JOURNAL OF SURGICAL RESEARCH 14, 133–138 (1973)

Experimental Intestinal Ischemia: Provocative Absorption Studies Following Gradual Celiac and Superior Mesenteric Artery Occlusion

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OBJECTIVE DOCUMENTATION of chronic intestinal ischemia usually proves an elusive, if not impossible, task. Despite the increasing frequency of arteriographic demonstrations of splanchnic arterial occlusive lesions these studies have not provided means of defining the functional adequacy or inadequacy of intestinal blood flow. This investigation attempted to establish criteria relating intestinal function to alterations in blood flow.

Manifest by abdominal angina, chronic intestinal ischemia is most often the result of arteriosclerotic occlusion of the proximal celiac, superior or inferior mesenteric arteries. Involvement of at least two of these three vessels is usually prerequisite to development of this disorder. One vessel occlusion is rarely associated with chronic symptomatic intestinal ischemia. If the discomfort of abdominal angina is the result of ischemia, then decreased intestinal blood flow at that particular time, which is usually during the postprandial period, should be demonstrable. Such a presumption was the basis for *d*-xylose absorption studies following provocative feedings in experimental animals with chronic celiac and superior mesenteric artery occlusions.

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Supported in part by U.S. Public Health Service Training Grant NIH-GM-00970, and the Hester Spencer Doan Fund.

Presented at the Sixth Annual Meeting of the Association for Academic Surgery. Nov. 2, 1972. New Orleans, LA.

Submitted for publication Nov., 1972

METHODS

Healthy adult dogs of both sexes weighing 17 to 25 kg with arteriographic confirmation of a normal splanchnic arterial circulation were studied. Gastrointestinal or renal disease which might have influenced absorption studies was not encountered. All animals were maintained on a standard dry meal diet and water throughout the investigation.

Five hour base line absorption studies with ingestion of 500 mg/kg of *d*-xylose were undertaken after fasting the dog overnight. *d*-Xylose dissolved in distilled water, 1 g/20 ml, was administered through lavage feeding tubes. Hourly blood levels of this pentose were determined by photometric quantitation of a *d*-xylose-*o*-toluidine complex at a wave length of 475 nm. Tests were performed both with and without a 100 g provocative meal of raw, lean beef cubes given 1 hr after ingestion of the d-xylose. Baseline and provocative studies were carried out on successive days.

Ameroid constrictors consisting of hygroscopic casein resin plastic cylinders were used to produce gradual vascular occlusions. The core of the constrictor, 6.0 mm in

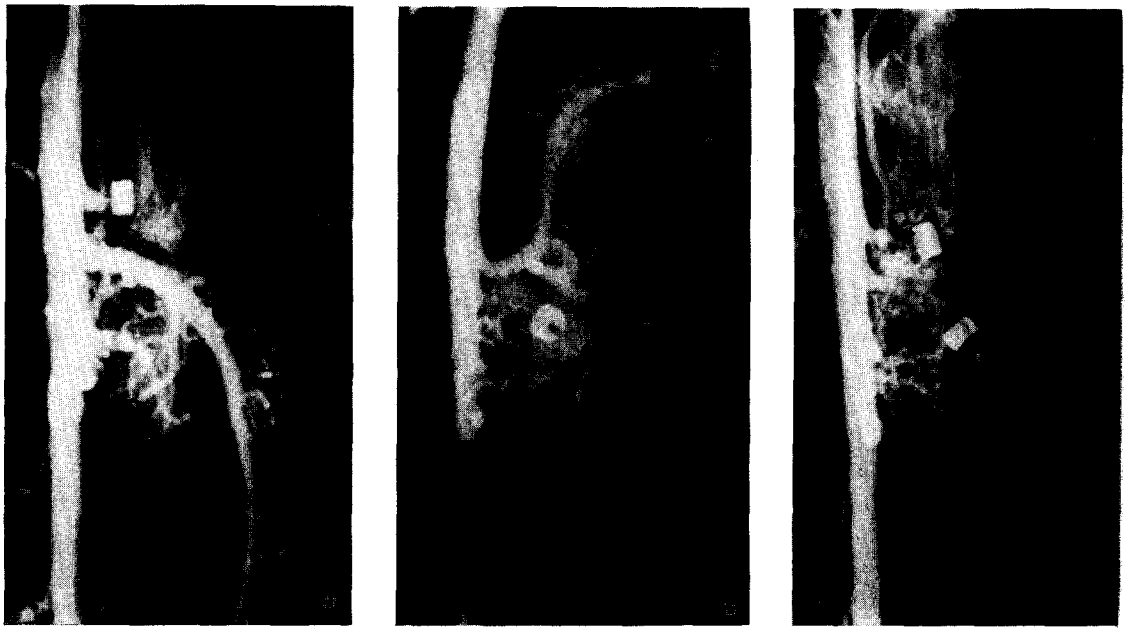

Fig. 1. Arteriographic appearance of splanchnic arteries 1 mo after application of constrictors revealing total occlusion of the celiac artery (a), superior mesenteric artery (b), and both celiac and superior mesenteric arteries (c).

height with an 8.0 mm o.d. and 3.0 mm i.d., was encased by a stainless steel sleeve. These devices were gas sterilized with ethylene chloride. Placement about the proximal celiac and superior mesenteric arteries entailed judicious dissection of the vessels for a short distance, avoiding excessive disturbance of splanchnic neural tissue or the artery's proximal branches. An extraperitoneal approach to the celiac artery through the posterior flank and a transperitoneal exposure of the superior mesenteric artery through an anterior abdominal incision were utilized. Serial arteriograms revealed gradual obliteration of the vessels over a 12 to 18 day period. One month after constrictor application documentation of complete occlusion was obtained by lateral aortography, using a retrograde femoral route (Fig. 1).

A second series of *d*-xylose absorption studies 2 mo postoperative were obtained, again with and without provocative meat meals. Three groups of dogs were investigated, of which one has been previously reported [9]. Ten dogs had celiac artery occlusion (Group I); five dogs underwent superior mesenteric artery occlusion (Group II); and five additional dogs had both celiac and superior mesenteric artery occlusion (Group III).

RESULTS

Comparison of the blood *d*-xylose levels in each group before and after arterial occlusion was undertaken (Tables 1, 2 and 3). Differences in results were subjected to analysis of variance using each dog as his own control.

No evidence existed of *statistically significant* *d*-xylose absorption enhancement or impairment following provocative feedings in any of the control animals prior to initiating gradual arterial occlusions. (I_{cx}:I_{cp}, II_{cx}:II_{cp}, III_{cx}:III_{cp}). Provocative meals did not, therefore, appear to affect *d*-xylose absorption in the presence of an intact splanchnic circulation.

Group I (Table 1). Celiac artery occlusion did not alter absorption when *d*-xylose was administered alone without the meat meal (I_{cx}:I_x). Routine *d*-xylose absorption tests are thus of no use in documenting celiac artery obstruction.

Table 1. Mean Blood d-xylose Levels (mg/100 ml) with Provocative Absorption Studies Prior to and Following Gradual Celiac Artery Occlusion (Group I)

Time (hr)	Control subjects				Ischemic subjects			
	I_{cx} (*d*-xylose)	I_{cp} (*d*-xylose meat meal)	$\Delta I_{cx}:I_{cp}$[a]	*P*	I_x (*d*-xylose)	I_p (*d*-xylose meat meal)	$\Delta I_x:I_p$[a]	*P*
1	85.6	80.9	−4.7	—	86.0	88.7	+2.7	—
2	76.1	80.3	+4.2	ns	67.1	59.4	−7.7	<0.01
3	43.5	40.6	−2.9	ns	37.4	27.8	−9.6	<0.05
4	25.4	23.1	−2.3	ns	21.3	13.1	−8.2	<0.01
5	15.3	12.2	−3.1	ns	13.0	6.2	−5.8	<0.01

[a] Differences subjected to analysis of variance: ns = not significant ($P > 0.1$).

Table 2. Mean Blood d-xylose Levels (mg/100 ml) with Provocative Absorption Studies Prior to and Following Gradual Superior Mesenteric Artery Occlusion (Group II)

Time (hr)	Control subjects				Ischemic subjects			
	II_{cx} (*d*-xylose)	II_{cp} (*d*-xylose meat meal)	$\Delta II_{cx}:II_{cp}$[a]	*P*	II_x (*d*-xylose)	II_p (*d*-xylose meat meal)	$\Delta II_x:II_p$[a]	*P*
1	57.2	58.2	−1.0	—	76.0	69.6	−6.4	—
2	51.4	45.4	−6.0	ns	47.6	51.8	+4.2	ns
3	29.6	25.2	−4.4	ns	28.4	26.6	−1.8	ns
4	20.8	16.6	−4.2	ns	16.2	15.0	−1.2	ns
5	11.8	9.4	−2.4	ns	9.6	8.2	−1.4	ns

[a] Differences were not significant, ns, ($P > 0.1$).

Effects of the provocative meal became apparent when ingestion of meat resulted in impaired *d*-xylose absorption among ischemic dogs compared to controls ($I_{cp}:I_p$). Mean differences in blood *d*-xylose levels during the postprandial period at 2, 3, 4 and 5 hr were 20.9, 12.8, 10.0, and 6.0 mg/100 ml, respectively. These findings were significant with $0.01 < P < 0.05$ in all instances except at 4 hr where $P < 0.01$. The practical value of these observations remain limited inasmuch as premorbid clinical studies, similar to control experimental studies, would be unavailable.

Provocative feedings most importantly were associated with diminished *d*-xylose absorption when compared to administration of the pentose alone among ischemic dogs ($I_x:I_p$). Mean blood *d*-xylose level decreases encountered at 2, 3, 4 and 5 hr were 7.7, 9.6, 8.2, and 5.8 mg/100 ml, respectively. In each instance $P < 0.01$, except at 3 hr where $0.01 < P < 0.05$. These later observations may be relevant to those clinical situations in which isolated celiac artery stenoses are thought to cause symptomatic intestinal ischemia.

Group II (Table 2). Superior mesenteric artery occlusion did not cause statistically significant alterations of *d*-xylose absorption when comparing control to ischemic animals, both with ($II_{cp}:II_p$) and without ($II_{cx}:II_x$) provocative feedings. Administration of meat meals among the ischemic dogs resulted in a mean blood *d*-xylose increase of 4.2 mg/100 ml at 2 hr and decreases of 1.8, 1.2, and 1.4 mg/100 ml at 3, 4, and 5 hr ($II_x:II_p$). With $P > 0.1$, no statistical significance was accorded these findings. Routine or provocative *d*-xylose absorption studies in the experimental animal with superior mesenteric artery occlusion were of no diagnostic value.

Group III (Table 3). Coexistent celiac and superior mesenteric artery occlusion was not associated with statistically signifi-

Table 3. Mean Blood d-xylose Levels (mg/ml) with Provocative Absorption Studies Prior to and Following Gradual Celiac and Superior Mesenteric Artery Occlusion (Group III)

	Control subjects				Ischemic subjects			
Time (hr)	III_{cx} (*d*-xylose)	III_{cp} (*d*-xylose meat meal)	$\Delta III_{cx}:III_{cp}$[a]	*P*	III_x (*d*-xylose)	III_p (*d*-xylose meat meal)	$\Delta III_x:III_p$[a]	*P*
1	82.2	74.8	−8.0	—	74.4	73.0	−1.4	—
2	84.4	94.0	+9.6	ns	58.2	58.8	+0.6	ns
3	52.0	48.4	−3.6	ns	45.0	34.0	−11.0	ns
4	30.0	28.2	−1.8	ns	28.0	19.4	−8.6	ns
5	18.0	16.4	−1.6	ns	18.2	6.2	−12.0	<0.05

[a] Differences subjected to analysis of variance; ns = not significant ($P > 0.1$).

cant differences in absorption of *d*-xylose when that substance was administered alone ($III_{cx}:III_x$). The rather large difference in mean *d*-xylose levels encountered at 2 hr in these later studies was unexplained.

Provocative feedings after celiac and superior mesenteric artery occlusion resulted in decreased *d*-xylose absorption ($III_{cp}:III_p$). Mean blood *d*-xylose levels in this situation were diminished 35.2, 14.4, 8.8, and 10.2 mg/100 ml at 2, 3, 4 and 5 hr, with $0.01 < P < 0.05$ at 2 and 5 hr and $0.05 < P < 0.1$ at 3 and 4 hr.

Among the ischemic dogs with celiac and superior mesenteric artery occlusion the provocative meat meal caused greater decreases in *d*-xylose absorption, ($III_x:III_p$), than were observed in similar studies following celiac artery occlusion ($I_x:I_p$). Mean blood *d*-xylose levels were decreased 11.0, 8.6, and 12.0 mg/100ml at 3, 4 and 5 hr. However, because of the small number of experimental subjects in the group and inconsistent patterns of absorption, statistical significance was evident only at the last test hour. Analysis of variance in these studies revealed $P > 0.1$ at 3 and 4 hr, and $0.01 < P < 0.05$ at 5 hr.

None of the animals in any group lost weight during the course of the investigation. Overt manifestations of gastrointestinal disease were not observed, and immediate side effects of ingesting the *d*-xylose solution (regurgitation and diarrhea) did not occur.

DISCUSSION

Reliable and simple clinical means of measuring tissue blood flow in the gastrointestinal tract are nonexistent. One might predict studies of intestinal motor function or certain absorption processes to yield *indirect* evidence reflective of altered intestinal blood flow. Earlier experimental studies have supported this concept, yet extrapolations to the clinical setting of chronic intestinal ischemia did not evolve. The present investigation attempted to bridge the gap by: (a) utilization of constricting devices providing gradual progressive arterial occlusions; (b) assessing an apparent flow dependent function (*d*-xylose absorption), and (c) obtaining of base line as well as provocative studies that allowed each animal to act as his own control, and made possible recognition of statistically significant smaller differences in absorption.

d-Xylose, because of its relative metabolic inertness [12], lends itself well to studies of intestinal carbohydrate absorption. Most ingested *d*-xylose is preferentially absorbed in the jejunum [5]. Recently, *d*-xylose absorption has been shown to include an active transport mechanism [1] but passive *d*-xylose transport (diffusion and convection), in contrast to active transport was believed most responsible for absorption with the quantity and manner of *d*-xylose administration in the present study [7].

Intestinal absorption of *d*-xylose has been related to blood flow under certain circumstances [11]. In chronic intestinal ischemia impaired absorption may follow cellular hypoxia with dysfunction of active transport mechanisms or *d*-xylose concentration differences favoring passive absorption may become less as accumulation of the carbohydrate in the bowel wall occurs. Speculation that intestinal blood flow is a potential rate-limiting factor of the absorptive process, and the conclusion that *d*-xylose absorption is proportionate to blood flow, awaits proof of *in vivo* investigations. Until such confirmatory evidence is available this remains an acceptable hypothesis.

Measurement of urinary *d*-xylose, representing a predictable percentage of the amount ingested, is a common test of intestinal absorption. Blood levels of this pentose in dogs have been shown to be linearly related to its renal excretion [2]. Quantitating blood *d*-xylose levels provides an additional means of evaluating its intestinal absorption. Sampling venous blood from indwelling catheters avoided the obvious problems of obtaining timed urine collections in dogs. It is important to note that reliability of results were felt in part due to use of trained dogs who were not disturbed from their resting state as blood specimens were obtained during the 5 hr test periods.

Direct determination of *d*-xylose blood levels involved spectrophotometric quantitation of a *d*-xylose-*o*-toluidine complex [3]. This analysis was considered more specific and technically less cumbersome than the *p*-bromoaniline method [8] that has received wide acceptance in the past.

Pathophysiologic sequellae of chronic splanchnic arterial occlusive disease are poorly understood. A few comments pertinent to interpreting the results of the present investigation warrant consideration.

It has been theorized that a "steal" of blood from the superior mesenteric to celiac arterial bed occurs in the presence of an isolated celiac artery stenosis. In this situation the superior mesenteric arterial inflow is alleged to be inadequate in maintaining peripheral intestinal perfusion because of excessive outflow through collaterals to the celiac circulation during the postprandial period. The assumption that inflow is restricted in this setting presumes existence of a functionally significant stenosis (relative or real) involving the superior mesenteric artery. Facts concerning critical stenoses of splanchnic arteries with concomitant occlusions make this a most improbable event [6].

A second hypothesis has been proposed that relates the potential–kinetic energy changes accompanying abnormally high blood flow velocities within the proximal superior mesenteric artery to diminished pulsatile flow in the distal mesenteric branches [10]. It is believed that redistribution of blood flow within the different regions of bowel wall can occur independent of changes in resistance [4]. Despite normal volume flow in these circumstances the altered perfusion away from mucosal to the submucosal-muscularis region, may account for postprandial impairment of *d*-xylose absorption as observed in this present investigation. That the permissive effect of collaterals on proximal superior mesenteric artery blood flow velocities affects the distal circulation received indirect support from this study. A number of animals undergoing provocative testing during a 4 to 6 wk period following the onset of gradual celiac artery stenoses demonstrated progressively greater reductions in *d*-xylose absorption that corresponded with development of collateral vessels. Although the experimental results are interpreted to represent effects of altered mucosal blood flow, the possibilities of varied intestinal motility with increased transit times or changes in intraluminal concentrations of *d*-xylose with altered enteric secretion rates affecting absorption are not discounted.

Controversy surrounds the clinical entity of chronic intestinal ischemia. This is par-

ticularly true of those cases attributed to isolated celiac artery stenosis [10]. Most skepticism results from the clinical vagaries ascribed to these diseases and an inability to accurately assess the presence of the ischemic state. The authors find agreement with much of the critical concern expressed in regard to chronic intestinal ischemia. However, it is suggested that investigations should be conducted concerning specific functional derangements associated with splanchnic artery occlusions before undertaking elaboration of more theories.

SUMMARY

Intestinal absorption of *d*-xylose was studied during the postprandial period after ingestion of a provocative meat meal in experimental animals with chronic celiac and superior mesenteric artery occlusions. Statistically significant impairment of *d*-xylose absorption occurred in the presence of celiac artery occlusion. In theory this was attributed to the effect of collateral circulation upon blood flow velocity within the superior mesenteric artery and altered perfusion of its distal branches.

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