EDITORIALS

CT Colonography: Progress Toward Colorectal Evaluation Without Catharsis

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The rapid development of computed tomography (CT) colonography (CTC) challenges us to see substantial gains amid the numerous technical innovations. The study by Ianaccone et al.[1] evaluates a noncathartic, tagging technique of CTC that has the potential to positively impact patient compliance with colorectal-screening guidelines.

In this study, a total of 203 patients at defined risk of colorectal cancer were evaluated prospectively with CT and colonoscopy. Patients 35 years or older were recruited based on criteria ranging from average risk of screening to positive colorectal symptoms. In total, 98 (48.3%) patients were recruited for evaluation of symptoms and 105 (51.7%) patients were asymptomatic. The novel aspects of this study were its use of a noncathartic bowel preparation, the relaxation of preexamination dietary restrictions, and the use of a single-tagging iodinated agent (Gastrografin; [Schering, Berlin, Germany] 200 mL). The study used a state-of-the-art technique for CT acquisition, including use of ultra–low-dose x-ray protocol (10 mA) and narrow-beam collimation (2.5 mm). After tagging without electronic stool subtraction, the CT data were evaluated independently by 3 trained radiologists by using the most commonly available technique of a 2-dimesional multiplanar image display as the primary evaluation (detection) with 3-dimensional endoscopic views for problem solving (characterization). The reference standard consisted of the optimized technique of segmental unblinding at colonoscopy with CT results, in which the colonoscopy did not serve as its own gold standard.[2,3] Optical colonoscopy was performed 3–7 days after the CT examination, after patients underwent a bowel preparation of 2 L of polyethylene glycol and bisacodyl the day before colonoscopy. Study results of multiobserver diagnostic performance on a per-polyp analysis were reported as an average sensitivity of 86% for polyps ≥6mm and 95.5% for polyps ≥8 mm. On a per-patient analysis, the sensitivity rate averaged 89.9% and the specificity rate averaged 92.2%. Interobserver agreement ranged from κ scores of 0.61–0.74 on a per-polyp basis to 0.79–0.91 on a per-patient basis.

Beginning in 2000, tagging-based techniques for CTC have been evaluated in pilot data by using barium or iodinated agents, with varying degrees of noncathartic regimens.[4–6] The goal of tagging is to impart a homogenous high density to both stool and residual fluid to increase the contrast between stool and distinct soft tissue elements of polyps and haustral folds. Untagged fecal matter is a well-recognized source of false-positive diagnoses in CTC. Furthermore, untagged residual colonic fluid can immerse and decrease the ability to detect true polypoid lesions, thus producing false negative findings. Callstrom et al.[4] first reported the use of 2% barium sulfate as a tagging regimen for noncathartic CTC; these investigators observed optimal results when tagging continued during a 48-hour period. Lefere et al.[5] also reported improved specificity of colorectal polyp detection in a comparison of 100 patients, using barium tagging and a fluid- and fiber-restricted regimen. Zalis et al.[6] have evaluated the use of nonionic iodinated compounds as tagging agents, and further used computerized subtraction to effect noncathartic, postacquisition cleansing of the colon. Once tagged, electronic subtraction of high-density material (stool or fluid) above a specific numerical threshold can be performed. Subtraction can help to preserve a full 3-dimensional fly-through review of the colon (because the fluid and stool are not compromising visibility) and may reduce reader eye fatigue. Although the additional step of electronic subtraction of tagged structures can introduce artifacts into the CT datasets,[6,7] these artifacts appear minimized with recent software improvements.[8] The evaluation of electronic subtraction is in its early stages and thus this technique has not yet emerged in standard practice of CTC. Although the large trial of Pickhardt et al.[9] used tagging with both barium and iodinated agents followed by subtraction, these steps were implemented in combination with full cathartic cleansing and a clear-liquid diet. Overall, these data suggest trends, including (1) tagging is feasible and well tolerated by subjects and (2) as seen in pilot data, the sensitivity of CTC with noncathartic tagging appears to be comparable with standard CTC for detection of polyps, whereas specificity may be improved with tagging.

The primary innovation evaluated in this study was the use of a preexamination fecal and fluid-tagging regimen that replaced the standard bowel cathartic regimen in the largest prospective cohort to date. Importantly, there was a decrease in dietary restriction without the use of catharsis. Subjects were able to choose their diet, with no restrictions on the amount of food or fluid intake, with the exception of avoidance of fiber-rich foods (e.g., fruit, vegetables, whole grain breads, and cereals). Catharsis was not used before the CT, and a traditional catharsis was performed before the subsequent colonoscopy. It is well recognized that the bowel preparation is one of the major barriers for patient compliance to undergo colorectal screening.[10] The overall unpleasantness of the bowel preparation has been reported to have higher ratings than that of the CT colonography or colonoscopy examinations.[11] In this study, 79.8% of the subjects returned questionnaires regarding patient preference for the bowel preparation: 88.3% of patients preferred fecal tagging preceding the CT colonography examination, 7.4% preferred the cathartic preparation preceding the colonoscopy, and 4.3% of patients had no preference. The lack of catharsis certainly has distinct advantages for specific patient cohorts, such as renal or diabetic patients, in whom electrolyte shifts can be harmful. The current results confirm the previously observed high accuracy of CTC for detection of polyps and strongly suggest that CTC can address the compliance barrier of cathartic bowel preparation.

The tagging performed with use of a single iodinated agent for both fecal and fluid tagging represents an important achievement. Whereas the enteric contrast agent, barium sulfate, requires emulsifiers to keep it in suspension, iodinated agents readily dissolve in aqueous solution. Because emulsifiers are invariably diluted during transit in the small bowel, the homogeneity and thoroughness of tagging observed in the colon may, in theory, be compromised. Active efforts to improve these agents continue to be made. The solubility of iodinated agents is more relevant for patients because it means that the agents can be readily dissolved in suitable beverages, such as soft drinks or juices, increasing ease of ingestion. In this study, analysis of image quality of tagging per colonic segment (i.e., ratings based on the worst area, not average, in long tortuous segments), showed results ranging from 80% in the transverse colon to 85% in the ascending colon. On a per-patient basis, fecal material was judged to have excellent tagging (i.e., homogenous labeling with clear differentiation between fecal material and the colonic mucosa) in 98.5% of patients. The validation of effective tagging in this study is based on strong results of diagnostic performance for detection of polyps and the high scores assigned by readers of image quality of stool tagging.

What are some of the concerns for this new tagging technique? One concern is the incidence of gastrointestinal symptoms, which occurred in 10% of patients in this study cohort. The authors chose to administer a commonly used ionic iodinated contrast rather than the more recently developed nonionic contrast materials. Although ionic agents such as Gastrografin may have the benefit of a mild cathartic-like action in the bowel, their high osmolarity is associated with gastrointestinal side effects. The newer nonionic agents show improved side effect profiles because of markedly lower osmolarity. Another concern is the large volume of the tagging agent used in this protocol, which may impair patient compliance in more widespread use. Namely, a total of 20 mL of contrast for each of the 5 doses per day of tagging was administered over 2 days, for a total of 200 mL of contrast. Pilot studies using agents with similar concentration of iodine suggest that lower iodine doses may be adequate for tagging.[6] Investigators continue to evaluate the balance between decreasing the amount of tagging needed and increasing the liberty of eating a more nonrestricted diet without catharsis. Although the observations of Iannaccone et al.[1] suggest an excellent performance for detection of clinically significant lesions by using new tagging techniques, more widespread implementation of tagging will merit further refinement of stool-tagging regimens.

How does this study compare with important aspects of study design of the other large clinical trials reported to date? In the largest and most successful study to date, Pickhardt et al.[9] evaluated a screening cohort of 1233 patients using a strict clear-liquid diet, rigorous catharsis (Phospha-soda [G.B. Fleet Inc., Lynchburg, VA] 90 mL; Bisacodyl [G.B. Fleet Inc.] 10 mg), stool and liquid tagging with both barium (500 mL total) and Gastrografin (120 mL), electronic stool subtraction, and 3-dimensional review as a primary image display among trained radiologists. In this study, the sensitivity rate was 88.7% for detection of adenomatous polyps $\geq$6 mm and 93.9% for polyps $\geq$8 mm in size; the specificity rate was 79.6% to detect patients with $\geq$6 mm polyps and 92.2% for patients with polyps $>$8 mm.[9] Two other large trials, which reported decreased diagnostic performance results[12,13] and decreased interobserver agreement,[13] differed across multiple factors but neither study used tagging agents. Importantly, differences in image-display techniques were reported in these studies. In the setting of comparing studies using tagged techniques, 2-dimensional multiplanar reformation (MPR) as a primary review with 3-dimensional endoscopic views for problem solving (current study of Ianaccone et al.[1]) had similar

results with 3-dimensional endoscopic review as a primary review (Pickhardt et al.[9]) for diagnostic performance. The complementary use of 2-dimensional MPR and 3-dimensional endoscopic views continues to be stressed by investigators of CT colonography.

Another important strength to compare in this study was the use of an ultra–low-dose CT protocol (10 mA). Radiation dose has been raised as a concern for the widespread applicability of CT colonography as a screening technique. Given the high contrast to noise present in the air–soft tissue polyp interface, decreased dose ranges can be exploited for polyp detection. Recent studies that used multidetector CT protocols have significantly decreased estimated absorbed x-ray dose to less than that required for barium enema.[14–17] In 2002, Macari et al.[14] reported successful results in a prospective cohort of 105 patients using a low-dose, multidetector row CT protocol of 50 effective mA (1-mm slice thickness), imparting effective doses of 5.0 mSv and 7.8 mSv for men and women, respectively. In 2003, further reduced CT radiation dose was reported in a prospective cohort of 158 patients using 10 effective mA (2.5-mm slice thickness), with simulated effective doses of 1.8 mSv and 2.4 mSV in men and women, respectively.[15] In comparison, Pickhardt et al.[9] used a CT protocol of 100 mA (1.25—2.5-mm slice thickness). The current study further validates the use of a low x-ray–dose technique.

In summary, the study of Ianacconne et al.[1] highlights the potential of CT colonography to provide highly accurate structural evaluation of the colon while simultaneously minimizing the duress of preexamination bowel preparation, dietary restriction, and radiation exposure. Further refinements in the amount and type of tagging agent, as well as exploration of improved electronic subtraction techniques, are under current investigation. However, the present study represents an important step toward simplification of the bowel preparation, which is one of the most important barriers for colorectal screening. Thus, noncathartic CT colonography may represent an important benefit for patients. Furthermore, such advances may also foster collaboration between radiologists and gastroenterologists, for if in the future CT colonography facilitates greater numbers of individuals to undergo noninvasive screening, colonoscopy will remain the therapeutic method for resection of clinically significant polyps.

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Cooling the Patient With Acute Liver Failure

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Acute liver failure (ALF) is a rare disease, with an estimate of 2000 cases per year in the United States. However, it is a worldwide problem, affecting previously healthy individuals and placing great demands on the provision of intensive care. Although multiorgan failure is increasingly recognized as the cause of death, brain edema and intracranial hypertension are unique complications of the syndrome, especially in patients with hyperacute liver failure, in whom less than a week elapse between the onset of symptoms and the development of hepatic encephalopathy.

In this issue of GASTROENTEROLOGY, Jalan et al.[1] show that moderate hypothermia (33°C) was able to control the elevated intracranial pressure (ICP) in 14 patients with ALF and intracranial hypertension who had failed standard medical therapy, allowing the performance of emergency liver transplantation. Such surgery can be lifesaving but the decision to operate can be quite challenging.[2] Uncertainty is not the case in the patients treated by Jalan et al.,[1] in whom death could be expected within a short period of time. Although this series expands on an earlier report from this group,[3] additional insight into the mechanisms responsible for the benefits of hypothermia are provided. At a time when bioartificial liver support systems have not fulfilled their promise,[4] the possibility that a relatively simple and inexpensive measure could bridge patients with ALF to emergency transplantation is particularly attractive.

Hypothermia is used in several other critical conditions associated with an elevated ICP; it has been recommended as standard of care after resuscitation from an out-of-hospital cardiac arrest.[5] However, the potential use in ALF is not a simple extrapolation from the practice of other disciplines—it is the result of laboratory and clinical investigations that during the past 20 years have provided insight into the pathogenesis of brain edema. Three major elements need to be considered; they are all affected by hypothermia to a varying extent.

An Osmotic Alteration in the Brain

Hyperammonemia is linked to osmotic changes in brain. This relationship was highlighted in a study where arterial ammonia levels >200 μg/dL were associated with the development of brain herniation.[6] In the current study, Jalan et al.[1] reports that moderate hypothermia is associated with a decrease in arterial ammonia levels. The mechanism for this effect has not been elucidated but, on a theoretical basis, could imply effects on the splanchnic release of ammonia, which is increased in ALF.[7] More on hypothermia and the liver is discussed later.

Once in brain, ammonia is detoxified in cortical astrocytes to form glutamine, a reaction catalyzed by glutamine synthetase. Glutamine levels increase several-fold in the brain, as assessed by magnetic resonance spectroscopy in human ALF.[8] Like other amino acids, such as taurine, or polyols, such as myo-inositol, glutamine is also an organic osmolyte. Astrocyte swelling occurs as a result of the increase in intracellular osmolarity induced by glutamine, a process that activates compensatory mechanisms, including a reduction in the levels of myo-inositol and taurine.[9] Mild hypothermia (35°C) in a rat model of ALF prevented the development of brain edema and was associated with unchanged levels of myoinositol and taurine.[10] Although not directly measured, it can be surmised that hypothermia decreased the extent of astrocyte swelling.

Cerebral Hemodynamics

An ammonia infusion to rats with portacaval anastomosis results in a predictable increase in brain water, a rise prevented by the application of temperatures of 33°C and 35°C.[11] The development of brain edema was associated with cerebral hyperermia, and the increase in cerebral blood flow was prevented by both mild and