Factors Other Than Major Vascular Occlusion That Contribute to Intestinal Infarction

PAUL H. JORDAN, JR.,* M.D., DEMETRI BOULAFENDIS, M.D., G. A. GUINN, M.D.

From the Cora and Webb Mading Department of Surgery, Baylor College of Medicine and the Surgical Services of the Veterans Administration, Houston, Texas

A VARIETY of conditions contribute to intestinal ischemia [2, 4, 11] other than occlusion of the mesenteric vasculature. About one fourth of instances of mesenteric infarction are attributable to nonocclusive factors.[12] Low cardiac output or reduced blood volume or both may contribute to the etiological factors resulting in poor tissue perfusion. Tissues develop signs of clinical ischemia in response to those factors depending on 1) inherent sensitivity to anoxia (brain, kidneys, liver, gut and extremities),[3, 10] 2) the presence of infection and 3) the degree of involvement of blood vessels with atherosclerosis. We observed over a period of five years, 16 cases in which some factor other than vascular occlusion was singularly responsible for bowel necrosis or contributed to necrosis by further reduction of blood flow already compromised by vascular disease. Five patients reported in this paper are examples of bowel necrosis that occurred as a consequence of poor tissue perfusion for reasons other than disease of the mesenteric vasculature.

Case Reports

Acute Myocardial Infarction

Case 1. A 67-year-old diabetic had vascular insufficiency of his left lower extremity. His blood pressure was was 130 mm. Hg systolic and 100 mm. Hg diastolic. He had a normal cardiac rate and rhythm and no murmurs. Laboratory studies were as follows: Hemoglobin 14.7 Gm., hematocrit 43%, WBC 13,750 per mm^3, BUN 18 mg., creatinine 1.1 mg. and fasting blood sugar 258 mg. Electrocardiogram showed evidence of an old anterior myocardial infarction. Three days after an uneventful aortogram, the patient complained of pain in the left chest. He had profuse diaphoresis and became cold and cyanotic. Blood pressure fell to 80 mm. Hg systolic and 40 mm. Hg diastolic and pulse rate increased to 120 a minute. An acute anterior myocardial infarction was diagnosed by serial electrocardiography. Hypotension persisted approximately 9 hours. The abdomen then became distended and he vomited coffee-ground material. He complained of lower abdominal pain and tenderness and passed a bloody stool. Following the onset of abdominal symptoms, the laboratory findings were: Hemoglobin 16.5 Gm., hematocrit 48.5% and WBC 27,750 per mm^3. Temperature was 101.8° F. Digitalization and tracheostomy were carried out. Exploratory laparotomy revealed a gangrenous left colon although both superior and inferior mesenteric vessels were patent. A left colectomy and colostomy were done. The patient remained hypotensive and died 18 hours later. Pathologic examination showed atherosclerosis of the mesenteric arteries, but no arterial or venous occlusion. There was an old and recent myocardial infarction with severe coronary artery disease.

Comment. Although this patient had generalized atherosclerosis including the mesenteric vessels, the problem of intestinal viability was primarily related to hypotension associated with acute myocardial infarction and not with the vascular disease or the aortography performed 3 days previously.

Submitted for publication May 20, 1969.

* 1200 Moursund Avenue, Houston, Texas 77025.

Absence of obstruction in the mesenteric arteries and the occurrence of bowel symptoms 9 hours after the onset of hypotension and recognition of an acute myocardial infarction suggest that the gangrenous colon resulted from poor tissue perfusion superimposed on the vascular narrowing of atherosclerosis. This case demonstrates the compensation that can be made for reduction in the cross-sectional area of the vascular supply of the intestine so long as the blood pressure is adequate to provide perfusion above the critical level required to prevent infarction.

Injudicious Use of Diuretics

Case 2. A 52-year-old man had a history for 7 weeks of acute congestive heart failure. For 3 weeks before admission, he was treated with digitalis and diuretics which resulted in a 22-pound weight loss. His blood pressure was 120 mm. Hg systolic and 106 mm. Hg diastolic. Pulse rate was 100 a minute. He had bilateral basilar rales, cardiomegaly with a Grade IV/VI pansystolic murmur and a gallop rhythm. There was venous distension in the neck; the liver was three fingerbreadths below the right costal margin and there was pitting edema of the legs. There was no abdominal tenderness. Chest x-ray showed cardiomegaly and pulmonary congestion.

He was treated intensively with digitalis and diuretics and lost an additional 10 pounds in 3 days. After 2 days of treatment, the hematocrit rose from 47 to 52% and the hemoglobin from 14.5 to 16.5 Gm. The WBC was 14,800 per mm^3. After the third day, the patient complained of lower abdominal pain and tenderness. He had nausea, vomiting and a bloody bowel movement. Blood pressure was 110 mm. Hg systolic and 70 mm. Hg diastolic. Pulse was 120 per minute and temperature was 101° F. He developed abdominal distension and signs of peritonitis. His urine was concentrated and output was low. At this time hematocrit was 58%, hemoglobin 17.5 Gm. and WBC 23,000 per mm^3. At operation, 6 feet of gangrenous small bowel and right colon were resected. The superior and inferior mesenteric arteries were unobstructed. Much of the specimen was frankly gangrenous and large areas of hemorrhage were present in the remaining portion. Microscopic studies confirmed these findings and also the presence of fresh thrombi throughout mesenteric vessels which were uninvolved with atherosclerosis. The patient died on the twenty-eighth postoperative day.

Comment. At autopsy, cardiac hypertrophy and acute left ventricular myocardial infarction with only minimal atherosclerotic changes of the blood vessels were found. In our opinion, overly vigorous treatment with diuretics and digitalis was suggested by the loss of 23 pounds before hospitalization and 10 pounds in the 3 days after hospitalization. The rise in the hematocrit and hemoglobin prior to abdominal symptoms indicates the degree of hemoconcentration and indirectly of hypovolemia which developed.

In this case, the mesenteric vessels were unobstructed by atherosclerosis and necrosis appeared unrelated to disease of the mesenteric vasculature but rather related to a combination of factors in which congestive heart failure played a prominent role. Vascular stasis in the gut wall resulting from myocardial failure led to thrombus formation of the small vessels. This was greatly facilitated by the hypovolemia and hemoconcentration that developed as a consequence of intensive treatment with diuretics and digitalis. This hypothesis is supported by findings of no disease in the mesenteric vasculature except for recent thrombi and a predominance of hemorrhagic necrosis of the intestinal wall. Similar findings of hemorrhagic infarction and thrombi in the kidneys, liver, brain and lungs where the vessels were uninvolved with atherosclerosis lends further support to this hypothesis.

Hemorrhagic Shock

Case 3. This 73-year-old man was admitted to the hospital in shock with evidence of gastrointestinal bleeding. Six hours prior to admission, he complained of abdominal pain. While in the emergency room, he vomited coffee-ground material and passed blood per rectum. In 1953, a perforated duodenal ulcer was closed. He was sweating profusely and his breathing was labored. Blood pressure was 68 mm. Hg systolic and 40 mm. Hg diastolic. Pulse was 108 per minute and irregular.

The abdomen was rigid with generalized guarding and absent bowel sounds. His rectum was filled with blood clots. Laboratory examination revealed hemoglobin 13.3 Gm., hematocrit 40% and WBC 20,300 per mm^3. with a shift to the left.

Abdominal exploration disclosed gangrene of the entire colon although the superior and inferior mesenteric arteries were not obstructed. Total colectomy, except for the rectum, and ileostomy were performed. Two weeks later, the patient again bled from the gastrointestinal tract. A large posterior penetrating duodenal ulcer, which had been overlooked at the first operation, was found. Vagotomy, oversew of the ulcer bed and pyloroplasty were performed. The patient died 48 days after the first operation as a consequence of infection.

Examination of the gangrenous colon revealed patency of the mesenteric vessels even though they were narrowed by atherosclerosis. Autopsy confirmed the patency of the major mesenteric vessels which were involved with some atherosclerosis.

Comment. In retrospect, this elderly patient was in shock as a result of a bleeding duodenal ulcer when admitted to the hospital. The history and rectal bleeding suggested the diagnosis of necrotic bowel which he had. Being impressed by the obvious lesion and the urgency of the occasion, a large posterior duodenal ulcer, which subsequently rebled, was overlooked at the first operation. The history of a perforated duodenal ulcer and the magnitude of the gastrointestinal bleeding on this occasion should have forewarned the surgeon that a source of bleeding other than necrotic bowel was possible.

As a result of atherosclerosis, the circulation of the colon prior to bleeding was probably decreased. With massive bleeding from the duodenal ulcer, one must assume that necrosis occurred because perfusion of the colon, already reduced, fell below the critical level for viability.

Congestive Heart Failure

Case 4. A 53-year-old man had severe congestive heart failure. When symptoms began 3 years before, coronary angiograms were normal and the diagnosis was cardiomyopathy. Symptoms were progressive but became worse 2 weeks before admission. He was moderately dyspneic, edematous, cold and cyanotic on admission. Pulse was 120 per minute and blood pressure was 94 mm. Hg systolic and 70 mm. Hg diastolic. He had a gallop rhythm and hepatomegaly.

On the following day, the patient became acutely ill with abdominal pain, tenderness and rigidity and jaundice. Blood pressure was 68 mm. Hg systolic and 44 mm. Hg diastolic, pulse was 140 per minute and temperature was 102° F.

At operation, a large portion of gangrenous small bowel was resected and an anastomosis between proximal jejunum and distal ileum performed. The arteries were involved with atherosclerosis but no thrombi were seen. The patient developed anuria and died 72 hours after operation. Autopsy revealed focal areas of edema and hemorrhagic infarction of colon and small bowel. The serosa and muscular layers were intact. Only slight atheromatous changes were seen in the major branches of the aorta. The heart was markedly dilated and there was extensive endocardial fibrosis.

Comment. When this patient entered the hospital with symptoms of severe congestive heart failure, he had no abdominal complaints. He had hypotension and tachycardia which most likely resulted in low cardiac output and poor tissue perfusion. Vascular stasis associated with heart failure compounded by compensatory vasoconstriction and/or the presence of atheromatous disease may have sufficiently reduced mesenteric blood flow to cause gangrenous bowel and ultimately death.

Hemoconcentration of Uncertain Origin

Case 5. A 74-year-old man with a complete heart block for 10 years had orthopnea and dyspnea at rest. His pulse was 28 per minute and irregular. Blood pressure was 160 mm. Hg systolic and 80 mm. Hg diastolic. The patient was taking Isuprel and Esidrex until the time of operation. His pulse rose to 72 per minute and blood pressure fell to 120 mm. Hg systolic and 80 mm. Hg diastolic at the time of implantation of a pacemaker. After operation, but on the same day, blood pressure averaged 150 mm. Hg systolic and 100 mm. Hg diastolic; pulse ranged between 72 and 84 per minute; temperature rose to 101.8° F.; the hematocrit was 57% and the hemoglobin was 19 Gm.

The patient had a septic course for 4 days. At operation, a gangrenous transverse colon, descend-

ing colon and 4 feet of mid-jejunum were resected. Jejuno-jejunostomy and right colostomy were performed.

The operative specimen was remarkable for the vascular congestion which involved all layers of the small and large bowel. There were focal areas of hemorrhage on the serosal and mucosal surfaces but no ulcerations. The mesenteric vessels were congested but none were obstructed with thrombus. The microscopic findings were those of hemorrhage, edema and acute inflammation through all layers of the intestinal wall. There were areas of hemorrhage and necrosis in the mucosa interspersed with focal areas of normal mucosa. There was vascular congestion in the mesentery but no evidence of vascular thrombosis.

The patient continued with a septic course. He developed high renal output failure and died 12 days postoperatively. Autopsy showed cardiac hypertrophy and diffuse myocardial fibrosis. There was diffuse atherosclerosis of moderate degree but no major vascular occlusion.

Comment. The explanation for bowel necrosis in this patient is less obvious than in the other patients. He did not have severe atherosclerosis and no major branch of the aorta was obstructed. The important observation was the extensive vascular congestion of the small and large intestine and their mesenteries. It seems likely that this was related to the severe hemoconcentration which was noted after insertion of the pacemaker. This might best explain the vascular congestion and the patchy distribution of necrosis rather than the presence of necrosis confined to a major vascular trunk. The reason for the hemoconcentration is unclear for no diuresis occurred with improvement in cardiac function. It is more likely that the patient had developed hemoconcentration preoperatively as a result of diuretic therapy. This cannot be ascertained with certainty for hematocrit and hemoglobin determinations were not obtained preoperatively.

Discussion

A variety of clinical conditions other than vascular occlusion contribute to bowel infarction. The pathophysiology of mesenteric ischemia that results from these factors has not been clearly established. Hemorrhagic shock and other conditions associated with low cardiac output, namely, arrhythmias, aortic stenosis, aortic insufficiency, acute myocardial infarction, myocardiopathies and congestive heart failure are the nonocclusive factors most frequently associated with bowel infarction. Hypovolemia and hemoconcentration are additional factors emphasized in this paper. In older patients, arteriosclerosis which by itself does not reduce blood flow sufficiently to cause gangrene may contribute to its development when associated with these other factors.

Pemmer and Berheim [16] considered shock as a cause of gastrointestinal ischemia. It has been demonstrated that bleeding dogs to shock levels and permitting them to remain in such a state for 4 to 5 hours results in bowel infarction and death [14] while survival can be insured by extracorporeal perfusion of the superior mesenteric artery. Schweinburg [18] showed that the mortality in shocked dogs was reduced by one half if the dogs were pretreated orally with nonabsorbable antibiotic agents. Fine [5] later showed that the toxic factor in plasma of shocked dogs was an endotoxin and he postulated that prolonged shock through vasoconstriction impairs the endotoxin-detoxifying function of the reticuloendothelial system. Ming [15] studied 75 cases of nonocclusive mesenteric ischemia at autopsy and found that shock had been present in 80 per cent. In 35 of 62 cases, post-mortem blood cultures were positive. It has been suggested that toxins from these organisms exert a vasoconstrictive effect and further contribute to intestinal necrosis produced by shock.[19]

Lillihei [14] described the physiologic response of dogs to ischemic bowel. The survival in dogs after vascular occlusion is shortened if recirculation to the portion of gangrenous bowel is reinstituted. Dissemination of toxic products is less and the animals live longer if circulation is not re-

stored. The reported mortality for "non-occlusive" intestinal infarction is near 100 per cent. This high mortality may result from reperfusion and distribution of toxic material from the dead bowel in response to the treatment of the condition which initially caused the necrosis. How this information can be applied to the preoperative preparation of man, in whom gangrene has resulted from low perfusion, is unknown.

Corday[5] observed angiospasm of the mesenteric arteriols during hypotension, arrhythmias, congestive heart failure and during administration of vasopressors in dogs. He postulated that shunting of blood from the mesenteric circulation to more vital structures, such as brain and myocardium resulted in ischemia of the gastrointestinal tract during periods of hypotension. This supports Fishberg's[6] theory of selective vasoconstriction as a cause of bowel infarction. Since poor tissue perfusion may produce splanchnic vasospasm, the infarction in some of our patients may have been due to the accumulative effect of reduced cardiac output and the resulting vasoconstriction of relatively normal vessels rather than the primary condition being superimposed on reduced blood flow through nonobstructed but nonresponsive arteriosclerotic vessels. Laufman and Method[13] reported that secondary muscular spasm in response to ischemia further reduces effective blood supply to the intestine. Once this vicious cycle is in motion, intestinal bacteria begin to thrive and gangrene with toxemia occurs in the event of low cardiac output for any reason.

Berger and Byrne[1] noted a correlation between intestinal gangrene and congestive heart failure and also pointed out that compensatory splanchnic vasospasm may shunt enough blood from the splanchnic bed to precipitate bowel infarction.

Fogarty and Fletcher[7] were of the opinion that the triad of congestive heart failure, digitalis intoxication and increased red cell mass or increased viscosity often differentiated "non-occlusive" from occlusive mesenteric ischemia. Other factors have been proposed as the cause of "non-occlusive" mesenteric ischemia. The vasoconstrictive effect of digitalis on the splanchnic bed and its toxicity and resulting arrhythmias have been implicated.[8, 17] Hypersensitivity and allergic phenomena have been suggested.[9]

Clinical Aspects

Symptoms vary with the disease responsible for poor perfusion. Abdominal complaints occur secondarily and depend on the degree of mesenteric vascular insufficiency. Transient abdominal angina with nausea, vomiting, diarrhea and abdominal distention lasting from several hours to several weeks may be reversible if recognized early and vigorous treatment of the basic disease initiated. Hematemesis and blood in the stool are common in later stages when gangrenous changes are in progress and signs of peritonitis and shock have occurred.

The gross appearance of the gastrointestinal tract at the operating table is variable. Changes may be so early as to cause uncertainty regarding the vascular status of the bowel. Pathological changes vary from edema to vascular congestion and hemorrhage to necrosis involving the mucosa or entire wall. Ischemic changes frequently do not follow the distribution of a major mesenteric artery. Instead, they may be patchy in distribution involving large areas of the gastrointestinal tract. Other abdominal organs may also present ischemic changes.

Patients prone to develop this condition are those 1) with longstanding congestive heart failure taking digitalis and diuretics, 2) with valvular disease and low cardiac output, 3) with digitalis intoxication and cardiac arrhythmias, 4) who are in shock or who have prolonged hypovolemia or hemoconcentration for reasons as diverse

as myocardial infarction, gastrointestinal bleeding and pancreatitis and 5) with prolonged, postoperative hypotension.

Fully developed, the disease becomes a surgical emergency even though the mortality is nearly 100 per cent. With greater awareness of the mechanisms responsible, we should be more competent in prevention and recognition during the incipient stages when treatment may be more effective.

Summary

A variety of conditions which have in common, low perfusion of splanchnic vessels, can produce "non-occlusive" mesenteric ischemia. Five cases of "non-occlusive" intestinal infarction of diverse etiology which included 1) acute myocardial infarction, 2) injudicious use of diuretics, 3) hemorrhagic shock, 4) congestive heart failure and 5) hemoconcentration of uncertain origin are reported. The factor responsible for ischemia may be superimposed on a state of arteriosclerotic vascular disease in which tissue perfusion of the gut has been reduced to a near critical level. Early clinical recognition and intensive management of these factors is required to prevent the development of "non-occlusive" mesenteric ischemia. Once gangrene has developed, expedient operation with postoperative emphasis on the cardiovascular and hemodynamic status is essential if there is to be improvement in treatment of this universally fatal complication.

References

1. Berger, R. L. and Byrne, J. J.: Intestinal Gangrene Associated with Heart Disease. Surg. Gynec. Obstet., 112:529, 1961.
2. Brawley, R. K., Roberts, W. C. and Morrow, A. G.: Intestinal Infarction Resulting from Non-obstructive Mesenteric Arterial Insufficiency. Arch. Surg., 92:374, 1966.
3. Corday, E., Irving, D. W., Gold, H., Bernstein, H. and Skelton, R. B. T.: Mesenteric Vascular Insufficiency: Intestinal Ischemia Induced by Remote Circulatory Disturbances. Amer. J. Med., 33:365, 1962.
4. Ende, N.: Infarction of the Bowel in Cardiac Failure. New Eng. J. Med., 258:879, 1958.
5. Fine, J., Frank, E. D., Ravin, H. A., Rutenberg, S. H. and Schweinburg, F. B.: The Bacterial Factor in Traumatic Shock. New Eng. J. Med., 260:214, 1959.
6. Fishberg, A. M.: Redistribution of Blood in Heart Failure. J. Clin. Invest., 17:510, 1938.
7. Fogarty, T. J. and Fletcher, W. S.: Genesis of Non-occlusive Mesenteric Ischemia. Amer. J. Surg., 111:130, 1966.
8. Gazes, P. C., Holmes, C. R., Moseley, V. and Pratt-Thomas, H. R.: Acute Hemorrhage and Necrosis of the Intestines Associated with Digitalization. Circulation, 23:358, 1961.
9. Germuth, F. G., Pace, M. G. and Tippett, J. C.: Comparative Histologic and Immunologic Studies in Rabbits of Induced Hypersensitivity of the Serum Sickness Type. II. The Effect of Sensitization to Homologous and Cross-Reactive Antigens on the Rate of Antigen Elimination and the Development of Allergic Lesions. J. Exp. Med., 101:135, 1955.
10. Hardy, J. D. and Fikri, A.: Ischemic Gangrene without Major Organic Vascular Occlusion: An Enlarging Concept. Surgery, 50:107, 1961.
11. Irving, D. W. and Corday, E.: Effect of Cardiac Arrhythmias on the Renal and Mesenteric Circulation. Amer. J. Cardiol., 8:32, 1961.
12. Jenson, C. B. and Smith, G. A.: A Clinical Study of 51 Cases of Mesenteric Infarction. Surgery, 40:930, 1956.
13. Laufman, H. and Method, H.: Role of Vascular Spasm in Recovery of Strangulated Intestine. Surg. Gynec. Obstet., 85:675, 1947.
14. Lillehei, R. C., Goott, B. and Miller, F. A.: The Physiological Response of the Small Bowel of the Dog to Ischemia Including Prolonged *in vitro* Preservation of the Bowel with Successful Replacement and Survival. Ann. Surg., 150:543, 1959.
15. Ming, Si-Chun: Hemorrhagic Necrosis of the Gastrointestinal Tract and Its Relation to Cardiovascular Status. Circulation, 32:332, 1965.
16. Penner, A. and Bernheim, A. I.: Acute Postoperative Enterocolitis: A Study on the Pathologic Nature of Shock. Arch. Path., 27:966, 1939.
17. Polansky, B. J., Berger, R. L. and Byrne, J. J.: Massive Non-occlusive Intestinal Infarction Associated with Digitalis Toxicity. Circulation, 30, Suppl. III:141, 1964.
18. Schweinburg, F. B., Shapiro, P. B., Frank, E. D. and Fine, J.: Host Resistance in Hemorrhagic Shock. IX Demonstration of Circulating Lethal Toxin in Hemorrhagic Shock. Proc. Soc. Exp. Biol. Med. 95:646. 1957.
19. Thal, A. and Egner, W.: Local Effects of Staphylococcal Toxin: Studies on Blood Vessels with Particular Reference to Phenomenon of Dermonecrosis. A.M.A. Arch. Path., 57:392, 1954.