Cardiac Manifestations of Adrenal Insufficiency

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It is estimated that the prevalence of primary adrenal insufficiency (Addison disease) is 1 in 10,000 people. There are multiple case reports and several studies that suggest a correlation between Addison disease and abnormalities of cardiac function. The pathophysiology of cardiac abnormalities in this condition is incompletely understood. This review explores what is currently known about the cardiac manifestations of Addison disease.

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KEY WORDS
Addison disease • Adrenal insufficiency • Cortisol • Congestive heart failure • Glucocorticoid replacement

Primary adrenal insufficiency (Addison disease) is estimated to occur in 1 in 10,000 people. The majority of cases of Addison disease are due to the development of autoantibodies against steroid 21-hydroxylase, the cytochrome P450 enzyme that is required for the adrenal glands to synthesize cortisol and aldosterone. Other etiologies are summarized in Table 1. The result of adrenal insufficiency is always a reduction of circulating corticosteroids and sometimes a reduction of mineralocorticoids and androgens (particularly in primary adrenal insufficiency). The role of glucocorticoids and mineralocorticoids in regulating intravascular volume is important and well established. Patients with primary adrenal insufficiency typically present with findings such as hyponatremia, hyperkalemia, and intravascular volume depletion.1

The direct effect on the cardiomyocyte is less clear. Cortisol has a permissive effect on synthesis of catecholamines that agonize sympathetic nervous
system adrenergic receptors\textsuperscript{3} and may have direct inotropic effects.\textsuperscript{4} High cortisol levels are required by the adrenal medulla to synthesize epinephrine. Cortisol also inhibits the action of catechol-O-methyltransferase, an enzyme that inactivates epinephrine. Cortisol induces transcription and expression of $\alpha_1$-adrenergic receptors in smooth muscle cells\textsuperscript{5}; function of the adrenergic receptor is dependent on the presence of cortisol.\textsuperscript{6} Thus, smooth muscle response to catecholamines requires the presence of cortisol.\textsuperscript{7} In addition to its well-known action in renal sodium handling, cortisol is also thought to regulate blood pressure by inhibiting intravascular nitric oxide synthase and by promoting the vasoconstrictor effects of erythropoietin.\textsuperscript{8}

Aldosterone is known to promote fibrosis in the heart in the presence of a high-sodium diet.\textsuperscript{9} This knowledge has led to the routine administration of mineralocorticoid receptor antagonists in advanced heart failure.\textsuperscript{10} Patients with congestive heart failure (CHF) also have abnormal cortisol metabolism, as the normal circadian rhythm of plasma cortisol levels has been reported to be abolished in patients with CHF.\textsuperscript{11}

### Cardiac Involvement in Acute Adrenal Crisis

There have been multiple reports of cardiomyopathy as the initial presentation in both adult and pediatric patients with untreated adrenal insufficiency (Table 2).\textsuperscript{12-19} Cardiomyopathy has been the primary clinical presentation in patients with polyglandular autoimmune syndrome (PAS) types 1\textsuperscript{20} and 2,\textsuperscript{21} both of which have adrenal insufficiency among the constellation of findings. In the case of the patient with PAS-1, the child recovered completely after repletion with calcium, calcitriol, and hydrocortisone. The patient with PAS-2 progressed to heart transplantation, although he also had type 1 diabetes, a major independent risk factor for coronary heart disease. A patient with panhypopituitarism and adrenal insufficiency from Sheehan syndrome was described as having severe CHF and reduced left ventricular (LV) systolic function.\textsuperscript{22} There are reports of patients with both primary and secondary adrenal insufficiency developing Takotsubo (apical-ballooning) cardiomyopathy.\textsuperscript{23-25}

Untreated adrenal insufficiency may cause significant electrocardiographic abnormalities, at least in part due to hyperkalemia. ST depression and T-wave inversions have been reported in patients with Addisonian crisis.\textsuperscript{26} In two reported cases, cardiac arrest was the presenting symptom of adrenal crisis.\textsuperscript{27,28} Cardiac arrest is likely to arise either from metabolic derangements, most notably

### Table 1

**Etiologies of Primary Adrenal Insufficiency**

<table>
<thead>
<tr>
<th>Autoimmune</th>
<th>Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated adrenalitis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Polyglandular autoimmune syndrome type I</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>Polyglandular autoimmune syndrome type II</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Adrenal hemorrhage or infarction</td>
<td>Disseminated fungal infection</td>
</tr>
<tr>
<td><strong>Metastatic cancer</strong></td>
<td>African trypanosomiasis</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
</tr>
<tr>
<td>Azole antifungals</td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital adrenal hypoplasia</td>
<td></td>
</tr>
<tr>
<td>Familial glucocorticoid deficiency</td>
<td></td>
</tr>
<tr>
<td>Impaired steroid biosynthesis</td>
<td></td>
</tr>
<tr>
<td>Impaired cholesterol biosynthesis</td>
<td></td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
</tr>
</tbody>
</table>

In addition to its well-known action in renal sodium handling, cortisol is also thought to regulate blood pressure by inhibiting intravascular nitric oxide synthase and by promoting the vasoconstrictor effects of erythropoietin.
hyperkalemia or from severe hypovolemia causing cardiovascular collapse. Prolongation of the QT interval resulting in torsade de pointes and cardiac arrest has been described in a patient with adrenal insufficiency. The QT interval corrected with administration of replacement glucocorticoids. Patients with Addison disease demonstrate an abnormal pressor response to 35% CO2 challenge when glucocorticoids are withheld for 48 hours. There has also been a suggestion that pericarditis and adrenal insufficiency may be linked.

### Hemodynamic Consequences of Adrenal Insufficiency

In an animal study of adrenalectomized rats, stroke volume index and cardiac index were both noted to be decreased. After several weeks, the adrenalectomized rats were found to have significantly decreased response in mean arterial blood pressure to an epinephrine bolus when compared with sham-operated rates. Interestingly, there was no significant difference in plasma concentrations of Na+, K+, or Cl− that could account for these hemodynamic changes. A study of 12 adrenalectomized dogs demonstrated low coronary blood flow, which increased to normal rates with cortisol replacement, along with concurrent rises in myocardial oxygen consumption.

### Table 2: Published Cases of Cardiac Manifestations in Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Age (years)</th>
<th>Etiology of Adrenal Insufficiency</th>
<th>Cardiac Manifestation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiltshire EJ et al12</td>
<td>8 F</td>
<td>Idiopathic primary</td>
<td>CMP, CHF, shock</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Eto K et al13</td>
<td>62 M</td>
<td>Empty sella</td>
<td>CHF, CMP, QT prolongation</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Al Jarallah AS14</td>
<td>2 M</td>
<td>Impaired steroid biosynthesis</td>
<td>Dilated CMP, CHF</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Derish M et al15</td>
<td>11 M</td>
<td>Idiopathic primary</td>
<td>CHF, CMP, cardiogenic shock</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Conwell LS et al16</td>
<td>13 F</td>
<td>Autoimmune adrenalitis</td>
<td>CHF, CMP</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Hachova A et al17</td>
<td>34</td>
<td>PAS-2</td>
<td>CMP, Nonspecific ST segment changes</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Mekontso-Dessap A et al18</td>
<td>42 F</td>
<td>Unspecified</td>
<td>CHF, dilated CMP (EF 35%), shock</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Walker and Butt19</td>
<td>6 M</td>
<td>Adrenoleukodystrophy</td>
<td>Shock, dilated CMP</td>
<td>Death</td>
</tr>
<tr>
<td>Wani Al et al20</td>
<td>Not given</td>
<td>PAS-1</td>
<td>Dilated CMP</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Nielsen TD et al21</td>
<td>32 M</td>
<td>PAS-2</td>
<td>Dilated CMP, CHF</td>
<td>Required cardiac transplant</td>
</tr>
<tr>
<td>Bao SS et al22</td>
<td>35 F</td>
<td>Sheehan syndrome</td>
<td>Dilated CMP, CHF</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Punnam SR et al23</td>
<td>71 F</td>
<td>Unspecified/withdrawal of glucocorticoids in chronic Addison disease</td>
<td>Takotsubo CMP</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Ukita C et al24</td>
<td>69 F</td>
<td>ACTH deficiency</td>
<td>Takotsubo CMP</td>
<td>Resolved with replacement</td>
</tr>
<tr>
<td>Gotyo N et al25</td>
<td>70 M</td>
<td>Idiopathic ACTH deficiency</td>
<td>Takotsubo CMP, Torsade de pointes</td>
<td>Resolved with replacement</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; CHF, congestive heart failure; CMP, cardiomyopathy; EF, ejection fraction; PAS-1, polyglandular autoimmune syndrome type I; PAS-2, polyglandular autoimmune syndrome type II.
Cardiac Manifestations of Adrenal Insufficiency continued

and carbon dioxide production.\textsuperscript{33} The observed changes may reflect increased systemic blood pressure, cardiac output, and cardiac work due to glucocorticoid replacement.

In a series of six human patients who presented with severe hemodynamic compromise to a critical care setting, right heart catheterization revealed low cardiac index in four patients. LV systolic work index was found to improve with infusion of fluid and glucocorticoid replacement.\textsuperscript{34} It is important

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to consider, in both the animal and human subjects, that severe hypovolemia will usually result in reduced cardiac output regardless of ventricular contractile state.

Cardiovascular Effects of Glucocorticoid and Mineralocorticoid Excess
Circadian rhythms of endogenous cortisol secretion in a healthy individual are complex and difficult to replicate pharmacologically. The challenge of cortisol-replacement therapy is to administer enough drug to alleviate symptoms and metabolic abnormalities while not giving more than is needed. However, it is possible that any given patient may be receiving more than the background population.\textsuperscript{36} Glucocorticoid supplementation is likely causing significant cardiovascular consequences.

The major adverse effects of glucocorticoids on the cardiovascular system are hyperlipidemia and hypertension, both of which are well established as direct risk factors for the development of coronary artery disease. Glucocorticoid supplementation has been associated with CHF.\textsuperscript{36,37} Therefore, it is reasonable to assume that patients who are receiving more-than-physiologic doses of glucocorticoids may be subjected to these adverse effects, resulting in excess cardiovascular morbidity and mortality.

Cardiac Outcomes in Chronic Adrenal Insufficiency
It is commonly held that patients with Addison disease who are properly diagnosed and treated have a normal survival rate. However, in 2006, a Swedish population study of 1675 patients with Addison disease found that these patients had a twofold higher risk ratio for death of adrenal replacement therapy did not predict CHF. In a series of seven patients with untreated chronic Addison disease, LV end-diastolic and end-systolic dimensions were reduced compared with healthy control subjects.\textsuperscript{40} This effect reversed with glucocorticoid replacement and is presumably due to volume depletion.

Glucocorticoid replacement is far from an exact science. Replacement dose is primarily determined based on the presence of clinical symptoms due to lack of sufficient objective assessment for monitoring replacement.\textsuperscript{41} Serum adrenocorticotropic hormone, urinary 24-hour free cortisol, serum cortisol-binding globulin, and timed serum cortisol levels have all failed to provide adequate accuracy to guide replacement dosing. This raises the distinct possibility of low-grade under-dosing leading to subclinical glucocorticoid deficiency. Clinical practitioners tend to give the lowest effective dose of glucocorticoid replacement in order to avoid consequences of over-replacement, including impaired glucose tolerance,\textsuperscript{42} obesity, and osteoporosis.\textsuperscript{43} It is yet unknown if chronic subclinical glucocorticoid under-replacement leads to long-term cardiovascular effects, particularly risk of dilated cardiomyopathy.

Cardiac Imaging in Addison Disease
In a study of seven patients with newly diagnosed Addison disease, two-dimensional echocardiography was undertaken both prior
to and after medical treatment. Both LV end-systolic and end-diastolic dimensions were reduced when compared with untreated control subjects. Chamber size normalized after medical treatment; mitral valve prolapse without regurgitation was seen in four of seven patients. These changes were thought to be due to the hypothalamic effect of untreated adrenal insufficiency. Of note, the only measure of cardiac function in this study was M-mode fractional shortening.

Conclusions
The available evidence suggests that there may be an increased incidence of cardiac abnormalities in patients with adrenal insufficiency. Most directly observed cardiac abnormalities in patients with adrenal insufficiency have been secondary to reduced plasma volume and electrolyte disturbances, and not due to a direct effect of either chronically low or high (due to over-repletion) levels of cortisol or aldosterone. The one limited study that assessed echocardiographic features of Addisonian patients did not find any functional abnormalities. However, to our knowledge, this has not been examined using state-of-the-art techniques for ventricular assessment such as strain-rate quantification or three-dimensional volume rendering, which may be sensitive in detecting more subtle forms of subclinical ventricular dysfunction. It could be useful to conduct such a study to determine if patients with adrenal insufficiency are at high risk for systolic dysfunction.

References

MAIN POINTS

- It is estimated that the prevalence of primary adrenal insufficiency (Addison disease) is 1 in 10,000 people. There are multiple case reports and several studies that suggest a correlation between Addison disease and abnormalities of cardiac function. The result of adrenal insufficiency is always a reduction of circulating corticosteroids and sometimes a reduction of mineralocorticoids and androgens.

- High cortisol levels are required by the adrenal medulla to synthesize epinephrine. Smooth muscle response to catecholamines requires the presence of cortisol. Patients with congestive heart failure (CHF) also have abnormal cortisol metabolism, as the normal circadian rhythm of plasma cortisol levels has been reported to be abolished in patients with CHF.

- Untreated adrenal insufficiency may cause significant electrocardiographic abnormalities, at least in part due to hyperkalemia. Cardiac arrest is likely to arise either from metabolic derangements, most notably hyperkalemia or from severe hypovolemia causing cardiovascular collapse.

- Glucocorticoid replacement is far from an exact science. Replacement dose is primarily determined based on the presence of clinical symptoms due to lack of sufficient objective assessment for monitoring replacement. It is yet unknown if chronic subclinical glucocorticoid under-replacement leads to long-term cardiovascular effects, particularly risk of dilated cardiomyopathy.

The authors declare no real or apparent conflicts of interest.