Caffeine has a half-life of 2 to 12 hours, is nearly 100% bioavailable, and reaches maximal concentrations in the body.
within an hour of ingestion. It has a relatively low volume of distribution and low plasma protein binding. The effects of caffeine on the cardiovascular system are summarized in Table. Caffeine is a nonselective competitive antagonist of adenosine receptors (A₁ and A₂A), which are found on the myocardium and coronary endothelium. Antagonism of these receptors results in decreased heart rate and positive chronotropic and dromotropic effects. Caffeine also acts as a phosphodiesterase inhibitor to cause significant inotropic effects via the calcium-induced calcium release process. As caffeine is metabolized in the liver, it is converted to theophylline, which in turn may cause adverse cardiac effects at high levels through blockade of adenosine receptors, resulting in increased adrenergic activity and increased catecholamine release.²

Caffeine toxicity also precipitates hypotension via direct and indirect mechanisms on the vascular smooth muscle cells. Caffeine directly inhibits myosin light chain kinase and
indirectly activates the nitric oxide synthase enzyme, which leads to vasodilation. Furthermore, the blockade of adenosine receptors increases catecholamine release, stimulating $\beta$-1 and $\beta$-2 receptors. Beta-1 receptor stimulation leads to tachydysrhythmias, incomplete diastolic filling times, decreased cardiac output, and ultimately hypotension. Stimulation of $\beta$-2 receptors on the peripheral vasculature adds to the vasodilatory effects.

Currently, there is no standardized management for caffeine overdose. The literature consists of widely different treatment strategies that vary on a case-to-case basis. Effective management should address prevention of further metabolism, the overwhelming adrenergic surge, and the multifactorial etiologies of caffeine-induced hypotension. Blockade of the hyperadrenergic response with short acting $\beta$1 antagonists, such as esmolol, has led to successful outcomes. Activated charcoal, intralipid
infusion, and subsequent hemodialysis are all useful interventions that prevent further caffeine metabolism and subsequent systemic effects. Intravenous fluid resuscitation with isotonic fluid can be administered to treat the hypotension. Additional vasopressor support may also be needed. Alpha-adrenergic receptor stimulation increases vascular tone. Phenylephrine and norepinephrine can be used to obtain α-1 agonism to improve blood pressure. Phenylephrine, in particular, is beneficial in that it is both a potent alpha agonist and causes reflex bradycardia to promote hemodynamic stability.

In summary, the patient experienced multiple episodes of ventricular tachyarrhythmias/fibrillation in the setting of isolated massive caffeine overdose. The ventricular arrhythmias were a result of caffeine toxicity on the cardiovascular system because of adenosine antagonism, endogenous catecholamine release, and phosphodiesterase inhibition, leading to increased cAMP availability. Management should focus on blocking the hyperadrenergic response with a short-acting β1-antagonist, removal of excess caffeine using activated charcoal, intralipid infusion and hemodialysis, and supporting hemodynamics with intravenous fluid resuscitation and vasopressors, such as phenylephrine or norepinephrine.

**Table. Effects of Caffeine on the Cardiovascular System**

<table>
<thead>
<tr>
<th>Location</th>
<th>Receptor</th>
<th>Mechanism</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium</td>
<td>A1</td>
<td>Nonselective competitive antagonism</td>
<td>(+) Chronotropy</td>
</tr>
<tr>
<td></td>
<td>β1</td>
<td>Stimulation of sympathetic NS</td>
<td>Decreased CO</td>
</tr>
<tr>
<td>PDE</td>
<td></td>
<td>Nonselective antagonism</td>
<td>(+) Inotropy</td>
</tr>
<tr>
<td>Coronary endothelium</td>
<td>A2A</td>
<td>Nonselective competitive antagonism</td>
<td>(+) Coronary vasoconstriction</td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>MLCK</td>
<td>Direct inhibition, increases MLCP</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>β2</td>
<td>Stimulation of sympathetic NS</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Endothelium</td>
<td>Ryanodine</td>
<td>Production of NO</td>
<td>Vasodilation</td>
</tr>
</tbody>
</table>

A indicates adenosine; β, beta; CO, cardiac output; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NO, nitric oxide; NS, nervous system; and PDE, phosphodiesterase.

**References**


**Disclosures**

None.

**Key Words:** caffeine ▪ caffeine overdose ▪ caffeine toxicity ▪ ventricular fibrillation ▪ ventricular tachycardia
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