The Cardiovascular Effects of Corticosteroids

By MAX H. WEIL, M.D., PH.D.

Biochemical derangements resulting from adrenal cortical hyperfunction or from critical reduction of the endogenous corticosteroid hormone supply are sometimes overshadowed by major disturbances of cardiovascular function. Arterial hypertension and congestive heart failure may be the predominant presenting clinical features in patients with adrenal cortical hyperfunction. During acute illness or following minor injury, hypotension and shock have been known to signal the presence of previously undiagnosed adrenal cortical insufficiency. When adrenocortical steroids are used as drugs in patients with normal adrenal output, they cause changes in cardiovascular function that appear as unwelcome side effects simulating the features of Cushing's syndrome. Nevertheless, these drugs are of practical value in the treatment of selected patients with cardiovascular diseases, including carditis, congestive heart failure, orthostatic hypotension, and bacterial shock. This review concerns itself with the effects of corticosteroids on the cardiovascular system and indications for their clinical use in treatment of patients with cardiovascular disturbances.

Cardiodynamic Effects

Observations on the Normal Myocardium

Naylor,1 studying the metabolism of the isolated toad heart, reported that 9a fluoro-hydrocortisone (9a FF) evokes an inotropic response resembling the action elicited by digitalis. In the isolated perfused guinea pig heart, however, Nasmyth2 found that hydrocortisone depresses amplitude as well as the rate of cardiac contractions. These reports have been variously cited as evidence for or against the use of steroids in myocardial failure. But a third study by Nahas and co-workers,3 using the isolated perfused heart-lung preparation of the dog, provides support for neither of the two interpretations. Infusion of 10 mg. of hydrocortisone succinate into the cardiopulmonary circuit did not cause significant alteration of function as reflected in measurements of cardiac output, outflow pressure, or electrocardiogram. Present evidence does not indicate that the administration of corticosteroids materially alters contractility of the heart muscle.

The protracted use of corticosteroid drugs may influence myocardial function by promoting shifts in electrolyte and fluid balance. In this respect the loss of intracellular potassium from the myocardium during steroid therapy is especially important. The reciprocal relationship between potassium concentration and the myocardial action of digitalis glycosides has significant biological and clinical implications. In studies with rats, severe deficiency of potassium resulted in histologically demonstrable injury to the myocardium,4 and Selye5 has produced necrosis of the heart muscle in rats treated with desoxytocicosterone or hydrocortisone. These findings have received considerable attention, but it should be borne in mind
that the special conditions of Selye's experiments exclude any direct clinical implications for the human patient.

**Electrocardiographic Effects**

Corticosteroids accelerate atrioventricular conduction. Lown and associates found that the average P-R interval in 34 patients with adrenal cortical hyperfunction was 0.136 second compared to a value which averaged 0.158 second in 539 control subjects. The atrioventricular conduction time was found to be inversely related to the concentration of urinary 17-ketosteroids. Corresponding changes were produced by the exogenous administration of glucocorticoid. Conversely, the P-R interval of a group of 50 patients with adrenal cortical insufficiency was significantly prolonged and 10 of the subjects exhibited first-degree heart block. Replacement therapy with cortisone decreased the P-R interval, but desoxycorticosterone had no such effect.

The mechanism by which the steroid hormones increase the speed of atrioventricular conduction is not known. Changes in potassium concentration do not explain the effect on the P-R interval. Both Lown and Friedberg and their associates suggest that steroids accelerate the speed of conduction by increasing the effectiveness of adrenergic stimuli. The possibility that adrenal steroids might potentiate sympathetic and particularly vasopressor activity will be reviewed at somewhat greater length in connection with their role in the treatment of shock.

**Myocarditis**

The benefit derived from corticosteroids during the treatment of inflammatory diseases of the myocardium is due to the anti-inflammatory effect of the hormone; thus the clinical manifestations of acute rheumatic myocarditis (and also endocarditis and pericarditis) are dramatically controlled. While the hormones may be lifesaving in patients with pancarditis and myocardial failure, their use in preference to salicylates under less critical circumstances is controversial. Present evidence—based entirely on statistical evaluation of clinical observations—favors the viewpoint that the hormones are singularly effective in suppressing the acute inflammatory process which accounts for myocardial failure. But there is no proof that they afford protection against chronic valvular deformities.

**Myocardial Infarction**

Corticosteroids have been recommended as adjuncts in the treatment of acute myocardial infarction. In one series of experiments with dogs the animals treated with cortisone showed decreased mortality, increased vascularity of the myocardium, and a smaller area of residual fibrosis in comparison to untreated controls. Detailed studies by three other groups of experienced observers failed to confirm these beneficial effects. Nevertheless, according to a number of clinical reports, particularly in the European literature, the use of corticosteroids in the treatment of myocardial infarction with or without shock is advocated. These agents are said to reduce fever and leukocytosis and sometimes to reverse the conduction defects associated with myocardial infarction. It is also reported that patients in shock responded more readily to vasopressor agents. The assumption is then made that the severe inflammatory reaction which occasionally accompanies necrosis of the heart muscle may itself threaten survival. The argument further contends that if the systemic response to inflammation is minimized, the metabolic demands on the already injured heart are correspondingly reduced. In each instance, conclusions were based on analyses of individual cases and no comparisons with patients who served as untreated controls were presented. It is hoped that a more objective evaluation of the merits of corticosteroids in the treatment of myocardial infarction may soon clarify the issue.

At present, the use of steroids in the treatment of myocardial infarction must still be regarded as experimental. However, two possible exceptions warrant special consideration. Dressler describes a "post-myocardial
infarction syndrome” characterized by protracted or recurrent fever, chest pain of the pleuropericardial type, and tendency to relapse. A pericardial friction rub is frequently heard and the presence of pleural effusion can be roentgenographically demonstrated in many cases. This condition is very similar to the pleuropericardial syndrome that follows cardiotomy or traumatic injury of the pericardium; both bear close resemblance to manifestations of acute connective tissue diseases. If salicylates do not afford relief, steroids usually provide prompt suppression of symptoms. Another possible indication for the use of steroids is in the treatment of acute or chronic heart block following myocardial infarction. A marked reduction in ventricular rate may compromise both the coronary and the cerebral blood flow. The dangers of cardiac arrest, myocardial failure, and acute cerebral anoxia (Stokes-Adams syndrome) suggest an ominous prognosis. Corticosteroids have occasionally been found dramatically effective in restoring atrioventricular conduction and abolishing symptoms, but such encouraging results are actually obtained only in isolated instances.

**Congestive Heart Failure**

The mineraloid effect of the adrenal steroid hormone is responsible for conservation of sodium in the kidneys, and increased elimination of potassium. Reabsorption of sodium leads to a proportionately greater retention of water, and the excess fluid is stored primarily in the interstitial and intravascular spaces. Gradual overfilling of the interstitial compartments produces edema. Excess of fluid in the intravascular spaces acts as a distending force which, like over-transfusion, results in elevation of blood pressure and cardiac enlargement, and it may threaten the life of the patient by producing congestive heart failure. These features have been observed in patients with adrenal cortical hyperfunction and can be experimentally demonstrated in animals, especially when a steroid with primary mineralocorticoid action is used.

However, a remarkable effect was observed in some patients with congestive heart failure. Rather than increasing severity of heart failure, administration of ACTH resulted in salt and water diuresis, augmented responsiveness to mercurial diuretic, and improved clinical status. The mechanism of this paradoxical response is not fully understood. In the dog, cortisone accelerates for a short time the glomerular filtration rate and sodium loss, but these effects do not usually occur in man. Administration of glucocorticoid or ACTH is most effective in patients with “refractory” heart failure of long duration, in whom aldosterone activity is already close to maximal. In a final effort to maintain adequate blood flow, the vascular volume is further increased, resulting in damaging loss of normal osmolarity of body fluids. It is postulated that under these circumstances diuresis is effected through inhibition of ADH. This coincides with the observation that loss of excess fluid is associated with reversal of the dilutional syndrome.

The vast majority of patients are not in the final stages of cardiac decompensation, and steroids intensify the severity of congestive heart failure. When the decision is made to use these drugs, the newer synthetic derivatives such as prednisolone are preferred because they minimize salt and water retention.

**Effects on Hypotensive States**

**Postural Hypotension**

The autonomic nervous system provides vasomotor reflexes that reduce postural influences on the distribution of blood in the vascular system. Loss of vasoconstrictive reflexes results in postural (orthostatic) hypotension. Hickler and associates were able to control the symptoms of this condition by oral administration of fluorohydrocortisone (9α FF). A reduction in the amount of norepinephrine released by the sympathetic nerve endings was demonstrated, but this was not altered by the steroid therapy. The beneficial effects of 9α
FF were most likely due to increased intravascular volume, which compensated for excessive loss of blood into dependent vascular beds when the patient assumed the upright posture. However, the possibility that the steroid potentiates the vasomotor activity of adrenergic nerves cannot be excluded.

**Shock**

**The Role of Adrenal Insufficiency**

Corticosteroid hormones are able to reverse shock from adrenal insufficiency, due to previous suppression with steroids or caused by primary adrenal failure during stress; this fact is well documented in patients and confirmed by controlled studies in experimental animals. Following intravenous injection of a soluble preparation of hydrocortisone, early improvement may be confidently expected.

These observations in patients with adrenal insufficiency prompted the use of steroids in the treatment of shock due to a diversity of causes. Many assumed that adrenal insufficiency is a major factor in the progression and irreversibility of shock. Objective studies failed to confirm that adrenal insufficiency was involved, however, either in the causation or the progression of shock. To the contrary, Melby found that the plasma cortisol concentration in patients under the stressful conditions of bacteremic shock is markedly elevated. Responsiveness of the adrenal gland to exogenous corticotropin is maintained; thus shock is clearly not due to adrenal failure.

**Bacterial Shock**

Nevertheless, abundant case history data are now available pointing to the effectiveness of steroids in large doses for the treatment of shock associated with bacteremia. Since in addition to the administration of corticosteroids a number of different therapeutic procedures are usually involved, it has not as yet been possible to determine the ultimate benefit provided by the steroid alone. However, when lethal amounts of endotoxin are injected into mice, rats, and dogs to simulate the conditions that are believed responsible for bacteremic shock, recovery is markedly improved by treatment with steroids. Maximal effectiveness requires early administration of large doses. In order to obtain the greatest number of survivors the necessary dose is many times greater than that needed for optimal replacement of adrenal cortical hormones in the adrenalectomized animal under stress. The relationship of the specific dose of prednisolone to 24-hour survival in experiments with mice is graphically illustrated in figure 1. Since no hormonal deficiency exists, the corticosteroids are regarded as having pharmacologic effects. By their physical presence in high concentration, they appear to protect tissues against the damaging effects of the bacterial toxin. It is hoped that research presently being pursued in several laboratories, including our own, will lead to a more complete understanding of the mechanism of this protection.

**Shock due to Other Causes**

The opinions differ as to the effectiveness of steroids in hemorrhagic shock. Knapp and Howard were unable to increase survival of dogs in “irreversible” hemorrhagic shock, but Connolly reported favorable results with early use of large amounts of hydrocortisone.

In the treatment of acute anaphylactic shock, epinephrine remains the drug of choice.

![Graph](http://circ.ahajournals.org/)

**Figure 1**

The relationship between dose of corticosteroid and survival in therapy of shock produced by a lethal injection of Escherichia coli endotoxin. Corticosteroid was injected 15 minutes and again 4 hours after endotoxin.
The protracted state of hypotension, however, which is associated with severe hypersensitivity reactions, is favorably affected by administration of corticosteroids.60, 61

Steroids are sometimes used to protect in a "nonspecific manner" against hypotension-producing insults. However, in experiments with mice, corticosteroids increased the mortality in animals injected with ganglion-blocking drugs as well as mice scalded with hot water.53, 62 Until additional information becomes available, the use of corticosteroids should be limited to shock associated with infection, shock due to hypersensitivity, and possibly hemorrhagic shock unresponsive to transfusion.

Influence on the Effectiveness of Vasopressor Agents

The vasopressor effect of norepinephrine is markedly increased when steroids are administered to an adrenalectomized animal.63 A lesser degree of potentiation is reported for human subjects with intact adrenal glands.64, 65 These observations help to increase our understanding of the protracted hypotensive states of patients with Addison's disease, and the dramatic effects of corticosteroid on arterial pressure. In patients with shock unrelated to adrenal insufficiency in whom responsiveness to vasopressor amines is markedly decreased, steroids are sometimes used with the expectation that pressor effect will be potentiated. Spink53 reported that in dogs with endotoxin shock large doses of corticosteroid reduced the amounts of metaraminol required to maintain arterial pressure at physiologic levels. Studies on patients in shock after myocardial infarction, however, have not demonstrated clearly that pressor effect is increased for an hour after large doses of soluble steroids are administered intravenously.66, 67 Studies are in progress at the present time to assess in patients with shock the hemodynamic effects of vasopressor agents and corticosteroids, separately and in combination. Preliminary observations68 following intravenous injections of dexamethasone indicate that cardiac output is increased but this is accompanied by a reduction rather than a rise in arterial pressure.

Summary and Conclusions

The cardiovascular actions of corticosteroids and indications for their use in cardiovascular diseases have been reviewed. Corticosteroids have little direct effect on the heart except that they characteristically accelerate atrioventricular conduction. This has been put to practical use in the treatment of heart block. As anti-inflammatory agents, these hormones are used for the control of symptoms caused by pericarditis or myocarditis, especially when associated with acute rheumatic fever. In the treatment of acute myocardial infarction, their use must still be regarded as experimental.

Fluid retention produced by the mineralocorticoid action leads to symptomatic improvement of patients with postural hypotension. Under special circumstances corticosteroids may initiate diuresis in patients with advanced congestive heart failure.

The adrenocortical hormones are now widely used in the treatment of acute hypotension (shock) states. They provide specific treatment in those very rare instances when shock is due to acute adrenal insufficiency. In the vast majority of patients, however, adrenal insufficiency is not the cause for shock. When administered in very high doses for their pharmacologic effect in patients with septic shock, adrenocortical hormones oppose the detrimental hemodynamic actions of bacterial endotoxin and thereby improve survival. Their use is also indicated in treatment of protracted hypotension associated with severe hypersensitivity reactions. However, there is as yet not adequate evidence of beneficial effect in the management of patients with shock caused by hemorrhage or trauma.

References


31. RIEMER, A. D.: The effect of prednisone in

Circulation, Volume XXV, April 1962


The Cardiovascular Effects of Corticosteroids
MAX H. WEIL

_Circulation_. 1962;25:718-725
doi: 10.1161/01.CIR.25.4.718

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/25/4/718.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/