Effects and Mechanism of Action of Aminophylline on Cardiac Function and Regional Blood Flow Distribution in Conscious Dogs

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SUMMARY The effects of aminophylline, 1 mg/kg/min infused intravenously for 10 minutes, were examined on left ventricular (LV) diameter, pressure, and indexes of myocardial contractility, as well as systemic, coronary, and regional hemodynamics in conscious dogs. Aminophylline increased mean arterial pressure 12 ± 2%, LV systolic pressure 8 ± 1%, LV dp/dt 20 ± 2%, velocity of myocardial fiber shortening 13 ± 2% and heart rate 5 ± 2%, and reduced LV end-diastolic diameter 2 ± 0.5%. Vascular resistance rose in the systemic bed 13 ± 5%, the coronary bed 26 ± 3%, the mesenteric bed 26 ± 5% and the iliac bed 36 ± 4%, but did not rise in the renal bed. Both β-adrenergic receptor blockade with propranolol and chronic treatment with reserpine attenuated but did not abolish the positive inotropic response induced by aminophylline. Alphaadrenergic receptor blockade with phentolamine prevented aminophylline-induced vasoconstriction in the systemic, coronary, mesenteric and iliac beds. In contrast to the vasoconstriction with i.v. aminophylline, when the drug was infused directly into the iliac artery, it elicited marked iliac vasodilation. Thus, in the intact conscious dog, i.v. aminophylline, in a dose that had little effect on heart rate, increased LV contractility and reduced preload. The increase in contractility was dependent in part on intact β-adrenergic nervous activity and endogenous catecholamine stores. The increases in systemic, coronary, iliac and mesenteric resistances involved α-adrenergic mechanisms. These actions appear to involve autonomic mechanisms, because the only direct effect of aminophylline on the iliac artery was marked vasodilation.

THEOPHYLLINE, ethylenediamine (aminophylline) is widely used in the treatment of cardiovascular and respiratory disease. In part, the therapeutic rationale is based on the concept that aminophylline is a potent vasodilator. It has been shown to decrease total systemic, 2 renal, 3 and, in particular, coronary 4, 6, 7 vascular resistances in anesthetized animal preparations. Ritchie 8 noted that experimentally, it can be demonstrated that the xanthines dilate coronary arteries and increase coronary blood flow, and this finding has led to their use in treating coronary artery disease. The most widely used methylated xanthine derivative is aminophylline, which is a combination of theophylline and ethylenediamine. The latter substance, believed to be therapeutically inert, increases the solubility of theophylline. 12 Because aminophylline is widely used clinically and because of the observation that the effects of many interventions differ substantially in anesthetized and conscious animals, 19 we studied this drug in intact, conscious dogs.

A primary goal of this study was to determine the effects of aminophylline on regional blood flow distribution using techniques designed to yield continuous direct measurements in healthy, conscious animals in which the effects of anesthesia and surgical trauma on circulatory and reflex control were absent. To understand the action of aminophylline on the coronary circulation, we felt it important to determine the effects of the drug on left ventricular (LV) function. Once the descriptive aspects of the circulatory effects of aminophylline were established in the conscious dogs, its mechanism of action was analyzed by repeating experiments in the presence of autonomic blockade. Finally, to separate the direct from the reflex effects of the drug, aminophylline was infused intra-arterially into the iliac bed, where the direct effects would not be complicated by secondary effects arising from activation of either central or peripheral components of the autonomic nervous system.

Methods

Thirty-two mongrel dogs (19–32 kg) were studied in the conscious state. In 13 dogs, through a left thoracotomy in the fifth intercostal space using pentobarbital sodium (30 mg/kg, i.v.) anesthesia, miniature pressures gauges (P 22, Konigsberg Instruments, Inc.) were implanted within the left ventricle through a stab wound in the apex and ultrasonic diameter transducers were implanted on opposing anterior and posterior walls of the left ventricle. Heparin-filled catheters were implanted in the left atrium and aorta. In 11 of these dogs ultrasonic flow transducers were implanted around the left circumflex coronary artery. In seven other dogs, electromagnetic flow probes were implanted on the ascending aorta and catheters were placed in the aorta. In 12 other dogs, through a midline laparotomy, using pentobarbital sodium (30 mg/kg, i.v.) anesthesia, Doppler ultrasonic or electromagnetic flow transducers (Zepeda Instruments, Inc.) were placed around superior...
mesenteric (eight dogs), left renal (12 dogs) and left iliac (10 dogs) arteries. Heparin-filled catheters were implanted in the aorta and hydraulic cuff occluders were implanted distal to all electromagnetic flow transducers on the peripheral arteries.

Arterial pressure was measured using the previously implanted heparin-filled catheters and a Statham P23Db strain-gauge manometer (Statham Instrument Division, Gould, Inc.). Miniature pressure gauges were calibrated in vitro and in vivo against Statham P23Db strain-gauge manometers connected to the left atrial and aortic catheters. At the time of autopsy, the position of the gauges within the ventricular cavity was confirmed. An improved ultrasonic transit time dimension gauge was used to measure LV diameter.\(^{14}\)

The instrument generates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of about 1.5 \times 10^8 \text{mm/sec} between the 3-MHz piezoelectric crystals, giving a record of instantaneous internal LV diameter. At a constant room temperature the thermal drift of the instrument is minimal, i.e., <0.01 mm in 6 hours, and the frequency response is flat to 60 Hz. Any drift in the measurement system, in the instrument electronics, the data tape recorder and the oscillograph that displayed data were eliminated during the experiment by periodic calibrations. This involved substitution of pulses of precisely known duration from a crystal-controlled pulse generator having a basic stability of 0.001%. The position of the ultrasonic transducers was confirmed at the time of autopsy. Blood flows were measured with either an ultrasonic Doppler flowmeter system or an electromagnetic flowmeter system (Benton Instruments). The ultrasonic Doppler flow system, which has been described in detail previously, has a reliable zero reference.\(^{15,16}\) and in these experiments, zero blood flow was determined repeatedly and was confirmed by calibration when the dog was sacrificed.

The electromagnetic flowmeter system was used to measure blood flow in the ascending aorta and in the iliac and mesenteric arteries. When the electromagnetic flowmeter was used to measure blood flow in the peripheral beds, zero flow was determined by infusing a previously implanted hydraulic occlusive cuff. In the measurement of aortic blood flow, zero was assumed to occur during late diastole.

The experiments were conducted 2–7 weeks after recovery from operation when the dogs appeared vigorous and healthy. While the dogs were resting quietly, continuous recordings of LV pressure and diameters, dP/dt and dD/dt (i.e., the velocity of myocardial fiber shortening), regional blood flows, arterial pressure and heart rate were taken in the control state, as well as during and after administration of aminophylline (Aminophyllin, Searle Laboratories). Aminophylline was infused intravenously in a dose of 1 mg/kg/min for 10 minutes in the absence of autonomic blockades, after \(\beta\)-adrenergic receptor blockade with propranolol (1 mg/kg), after \(\alpha\)-adrenergic receptor blockade with phentolamine (1 mg/kg), after both \(\alpha\)- and \(\beta\)-adrenergic receptor blockade, and after endogenous catecholamine deple-

The adequacy of \(\beta\)-adrenergic blockade was tested with isoproterenol (1 \(\mu\)g/kg i.v.), that of \(\alpha\)-adrenergic blockade was tested with norepinephrine (1 \(\mu\)g/kg i.v.), and that of catecholamine depletion with reserpine was tested during a terminal experiment by electrical stimulation of the left stellate ganglion. In nine intact dogs, aminophylline (2.5 mg/kg/min) was infused intravenously for 10 minutes in the absence of autonomic blockade. In five intact dogs in which iliac blood flow and arterial pressure were measured, aminophylline was infused intra-arterially, 0.04 \(\mu\)g/kg/min for 10 minutes through a catheter placed in the iliac artery retrogradely, via a branch of the femoral artery, under local anesthesia. To rule out the possibility that any of the observed changes in response to aminophylline were spontaneous and not due to the drug, at least 15 minutes of stable control measurements were recorded before drug administration. Moreover, saline infusions of a volume similar to the amount administered with the drug did not alter hemodynamics. Furthermore, because of the long-acting effects of aminophylline, each infusion of the drug was conducted on a different day. Finally, six control experiments and six experiments with autonomic blockade were repeated on separate days and yielded similar results, indicating that tachyphylaxis was not a major problem.

The data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph. A cardiotachometer triggered by the pressure pulse provided instantaneous, continuous records of heart rate. Continuous records of dP/dt and dD/dt were derived from the LV pressure and diameter signals using Philbrick operational amplifiers (Teledyne Philbrick), connected as differentiators and with frequency responses of 700 Hz and 140 Hz, respectively. However, when used in conjunction with the multichannel oscillographic recorder, the frequency response was 60 Hz for both differentiators. A triangular wave signal with a known slope was substituted for pressure and diameter signals to directly calibrate the dP/dt and dD/dt signals. Electronic resistance-capacitance filters with 2-second time constants were used to derive mean arterial blood pressure and mean regional and coronary blood flows, while an 8-second time constant was used to derive mean aortic flow. Mean regional vascular resistances were calculated as quotients of mean arterial pressure and regional blood flows. Late diastolic coronary resistance was calculated as the quotient of late diastolic arterial pressure and late diastolic coronary blood flow.

Multiple responses were compared to control values using the two-way analysis of variance and comparisons between groups were analyzed using one way analysis of variance. When only one response was analyzed (i.e., peripheral flows and resistances, after \(\alpha\)-adrenergic blockade), the paired \(t\) test was used within groups of animals and one-way analysis of variance was used to compare responses between groups.\(^{17}\)
Results

Intravenous Aminophylline Infusion
(1.0 mg/kg/min for 10 minutes)

Data were recorded continuously but analyzed and presented as change from control at 3–4 minutes of infusion, 9–10 minutes of infusion (referred to as “during infusion”) and 9–10 minutes after termination of the infusion (referred to as “after infusion”). All responses after autonomic blockades are compared with effects of aminophylline in intact dogs during infusion. All changes presented in the Results section are statistically significant unless specifically stated otherwise. Specific confidence levels are listed in figures and tables. Control values are noted in figures and tables.

Left Ventricular and Coronary Dynamics

Intact Dogs

Left ventricular dynamics (table 1). Aminophylline increased mean arterial pressure 11.6 ± 1.7% and LV systolic pressure 7.5 ± 1.3%; both remained elevated after infusion. Heart rate rose slightly during infusion but was not significantly elevated after infusion. LV end-diastolic diameter fell by 1.7 ± 0.3% and remained decreased after infusion. Aminophylline increased LV dP/dt 19.9 ± 2.4% and dD/dt 12.9 ± 1.7% during infusion, and these variables remained elevated after infusion.

Coronary dynamics (table 2). Aminophylline decreased mean coronary flow 7.8 ± 2.1% during infusion and flow continued to decline 11.7 ± 2.8% after infusion. Late diastolic coronary resistance increased (25.7 ± 2.5%) during infusion and rose further (37.8 ± 6.8%) after infusion (fig. 1).

When a larger dose of aminophylline was infused (2.5 mg/kg/min for 10 minutes) and increased heart rate substantially (29.9 ± 7.0%), mean coronary blood flow increased (36.8 ± 7.1%) and late diastolic coronary resistance decreased (24.7 ± 6.0%) (table 3).

Beta-adrenergic Receptor Blockade
(Aminophylline 1.0 mg/kg/min for 10 minutes)

Left ventricular dynamics. In the presence of β-adrenergic receptor blockade, aminophylline increased mean arterial pressure (5.5 ± 1.4%), significantly less (p < 0.05) than in the absence of blockade. LV systolic pressure and heart rate did not change significantly. However, LV end-diastolic diameter fell (1.5 ± 0.2%). LV dP/dt increased 6.4 ± 0.7% and dD/dt increased 7.4 ± 1.5%, significantly less (p < 0.01) than the increases in the unblocked state (fig. 2).

The difference between the effects of aminophylline on LV dP/dt and velocity were even more apparent when the actual changes were examined. In non-blocked dogs, aminophylline increased LV dP/dt by 740 ± 100 mm Hg/sec and velocity by 10.5 ± 1.5 mm/sec. After β blockade, aminophylline increased LV dP/dt by only 220 ± 31 mm Hg/sec and velocity by 4.2 ± 0.9 mm/sec.

Coronary dynamics. In the presence of β-adrenergic receptor blockade, aminophylline decreased mean coronary blood flow and increased late diastolic coronary vascular resistance to the same extent as in the unblocked state (fig. 3).

Alpha- and β-adrenergic Receptor Blockade
(a minophylline 1.0 mg/kg/min for 10 minutes)

Left ventricular dynamics. In the presence of combined α- and β-adrenergic receptor blockade, aminophylline induced no significant changes in mean arterial pressure, LV systolic pressure or heart rate. LV end-diastolic diameter decreased by 4.6 ± 0.5%, which was significantly greater (p < 0.01) than that observed when aminophylline was infused either in the

<table>
<thead>
<tr>
<th>Table 1. Effects of Aminophylline, 1 mg/kg/min i.v. for 10 Minutes</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Mean arterial pressure (mm Hg) n = 13</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg) n = 13</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec) n = 13</td>
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<tr>
<td>Velocity (mm/sec) n = 10</td>
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<tr>
<td>LV end-diastolic diameter (mm) n = 10</td>
</tr>
<tr>
<td>LV stroke shortening (mm) n = 10</td>
</tr>
<tr>
<td>Heart rate (beats/min) n = 13</td>
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</tbody>
</table>

*p < 0.05 significantly different from control.
†p < 0.01 significantly different from control.
Abbreviation: LV = left ventricular.
unblocked state or in the presence of β-adrenergic blockade alone. In the presence of combined α- and β-adrenergic receptor blockade, aminophylline increased LV dP/dt (5.6 ± 1.8%) and dD/dt (6.3 ± 1.4%), changes similar to those after β blockade and significantly less (p < 0.01) than those observed in the unblocked state (fig. 2).

**Coronary dynamics.** When aminophylline was in-

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**Table 2. Effects of Aminophylline, 1 mg/kg i.v. for 10 Minutes, on Resistances and Flows**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3-min infusion</th>
<th>9-min infusion</th>
<th>9 min after infusion</th>
</tr>
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<tbody>
<tr>
<td><strong>Systemic resistance</strong></td>
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<tr>
<td>(mm Hg/l/min)</td>
<td>n = 7</td>
<td>42 ± 3.9</td>
<td>8.0 ± 1.9†</td>
<td>12.8 ± 4.6*</td>
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<tr>
<td><strong>Systemic flow</strong></td>
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<tr>
<td>(l/min)</td>
<td>n = 7</td>
<td>2.3 ± 0.2</td>
<td>−2.6 ± 1.8</td>
<td>−2.4 ± 2.4</td>
</tr>
<tr>
<td><strong>Diastolic coronary resistance</strong></td>
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<td></td>
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<tr>
<td>(mm Hg/ml/min)</td>
<td>n = 11</td>
<td>1.79 ± 0.15</td>
<td>12.8 ± 1.9†</td>
<td>25.7 ± 2.5†</td>
</tr>
<tr>
<td><strong>Mean coronary flow</strong></td>
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<td></td>
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<tr>
<td>(ml/min)</td>
<td>n = 11</td>
<td>44.3 ± 2.8</td>
<td>−5.3 ± 1.2†</td>
<td>−7.8 ± 2.1†</td>
</tr>
<tr>
<td><strong>Iliac resistance</strong></td>
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<td></td>
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<tr>
<td>(mm Hg/ml/min)</td>
<td>n = 10</td>
<td>0.66 ± 0.07</td>
<td>7.7 ± 2.8*</td>
<td>35.8 ± 3.7†</td>
</tr>
<tr>
<td><strong>Iliac flow</strong></td>
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</tr>
<tr>
<td>(ml min)</td>
<td>n = 10</td>
<td>158 ± 13</td>
<td>−6.6 ± 2.1*</td>
<td>−18.9 ± 2.1†</td>
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<tr>
<td><strong>Mesenteric resistance</strong></td>
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<tr>
<td>(mm Hg/ml/min)</td>
<td>n = 8</td>
<td>0.38 ± 0.02</td>
<td>1.6 ± 1.7</td>
<td>25.6 ± 4.9†</td>
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<tr>
<td><strong>Mesenteric flow</strong></td>
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<tr>
<td>(ml/min)</td>
<td>n = 8</td>
<td>245 ± 16</td>
<td>−1.0 ± 1.6</td>
<td>−12.7 ± 3.0†</td>
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<tr>
<td><strong>Renal resistance</strong></td>
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<tr>
<td>(mm Hg/ml/min)</td>
<td>n = 12</td>
<td>0.77 ± 0.03</td>
<td>−8.6 ± 1.3†</td>
<td>4.0 ± 3.6</td>
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<tr>
<td><strong>Renal flow</strong></td>
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<tr>
<td>(ml/min)</td>
<td>n = 12</td>
<td>127 ± 5.2</td>
<td>9.8 ± 1.7†</td>
<td>6.3 ± 2.5*</td>
</tr>
</tbody>
</table>

* p < 0.05 significantly different from control.
† p < 0.01 significantly different from control.

**Table 3. Effects of Aminophylline, 2.5 mg/kg/min i.v. for 10 Minutes**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3-min infusion</th>
<th>9-min infusion</th>
<th>9 min after infusion</th>
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<tbody>
<tr>
<td><strong>Mean arterial pressure</strong></td>
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<tr>
<td>(mm Hg)</td>
<td>n = 9</td>
<td>92 ± 3.0</td>
<td>6.8 ± 1.1†</td>
<td>10.5 ± 1.8†</td>
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<tr>
<td><strong>LV systolic pressure</strong></td>
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<tr>
<td>(mm Hg)</td>
<td>n = 9</td>
<td>125 ± 4.0</td>
<td>8.6 ± 1.4†</td>
<td>11.7 ± 2.2†</td>
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<tr>
<td><strong>LV dP/dt</strong></td>
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<tr>
<td>(mm Hg/sec)</td>
<td>n = 9</td>
<td>3770 ± 160</td>
<td>20.2 ± 3.6†</td>
<td>52.5 ± 9.8†</td>
</tr>
<tr>
<td><strong>Velocity</strong></td>
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<td></td>
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<tr>
<td>(mm/sec)</td>
<td>n = 7</td>
<td>76.0 ± 8.0</td>
<td>—</td>
<td>18.2 ± 3.3†</td>
</tr>
<tr>
<td><strong>LV end-diastolic diameter</strong></td>
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<tr>
<td>(mm)</td>
<td>n = 7</td>
<td>33.33 ± 1.80</td>
<td>—</td>
<td>−5.9 ± 1.7*</td>
</tr>
<tr>
<td><strong>LV stroke shortening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(mm)</td>
<td>n = 7</td>
<td>10.6 ± 0.97</td>
<td>—</td>
<td>5.0 ± 3.4</td>
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<tr>
<td><strong>Heart rate</strong></td>
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<tr>
<td>(beats/min)</td>
<td>n = 9</td>
<td>88 ± 4.0</td>
<td>13.9 ± 4.7*</td>
<td>29.9 ± 7.0†</td>
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<tr>
<td><strong>Mean coronary flow</strong></td>
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<td></td>
</tr>
<tr>
<td>(ml/min)</td>
<td>n = 7</td>
<td>43.1 ± 2.6</td>
<td>14.9 ± 2.6†</td>
<td>36.8 ± 7.1†</td>
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<tr>
<td><strong>Late diastolic coronary resistance</strong></td>
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<tr>
<td>(mm Hg/ml/min)</td>
<td>n = 7</td>
<td>1.94 ± 0.14</td>
<td>−9.0 ± 2.8*</td>
<td>−24.7 ± 6.0†</td>
</tr>
</tbody>
</table>

* p < 0.05 significantly different from control.
† p < 0.01 significantly different from control.

Abbreviation: LV = left ventricular.
FIGURE 1. The effects of i.v. aminophylline (1.0 mg/kg/min) are shown on left ventricular (LV) pressure, LV dP/dt, mean arterial pressure, phasic and mean coronary blood flow and mean coronary resistance in a conscious dog during the control period, 9 minutes during infusion and 9 minutes after infusion. During and after aminophylline infusion, mean arterial pressure, LV pressure and dP/dt increased, mean coronary blood flow decreased and coronary resistance increased.

Fused in the presence of combined α- and β-adrenergic receptor blockade, the decreases in mean coronary blood flow and increases in late diastolic coronary resistance were abolished (fig. 3). These effects differed significantly (p < 0.01) from those in the untreated dogs or those after β-adrenergic blockade alone. In two experiments aminophylline was infused in the presence of α-adrenergic receptor blockade alone. In these experiments the aminophylline-induced coronary vasoconstriction was also abolished, i.e., coronary flow rose by 23% in each and coronary resistance fell by 23% and 14% in the two experiments.
Reserpine-induced Catecholamine Depletion  
(aminophylline 1.0 mg/kg/min for 10 minutes)

After pretreatment with reserpine, aminophylline did not significantly alter mean arterial pressure (control = 81.0 ± 3.0 mm Hg), heart rate (control = 59 ± 7 beats/min) or end-diastolic length (control = 32.46 ± 1.18 mm), but increased LV dp/dt 10.3 ± 2.0% (from 3010 ± 260 mm Hg/sec) and dD/dt 5.6 ± 2.9% (from 61.0 ± 6.7 mm/sec). These changes were significantly less ($p < 0.01$) than those when aminophylline was infused in the unblocked state. The effects of reserpine pretreatment resembled those of β-blockade on the response to aminophylline.

Systemic, Iliac, Mesenteric and Renal Flows  
and Resistances after i.v. Aminophylline  
(1.0 mg/kg/min for 10 minutes)

Intact Dogs

Systemic bed. Flow did not change significantly from control during or after infusion. However, systemic resistance increased 12.8 ± 4.6% during infusion and rose further, 21.6 ± 8.2% above control, after infusion (table 2, fig. 4).

Iliac bed. Iliac flow decreased 18.9 ± 2.1% during infusion and remained depressed 20.1 ± 3.3% below control after infusion. Iliac resistance increased 35.8
± 3.7% during infusion and increased further, 44.6 ± 5.8% above control, after infusion (table 2, fig. 4).

Mesenteric bed. Mesenteric flow decreased 12.7 ± 3.0% during infusion and remained depressed (11.5 ± 1.7%) after infusion (table 2, fig. 4). Resistance increased 25.6 ± 4.9% during infusion and remained elevated (27.7 ± 3.5%) after infusion (table 2, fig. 4).

Renal bed. Initially and transiently, renal flow increased 9.8 ± 1.7% and renal resistance decreased 8.6 ± 1.3%. However, at 9–10 minutes during infusion, renal flow remained elevated 6.3 ± 2.5%, while resistance had returned toward control. After infusion, renal flow did not differ from control; however, renal resistance was elevated 8.6 ± 3.7% above control (table 2, fig. 4).

Alpha-adrenergic Receptor Blockade

In the presence of α-adrenergic receptor blockade, aminophylline increased systemic flow 9.7 ± 2.8% from 3.03 ± 0.28 l/min and reduced systemic resistance 7.1 ± 3.2% from 31.85 ± 2.53 mm Hg/l/min. These effects were significantly different (p < 0.01) from those in the unblocked state (fig. 5).

Iliac bed. In the presence of α-receptor blockade alone, the vasoconstrictor effects of aminophylline were reversed to vasodilatation, with a decrease in iliac resistance (18.0 ± 6.0% from 0.53 ± 0.04 mm Hg/ml/min). The effects were significantly different (p < 0.01) from those in the unblocked state (fig. 5).

Mesenteric bed. In the presence of α-receptor blockade alone, aminophylline induced no significant changes in either mesenteric flow or resistance. These effects were significantly different (p < 0.01) from those in the unblocked state (fig. 5).

Renal bed. In the presence of α-receptor blockade alone, aminophylline induced no significant changes in either renal flow or resistance. Thus, at the end of infusion, renal resistance was unaltered either in the presence or absence of α-adrenergic receptor blockade (fig. 5).

Intra-arterial Aminophylline
(0.4 µg/kg/min for 10 minutes)

Aminophylline was infused into the iliac artery in five dogs. During the infusion, mean arterial pressure and heart rate did not change. Iliac blood flow increased 63.5 ± 5.4% (from 94.4 ± 16.6 ml/min), while iliac resistance fell 37.3 ± 3.0% (from 1.04 ± 0.13 mm Hg/ml/min). These effects were significantly different (p < 0.01) from the decrease in iliac flow and increase in iliac resistance when aminophylline was infused systemically (fig. 6).
Discussion

The concept that aminophylline is a potent coronary and peripheral vasodilator is based primarily on experiments in anesthetized animal preparations. These experiments have demonstrated vasodilation, when the drug was administered intravenously, in the systemic, renal and coronary vascular beds. When aminophylline was administered directly into the renal or coronary beds, it caused even more striking dilation. In contrast to these experiments in anesthetized animals, the results of the present investigation, conducted in intact, conscious dogs indicate that the predominant effect of intravenously administered aminophylline is to constrict the systemic, coronary, mesenteric and iliac beds. Only the renal bed showed modest and transient vasodilation. Other studies of the effects of aminophylline in intact, conscious normal human subjects have failed to show substantial vasodilation. For instance, Howarth et al. found that aminophylline induced only a transient increase in cardiac output, which then fell below control levels. Similarly, Davis and Shock found that renal plasma flow increased only transiently with aminophylline. Finally, Maxwell et al. found that aminophylline induced coronary vasoconstriction in normal human subjects. Thus, a clear difference appears to exist between the effects of aminophylline in intact conscious animals and man and in anesthetized animal preparations. Whether a difference exists between the effects of the drug in the presence and absence of cardiovascular disease has not been determined.

The finding that aminophylline induced vasoconstriction in the coronary bed was particularly surprising because of the concomitant increases in myocardial contractility and arterial pressure, which would be expected to augment myocardial oxygen demand and thereby result in metabolically mediated coronary vasodilation, implying that the vasoconstrictor influence was indeed powerful. The coronary vasoconstriction induced by aminophylline was abolished by α-adrenergic blockade, indicating that this effect was sympathetically mediated. When a larger dose of aminophylline was infused (i.e., 2.5 mg/kg/min intravenously for 10 minutes), both heart rate and the indexes of myocardial contractility rose substantially. With this dose of drug there was a substantial increase in coronary blood flow, with a fall in late diastolic coronary resistance (table 3). Thus, in intact, conscious dogs, aminophylline in a dose that did not alter the heart rate substantially caused α-adrenoergically mediated coronary vasoconstriction. However, in a dose of the drug that caused larger increases in contractility and heart rate, and therefore greater increases in myocardial metabolism, net coronary vasodilation was observed.

When the drug is administered systemically, an action on the autonomic nervous system might outweigh the direct effects of the drug. The studies on the iliac circulation support the concept that aminophylline exerts two distinct effects on the peripheral vascular bed: an indirect vasoconstrictor effect involving α-adrenergic mechanisms and a direct vasodilator effect. In these experiments, effects of intra-arterial and i.v. aminophylline were opposite (fig. 6). Aminophylline is a potent vasodilator when administered directly into the iliac artery. However, when given systemically, in the intact animal, it causes potent iliac vasoconstriction that appears to involve an α-adrenergic mechanism, as it can be abolished by phentolamine. Thus, the drug not only exerts differing actions when administered to intact, conscious or anesthetized preparations, but also when it is administered intravenously or intra-arterially.

In the present study, aminophylline elicited dose-related increases in cardiac rate and contractility, i.e., LV dp/dt, LV dD/dt and myocardial fiber shortening per stroke. The positive inotropic effects of the drug have been clearly demonstrated in isolated atrial and papillary muscle and also in the isolated heart and in anesthetized dog preparations. Aminophylline reduces the left ventricular filling pressure in patients with and without heart disease. Findings compatible with those in the present study in which LV end-diastolic diameter fell.

We felt the mechanism of the aminophylline-induced increase in myocardial contractility should be investigated further. Aminophylline acts as a competitive inhibitor of cyclic nucleotide phosphodiesterase, the enzyme that catalyzes the conversion of cyclic AMP to 5'-AMP, and also acts on membranes of the sarcoplasmic reticulum, and thus influences the intracellular movement of calcium.

After β-adrenergic blockade, the augmentation of the indexes of contractility, LV dp/dt and dD/dt induced by the drug were substantially reduced, implying that a portion of the increase in contractility involved β-adrenergic mechanisms. This observation in intact conscious dogs contrasts strikingly with experiments using right ventricular papillary muscle and.
isolated guinea pig atria\textsuperscript{22} and frog hearts,\textsuperscript{26} in which $\beta$ blockade did not influence the positive inotropic action of the drug. To leave $\beta$-adrenergic receptors intact but to investigate further the role of adrenergic mechanisms, dogs were pretreated with reserpine to deplete endogenous catecholamine stores. Under these conditions the aminophylline-induced increases in myocardial contractility were again attenuated to the levels after $\beta$ blockade. These experiments support the concept that the positive inotropic response to aminophylline is in part caused by activation of the sympathetic nervous system, while not being totally dependent on the $\beta$-adrenergic receptor. Again, this finding contrasts with previous studies on right ventricular papillary muscle\textsuperscript{25} and isolated rat atria,\textsuperscript{21} in which the positive inotropic responses to aminophylline were not prevented by reserpine pretreatment. If aminophylline activates sympathetic nerves in the intact, conscious animal, then this action would reconcile the apparent differences between our results and those obtained in isolated muscle or heart preparations devoid of normal autonomic innervation. Thus, from our experiments it appears that a portion of the positive inotropic response to aminophylline is related to the release of endogenous catecholamine stores, and possibly to an augmentation of their action by inhibition of phosphodiesterase.

The concept that there may be both c-AMP and non-c-AMP-mediated components to the aminophylline-induced positive inotropic response was initially proposed by Marcus et al.\textsuperscript{24} Theophylline enters myocardial tissue very rapidly, but the development of increases in myocardial twitch tension proceeds even faster than the uptake of drug by the heart.\textsuperscript{32, 33} This suggests that the drug acts on some component of the cell other than the intracellular space, perhaps the sarcolemma, because theophylline increases the slow inward calcium current during the cardiac action potential.\textsuperscript{24} Several authors have suggested that aminophylline-induced alterations in calcium flux might be at least part of the mechanism of the positive inotropic response.\textsuperscript{32, 26, 37} Our studies suggest that in conscious animals with intact reflexes, a portion of the positive inotropic response after aminophylline infusion is dependent on intact adrenergic nervous activity and endogenous catecholamine stores, presumably by inhibiting the breakdown of c-AMP formed in the heart from norepinephrine released by nerve endings during normal impulse traffic, while another portion seems independent of these factors and is possibly caused by alterations in calcium influx.

The mechanism of action of aminophylline on the vascular beds remains speculative. It is unlikely that an action on the systemic arterial baroreceptor system caused the increases in systemic, coronary, iliac and mesenteric resistances, because aminophylline caused an increase in arterial pressure that would elicit arterial baroreceptor-induced vasoconstriction in the regional beds. The influence of aminophylline on intracardiac low pressure receptors was not investigated but cannot be excluded, because a fall in preload consistently occurred after administration of the drug. The drug stimulates nervous activity centrally\textsuperscript{12} and at sympathetic ganglia,\textsuperscript{35-37} and the integrated cardiovascular response to systemic aminophylline could result from stimulation of the central nervous system, which elicits $\alpha$ adrenergically mediated constriction of the systemic and regional vasculature and a portion of the positive inotropic response. These effects predominate over the direct dilator effects of the drug on vascular smooth muscle and augment the nonsympathetically mediated positive inotropic response.

In conclusion, in the intact conscious dog, i.v. aminophylline in a dose that does not alter heart rate substantially increases LV contractility and reduces preload. The stimulation of myocardial contractility is dependent, in part, on intact $\beta$-adrenergic nervous activity and endogenous catecholamine stores. The moderate increases in systemic, coronary, iliac and mesenteric resistances appear to involve $\alpha$-adrenergic mechanisms. In the coronary bed, vasoconstriction was noted only at the lower dose; with a large dose, and concomitant greater stimulation of myocardial oxygen demands, net coronary vasodilation was observed. The only vasodilator effect of the drug was observed on the renal bed, where it was minor. The direct effect of aminophylline on the iliac vascular bed is vasodilation, but when the drug is given systemically it causes iliac vasoconstriction. Thus, aminophylline exerts differing effects when administered to conscious and anesthetized animals, and its influence on the cardiovascular system is dependent on the dose and route of administration of the drug.

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References

8. Wegria R, Essex HE, Herrick JF, Mann FC: The simultaneous action of certain drugs on the blood pressure and on the flow in
the right and left coronary arteries. Am Heart J 20: 557, 1940
10. Moore, KL, Lu FC: Effects of epinephrine, aminophylline, nitroglycerine, and papaverine on coronary inflow and on heart contraction, as recorded concurrently. J Pharmacol Exp Ther 99: 286, 1950
25. Kasper W, Greiner H, Grosse N, Scholz H: Inability of propanolol to change the effects of theophylline on myocardial mechanics. (abstr) Naunyn-Schiemedebergs Arch Pharmacol 289 (suppl R27), 1975
27. Verma SC, McNell H: Actions and interactions of theophylline and imidazole on cardiac contractility, phosphorylase activation, and cyclic AMP. Arch Int Pharmacodyn 221: 4, 1976
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