies have shown an improved blood flow in the injured cat spinal cord as a result of high-dose MP administration (9).

One possible explanation for the enhancement of regional blood flow in low flow states by high doses of glucocorticoid may be an antagonism of vasoconstrictor influences as alluded to above. Of particular interest, in view of the increased sympathetic nervous tone and adrenal medullary release of epinephrine in shock, have been the elegant studies by Altura and Altura (5) which have disclosed that large concentrations of glucocorticoid (e.g., MP or hydrocortisone) attenuate epinephrine-induced constriction of rat mesenteric arterioles in both *in vivo* and *in vitro* preparations. Furthermore, this effect has been found by the same investigators to correlate with an improved survival in hemorrhagically shocked rats when given a massive 30-mg/kg iv MP dose.

The present study has taken this aspect of the acute cardiovascular pharmacology of massive dose glucocorticoid administration a step further by examining the effects of a 30-mg/kg iv bolus MP injection on blood pressure and heart rate in normotensive cats. Moreover, this report compares the acute effects of the large MP dose on the cardiovascular responses to separate systemic administration of norepinephrine and isoproteronol. The results confirm previous findings by others (5) of a depressed α adrenergic responsiveness while also demonstrating a significant steroid pressor response and a modification of β-adrenergic receptor sensitivity.

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Materials and Methods. *General.* Adult cats of either sex were employed in this study. The animals were anesthetized with 80 mg/kg alpha chloralose iv (Sigma Chemical Co., St. Louis, Mo.), a tracheotomy was performed, positive pressure ventilation with room air instituted, and complete neuromuscular paralysis initiated using 3 mg/kg gallamine triethiodide iv (Sigma). One carotid artery was cannulated for blood pressure recording on a Gould 2600 Recorder and an iv line was placed in a brachial vein for test drug administration.

Experimental protocol. Each animal first received a single 10-μg/kg iv bolus of NE hydrochloride (10 μg/ml) (Sigma). After the cardiovascular effects of NE had completely abated in each animal (20 min), a single 10-μg/kg rapid iv dose of ISO hydrochloride (10 μg/ml) (Vitarine Co., New York, N.Y.) was given. Twenty minutes after ISO, by which time its effects had disappeared, each animal received a single 30-mg/kg iv bolus of MP sodium succinate (60 mg/ml) (Solu-Medrol, Upjohn, Kalamazoo, Mich). This MP dose was specifically chosen based on the results of other studies (1, 3–7, 9, 10). At 20 and 40 min, respectively, after the MP dose, the NE and ISO test administrations were repeated.

The actions of MP, and NE and ISO before and after MP, were measured on the systolic and diastolic blood pressures, the pulse pressure (i.e., systolic minus diastolic), and the heart rate. The actions of NE and ISO on each parameter were statistically compared before vs after MP using a paired *t* test (two tailed) at measurement points of 5, 15, 30, 60, 90, and 120 sec. In addition, repeated-measures analysis of variance was employed to compare the differences in the overall time courses of the NE and ISO effects before vs after MP.

Results. *Acute cardiovascular actions of methylprednisolone.* Rapid iv administration of the 30-mg/kg MP dose produced an immediate increase in the systolic, diastolic, and pulse pressures as shown in Fig. 1 which illustrates the early time course of these responses. Interestingly, heart rate was neither directly nor reflexly affected. Table I shows that this response pattern persisted throughout the experiment as measured at 20 and 40 min after MP administration.

It should be noted that in numerous other experiments by the authors with chloralose-

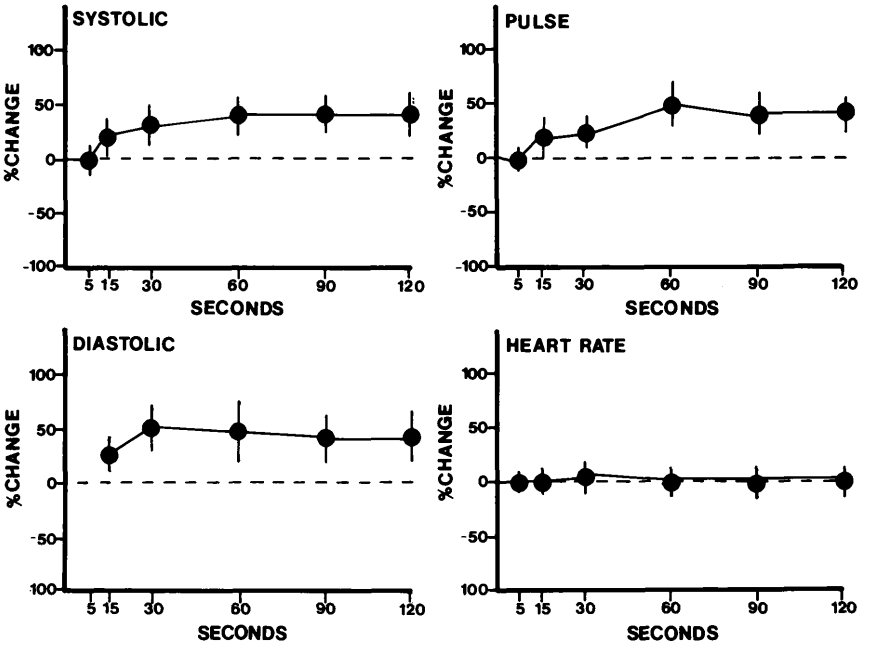

FIG. 1. Acute effects of a single 30-mg/kg iv bolus of methylprednisolone sodium succinate in six cats on systolic and diastolic blood pressures, pulse pressure, and heart rate during the first 2 min after injection.

TABLE I. ACUTE CARDIOVASCULAR EFFECTS OF A 30-mg/kg iv BOLUS OF METHYLPREDNISOLONE SODIUM SUCCINATE (MEAN ± SE)[a]

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse pressure (mm Hg)	Heart rate (beats/min)
Before MP (control)	85.2 ± 7.9	48.0 ± 6.9	37.2 ± 5.4	146.7 ± 9.5
20 min after MP (just prior to second NE injection)	120.0 ± 8.6	66.3 ± 8.3	53.7 ± 6.4	144.0 ± 9.5
$P<$[b]	0.005	0.01	0.02	0.6
40 min after MP (just prior to second ISO injection)	115.8 ± 8.7	61.5 ± 8.9	54.3 ± 5.9	139.7 ± 9.9
$P<$[b]	0.02	0.05	0.1	0.6

[a] Six animals.
[b] Paired t test (two-tailed) between values for control and 20 min, or control and 40 min after MP bolus.

anesthesized cats, the blood pressure and heart rate have been found to be quite stable thus indicating that the acute effects of the large MP dose are real. Furthermore, administration of the MP vehicle (0.5 ml/kg) in three cats did not produce any appreciable cardiovascular responses (not shown in table or figures).

Effect of methylprednisolone on norepinephrine responsiveness. Figure 2 displays the time course of the cardiovascular actions of

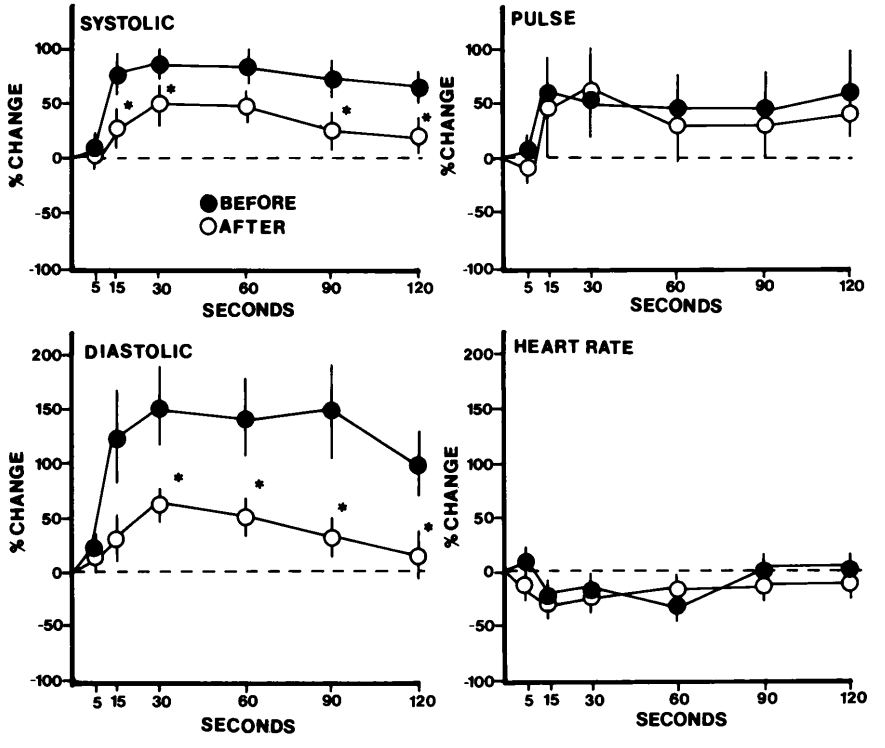

FIG. 2. Comparison of the effects of a single 10-μg/kg iv injection of norepinephrine in six cats on systolic and diastolic blood pressures, pulse pressure, and heart rate before and 20 min after a single iv bolus of methylprednisolone sodium succinate. Asterisks indicate $P < 0.05$ by paired t test at individual measurement points. The overall systolic and diastolic blood pressure responses were significantly blunted, as determined by repeated-measures analysis of variance, $P < 0.005$ ($F = 13.78$, df = 1, 10) and $P < 0.001$ ($F = 159.90$, df = 1, 10), respectively. Baseline values in millimeters of mercury or beats per minute are given in Table I.

NE before and 20 min after MP. Glucocorticoid treatment caused a dramatic blunting of the normal increase in both the systolic and diastolic blood pressures seen with NE. These effects were highly significant both by paired *t* test at individual time points and by repeated-measures analysis of variance (see figure legend). However, the increase in the pulse pressure and the reflex bradycardia caused by NE were unaltered by MP.

Considering the possibility that the NE-induced elevation in systolic and diastolic blood pressure may have been decreased only as a result of the higher baselines pressures caused by the 30-mg/kg MP dose (Table I), coefficients for the possible negative correlation between the systolic and diastolic baseline values and the percentage increase in each experiment were calculated using a least-squares regression analysis. The correlations for the systolic and diastolic effects of NE after MP were only −0.2 and −0.3, respectively, indicating that the decreased responsiveness to NE after MP was unrelated to the higher baseline systolic and diastolic blood pressures caused by the steroid.

Effect of methylprednisolone on isoproterenol responsiveness. Figure 3 shows the time course of the blood pressure and positive chronotropic actions of ISO before and after MP. The mean rise in systolic pressure seen with ISO was significantly decreased by MP administration as determined by repeated-measures analysis of variance. In contrast, the fall in diastolic pressure caused by ISO appeared to be enhanced and prolonged as a consequence of MP treatment. This difference failed to reach statistical significance, however. The normal widening in the pulse pressure by ISO was also blunted following MP treatment and this effect was significant by paired *t* test at the 5-sec measurement time, but not later,

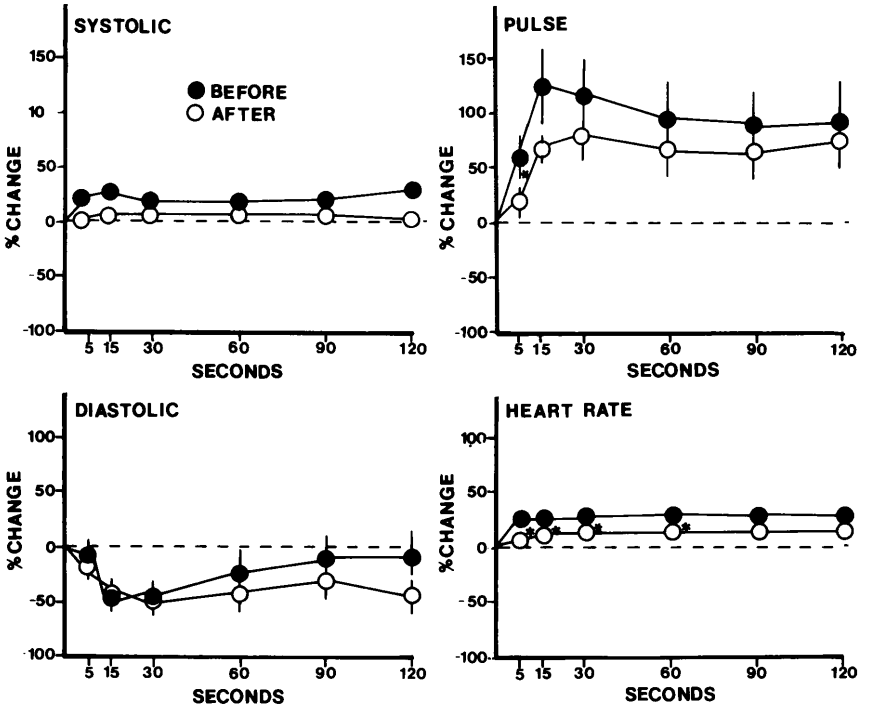

FIG. 3. Comparison of the effects of a single 10-μg/kg iv injection of isoproterenol in six cats on systolic and diastolic blood pressures, pulse pressure, and heart rate before and 40 min after a single 30-mg/kg iv bolus of methylprednisolone sodium succinate. Asterisks indicate $P < 0.05$ by paired *t* test. The systolic blood pressure and the heart rate response, over the first 60 sec, were significantly blunted as determined by repeated-measures analysis of variance, $P < 0.025$ ($F = 7.27$, df = 1, 10) and $P < 0.05$ ($F = 6.59$, df = 1, 10), respectively. Baseline values in millimeters of mercury or beats per minute are given in Table I.

suggesting that MP may have slowed the onset of the vascular response to ISO.

The positive chronotropic effects of ISO during the first 60 sec after injection, were significantly depressed by MP as determined by repeated-measures analysis of variance.

Discussion. The most striking feature of the present results is the decrease in the vasoconstrictor (i.e., diastolic blood pressure) responsiveness to NE caused by the acute iv administration of a 30-mg/kg dose of MP. This finding in nonshocked cats is consistent with the results of Altura and Altura (5) who demonstrated a similar decrease in the vasoconstrictor effects of epinephrine after an identical glucocorticoid dose in rats that were previously subjected to severe hemorrhage.

The present study has additionally revealed an effect of MP to attenuate the NE-induced increase in systolic blood pressure. This could be the consequence of either a smaller increase in venous return in response to NE, as a result of an attenuated α receptor mediated venoconstrictor action after MP, or to a decreased direct cardiac β-receptor activation by NE, following the glucocorticoid. While both mechanisms may be involved, the concomitant attenuation of some of the cardiovascular effects of the selective β-receptor agonist ISO, suggests that the sensitivity of both general types of adrenergic receptors may be decreased by the steroid.

The apparent depression of cardiovascular β-adrenergic receptor responsiveness by a large MP dose, in addition to decreasing α-receptor sensitivity, is complicated by experimental evidence that this aspect of the glucocorticoid effect may be selective for cardiac β 1 receptors. For instance, only the effect of ISO to increase systolic blood pressure and heart rate were blunted, while the action of ISO to reduce diastolic pressure secondary to a fall in peripheral resistance (i.e., β-2 receptor activation in skeletal muscle vascular beds) was, if anything, slightly increased.

Regarding the molecular mechanism of the acute attenuation of vascular α and cardiac β 1 receptors by MP, a few studies have shown that glucocorticoid administration can modulate the number, or activity, of a variety of cellular receptors (15). Glucocorticoids can presumably accomplish this by either altering receptor synthesis and turnover or through an effect on the phospholipid environment adjacent to the receptor. In regards to the first possibility, recent studies have demonstrated a dexamethasone-induced decrease in β-adrenergic receptor number in cultured muscle cells (16). However, this required chronic exposure to the glucocorticoid, but only a nanomolar concentration. On the contrary, the rapid nature of the dampening of α- and β-1 adrenergic sensitivity reported here, together with the apparent need for an MP dose as high as 30 mg/kg (5) supports the latter possibility of a direct membrane action of the steroid. In view of the report that MP also inhibits potassium chloride- and calcium chloride-induced contraction of vascular smooth muscle (5), the precise nature of the membrane effect on adrenergic receptor responsiveness may involve an attenuated depolarization and depolarization-triggered calcium entry into vascular smooth muscle and perhaps cardiac muscle as well. Consistent with this interpretation, other investigators have observed that MP does not interfere with the venous smooth muscle mechanical response to sympathetic nerve stimulation, but instead reduces the electrical response (17, 18). This direct effect of MP on vascular cell membranes and on the heart merits further study.

Although acute administration of MP was associated with a decrease in the vasoconstrictor action of NE and the cardiac stimulant action of ISO, the iv bolus injection of the glucocorticoid itself produced a sustained increase in systolic, diastolic, and pulse pressures. A similar elevation in blood pressure was found by Altura and Altura (5) when the identical MP dose was infused into hemorrhagically shocked rats. Furthermore, these investigators observed that the steroid-induced increase in blood pressure occurred simultaneously with a decreased vasoconstrictor response not only to catecholamine, but also vasopressin, angiotensin, serotonin, potassium chloride, and calcium chloride. Thus, the increase in blood pressure caused by MP may be the result of a direct effect of the steroid to enhance vascular smooth muscle contractility, or to an increase in cardiac output secondary to a positive inotropic action that is unrelated to β-1 adrenergic receptor activation since this appears to be decreased. Indeed, an increase in cardiac output, concomitant with

a decrease in peripheral vascular resistance in response to large glucocorticoid doses, has been reported in man (14).

In conclusion, the present study demonstrates that the acute cardiovascular effects of a large iv dose of glucocorticoid (e.g., MP) and the effects on cardiovascular adrenergic receptor responsiveness are more complex than previously thought. Thus, in the utilization of high-dose steroid therapy in various clinical conditions (e.g., shock, CNS trauma, and possibly stroke), a composite cardiovascular action may be observed which in relation to adrenergic mechanisms involves both a dampened cardiac β 1 receptor and vascular α receptor responsiveness. This, however, may occur together with a directly mediated increase in blood pressure that appears to be secondary to an increase in cardiac output.

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