Comparison of carbon dioxide and air insufflation use by non-expert endoscopists during endoscopic retrograde cholangiopancreatography

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Running head: CO2 insufflation during ERCP

Abstract

Background: ERCP are subject to several complications which include a lengthy procedure time, technical difficulty, and active bowel movement induced by air insufflation. In ERCP performed by non-expert endoscopists who are prone to excessive luminal insufflation, insufflation with carbon dioxide (CO2) may provide better and safer outcomes. We aimed to assess the efficacy and safety of CO2 insufflation during ERCP by non-expert endoscopists.

Methods: This study included 208 consecutive patients who received ERCP, excluding those in poor general health or with obstructive lung disease. The first operator for each patient was a non-expert endoscopist having done 50 or less ERCP procedures. Primary outcomes were the changes in cardiopulmonary state during ERCP. Secondary outcomes were ERCP complications. We designed a single center, randomized, prospective, double-blind, controlled trial with CO2 and air insufflation during ERCP.

Results: CO2 insufflation did not affect overall procedure progression or results. A positive correlation was observed between procedure time and change in maximal systolic blood pressure from baseline among patients in the air insufflation group, but not in the CO2 insufflation group (correlation coefficient 0.408 vs. 0.114, change in the maximal systolic blood pressure from baseline +4.2 vs. +1.2 mmHg/ 10 minutes). This was consistent with our findings in patients treated by the first operator alone. The occurrence rate of post-ERCP pancreatitis tended to be lower in the CO2 group than the air group (4/102 [3.9%] vs. 0/106 [0%], P=0.056).

Conclusions: CO_2 insufflation during ERCP by non-expert endoscopists is recommended from the standpoints of efficacy and safety.

Keywords: carbon dioxide, ERCP, post-ERCP pancreatitis, non-expert endoscopist

Introduction

ERCP and its related procedures have become essential techniques in the examination and treatment of pancreato-biliary diseases. However, such procedures are more complicated than traditional examination techniques, resulting in post ERCP-pancreatitis among other serious complications. Procedure-related complications are more frequently seen when ERCP is performed by a non-expert interventionalist, which has raised a need for the development of improved safety measures. [1, 2] Most notably, prolonged examination time and over-insufflation during ERCP by non-experts may trigger active bowel movement and result in unsuccessful tests and complications.

The advantage of insufflation with CO2 instead of air during endoscopy has been well established[3-8]. CO2 is absorbed by the body faster than air and is rapidly excreted through respiration[9]. CO2 insufflation is especially favored in time-consuming endoscopic procedures, such as double-balloon enteroscopy, endoscopic submucosal dissection, and ERCP[10-11]. Furthermore, it was reported that insufflation with CO2 could reduce procedure-related abdominal pain and complications compared with air insufflation due to less bowel hyperextension. Several studies showed that ERCP with CO2 insufflation decreased the incidence and severity of post-procedural abdominal pain and did not affect the incidence of post-ERCP pancreatitis[12-15]. However, as these reports did not weigh its merits with regard to operator experience, it is plausible that CO2 insufflation may be of greater benefit when used during ERCP by non-expert operators. There have been no previous reports about changes in cardiopulmonary state and complication rate during ERCP by non-expert endoscopists as well.

The present trial was conducted to assess the usefulness of CO2 insufflation during ERCP by non-experts, focusing on the efficacy and safety parameters of changes in cardiopulmonary state during ERCP and occurrence of complications.

Methods

Study design

This study was designed as a prospective, single center, double-blind, randomized, control trial. Patients were assigned to one of two groups: the CO2 insufflation group or the air insufflation group. The study protocol was approved by the institutional review board. All participants provided informed consent prior to study enrollment.

Patients

Between November 2010 and September 2011, 208 consecutive adult patients undergoing ERCP for pancreato-biliary disease at Shinshu University Hospital were enrolled in this study. Each first operator was a non-expert endoscopist having done 50 or less ERCP procedures.

The exclusion criteria for patients were as follows: (1) no informed consent, (2) younger than 20 years of age, (3) chronic obstructive pulmonary disease, (4) pregnancy, (5) use of sedative drugs within 12 hours prior to ERCP, (6) receiving endoscopic ultrasonography or gastrointestinal endoscopy within 12 hours before or after ERCP, (7) receiving ERCP at a non-urgent time, (8) use of a double-balloon enteroscope for ERCP, (9) inaccessibility of the papilla of Vater for endoscopic examination, (10) poor general status requiring ERCP by an expert endoscopist (consciousness disorder, systolic blood pressure <80 mmHg, body temperature >39°C, or pulse oxymeter [SpO2] <90%), and (11) judged as inappropriate by a doctor.

Randomization and blinding of the study

Enrolled patients were randomized into two groups designated as the CO_2 insufflation group (CO_2 group, n=106) and the air insufflation group (air group, n=102) by a computer-generated sequence just before ERCP. The procedure room set-up was virtually identical for each procedure.

Endoscopic retrograde cholangiopancreatography

All patients underwent ERCP and related procedures in a prone position after receiving 5 mg midazolam and 7.5 mg pentazocine hydrochloride intravenously for deep conscious sedation. The operator and assistants checked the sedation level of each patient and increased the doses of sedatives accordingly until deep sedation was achieved. Administration of anti-spastic drugs by intramuscular injection of 20 mg scopolamine butylbromide or 1 U.S.P glucagon and introduction of 2 l/min oxygen by a nasal tube were also performed if the need arose. Bile or pancreatic duct cannulation was performed using standard methods with an ERCP catheter (PR-4Q-1, Olympus, Tokyo, Japan). After cannulation, routine procedures, such as sphincterotomy, biceps, biliary stenting, or intraductal ultrasonography, were performed on each patient.

Expert endoscopists assumed control of ERCP sessions when procedure duration endangered the health of the patient. As each first operator was a novice endoscopist, an expert endoscopist took control of the procedure at any time when it did not progress for 10 minutes.

Clinical care and assessment

All patients were routinely measured for SpO2, pulse rate, and arterial blood pressure using a bedside monitor before administration of sedative drugs and every 5 minutes thereafter during procedures. If the patient showed pain or anxiety by unintentional body movement, additional sedatives were administered until deep sedation was re-established. If bowel movements increased during procedures, additional anti-spastic drugs were administered. Oxygen supply by a nasal tube was performed at 2l/min and routinely adjusted to maintain a SpO2 level of 95% during procedures. The change in maximal systolic blood pressure from baseline was defined as the maximal systolic blood pressure during ERCP minus the systolic blood pressure before administration of sedative drugs. This change in cardiopulmonary state was set as the primary end point. Total examination time was routinely recorded and defined as the time period from insertion to pullout of the scope. Measurements of arterial pCO2 and transcutaneous pCO2 were not performed in this study because previous studies on CO2 insufflation during ERCP, colonoscopy, and double-balloon enteroscopy did not show any increases in these parameters[12-14, 16, 17].

Blood cell counts and serum amylase values were evaluated immediately before and 2 hours and the following morning after ERCP. ERCP complications were defined according to Cotton's criteria[18]. ERCP complications were defined as the secondary end point in this study.

Statistical methods

The Fisher's exact and Pearson's chi-square tests were adopted to test for differences between subgroups of patients. To compare continuous data, the Mann-Whitney U test was employed. All tests were performed using the IBM SPSS Statistics Desktop for Japan ver. 19.0 (IBM Japan Inc., Tokyo, Japan). P values of less than 0.05 were considered to be statistically significant.

Sample size

ERCP-related complication rates have been reported by prospective studies to range from 4.2% to 16.8%[19-30]. The occurrence of hypotension during ERCP with midazolam sedation was reported to be from 2.0% to 9.8%, and that of hypoxia was determined to be from 8.2 to 31.3%[31-35]. Since the first operator in this study was a non-expert endoscopist, we predicted complication rates for hypotension or hypoxia to be approximately 20% each. In another study[13], the incidence of post-ERCP pain with CO_2 insufflation was approximately half of that with insufflation with air. Under these conditions, we estimated that analysis of over 100 patients per treatment group were required to provide 80% detection power at an α significance value of 0.05.

Results

Patients

A total of 208 patients requiring urgent ERCP were enrolled in this study and separated into 102 patients who received air insufflation and 106 patients who received CO_2 insufflation (**Fig. 1**). There were no statistical differences with regard to age, sex, incidence of first ERCP, prior sphincterotomy, or prior post-ERCP pancreatitis between the two groups (**Table 1**). The prevalences of final diagnosis and ERCP-related procedures were also similar between the groups (**Table 2, 3**).

Time and success rate of procedures

There were no statistical differences in procedure time or success rate between the two groups. The progress of ERCP and related procedures was not affected by CO_2 insufflation (**Table 4**).

Changes in cardiopulmonary state during ERCP

There were no statistical differences regarding the addition of anti-spastic or sedative drugs between the two groups. However, oxygen supply demand tended to be lower in the CO_2 group than in the air group ($p=0.088$) (**Table 4**).

A positive correlation was observed between procedure time and change in maximal systolic blood pressure from baseline among patients in the air insufflation group, but not in the CO_2 insufflation group (correlation coefficient 0.408 vs. 0.114, change in the maximal systolic blood pressure from baseline +4.2 vs. +1.2 mmHg/10 minutes) (Fig. 2A). It was the same result in patients treated by the first operator alone (Fig. 2B). Although procedure time was long for these operators, there was no significant change in blood pressure elevation in the CO_2 insufflation group.

Adverse events

No statistical differences were observed in white blood cell count and serum amylase level comparisons between the two groups (**Table 4**). Overall, adverse events occurred in 7/208 patients (3.3%; 6 in the air group and 1 in the CO_2 group), and were significantly higher in the air group ($P=0.048$). Post-ERCP pancreatitis occurred in 4/208 patients (1.9%; 3 mild and 1 severe), all of whom were in the air group, albeit not significantly different ($P=0.056$). Other adverse events were an allergy in 1 patient in each group and vagovagal reflex in 1 air group patient. No serious cardiopulmonary complications occurred (**Table 5**).

Discussion

ERCP requires a lengthy procedure time with high levels of sedation and a potentially high amount of air insufflation, which makes CO2 an attractive candidate to improve outcome and safety. The utility of CO2 insufflation during ERCP was reported in previous studies of non-uniformly experienced operators, indicating reductions in abdominal distention and nausea compared with air insufflation[12-15]. Furthermore, CO2 insufflation in enteroscopy and related procedures was shown to reduce bowel hyperextension accompanying luminal over-insufflation, since distended bowels would frequently limit or prevent the flexibility and controllability of the endoscope. In ERCP for patients with a very small papilla of Vater, body movement and active bowel movement during procedures introduce not only operation difficulty, but also edema in the papilla, which in turn may result in post-ERCP pancreatitis. In a previous study, CO2 insufflation during ERCP mitigated abdominal distention and nausea after procedures, but adverse events, such as post-ERCP pancreatitis, were not affected. The present study assessed the utility and safety of CO2 insufflation in ERCP operations done by non-experts and showed that CO2 may reduce complications and the risk of post-ERCP pancreatitis.

Since novice operators tend to over-insufflate during ERCP, insufflation with CO2 may have reduced the demand for oxygen in comparison with air insufflation in our study, but procedure time and success rate were not affected. CO_2 insufflation may have also lowered upward pressure on the diaphragm by reducing pressure changes in the intestinal lumen and intra-abdominal pressure, which reduced pain during ERCP.

The frequency of complications associated with ERCP and related procedures with air insufflation in our study (5.9%) was similar to that previously reported in a recent systematic survey of prospective studies (6.85%)[36) However, the complication rate with CO_2 insufflation in our cohort (0.9%) was clearly lower. CO_2 insufflation during ERCP appeared to reduce the incidence post-ERCP pancreatitis in comparison with air insufflation in the present study. This may be due to the reasons of 1) CO_2 insufflation reduced edema in the papilla of Vater by limiting body movement accompanying pain, as well as movement of the intestinal tract, and 2) CO_2 insufflation reduced the pressure in the intra-pancreatic duct by limiting bowel hyperextension.

In ERCP with prolonged procedure times, we observed that CO_2 insufflation reduced the negative effects of this procedure on dynamic blood circulation. We also demonstrated that CO_2 insufflation reduced pain not only after, but also during, ERCP, although previous studies showed that CO_2 reduced abdominal distention and nausea after ERCP only[12-15)].

Although we decided to recruit procedures being started by a non-expert, eventually only half of the cases in each group were completed by the non-expert alone. The complexity of ERCP-related procedures may thus affect the final clinical outcomes from the study. In our investigation, ERCP for patients in poor general condition and those done by an expert endoscopist were excluded. Thus, it remains unclear whether CO2 insufflation is more useful in patients in poor health due to factors like acute cholangitis or elderly age.

Conclusion

CO2 insufflation during ERCP by non-expert endoscopists could be considered from the standpoints of efficacy and safety.

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Table 1. Characteristics of the study population

	Type of insufflation during ERCP		
	Air (n=102)	CO_2 (n=106)	*p* value*
Age (years) [a]	63.5 (26-87)	65.0 (27-93)	0.372
Male [b]	74 (72.5%)	71 (67.0%)	0.451
First ERCP [b]	26 (25.5%)	22 (20.8%)	0.511
Prior sphincterotomy [b]	60 (58.8%)	56 (52.8%)	0.405
Prior post-ERCP pancreatitis [b]	11 (10.7%)	5 (4.7%)	0.167
Comorbidities			
Ischemic heart disease [b]	7 (6.9%)	8 (7.5%)	0.938
Hypertension [b]	13 (12.7%)	20 (18.9%)	0.227
Atrial fibrillation [b]	2 (2.0%)	4 (3.8%)	0.683
Diabetes [b]	21 (20.6%)	13 (12.3%)	0.105
Previous abdominal surgery [b]	35 (34.3%)	40 (37.7%)	0.607
Cerebrovascular disease [b]	7 (6.9%)	5 (4.7%)	0.714

a: Data are expressed as median (range).

b: Data are expressed as a positive number (%).

* *p* values were calculated using the Mann-Whitney U test and Pearson's chi-square test.

Table 2. ERCP characteristics

	Type of insufflation during ERCP		
	Air (n=102)	CO_2 (n=106)	*p* value*
Diagnostic ERCP	14 (13.7%)	15 (14.2%)	1.000
Endoscopic procedure			
Forceps biopsy of biliary tract	10 (9.8%)	15 (14.1%)	0.335
Brush cytology of pancreatic duct	2 (2.0%)	2 (1.9%)	1
Aspiration cytology of pancreatic juice	0 (0%)	3 (2.8%)	0.246
IDUS of biliary tract	13 (12.7%)	17 (16.0%)	0.323
IDUS of pancreatic duct	2 (2.0%)	4 (3.8%)	0.683
Biliary sphincterotomy	11 (10.8%)	14 (13.2%)	0.672
Pancreatic sphincterotomy	3 (2.9%)	3 (2.8%)	1.000
Papillary balloon dilatation	2 (2.0%)	1 (0.9%)	0.616
Endoscopic nasobiliary drainage	20 (19.6%)	16 (15.1%)	0.425
Endoscopic nasopancreatic drainage	2 (2.0%)	0 (0%)	0.244
Biliary plastic stenting	25 (24.5%)	29 (27.4%)	0.582
Pancreatic plastic stenting	10 (9.8%)	13 (12.3%)	0.694
Biliary metallic stenting	9 (8.8%)	6 (5.7%)	0.430
Removal of CBD stones	15 (14.7%)	14 (13.2%)	0.842
Removal of pancreatic stones	5 (4.9%)	10 (9.4%)	0.285

CBD: common bile duct, IDUS: intra-ductal ultrasonography

* *p* values were calculated using Pearson's chi-square test.

Table 3. Final diagnosis

	Type of insufflation during ERCP		
	Air (n=102)	CO_2 (n=106)	p value*
Final diagnosis			0.444
CBD stones	22 (21.6%)	24 (22.6%)	
Benign BD stricture	20 (19.6%)	23 (21.7%)	
Pancreatic stones	23 (22.5%)	23 (21.7%)	
Cholangiocarcinoma	10 (9.8%)	11 (10.4%)	
BD stricture by lymph nodes	8 (7.8%)	6 (5.7%)	
Pancreatic cancer	7 (6.9%)	4 (3.8%)	
GB cancer	4 (3.9%)	5 (4.7%)	
IPMN	2 (2.0%)	3 (2.8%)	
GB stones	2 (2.0%)	4 (3.8%)	
Pancreatic divisum	2 (2.0%)	0 (0%)	
Autoimmune pancreatitis	0 (0%)	2 (1.9%)	
Other	2 (2.0%)	1 (0.9%)	

CBD: common bile duct, BD: bile duct, GB: gall bladder, IPMN: intra-ductal mucinous neoplasm

* p values were calculated using Pearson's chi-square test.

Table 4. Duration and success rate of procedures and rates of additional sedatives, anti-spastic drugs, and oxygen supply

	Type of insufflation during ERCP		
	Air (n=102)	CO_2 (n=106)	*p* value*
Achieved by first operator alone [a]	49 (48.0%)	53 (50.0%)	0.777
Total examination time [b]	31.7 (6-139)	34.4 (8-134)	0.205
Success rate of insertion into bile or pancreatic duct [a]	99 (97.1%)	104 (98.1%)	0.620
Rate of additional anti-spastic drugs [a]	0 (0%)	0 (0%)	1.000
Rate of additional sedative drugs [a]	45 (44.1%)	53 (50.0%)	0.396
Rate of increased oxygen supply [a]	14 (13.7%)	7 (6.6%)	0.088
White blood cell count > ULN (9130 /μl)			
2 hours after ERCP [a]	19 (18.8%)	16 (15.1%)	0.578
Morning after ERCP [a]	13 (12.7%)	8 (7.5%)	0.254
Serum amylase > 3xULN (381 IU/l)			
2 hours after ERCP [a]	6 (5.9%)	4 (3.8%)	0.530
Morning after ERCP [a]	11 (10.8%)	6 (5.7%)	0.211

ULN: upper limit of normal

[a]: Data are expressed as median (range).

[b]: Data are expressed as a positive number (%).

* *p* values were calculated using Pearson's chi-square test.

Table 5. Adverse events

	Type of insufflation during ERCP		
	Air (n=102)	CO_2 (n=106)	*p* value*
Post-ERCP pancreatitis	4 (3.9%)	0 (0%)	0.056
Mild	3	0	
Moderate	0	0	
Severe	1	0	
Allergy	1 (1.0%)	1 (0.9%)	0.978
Vagovagal reflex	1 (1.0%)	0 (0%)	0.307
Total	6 (5.9%)	1 (0.9%)	0.048

* *p* values were calculated using Pearson's chi-square test.

Figure legends

Figure 1.

Flowchart diagram of study participants

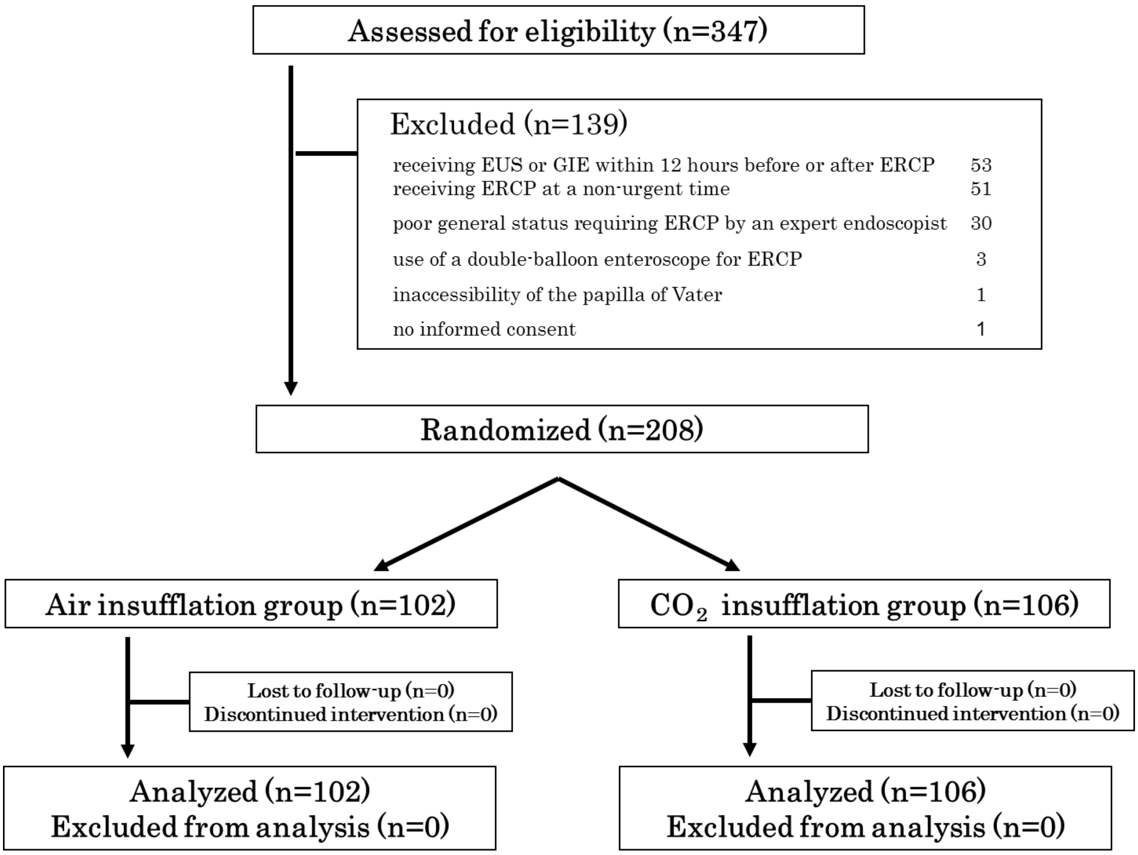
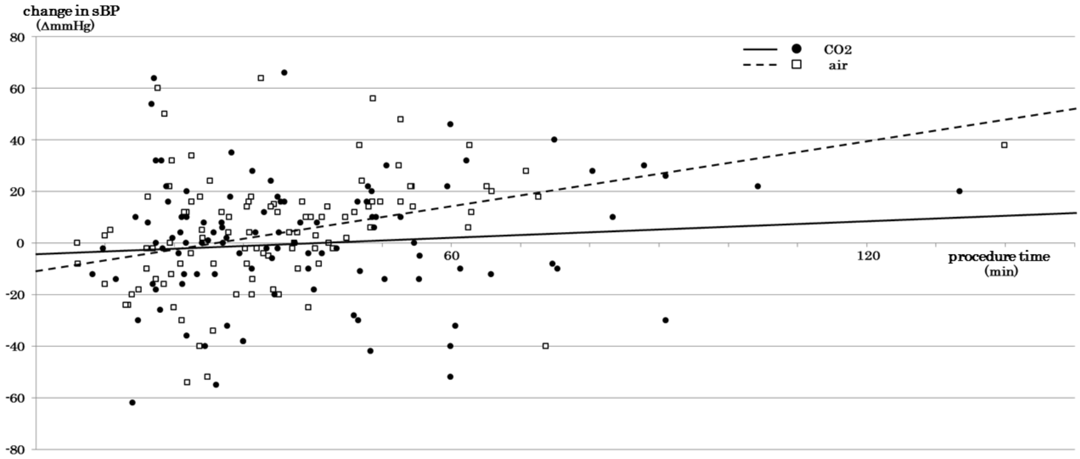


Figure 2.

A: Correlation between procedure time and change in sBP in all patients. In the CO_2 insufflation group, the change in sBP was +1.2 mmHg/10 minutes (correlation coefficient: 0.114, p=0.052). In the air insufflation group, sBP was +4.2 mmHg/10 minutes (correlation coefficient: 0.408, p =<0.001). B: Correlation between procedure time and change in sBP in patients treated by the first operator alone. In the CO_2 insufflation group, the change in sBP was +0.6 mmHg/10 minutes (correlation coefficient: -0.005, p=0.973). In the air insufflation group, sBP was +5.4 mmHg/10 minutes (correlation coefficient: 0.342, p=0.018). The change in sBP was defined as the change in maximal systolic blood pressure from baseline. sBP: systolic blood pressure.

A


change in sBP
(ΔmmHg)
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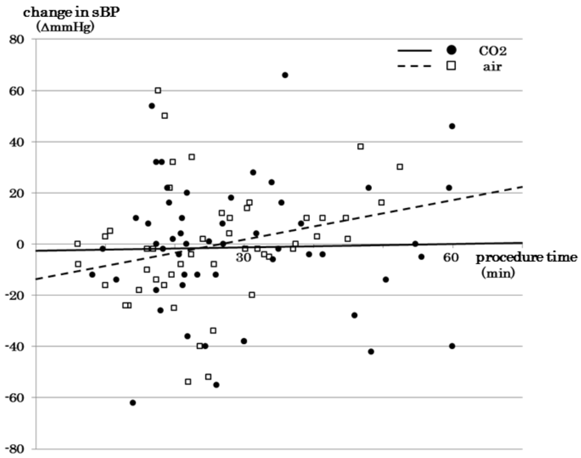
60
40
20
0
-20
-40
-60
-80
60
120
procedure time
(min)
CO2
air

B


change in sBP
(ΔmmHg)
80
60
40
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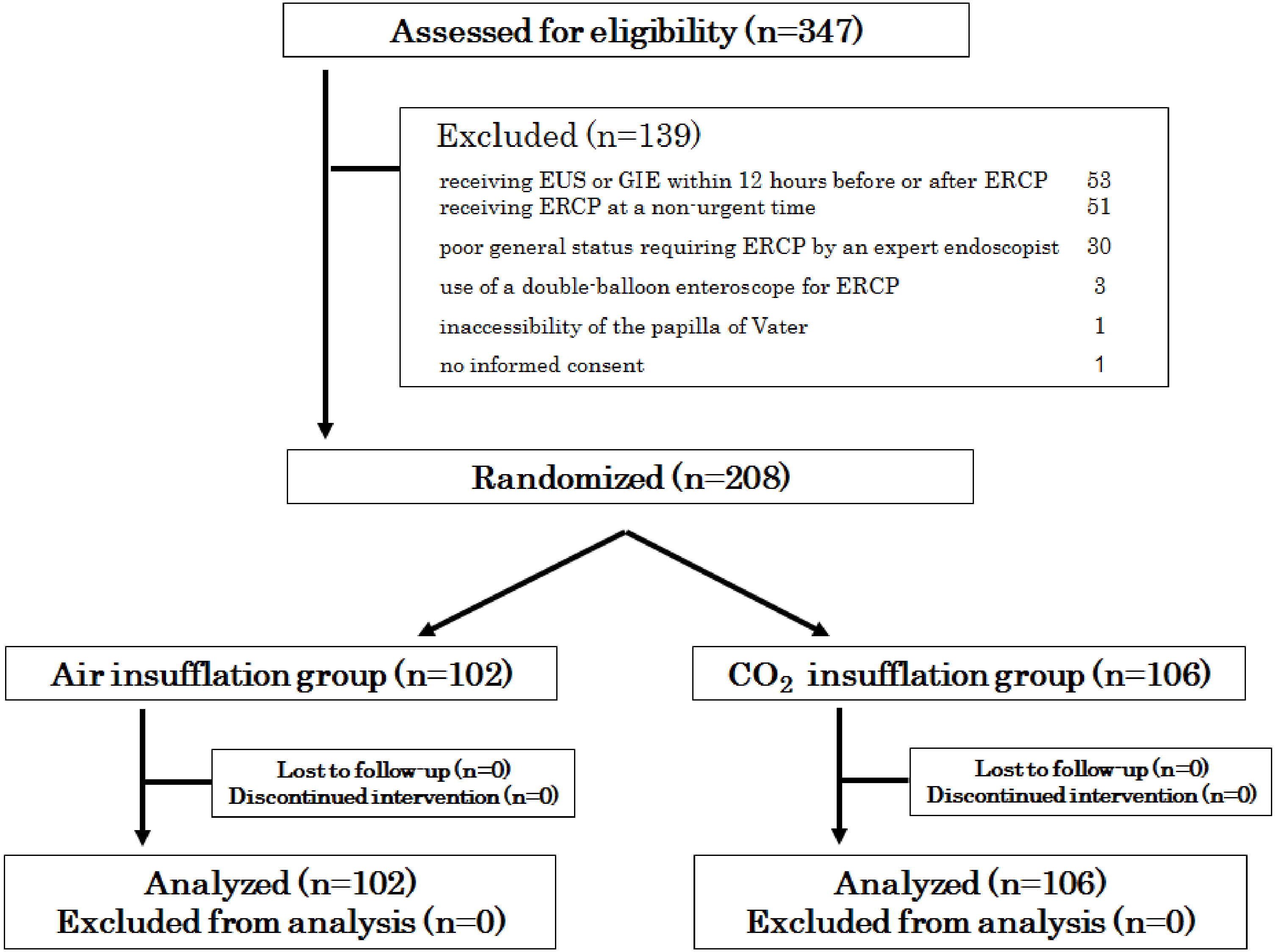
0
-20
-40
-60
-80
30
60
procedure time
(min)
CO2
air



Assessed for eligibility (n=347)
Excluded (n=139)
receiving EUS or GIE within 12 hours before or after ERCP 53
receiving ERCP at a non-urgent time 51
poor general status requiring ERCP by an expert endoscopist 30
use of a double-balloon enteroscope for ERCP 3
inaccessibility of the papilla of Vater 1
no informed consent 1
Randomized (n=208)
Air insufflation group (n=102)
CO_2 insufflation group (n=106)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Analyzed (n=102)
Excluded from analysis (n=0)
Analyzed (n=106)
Excluded from analysis (n=0)

Figure 1.

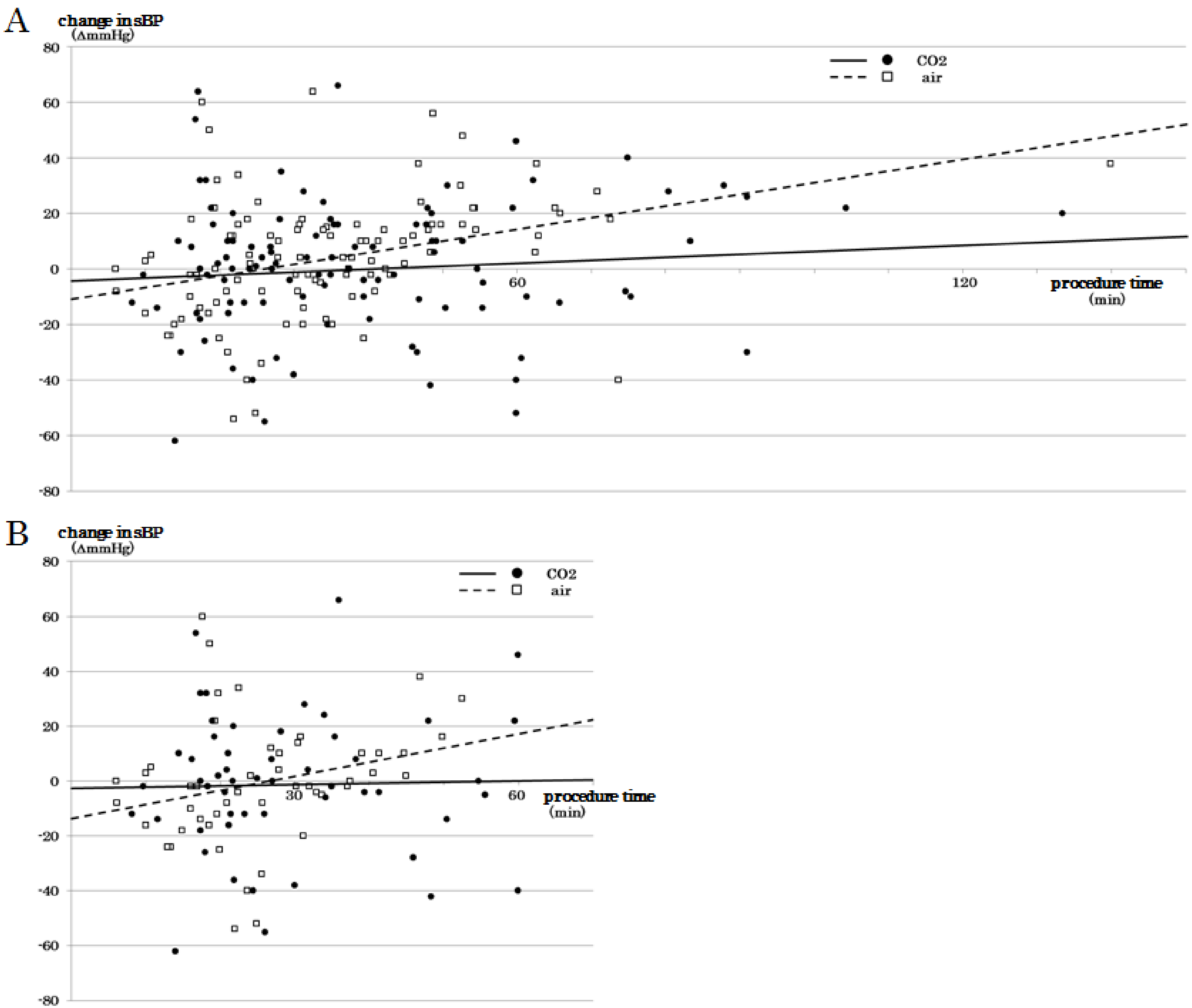

A
change in sBP
(ΔmmHg)
80
60
40
20
0
-20
-40
-60
-80
60
120
procedure time
(min)
CO2
air
B
change in sBP
(ΔmmHg)
80
60
40
20
0
-20
-40
-60
-80
30
60
procedure time
(min)
CO2
air

Figure 2.