学位論文（博士）

Pancreatobiliary flow dynamics: Association between bile and pancreatic juice evaluated with cine-dynamic magnetic resonance cholangiopancreatography using spatially selective inversion recovery pulse.

（膵液・胆汁の排出動態：空間選択的 IR パルス併用 cine dynamic MRCP による胆汁と膵液の関連性の評価）

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医学専攻　放射線医学講座

令和３年１０月

学位論文の関連論文の研究背景及び要旨

所属　放射線医学講座
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〔題名〕

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〔研究背景〕

胆道系と膵臓は、発生や解剖、病理組織学的に密接な関係がある。胆汁と膵液の排出は、主に主膵管と総胆管の合流部を取り囲む Oddi 括約筋により調節されていると考えられているが、胆汁と膵液の生理的な流れのパターンや相互関係については十分に解明されていない。これまでの研究で、空間選択的 IR パルス併用 cine dynamic MRCP を用いて、膵液と胆汁の生理的な流れや、肝外胆管拡張や胆摘後、慢性膵炎などの様々な病態における膵液と胆汁の排出動態の変化について評価されてきた。いずれも膵液と胆汁の排出動態を別々に評価しているが、膵液と胆汁の排出タイミングは必ずしも一致しないことがわかっている。胆道狭窄や括約筋機能不全、膵胆管合流異常など、様々な病態で膵液や胆汁の排出動態は変化するため、膵液や胆汁の生理的な排出動態の相互関係を解明することは臨床的に有用である。さらに、膵炎を伴わない主膵管拡張の患者における膵液と胆汁の排出動態の変化についても、まだ明らかになっていない。したがって本研究では、肝外胆管や主膵管に疾患のない患者を対象に、空間選択的 IR パルス併用 cine dynamic MRCP を用いて、胆汁と膵液の生理的な流れのパターンを同時に評価し、膵炎を伴わない主膵管拡張のある患者と比較することを目的とした。

〔要旨〕

方法：2019 年 1 月から 12 月の間に cine dynamic MRCP を含む腹部 MRI 検査を施行され、胆汁や膵液の生理的な流れに影響を与えるような疾患のない 104 名の患者を対象とした。この中で、主膵管および肝外胆管の拡張がない 85 名の患者を正常群とし、主膵管拡張（>3mm）が見られた 19 名の患者を膵管拡張群とした。

3 テスラの MRI（Vantage Galan ZGO，Canon Medical Systems）を使用した。まず 50mm 厚の 1 回の息止め 2D MRCP 画像に、20mm 幅の空間選択的 IR パルスを主膵管と下部総胆管にできるだけ直交する角度で印加して撮像した。IR パルス内では、流れのない膵液や胆汁は信号抑制され無信号となり、流れのある膵液や胆汁は高信号に描出される。一方、IR パルス外の胆汁と膵液の逆行性の流れは低信号域として描出される。この 5 秒間の呼吸停止 MRCP 撮像を 15 秒間隔で繰り返し、5 分間で 20 回の連続撮像を行った（cine dynamic MRCP）。

各患者 20 枚の cine dynamic MRCP 画像において、IR パルス内外で観察された膵液と胆汁の順行性と逆行性の流れの頻度と、移動距離に基づいた 5 段階の排出グレード（グレード 0：排出なし、グレード 1：5mm 未満、グレード 2：5〜10mm、グレード 3：11〜15mm、グレード 4：15mm 以上）を 3 人の放射線科医が評価し、排出グレートの合計を 20 で割った平均排出グレードを解析に用いた。さらに、各画像で観察された膵液と胆汁の流れを 4 つの膵液の流れのパターン（順行性：P_A、逆行性：P_R、順行性＋逆行性：P_{A+R}、流れなし：P_N）と 4 つの胆汁の流れのパターン（順行性：B_A、逆行性：B_R、順行性＋逆行性：B_{A+R}、流れなし：B_N）を組み合わせた 16 パターン（P_A - B_A、P_A - B_R、P_A - B_{A+R}、P_A - B_N、P_R - B_A、P_R - B_R、P_R - B_{A+R}、P_R - B_N、P_{A+R} - B_A、P_{A+R} - B_R、P_{A+R} - B_{A+R}、P_{A+R} - B_N、P_N - B_A、P_N - B_R、P_N - B_{A+R}、P_N - B_N）に分類し（図 1-3）、各患者群の全画像のうち、各流れのパターンが何回観察されたかを評価した。

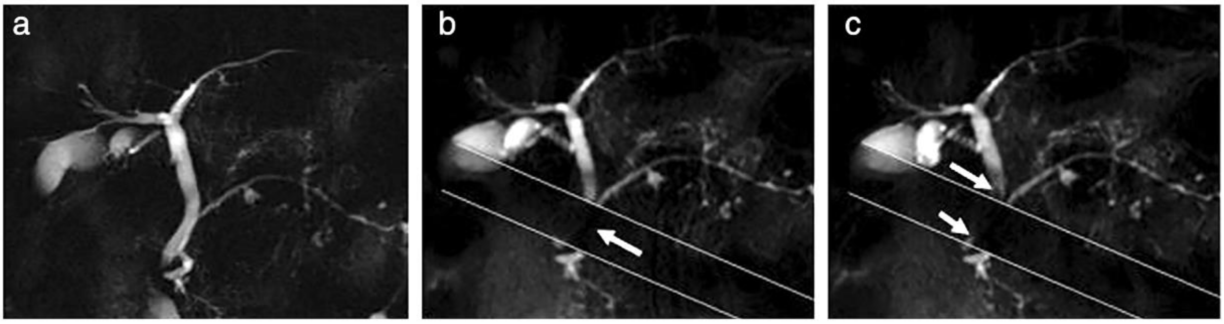

図１ (a) MRCP 画像、(b,c) cine dynamic MRCP 画像

(b) P_N - B_N パターン、(c) P_N – B_R パターン（逆行性の胆汁排出グレード 1）

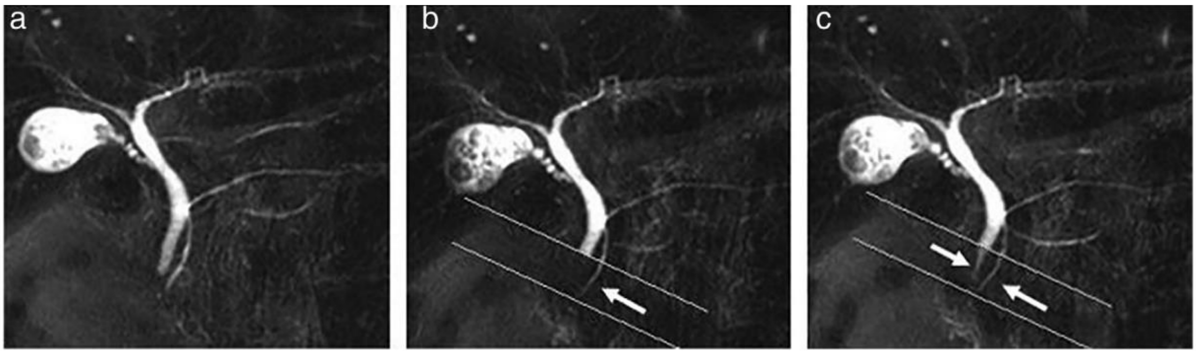

図２ (a) MRCP 画像、(b,c) cine dynamic MRCP 画像

(b) P_A - B_N パターン（順行性の膵液排出グレード 4）、(c) P_A – B_A パターン（順行性の膵液排出グレード 4、順行性の胆汁排出グレード 3）

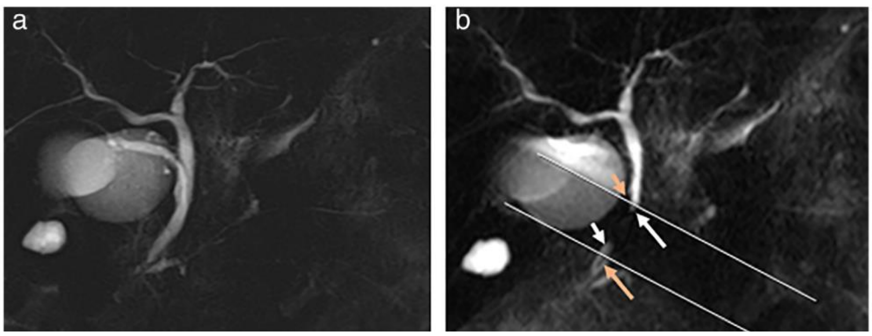

図３ (a) MRCP 画像、(b) cine dynamic MRCP 画像

(b) P_N – B_{A+R} パターン（順行性・逆行性の胆汁排出グレード 1）

統計解析には Spearman の順位相関係数、Kruskal-Wallis 検定，Mann-Whitney U 検定、X^2 検定、Fisher の正確確率検定を用いた。

結果： 正常群では、P_A - B_N パターンの頻度が最も高く（29%）、次いで P_N - B_N パターン（23%）、P_A - B_A パターン（22%）であった。膵液と胆汁が同じ流れのパターンを示したのは 47%（P_A - B_A：22%、P_R - B_R：2%、P_N - B_N：23%）で、53%が異なる流れのパターンを示した。膵管拡張群では、P_N - B_N パターンが最も多く（56%）、次いで P_A - B_N パターン（16%）であった（表 1）。

	Normal group (n = 85)	Dilated pancreatic duct group (n = 19)	*p* value
Number of images	1700	380	
Flow pattern			
P_A–B_A	367 (22)	28 (7)	<0.001
P_A–B_R	95 (6)	8 (2)	0.005
P_A–B_{A+R}	47 (3)	0 (0)	0.001
P_A–B_N	485 (29)	59 (16)	<0.001
P_R–B_A	3 (0.2)	1 (0.3)	0.554
P_R–B_R	33 (2)	3 (0.8)	0.120
P_R–B_{A+R}	1 (0.06)	0 (0)	0.817
P_R–B_N	6 (0.4)	6 (2)	0.012
P_{A+R}–B_A	0 (0)	1 (0.3)	0.183
P_{A+R}–B_R	1 (0.06)	1 (0.3)	0.332
P_{A+R}–B_{A+R}	0 (0)	1 (0.3)	0.183
P_{A+R}–B_N	0 (0)	1 (0.3)	0.183
P_N–B_A	107 (6)	26 (7)	0.693
P_N–B_R	145 (9)	31 (8)	0.814
P_N–B_{A+R}	17 (1)	2 (0.5)	0.297
P_N–B_N	393 (23)	212 (56)	<0.001

Data are given as the number of the flow pattern observed with percentages in parentheses.

表 1　正常群と膵管拡張群での膵液と胆汁の流れのパターンの比較

Cine-dynamic MRCP 所見を正常群と膵管拡張群で比較したところ（表 2）、膵管拡張群は正常群と比べ、膵液の順行性の流れの頻度と排出グレードが有意に低かった（頻度：3 回 vs. 13 回、排出グレード：0.25 vs. 0.9）。また、胆汁の順行性の流れの頻度と排出グレードも有意に低かった（頻度：2 回 vs. 6 回、排出グレード：0.1 vs. 0.35）。一方、膵液と胆汁の逆行性の流れの頻度と排出グレードに有意差は見られなかった。

	Normal Group (n = 85)	Dilated Pancreatic Duct Group (n = 19)	P value
Age (y)	71 (62–77)	75 (69–79)	0.072
Diameter of main pancreatic duct (mm)	2 (2–3)	4 (4–5.5)	<0.001
Diameter of common bile duct (mm)	6 (5–8)	7 (5.5–8)	0.210
Frequency of antegrade pancreatic juice flow observed	13 (8–16)	3 (0–9)	<0.001
Secretion grade of antegrade pancreatic juice flow	0.9 (0.5–1.4)	0.25 (0–0.48)	<0.001
Frequency of reversed pancreatic juice flow observed	0 (0–0)	0 (0–0)	0.931
Secretion grade of reversed pancreatic juice flow	0 (0–0)	0 (0–0)	0.995
Frequency of antegrade bile flow observed	6 (1–10)	2 (0–5.5)	0.008
Secretion grade of antegrade bile flow	0.35 (0.1–0.6)	0.1 (0–0.28)	0.006
Frequency of reversed bile flow observed	3 (1–6)	1 (0–5)	0.092
Secretion grade of reversed bile flow	0.2 (0.05–0.4)	0.05 (0–0.28)	0.129

Data are median with 25th and 75th percentiles in parentheses.

表２　正常群と膵管拡張群での MRI 所見の比較

考察:主膵管と総胆管は乳頭部で合流し十二指腸に注ぐことから、通常は膵液と胆汁の排出タイミングは連動していると想定される。しかし、本研究では正常群の 53%で膵液と胆汁の排出は連動しておらず、これは各流れを誘発するトリガーの違いが影響している可能性がある。今回観察された胆汁と膵液の流れのパターンの頻度は、膵管・胆管内圧や括約筋機能などの生理的な相互関係を反映していると考えられ、例えば正常群で最も頻度が高い P_A - B_N パターンは、通常膵管内圧が総胆管内圧より高く、括約筋圧よりも容易に高くなることで、膵液が高頻度に排出されることによると思われる。

膵管拡張群では、膵液だけでなく胆汁の順行性の流れも減少していた。膵管拡張と胆汁排出との関連ははっきりしないが、膵実質の障害により胆汁分泌が低下することが報告されている。対象患者の大部分が膵管内乳頭粘液性腫瘍（IPMN）を有しており、IPMN は病理学的に膵実質の軽度から中等度の線維化や腺房萎縮などの慢性膵炎の像を示すことから、軽微な慢性膵炎の結果として、膵液と胆汁の順行性の流れの減少が起こった可能性が考えられる。

結語:空間選択的 IR パルス併用 cine dynamic MRCP により、胆汁と膵液の生理的な流れの様々なパターンを可視化することができ、その中の 53%が膵液と胆汁が異なる流れのパターンを示した。胆汁と膵液の排出動態は主膵管拡張により変化することが予想されるため、正常な胆汁と膵液の流れのパターンを認識しておくことは重要である。

Pancreatobiliary Flow Dynamics: Association Between Bile and Pancreatic Juice Evaluated With Cine-Dynamic Magnetic Resonance Cholangiopancreatography Using Spatially Selective Inversion Recovery Pulse

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Background: The physiological flow patterns and the reciprocal relationship between pancreatic juice and bile excretion dynamics have not been clearly elucidated by imaging.
Purpose: To assess the physiological flow patterns of bile and pancreatic juice simultaneously in order to clarify the pancreatobiliary flow dynamics using cine-dynamic magnetic resonance cholangiopancreatography (MRCP) with a spatial selective inversion recovery (IR) pulse.
Study Type: Retrospective.
Population: A total of 85 patients with physiologically normal pancreatobiliary flow without ductal dilatation (normal group) and 19 patients with dilated pancreatic duct.
Field Strength/Sequence: A 3 T, fast spin echo sequence with IR pulse to nullify the signal of static pancreatic juice and bile.
Assessment: The frequency and secretion grade of the antegrade and reverse flow of the pancreatic juice and bile on cine-dynamic MRCP were visually evaluated. Additionally, the reciprocal relationship between pancreatic juice and bile flow was evaluated based on its flow patterns.
Statistical Tests: Spearman's rank correlation coefficient analysis and the Kruskal–Wallis and Mann–Whitney *U* tests were used. *P* values of <0.05 were considered to indicate statistical significance.
Results: In the normal group, the antegrade pancreatic juice flow and no bile flow pattern was most frequently observed (29%), followed by the no pancreatic juice flow and no bile flow pattern (23%), the antegrade pancreatic juice flow and antegrade bile flow pattern (22%), and the no pancreatic juice flow and reverse bile flow pattern (9%). The flow of the pancreatic juice and bile were synchronized with each other in 47%, while they were not in 53%. In the dilated pancreatic duct group, the mean secretion grade of the antegrade bile and pancreatic juice flow was significantly lower than in the normal group.
Data Conclusion: Cine-dynamic MRCP with a spatially selective IR pulse can visualize the variations of the physiological flow patterns of bile and pancreatic juice including 53% of unsynchronized patterns.
Level of Evidence: 4
Technical Efficacy: Stage 5

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The biliary system and pancreas show closely related development, anatomy and histopathological findings.[1] The common bile duct joins the main pancreatic duct to frequently form a common channel before opening into the duodenum at the ampulla of Vater.[2] The excretion of pancreatic juice and bile is thought to be regulated by the sphincter of Oddi surrounding the junction of the common bile duct and pancreatic duct.[3] However, the physiological flow patterns and relationship between pancreatic juice and bile excretion dynamics are not well understood.

Some studies have evaluated the excretion flow dynamics of pancreatic juice and bile using cine-dynamic magnetic resonance cholangiopancreatography (MRCP) with a spatially selective inversion recovery (IR) pulse.[4,5] These studies demonstrated that the secretion of bile and pancreatic juice was irregular and that reverse bile flow in the extrahepatic bile duct was a physiological phenomenon. These studies also showed that the frequency of antegrade bile flow was decreased in patients with extrahepatic bile duct dilatation, while that of reverse bile flow was not. In addition, cine-dynamic MRCP with a spatially selective IR pulse technique has been applied in several clinical investigations. For instance, it has been reported that this technique was useful for the early diagnosis of chronic pancreatitis as well as the assessment of its severity.[6,7] Another study showed that antegrade bile flow was observed more frequently in patients after cholecystectomy, probably due to the increased internal pressure of the extrahepatic bile duct.[8] In these studies, the flow dynamics of pancreatic juice and bile were evaluated separately; however—in the clinical setting—it has been noted that the timing of pancreatic juice and bile excretion is not always linked. It would be clinically useful to elucidate the relationship in the physiological flow dynamics of pancreatic juice and bile because the pancreatobiliary flow dynamics can change in various pathological conditions, including biliary stricture, sphincter dysfunction, and anomalous union of the pancreatobiliary duct with reflux.[9,10] Additionally, the changes in the bile and pancreatic flow dynamics in patients with main pancreatic duct dilatation without pancreatitis are still unclear.

Thus, the purpose of this study was to assess the physiological flow patterns of bile and pancreatic juice simultaneously using cine-dynamic MRCP in patients without diseases involving the extrahepatic bile duct or main pancreatic duct and to compare them with patients having main pancreatic duct dilatation without pancreatitis.

Materials and Methods

Study Population

This retrospective study was approved by our institutional review board, and the need for informed consent from the patients was waived. An imaging database was searched for patients who underwent abdominal MRI examinations between January 2019 and December 2019. The inclusion criteria were as follows: 1) suspicion of hepatobiliary or pancreatic disease based on the patient's clinical history or previously performed ultrasonography or computed tomography (CT) and 2) patient underwent cine-dynamic MRCP as a part of our hepatobiliary and pancreatic MRI examination protocol. The patients without disease that could affect the physiological flow of the bile or pancreatic juice were considered as patients with "physiologically normal" pancreatobiliary flow dynamics. Of these, the patients who had no dilatation of the main pancreatic duct or extrahepatic bile duct were enrolled as the normal group. Additionally, the patients who had dilation of the main pancreatic duct (>3 mm)[11] were enrolled as the dilated pancreatic duct group. In the normal group, the patients were classified into three groups according to age as follows: group 1, ≤65 years; group 2, 66–75 years; and group 3, ≥76 years.

MRI Protocol

MRI was performed with a 3 T clinical MRI system (Vantage Galan ZGO, Canon Medical Systems, Tochigi, Japan) equipped with a 16-channel body coil. Patients fasted for at least 4 hours before the MRI examination. Before the start of the MRI examination, each patient orally ingested 36 mg of manganese chloride tetrahydrate (Bothdel Oral Solution 10, a package of 250 mL; Kyowa Hakko Kirin, Tokyo, Japan) to reduce bowel peristalsis-related artifacts. First, a breath-hold, thick-slab two-dimensional MRCP image was obtained in the coronal plane as a reference, using a fast spin-echo sequence. The imaging parameters of this sequence were as follows: repetition time (TR)/echo time (TE), 5000/507 msec; echo train spacing, 6.5 msec; slice thickness, 50 mm; acquisition matrix, 512 × 512; field of view (FOV), 350 × 350 mm; and bandwidth, 558 Hz/pixel. Next, using the same sequence, a spatially selective IR pulse (inversion time, 2200 msec) of 20 mm in width was placed as perpendicularly as possible to the main pancreatic duct and lower common bile duct to nullify the signal of the static pancreatic juice and bile.[4,5] MRCP with a spatially selective IR pulse was repeatedly performed every 15 sec (5 sec imaging and 10 sec) for 5 minutes to acquire a series of single-shot MRCP images (20 images total), and a series of these MRCP images were displayed in cine-dynamic fashion (cine-dynamic MRCP).

Image Evaluation

Cine-dynamic MRCP images were evaluated independently by three radiologists (K.I., M.T. and M.H., with 33, 19, and 6 years of clinical experience, respectively). The reviewers were blinded to any clinical information of the patients, and any interpretation discrepancies were resolved by reaching a consensus. MR images were evaluated for the frequency and the movement distance of the antegrade and reverse flow of the pancreatic juice and bile observed in the main pancreatic duct and common bile duct of each patient over the 5-minute imaging period (20 images). The secretion grade was categorized based on the movement distance of the pancreatic juice and bile using the 5-point secretion grading score (grade 0, no secretion; grade 1, <5 mm; grade 2, 5–10 mm; grade 3, 11–15 mm; grade 4, > 15 mm).[5] The mean secretion grade for each patient was defined as follows: (total of grading score)/20.

In addition, the reviewers classified the flow pattern of the pancreatic juice and bile observed on each image of the cine-dynamic MRCP series; the four pancreatic juice flow patterns

TABLE 1. Comparison of the Flow Patterns of the Pancreatic Juice and Bile Between the Normal Group and the Dilated Pancreatic Duct Group

	Normal group (n = 85)	Dilated pancreatic duct group (n = 19)	*p* value
Number of images	1700	380	
Flow pattern			
P_A–B_A	367 (22)	28 (7)	<0.001
P_A–B_R	95 (6)	8 (2)	0.005
P_A–B_{A+R}	47 (3)	0 (0)	0.001
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P_R–B_R	33 (2)	3 (0.8)	0.120
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P_R–B_N	6 (0.4)	6 (2)	0.012
P_{A+R}–B_A	0 (0)	1 (0.3)	0.183
P_{A+R}–B_R	1 (0.06)	1 (0.3)	0.332
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P_N–B_A	107 (6)	26 (7)	0.693
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P_N–B_N	393 (23)	212 (56)	<0.001

Data are given as the number of the flow pattern observed with percentages in parentheses.

(antegrade pancreatic juice flow, P_A; reverse pancreatic juice flow, P_R; simultaneously observed antegrade and reverse flow of pancreatic juice, P_{A+R}; no flow of pancreatic juice, P_N), and the four bile flow patterns (antegrade bile flow, B_A; reverse bile flow, B_R; simultaneously observed antegrade and reverse flow of bile, B_{A+R}; no flow of bile, B_N), and finally the 16 patterns by the combination of the

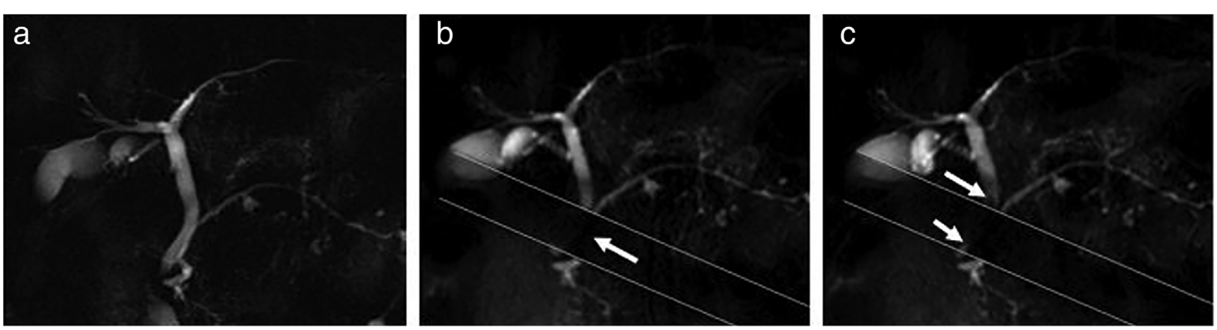

FIGURE 1: A 78-year-old woman with branch-duct intraductal papillary mucinous neoplasms in the normal group. (a) MRCP image without a spatially selective IR pulse obtained as a reference image. (b,c) Representative images of the no pancreatic juice flow and no bile flow (P_N–B_N) pattern and the no pancreatic juice flow and reverse bile flow (P_N–B_R) pattern observed during cine-dynamic MRCP with a spatially selective IR pulse. (b) The static pancreatic juice and bile within the area of the spatially selective IR pulse (the area of 20 mm width between the parallel white lines) was shown as low signal intensity (arrow). The flow pattern of the pancreatic juice and bile was classified as P_N–B_N pattern. (c) The reversed flow of the bile was observed as low signal intensity outside the area of the spatially selective IR pulse (long arrow) and was also observed as high signal intensity coming from papilla Vater side within the area of the spatially selective IR pulse (short arrow) on the cine-dynamic MRCP image with a spatially selective IR pulse. The secretion grade of the reversed bile flow was categorized as grade 1. The flow pattern of the pancreatic juice and bile was classified as P_N–B_R pattern.

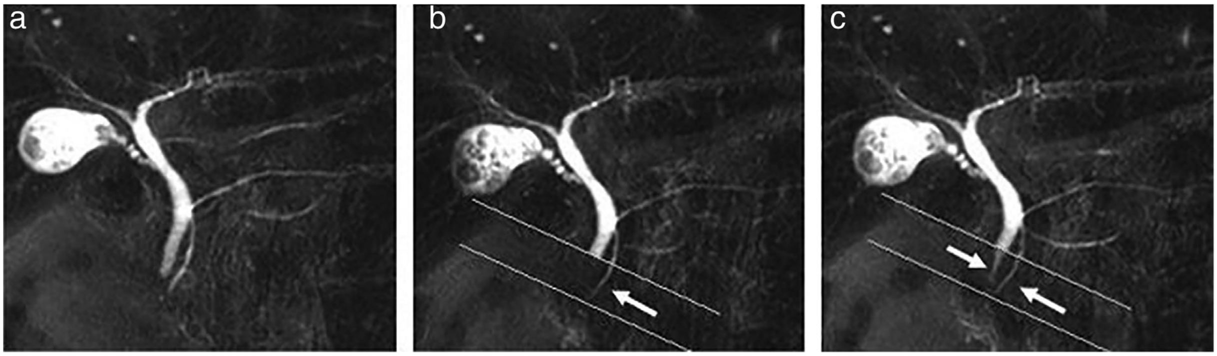

FIGURE 2: A 54-year-old woman with cholelithiasis in the normal group. (a) MRCP image without a spatially selective IR pulse obtained as a reference image. (b,c) Representative images of the antegrade pancreatic juice flow and no bile flow (P_A–B_N) pattern and the antegrade pancreatic juice flow and antegrade bile flow (P_A–B_A) pattern observed during cine-dynamic MRCP with a spatially selective IR pulse. (b) The antegrade flow of the pancreatic juice was observed as high signal intensity (arrow) within the area of the spatially selective IR pulse. The secretion grade of the antegrade pancreatic juice flow was categorized as grade 4. The flow pattern of the pancreatic juice and bile was classified as P_A–B_N pattern. (c) The antegrade flow of the pancreatic juice and bile was observed as high signal intensity (arrows). The secretion grade of the antegrade flow of the pancreatic juice and bile was categorized as grade 4 and grade 3, respectively. The flow pattern of the pancreatic juice and bile was classified as P_A–B_A pattern.

four pancreatic juice flow patterns and the four bile flow patterns as follows: P_A–B_A, P_A–B_R, P_A–B_{A+R}, P_A–B_N, P_R–B_A, P_R–B_R, P_R–B_{A+R}, P_R–B_N, P_{A+R}–B_A, $P_{A+R}B_R$, P_{A+R}–B_{A+R}, P_{A+R}–B_N, P_N–B_A, P_N–B_R, P_N–B_{A+R}, and P_N–B_N. The reviewers also evaluated how often each flow pattern was observed in all of the images of each patient group. The maximal diameter of the common bile duct and main pancreatic duct was measured by two radiologists (M.T. and M.H., with 19 and 6 years of clinical experience, respectively), perpendicularly to the long axis on MRCP images without the IR pulse using an electronic caliper. The mean measurements of the two observers were used for analysis.

Statistical Analysis

Statistical analyses were performed using the SPSS software program (version 20.0 for Windows; IBM Corp., Armonk, NY, USA). Interobserver agreement among the three radiologists was evaluated using Fleiss κ statistics. The κ values were interpreted as follows: less than 0.40, poor agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.80 or higher, excellent agreement. A Spearman's rank correlation coefficient analysis was performed to evaluate the correlation between the MRI measurements and age. Kruskal–Wallis and Mann–Whitney *U* tests were used for comparison of MRI measurements among the groups. For the comparison of the flow patterns of the pancreatic juice and bile among the groups, the chi-squared and Fisher's exact test were performed. *P* values of <0.05 were considered to indicate statistical significance.

Results

One hundred ninety-three consecutive patients met our inclusion criteria. Among these patients, 89 patients were excluded for one of the following reasons: pancreatobiliary or duodenal disease, or conditions that could affect the physiological flow of bile or pancreatic juice ($n = 39$); unclear visualization of the common bile duct or main pancreatic duct due to artifacts or duct obstruction ($n = 29$); large tumor of the pancreatic head that interfered with the evaluation of the bile or pancreatic juice flow on cine-dynamic MRCP ($n = 11$); displacement or unclear visualization of a spatially selective IR pulse ($n = 8$); and incomplete cine-dynamic

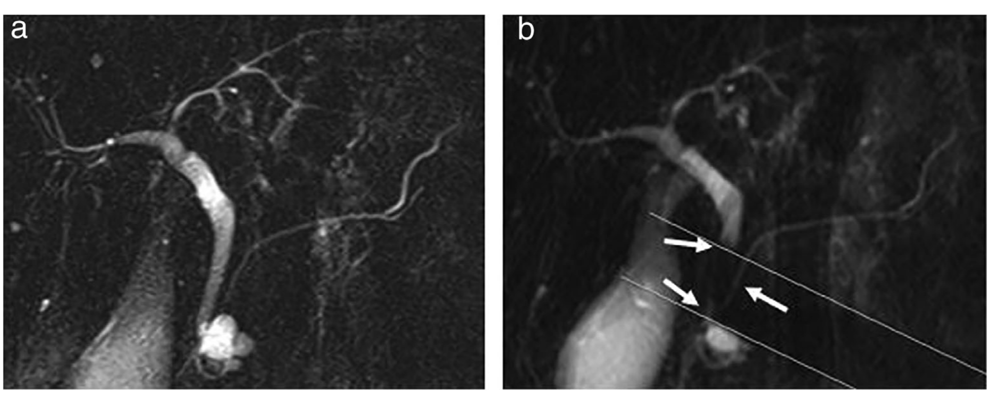

FIGURE 3: A 52-year-old woman with branch-duct intraductal papillary mucinous neoplasms in the normal group. (a) MRCP image without a spatially selective IR pulse obtained as a reference image. (b) Representative image of the antegrade pancreatic juice flow and reverse bile flow (P_A–B_R) pattern observed during cine-dynamic MRCP with a spatially selective IR pulse. The antegrade pancreatic juice flow and the reversed bile flow (oppositely directed flow) were observed simultaneously (arrows) on the cine-dynamic MRCP image with a spatially selective IR pulse. The secretion grade of the antegrade pancreatic juice flow and the reversed bile flow was categorized as grade 4 and grade 1, respectively. The flow pattern of the pancreatic juice and bile was classified as P_A–B_R pattern.

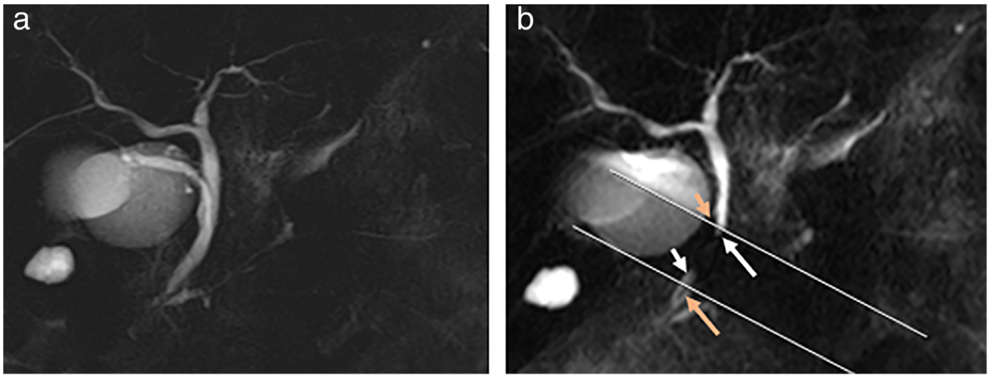

FIGURE 4: A 66-year-old woman with cholelithiasis in the normal group. (a) MRCP image without a spatially selective IR pulse obtained as a reference image. (b) Representative image of the no pancreatic juice flow and simultaneously observed antegrade and reverse flow of bile (P_N–B_{A+R}) pattern observed during cine-dynamic MRCP with a spatially selective IR pulse. The antegrade bile flow (long arrows) and the reversed bile flow (short arrows) were observed simultaneously (oppositely directed flow) on the cine-dynamic MRCP image with a spatially selective IR pulse. The antegrade bile flow (long arrows) is shown as flow-in high signal (white long arrow) within the area of the IR pulse and flow-out low signal (red long arrow) just outside the area of IR pulse. Conversely, the reversed bile flow (short arrows) was observed within the area of the IR pulse as flow-in high signal (white short arrow) from papilla vater side, and shown as flow-out low signal (red short arrow) just outside the area of IR pulse. The secretion grade of both the antegrade bile flow and the reversed bile flow was categorized as grade 1. The flow pattern of the pancreatic juice and bile was classified as P_N–B_{A+R} pattern.

MRCP ($n = 2$). Finally, 104 patients were included in this study. Among these, 85 patients (male, $n = 45$; female, $n = 40$; median age, 71 years [range, 40–88 years]) were enrolled as the normal group. These included patients with hepatobiliary diseases ($n = 42$), including adenomyomatosis ($n = 16$), cholelithiasis ($n = 15$), hepatic hemangioma ($n = 3$), liver cyst ($n = 3$), benign intrahepatic biliary stricture ($n = 1$), peribiliary cyst ($n = 1$), cholecystitis ($n = 1$), fatty liver ($n = 1$), and hepatocellular carcinoma ($n = 1$); patients with pancreatic diseases ($n = 35$) such as branch-

TABLE 2. Comparison of the MRI Findings and Measurements Between the Normal Group and the Dilated Pancreatic Duct Group

	Normal Group ($n = 85$)	Dilated Pancreatic Duct Group ($n = 19$)	P value
Age (y)	71 (62–77)	75 (69–79)	0.072
Diameter of main pancreatic duct (mm)	2 (2–3)	4 (4–5.5)	<0.001
Diameter of common bile duct (mm)	6 (5–8)	7 (5.5–8)	0.210
Frequency of antegrade pancreatic juice flow observed	13 (8–16)	3 (0–9)	<0.001
Secretion grade of antegrade pancreatic juice flow	0.9 (0.5–1.4)	0.25 (0–0.48)	<0.001
Frequency of reversed pancreatic juice flow observed	0 (0–0)	0 (0–0)	0.931
Secretion grade of reversed pancreatic juice flow	0 (0–0)	0 (0–0)	0.995
Frequency of antegrade bile flow observed	6 (1–10)	2 (0–5.5)	0.008
Secretion grade of antegrade bile flow	0.35 (0.1–0.6)	0.1 (0–0.28)	0.006
Frequency of reversed bile flow observed	3 (1–6)	1 (0–5)	0.092
Secretion grade of reversed bile flow	0.2 (0.05–0.4)	0.05 (0–0.28)	0.129

Data are median with 25th and 75th percentiles in parentheses.

TABLE 3. Comparison of the MRI Findings and Measurements Among the Three Age-Range Groups

	Group1 ($n = 27$)	Group 2 (i = 34)	Group 3 ($n = 24$)	*P* value
Age range (y)	≤65	66–75	≥76	
Diameter of main pancreatic duct (mm)	2 (2–2)	2 (2–3)	2.75 (2–3)	0.018
Diameter of common bile duct (mm)	6 (4–7)	6.75 (6–7.88)	7 (5.88–8)	0.099
Frequency of antegrade pancreatic juice flow observed	14 (10.5–17)	13 (9–16)	11.5 (3.75–15.25)	0.154
Secretion grade of antegrade pancreatic juice flow	0.95 (0.63–1.7)	0.98 (0.65–1.39)	0.63 (0.24–1.26)	0.167
Frequency of reversed pancreatic juice flow observed	0 (0–0)	0 (0–1)	0 (0–0)	0.487
Secretion grade of reversed pancreatic juice flow	0 (0–0)	0 (0–0.05)	0 (0–0)	0.519
Frequency of antegrade bile flow observed	7 (3–11)	7.5 (2.25–10.75)	4 (0–8.25)	0.188
Secretion grade of antegrade bile flow	0.4 (0.15–0.73)	0.4 (0.11–0.55)	0.25 (0–0.53)	0.515
Frequency of reversed bile flow observed	4 (1–7)	3 (1–6)	3 (0–5)	0.765
Secretion grade of reversed bile flow	0.2 (0.05–0.4)	0.23 (0.063–0.35)	0.18 (0–0.35)	0.878

Data are median with 25th and 75th percentiles in parentheses.

duct intraductal papillary mucinous neoplasms ($n = 30$), pancreatic neuroendocrine tumor ($n = 3$), primary pancreatic lymphoma ($n = 1$), and pancreatic lipoma ($n = 1$); and patients with no diseases ($n = 8$). The remaining 19 patients (male, $n = 13$; female, $n = 6$; median age, 75 years [range, 57–85 years]) were enrolled as the dilated pancreatic duct group. The underlying diseases in these patients included intraductal papillary mucinous neoplasms ($n = 13$), pancreatic cyst ($n = 1$), pancreatic gastrointestinal stromal tumor ($n = 1$), and pancreatic ductal dilatation of unknown cause ($n = 4$).

The interobserver agreement for the frequency of observation of antegrade and reverse pancreatic juice flow and the grade of the moving distance of antegrade and reverse pancreatic juice flow with cine-dynamic MRCP was excellent (κ value = 0.959). The interobserver agreement for the detection of antegrade and reverse bile flow and the grade of the moving distance of antegrade and reverse bile flow was also excellent (κ value = 0.922).

The results of the flow patterns of the pancreatic juice and bile are shown in Table 1 and Figures 1–4. The P_A–B_N pattern was the most frequent flow pattern in the normal group (29%, 485/1700 images), followed by the P_N–B_N pattern (23%, 393/1700 images) and P_A–B_A pattern (22%, 367/1700 images). In the normal group, the flow of the pancreatic juice and bile were synchronized with each other in 47% of the observations (P_A– B_A pattern: 22%, P_R–B_R pattern: 2%, and P_N–B_N pattern: 23%), while they were not synchronized in 53%. Conversely, in the dilated pancreatic duct group, the P_N–B_N pattern was the most frequent flow pattern (56%, 212/380 images), followed by the P_A–B_N pattern (16%, 59/380 images), indicating that several flow patterns, including the P_A pattern were less likely to be observed in the dilated pancreatic duct group than in the normal group, while the P_N–B_N pattern was more likely to be observed in the dilated pancreatic duct group than in the normal group.

In the comparison of MRI findings and measurements between the normal group and the dilated pancreatic duct group (Table 2), the diameter of the main pancreatic duct in the dilated pancreatic duct group (4 [range, 4–5.5] mm) was significantly larger than that in the normal group (2 [range, 2–3] mm), while the diameter of the common bile duct and age did not differ to a statistically significant extent ($P = 0.210$ and $P = 0.072$, respectively). Regarding the cine-dynamic MRCP findings, the frequency and mean secretion grade of the antegrade pancreatic juice flow were significantly lower in the dilated pancreatic duct group than in the normal group (frequency, 3 [range, 0–9] times vs. 13 [range, 8–16] times; mean secretion grade, 0.25 [range, 0–0.48] vs. 0.9 [range, 0.5–1.4]). Additionally, the frequency and mean secretion grade of the antegrade bile flow in the dilated pancreatic duct group were significantly lower in comparison to the normal group (frequency, 2 [range, 0–5.5] times

TABEL 4. Comparison of the Flow Patterns of the Pancreatic Juice and Bile Among the Three Age-Range Groups

	Group1 (n = 27)	Group 2 (n = 34)	Group 3 (n = 24)	*P* value
Age range (y)	≤65	66–75	≥76	
Number of images	540	680	480	
Flow pattern				
P_A–B_A	133 (25)	157 (23)	77 (16)	0.002
P_A–B_R	42 (8)	40 (6)	13 (3)	0.002
P_A–B_{A+R}	12 (2)	29 (4)	6 (1)	0.006
P_A–B_N	159 (29)	195 (29)	131 (27)	0.745
P_R–B_A	3 (0.6)	0 (0)	0 (0)	0.054
P_R–B_R	4 (0.7)	16 (2)	13 (3)	0.046
P_R–B_{A+R}	1 (0.2)	0 (0)	0 (0)	0.600
P_R–B_N	2 (0.4)	3 (0.4)	1 (0.2)	0.884
P_{A+R}–B_A	0 (0)	0 (0)	0 (0)	-
P_{A+R}–B_R	0 (0)	0 (0)	1 (0.2)	0.282
P_{A+R}–B_{A+R}	0 (0)	0 (0)	0 (0)	-
P_{A+R}–B_N	0 (0)	0 (0)	0 (0)	-
P_N–B_A	28 (5)	47 (7)	32 (7)	0.432
P_N–B_R	49 (9)	42 (6)	54 (11)	0.008
P_N–B_{A+R}	9 (2)	8 (1)	0 (0)	0.024
P_N–B_N	98 (18)	143 (21)	152 (32)	<0.001

Data are given as the number of the flow pattern observed with percentages in parentheses.

vs. 6 [range, 1–10] times; mean secretion grade, 0.1 [range, 0–0.28] vs. 0.35 [range, 0.1–0.6]). In contrast, when the normal group and the dilated pancreatic duct group were compared, the differences in the frequency and mean secretion grade of the reverse flow of the pancreatic juice (frequency, $P = 0.931$; mean secretion grade, $P = 0.995$) and bile (frequency, $P = 0.092$; mean secretion grade, $P = 0.129$) were not significant.

In the normal group, the mean secretion grade of antegrade pancreatic juice flow significantly decreased with age ($r = -0.222$), while no significant correlation was found between the frequency of antegrade pancreatic juice flow and age ($r = -0.205$, $P = 0.060$; 95% confidence intervals of -0.406 to 0.015). The frequency and mean secretion grade of reverse pancreatic juice flow (frequency, $r = 0.067$, $P = 0.541$; mean secretion grade, $r = 0.060$, $P = 0.588$), antegrade bile flow (frequency, $r = -0.158$, $P = 0.149$; mean secretion grade, $r = -0.122$, $P = 0.267$) and reverse bile flow (frequency, $r = -0.034$, $P = 0.758$; mean secretion grade, $r = -0.016$, $P = 0.882$) also showed no significant correlation with age. Additionally, the diameter of the main pancreatic duct ($r = 0.323$) and that of the common bile duct ($r = 0.251$) were significantly and positively correlated with age.

In the comparison among the three age-range groups (Tables 3 and 4), the diameter of the main pancreatic duct in group 3 (2.75 [range, 2–3] mm) was significantly larger than that in group 1 (2 [range, 2–2] mm) and group 2 (2 [range, 2–3] mm), while no significant difference in the diameter of the common bile duct was observed ($P = 0.099$). Regarding the cine-dynamic MRCP findings, there were no significant differences in the frequency or mean secretion grade of the antegrade and reverse flow of the pancreatic juice and bile among the three groups. However, the frequency and mean secretion grade of the antegrade flow of the pancreatic juice (frequency, $P = 0.154$; mean secretion grade, $P = 0.167$) and bile (frequency, $P = 0.188$; mean secretion grade, $P = 0.515$) tended to be lower in group 3 than in groups 1 and 2. Reflecting this tendency, in particular, the proportion of the P_A–B_A pattern in all images of group 3 (16%, 77/470 images) was significantly lower in comparison to that in group 1 (25%, 133/540 images) and group 2 (23%, 157/680 images). Conversely, the P_N–B_N pattern was significantly more frequently observed in group 3 (32%, 152/480 images) than in group 1 (18%, 98/540 images) or group 2 (21%, 143/680 images).

Discussion

Findings of our study showed the many variations of the physiological flow patterns of bile and pancreatic juice. In the normal group, the P_A–B_N pattern was the most frequent flow pattern, followed by the P_N–B_N pattern and P_A–B_A pattern. The flow of the pancreatic juice and bile were synchronized with each other in 47%, while they were not in 53%.

Since the common bile duct and the main pancreatic duct are confluent at the papilla, forming a common channel, and pancreatic juice and bile are excreted into the duodenum from there, it may be assumed that the timing of the excretion of pancreatic juice and bile is usually linked. However, the findings of our study showed that the physiological flow of pancreatic juice and bile were not synchronized with each other in 53% of the observations, with many variations in the timing and direction in the normal group. These unsynchronized variations may be associated with differences in the triggers that induce the flow of pancreatic juice and bile, respectively.[12,13]

The flow of pancreatic juice and bile appear to be primarily controlled by the "shutter" functions of the sphincter of Oddi with basal pressure of 15 mmHg.[2,11] However, in the P_A–B_N pattern, given that the main pancreatic duct pressure is usually greater than the common bile duct pressure,[14] the pancreatic juice appeared to have flowed out into the duodenum dominantly, triggered by an increase in intrapancreatic ductal pressure, which frequently exceeded the basal pressure of Oddi. In contrast, intrabile duct pressure is ordinarily lower than the basal pressure of Oddi due to the buffer function of the gallbladder in the collection of bile. However, in the P_N–B_A pattern, the bile is likely to flow out into the duodenum dominantly, triggered by contraction of the gallbladder, which increases the internal pressure of the bile duct.[15]

In contrast, regarding the reverse flow of the pancreatic juice and bile, which may be the counteractive flow induced by contraction of the sphincter of Oddi, the bile can be more likely than pancreatic juice to show retrograde flow due to the low intrabile duct pressure,[14] which may be a reason for the relatively high frequency of the P_N–B_R pattern. Thus, our findings suggest that the occurrence of each variation in the flow patterns of the pancreatic juice and bile visualized by cine-dynamic MRCP with a spatially selective IR pulse may be reasonable, mainly reflecting the physiological interrelationship between the Oddi function and the intraductal pressure. Recognition of these normal variations would be essential since the flow dynamics patterns of the bile and pancreatic juice are expected to change depending on pathological conditions, such as functional disorder of the sphincter of Oddi, dysfunction of gallbladder contractility, and pathological changes in intraductal pressure[16–18] although these presumptions need to be confirmed in the clinical study using patients with these pathologic conditions as the next step.

In this study, notable variations in the flow patterns of the pancreatic juice and bile, the P_A–B_R pattern, and the P_R–B_A pattern, were observed in the normal group. These flow patterns might imply the findings of pancreatobiliary and biliopancreatic reflux. This two-way regurgitation usually occurs in patients with a long common channel, such as anomalous union of pancreaticobiliary duct, in whom the sphincter action does not functionally affect the pancreaticobiliary junction.[19] However, pancreatobiliary and biliopancreatic reflux can also occur in patients with a morphologically normal pancreaticobiliary junction, and previous studies showed that such cases included dysfunction of the sphincter of Oddi, common bile duct dilatation, choledocholithiasis, periampullary diverticula, as well as patients who have undergone endoscopic sphincterotomy or endoscopic papillary balloon dilatation.[9,10,20–22] Thus, the patients with these patterns in the normal group might have occult pancreatobiliary and biliopancreatic reflux caused by occult dysfunction of the sphincter of Oddi. Because occult pancreatobiliary and biliopancreatic reflux are associated with various pancreaticobiliary diseases, including biliary cancer and acute pancreatitis,[9,19,23] the early detection of this regurgitation would be important for optimal patient management such as careful follow-up and effective treatment of the sphincter of Oddi dysfunction. Thus, cine-dynamic MRCP with a spatially selective IR pulse might have the potential to make an early and non-invasive diagnosis of occult pancreatobiliary and biliopancreatic reflux.

Our results suggest that the antegrade pancreatic juice flow in patients with main pancreatic duct dilatation was stagnant or slowed down in comparison to the patients in the normal group. In addition, a decrease of antegrade bile flow was observed in patients with main pancreatic duct dilatation in spite of the absence of common bile duct dilatation. Reflecting these changes in the antegrade flow of the pancreatic juice and bile, several flow patterns—especially those including the P_A pattern—were less frequently observed, while the P_N–B_N pattern was more frequently observed in patients with main pancreatic duct dilatation than in patients without diseases of the main pancreatic duct or extrahepatic bile duct. Although the relationship between pancreatic duct dilatation and bile flow has not been clearly elucidated, a previous study showed that bile secretion was decreased in the presence of pancreatic damage, such as fibrosis and degeneration of the pancreas.[24] The exact cause of main pancreatic duct dilatation in this study group was unknown. However, in the dilated pancreatic duct group, the majority of patients had intraductal papillary mucinous neoplasms, which have been often associated with pancreatitis, although there were no patients with clinical pancreatitis. In addition, the pathology of intraductal papillary mucinous neoplasms has shown that the pancreatic parenchyma close to the dilated pancreatic duct usually shows mild-to-moderate fibrosis and acinar atrophy, which are typical of obstructive chronic pancreatitis microscopically.[25] Thus, a decrease of the antegrade flow of bile and pancreatic juice in patients with pancreatic duct dilatation could occur as a result of subtle chronic pancreatitis.

Regarding the relationship with age, our results indicate that—with the exception of antegrade pancreatic juice flow—the physiological flow of pancreatic juice and bile is not affected by aging, and our findings are in accordance with those of previous studies.[5,26]

Limitations

First, this study was retrospective and the number of patients in the dilated pancreatic duct group was relatively small. Second, the median age of the dilated pancreatic duct group was higher than that of the normal group. Hence, the accumulation of more data with a large age-matched patient population is needed to confirm our results. The age of patients in the normal group was also relatively high, and this group included patients with various hepatobiliary or pancreatic diseases; however, these diseases were not considered to affect the physiological flow of the bile or pancreatic juice. Thus, our results shown as the physiological flow patterns of bile and pancreatic juice may be not representative across a broader population. Although it was not practical to perform MRI examinations, including cine-dynamic MRCP, in patients without pancreatobiliary disease, it will be better to be tested on normal volunteers to confirm our results in the further study. Third, MRI examinations were performed under a fasting condition in this study, and the influence of food intake was not considered. The food intake could obviously affect the flow dynamics of the bile and pancreatic juice because of the increased secretion of bile and pancreatic juice and the activation of gallbladder contractility.[15,27] Finally, regarding the reverse flow of bile and pancreatic juice, the contents of the common bile duct and main pancreatic duct could not be directly confirmed. The contents may include bile, pancreatic juice, duodenal fluid, or their mixture.[28] Thus, further evaluation in combination with the measurement of the amylase level in bile and computed tomography combined with drip infusion cholangiography is needed to validate our results.[19]

Conclusion

Cine-dynamic MRCP with a spatially selective IR pulse can visualize the variations of the physiological flow patterns of bile and pancreatic juice In the present study, the flow of pancreatic juice and bile were not synchronized with each other in 53% of the observations. It is essential to recognize these normal variations because the flow dynamic patterns of the bile and pancreatic juice are expected to change depending on the presence of main pancreatic duct dilatation and may also be affected by functional disorder of the sphincter of Oddi.

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