Thieme

Water exchange for screening colonoscopy increases adenoma detection rate: a multicenter, double-blinded, randomized controlled trial

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submitted 12.7.2016
accepted after revision 20.12.2016

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DOI http://dx.doi.org/10.1055/s-0043-101229
Published online: 10.3.2017 | Endoscopy 2017; 49: 456–467

ISSN 0013-726X

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ABSTRACT

Background and study aims Single-center studies, which were retrospective and/or involved unblinded colonoscopists, have suggested that water exchange, but not water immersion, compared with air insufflation significantly increases the adenoma detection rate (ADR), particularly in the proximal and right colon. Head-to-head comparison of the three techniques with ADR as primary outcome and blinded colonoscopists has not been reported to date. In a randomized controlled trial with blinded colonoscopists, we aimed to evaluate the impact of the three insertion techniques on ADR.

Patients and methods A total of 1224 patients aged 50–70 years (672 males) and undergoing screening colonoscopy were randomized 1:1:1 to water exchange, water immersion, or air insufflation. Split-dose bowel preparation was adopted to optimize colon cleansing. After the cecum had been reached, a second colonoscopist who was blinded to the insertion technique performed the withdrawal. The primary outcome was overall ADR according to the three insertion techniques (water exchange, water immersion, and air insufflation). Secondary outcomes were other pertinent overall and right colon procedure-related measures.

Results Baseline characteristics of the three groups were comparable. Compared with air insufflation, water exchange achieved a significantly higher overall ADR (49.3%, 95% confidence interval [CI] 44.3%–54.2% vs. 40.4% 95%CI 35.6%–45.3%; P =0.03); water exchange showed comparable overall ADR vs. water immersion (43.4%, 95%CI 38.5%–48.3%; P =0.28). In the right colon, water exchange achieved a higher ADR than air insufflation (24.0%, 95%CI 20.0%–28.5% vs. 16.9%, 95%CI 13.4%–20.9%; P =0.04) and a higher advanced ADR (6.1%, 95% CI 4.0%–9.0% vs. 2.5%, 95%CI 1.2%–4.6%; P=0.03). Compared with air insufflation, the mean number of adenomas per procedure was significantly higher with water exchange (P=0.04). Water exchange achieved the highest cleanliness scores (overall and in the right colon). These variables were comparable between water immersion and air insufflation.

Conclusions The design with blinded observers strengthens the validity of the observation that water exchange, but not water immersion, can achieve significantly higher adenoma detection than air insufflation. Based on this evidence, the use of water exchange should be encouraged.
Trial registered at ClinicalTrials.gov (NCT02041507).

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world, with nearly 1.4 million new cases diagnosed in 2012 [1].

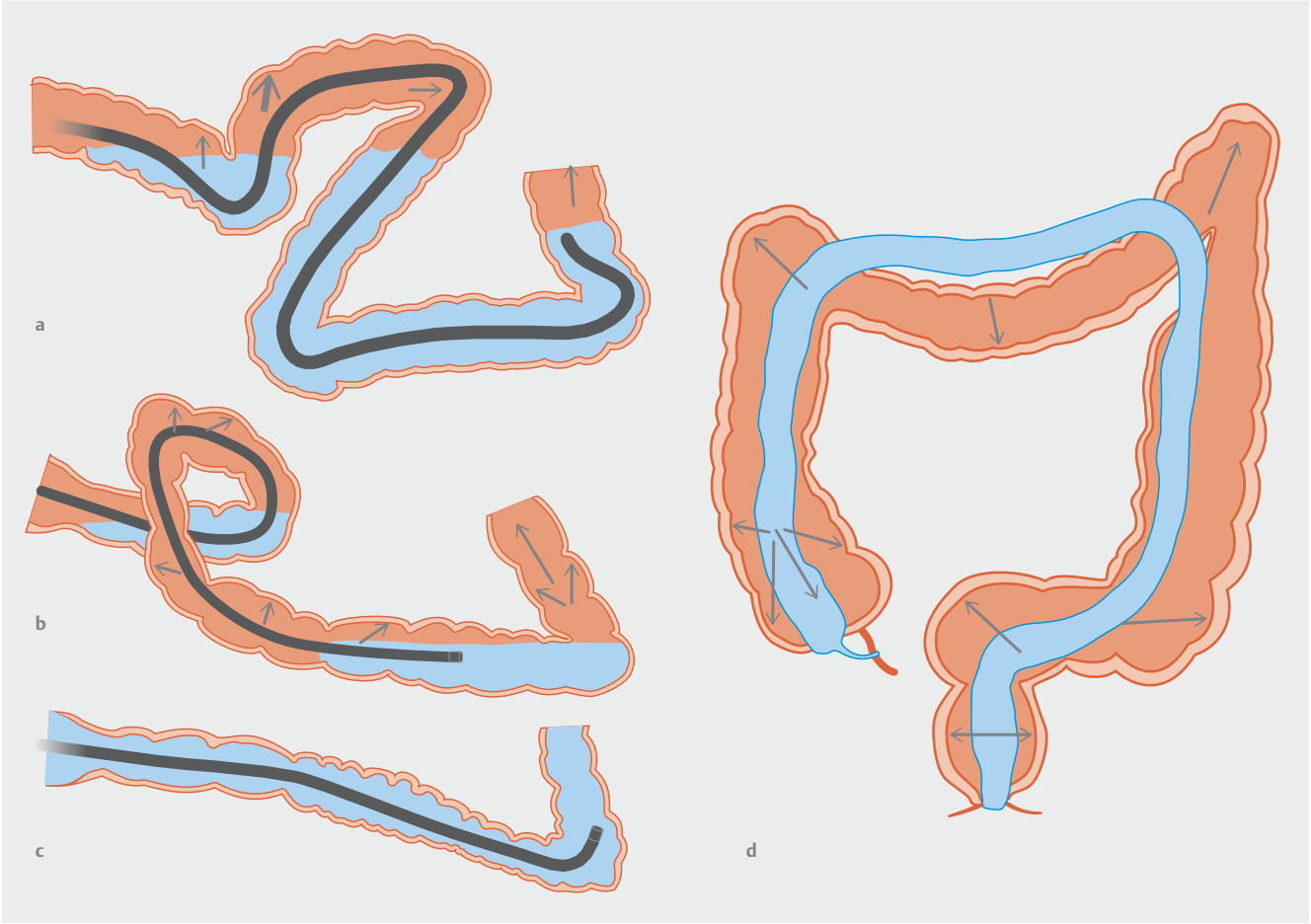
Low adenoma detection rate (ADR; the proportion of patients with at least one adenoma found in the colon) is correlated with the risk of postcolonoscopy CRC [2]. Considering that the effectiveness of colonoscopy hinges on the detection and removal of cancer precursors, novel approaches to improve ADR are desirable.

Air insufflation colonoscopy has been reported to fail to prevent some postscreening right-sided CRC incidence and mortality [3, 4]. Its decreased effectiveness in the proximal colon (cecum to splenic flexure) compared with the distal colon may be related to nonmodifiable factors, such as unique biological features of right-sided cancers [5] or to modifiable deficiencies of screening colonoscopy [6, 7].

Small polyps with flat or depressed morphology and containing advanced histology are more common in the proximal colon than in the distal colon [8]. These small presumptive precursors of cancer are possibly more easily obscured by residual feces, and are more likely to be missed during colonoscopy [8, 9].

Water-aided colonoscopy, in which water is infused in lieu of gas insufflation to distend the lumen during the insertion phase, can be broadly subdivided into water immersion and water exchange. Water immersion is characterized by the infusion of water to facilitate cecal intubation, with limited use of insufflation when necessary, and removal of residual water predominantly during withdrawal [10 – 13]. Water exchange is characterized by the gasless insertion to the cecum in clear water, minimizing distension and maximizing cleanliness during insertion. Removal of residual water is done predominantly during this phase (▶ **Fig. 1a – d**) [10, 11].

Compared with air insufflation, the impacts of water immersion and water exchange differ. Water immersion did not significantly increase ADR [11], whereas previous studies suggest that water exchange might increase ADR [14 – 16], particularly for small size lesions in the proximal colon [11, 14 – 17], providing salvage cleansing and improving bowel preparation [15,



▶ **Fig. 1** The three insertion techniques. **a,b** If air is insufflated or if water is infused as an adjunct to insufflation, the colon is elongated and pushed upwards (arrows), sharpening bends at flexures and/or causing looping. **c** When water is infused in an airless lumen, the colon is not elongated and the sigmoid is straightened, allowing an easier passage into the descending colon. **d** With the colon filled with the amount of water strictly necessary to allow instrument insertion (blue colon lumen), water exchange does not elongate the bowel, and bends and flexures are smoother and easier to negotiate. In contrast, insufflated or residual air (pink colon) elongates and distends the colon, making the procedure more difficult.

17]. Limitations of the studies included their retrospective analysis [11, 14, 17], investigators unblinded to the insertion method [15, 16], and lack of a direct comparison between water exchange, water immersion, and air insufflation with ADR as the primary outcome [11, 14 – 17].

In the current head-to-head comparison of the three techniques with blinded colonoscopists, we aimed to evaluate the impact of the three insertion techniques on ADR. We were also interested in the impact of water exchange in further improving colon cleansing.

Patients and methods

This study was a prospective, double-blinded, multicenter, randomized controlled trial conducted at three endoscopy centers (two in Italy and one in the Czech Republic), with planning assistance provided by a US proponent of water exchange (F. W. L.). From February 2014 through March 2016, consecutive asymptomatic individuals aged 50 – 70 years and undergoing colonoscopy after a positive fecal occult blood test or as primary screening test were considered for eligibility. Exclusion criteria included previous colonoscopy within 5 years, surveillance colonoscopy, previous colorectal surgery, indication for a proctosigmoidoscopy or bidirectional endoscopy, history of inflammatory bowel disease, patient refusal or inability to provide informed consent, and inadequate consumption of bowel preparation. Patients meeting the inclusion criteria who signed an informed consent were enrolled and randomized. The study protocol was approved by the respective local ethics committees and registered at ClinicalTrials.gov (NCT02041507).

Study procedures

Initial standardization of the water exchange method was carried out by hands-on coaching of the principal investigators at each center (S. C., P. F., and F. R.) by F. W. L. Procedures were performed by 11 board-certified endoscopists experienced in all insertion techniques and who had participated in previous water-aided colonoscopy studies. High-definition, wide-angle, adult video colonoscopes (Olympus HD 180 – 190 series; Olympus Corp., Hamburg, Germany) were used. The need to switch to a smaller-caliber colonoscope was considered as intention-to-treat failure.

Instructions on the split-dose bowel preparation (4 L or low-volume polyethylene glycol solution) were provided to all patients in a rigorous manner. Colonoscopists were blinded to the colon preparation used.

All patients were offered conscious sedation (intravenous midazolam, plus fentanyl or meperidine). Medication was administered before the examination or on-demand at the patient's request during the procedure if they experienced discomfort or pain. Before starting the procedure, demographic and clinical data of the patients were recorded.

The patients, but not the colonoscopists and the assisting nurses, were blinded to the insertion method with the monitors placed out of patients' view. In order to overcome the limitation in previous studies of an unblinded colonoscopist performing withdrawal inspection, the withdrawal in the current study was performed by a second colonoscopist, who was blinded to the insertion technique used, after the endoscope had reached the cecum. In the air insufflation and water immersion arms, suction marks were produced at the mid transverse colon, hepatic flexure, and cecum to mimic the same marks frequently produced by the water exchange technique.

Polyps found during the insertion phase were noted during colonoscopy, but permanent records were not kept. If a polyp was seen at insertion but not at withdrawal, the second colonoscopist was asked to re-examine the colon segment containing the missed lesion (segmental unblinding). To assess the adequacy of blinding, the patient and the second colonoscopist were asked at the end of each examination to guess which insertion method had been used. If less that 66 % of these answers were correct, then adequate blinding was considered to have been achieved.

Colonoscopy began with the patients in the left lateral position. In the water exchange and water immersion groups, the air pump was turned off before starting the procedure in order to avoid inadvertent insufflation. During the insertion phase, patients randomized to the water-aided colonoscopy groups had air and residual water or feces present in the rectum aspirated, and then the colon was irrigated with water at 37 °C using flushing pumps (Olympus OFP2; Olympus Corp.). There was no restriction placed on the overall volume of water infused to achieve adequate lumen distension.

Water immersion involved an infusion of water during the insertion phase of colonoscopy mainly to open the colonic lumen and progress to the cecum, without attempting to maximize colon cleanliness. Residual air pockets were not removed [12, 13, 18] and were used to bypass colon content [13]. Infused water and residual feces were suctioned predominantly during withdrawal [12, 13, 18]. Three insufflations of no more than 10 seconds each were allowed to enable the colonoscopists to advance the colonoscope through the lumen that could not be seen clearly [12, 18]. Further use of insufflation was considered as intention-to-treat failure [12].

Water exchange entailed the infusion and simultaneous suction of water to open the lumen in order to allow passage of the instrument in clear water. Suction of infused water was also applied when colonoscope insertion proceeded smoothly in order to maximize cleanliness and minimize distension [10, 16]. Air pockets, when encountered, were always aspirated [10, 16, 18]. In a collapsed colon, turbulence created at the tip of the instrument facilitates the removal of residual feces, providing incidental salvage cleansing during instrument insertion.

In the air insufflation group, colonoscopy was performed in the usual fashion, with minimal insufflation required to aid insertion. Cleaning, done predominantly during withdrawal, could also be carried out during insertion in some cases at the discretion of the colonoscopist [18].

Cecal intubation was defined as the passage of the scope tip beyond the ileocecal valve with visualization of the cecal appendix. After cecal intubation, as much residual water as possible was aspirated before beginning the withdrawal phase. In all arms, withdrawal lasted at least 6 minutes and was done using air insufflation to obtain adequate distension. A stopwatch was

used to time the procedures. Polyp resection was done during withdrawal in all groups. All proximal colon polyps were removed irrespective of their size and appearance.

Colon cleanliness was assessed using the Boston Bowel Preparation Scale (BBPS) [19]. Cardiopulmonary function was monitored throughout. The amount of water infused and suctioned during insertion and withdrawal, and adverse outcomes were recorded.

Polyp location and classification

Polyps were counted and their location marked on a data sheet. Size was determined by comparison with standard biopsy forceps (Radial Jaw 4; Boston Scientific Corp., Marlborough, Massachusetts, USA). Pathology reports were reviewed to cross-check polyp size, and to evaluate ADR, mean adenomas per procedure (MAP; total number of adenomas detected divided by the number of colonoscopies), mean adenomas per positive procedure (MAP+; total number of adenomas detected divided by the number of colonoscopies in which at least one adenoma was detected), proportions of individuals with advanced adenomas (diameter ≥ 10 mm, or high grade dysplasia, or ≥ 20 % villous components), and sessile serrated adenomas (SSA). Adenomas found during segmental unblinding were counted separately for ADR.

Study end points

The primary outcome was overall ADR. Secondary outcomes included right colon ADR, overall and right colon advanced ADR, MAP (entire and right colon), MAP+, SSA distribution, and colon cleanliness. Procedural outcomes, patient satisfaction with the procedure, and willingness to repeat the examination were also evaluated.

Statistical analysis

Analyses were performed as randomized using Minitab 16.1.1 software (Minitab Ltd., Coventry, UK). Standard descriptive statistics were used to assess the distribution of the study variables and to compare them. Normally distributed variables are summarized as means and standard deviation, and non-normally distributed variables are described with medians and interquartile range. Overall *P* values for categorical variables were obtained by chi-squared test or Fisher's exact test, as appropriate. When the overall comparison was significant, post hoc pairwise comparisons were performed. Overall *P* values for continuous variables were obtained by Kruskal – Wallis test and when the overall comparison was significant, post hoc pairwise comparisons were performed. All reported *P* values for pairwise comparisons were adjusted using the Bonferroni correction. A *P* value of < 0.05 was considered to be statistically significant.

Published studies reported separate comparisons of water exchange vs. air insufflation, or water immersion vs. air insufflation, with ADR as a secondary outcome. Based on the observed increase in ADR by water exchange vs. air insufflation of 8.3 % [14], 11.0 % [15], and 10.9 % [16] in screening settings, and taking into account that at the three centers involved in the current study the colonoscopists' aggregated screening ADR was 40.1 %, a sample size of 385 patients per arm could allow for an 80 % power to detect as statistically significant ($\alpha = 0.05$, two-sided test) a 10 % absolute increase in the detection rate of adenomas between water exchange and air insufflation. We considered the 10 % increase to be clinically relevant.

Aggregated data of studies comparing water immersion and air insufflation in patients with mixed indications showed that water immersion was associated with both increases and decreases in overall ADR, and the net change was a significant reduction (−4.4 %, $P = 0.02$) [14]. The two studies that compared water immersion vs. air insufflation in predominantly screening and surveillance patients reported an aggregated 6 percentage point increase in ADR by water immersion (air insufflation 35.3 %; water immersion 41.3 %) [13, 20]. Based on these observations, a sample of 1066 patients per arm would be required (at $\alpha = 0.05$, 80 % power) to show a possible significant increase in ADR of water immersion vs. air insufflation; and a sample of 2447 patients per arm would be required to show a significant difference in ADR between water exchange and water immersion.

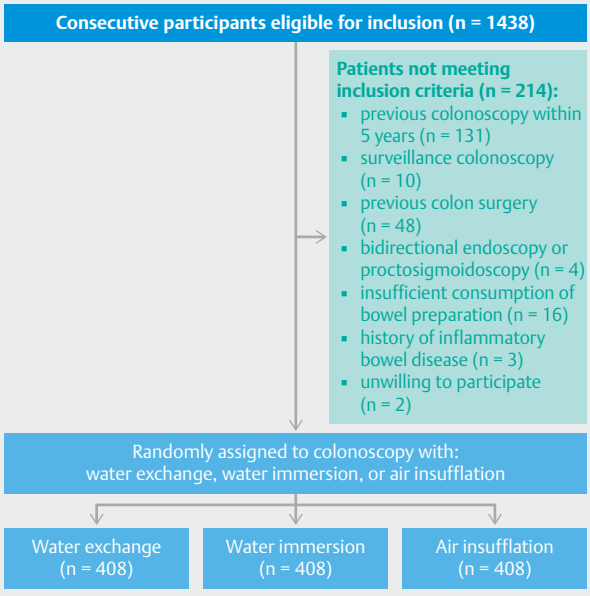
We then designed the current study to test the hypothesis that water exchange, but not water immersion, would significantly increase ADR compared with air insufflation. Such a head-to-head comparison of the three insertion techniques has not been previously reported. We also anticipated a drop-out rate of 6 % (unsuccessful intubation and inspection due to technical difficulty, poor bowel preparation or complications). A computer-generated randomization list with permuted block design with variable block sizes of 3 and 6 yielded a final enrollment of 408 patients per arm. Concealment of allocation was achieved using opaque sealed envelopes.

Results

Patients and procedural data

Overall, 1224 patients were randomized 1:1:1 to water exchange, water immersion, or air insufflation (▶ **Fig. 2**). Most procedures were performed following a positive fecal occult blood test or as primary colonoscopy (▶ **Table 1**).

▶ **Table 2** details the procedural outcomes. Cecal intubation rates, withdrawal time in cases without polypectomy/biopsy, and total procedure times were comparable. Water exchange showed a significantly longer insertion time than water immersion and air insufflation ($P = 0.002$). Cleansing scores and proportions of excellent cleanliness (overall BBPS ≥ 8, right colon BBPS = 3) were significantly higher in the water exchange group. Water immersion did not increase BBPS scores compared with air insufflation. Patient satisfaction with the procedure and willingness to repeat were comparable. Water exchange achieved the highest proportion of unsedated procedures, which was significant compared with air insufflation ($P = 0.03$). Colonoscopist and patient guesses about the insertion technique used were approximately 33 % and < 37 %, respectively. Overall volumes of water infused and aspirated during insertion and withdrawal attested to the correct application of water exchange and water immersion.



▶ **Fig. 2** Study flow chart.

Primary outcome: overall ADR

Overall ADR is reported in ▶ **Table 3**. Data are presented as proportions with 95% confidence intervals (CIs). Compared with air insufflation (40.4%, 95%CI 35.6%–45.3%), water exchange (49.3%, 95%CI 44.3%–54.2%) but not water immersion (43.4%, 95%CI 38.5%–48.3%) achieved significantly higher overall ADR ($P = 0.03$ and $P > 0.99$, respectively).

Secondary outcomes

Compared with air insufflation, water exchange, but not water immersion, achieved significantly higher ADR and advanced ADR in the right colon (▶ **Table 3**). ▶ **Table 3** also shows that water exchange achieved the highest proportions of detected adenomas in the entire colon and in the right colon across all size categories, as well as the highest overall advanced ADR; however, the data were not statistically significantly different. Compared with air insufflation, water exchange, but not water immersion, achieved a significantly higher MAP in the entire colon. Right colon MAP and entire colon MAP + were comparable among the three study arms.

The analysis of SSA distribution in the entire colon was as follows: water exchange 20 (4.9%; 95%CI 3.1%–7.5%), water immersion 9 (2.2%; 95%CI 1.0%–4.3%), and air insufflation 15 (3.7%; 95%CI 2.1%–6.1%). In the right colon, SSA distribution was as follows: water exchange 10 (2.5%; 95%CI 1.2%–4.6%), water immersion 6 (1.5%; 95%CI 0.6%–3.3%), and air insufflation 8 (2.0%; 95%CI 0.9%–3.9%). In the entire and right colon, data were comparable ($P = 0.12$ and $P = 0.60$, respectively).

Per-center analyses

We analyzed ADR and colon cleanliness separately for each center. Compared with air insufflation, water exchange significantly increased ADR at the two centers ($P = 0.03$ and $P = 0.02$, respectively) that also showed significantly higher BBPS scores by water exchange (both overall $P < 0.001$). At the third center, the volume of water (median 300 mL) used to implement water exchange was about one-half of that used at the other centers, and ADR (overall $P = 0.18$) as well as BBPS scores (overall $P = 0.69$) were comparable among study groups.

▶ **Table 1** Demographics details and indications for colonoscopy.

Variable	Water exchange n = 408	Water immersion n = 408	Air insufflation n = 408
Sex, n (%)			
▪ Female	184 (45.1)	185 (45.3)	183 (44.9)
▪ Male	224 (54.9)	223 (54.7)	225 (55.1)
Age, mean (SD), years	61.4 (6.2)	61.0 (6.3)	60.9 (6.2)
Body mass index, mean (SD), kg/m^2	26.4 (4.1)	26.4 (4.4)	26.6 (4.4)
Previous abdominal surgery, n (%)	150 (36.8)	126 (30.9)	154 (37.7)
Family history of colorectal cancer, n (%)	47 (11.5)	47 (11.5)	45 (11.0)
Indications for colonoscopy, n (%)			
▪ Screening FIT +	242 (59.3)	242 (59.3)	222 (54.4)
▪ Screening FOBT +	18 (4.4)	19 (4.7)	19 (4.7)
▪ Primary colonoscopy	148 (36.3)	147 (36.0)	167 (40.9)

FIT + , positive fecal immunochemical test; FOBT + , positive fecal occult (guaiac-based) blood test.

▶ **Table 2** Procedural data.

	Water exchange n = 408	Water immersion n = 408	Air insufflation n = 408	*P* value[1]			
				Overall	Pairwise comparison		
					Water exchange vs. Water immersion	Water exchange vs. Air insufflation	Water immersion vs. Air insufflation
Cecal intubation rate (based on original group assignment), n (%) [95 %CI]	387 (94.9) [92.3 – 96.7]	377 (92.4) [89.3 – 94.7]	386 (94.6) [91.8 – 96.4]	0.70	NC	NC	NC
Cecal intubation rate (final), n (%) [95 %CI]	402 (98.5) [96.7 – 99.4]	400 (98.0) [96.0 – 99.1]	399 (97.8) [95.7 – 98.9]	0.73	NC	NC	NC
Cecal intubation time[2], median (IQR), minutes	9.0 (6.6 – 12.0)	8.0 (5.5 – 11.4)	8.0 (5.3 – 12.0)	0.002	0.01	0.01	> 0.99
Withdrawal time[3], cases without polypectomy, median (IQR), minutes	9.0 (7.0 – 11.0)	9.0 (7.0 – 11.0)	8.0 (7.0 – 10.0)	0.08	NC	NC	NC
Total procedure time[4], median (IQR), minutes	21.0 (17.0 – 30.0)	22.0 (17.0 – 28.7)	20.5 (15.0 – 28.2)	0.06	NC	NC	NC
Colon cleanliness							
▪ BBPS, median (IQR)	9.0 (7.0 – 9.0)	8.0 (6.0 – 9.0)	8.0 (6.0 – 9.0)	< 0.001	< 0.001	< 0.001	> 0.99
▪ BBPS ≥ 8, n (%) [95 %CI]	275 (67.4) [62.8 – 71.9]	227 (55.6) [50.7 – 60.4]	227 (55.6) [50.7 – 60.4]	< 0.001	0.003	0.003	> 0.99
▪ Right colon BBPS, median (IQR)	3.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	< 0.001	< 0.001	< 0.001	> 0.99
▪ Right colon, BBPS = 3, n (%) [95 %CI]	243 (59.6) [40.3 – 61.1]	186 (45.6) [23.3 – 45.7]	190 (46.6) [21.2 – 45.4]	< 0.001	< 0.001	< 0.001	> 0.99
Sedation practice, n (%)							
▪ None	249 (61.0)	235 (57.6)	213 (52.2)	0.04	0.95	0.03	0.37
▪ Conscious sedation	159 (39.0)	173 (42.4)	195 (47.8)				
Adverse events, n (%)							
▪ Cardiorespiratory[5]	5 (1.2)	4 (1.0)	5 (1.2)	0.93	NC	NC	NC
▪ Bleeding[6]	5 (1.2)	6 (1.5)	3 (0.7)	0.60	NC	NC	NC
▪ Other							
Overall satisfaction with procedure[7], median (IQR)	10.0 (9.0 – 10.0)	10.0 (9.0 – 10.0)	10.0 (9.0 – 10.0)	0.13	NC	NC	NC
Willingness to repeat examination, n (%)	389 (95.3)	390 (95.6)	386 (94.6)	0.57	NC	NC	NC

▶ **Table 2** (Continuation)

	Water exchange n = 408	Water immersion n = 408	Air insufflation n = 408	*P* value[1]			
				Overall	Pairwise comparison		
					Water exchange vs. Water immersion	Water exchange vs. Air insufflation	Water immersion vs. Air insufflation
Investigators guessed insertion method, n (%)	119 (29.2)	135 (33.1)	116 (28.4)	0.30	NC	NC	NC
Patients guessed insertion method, n (%)	109 (26.7)	86 (21.1)	151 (37.0)	<0.001	0.17	0.01	<0.001
Infused water during insertion, median (IQR), mL	550 (350 – 800)	400 (250 – 500)	0 (0 – 50)	<0.001	<0.001	<0.001	<0.001
Aspirated water during insertion, median (IQR), mL	500 (350 – 700)	50 (0 – 200)	100 (0 – 200)	<0.001	<0.001	<0.001	>0.99
Infused water during withdrawal, median (IQR), mL	100 (50 – 300)	100 (50 – 200)	100 (50 – 250)	0.50	NC	NC	NC
Aspirated water during withdrawal, median (IQR), mL	200 (100 – 400)	400 (250 – 600)	200 (100 – 350)	<0.001	<0.001	0.73	<0.001

CI, confidence interval; IQR, interquartile range; BBPS, Boston Bowel Preparation Scale; NC, not calculated when the *P* value for the overall comparison among the three groups was not statistically significant.

[1] Overall *P* values for categorical variables were obtained by chi-squared test. When the overall comparison was significant, post hoc pairwise comparisons were performed. Overall *P* values for continuous variables (cecal intubation time, withdrawal time, cases without polypectomy, total procedure time, BBPS, overall satisfaction about procedure, infused water during insertion, aspirated water during insertion, infused water during withdrawal, and aspirated water during withdrawal) were obtained by Kruskal – Wallis test. When the overall comparison was significant, post hoc pairwise comparisons were performed. All *P* values for pairwise comparisons shown in the table have been adjusted by the Bonferroni correction.

[2] Cecal intubation time was defined as the time for passage of the colonoscope from the rectum to the cecum, including time spent infusing water.

[3] Withdrawal time was defined as the time for passage of the colonoscope from the cecum to the rectum

[4] Total procedure time was the sum of the cecal intubation time and the withdrawal time.

[5] Transient oxygen desaturation (<85 % for > 15 seconds) or vagal reaction (heart rate < 60, excessive sweating, nausea and/or vomiting).

[6] Major bleeding episodes requiring immediate or delayed endoscopy therapy.

[7] Score based on numeric rating scale (0 = not satisfied, 10 = very satisfied).

▶ **Table 3** Adenoma detection in the entire colon and in the right colon.

	Water exchange n = 408	Water immersion n = 408	Air insufflation n = 408	*P* value[1]			
				Overall	Pairwise comparison		
					Water exchange vs. Water immersion	Water exchange vs. Air insufflation	Water immersion vs. Air insufflation
Overall ADR, n (%) [95 %CI]	201 (49.3) [44.3 – 54.2]	177 (43.4) [38.5 – 48.3]	165 (40.4) [35.6 – 45.3]	0.04	0.28	0.03	> 0.99
▪ Size category in mm, n (%) [95 %CI]							
– ≤ 5	138 (33.8) [29.3 – 38.7]	128 (31.4) [26.9 – 36.2]	114 (27.9) [23.7 – 32.6]	0.19	NC	NC	NC
– 6 – 9	53 (13.0) [10.0 – 16.7]	45 (11.0) [8.2 – 14.6]	52 (12.7) [9.8 – 16.5]	0.65	NC	NC	NC
– ≥ 10	67 (16.4) [13.0 – 20.5]	59 (14.5) [11.3 – 18.3]	47 (11.5) [8.7 – 15.1]	0.13	NC	NC	NC
Right colon ADR, n (%) [95 %CI]	98 (24.0) [20.0 – 28.5]	78 (19.1) [15.4 – 23.3]	69 (16.9) [13.4 – 20.9]	0.03	0.28	0.04	> 0.99
▪ Size category in mm, n (%) [95 %CI]							
– ≤ 5	73 (17.9) [14.4 – 22.0]	63 (15.4) [12.1 – 19.4]	51 (12.5) [9.5 – 16.2]	0.10	NC	NC	NC
– 6 – 9	18 (4.4) [2.7 – 7.0]	15 (3.7) [2.2 – 6.1]	17 (4.2) [2.5 – 6.7]	0.86	NC	NC	NC
– ≥ 10	19 (4.7) [2.9 – 7.3]	13 (3.2) [1.8 – 5.5]	9 (2.2) [1.1 – 4.3]	0.15	NC	NC	NC
Overall advanced[2] ADR, n (%) [95 %CI]	79 (19.4) [15.7 – 23.6]	70 (17.2) [13.7 – 21.2]	58 (14.2) [11.0 – 18.0]	0.14	NC	NC	NC
Right colon advanced[2] ADR, n (%) [95 %CI]	25 (6.1) [4.0 – 9.0]	18 (4.4) [2.7 – 7.0]	10 (2.5) [1.2 – 4.6]	0.04	0.82	0.03	0.37
MAP (SD)[3]	0.88 (1.2)	0.86 (1.6)	0.72 (1.2)	0.04	0.39	0.04	0.93
Right colon MAP (SD)[4]	0.31 (0.7)	0.31 (0.9)	0.25 (0.8)	0.07	NC	NC	NC
MAP + (SD)[5]	1.79 (1.2)	1.98 (1.9)	1.79 (1.3)	0.69	NC	NC	NC

ADR, adenoma detection rate; CI, confidence interval; MAP, mean adenomas per procedure; MAP + , mean adenomas per positive procedure; NC, not calculated when the *P* value for the overall comparison among the three groups was not statistically significant.

[1] Overall *P* values for categorical variables were obtained by chi-squared test. When the overall comparison was significant, post hoc pairwise comparisons were performed. Overall *P* values for continuous variables (MAP, right colon MAP, and MAP +) were obtained by Kruskal – Wallis test. When the overall comparison was significant, post hoc pairwise comparisons were performed. All *P* values for pairwise comparisons shown in the table have been adjusted by the Bonferroni correction.

[2] Advanced adenomas: adenomas ≥ 10 mm in diameter, or high grade dysplasia, or with ≥ 20 % villous components.

[3] Median (interquartile range, IQR) for water exchange, water immersion, and air insufflation were all equal to 0 (0 – 1.0).

[4] Median (IQR) for water exchange, water immersion, and air insufflation were all equal to 0 (0 – 0).

[5] Median (IQR) for water exchange, water immersion, and air insufflation were all equal to 1.0 (1.0 – 2.0).

Segmental unblinding and failed polyp retrieval

The distribution and number of polyps not found by the second colonoscopist during withdrawal and subsequently identified by unblinding were comparable among the groups: 3 water exchange, 2 water immersion, and 2 air insufflation. Of these polyps, one each in the water exchange and water immersion groups contributed to right colon ADR, and one air insufflation case contributed to distal colon ADR.

Some diminutive polyps (2 water exchange, 2 water immersion, and 3 air insufflation cases) were not retrieved after resection. Assuming they were adenomas, ADR in the water immersion group was not affected (the polyps were lost in a patient with other adenomas that contributed to the ADR). The water exchange and air insufflation arms lost 1 and 2 cases, respectively, that could have contributed to the ADR in these arms.

Adverse events

Adverse events were comparable among groups (▶ **Table 2**). There were 14 cardiorespiratory and 14 post-polypectomy bleeding episodes. All were managed successfully during the procedure. Three water immersion bleeding cases, all with large polyps resected, were admitted for observation. The clinical course was uneventful.

Discussion

In this head-to-head comparison of water exchange, water immersion, and air insufflation with colonoscopy by blinded colonoscopists carried out in patients undergoing CRC screening, the water exchange technique, compared with the air insufflation group, significantly enhanced the detection of adenomas in the entire colon, adenomas and advanced adenomas in the right colon, and MAP in the entire colon. In addition, water exchange significantly enhanced colon cleanliness, overall and in the right colon, even when a split-dose bowel preparation regimen was used.

The results of the current study are relevant for the following reasons. First, our study confirms previous observations that water exchange can increase the detection rate of clinically relevant neoplastic lesions [11, 16 – 18, 21], which is well known to be associated with a higher CRC protection rate [22, 23]. Indeed, ADR is an important colonoscopy quality indicator [7] related to the risk of interval cancer [2], which is predicted by a low ADR [2]. Interval cancers are more likely to be found in the right colon [24], and occur partly as a result of missed lesions [24, 25]. These right colon, small, nonpolypoid [26] CRC precursors have advanced histology more often than distal ones [8, 26]. The enhancement in lesion detection in the entire colon and the right colon by water exchange could play a role in curbing interval cancer incidence and mortality. It has been estimated that each 1 % increase in ADR predicts a 3 % decrease in the risk of interval cancer and a 5 % decrease in the risk of a fatal interval cancer [2].

In addition, the increase in MAP in the entire colon by water exchange is notable. Compared with ADR, MAP is a better reflection of inspection over the entire length of the colon, and is considered to be a promising adjunct to ADR to further enhance colonoscopy quality assurance [7, 27, 28].

Second, as previously reported [15, 17, 18, 21], water exchange significantly increased colon cleanliness to excellent levels both in the entire colon and the right colon, which ultimately led to an increase in ADR and MAP. Colon cleanliness is another important colonoscopy quality indicator [7]. The improvement in the right colon was particularly notable because in this segment it is more difficult to achieve adequate bowel preparation [29]. Whereas suboptimal bowel preparation has been shown to be associated with low ADR [30, 31], excellent bowel cleanliness has been linked to high adenoma detection, especially for diminutive lesions [32].

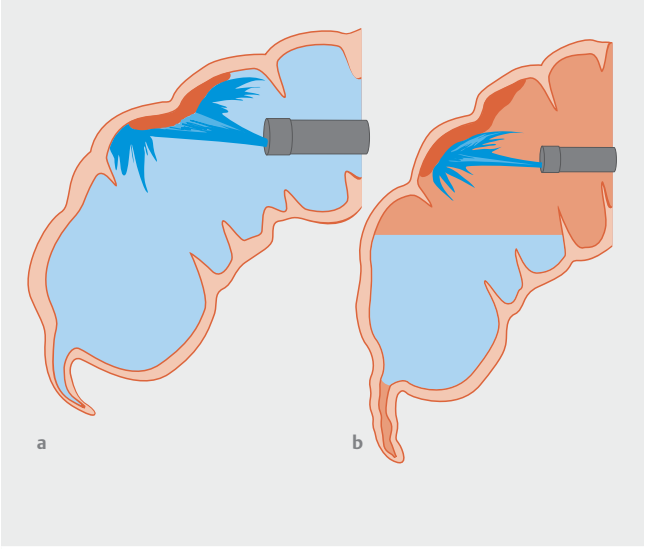
In our study, the salvage cleansing effect of water exchange and the enhancement of colon cleanliness (right colon included), subjective to interoperator variability, are confirmed by the objective outcomes of a higher entire colon and right colon ADR, as well as entire colon MAP, achieved by water exchange.

Third, split-dose preparation was rigorously implemented, and yet water exchange significantly enhanced colon cleanliness, as previously described [18]. Split-dose bowel preparation has been reported to increase colon cleanliness and ADR, especially in the right colon [33]. Reasonably, novel approaches that further enhance bowel cleanliness, facilitating inspection of the colon especially in its right segments, would yield a higher lesion detection to optimize the quality of colonoscopy in colon cancer prevention. The hypothesis that the increase in right colon ADR by water exchange may result in a reduction in right colon interval cancer deserves to be tested.

In the current analysis, water exchange increased ADR and MAP in the entire colon and ADR in the right colon. The confirmation of the primary and secondary hypotheses that water exchange increases overall ADR, right colon ADR, and entire colon MAP, respectively, further improving colon cleanliness after split-dose preparation, provides evidence that water exchange can enhance the quality of screening colonoscopy.

In the current study the cohort of patients with a positive fecal immunochemical test or fecal occult blood test constituted 62.3 % of the total sample. In this selected cohort of high-risk patients, adenomas occur more frequently than in average-risk screening patients [34, 35]. It is possible that, in our study, excellent bowel cleanliness enhanced ADR further because lesions, more visible in a cleaner colon, occurred more frequently. And yet, water exchange significantly improved cleanliness, ADR and MAP.

There are several plausible mechanisms for the increase in lesion detection by water exchange. Compared with air insufflation, water exchange has consistently shown a significant increase in bowel cleanliness [21, 36 – 40], even in the right colon [21, 36 – 39], when same-day or split-dose preparation was used [21, 36 – 40]. In the current study, the median volume of water infused during withdrawal was similar (100 mL) across the three arms. Conversely, there was a significant difference in volumes of water infused during insertion using water exchange when compared with the other two arms. In a deflated bowel, the turbulence created by the jet of infused water and water removal by suction near the tip of the colonoscope is ef-



▶ **Fig. 3** Cleansing effects using air insufflation or water-assisted insertion. **a** In the water-filled and deflated colon, the jet stream of water is very effective in creating turbulence that removes residual feces and debris from the mucosa. **b** The same area is wider and more difficult to clean when the bowel is stretched by inflated air or by residual air pockets.

fective in dislodging residual feces and debris adherent to the mucosa for removal by aspiration (▶ **Fig. 3a**) [38]. In contrast, in a distended bowel (using air insufflation or water immersion) the water jet can only clean a small area (size of the jet) of the mucosa at any time (▶ **Fig. 3b**).

It was hypothesized that the larger volume of infused water, along with the mechanism of turbulence created by water exchange, might represent the main driver for a better colon salvage cleansing and subsequent higher ADR [14]. The current study provided data in support of this hypothesis. In fact, we observed different performance using water exchange at the three centers: at the center in which a lower insertion volume of water was used in water exchange, no significant difference in ADR was achieved. The smaller volume exchanged also resulted in a loss of salvage cleaning, as BBPS was not improved. These observations imply that the salvage cleaning provided by water exchange during insertion is critical to its success in improving ADR, improvement mainly related to the increased detection of small lesions.

Intraprocedural cleansing has been reported to account for a 19.2% of the total withdrawal time of air insufflation colonoscopy [41]. Experience in other settings, especially the aviation industry, clearly shows that multitasking and attention switching have a detrimental impact on the outcome of the principal task [42,43]. It has been demonstrated that, during the withdrawal phase of water exchange procedures, only scarce amount of water is left to be aspirated. There are fewer distractions relating to washing and cleaning [44]; therefore, multitasking and attention switching are minimized and the colonoscopists can do a more focused search for lesions with fewer distractions or disruptions of this activity [18,21,44].

Water exchange does not require a steep learning curve [45], and is certainly suitable for broad application [46]. However, more procedures are required to learn all of its nuances compared with, for example, water immersion [12,13].

Of note in the current study, compared with air insufflation, water exchange significantly decreased the need for sedation, as previously reported [12,38,39], and yet increased ADR, MAP, adenoma, and advanced adenoma detection rates in the right colon.

Our study has a number of strengths. First, unlike previous reports, the insertion and withdrawal phases of colonoscopy were done by different colonoscopists, thus eliminating the possible bias associated with knowledge of the insertion method. Second, our analysis has the largest sample of patients recruited in routine clinical settings in different community hospitals at multinational sites using the three insertion techniques. Third, instructions on the split-dose colon preparation were provided to all patients in a rigorous manner, and water-aided methods were correctly implemented. Fourth, the colonoscopists appeared to have used unbiased withdrawal techniques in all groups, with comparable withdrawal times of procedures without polypectomy and comparable MAP+across study groups. Fifth, the colonoscopist and patient guesses about insertion technique confirmed that adequate blinding had been achieved.

Nonetheless, there are some limitations associated with this study. Records of polyps encountered during insertion were not retained and analyzed [21]. At each center, high-definition Olympus 180, 185, and 190 series colonoscopes were available, but we did not record their use prospectively; therefore we cannot provide information about an association of a specific instrument model with ADR of any type. At one center, water exchange was performed with smaller volumes of water exchanged compared with the other two centers, without maximizing cleanliness during insertion. The lower volumes of water used might have decreased the impact on adenoma detection.

In conclusion, in a European population of screening patients, water exchange was associated with higher overall ADR, right colon ADR and advanced ADR, as well as entire colon MAP. Water exchange further improved colon cleanliness after split-dose bowel preparation. Our findings may be relevant in addressing the issue of missed adenomas, particularly in the cecum and the ascending colon. The design with blinded colonoscopists strengthens the validity of the observation that water exchange, but not water immersion, can achieve significantly higher adenoma detection than air insufflation. Based on this evidence, the use of water exchange should be encouraged.

Acknowledgments

This study was supported by the European Society of Gastrointestinal Endoscopy (ESGE) Research Grant 2013.
The authors are grateful to all personnel for their contribution to recruitment and endoscopy procedures: E. Berenato, P. Binárová, M. Bolková, C. Cardia, E. Carpani, P. Cerronis, E. Clerici, C. Denna, T. Guiso, Z. Ilčíková, J. Kotová, Š. Kostková, A. Macúrová, F. Magnanimo, L. Marelli, M. Matznerová, M. Medas, A.

Santalmasi, I. Šínovská, G. Tatti, A. Trčková, L. Treppete, L. Válková, T. Villa.

Competing interests

None

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