Digoxin Induced Intestinal Vasoconstriction

The Effects of Proximal Arterial Stenosis and Glucagon Administration

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SUMMARY

Previous studies have shown that intravenous cardiac glycosides produce mesenteric vasoconstriction (MVC). The possibility that this might critically compromise blood flow in patients with mesenteric vascular disease was suggested. To evaluate whether MVC occurs with intravenous cardiac glycosides in the presence of proximal mesenteric artery stenosis, blood flow in the superior mesenteric artery (SMA) of thirteen dogs was measured with a Doppler flowmeter. The SMA was constricted and pressures were measured in the aorta, SMA, and superior mesenteric vein. Superior mesenteric vascular resistance (SMVR) was calculated by dividing the pressure difference between the SMA and superior mesenteric vein by the total blood flow to the superior mesenteric vasculature and was reported as mm Hg/cc-min. Blood flow was measured simultaneously by a drop rate meter in the vein of a surgically isolated intestinal segment supplied by a single arterial arcade. Venous outflow pressure from this segment was also monitored, which allowed calculation of isolated gut segment resistance (IGSR) in mm Hg/cc-min per 100 g gut. Stenosis of the SMA produced pressure gradients of 10 to 75 mm Hg and decreased resting blood flow by as much as 82%. Digoxin produced an increase in both SMVR and IGSR throughout the 30 to 120 minute period of the study in thirteen dogs despite the presence of severe grades of SMA stenosis. There was no relationship between the degree of proximal SMA stenosis and the magnitude of resistance change due to digoxin. To determine if this MVC was reversible, glucagon was administered to eleven dogs 30 to 60 minutes after digoxin and completely overcame the constriction. Thus, digoxin produced MVC in the presence of proximal SMA stenosis. This MVC was pharmacologically reversible. These data suggest that intravenous digoxin might contribute to intestinal ischemia in patients with preexisting vascular disease.

Additional Indexing Words:
Nonocclusive mesenteric infarction
Mesenteric vascular resistance

THE ADMINISTRATION of cardiac glycosides results in mesenteric vasoconstriction in dogs,1-3 monkeys4-7 and humans.4-7 Digitalis also produces contraction of vascular smooth muscle in vitro8 and in vivo.9 It has been suggested that this phenomenon may be important in the pathogenesis of intestinal ischemia and hemorrhagic infarction in patients with preexisting mesenteric vascular disease, especially since the majority of patients suffering from non-
occlusive mesenteric infarction are elderly patients receiving digitalis.10,11

However, there are no data on the effect of digitalis in the presence of a preexisting compromised vascular supply in which the normal autoregulatory mechanisms might produce, in some cases, a state of decreased vascular tone or relative vasodilation. Several investigators have demonstrated autoregulatory mechanisms in the splanchnic vasculature.12-16 Mesenteric vasoconstriction produced by other drugs, such as norepinephrine, has been shown to be partially overcome by a phenomenon which is termed autoregulatory escape.17 The possibility exists, therefore, that decreased blood flow and perfusion pressure, and the associated autoregulatory decrease in vascular tone, might, in some manner, moderate the mesenteric vasoconstriction associated with digitalis administration.

Another possibly useful moderating influence on digitalis-induced mesenteric vasoconstriction may be other pharmacologic agents. Because the mesenteric
vasoconstriction produced by digitalis may be harmful in some patients, a pharmacologic agent with the ability to overcome this increase in vascular resistance may have some clinical utility. Glucagon, a drug which has a positive inotropic effect on the heart which is additive to that of digitalis, also has been shown to produce mesenteric vasodilatation. It is possible, therefore, that glucagon, if used along with digitalis, may add to the desired clinical effect, i.e., the positive inotropic effect on the heart, while moderating the mesenteric vascular effect of cardiac glycosides. This study was designed to determine whether mesenteric vasoconstriction occurs after digoxin administration in the presence of a severe stenosis of the proximal superior mesenteric artery, whether the presence or absence of autoregulation modifies this response, and whether glucagon can alter or overcome mesenteric vasoconstriction.

Methods

Mongrel dogs weighing 18–30 kg were anesthetized with pentobarbital (50 mg/kg). Orotracheal intubation was performed and respiration was controlled with a Harvard respirator. Heparin (1 mg/kg) was administered. All pressures were monitored with Statham P23Dd pressure transducers. A midline abdominal incision was made. A femoral artery and vein were cannulated and the tip of the arterial catheter was placed in the abdominal aorta at the approximate position of the origin of the superior mesenteric artery (SMA) as determined by palpation. This catheter was used to measure aortic pressure. The proximal SMA was isolated and a Doppler flowmeter probe was placed around it. A variable snare constrictor was placed around the SMA just distal to the flowmeter probe and care was taken not to include any arterial branches between the constrictor and the flowmeter probe. A proximal branch of the SMA and its accompanying vein were cannulated for pressure monitoring.

One segment of the ileum or jejunum, supplied from the SMA by a single arterial arcade, was surgically isolated and its venous outflow was directed through a drop rate meter similar to one previously described. Pressure in this venous outflow line was monitored. All data were recorded continuously on a Brush Model 200 eight-channel recorder.

The snare around the SMA was tightened to produce a pressure gradient between the aorta and the distal SMA. It was adjusted to produce a low (<25 mm Hg), moderate (25–50 mm Hg), or high (>50 mm Hg) pressure gradient. After 10 min of stabilization the snare was fixed in place for the duration of the experiment.

Thus, as illustrated in figure 1, we were able to determine two separate indices of mesenteric vascular tone, the superior mesenteric vascular resistance (SMVR), and the isolated gut segment vascular resistance (IGSR).

The SMVR was calculated as the pressure drop across the superior mesenteric vascular bed divided by the blood flow to the superior mesenteric vascular bed and reported in resistance units (RU = mm Hg/cc-min). The pressure drop for this calculation was obtained by subtracting the observed superior mesenteric venous pressure from the observed pressure in the SMA distal to the snare. The blood flow through the mesenteric vasculature was obtained by subtracting the flow through the isolated gut segment from the flow measured by the Doppler flowmeter on the SMA. SMVR = (SMA — SMVP) (QSMA — QIGS)².²¹

The IGSR was calculated as the pressure drop across the isolated gut segment divided by the flow through the isolated gut segment adjusted to flow per 100 g of gut. The pressure for this calculation was obtained by subtracting the pressure measured in the isolated gut segment venous outflow line from the pressure measured in the SMA distal to the snare. The gut segment was weighed immediately at the end of each experiment and the flow for the IGSR was calculated by multiplying the flow measured in the drop rate meter by 100 g divided by the wet weight of the gut segment. This was reported in resistance units (RU = mm Hg/cc-min per 100 g gut). IGSR = (SMA — IGVP) (QIGS X gut weight)² X 100.

These two resistance calculations involved two different flow measurements (Doppler flowmeter and drop rate meter) and two different venous pressure measurements (superior mesenteric venous pressure and isolated gut segment venous outflow pressure). The superior mesenteric venous pressure was allowed to vary throughout the experiment while the isolated gut segment venous pressure was closely fixed by the height of the opening of the venous outflow line relative to the systemic veins.

The observation of two independent indices of mesenteric vascular resistance decreased the possibility that a change

Figure 1

Graphic representation of the experimental preparation. The abdominal aorta and portal vein are pictured along with a representation of the small intestines. One segment of the intestine is isolated and blood flow and venous pressure are measured (isolated gut segment). Total blood flow to the intestine supplied by the superior mesenteric artery is measured by a Doppler flowmeter probe. Mesenteric arterial pressure distal to the snare, aortic pressure, and superior mesenteric venous pressure are also measured.
observed in vascular tone or blood flow could be due to experimental technique. Also, since changes in portal or superior mesenteric venous tone and pressure can have a marked effect on the mesenteric arterial resistance, this could be part of the mechanism by which digitalis affects mesenteric vascular resistance. By measuring vascular resistance with two methods, in one of which the venous pressure is held constant (IGSR), while in the other venous pressure is allowed to vary (SMVR), this possible contribution to the alteration of mesenteric vascular resistance could be evaluated.

After stabilization of all parameters (10–30 min) digoxin (0.01 mg/kg) was injected intravenously in a bolus. Resistances were calculated every five minutes. In eleven dogs glucagon (1 mg intramuscularly) was injected 30–60 min after the administration of digoxin and measurements were continued for 30 min more. In two control dogs without constriction in the proximal SMA, intravenous digoxin was administered and measurements were continued for two hours; no glucagon was given to these animals. Two additional animals, prepared in the same way, with high grade stenoses in proximal SMA, were given a lower dose (0.005 mg/kg) of digoxin after data were observed for one hour. This one hour period of observation of data allowed determination of the effects of proximal arterial constriction alone on mesenteric vascular resistance. Calibration of the drop rate meter was done by timed collection into a graduated cylinder at various intervals throughout each experiment. Calibration of the Doppler flowmeter was performed at the termination of each experiment in situ on the SMA, again, by timed collection of SMA flow into a graduate cylinder. Lead II of the electrocardiogram was monitored continuously in each experiment.

All data are reported as the mean ± 1 SEM. Correlation coefficients were computed in order to detect, if possible, relations between the gradient produced by the snare on the SMA and changes in either SMVR or IGSR. Paired t-tests were used to determine the significance of differences, compared to their control values, in the resistance values observed after pharmacologic interventions.

Results

Mesenteric Vascular Resistance

Control SMVR varied from 0.30 to 2.3 RU (mean = 0.83 ± 0.10 RU). As can be seen in figures 2 and 3, digoxin produced a significant rise in vascular resistance (P < 0.01) to a mean of 1.10 ± 0.12 RU. In individual experiments an increase in resistance occurred in all but one dog. Control IGSR varied from 3.4 to 17.3 RU (mean = 7.2 ± 1.3 RU). Digoxin produced an increased resistance in all isolated gut segments to a mean of 10.2 ± 0.7 RU. We were unable to demonstrate a significant correlation between the magnitude of the proximal SMA gradient and the magnitude of the resistance changes (IGSR: r = −0.16; SMVR: r = −0.39; N = 11).

As can be seen in table 1, the autoregulatory response of the mesenteric vascular beds to SMA constriction proved to be quite variable among the dogs and even within the same animal. In four experiments SMVR decreased after constriction of the SMA. In the other seven experiments SMVR increased following constriction of the SMA. In the isolated gut segments four preparations exhibited vasodilatation following constriction of the SMA and seven preparations ex-

![Figure 2](attachment://image.png)

The response of vascular resistance in individual experiments to digoxin and glucagon administration. Each line represents an individual experiment; solid lines represent calculated superior mesenteric vascular resistance (SMVR) and dashed lines represent isolated gut segment resistance (IGSR). The low gradient experiments are shown on top of the figure, the moderate gradient experiments in the middle, and the high gradient experiments on the bottom. Control values were calculated after stabilization following superior mesenteric artery stenosis. All values are represented as the percent of this control. Resistances calculated 30 min after digoxin administration are shown on the center vertical line and those calculated 15–30 min after glucagon administration are shown on the far right vertical line. Digoxin produced significant vasoconstriction in each group (P < 0.01, t-test) and glucagon produced significant vasodilatation (P < 0.01, t-test). No significant differences were found between the two groups.
DIGOXIN AND GUT VASOCONSTRICTION

hibited vasoconstriction. There was only one experiment (no. 11), however, in which both IGSR and SMVR decreased after SMA constriction. In four experiments both resistance measurements increased following SMA constriction, and in six experiments the two measurements of vascular resistance moved in opposite directions with SMA constriction. In the experiments done with a low SMA gradient, one of the six observations demonstrated vasodilatation following SMA constriction; in the moderate gradient three of eight observations showed vasodilatation; and in the high gradient experiments four of eight observations showed vasodilatation following SMA constriction. However, as demonstrated in figure 4, digoxin produced vasoconstriction of similar magnitudes in all preparations regardless of the vascular response to SMA constriction.

Mesenteric Blood Flow

Constriction of the SMA with a snare produced a decrease in blood flow both in the SMA and in the IGS in all animals. The magnitude of this change was related to the gradient produced by the snare (r = 0.65). Mean SMA flow prior to constriction was 209 ± 29 cc/min and decreased to 143 ± 26 cc/min. Mean SMA flow in the low gradient (< 25 mm Hg) experiments fell 23 ± 6.8% (N = 3) following constriction of the SMA; in the moderate gradient (25–50 mm Hg) experiments SMA flow fell 13 ± 6.9% (N = 4); and in the high gradient (>50 mm Hg) experiments SMA flow fell 53 ± 11% (N = 4). Mean IGS flow prior to constriction was 18.4 ± 2.6 cc/min and decreased to 12.7 ± 1.8 with SMA constriction. Mean IGS flow in the low gradient preparations fell 11.7 ± 1.9% (N = 3); in the moderate gradient dogs IGS flow fell 18.7 ± 5.4% (N = 4); and in the high gradient experiments IGS flow fell 49.0 ± 3.9% (N = 4) following constriction of the SMA.

The administration of digitalis was followed by a further decrease in both flows in all dogs (fig. 5) except one in which mean blood pressure rose throughout the experiment from 115 mm Hg to 145 mm Hg. Vascular resistances rose in this animal after digoxin in both SMVR and IGSR. Mean blood pressures in all other experiments remained relatively stable.

![Figure 3](image-url)

The response of vascular resistance (mean ± SEM), to digoxin and glucagon administration. Superior mesenteric vascular resistance (SMVR) is shown on the left half of the figure and isolated gut segment resistance (IGSR) is shown on the right half. The units shown are resistance units as described in the text. The differences between control and digoxin values and between digoxin and glucagon values in both resistance calculations are significant (P< .01, t-test). The differences between control and glucagon values are not significant. Control calculations were made after superior mesenteric artery stenosis, digoxin calculations were made 30 min after digoxin administration, and glucagon calculations were made 15–30 min after glucagon administration.

![Figure 4](image-url)

The response of vascular resistance to digoxin administration in those preparations exhibiting autoregulation with superior mesenteric artery constriction compared to those preparations which did not exhibit autoregulation. The isolated gut segment resistance (IGSR) is shown on the left of the figure and the superior mesenteric vascular resistance (SMVR) is shown on the right. Resistance is represented as the percent increase above control and was calculated 30 min after digoxin administration. No significant differences were found between nonautoregulating vasculature and autoregulating vasculature in either resistance calculation.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Low gradients (25 mm Hg)</th>
<th>Moderate gradients (25–50 mm Hg)</th>
<th>High gradients (50 mm Hg)</th>
</tr>
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<tr>
<td></td>
<td>1  2  3</td>
<td>4  5  6  7</td>
<td>8  9  10  11</td>
</tr>
<tr>
<td>SMVR</td>
<td>+  +  +  +  +  +</td>
<td>+  +  +  +  +  +  +</td>
<td>+  +  +  +  +  +  +  +</td>
</tr>
<tr>
<td>IGSR</td>
<td>+  +  -  +  +  +</td>
<td>+  +  -  +  +  +  +</td>
<td>+  +  -  +  +  +  +  +</td>
</tr>
</tbody>
</table>

+ = vasoconstriction following SMA constriction.
- = vasodilatation following SMA constriction.
The response of mesenteric blood flow to superior mesenteric artery constriction and pharmacologic intervention. The flow in the main superior mesenteric artery (SMA) is shown on the left and the flow in the isolated gut segment is shown on the right. The control bars represent flow measured before any interventions were performed; the constrict bars represent flow measured after constriction of the superior mesenteric artery; the after digoxin bars represent flow measured 30 min after digoxin administration; and the after glucagon bars represent flow measurements made 15-30 min after glucagon administration. Each intervention shown produced a significant change in flow (P < 0.01, t-test) from the preceding state in both SMA and IGS flow. No significant differences were found between the corresponding constrict and after glucagon measurements.

Glucagon Administration

Glucagon administration 30-60 min after digoxin injection was followed in 10-15 min by a significant decrease (P < 0.01) in both SMVR and IGSR in all animals (figs. 2 and 3). Following glucagon injection flow in the SMA increased in all animals (P < 0.05) and flow in the IGS increased in eight of the eleven animals (P < 0.05) as seen in figure 5. The mean values of both flow measurements and of both resistance calculations following glucagon administration were similar to the values found before injection of digoxin. Glucagon administration, as could be expected, produced a transient fall in systemic arterial pressure lasting 10-15 min in eight of the eleven dogs. This change was not statistically significant.

There were no changes in systemic arterial pressure attributable to digoxin injection. The EKG revealed no changes in rate or rhythm with digoxin administration. There were no consistent changes in the superior mesenteric venous pressure with digoxin or glucagon administration. In two additional dogs in which glucagon was not given and SMA constriction was not produced, digoxin resulted in an increase in both IGSR and SMVR which persisted for at least two hours. Finally, in two dogs in which high gradient stenoses were produced, resistances were observed for a period of one hour and, following this, a lower dose of digoxin (0.005 mg/kg) was given. Neither SMVR nor IGSR changed significantly during the one hour observation period prior to digoxin administration.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Constrict</th>
<th>30 min after digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMVR*</td>
<td>0.59</td>
<td>0.66</td>
<td>0.80</td>
</tr>
<tr>
<td>IGSR†</td>
<td>20.8</td>
<td>19.1</td>
<td>29.2</td>
</tr>
<tr>
<td>SMVR*</td>
<td>0.98</td>
<td>0.76</td>
<td>0.83</td>
</tr>
<tr>
<td>IGSR†</td>
<td>10.7</td>
<td>12.2</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*mm Hg/cc-min
†mm Hg/cc-min/100 g gut

However, following digoxin administration, resistances increased (table 2) and blood flows decreased, both in vascular beds in which autoregulation occurred and in those in which autoregulation was not seen.

Discussion

Digitalis administration has been shown to produce vasoconstriction in the mesenteric vasculature in dogs, monkeys, normal humans and humans in left ventricular failure. This arteriolar constriction has been suggested to be a possible contributing factor in the production of nonocclusive intestinal infarction, especially in the presence of other conditions, such as shock or mesenteric atherosclerosis, which might decrease splanchnic blood flow. This study demonstrates that mesenteric vasoconstriction and decreased mesenteric blood flow occur following intravenous digoxin administration in dogs in which a significant proximal mesenteric arterial obstruction and a significant decrease in mesenteric blood flow were present prior to digitalis administration. Thus, the administration of digitalis glycosides can cause splanchnic vasoconstriction and further decrease blood flow in dogs under conditions which might be expected to be associated with an already compromised mesenteric vasculature. Similar conclusions have been reported in studies of endotoxic and hemorrhagic shock in dogs.

Autoregulation in the mesenteric vasculature is a complex phenomenon. In some experimental conditions the mesenteric vasculature has reacted completely passively to changes in perfusion pressure and demonstrated no autoregulatory changes in vascular resistance at all. Johnson studied the dog intestinal vasculature and found autoregulation to be present in 75% of his preparations and absent in 25%. In those preparations which exhibited autoregulation, a reduction in arterial pressure was usually accompanied by a decrease in flow, and only modest autoregulation (a slight decrease in vascular resistance) was observed. In the 25% of the preparations which did not exhibit autoregulation an increase in resistance was noted with decreasing perfusion pressure. The presence of
vasodilatation in eight of 22 (36.4%) observations in our experimental series following SMA constriction is consistent with Johnson’s findings on autoregulation of the intestine, considering that the decrease in mesenteric arterial pressure, and hence, stimulus to autoregulation was less in our experiments. In our study, autoregulation was demonstrated in more of the experiments in the group with high initial SMA gradients (50%) than in the group with low gradients (17%). The intestine is a complex organ with vascular components supplying secretory, muscular, mucosal and supportive tissues each with its own individual metabolic and circulatory requirements. As a result, the net circulatory response to hemodynamic alterations in the vasculature supplying these different tissues is very complex. We have no explanation for the observation that in six experiments autoregulation was observed in only one of the two vascular beds being studied simultaneously (SMVR or IGSR) (table 1). This study demonstrated that vasoconstriction produced by digoxin administration was the same in preparations that exhibited autoregulation and in preparations that did not demonstrate autoregulation.

The effects of intravenous cardiac glycosides on the portal or mesenteric venous systems were not directly measured in these experiments. However, the design of these experiments allows a determination of any contribution of this venous system to changes in vascular resistance or blood flow. Two parallel circulations were studied, in one of which the portal mesenteric venous system was intact (total superior mesenteric vasculature), while in the other (isolated gut segment) this system was excluded from the circulation. Since both circulations responded in a similar manner and with a similar magnitude of response to all interventions, we can conclude that any changes in the portal venous system which may have occurred did not contribute to our experimental results.

Delayed mesenteric vasoconstriction has been reported to occur in the canine intestinal vasculature following SMA constriction alone. This was shown to begin 30 to 300 min after stabilization following partial occlusion of the SMA. Since in our study digoxin was injected immediately following stabilization of pressures and flow after SMA constriction, and maximal mesenteric vasoconstriction occurred in all cases within 15 min, the delayed vasoconstriction described could not have produced our results following digoxin injection. This phenomenon may, however, have contributed to mesenteric vasoconstriction in the later stages of our experiments and may contribute to the clinical entity of nonocclusive mesenteric infarction. It is of interest, therefore, that glucagon, administered at a time when this phenomenon could conceivably have been operative, was able to overcome the vasoconstriction in all instances.

The specific cardiac glycoside and dose chosen for these experiments were used for several reasons. Digoxin was chosen because it is a very commonly used digitalis glycoside for rapid digitalization. The dose of digoxin used (0.01 mg/kg) was chosen for its similarity (per kg body weight) to commonly used clinical schedules for rapid intravenous digitalization. This dose is significantly less than the dose used in previous experiments demonstrating digitalis-induced mesenteric vasoconstriction.

These experiments were done on anesthetized dogs with an open abdominal incision. There is evidence that mesenteric vasoconstriction following digitalis administration in awake, alert, chronically instrumented dogs may produce splanchnic vasoconstriction of shorter duration and lesser magnitude than that produced in the anesthetized animal. However, in awake unanesthetized humans, with or without left ventricular failure, the pattern of mesenteric vascular response to the intravenous administration of cardiac glycosides has been shown to be similar to that described in these experiments. This would suggest that patients may respond to intravenous digitals with significant mesenteric vasoconstriction. Thus, in clinical situations such as shock or atherosclerotic obstructive disease of the proximal splanchnic vasculature, intravenous digitals may contribute to further reduction of the mesenteric blood supply.

Glucagon, a drug which is known to reduce mesenteric vascular resistance, has been shown in this study to overcome completely the effects of digitals on the intestinal vasculature and to return mesenteric vascular resistance and blood flow approximately to control values. Whether this pharmacologic reversal of digitals-induced mesenteric vasoconstriction has clinical use or effectiveness remains to be seen. However, glucagon, which has a known positive inotropic effect on the heart and has been shown to be useful in conjunction with digitals in some clinical situations, might, in the presence of possible mesenteric vascular insufficiency, protect against further mesenteric ischemia when used together with intravenous digitals.

In conclusion, these experiments demonstrate that intravenous digoxin produces sustained mesenteric vasoconstriction and decreased blood flow in the mesenteric vasculature in the presence of severe stenosis of the proximal arterial supply to the intestine. This vasoconstriction is similar in magnitude whether mesenteric vascular autoregulation was present or absent. Glucagon, a drug with positive inotropic effects on the heart, is able to overcome digoxin-induced mesenteric vasoconstriction and in-

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crease mesenteric blood flow in the presence of severe stenosis of the proximal arterial supply to the intestine.

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References
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