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Simultaneous Dual-contrast Imaging of Small Bowel with Iodine and Bismuth using Photon-counting-detector CT: A Feasibility Animal Study

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Abstract

Objectives: Dual-energy and multi-energy computed tomography (DECT/MECT) has the potential to simultaneously visualize two contrast agents in the small bowel: arterial enhancement of iodine in the bowel wall and enteric enhancement of bismuth in the bowel lumen. The purpose of this study is to explore its feasibility in a swine study using a research whole-body photon-counting-detector (PCD) CT system.

Materials and Methods: A phantom study was initially performed to evaluate the quantification accuracy of iodine and bismuth separation from a single PCD-CT scan, which also served as the calibration reference for material decomposition of *in vivo* swine PCD-CT data. In the animal study, a test bolus scan was first performed to determine the time-attenuation curve for the arterial enhancement, based on which the timing of the PCD-CT dual-contrast scan was determined. A 600 mL homogeneous bismuth-saline solution (180 mL Pepto-Bismol + 420 mL normal saline) was orally administered to the pig using esophageal intubation. Approximately one hour after bismuth administration, 40 mL iodine contrast (Omnipaque 350, 5 mL/s) was injected intravenously. A PCD-CT scan was performed 13 seconds after the initiation of the contrast injection to simultaneously capture the arterial enhancement of iodine and the enteric enhancement of bismuth. To provide optimal material separation and quantification, all PCD-CT scans in both phantom and animal studies were operated at 140 kV with four energy thresholds of 25, 50, 75, and 90 keV.

Results: Using a generic image-based material decomposition method, the iodine and bismuth samples were successfully delineated and quantified in the phantom images with a root-mean-square-error of 0.20 mg/mL in iodine measurement and 0.12 mg/mL in bismuth measurement. In the pig study, the enhancing bowel wall containing iodine and the small bowel loop containing bismuth were not differentiable in the original PCD-CT images. However, they were clearly distinctive from each other in the iodine- and bismuth-specific images after material

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decomposition, as reviewed by an abdominal radiologist. In addition, quantitative analysis showed that the misclassification between the two contrast materials was less than 1.0 mg/mL.

Conclusions: Our study demonstrated the feasibility of simultaneous imaging of iodine and bismuth in small bowel of swine using PCD-CT.

Keywords

Contrast materials; photon-counting-detector (PCD); multi-energy CT (MECT); material decomposition

1. Introduction

Simultaneous imaging of two or more contrast agents using dual-energy CT (DECT) or multi-energy CT (MECT) has received much attention recently [1–14]. One promising application that may be clinically useful involves iodine and bismuth for small bowel imaging [10–12]. In this application, iodine and bismuth are administered via intravascular and enteric routes, respectively, to achieve simultaneous arterial enhancement of iodine in the vascularized bowel wall and enteric enhancement of bismuth in the intestinal lumen. Simultaneous imaging of these two contrast agents by a single CT scan, followed by material decomposition, is capable of differentiating arterial enhancement and enteric enhancement with perfect or near perfect image co-registration [10, 12]. The ability to change the visual display of the gut lumen and bowel wall using material classification may have unique advantages in a number of clinical scenarios, e.g., patients with two suspected diseases for which the selection of oral contrast would be entirely different for each disease (e.g., the Crohn's patient who has had a colonic resection for colon cancer); patients with imaging findings that could be clarified if positive enteric contrast could be distinguished from intravenous contrast (e.g., high density contrast adjacent to bowel in the setting of trauma); and most commonly, patients without a known small bowel diagnosis, for which an imaging approach that can permit separate visualization of the bowel lumen and bowel wall may provide advantages of positive and neutral enteric contrast agents.

DECT was first used in a few phantom and animal studies to simultaneously image iodine and bismuth [10–12]. For example, luminal bismuth and mural iodine filled in a small-bowel phantom were successfully differentiated using DECT to identify hyper-enhancing, hypo-enhancing, and non-enhancing polyps of different sizes [11]. In two different rabbit abdominopelvic models, intraluminal bismuth contrast medium and intravascular iodine contrast medium in bowel wall were scanned and separated into different contrast-specific images for better visualization [10, 12]. Increased diagnostic accuracy and confidence by radiologists were indicated. The material separation demonstrated in these studies, while appearing to be successful, has also revealed significant limitations hindering its potential clinical applications such as in small bowel imaging. For example, the material decomposition method employed in the studies using DECT was essentially performed based on two basis materials given only two x-ray beam measurements in DECT. Though the two-material decomposition method was capable of separating iodine and bismuth, it involved at least two steps to separate iodine, bismuth, and the background material, and did not fully utilize the k-edge property of bismuth, leading to either qualitative or pseudo-

quantitative results [10–12]. To perform quantitative three-material decomposition using DECT, an additional physical constraint such as mass or volume conservation has to be incorporated to solve the three-material problem [15].

In a recent study, energy-resolved photon-counting detector (PCD) based multi-energy CT (MECT) with four x-ray energy bins was used to differentiate intravascular (iodine and gadolinium) and enteric (bismuth) contrast materials in a canine study [6]. In the above study, separation of the bismuth inserts placed underneath the animal was clearly observed in the bismuth-specific image, but the 60 mg bismuth subsalicylate orally administered 24–72 hours prior to the PCD based MECT (PCD-CT) scan was not noticeable in the small intestine in both original PCD-CT and bismuth-specific images. To validate the feasibility of using iodine and bismuth in CT small bowel imaging, the dual-contrast imaging protocol needs to be well designed.

To address the limitations of the aforementioned studies, phantom experiments were recently performed to determine the quantitative accuracy and dose efficiency of simultaneous dual-contrast imaging using both DECT and PCD-CT with an image domain three-material decomposition method [16, 17]. It was demonstrated that dual-contrast imaging tasks involving iodine and bismuth, such as in small bowel imaging, was highly accurate and had a much better noise property and dose efficiency than that in other tasks such as iodine and gadolinium in biphasic liver imaging. Motivated by the phantom results and to further address the limitations of the previous studies such as the visualization of the small bowel lumen and wall using two separate contrast agents, a swine study is performed in this work to evaluate its feasibility in small bowel imaging using a PCD-CT system with a newly designed dual-contrast imaging protocol.

2. Materials and Methods

2.1. PCD-CT System

A research whole-body PCD-CT system (SOMATOM CounT, Siemens Healthineers, Forchheim, Germany) was employed in this study. The system was designed based on the same platform as the second-generation dual-source, dual-energy CT system (SOMATOM Definition Flash, Siemens Healthineers, Forchheim, Germany), with the second EID replaced by a PCD. The system therefore, consists of two independent subsystems, namely the EID subsystem with a full scan field of view (FOV) of 50 cm and the PCD subsystem with a scan FOV of 27.5 cm. Up to four energy thresholds are available in the PCD subsystem to enable MECT data acquisition. Additional technical details of the PCD-CT system can be found elsewhere [18–26].

2.2. Phantom Experiment

A phantom experiment was designed to evaluate the quantification accuracy of separating iodine and bismuth by a single PCD-CT scan, and to serve as calibration references for material decomposition in the following animal study. Three iodine samples (4, 7.5, and 15 mg/mL), three bismuth samples (5, 7.6, and 10 mg/mL), and two iodine/bismuth mixtures (4/5 and 7.5/7.6 mg/mL) were prepared using iohexol (Omnipaque 350, GE Healthcare,

Princeton, NJ) and bismuth subsalicylate (Pepto-Bismol, PROCTER & GAMBLE, Mason, OH) [10–12]. All samples were arranged in an equiangular fashion and placed in a 25 cm (lateral dimension) water tank. The phantom was scanned by the PCD subsystem at 140 kV with four energy thresholds of 25, 50, 75, and 90 keV, which were previously determined to yield optimal material decomposition performance [6, 27, 28]. Data acquisition and image reconstruction parameters for the phantom experiment are summarized in Table 1.

The phantom MECT images were processed using a generic image-based material decomposition method to determine the basis material concentrations at each location by solving a system of linear equations [29]. Three basis materials namely iodine, bismuth, and background (water-like) were used. Noise reduction techniques were not employed in the material decomposition process in order to reflect the inherent noise properties of PCD-CT involving two contrast agents. After material decomposition, a circular region of interest (ROI) was drawn on each contrast sample in material-specific images to measure the mean concentration value and the standard deviation. In addition, root-mean-squared error (RMSE) between measured concentrations and nominal values was calculated.

2.3. Swine Study

2.3.1 Animal Preparation—With the approval from our institutional animal care and use committee (IACUC), a female 3-month-old domestic pig (35 kg) was anesthetized using Telazol (5 mg/kg) as well as Xylazine (2 mg/kg), and maintained with isoflurane (1–3%) and oxygen through tracheal intubation throughout the entire study. The pig was placed in supine feet-first position on the scan table. Physiological parameters of the pig including heart rate, blood pressure, anesthesia, respiration, and body temperature were continuously monitored. Two sheaths were placed, one in the right femoral vein to provide the access point for intravascular iodine injection, and the other in the femoral artery for blood pressure readings. End expiration breath-hold was enabled through suspended ventilation during CT acquisitions. Non-contrast scans were first performed using both EID and PCD subsystems to determine the scan range as well as the proper radiation dose level, which also served as the baseline for the following CT scans with contrast agents.

2.3.2 Test Bolus to Determine Optimal Arterial Enhancement—A test bolus scan was performed to determine the timing of the optimal arterial enhancement. A total amount of 40 mL iohexol followed by 20 mL saline, was administered into the right femoral vein at an injection rate of 5 mL/s. Right after the start of the contrast injection, a series of single-energy CT (SECT) acquisitions (0.5 s rotation, 2.5 s cycle time, 15 axial scans) was performed at the upper abdominal level to visualize the vascular contrast enhancement using the EID subsystem at 120 kV. After reconstructions, a ROI was drawn within the abdominal aorta in a representative slice to measure the average CT number and to determine the time-dependent arterial enhancement curve (Figure 1), which was used to provide the timing information for the single-scan, dual-contrast PCD-CT imaging protocol. In the current swine study, the animal was anesthetized during scans, and euthanized immediately after CT scanning, so the contrast dose level did not pose a serious concern. We used the test bolus at the same iodinated contrast volume as in the subsequent dual-contrast scan in an effort to provide sufficient conspicuities of the hepatic arteries. The benefit of doing so is that the

enhanced vessels could be clearly identified to accurately determine the time-dependent arterial enhancement curve. In patient studies, a much smaller amount would be used. The test bolus could also be replaced with bolus tracking methods.

2.3.3 Dual-contrast Imaging Protocol—A 600 mL homogeneous bismuth-saline solution (180 mL Pepto-Bismol + 420 mL normal saline) was orally administered to the pig through a stomach esophageal intubation, followed by EID subsystem (SECT at 120 kV) test scans performed every 20 mins until the swine small bowel was opacified. Luminal small bowel bismuth opacification was sufficient for abdominopelvic scanning at one hour, at which time intravenous contrast was administered. Via the right femoral vein, 40 mL bolus of iohexol followed by 20 mL saline flush was injected at a flow rate of 5 mL/s PCD-CT imaging was initiated 13 s after the initiation of the iodine injection to simultaneously capture the arterial enhancement (iodine) and luminal enteric opacification (bismuth), as summarized in Figure 2. PCD-CT data acquisition and image reconstruction parameters were identical to the phantom study (Table 1).

2.3.4 Material Decomposition and Image Analysis—The same image-based material decomposition method was implemented on the images acquired from the above PCD-CT scan to differentiate and quantify iodine and bismuth contrast materials, which correspond to arterial enhancement and enteric opacification, respectively. Compared to the material decomposition implemented in the phantom study, the background material was changed from water to soft tissue in the animal study to ensure quantitative accuracy [6].

All PCD-CT images were reviewed by a senior abdominal radiologist with 21 years of experience in the imaging of small bowel inflammatory and neoplastic conditions at CT and MR enterography. The radiologist was then asked to confirm the separation of small bowel wall containing iodine and small bowel lumen containing bismuth on the iodine- and bismuth-specific images, respectively. To quantitatively evaluate the separation and the misclassification between two contrast materials, two ROIs for iodinated intravenous/intramural opacification and two for luminal opacification with bismuth were drawn on the ileal wall and the ileal lumen, respectively. For each ROI, the mean CT number or mass concentration ($\pm$ standard deviation) was measured on all the PCD-CT energy bin images, as well as the bismuth only and iodine only images.

3. Results

3.1. Phantom Experiment

Figure 3a shows the PCD-CT image reconstructed from the threshold-low data, which corresponds to the energy window of [25 140] keV. The CT number of both iodine and bismuth samples increased with the increase of concentration and the two contrast materials could not be visually differentiated. After three-material decomposition, iodine and bismuth samples could be clearly delineated and quantified, as demonstrated in the fused color map of iodine-specific and bismuth-specific images in Figure 3b. All measurements of mean concentration value and the standard deviation were summarized in Figure 3c and 3d for iodine and bismuth samples, respectively. The RMSE values between measured

concentrations and nominal values were calculated as 0.20 mg/mL for iodine and 0.12 mg/mL for bismuth.

3.2. Swine Study

Figure 4a shows a non-contrast PCD-CT image at [25 140] keV, which can be used as a baseline reference for the contrast enhanced images. Figure 4b shows a [25 140] keV image, which was acquired from a single PCD-CT scan after administration of the oral bismuth and intravenous iodine contrast materials. Before material decomposition, the radiologist indicated that both the arterial enhancement of iodine in small bowel wall and the enteric enhancement of bismuth in small bowel lumen were observed but not completely distinguishable from each other. For example, the small bowel loop containing bismuth (green arrow) and the adjacent iodine-enhancing bowel wall (red arrows) had similar contrast enhancement that were not differentiable. Notable distinction between these two structures, however, was revealed in the iodine-specific (Figure 4c) and bismuth-specific (Figure 4d) images after three-material decomposition, which was also confirmed by the radiologist. Four ROIs, two on the ileal wall (#1 and #2) and two on the ileal lumen (#3 and #4), were drawn on Figure 4b–4d, and the measurements of the mean values as well as the standard deviations were summarized in Table. 2. Of note, the misclassification of one contrast agent on the material-specific image containing the other contrast agent was less than 1.0 mg/mL. Furthermore, the fused color map showing both contrast materials provides a better representation of the distinction between iodine and bismuth, as shown in Figure 5. Note that any non-basis materials such as the bony structures (e.g. spine and ribs in Figures 4 and 5) were decomposed into different basis material maps according to their physical properties (e.g. atomic number and density) and the impact of the volume conservation which was incorporated into the material decomposition algorithm [29, 30].

4. Discussions

A swine study was performed to explore the feasibility of simultaneous imaging of iodine and bismuth in small bowel using a PCD-CT system with a newly designed dual-contrast imaging protocol. Results showed clear separation between the small bowel lumen containing bismuth and the adjacent enhancing bowel wall containing iodine, and accurate quantification of each contrast material. Simultaneous imaging of iodine and bismuth may be potentially considered for several clinical applications. For example in the identification of small-bowel pathologies, the conspicuity of certain types of small-bowel polyps containing iodine may be increased after separating them from the positive enteric contrast agent such as bismuth in the small bowel lumen [11]. Another potential application is to facilitate the diagnosis of bowel injuries, in which approximately 20% have been reported with extravasation of enteric luminal contrast material. In this scenario, simultaneous imaging of vascular contrast material such as iodine and enteric luminal contrast material such as bismuth, followed by material decomposition to separate these two materials, may distinguish extravasated bismuth due to bowel perforation and vascular iodine due to bleeding [31]. Study shows that with simultaneous imaging of iodine and bismuth, traumatic fluid collections, which were misdiagnosed repeatedly with conventional SECT, were diagnosed correctly with a single-scan DECT protocol [10]. This is clinically impactful in

identifying the source of extravasation in bowel injuries. In addition, clear separation between positive oral and intravenous contrast media may provide meaningful volume-rendered or three-dimensional rendering of the abdominopelvic vasculature by removing oral contrast media which normally obscures crucial assessments of bowel wall enhancement in SECT [12, 32].

Simultaneous imaging of iodine and bismuth contrast agents using a single DECT or MECT scan has been investigated in several studies, where the iodine representing arterial enhancement and bismuth representing enteric enhancement could be separated [10–12, 15–17, 29]. To our knowledge, in the only large-animal study reported so far for simultaneous imaging of iodine and bismuth using PCD-CT, enteric bismuth subsalicylate was orally administered and intravascular iodine as well as gadolinium was sequentially injected in a canine [6]. This study showed separation of iodine and gadolinium in the kidney, but did not reveal any bismuth in the small bowel lumen. Hypothetically there are two potential reasons: first, only 60 mg bismuth subsalicylate was administered in the above canine. To achieve reasonable enteric enhancement, a total amount of 180 mL Pepto-Bismol, equivalent to 6300 mg bismuth subsalicylate was needed in our swine study. Even considering the difference between two animals, only 60 mg bismuth subsalicylate is unlikely to provide sufficient enteric enhancement (note that the dosage of bismuth subsalicylate used in the current study and the potentially associated toxicity issues are discussed later). Second, the bismuth subsalicylate was orally administered in the canine study 24–72 hours prior to the PCD-CT scan without knowing the uptake profile of bismuth subsalicylate in the small intestine. With such a long delay, the administered bismuth subsalicylate may already leave the small intestine. In our study, we found that a shorter delay of approximately one hour already yields sufficient bismuth enteric enhancement (100–200 HU) in small bowel lumen.

Bismuth based enteric contrast material was selected in this study for the following reasons. As a complementary contrast material, bismuth (atomic number: 83; k-edge: 90.5 keV) is clearly distinguishable from iodine (atomic number: 53; k-edge: 33.2 keV); the iodinated contrast media have been routinely used in CT clinical practice. Bismuth subsalicylate is widely available and relatively inexpensive. For example, the bismuth subsalicylate used in this study is the active ingredient in the popular medication Pepto-Bismol for treating temporary discomforts of the stomach and gastrointestinal tract, and has been previously used in experimental studies as an enteric CT contrast [6, 10–12, 15–17, 29]. Barium sulfate is the most commonly used positive gastrointestinal contrast agent in conventional CT enterography; barium exhibits similar attenuation characteristics (atomic number: 56; k-edge: 37.4 keV) as iodine [1, 11]. Though delineation between iodine and barium is possible in small animals such as mice using PCD-CT, they are indistinguishable in larger subjects since their k-edges are only 4 keV apart [1] and most of the low-energy photons are absorbed by the body. Other types of High-Z intravenous or enteric contrast materials such as those based on tantalum, hafnium, tungsten, or rhenium are also under active investigations [33, 34].

There are several limitations in this study. First, this was an exploratory phantom and animal study to demonstrate the feasibility of using PCD-CT to materially classify and permit visualization of the gut lumen and gut wall using two contrast agents, namely iodine and

bismuth. As such, the sample size (one pig) was limited (under-sampled) for any meaningful statistical analysis at the current investigation stage. Additional statistical analysis would require a comprehensive study involving a large number of subjects and disease models to evaluate its diagnostic value, which was beyond the scope for this pilot study. Second, there is currently no bismuth-based enteric agents approved by Food and Drug Administration for use in clinical practice; this limits the immediate translation of our proposed technique for clinical use in humans, where an oral contrast agent delivery protocol would need to be optimized. The major concern is the toxicity and potential adverse effects of bismuth subsalicylate, in particular with the amount of bismuth required for optimal CT imaging [31, 35–37]. For example, 180 mL Pepto-Bismol was used in the current study to achieve 100–200 HU enteric enhancement in small bowel lumen at the PCD-CT image at [25 140] keV. This amount, however, has already exceeded the maximum allowed dose (120 mL) of Pepto-Bismol within 24 hours as prescribed in the product label. Also, Pepto-Bismol should not be used in children younger than 12 years of age. The required dose of bismuth subsalicylate may be reduced given continuously improved material-specific imaging performance of using MECT technologies, for example, in terms of better spatial resolution and lower detection capability. Finally, the filling of bismuth subsalicylate in small bowel lumen was imaged at about one hour after the oral administration. This time delay between enteric contrast administration and PCD-CT scan was sufficient for the purpose of this feasibility study. However, a more rigorous study is needed to comprehensively investigate the time-attenuation properties of bismuth subsalicylate in different organs such as stomach, small intestine, large intestine, and kidney, which may be determined by repeating CT scans with reasonable delays (e.g. every 20 minutes) over a large time scale.

The results demonstrated in the current animal feasibility study may be further improved from the following two aspects. First, current investigational whole-body PCD-CT system suffers from severe spectral distortions caused by many physical non-idealities of the PCD itself [38–40], resulting in inefficient radiation dose of simultaneous imaging of iodine and bismuth by the current PCD-CT system compared to the conventional SECT protocol [16]. As ongoing research topics, corrections for these non-ideal effects may further improve the material-specific imaging performance [41, 42]. Second, a generic image-based method without incorporating any denoising steps either before or within the material decomposition process was employed to demonstrate the inherent noise property in simultaneous imaging of iodine and bismuth with a single PCD-CT scan. Novel material decomposition methods have been reported providing better material-specific imaging performance compared to the generic method [22, 43–45]. These methods may be employed to further improve the material-specific imaging performance.

5. Conclusion

In this exploratory study, the feasibility of simultaneous imaging of iodine and bismuth contrast materials in small bowel imaging was demonstrated in swine using a PCD-CT system. With an in-house designed single-scan dual-contrast PCD-CT imaging protocol, the arterial enhancement of iodine in small bowel wall and the enteric enhancement of bismuth in small bowel lumen could be separated in the material-specific images. With further investigations of the dosage, contrast toxicity, and time-attenuation property in small bowel

of bismuth subsalicylate, and continuous improvements of MECT imaging technologies, our findings in this feasibility study may translate to clinical application of MECT for improved small bowel imaging.

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Figure 1.

- (a) Time-dependent arterial enhancement curve was determined based on the average contrast enhancement measured within a circular ROI drawn within the abdominal aorta on a representative slice; the enhancement curve shows the peak arterial enhancement at 19.5 s;
- (b) an example SECT image acquired at peak enhancement indicating the contrast enhancement in arteries and the ROI selection.

Figure 2.

Timing of bismuth and iodine administration and single-scan PCD-CT protocol; note that the PCD-CT scan was started 5~6 seconds prior to the peak arterial enhancement to fully capture the entire enhancement peak due to the duration of PCD-CT scan itself.

Figure 3.

(a) Water phantom with contrast samples and concentration value (in mg/mL) labeled; (b) fused color map of iodine-specific and bismuth-specific images indicating that these two contrast materials could be clearly identified and quantified; (c) measured iodine concentrations (mean $\pm$ standard deviation) versus nominal values; (d) measured bismuth concentrations (mean $\pm$ standard deviation) versus nominal values.

Figure 4.

(a) Image acquired from a non-contrast PCD-CT scan at [25 140] keV; (b) image acquired from a PCD-CT scan at [25 140] keV after oral administration of bismuth and intravenous injection of iodine; (c) iodine-specific and (d) bismuth-specific images after material decomposition; note that the small bowel loop containing bismuth (green arrow) and the adjacent enhancing bowel wall (red arrows) were not differentiable in (b) but clearly separated from each other in the contrast-specific images (c-d).

Figure 5.
Fused color map of iodine-specific and bismuth-specific images generated from material decomposition using PCD-CT images

Table 1.

Data acquisition and image reconstruction parameters in PCD-CT scan

Acquisition mode (collimation)	Chess (32 × 0.5 mm)
Voltage (kV)	140
Thresholds (keV)	25, 50, 75, and 90
CTDIvol (mGy)	24
Pitch	0.6
Rotation time (s)	0.5
Scan/Recon FOV (mm)	275/275
Slice-thickness/increment (mm)	3.0/2.0
Reconstruction Kernel	D30

Table 2.

Quantitative measurement on PCD-CT images (unit: HU) and material-specific images (unit: mg/mL)

ROI	PCD-CT Image: [25 50] keV	PCD-CT Image: [50 75] keV	PCD-CT Image: [75 90] keV	PCD-CT Image: [90 140] keV	Iodine-specific Image	Bismuth-specific Image
#1 (ileal wall)	221.4 ± 21.8	158.6 ± 33.2	105.1 ± 22.8	73.1 ± 9.8	5.7 ± 1.3	0.2 ± 0.9
#2 (ileal wall)	217.3 ± 18.2	187.3 ± 18.4	100.6 ± 29.0	71.5 ± 25.7	6.7 ± 0.7	-0.2 ± 0.9
#3 (ileal lumen)	169.2 ± 31.9	165.5 ± 30.5	105.1 ± 27.6	188.9 ± 17.5	-0.2 ± 0.6	6.5 ± 0.5
#4 (ileal lumen)	162.2 ± 32.4	177.5 ± 28.8	133.1 ± 55.18	203.8 ± 26.5	-1.0 ± 0.9	7.6 ± 0.7