Cardiovascular Effects of Griseofulvin

By Earl E. Aldinger, Ph.D.

ABSTRACT
The intravenous administration of griseofulvin in doses of 3.0 mg/kg to 32 anesthetized open-chest dogs produced marked increments (43%) in isometric systolic force measured by a strain gauge. These changes were accompanied by an increase (22%) in heart rate and a decrease (25%) in blood pressure. The effect was unaltered by clamping the blood supply to and from the adrenal glands or by previous treatment with 1 mg/kg reserpine, 0.4 mg/kg propranolol HCl, 10 mg/kg hexamethonium chloride, 1 mg/kg phentolamine HCl or 2 mg/kg atropine. In 11 anesthetized open-chest rats and 7 isolated rabbit hearts, griseofulvin also increased the force of contraction. It may be inferred from these experiments that griseofulvin has a direct action on the cardiovascular system rather than one mediated through neurogenic or hormonal mechanisms. These cardiovascular changes may occur in patients in whom griseofulvin is used in the treatment of fungus diseases.

ADDITIONAL KEY WORDS
blood pressure propranolol isolated rabbit heart myocardial contractility reserpine heart rate dog rat

Intravenous administration of griseofulvin increases coronary blood flow in the heart in vivo and relaxes isolated coronary arterial segments in vitro (1). Clinical reports have indicated that this drug may be beneficial in the reduction of episodes of angina pectoris (2), in the relief of arterial spasm of the hand associated with onychomycosis (3), and such peripheral vascular disorders as the shoulder-hand syndrome (4). The increased blood flow appears to be a direct action of griseofulvin on vascular smooth muscle rather than one mediated through the central or autonomic nervous systems.

The object of the present investigation was to determine whether griseofulvin exerts any additional action on the cardiovascular system, particularly the myocardium.

Methods
Experiments were conducted on dogs, rats, and rabbits. Thirty-two mongrel dogs of both sexes, each weighing 10 to 15 kg, were anesthetized with 25 mg/kg sodium pentobarbital injected intravenously. Light surgical anesthesia was maintained with subsequent small, periodic doses. Ventricular contractile force, heart rate, aortic blood pressure, and in some experiments lead II of the ECG were recorded. The right femoral artery and vein were cannulated with PE 190 polyethylene tubing. The arterial cannula was inserted into the aorta to the level of the diaphragm for the measurement of blood pressure, and the venous cannula was inserted 5 or 6 cm into the inferior vena cava for administration of drugs. Following tracheotomy, the animals were intubated and ventilated mechanically by a Harvard respirator with room air. A midsternal thoracotomy was performed and a strain-gauge arch was sutured to the right ventricle (5). The muscle between the two points of attachment was stretched by approximately 30% of the end-diastolic length. Although right ventricular contractile force was measured, it has been shown that changes recorded from any given area of either ventricle are representative of changes in the entire heart (6).

The blood supply to and from the adrenal glands was clamped in 4 animals. Four dogs were previously treated with 1 mg/kg reserpine, 5 dogs with 0.4 mg/kg propranolol HCl, 3 dogs with 10 mg/kg hexamethonium chloride, 2 dogs with 1 mg/kg phentolamine HCl and 2 dogs with 2 mg/kg atropine to determine whether autonomic reflexes contributed to the cardiovas-
cular response to griseofulvin. The degree of beta- and alpha-receptor blockade was determined by test injections of 0.5 \( \mu \)g/kg isoproterenol and 1.0 \( \mu \)g/kg norepinephrine.

Dimethylformamide was used as the solvent for making a 1058 griseofulvin solution. The drug was injected into the inferior vena cava in doses of 0.5, 1, 2, and 3 mg/kg.

Eleven Sprague-Dawley female rats weighing 400 ± 15 g were used to determine whether any difference existed between their response to griseofulvin and that of dogs. Anesthesia was induced with sodium pentobarbital (40 mg/kg ip). A tracheotomy was performed and artificial respiration was provided by a rhythmic, motor-driven Harvard respirator. The right carotid artery and the jugular vein were cannulated with PE 20 polyethylene tubing for measurement of blood pressure and for administration of drugs, respectively. The heart was exposed through a midline thoracotomy and the ventricular contractile force was measured with a strain-gauge lever system (7). The lever system was attached with cotton sutures to an 8-mm segment of the right ventricle in a vertical plane from apex to valve. The segment of muscle between the two points of attachment was stretched to apply an initial tension of 8 g above end-diastolic tension because it resulted in an increase of the ratio of tension to length, whereas 10 g or more frequently resulted in a decrease of the ratio. Therefore, the tension-to-length ratio under observation was always situated in the uppermost segment (70 to 90%) of the ascending portion of the Starling curve. All variables were measured and recorded as in the dog experiments. Griseofulvin was injected in a volume of 0.02 to 0.1 ml (5 to 25 mg/kg).

Seven isolated rabbit hearts, three previously treated with reserpine, were used to determine the direct effect of griseofulvin on the myocardium. Rabbits that had been given heparin (3 mg/kg) were stunned by a blow on the back of the neck and the heart was immediately removed and connected to an Anderson heart perfusion apparatus (Metro Industries) and perfused with Chenoweth's solution at 37°C. Ventricular contractile force was measured with a strain gauge connected to the apex by a string. Griseofulvin was administered in a volume of 0.2 to 0.10 ml.

A Statham transducer (P23-D) was used to measure aortic blood pressure changes, and a tachometer utilizing impulses from the ventricular contractile force was used to measure heart rate. Aortic blood pressure, heart rate, ventricular contractile force, and ECG were recorded (Sanborn polyviso recorder model 154).

**Results**

**DOGS**

Griseofulvin administered intravenously produced marked changes in ventricular contractile force, aortic blood pressure and heart rate (Table 1). These responses were dose dependent up to 3 mg/kg; 1 mg/kg produced 40 to 50% of the maximum response and concentrations as high as 20 mg/kg evoked essentially the same response as 3 mg/kg. The administration of equal volumes of the vehicle produced no changes in the recorded variables. The decrease in diastolic blood pressure was greater than that observed in systolic blood pressure. The concomitant increase in ventricular contractile force, usually occurring 8 to 12 seconds after the fall in blood pressure, probably increases stroke volume, as indicated by the increment in pulse pressure, and, along with the increase in heart rate, tends to increase cardiac output and blood flow. The positive inotropic and heart rate response to griseofulvin (5 to 15 minutes) was considerably longer than the blood pressure changes (1 to 3 minutes). The changes shown in Figure 1 are typical of the cardiovascular response to 3 mg/kg griseofulvin.

![TABLE 1](http://circres.ahajournals.org/)

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose</th>
<th>Ventricular contractile force</th>
<th>Heart rate</th>
<th>Aortic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs*</td>
<td>3 mg/kg</td>
<td>42.9 ± 11</td>
<td>22.0 ± 12</td>
<td>-24.2 ± 8</td>
</tr>
<tr>
<td>Rats†</td>
<td>5 mg/kg</td>
<td>21.4 ± 8</td>
<td>18.3 ± 14</td>
<td>-27.4 ± 10</td>
</tr>
<tr>
<td>Rabbits‡</td>
<td>4 mg</td>
<td>26.2 ± 12</td>
<td>20.1 ± 16</td>
<td></td>
</tr>
</tbody>
</table>

*32 open-chest dogs, †11 open-chest rats, ‡7 isolated rabbit hearts. The values given for the ventricular contractile force, heart rate, and aortic blood pressure are the percent changes from control values ± sd.

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Changes in ventricular contractile force (VCF) in grams, blood pressure (BP) in mm Hg, and heart rate (HR) in beats per minute following the intravenous administration of 3.0 mg/kg of griseofulvin.

Changes in VCF, BP, and HR (abbreviations same as Fig. 1) following the intravenous administration of 0.5 μg/kg of isoproterenol (I) and 3.0 mg/kg of griseofulvin (G) before and after 0.3 mg/kg of propranolol (P).
Clamping the blood supply to and from the adrenal glands in three animals had no effect on the griseofulvin response. Previous treatment with 1 mg/kg reserpine (4 dogs) for 3 days prior to the experiment, 0.4 mg/kg propranolol HCl (5 dogs), 10 mg/kg hexamethonium chloride (3 dogs), 1 mg/kg phentolamine HCl (2 dogs) or 2 mg/kg atropine (2 dogs) had no effect on the response to griseofulvin. The percent increase following the administration of 3 mg/kg griseofulvin was actually greater after blockage of beta-receptor sites with 0.3 mg/kg propranolol (Fig. 2). This marked increment in ventricular contractile force following griseofulvin occurred in spite of complete blockade of the aortic blood pressure and heart rate and 75% blockade of the inotropic effect of isoproterenol. A dose of 0.4 mg/kg propranolol completely blocks the reflex increment in myocardial contractility that usually accompanies the hypotensive action of nitroglycerine. There were no significant ECG changes in any of the animals.

RATS
After the intravenous injection of small volume doses (.02 ml or 5 mg/kg) of griseofulvin, eleven rats responded with an increase (21%) in ventricular contractile force. A decrease (27%) in aortic blood pressure and an increase (18%) in heart rate were similar to those occurring in the dog. Table 1 summarizes these results. Figure 3A is typical of ventricular contractile force changes in the rat.

ISOLATED RABBIT HEARTS
The effect of griseofulvin (4 mg) on seven isolated rabbit hearts was, in general, the same as that observed in the intact rat heart. The average increase in ventricular contractile force was 26%; this was accompanied by a 20% increase in heart rate. The response of three rabbits which had been previously treated with reserpine was essentially the same as that of control rabbits, indicating a direct action of griseofulvin on the myocardium. Table 1 summarizes these results. Figure 3B is typical of ventricular contractile force changes in the isolated rabbit heart.

No changes in contractility were observed in either intact dog and rat hearts or isolated rabbit hearts following either the administration of the solvent dimethylformamide or 9.1% dextran in physiologic saline when given in a volume equal to the volume of 10% griseofulvin used in these experiments. The drugs were administered intravenously to the intact dogs and rats and via the aorta in the isolated rabbit heart preparation.

Discussion
The present study has shown that, in addition to increasing coronary blood flow, griseofulvin increases myocardial contraction and
heart rate and decreases blood pressure by a direct action on the myocardium and vascular smooth muscle.

The fall in blood pressure following the intravenous administration of griseofulvin, 8 to 12 seconds prior to the increment in ventricular contraction, indicates that griseofulvin produces peripheral vasodilation. Both systolic and diastolic blood pressure decreased markedly, with the greater reduction occurring in the diastolic pressure. The change in the pulse pressure and the increase in inotropic activity of the heart suggest that stroke volume has increased. A moderate increase in heart rate was always observed; cardiac output probably increased. These actions of griseofulvin were unaltered by pharmacologic blockade of autonomic ganglia and receptors; therefore the drug probably has a direct action on the cardiovascular system.

Experiments on rats produced essentially the same results as those observed in dogs. Isolated rabbit hearts, controls and those previously treated with reserpine, responded with an increase in myocardial contraction and rate.

The positive inotropic response to griseofulvin, lasting from 5 to 15 minutes, was considerably longer than the blood pressure changes (1 to 3 minutes). Rubin reported that the intravenous administration of 1.0 to 5.0 mg/kg of griseofulvin caused an increase in coronary blood flow lasting from 2 to 12 minutes (1). This approximates the duration of the positive inotropic response to the drug. There is no information to show whether the increase in coronary blood flow or increased cardiac contractility begins first.

Other drugs that evoke a cardiovascular response similar to those observed with griseofulvin are papaverine, isoproterenol, quinidine, nitroglycerine and aminophylline (8). However, studies in our laboratory have shown that the inotropic action of quinidine and nitroglycerine is abolished after sympathetic ganglionic blockade, suggesting that the inotropic effect was due to a reflex response to the fall in blood pressure. The cardiovascular actions of isoproterenol are blocked by beta-adrenergic receptor-blocking drugs (9). In our experience, the cardiac action of papaverine and aminophylline is only slightly altered following beta-receptor blockade, which suggests a mechanism of action resembling griseofulvin. There appears to be no structure-activity relationship to elucidate their similar cardiovascular action.

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References

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EARL E. ALDINGER

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